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Circular

Guidance documents for Zonal, Sub zonal & Port offices was prepared in 2011 and implemented since then. It sets out nature of work that Zonal, Sub zonal & Port offices generally carry out and the guidelines about the policy that should be followed in disposing of work & duties.

In recent times there are many changes in the procedures of Zonal, Sub zonal & Port offices activities due to introduction of new Rules and regulation, online system through SUGAM portal and delegation of some activity to state Drugs Authority etc. Hence it was needed to amend/revise the Guidance documents inline with the recent procedures followed by Zonal, Sub zonal & Port offices

To undertake the revision of Guidance documents for Zonal, Sub zonal & Port offices a team was constituted vide order ref.no. GBT/RS/SS/NRS/2023-24 dated.26.12.2023. The team submitted the draft document with respect to their responsibilities for preparation of first draft by team comprising of officials from CDSCO.

The guidance drafted & reviewed was shared with all officials (DDC (I) level) of CDSCO HQ/Zones/Sub-Zone/Port offices to provide comments/suggestions/inputs if any and the same was deliberated on 02.09.2024 virtually with all CDSCO Zonal, Sub zonal & Port offices & CDSCO(HQ) officials. Accordingly, revised and finalised Guidance documents for Zonal, Sub zonal & Port offices (revision: 01, 2024) is prepared to ensure uniform procedures in the execution of various regulatory process by Zonal/ Sub zonal & port offices of CDSCO.

(Dr.Rajeev Singh Raghuvanshi)
Drugs Controller General (India)

To,

All Zonal/Sub zonal/Port offices and IT cell for upload in the web site.

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Guidance Document
for
Functions and Responsibilities
of
Zonal, Sub-zonal & Port offices of CDSCO

Revision:01

Central Drugs Standard Control Organization

Directorate General of Health Services,

Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

2024

PREFACE

This is in consonance with the objective of the Drugs & Cosmetic Act 1940 and Rules thereunder and other functions of CDSCO wherever applicable.

These guidelines are intended for the guidance of Departmental offices only. It sets out the nature of work that the Zonal, Sub-Zonal and Port offices of the Central Drugs Standard Control Organization generally carry out and the guidelines about the policy that should be followed in disposing of the work & duties.

This guidance document is for internal work procedures within CDSCO offices and CDSCO (HQ) for bringing uniformity, transparency, predictability and accountability of all CDSCO offices for the functions/ activities executed. This guidance document does not supersede Rules and in case of any dispute, Rules shall prevail over guidance document.

While all conceivable item of work that pass through the Central Drugs Standard Control Organization at the Zone, Sub-Zone & Ports, have been included in these guidelines, there may be certain omissions. This guidance document is dynamic in nature and may be amended from time to time as per requirements after obtaining necessary approval from the competent authority.

INTRODUCTION

A guidance document for functions and responsibilities of Zonal, Sub-zonal & Port offices of CDSCO was published in the year 2011 to ensure that the activities of all the subordinate offices under the control of the Drugs Controller General (India) are implemented uniformly & rationally in consonance with the Drugs & Cosmetics Act & Rules thereunder so that the whole system functions transparently.

It is now felt necessary to revise the guidance document of 2011 to align the current practices, procedures of CDSCO with that in the guidance document. This includes amendment/ revision in various rules, implementation of online system of application, review, processing and issuance of permissions/ letters for various activities of the Zonal, Sub-zonal & Port offices. This is also required that all the activities of all the offices are linked with CDSCO (Head Quarter) and the day-to-day activity is recorded electronically and shared with the office of Drugs Controller General (India) and other subordinate offices in regular and time bound manner through a network of communication.

In view of the above objectives, the following current working procedures are suggested to be carried out by all the subordinate offices under the control of the Drugs Controller General (India).

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ORGANISATION SET-UP OF CENTRAL DRUGS STANDARD CONTROL ORGANISATION (CDSCO)

The Drugs Controller General (India) is the head of Central Drugs Standard Control Organisation (CDSCO). The CDSCO with its Headquarters in New Delhi has 08 Zonal offices, 07 Sub-Zonal offices, 08 Central Drugs Testing Laboratories and 09 Air Port & 19 Sea port Offices (including Inland Container Depots and excluding some notified ports) as given below:

BROAD FUNCTIONS & ACTIVITIES OF ZONAL & SUB ZONAL OFFICES

All the Zonal Offices are headed by Dy. Drugs Controller (India) who is assisted by Assistant Drugs Controller (India), Drugs Inspectors, Assistant Drugs Inspectors Technical Officers, Senior Technical Assistants & Technical Assistants for the technical work and a group of Ministerial staff including one Head Clerk and other subordinate staff in the administrative work. Different subzonal offices are headed by Dy. Drugs Controller (India)/ Assistant Drugs Controller (India) who is assisted by Assistant Drugs Controller (India) [in case where Dy. Drugs Controller (India) is heading the sub zonal office], Drugs Inspectors, Assistant Drugs Inspectors, Technical Officers, Senior Technical Assistants & Technical Assistants for the technical work. Port offices headed by Assistant Drugs Controller (India)/ Drugs Inspector/ Technical Officer are also under the direct control of the Dy. Drugs Controller (India) of the respective zone for technical as well as administrative function. Following are the broad functions, activities and duties of the zonal and sub-zonal offices:-

TECHNICAL FUNCTIONS:-

1. To scrutinize the application and participate in the joint inspection for issuance /revalidation of Certificate of Pharmaceutical Products (COPPs) as per WHO certification scheme after receiving the application from the manufacturing firm.
2. To scrutinize the application and participate in the joint inspection for grant /retention of license for manufacturing or risk based inspection atleast once in three-year as per GSR 1337(E) dated 27.10.2017.
3. To scrutinize the application and participate in the joint inspection for grant/renewal of Blood Center license.
4. To scrutinize the application and participate in the joint inspection for grant/retention of license for all biologicals (vaccine, anti-sera, r-DNA, biosimilars, blood products etc.) manufacturing units (both human as well as veterinary).
5. To scrutinize the application and participate in the joint inspection for grant/retention of license for LVP manufacturing units.
6. To scrutinize the application and carry out the inspection for grant/retention of license for Class C & D Medical Devices/ In-Vitro Diagnostic manufacturing unit under Medical Devices Rules, 2017.
7. To participate in the inspection of Clinical Trial facilities and BA/BE centers as directed by the Drugs Controller General (India) from time to time as per the provision of New Drugs & Clinical Trials Rules, 2019.
8. To carry out Surprise check/Raid jointly/independently on the basis of complaint received under Whistle Blower scheme and also from other sources.
9. To carry out risk based inspections of manufacturing/ testing facilities as per directives received from CDSCO(HQ).
10. To carry out joint inspection of Drug Testing Laboratory for the purpose of grant of approval for test / analysis of Drugs & Cosmetics.

11. To process the application for Written Confirmation (WC) for export of API to European Union as per EU Directives and their inspection, if required.
12. To follow up action on NSQ drugs with State Licensing Authorities in the respective zone as well as with other zonal offices.
13. Drawing of regular drugs samples from the manufacturing & sales / distribution premises including the Govt. establishment.
14. When the samples drawn by the Central Drugs Inspector are declared spurious / adulterated / grossly substandard etc., the cases are investigated and prosecutions are launched in the appropriate court after obtaining necessary sanction from the Drugs Controller General (India).
15. Information regarding cancellation/suspension of manufacture licenses or withdrawal of product permission by the State Licensing Authority is circulated to other State Licensing Authorities in the zone and other zonal offices.
16. Deputation of Drugs Samplers at various places of suspicious nature and collect samples through them as surrogate patient from the sales premises by way of survey to monitor the quality of drugs. Further surprise check/raid is to be carried out by the Drugs Inspectors in case these samples are declared as NSQ by the testing lab.
17. To pursue the court cases pending in different courts under the zone.
18. Technical survey as and when directed by the Drugs Controller General (India) from time to time.
19. To discuss all matter related to enforcement of the provisions of D&C Act & Rules thereunder with various State Drugs Controllers in the zone from time to time.
20. To monitor the statutory work of Drugs Inspector working under the zonal and sub-zonal offices.
21. To co-ordinate for answering the Parliament Questions and for obtaining the data from various State Licensing Authorities under the zonal and sub-zonal offices.
22. Preparation of Monthly / Quarterly / Annual Reports.
23. To co-ordinate with various international regulatory agencies for inspections conducted by various international regulatory agencies as and when directed.
24. To organize workshop, seminar etc. as directed.
25. To conduct the function of Drugs Controller General (I) as and when delegated by him under Rule 22 & 122L and other rules of the Drugs & Cosmetics Act. Presently, the following functions are delegated to respective zonal officers for carrying out on his behalf: -
    a. Permission for grant of license to manufacture drugs for the purpose of examination, test or analysis under the New Drugs & Clinical Trials Rules, 2019 in Form CT-11 for new drugs/investigational new drugs (Active Pharmaceutical Ingredients & formulations), CT-14 (Unapproved Formulations) and CT-15 (unapproved APIs) so as to obtain license from State Licensing Authority (SLA) of concerned State under Rules 89 of the Drugs and Cosmetics Rules, 1945 on Form-29 as per requirements (except biological drugs).
    b. Grant of license for import of small quantities of old drugs in Form-11 for the purpose of examination, test or analysis as provided under Rule 33 of the Drugs and Cosmetics Rules, 1945 and for import of small quantities of new drugs in CT-17 under the provisions of NDCT Rules, 2019 (except biological drugs).
    c. Grant of license for import of small quantities of unapproved new drugs in Form CT- 25 by Government Institutions or Autonomous Medical Institutions for treatment of patients under Rule 86 of New Drugs and Clinical Trial Rules, 2019.
    d. No objection certificates (Dual use NOC) for grant of permissions for import of dual use items, not for medicinal use as provided under Rule 89 of the Drugs and Cosmetics Rules.

e. No objection certificates for grant of permissions for manufacture for export only of unapproved / approved new drugs and drugs banned under Section 26-A of the Drugs and Cosmetics Act.
f. Grant of license for import of small quantities of drugs for personal use under Form 12B of the Drugs and Cosmetics Rules.

b. Any other functions as assigned by JDC(I)/ DCG(I) from time to time.

ADMINISTRATIVE FUNCTIONS:-

1. Maintenance of Service records/leave records of Gazetted and Non-Gazetted Staff.
2. Matters related to confirmation and filling of posts wherein concerned zonal officer is the appointing authority.
3. Promotion of staff, recruitment of staff, relieving of staff and maintenance of seniority of Non-Gazetted employees.
4. To arrange DPC for eligible candidates to give regular promotion and under MACP Scheme to Group C & D Staff.
5. Maintenance of Rosters for Group C & D posts.
6. Preparation of annual budgets /preliminary and final estimate of expenditure etc.
7. Sanction of increments/fixation of Pay etc.
8. Preparation of reports/replies concerning to the above administrative function.
9. Handling of Cash and Accounts and maintenance of its records.
10. Preparation and submission of all types of bills including arrears, loans, TA/DA and advances to Pay & Accounts Office and maintenance of its records.
11. Preparation of Accounts reports-Monthly, Quarterly, Half Yearly and annual and maintenance of its records.
12. Maintenance of G.P.F. Records in respect of Group-D employees and correspondence regarding G.P.F. in respect of other staff.
13. Reconciliation work of Cash & Accounts with concerned PAO.
14. Purchase of perishable and non-perishable store items and maintenance of its records.
15. Maintenance of all the documents.
16. To maintain the inventory and account of scientific books and journals etc.
17. Preparation of monthly, half yearly and annual return concerning to income tax through a qualified Chartered Accountant.
18. Annul Maintenance Contract (AMC) of office equipment and machineries etc.
19. All other administrative returns after receiving the queries from Directorate / Ministry from time to time.
20. Preparation of documents and bills in case of superannuation.
21. Reply under RTI Act.
22. Any other functions assigned by DCG(I) / DDC(I) from time to time

ACTIVITIES OF ZONAL & SUB-ZONAL OFFICES OF CDSCO AND TARGETED TIMELINES

The zonal / sub-zonal offices deal with various applications. The targeted time lines and subsequent actions for disposal of the applications received in the office of zonal/sub-zonal offices is as follows: -

Nature of application	Targeted time lines	First response & Action to be taken
Grant or renewal of Blood Centre license.	Targeted time line should be **21 working days** from the date of submission of the application for scrutiny of the documents.	In case some deficiencies are observed in the documents, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed to the State Licensing Authority with a copy endorsed to the applicant. On conformation of the date, inspection to be carried out and the application shall be disposed of.
Grant or retention of Vaccine manufacturing licenses	Targeted time line should be **30 working days** from the date of submission of the application for scrutiny of the documents.	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed to the State Licensing Authority with a copy endorsed to the applicant. On conformation of the date, inspection to be carried out and the application shall be disposed of.
Grant of Medical Devices Manufacturing licenses	Completion of scrutiny of online submission of application shall be carried out within **45 days.** Inspection for grant of licence or loan licence for Class C or Class D medical device shall be carried out within a period of **60 days** from the date of application. Grant of licence or loan licence to manufacture for sale or for distribution by the Central Licensing Authority, after receipt of the report shall be granted within a period of **45 days** from the date the inspection report has been received.	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed. On conformation of the date, inspection to be carried out and the application shall be disposed of.

Approval of Institution for carrying out Test on Drugs, Cosmetics and Raw materials as prescribed under Rule 150F of Drugs & Cosmetics Rules.	Targeted time line should be **21 working days** from the date of submission of the application for scrutiny of the documents.	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed to the State Licensing Authority with a copy endorsed to the applicant. On conformation of the date, inspection to be carried out and the application shall be disposed of.
Grant of LVP manufacturing licenses.	Targeted time line should be **21 working days** from the date of submission of the application for scrutiny of the documents.	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed to the State Licensing Authority with a copy endorsed to the applicant. On conformation of the date, inspection to be carried out and the application shall be disposed of.
Grant or retention of Bio-Tech/Biosimilar products/ blood products manufacturing licenses	Targeted time line should be **30 working days** from the date of submission of the application for scrutiny of the documents.	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed to the State Licensing Authority with a copy endorsed to the applicant. On conformation of the date, inspection to be carried out and the application shall be disposed of.
For inspection of BA/BE studies and Clinical Trial site.	Targeted time line should be **30 working days** from the date of submission of the application for scrutiny of the documents.	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed. On conformation of the date, inspection to be carried out and the application shall be disposed of.
Grant or revalidation of COPPs	Targeted time line should be **28 working days** from the date of submission of the application for scrutiny of the documents.	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed to the State Licensing Authority with a copy endorsed to the applicant. On conformation of the date, inspection to be carried out and the application shall be disposed of.
Issuance of COPPs for additional products	Targeted time line should be **21 working days** from the date of submission of the	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed to the State

	application for scrutiny of the documents.	Licensing Authority with a copy endorsed to the applicant. On conformation of the date, inspection to be carried out and the application shall be disposed of.
Grant/ renewal/ endorsement of Written Confirmation (WC)	Targeted time line should be **21 working days** where no inspection is required & **30 working days** where inspection is required from the date of submission of the application for scrutiny of the documents.	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed. On conformation of the date, inspection to be carried out and the application shall be disposed of.
Permission for grant of license to manufacture drugs for the purpose of examination, test or analysis under the New Drugs & Clinical Trials Rules, 2019 in Form CT-11 for new drugs/investigational new drugs (Active Pharmaceutical Ingredients & formulations), CT-14 (Unapproved Formulations) and CT-15 (unapproved APIs).	Targeted time line should be **15 working days** from the date of submission of the application for scrutiny of the documents.	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame otherwise tentative inspection date should be proposed as the case may be. On conformation of the date, inspection to be carried out and the application shall be disposed off.
NOC to be granted for cargo clearance at Port Offices of CDSCO	Activity: NOC to be granted only based on documents checks Timeline: 2-3 hours. Activity: NOC to be granted after document checks and physical inspection without involving lab-testing Timeline: 24-48 hours. Activity: NOC to be granted after document checks, physical inspection, drawing of samples and testing by a laboratory Timeline: 48-72 hours * In case of consignments where sampling is done, consignments may be released based on Latter of	In case some deficiencies in the documents is observed, notice of compliance should be forwarded to the applicants within this time frame and the application shall be disposed of.

	Guarantee submitted by the importer.	
For any other inspection communicated from the Office of the Drugs Controller General (India)	As directed by DCG(I).	Inspection should be completed as per the requirement.

(The complaints regarding drug products are to be disposed of as early as possible in coordination with concerned agencies).

The documents required to be submitted for various applications as mentioned above should be displayed in the notice board of the respective zonal office for perusal of the applicants and common public. The required documents for various applications are enclosed in this guidance document.

As soon as any document is received, the Zonal officer should mark the documents for scrutiny to the technical staff through online file processing portal viz Parichay/ SUGAM Portal /NSWS Portal/ MD Online portal. The concerned technical staff should submit his or her observations on the documents in a specified checklist.

Depending on the work load of the office, the technical staff may be asked to submit either directly his/her observations to the head zonal / sub-zonal officer or may be routed through Assistant Drugs Controller (I) or Drugs Inspector or Assistant Drugs Inspector or Sr. Technical Assistance. In case notice of compliance (NOC) to be issued to the applicants, the draft for approval (DFA) in this regard should also be prepared by the concerned technical staff and send along with the observations checklist for further necessary action through online file Parichay/ SUGAM Portal /NSWS Portal/ MD online Portal. If after scrutiny, the documents are found in order, the zonal officer should instruct the concerned technical staff to propose for a joint inspection to the State Licensing Authority. After the inspection date is proposed and the inspection was allotted to a particular inspector, the concerned file along with all the documents including observations checklist should be handed over to the concerned Drugs Inspector for joint inspection through online file processing portal Parichay/ SUGAM Portal /NSWS Portal/ MD Online Portal. The inspections may be carried out as per SOP. After the joint inspection is carried out by the Drugs Inspector, inspection report in the prescribed proforma (which are annexed) should be prepared. The concerned file along with the copy of joint inspection report should be submitted by the Drugs Inspector to the zonal / sub-zonal officer as the earliest through online file processing portal Parichay/ SUGAM Portal /NSWS Portal/ Md Online Portal. The zonal / sub-zonal officer should go through the report and record his/her observations on the report in writing and further necessary action as deemed fit shall be initiated by him/her.

CHAPTER-1

PROCEDURES FOR SAMPLING BY THE DRUGS INSPECTOR AND DRUGS SAMPLERS IN ZONAL/SUBZONAL OFFICE

Good quality medicines are essential for efficient disease management. Not of standard Quality (NSQ) and Spurious drugs can cause treatment failure and adverse reactions, increase morbidity and mortality, and contribute to the development of drug resistance. Vulnerable populations and patients with co-morbidities are at particular risk of being harmed from receiving substandard or spurious medicines. Poor-quality medicines also increase health care costs to both patients and the health system as a whole, wasting resources that could otherwise be used to benefit public health.

Drugs regulation in India is a complex process, where one side approval of new drugs, issuance of manufacturing license, wholesale license, retail license and their renewal/ retention are carried outby central and state regulatory authorities, which involves assessment of product technical documentation, inspection to ascertain manufacturers' compliance with the principles of Good Manufacturing Practices (GMP) and approval or issuance of approval & license as per Drugs & Cosmetics Act and Rules there under. Other side it also includes post-marketing surveillance (PMS) activities, such as maintenance of Market authorization/ registration through Post approval changes (PAC) for Biologicals, regular inspections of manufacturers, wholesalers and retailers, quality control testing, pharmacovigilance, routine sampling of products from the distribution channel and implementation of regulatory actions in the event of any quality problem reported to Drug Regulatory Authorities.

In general, sampling is carried out to assess the quality of drugs, cosmetic provided to patientsand generate the data that can help to formulate strategies and plans to ensure the continuous availability of good quality products in the market. Sampling also confirms that patients arereceiving satisfactory products and give reassurance that the regulatory system of the country is functional, or when there is a suspicion that patients are not receiving satisfactory medicines.

The Section 22 & 23 of the Drugs & Cosmetics Act 1940 prescribes the detail procedure for samples to be taken by Drugs Inspectors of Central and State drugs control as a part of routine drugs quality surveillance. Drugs sampling are costly tasks and limitations of resources may restrict the number of samples collected, parameters tested, techniques to be used for analysis or number of Drugs Inspector & Laboratory available to conduct the sampling and analysis respectively. Therefore, it is important to optimize the use of resources by focusing on parameters that pose a higher risk to patients and apply risk analysis during planning of the sampling.

From the past trends it is observed that there is no defined methodology for sample selection & location of sampling etc and was done randomly with the individual knowledge of Drug Inspectors. Often it was seen that sampled drugs are from big brands and collected from urban locations or sub urban locations only. The interior locations or rural distributions are not covered and thereby quality of drugs at distant

user/ last user was not being assessed. Cosmetics samples were not collected in some regions. There is no centralize database of sale outlets where NSQ / Spurious product were reported, such identified outlets are to be kept for regular vigilance.

The main objective of the sampling is to check the quality & efficacy of drugs & cosmetic available in the market with their approved specifications. This involves:

- Monitoring the quality of the API, Excipients and finished products of drugs, cosmetic and medical devices in all parts of the distribution chain throughout the authorised shelf-life.
- Ensuring that existing control methods are satisfactory.
- Investigating the Not of Standard Quality (NSQ) Product.
- Identifying Unapproved Products/ Without License sales outlets.
- Identifying Spurious drugs in distribution chain
- Identifying sales outlets where repetitive NSQ/ Spurious drugs are reported etc.

This guideline is mainly focused to utilize available information & identified risks for selection of sample & location to cover vast variety of drugs, cosmetic and medical devices moving in the market from manufacturing facility, wholesale outlet, retail outlet, government distribution channel etc. in urban, sub-urban, and rural locations. To maintain a centralized monthly NSQ/Spuriousdrug list and publishing on CDSCO website to avoid their further use.

This guideline will be useful for effective surveillance for quality & efficacy of drugs & cosmetic available in the market by adopting uniform drug sampling methodology for drugs inspectors underdrug regulatory authorities of state and central.

1. Sampling Plan:

Each drugs inspector with consultation of his controlling authority shall prepare a sampling plan on monthly basis & annual basis for finalizing the sampling locations to cover the entire jurisdiction/ area under their office. This will avoid communication gap between the officers and optimum utilization of resource to cover the maximum territory and all kind of product category withidentified risk and approached under this guidance document. Sampling plan shall include rural/ tribal areas and drugs used in areas of endemic for certain diseases, drugs for seasonal diseases etc.,

The annual sampling plan shall be shared with their headquarters of their offices for review and to avoid any repetitive sampling of one brand and to cover maximum variety of brand/category in proposed sampling schedule.

2. Selection of sample:

The selection of sample will depend on various factors, which may indicate possible higher risk to the quality of drug. The Drugs Inspectors shall draw samples of different therapeutic categories, different formulations, and different manufacturers from a one sales outlet by applying following identified risks,

it is not exhaustive and is only indicative.

a. Feedback/information from citizens, Healthcare professionals. Products on which efficacy information is received during interaction with Doctors/Medical Representatives / Chemists / Pharmacists / Consumers / Media /Public Domain.

b. Sampling schedule provided by CDSCO for specific therapeutic category drugs inspecific months (Yearly Joint Surprise Check schedule provided by CDSCO).

c. Use of Drugs Alert of CDSCO and State Drug Authorities for detail of frequent NSQ/ Spurious drugs and their manufacturing & sales outlets.

d. Seasonal changes in environmental conditions may have an influence on the quality of the medicine collected. It is possible that Spurious of antimalarial are more common during the malaria season and so on.

e. Brands of the same product sold at different prices and aimed at different market segments.

f. Drugs found procured or sold at huge discounts (in deviation to ethical market practices)

g. Products with high consumption volumes.

h. Products having low potency and narrow therapeutic index.

i. Drugs found with tampered label.

j. Products which are sold during specific seasons or pandemic.

k. Information from various disease control programmes can be used like NationalPrograms for De-worming, Universal vaccination etc.

l. Drugs manufactured by new manufacturers.

m. Products which are labeled / printed in suspicious manner. e.g. lack of required details, mistakes in spelling, illegible description etc.

n. Drugs with poor quality of primary packing (packing that comes indirect contact with the dosage form depending on the season and Products whose packing gives rise to suspicion of being low quality.

o. Products with one or more visible defects.

p. Brands which appears to be same/resemblance of other well-known or established brands.

q. Drugs for which proper purchase/sale record is not maintained (No purchase bills/ BatchNumber or Date of Manufacturing or Expiry does not tally with the bill/ proper salerecord not maintained especially if it is a wholesale concern).

r. Drugs that are usually sold/distributed to specific perceivably doctor attached counters and are not available in general counters.

s. Products which are in supply chain from different route other than regular/ authorize supply chain of manufacturer i.e. Super Stockiest – Stockiest – Wholesaler – Retailer.

t. Inter-State purchase by the whole seller or retailer and other than regular/ authorize supply chain of manufacturer.

The Drugs Inspector shall ensure that at least all the above identified risks are utilized in his sampling activities of 06 months. Further, not more than 03 samples are collected from one sale outlet and excess sampling, if any reasons shall be recorded and approved by the controlling authority.

3. Selection of Sampling Location:

The sampling location can be identified by applying following approaches; it is not exhaustive and is only indicative;

a. Frequent NSQ reports
b. Market complaints
c. Manufacturing and sales locations not yet sampled or last sampling was done morethan 01 years before by state or central drugs inspector.
d. Government Medical Store Depot.
e. Private/Public Sector manufacturing firms.
f. State, Central Government Hospitals/Institutes having local purchase by theHospital/Institute.
g. Wholesale/Retail sales premises.
h. Sale outlets having operation in morning and evening hours only.
i. Sales outlet located nearby school & colleges.
j. Sales outlet situated at border areas of district, state, and country.
k. Prevalence of the disease in region & season for which the target medicines areindicated.
l. Complexity of manufacturing,
m. Stability of the medicine – risk of quality deterioration under local conditions of storage, distribution and use.
n. Non-Compliance of manufacturers of the target medicines with GMP principles.
o. Complexity of distribution chain for the target medicines and likelihood of non- compliance with good distribution practices (GDP) principles and approved storage conditions during distribution and storage.

4. Number of Samples:

Each Drugs Inspector shall collect samples under the provision specified in the Section 22 & 23 of the Drugs & Cosmetics Act 1940. Each Drugs Inspector shall collect at least 10 samples in a month comprising of following;

a. 09 samples of drugs (API, Excipient and Formulations)
b. 01 sample of cosmetics/ Medical Device.

Also, each Drugs Inspector shall collect at least 01 sample of vaccine quarterly under Drugs and Cosmetic Act.

5. Quantity of samples

It is important that sufficient quantity of samples are collected & forwarded to laboratory so that all the parameters are tested and re-testing, if any required by laboratory before issuing of NSQ test report. The quantity of samples also varies with type of samples like API, Formulations (Tablets, Capsules, Liquid Oral, Injectable, Large Volume Parenteral, Ointment, Lotions etc), Cosmetics, medical devices etc., Please refer **Annexure 1-5** for quantity required for testing of various sample product category.

Sometime, retail outlets or rural sale outlet are not having sufficient quantity for complete testingand it become challenge to divide & pack sample in four equal portions. In this situation priority shall be given for tests like identification and assay under reduced testing to rule out spurious products. In such cases the sample portion can be divided in 02 equal portion preferably both with primary/secondary labels (one portion for Government analyst and other for producing in the court) and remaining 02 portions sufficient for performing reduced testing. This information shall be recorded in respective forms under Drugs, Cosmetics & Medical Devices Rules and covering letter to respective Government Analyst, where sample is sent for testing for reduced testing i.e. identification and assay only due to non-availability of full quantity.

6. Timelines:

It is important to avoid any procedure delay in testing and obtaining of test report from the laboratory, so that further use of identified NSQ products are stopped by issuing drug alert and product recall notice at the earliest for public awareness, irrespective to proceeding of Drugs Inspector as per provision under Drugs & Cosmetic Act & Rules there under. Following timelines are to be followed;

a. The Drugs Inspector shall plan the sampling in such a way that samples are forwarded to laboratory on the same day of sampling.
b. If delay happens due to transit from rural location or distant location to office, then sample shall be forwarded to laboratory by next day and not later than that.
c. The disclosure under section 18A of Drugs & Cosmetics Act & Rules there under for Name, Address, copy of purchase invoice and other particulars of the person from whom he acquired the drug or cosmetic shall be obtained during sampling to rule outthe possibility of Spurious drug. Further distribution chain establishment up to manufacturer level under section 18A of Drugs and Cosmetics Act is to be completed for all samples. This will be helpful to ensure the availability of true product in the marketand also to initiate quick actions for NSQ product declared by the Government Analyst.
d. The Drugs Inspector shall obtain the method of analysis & reference/working standards from manufacturer for sample belongs to patent & proprietary drugs or new drugs, without waiting for communication from laboratory and shall provide to the laboratory for timely testing of the product.

e. The head of state and central laboratories shall forward NSQ reports in excel sheet format as per Para 9 with copy of test report preferably before 10th of every month for uploading at CDSCO website under Drug/Device/Cosmetic NSQ Alert for vide public awareness.

f. The head of the field offices of the State and central drug authorities shall forward the monthly spurious alert as per following excel sheet format as per Para 9 for uploading atCDSCO website under Spurious Drug/Device/Cosmetic Alert for vide Public Awareness preferably before 10th of every month.

NOTE: CDSCO Drug Inspectors shall use SUGAM Lab Portal for generation of Form-17/ Form-17A/ Form-18 and forwarding through online (forms only) & offline (printed forms & samples) to the concerned laboratory.

7. Database / Monitoring:

Each Drugs Inspector shall maintain data of sampling and shall submit to their controlling authority on monthly basis for execution of sampling plan. The inputs from the monthly data of sampling shall be used for planning of next month's sampling plan. Following information are to be maintained;

a. Number of samples drawn and their process completion up to test report from laboratory and chain establishment up to manufacturer level.

b. Number of NSQs reported by laboratory and their action taken (Drugs Alert, Product Recall, Proposal to controlling Authority for Admin/Legal Action, Completed Action like Suspension/ Cancellation of license, Court Cases Number etc.)

c. The cases of Spurious products reported by laboratory in test report or identified underchain establishment up to manufacturer by the Drugs Inspectors and their action taken (Drugs Alert indicating all the locations, Product Recall / Seizure, Number of Arrest, Proposal to controlling Authority for Legal Action, Court Cases No.).

8. Each Drug Controlling office and Head Zonal/ Sub Zonal officers shall prepare a list on monthly basis for Wholesale/retail outlet with name of registered pharmacist and owner where Spurious products arereported/ distribution chain is broken for the provided invoice.

The above list shall be shared to their head office for preparation of centralized list of wholesaler / retailer outlets revealed in sale/distribution of Spurious products and to give wide publicity for public to avoid use of purchased medicine from these outlets.

9. NSQ / Spurious Alerts:

The NSQ reports received from state and central laboratories shall be reported in following excel sheet format with copy of test report preferably before 10th of every month for uploading at CDSCO website

under Drug/Device/Cosmetic NSQ Alert for vide public awareness.

NSQ Alert for month……							
Sr. No.	**Product / Drug Name**	**B. No.**	**Manufacturing date**	**Expiry Date**	**Manufactured By**	**NSQ Results**	**Reported by CDSCO/State Lab**

The samples identified as Spurious due to distribution chain breakage or reported by the manufacturer as Spurious shall be reported in following excel sheet format with copy of Drugs Inspector report indicating distribution chain break with manufacturer response indicating how to identify original product from reported Spurious. The head of the field offices of the State and central drug authorities shall forward the monthly spurious alert as per following excel sheet formatfor uploading at CDSCO website under Spurious Drug/Device/Cosmetic Alert for vide Public Awareness preferably before 10th of every month.

Spurious Alert for month…….							
Sr. No.	Product /Drug Name	B. No	Manufacturing/ Expiry Date	Manufactured By as per Label	Sale Outlets Involvedin distribution of Spurious Drug (Name & Address of outlet with Pin code and Pharmacist Namewith Registration number)	Response of Original Manufacturer stating how to identify the original product from reported Spurious product	Reportedby CDSCO/State/ Manufacturer
					1. Sampled At 2. 3. 4.Detail disclosed in Invoice is not verifiable due to non-existence of firm/ address and supply chain broke.		

10. Testing Laboratories:

Detail of Notified laboratories for Drugs, Cosmetics and Medical device at central and statelevel is already available in Rules and notification/ letters circulated time to time.

States which are not having their own testing laboratories has notified Central Drugs Testing laboratories and Central labs are testing samples of state drugs inspectors.

In some quality complaint cases where states neither have their own laboratory nor notified central laboratory for specific product category etc. shall request the respective CDSCO field office for sampling by the CDSCO inspector.

Recently, G.S.R 409(E) dated 2nd June, 2023-Medical Devices (Amendment) Rules, 2023 "State medical Devices Testing Laboratory" means a medical devices laboratory established or designated by the State Government under sub-rule (3) of rule 19".

Central Medical Device Testing Laboratory (CMDTL) for testing of Medical Devices under MDR 2017. Total 6 CMDTL are notified by MOH&FW under MDR 2017 for testing of devices in the country as per S.O 2237(E) dated 1st June 2018.

S.No	**Name of Laboratory**	**Category of medical device**
1	The National Institute of Biologicals, Noida	In-Vitro Diagnostics for human Immunodeficiency virus, Hepatitis B Surface Antigen and Hepatitis C Virus, Blood Grouping sera, Glucose Test Strip, Fully Automated Analyser Based Glucose Reagent
2	The Central Drugs Testing laboratory, Chennai	Condoms
3	The Central Drugs Laboratory, Kolkata	Surgical Dressings, Surgical Cotton, Surgical Bandages, Disinfectant
4	The Regional Drugs Testing Laboratory (RDTL), Guwahati	Disposable Hypodermic Syringes, Disposable Hypodermic Needle, Disposable Perfusion Sets, I.V. Cannulae
5	The Central Drugs Testing Laboratory, Mumbai	Intra Uterine Devices (IUD) and Falope Rings
6	The Regional Drugs Testing Laboratory, Chandigarh	Disposable Hypodermic Syringes, Disposable Hypodermic Needles, Disposable Perfusion Sets, Catheters, I.V. Cannulae, Scalp Vein Set, Ligatures, Sutures, Staplers, Surgical Dressing, Umbilical Tapes.".

Annexure-1

Quantity of Drugs Sample Required for Complete Analysis

S.No.	**Name of Drug Sample**	**Form-18Samples**	**Survey Samples**
1.	Tablets	100 Tablets	20 Tablets
2.	Capsules	100 Capsules	20 Capsules
3.	Syrups / Oral Liquids/Suspensions	12 Bottles	2 Bottles
4.	Injection (Ampoule) (1-10 ml)	40 Ampoules	10 Ampoules
	Injection (Ampoule) (10-100ml)	25 Ampoules	10 Ampoules
5.	Large Volume Parentrals (morethan 100 ml)	10 Bottles	2 Bottles
6.	Powder for injection (Sterile)	40 Vials	5 Vials
7.	Dry Powder for Oral/ Liquid Suspension	25 Bottles	5 Bottles
8.	Oral Rehydration Salt Sachets	30 Pcs	5 Pcs
9.	API Drug	2 x 10 gm	5 gm
10.	Ointment / Creams / Paste / Gel(Non Sterile)	12 Pcs	2Pcs
	Ointment / Creams / Paste / Gel (Sterile)	20pcs	5pcs
11.	Eye / Ear Drops	40 Vials/ pcs	5 Vials/ pcs
12.	Nasal Preparation	20 Vials	5 Vials
13.	Inhalers/ Spray	40 Pcs	5 Pcs
14.	Pessaries / Lozenges	60 Pcs	20 Pcs
15.	Empty Gelatine Capsules	500 Capsules	100 Capsules

Annexure-2

Quantity of Cosmetics Sample Required For Complete Analysis

S.N	Name of Cosmetic Sample	Form Cos 17 Samples	Survey Samples
1.	Skin Cream	3 x 50 gm	1 x 50 gm
2.	Hair Cream	3 x 50 gm	1 x 50 gm
3.	Shampoo	3 x 200 ml	1 x 200 ml
4.	Soap	3 x 150 gm	1 x 150 gm
5.	Transparent Toilet Soap	3 x 150 gm	1 x 150 gm
6.	Tooth Powder	3 x 50 gm	1 x 50 gm
7.	Shaving Cream	3 x 15 gm	1 x 15 gm
8.	Cosmetic Pencil	20 Pencils	5 Pencils
9.	Hair Dyes (Liquid, Gel & Cream)	3 x 100 ml	1 x 100 ml
10.	Powder Hair Dyes	4 x 20 gm	1 x 20 gm
11.	Liquid Toilet Soap	3 x 100 ml	1 x 100 ml
12.	Bathing Bar	3 x 75 gm	1 x 75 gm
13.	Hair Oil	3 x 50 ml	1 x 50 ml
14.	Lipstick	15 Packs	5 Packs
15.	Nail Polish	15 Packs	5 Packs
16.	Talcum Skin powder	3 Packs	1 Packs
17.	Kajal	10 Packs	1 Packs
18.	Any other cosmetic	3 Packs	1 Packs

Annexure-3

Quantity of vaccine sample required for complete analysis by Central Drugs Laboratory, Kasauli (Appellate Laboratory)

Sr. No.	Name of Product / Sample		Containers* (Doses)/ No. of unit Required
1.	Bacterial Vaccines	1.BCG Vaccine	10/20 doses x 60 vials
		2.Cholera Vaccine	1 dose x 50 containers
		3.DT / Td Vaccine	1 dose x 50 containers 5 doses x 10 containers 10 doses x 08 containers 20 doses x 08 containers
		4.DTP/ DTaP Vaccine	1 dose x 50 containers 5 doses x 10 containers 10 doses x 08 containers
		5.DTP Combination Tetravalent (DTP-HepB, DTP-Hib), DTP-IPV) Pentavalent (DTP HepB Hib, DTP- Hib IPV), Hexavalent (DTP HepB Hib IPV) (in whole cell or acellular Pertussis combinations)	1 dose x 50 containers 5 doses x 10 containers 10 doses x 08 containers
		6.Hib Vaccine	1 dose x 50 containers 5 doses x 10 containers
		7.Meningococcal Vaccine	1 dose x 50 containers 5 doses x 10 containers 10 doses x 08 containers
		8.Pneumococcal Vaccine	1 dose x 50 containers 4 doses x 15 containers 5 doses x 10 containers 10 doses x 08 containers
		9.Tetanus Vaccine	1 dose x 50 containers 5 doses x 10 containers 10 doses x 08 containers
		10.Typhoid Vaccine	1 dose x 50 containers 4 doses x 15 containers 5 doses x 10 containers 10 doses x 08 containers
2.	Surgical Suture	Surgical Suture	25 Strands

3.	Viral Vaccine	1. Measles Vaccine	1 Dose x 50 Containers 5 Dose x 30 Containers 10 Dose x 20 Containers
		2. Measles & Rubella Vaccine	1 Dose x 50 Containers 5 Dose x 30 Containers 10 Dose x 20 Containers
		3. Measles, Mumps & Rubella Vaccine,	1 Dose x 50 Containers 5 Dose x 30 Containers 10 Dose x 20 Containers
		4.Measles, Mumps ,Rubella & Varicella Vaccine	1 Dose x 50 Containers
		5. Rubella Vaccine	1 Dose x 50 Containers
		6. Hep-A Vaccine	1 Dose x 50 Containers 2 Dose x 35 Containers
		7. Hep-B Vaccine	1 Dose x 50 Containers 2 Dose x 35 Containers 10 Dose x 20 Containers
		8. Influenza Vaccine	1 Dose x 50 Containers
		9. J.E Vaccine	1 Dose x 50 Containers 5 Dose x 30 Containers
		10. Rotavirus Vaccine	1 Dose x 50 Containers 2 Dose x 35 Containers 5 Dose x 30 Containers
		11. HPV Vaccine	1 Dose x 50 Containers
		12. Varicella Vaccine	1 Dose x 50 Containers
		13. Yellow Fever Vaccine	1 Dose x 50 Containers 2 Dose x 35 Containers 5 Dose x 30 Containers
4.	Antisera Products	Snake Venom Antiserum	10 ml x 15 Vials
		Diphtheria Antitoxin	10 ml x 10 Vials
		Rabies Antiserum	05 ml x 15 Vials 2 ml x 20 Vials/Ampoules
		Scorpion Venom Antiserum	1 ml x 40 Vials 10 ml x 10 Vials
		Rabies (H) Monoclonal Antibody	2.5 ml x 20 Vials/Ampoules 1.25 ml x 30 Vials/Ampoules
		Tetanus Antitoxin	1 ml x 40 Vials/PFS/Ampoules
5.	Blood Products	Antithymocyte Globulin	5 ml x 15 vials
6	Toxin	*Clostridium botulinum toxin type A & Neurotoxin type A*	1 ml x 40 vials
7.	Rabies Vaccine		1 ml X 35 Vials

		0.5 ml X 50 Vials
8.	OPV	20 Doses X 20 Vials 10 Doses X 30 Vials
9.	IPV	5 Doses X 20 Vials 10 Doses X 20 Vials 1 dose X 20 Vials
10.	Malaria	2 Doses X 20 Vials
11.	nOPV	20 Doses X 20 Vials 50 Doses X 20 Vials

***Containers may be Vials/ Ampoules/ PFS/ etc.**

Annexure-4

Quantity of biological/ Medical Devices SAMPLES

(*Note: List is for reference purpose only, however please check website of NIB, Noida for current information)

NEW CODE	PRODUCT NAME	QUANTITY REQUIRED/ BATCH	
		TESTING	RETAINED
A.1.1	Glucose Reagent-Open Ended Chemistry	500 ml or 1000Tests with accessories	Nil
A.1.2	Glucose Reagent-Closed Chemisty System	1000 Tests or Reagent quantity enough for useover 25 working days vis-a-vis on-board shelf life of Reagent with accessories	Nil
A.2	Blood Glucose Test Strips	1200 Test Strips with accessories	350 Test Strips withaccessories
A.3	Glucometer Device	10 Nos. with accessories	02 Nos. withaccessories
B.1	ABD Pad	140 Tests	60 Tests
B.2	ABO confirmation card	144 Tests	72 Tests
B.3	ABO Rh Typing Card	144 Tests	72 Tests
B.4	Anti D (Verification ofWeak D byIAT)	2 vials	1 vial
B.5	**Anti Kp^b Reagent	2 vials	1 vial
B.6	Anti-A (Bulk)	1vial	1 vial
B.7	Anti-A (Concentrate Bulk)	1vial	1 vial
B.8	**Anti-A /B / D /K / control ABOcard	144 Tests	72 Tests
B.9	Anti-A Monoclonal	2 vials	1 vial
B.10	Anti-A1 (Lectin)	2 vials	1 vial

B.11	Anti-AB (Monoclonal)	2 vials	1 vial
B.12	Anti-B (Concentrate Bulk)	1 vials	1 vial
B.13	Anti-B (Bulk)	1 vials	1 vial
B.14	Anti-B (Monoclonal)	2 vials	1 vial
B.15	**Anti-C^w Reagent	2 vials	1 vial
B.16	Anti-D (RH1) (Totem)	2 vials	1 vial
B.17	Anti-D (IgG) Monoclonal	2 vials	1 vial
B.18	Anti-D (IgM) Monoclonal	2 vials	1 vial
B.19	Anti-D (IgM)(Bulk)	1vial	1vial
B.20	Anti-D (IgM) (Concentrate Bulk)	1vial	1 vial
B.21	Anti-D (IgM+IgG) (Bulk)	1vial	1 vial
B.22	Anti-D (IgM+IgG) (Concentrate Bulk)	1vial	1 vial
B.23	Anti-D (IgM+IgG) Monoclonal	2 vials	1 vial
B.24	**Anti-Fy^a Reagent	2 vials	1 vial
B.25	**Anti-Fy^b Reagent	2 vials	1 vial
B.26	Anti-H (Lectin)	2 vials	1 vial
B.27	Anti-Human Globulin	2 vials	1 vial
B.28	**Anti-Jk^a Reagent	2 vials	1 vial
B.29	**Anti-Jk^b Reagent	2 vials	1 vial
B.30	**Anti-k Reagent	2 vials	1 vial
B.31	**Anti-K Reagent	2 vials	1 vial
B.32	**Anti-Kp^a Reagent	2 vials	1 vial
B.33	**Anti-Le^a Reagent	2 vials	1 vial
B.34	**Anti-Le^b Reagent	2 vials	1 vial

B.35	**Anti-M Reagent	2 vials	1 vial
B.36	**Anti-N Reagent	2 vials	1 vial
B.37	**Anti-Pi Reagent	2 vials	1 vial
B.38	**Anti-s Reagent	2 vials	1 vial
B.39	**Anti-S Reagent	2 vials	1 vial
B.40	Blood Grouping Cards	144 Tests	72 Tests
B.41	Blood Grouping Rapid CardTest	144 Tests	72 Tests
B.42	Bovine Serum Albumin	2 vials	1 vial
B.43	CombiPack ABD MonoclonalAntibody	2 combipack	1 combipack
B.44	**Gel Card Anti-M	144 Tests	72 Tests
B.45	**Gel Card Anti-N	144 Tests	72 Tests
B.46	Gel Card Anti-A1 (Lectin)	144 Tests	72 Tests
B.47	**Gel Card Antigen Profile I	144 Tests	72 Tests
B.48	**Gel Card Antigen Profile II	144 Tests	72 Tests
B.49	**Gel Card Antigen Profile III	144 Tests	72 Tests
B.50	Gel Card Anti-H (Lectin)	144 Tests	72 Tests
B.51	Gel card for Direct AntiGlobulin test	144 Tests	72 Tests
B.52	*Gel card for new born	144 Tests	72 Tests
B.53	Gel Card forward & reverse grouping	144 Tests	72 Tests
B.54	Gel Card forward grouping	144 Tests	72 Tests
B.55	Gel Card Rh Subgroups	144 Tests	72 Tests
B.56	*Gel Cards ABO/Rh for NewbornsDVI Neg/Pos	144 Tests	72 Tests

B.57	Gel Cards Anti- A/B/AB/DVI Pos/DVINeg/Ctl	144 Tests	72 Tests
B.58	Gel Cards Anti-A/B/D/Rh subgroups	144 Tests	72 Tests
B.59	**Gel Cards Anti-C^w	144 Tests	72 Tests
B.60	Gel Cards Anti-D (Human)	144 Tests	72 Tests
B.61	Gel Cards Anti-DVI	144 Tests	72 Tests
B.62	**Gel Cards Anti Fy^a	144 Tests	72 Tests
B.63	**Gel Cards Anti Fy^b	144 Tests	72 Tests
B.64	**Gel Cards Anti Jk^a	144 Tests	72 Tests
B.65	**Gel Cards Anti Jk^b	144 Tests	72 Tests
B.66	**Gel Cards Anti K	144 Tests	72 Tests
B.67	**Gel Cards Anti-k	144 Tests	72 Tests
B.68	**Gel Cards Anti-Kp^a	144 Tests	72 Tests
B.69	**Gel Cards Anti-Kp^b	144 Tests	72 Tests
B.70	**Gel Cards Anti-Le^a	144 Tests	72 Tests
B.71	**Gel Cards Anti-Le^b	144 Tests	72 Tests
B.72	**Gel Cards Anti-Lu^a	144 Tests	72 Tests
B.73	**Gel Cards Anti-Lu^b	144 Tests	72 Tests
B.74	**Gel Cards Anti-Pi	144 Tests	72 Tests
B.75	**Gel Cards Anti-S	144 Tests	72 Tests
B.76	**Gel Cards Anti s	144 Tests	72 Tests
B.77	Gel Cards CrossmatchTesting (CT)	144 Tests	72 Tests
B.78	Gel Cards Neutral	144 Tests	72 Tests
B.79	**Gel Cards Rh subgroups +C^w + K	144 Tests	72 Tests
B.80	**Gel Cards Rh subgroups +K	144 Tests	72 Tests

B.81	Gel Cards Type + Screen	144 Tests	72 Tests
B.82	Microplate for forward & Reverse grouping	144 Tests	72 Tests
B.83	*Newborn casette for AntiA/AntiB/ Anti AB/ AntiD/ Control / Anti IgG	144 Tests	72 Tests
B.84	Sera/Gel Card for AHG & C3d	144 Tests	72 Tests
B.85	Gel cards for Anti-A, B, DVI- /Enzyme/AHG	144 Tests	72 Tests
B.86	Gel cards for DAT Anti-IgG-Dilution	144 Tests	72 Tests
B.87	Gel cards for LISS/Coombs +EnzymeTest	144 Tests	72 Tests
B.88	Gel cards for DC-Screening I	144 Tests	72 Tests
B.89	Gel cards for Reverse Grouping withAntibodyScreening	144 Tests	72 Tests
B.90	Anti-Human Globulin IgG	2 vials	1 vial
B.91	Anti-Human Globulin C3d	2 vials	1 vial
B.92	Rh Phenotype Card withAnti-D	144 Tests	72 Tests
B.93	Gel card for ABO/Rh for Patients	144 Tests	72 Tests
B.94	**Anti-Lu^a Reagent	2 vials	1 vial
B.95	**Anti-Lu^b Reagent	2 vials	1 vial
B.96	Starter pack for preparing CoombsControl Cells	2 Pack	1 Pack
B.97	Gel Card for DC Screening II	144 Tests	72 Tests
B.98	Gel Card for ABO Sub Grouping	144 Tests	72 Tests

C.1	Anti HBc IgM CLIA	150 Tests	150 Tests
C.2	Anti HBc IgM ELFA	150 Tests	150 Tests
C.3	Anti HBc IgM ELISA	96 Tests x 02 Kits	96 Tests x 02 Kits
C.4	HBe Ag CLIA	150 Tests	150 Tests
C.5	HBe Ag ELFA	150 Tests	150 Tests
C.6	HBe Ag ELISA	96 Tests x 02 Kits	96 Tests x 02 Kits
C.7	Anti HBs CLIA/HBs Ab CLIA	150 Tests	150 Tests
C.8	Anti HBs ELFA/HBs Ab ELFA	150 Tests	150 Tests
C.9	Anti HBs ELISA/HBs Ab ELISA	96 Tests x 02 Kits	96 Tests x 02 Kits
C.10	Anti-HBe CLIA/ HBe Ab CLIA	150 Tests	150 Tests
C.11	Anti-HBe ELFA/ HBe Ab ELFA	150 Tests	150 Tests
C.12	Anti-HBe ELISA/ HBe Ab ELISA	96 Tests x 02 Kits	96 Tests x 02 Kits
C.14	Dengue IgM ELISA	96 Tests x 02 Kits	96 Tests x 02 Kits
C.15	HBc IgM CLIA	150 Tests	150 Tests
C.16	HBc IgM ELFA	150 Tests	150 Tests
C.17	HBc IgM ELISA	96 Tests x 02 Kits	96 Tests x 02 Kits
C.18	HBc Total CLIA/Anti HBc Total CLIA	150 Tests	150 Tests
C.19	HBc Total ELFA / Anti HBc TotalELFA	150 Tests	150 Tests
C.20	HBc Total ELISA/Anti HBc Total ELISA	96 Tests x 02 Kits	96 Tests x 02 Kits
C.21	HBe Ag-Ab CLIA	250 Tests	250 Tests

C.22	HBe Ag-Ab ELFA	250 Tests	250 Tests
C.23	HBe Ag-Ab ELISA	96 Tests x 03 Kits	96 Tests x 03 Kits
C.24.1	HBsAg CLIA	700 Tests	700 Tests
C.24.2		400 Tests	400 Tests
C.25.1	HBsAg ELFA	700 Tests	700 Tests
C.25.2		400 Tests	400 Tests
C.26.1	HBsAg ELISA	96 Tests x 07 Kits	96 Tests x 07 Kits
C.26.2		96 Tests x 04 Kits	96 Tests x 04 Kits
C.27	HBsAg Confirmatory ELISA*	100 Tests	100 Tests
C.28.1	HBsAg Rapid (Strip/Cassette) {Lateral Flow (Immunochromatography)}	600 Tests	600 Tests
C.28.2		250 Tests	250 Tests
C.29.1	HCV Ab CLIA	700 Tests	700 Tests
C.29.2		400 Tests	400 Tests
C.30.1	HCV Ab ELFA	700 Tests	700 Tests
C.30.2		400 Tests	400 Tests
C.31.1	HCV Ab ELISA	96 Tests x 07 Kits	96 Tests x 07 Kits
C.31.2		96 Tests x 04 Kits	96 Tests x 04 Kits
C.32	HCV Ab Confirmatory/Supplemental Rapid	100 Tests	100 Tests
C.33.1	HCV Ab Rapid (Strip/Cassette) {Lateral Flow (Immunochromatography)}	600 Tests	600 Tests
C.33.2		250 Tests	250 Tests
C.34	HCV Ab RIBA	100 Tests	100 Tests

C.35	HCV Ab ConfirmatoryWestern Blot	100 Tests	100 Tests
C.36.1	HCV Ag-Ab ELFA	700 Tests	700 Tests
C.36.2		400 Tests	400 Tests
C.37.1	HCV Ag-Ab ELISA	96 Tests x 07 Kits	96 Tests x 07 Kits
C.37.2		96 Tests x 04 Kits	96 Tests x 04 Kits
C.38.1	HIV 1&2 Ab CLIA	700 Tests	700 Tests
C.38.2		400 Tests	400 Tests
C.39.1	HIV 1&2 Ab ELFA	700 Tests	700 Tests
C.39.2		400 Tests	400 Tests
C.40.1	HIV 1&2 Ab ELISA	96 Tests x 07 Kits	96 Tests x 07 Kits
C.40.2		96 Tests x 04 Kits	96 Tests x 04 Kits
C.41	HIV 1&2 Ab Confirmatory/ HIV 1& 2 Ab SupplementalRapid	100 Tests	100 Tests
C.42.1	HIV 1&2 Ab	600 Tests	600 Tests
C.42.2	Rapid (Strip/Cassette) {Lateral Flow (Immunochromatography)}	250 Tests	250 Tests
C.43	HIV 1&2 Ab Confirmatory WesternBlot	100 Tests	100 Tests
C.46.1	HIV Ag-Ab CLIA	700 Tests	700 Tests
C.46.2		400 Tests	400 Tests
C.47.1	HIV Ag-Ab ELFA	700 Tests	700 Tests
C.47.2		400 Tests	400 Tests
C.48.1 C.48.2	HIV Ag-Ab ELISA	96 Tests x 07 Kits 96 Tests x 04 Kits	96 Tests x 07 Kits 96 Tests x 04 Kits

C.49.1	HIV Ag-Ab Rapid (Strip/Cassette) {Lateral Flow (Immunochromatography)}	600 Tests	600 Tests
C.49.2		250 Tests	250 Tests
C.50.1	HIV TP Combo Rapid	700 Tests	700 Tests
C.50.2		350 Tests	350 Tests
C.51.1	HIV,HCV Combo Rapid	700 Tests	700 Tests
C.51.2		350 Tests	350 Tests
C.52.1	HIV,HCV,HBV Combo Rapid	800 Tests	800 Tests
C.52.2		450 Tests	450 Tests
C.54	Paclitaxel for HIV, HBsAg, HCV	01 Vial	01 Vial
C.55	Human Plasma/ Plasma Pool for Fractionation as per IP	03 Vials x 05 ml	03 Vials x 05 ml
C.56	Syphilis CLIA	300 Tests	300 Tests
C.57	Syphilis ELISA	96Tests x 03 Kits	96Tests x 03 Kits
C.58	Syphilis Rapid (Strip/Cassette) {Lateral Flow (Immunochromatography)}	250 Tests	250 Tests
C.59	Syphilis RPR	250 Tests	250 Tests
C.60	Syphilis TPHA	250 Tests	250 Tests
#C.61	Infection diagnostic testfor HBV(Qualitative)	36 Tests	36 Tests
#C.62	Infection diagnostic testfor HCV(Qualitative)	36 Tests	36 Tests
#C.63			

	Infection diagnostic testfor HIV-1(Qualitative)	98 Tests	98 Tests
#C.64	Blood donor Screening multiplex(HBV, HCV &HIV) Test (Qualitative)	146 Tests	146 Tests
#C.65	Viral load monitoring Kit for HBV	24 Tests	24 Tests
#C.66	Viral load monitoring Kit for HCV	24 Tests	24 Tests
#C.67	Viral load monitoringKit forHIV-1	76 Tests	76 Tests
C.69.1	HIV, HCV, Syphilis and HBsAg Combo Rapid (Device having Four individual sample addition wells)	600 Tests	600 Tests
C.69.2		250 Tests	250 Tests
C.70.1	HIV 1&2 Ab Rapid (Strip/Cassette) {Vertical Flow (Immunofiltration)}	600 Tests	600 Tests
C.70.2		250 Tests	250 Tests
C.71.1	HIV 1+2 (ImmunodotTest/ Dot Immuno Assay)	600 Tests	600 Tests
C.71.2		250 Tests	250 Tests
C.72.1	HIV Ag-Ab Rapid (Strip/Cassette) {Vertical Flow(Immunofiltration)}	600 Tests	600 Tests
C.72.2		250 Tests	250 Tests

C.73.1	HCV Ab Rapid (Strip/Cassette) {Vertical Flow (Immunofiltration)}	600 Tests	600 Tests
C.73.2		250 Tests	250 Tests
C.74	HBsAg Confirmatory CLIA**	100 Tests	100 Tests
D.1.1	Anti-D Immunoglobulin for Intravenous use	110 vials	60 vials
D.1.2		55 vials	30 vials
D.2.1	Anti-D (Rho) Immunoglobulin (Intramuscular)	50 vials	25 vials
D.2.2		100 vials	50 vials
D.3	Anti-Inhibitor Coagulant Complex	10 vials	05 vials
D.5.1	Hepatitis B Immunoglobulin (Intramuscular)	70 vials	40 vials
D.5.2		33 vials	25 vials
D.5.3		18 vials	12 vials
D.5.4	Hepatitis B Immunoglobulin (subcutaneous)	70 vials	50 vials
D.6.1	Hepatitis B Immunoglobulin (Intravenous)	110 vials	60 vials
D.6.2		55 vials	30 vials
D.6.3		05 vials	02 vials
D.7	Human Albumin	04 Bottles	02 Bottles
D.8	Human Coagulation Factor - IX	06 vials	04 vials
D.9	Human CoagulationFactor - IX (recombinant)	06 vials	02 vials
D.10.1	Human Coagulation Factor - VIII(Dried Human Antihaemophilic	08 vials	04 vials

	Fraction)		
D.10.2	Human Coagulation Factor - VIII(without vWF) (Dried Human Antihaemophilic Fraction)		
D.11	Human Normal Immunoglobulin(IM)	10 vials	05 vials
D.12	Human Normal Immunoglobulin (Intramuscular) (Bulk)	04 Bottles	02 Bottles
D.13.1	Human Normal	03 Bottles	02 Bottles
D.13.2	Immunoglobulin forIntravenous use	10 Bottles	08 Bottles
D.13.3		03 Bottles	02 Bottles
D.14	Human Plasma Protein Fraction	04 Bottles	02 Bottles
D.15	Human ProthrombinComplex (PTC)	10 Bottles	05 Bottles
D.16	Human Normal/Specific Immunoglobulin (IV) (Bulk)	03 Bottles	03 Bottles
D.17	Rabies Immunoglobulin	20 vials	10 vials
D.18	Human CoagulationFactor-VIII (recombinant)	06 vials	02 vials
D.19	Tetanus Immunoglobulin (Intramuscular)	50 vials	25 vials
D.20	Tetanus Immunoglobulin (Intramuscular) (Bulk)	04 Bottles	02 Bottles
D.21	Human Fibrinogen	05 vials	02 vials

D.22	Human Normal Immunoglobulin (IgG)(subcutaneous administration)	04 bottles	02 Bottles
D.23.1	Fibrin Sealant Kit	06 Kits	02 Kits
D.23.2	Fibrin Sealant Kit(without F-XIII)		
D.23.3	Fibrin SealantKit (without Fibrinogen)		
D.24	Anti-T Lymphocyte Immunoglobulinfor Human Use, Animal (lyophilized)	10 vials	10 vials
D.25	AntihemophilicFactor VIII (Recombinant PEGylated)	10 vials	10 vials
D.26	Anti-D Immunoglobulin (Intramuscular) Freeze Dried	50 vials	25 vials
E.1	Heparin Sodium injection	08 vials	06 vials
E.2	Human Chorionic Gonadotropin(HCG)Bulk	0.2g x 1 vial & 5mg x 5vials *Sample is required in separatevials containing quantity as mentioned Above	Nil
E.3.1	Human Chorionic Gonadotropin(HCG)injection	08 vials	06 vials
E.3.2		10 vials	07 vials
E.4	Menotropin (HumanMenopausal Gonadotropin) Bulk	2mg x 4 vials, 4mg x 1 vial& 5mgx 2 vials *Sample is required in separate vials containing quantity as mentioned above	Nil
*E.5.1		17 vials	14 vials
*E.5.2		14 vials	14 vials

*E.5.3	Menotropin (Human Menopausal Gonadotropin) injection	12 vials	10 vials
*E.5.4		12 vials	10 vials
E.6.1	Enoxaparin Sodium Injection	20 vials	20 vials
E.6.2		18 vials	18 vials
E.7.1	Recombinant HumanGrowth Hormone/Somatropininjection	12 vials	10 vials
E.7.2			
E.7.3			
E.7.4			
E.7.5			
E.7.6			
E.7.7		12 PFS/Vial	10 PFS/Vial
E.8.	Recombinant Streptokinase injection	12 vials	10 vials
E.9	Recombinant Human Follicle StimulatingHormone Injection	10 PFS 10 vials	10 PFS\ 10 vials
E.10	Streptokinase Bulk	25mg x 3 vials, 5mg x 5 vials, 10mgx 2 vials & 15mg x 1 vial *Sample isrequired in separate vialscontaining quantity as mentioned above	Nil
* E.11.1	Streptokinase injection	10 vials	08 vials
* E.11.2		09 vials	08 vials
# E.12.1	Tenecteplase for injection(TNK-TPA)	6 vials	2 vials
# E.12.2		6 vials	2 vials
# E.12.3		6 vials	2 vials
E.13	Urofollitropin Bulk	5mg x 3 vials & 2mg x 2vials *Sample is required in separatevials containing quantity as mentioned Above	Nil

# E.14.1	Urofollitropin injection	11 vials	08 vials
# E.14.2		11 vials	08 vials
E.15	Urokinase Bulk/Final	05mg x 8 vials *Sample is required in separate vials containing quantity as mentioned above	Nil
# E.16	Urokinase injection	11 vials	08 vials
# E. 17	Elaprase Injection	04 vials	04 vials
# E.18	VPRIV Injection	06 vials	06 vials
# E. 19	Replagal Injection	04 vials	04 vials
E.20	Human C1-Esterase Inhibitor	13 vials	08 vials
F.1.1	Biphasic Isophane Insulin(25/75)	25	10
F.1.2	Biphasic Isophane Insulin(25/75)	15	10
F.1.3	Biphasic Isophane Insulin(30/70)	25	10
F.1.4	Biphasic Isophane Insulin(30/70)	15	10
F.1.5	Biphasic Isophane Insulin(50/50)	25	10
F.1.6	Biphasic Isophane Insulin(50/50)	15	10
F.2	Dulaglutide	25	5
F.3	Exenatide	25	5
F.4.1	Filgrastim Injection (rh.GCSF)	15	5
F.4.2		15	10
F.5	Insulin Aspart bulk	2g x 2 aliquotes	Nil
F.6.1	Insulin Aspart	25	10
F.6.2		15	10
F.7.1	Insulin Aspart & Insulin aspart protamine suspension Mixed in 30/70mix	25	10

F.7.2	Insulin Aspart & Insulin aspart protamine suspension Mixed in 50/50 mix	25	10
F.8	Insulin Degludec	20	10
F.9	Insulin Degludec / InsulinAspart	30	10
F.10	Insulin Detemir	20	10
F.11.1	Insulin Glargine	25	10
F.11.2		25	10
F.11.3		15	10
F.12.1	Insulin Glulisine	25	10
F.12.2		15	10
F.13	Insulin Lispro bulk	2g x 2 aliquotes	Nil
F.14.1	Insulin Lispro	25	10
F.14.2		15	10
F.15.1	Insulin Lispro & InsulinLispro Protamine Suspension (Mixed in 25/75 Mix)	25	10
F.15.2	Insulin Lispro & InsulinLispro Protamine Suspension Mixed in50/50 Mix	25	10
F.16	Interferon alpha 2b injection	15	10
F.17.1	Isophane insulin (NPH)	25	10
F.17.2		15	10
F.18	Liraglutide (Glucagonlike Peptide-1)	20	10
F.19	Peg Filgrastim Injection (PegGCSF)	20	5
F.20	Peg Interferon alpha 2b inj	15	10
F.21	Peg Interferon Beta 1a inj	25	5

F.22	rh – Insulin bulk	2g x 2 aliquotes	Nil
F.23	rh- Erythropoietin bulk	2g x 2 aliquotes	Nil
F.24.1	rh. Erythropoietin injection	15	5
F.24.2		20	5
F.25	rh. Interferon beta 1a Injection	30	5
F.26.1	Soluble insulin (Regular)	25	10
F.26.2		15	10
F.27	Teriparatide (rh. Para ThyroidHormone- PTH)	15	10
F.28	Xultophy (Liraglutide & Degludec)	30	10
F.29	Peg Erythropoietin	20	10
F.30.1	Peg Interferon Beta 1a inj	30	5
F.30.2		30	5
F.31	Insulin Glargine Bulk	2g x 2 aliquotes	Nil
F.32	Recombinant interferonbeta 1binjection 250 µg/ ml	20 vials	5 vials
F.33	Darbepoetin Alpha Injection	25 vials	5 vials
H.1	Cell Culture Rabies vaccine	21 vials	10 vials
H.2.1	Hepatitis A		20 vials
		20 vials	
H.2.2		12 vials	12 vials
H.3.1	Hepatitits B	20 vials	20 vials
H.3.2		12 vials	12 vials
H.3.3		12 vials	12 vials
H.4	Japanese Encephalitis Vaccine(Human)	20 vials	20 vials

H.5.1	Measles Mumps & Rubella Vaccine	20 vials	20 vials
H.5.2		14 vials	14 vials
H.6.1	Measles Vaccine	20 vials	20 vials
H.6.2		14 vials	14 vials
H.7.1	Rubella vaccine	20 vials	20 vials
H.7.2		14 vials	14 vials
H.8	Bacillus Calmette Guerin (BCG)Vaccine	57 vials	57 vials
H.9.1	Haemophilus InfluenzaeType-b-(Hib)-TT Conjugate Vaccine	55 vials	55 vials
H.9.2		18 vials	18 vials
H.10	Oral Cholera Vaccine	20 vials	20vials
H.11	Oral Polio Vaccine	10 vials	10 vials
H.12.1	COVID-19 Vaccines (Covishield, Covaxin,ZyCoV-D)	40 vials	20 vials
H.12.2		10 vials	5 vials
H.12.3		10 vials	5 vials
H.13	Rabies Immunoglobulin(Equine)	20 vials	10 vials
H.14	Human Papilloma Virus Vaccine(r-DNA)	30 vials	15 vials
J.1.1	Adalimumab	10 PFS	10 PFS
J.1.2		11 PFS	11 PFS
J.1.3		10 PFS	10 PFS
J.2.1	Bevacizumab	5 vials	5 vials
J.2.2		5 vials	5 vials
J.3	Etarnercept	9 PFS	9 PFS
J.4	Pertuzumab	5 vials	5 vials
J.5.1	Ramucirumab	5 vials	5 vials
J.5.2		5 vials	5 vials
J.6	Ranibizumab	16 vials	16 vials

J.7.1	Rituximab	5 vials	5 vials
J.7.2		5 vials	5 vials
J.8.1	Trastuzumab	6 vials	6 vials
J.8.2		6 vials	6 vials
J.9.1	Anti-D Immunoglobulin, I.M (Monoclonal)	33 vials	33 vials
J.9.2		36 vials	36 vials
J.10.1	Human Hepatitis B Immunoglobulin (Intramuscular) (Monoclonal)	50 vials	50 vials
J.10.2		33 vials	33 vials
J.10.3		18 vials	18 vials
J.10.4		13 vials	13 vials
J.10.5		6 vials	6 vials
J.10.6		3 vials	3 vials
J.12.1	Tetanus Immunoglobulin (Monoclonal), Tetclone	33 vials	33 vials
J.12.2		18 vials	18 vials
J.13	Obinutuzumab	4 vials	4 vials
J.14	Omalizumab	9 vials	9 vials
J.15	Natalizumab	4 vials	4 vials
J.16	Pembrolizumab	4 vials	4 vials
J.17	Infliximab	10vials	10Vials
J.18	Mepolizumab	10vials	10Vials
J.19	Recombinant AntiRho-D Immunoglobulin Injection	100 vials	100 vials
J.20	Vedolizumab	09 vials	09 vials
J.21.1	Transtuzumab Emtansine	05 vials	05 vials
J.21.2		05 vials	05 vials
J.22	Inotuzumab Ozogamicin (Powder for solution forinfusion)	10vials	10Vials

J.23.1	Denosumab	12 PFS	12 PFS
J.23.2		12 vials	12 vials
J.24	Benralizumab	12 PFS	12 PFS
J.25.1	Durvalumab	09 vials	09 vials
J.25.2		05 vials	05 vials
J.26	Tocilizumab	05 vials	05 vials
J.27	Cetuximab	05 vials	05 vials
J.28	Brentuximab Vedotin	09 vials	09 vials
J.29	Evolocumab Injection	15 PFS	15 PFS
J.30	Nivolumab	09 vials	09 vials
J.31	Secukinumab	15 vials	15 vials
K.1	RT-PCR Kits for Diagnosis of COVID-19 (Validation)	160 Tests	160 Tests
K.2	RT-PCR Kits for Diagnosis of COVID-19(Batch Testing)	50 Tests	50 Tests
K.3	RNA Extraction Kits for Diagnosisof COVID-19 (Validaton)	50 Tests	50 Tests
K.4	RNA Extraction Kits for Diagnosisof COVID-19 (Batch Testing)	30 Tests	30 Tests
K.5	VTM for Diagnosis ofCOVID-19 (Validation)	20 Tests	20 Tests
K.6	VTM for Diagnosis of COVID-19(Batch Testing)	10 Tests	10 Tests
K.7	COVID Ab kit (IgG to S Protein)Rapid	250 Tests	250 Tests
K.8	COVID Ab kit (IgG to S Protein)CLIA	400 Tests	400 Tests
K.9	COVID Ab kit (IgG to N Protein)Rapid	250 Tests	250 Tests

K.10	COVID Ab kit (IgG to N Protein)CLIA	400 Tests	400 Tests
K.11	RT-LAMP Kit for Diagnosis ofCOVID-19(Validation)	160 Tests	160 Tests
K.12	RT-LAMP Kit for Diagnosis ofCOVID-19(Batch Testing)	50 Tests	50 Tests

Annexure-5

Quantity required for Complete Analysis of Medical Device Samples

s.no.	name of medical device	Form MD 38 samples	Survey samples
1.	Hypodermic Syringe	50pcs	10 pcs
2.	Hypodermic Needle/DisposableSyringe Needles	50 pcs	10 pcs
3.	Infusion Set/Transfusion Set	50 pcs	10 pcs
4.	IV Cannulas	50 pcs	10 pcs
5.	Roll Bandage/Surgical Dressings	20 pcs	10 pcs
6.	Sterile Gauze Swab	50 pcs	10 pcs
7.	Surgical Suture (absorbable)	50 pcs	30 pcs
8.	Surgical Suture (Non-absorbable)	50 pcs	30 pcs
9.	Medicated Tape (Band-aid)	100 pcs	20 pcs
10.	Absorbent Cotton Wool I.P.	200gm	100gm
11.	Catheter or Ryles Tube	30 pcs	10 pcs
12.	Tubing for Micros-surgery orEndoscope	50 pcs	10 pcs
13.	Male Rubber Latex Condoms	100 pcs	100 pcs
14.	Copper T	120 pcs	20 pcs
15.	Tubal Rings	100 pcs	20 pcs
16.	Blood Bags	10bags	5bags
17.	Absorbent Sponge	50 pcs	5 pcs

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CHAPTER-2

PROCEDURE TO CARRY OUT SURPRISE CHECK/RAID AND INVESTIGATION ON THE BASIS OF THE COMPLAINT.

Zonal & sub-zonal office receive complaints from some agencies and stake holders regarding movement of spurious/sub-standard drugs. If a spurious or sub-standard is detected by zonal or subzonal office, utmost care should be taken to connect the manufacturer through all distribution channel from the source of collection of the impugned drug. The moment manufacturer involvement is established, the documented evidence collected in this regard should immediately be sent to the concerned zonal officer under whose jurisdiction the manufacturing unit is located for further investigation through the Drugs Inspector of the said zone. It is advisable not to send the Drugs Inspector directly to the manufacturing unit or to the concerned State Licensing Authority for investigation without connecting the manufacturer with proper documented evidence.

CHAPTER-3

Procedures to be adapted by the zonal officers to discharge the various functions that has been delegated recently by the Drugs Controller General of India under Rule 22 of the Drugs & Cosmetic Rules

1. Permission for grant of license to manufacture drugs for the purpose of examination, test or analysis under the New Drugs & Clinical Trials Rules, 2019 in Form CT-11 for new drugs/investigational new drugs (Active Pharmaceutical Ingredients & formulations), CT-14 (Unapproved Formulations) and CT-15 (unapproved APIs), permission to grant of import license to manufacture drugs for the purpose of examination, test or analysis under the New Drugs & Clinical Trials Rules, 2019 in Form CT-17 and permission to grant of import license to manufacture drugs for the purpose of examination, test or analysis under the Drugs Rules in Form 11 so as to obtain license from State Licensing Authority (SLA) of concerned State under Rules 89 of the Drugs and Cosmetics Rules, 1945 on Form-29 as per requirements.
2. Issue of No. Objection certificate for the grant of permission for manufacture for export only of unapproved/ approved new drugs and drugs banned under section 26-A of the Drugs & Cosmetic Act.
3. Issue of Permit for import of small quantities of drugs for personal use under Form-12B of the Drugs & Cosmetic Rules.
4. Issue of No. Objection certificate for the grant of permission for import of dual use items, not for medicinal use.
5. Guidelines have been prepared separately on different topics subsequently.

CHAPTER-4

Procedure to be followed to maintain the records of all activities of Zonal & Sub-Zonal office

Following activities of the zonal / sub-zonal office (depicted below) should be recorded and the generated data in this regard should be preserved in graphical representation and to be forwarded to the head quarter as well as the zonal offices at regular interval e.g. monthly and yearly (as KPI).

Administrative	Technical
i. No. of receipts ii. No. of receipts processed and reply thereof iii. No. of receipt filed where no action is warranted. iv. No. of letters generated by this office v. Monthly expenditure statement. vi. No. of RTI applications received and disposed of.	i. No. of applications received a. For issuance / revalidation of COPPs. b. For grant / renewal of blood center licenses. c. For grant/ retention of manufacturing license. d. For grant/ retention of Class C & D Medical Devices / In-vitro Diagnostics e. For grant/ retention of Vaccine mfg. units f. For grant/ retention of LVPs units g. For grant of approval for Testing Laboratory. h. For grant of approval for Bio-Tech / Bio-Similar Products. i. For grant of approval for BA/BE centers and CRO Inspections as directed by DCG(I). j. For grant of permission in Form 11 as per Drugs Rules and Form CT-11, Form CT-14, Form CT-15 & Form CT-17 as per NDCT, 2019. k. For grant of permission in Form 12(B) for import l. For grant of NOC for export m. For grant of NOC for dual use items n. For grant of COPPs for additional product ii. No. of samples collected under the Act, No. of test reports received, No. of test reports pending. iii. No. of samples declared NSQ iv. No. of complaint received. v. No. of complaint attended. vi. No. of complaint where action was initiated vii. No of prosecution filed before various courts. viii No. of inspections carried out a. For issuance / revalidation of COPPs.

	b. For grant / renewal of blood center licenses. c. For grant / retention of Class C & D Medical Devices / IVD. d. For grant / retention of manufacturing license d. For grant / retention of Vaccine mfg. units e. For grant / retention of LVPs units f. For grant of approval for Testing Laboratory g. other inspections ix. Other activities (workshop, seminar, meetings, trainings organized / attended)

Chapter-5

Processing of application of CoPP, CLAA items and medical device and Inspection process

Part A

	TITLE			Division Name	Technical
	General Procedure to be followed during On Site Evaluation (OSE) by Drugs Inspectors			Document No.	SOP/001
				Revision No.	00
				Effective Date	
				Page No.	
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 OBJECTIVE:

The Central Drugs Standard Control Organization is responsible for laying down the standards of drugs, cosmetics, diagnostics and devices and enforcing the rules of Good Manufacturing Practice (GMP) in India for manufacturers of Finished Pharmaceuticals Products (FPP) and Active Pharmaceutical Ingredients (API). The objective of this document is to provide uniform enforcement procedures for onsite inspections to evaluate compliance of the quality system and infrastructure with nationally & internationally accepted GMP Standards (based on the reference document as prescribed in the D & C Act & Rules and WHO-GMP/TRS guidelines)

2.0. SCOPE:

This SOP sets out a uniform procedure for carrying out the notified inspections for following modules under the preview of D & C Act & Rules and WHO-GMP-TRS throughout India.

2.1. Routine Inspection
2.1.1. Inspections for grant/renewal of licenses under CLAA Scheme.
2.1.2. Inspections for issuance / revalidation of COPPs as per WHO Certification Scheme for use in international commerce only.
2.1.3 Inspections for approval of Testing Laboratories.
2.2. Follow up inspection
2.2.1. Compliance verification inspection to authenticate the results of corrective actions.
2.3. Special Inspection
2.3.1. UNOPS/RITES inspection for NCB/ICB.

3.0 RESPONSIBILITIES:

3.1. It is the responsibility of concerned Drugs Inspector(s)/inspection team member(s) who carry out the aforesaid inspection to follow this SOP.

4.0. EXTERNAL EXPERTS OTHER THAN DRUGS INSPECTORS:

4.0.1. The Field expert may join the team as necessary, for example:-

4.0.1.1. For biologicals including vaccines — a biological products specialist;

4.0.1.2. A blood Bank Expert for blood Bank inspection.

4.0.1.3. Bio-tech expert for products like rDNA, monoclonal etc.

4.0.1.4. Clinical Pharmacologist or other experts for BA/BE centres or CROs.

5.0. PROCEDURES

5.1. PREPARING FOR THE INSPECTION

5.1.1. Receipt of File of the firm to the deputed inspection team member(s).

5.1.2. A review should be made relating to the firm to be visited from the documents available in the office file. This may include:-

5.1.2.1. Drug Manufacturing Licence.

5.1.2.2. The marketing Authorization for the applied products.

5.1.2.3. Site Master File

5.1.2.4. Evaluation of i. Product records (process validation and stability studies), ii. Reports of adverse Drugs reaction, iii. Market complaint, iv. Product recall record, v. NSQ reports available in the office file, vi. Discrepancies pointed out in previous inspection reports.

5.1.3. Preparation of the day wise inspection plan (1-3 days) as per Annexure A

5.1.4. Communication with the Local Authority for access to the site of inspection and regarding the Schedule of inspection.

5.2 **CONDUCT OF INSPECTORS DURING INSPECTION**

5.2.1 The inspectors are public servant within the meaning of Sec. 21 of IPC and should behave accordingly.

5.2.2. Inspector shall act according to the procedures for handling of confidential information. All information observed or passed to the inspector is confidential and shall not be disclosed to anybody other than his controlling authority.

5.2.3. Inspector shall neither carry with him any written or printed materials relating to other units nor disclose any information relating to another company.

5.2.4. The inspector's task is not only to point out deficiencies but also to provide guidance based on scientific evidence.

5.3. OPENING SESSION

5.3.1. **At the opening session: -**

The inspection usually begins with a meeting between the inspector(s), representatives of the firm or plant management and those responsible for the product or areas to be inspected.

5.3.1.1. The inspectors shall identify themselves and describe their jobs;

5.3.1.2. The inspection team shall give a written day wise plan for the inspection schedule as per **Annexure- A**.

5.3.1.3. The inspector(s) shall inform to the firm management to ensure presence of concerned in-charge of the respective areas as per inspection plan. 5.3.1.4. The inspectors shall state which documents they need to examine once they have completed their preliminary tour of the site.

5.4 Conduct of Inspection

5.4.1. There will be a preliminary tour of the site to allow the inspectors to get a general orientation of the site. It is recommended that the inspecting team start the plant tour as soon as possible after arrival. It is advisable to follow the inspection plan as per material flow.

5.4.2. Over the course of the inspection the inspectors shall review all procedures, production and laboratory records, validations and any other record or documentation relating to production and control of the production process.

5.4.3. It is advisable to check the items that are specific to certain areas of the facility, such as, Sampling /Dispensing of RM/PM, in process testing and working documents at the point of operation.

5.4.4. The inspection shall also include detailed tours of all production facilities, laboratories, stores, utilities, the plant's record and documentation centre.

5.4.5. The following specific issues shall be investigated, inter alia:

5.4.5.1 The suitability of the facility for its purpose, including the orderliness of its Lay-out for man and material movement, equipment and cleanliness;

5.4.5.2 The production equipment —its qualification/validation, calibration and cleanliness, preventive maintenance, daily equipment usage logs.

5.4.5.3. Whether production records are fully maintained and in real time.

5.4.5.4. Critical systems: HVAC, water system, filtered compressed air, drainage, ETP and any other relevant systems.

5.4.5.5. The documents such as master formulae, test specifications, Standard Operating Procedures, batch records (including protocols of analysis and documents relating to the control of printed material and labelling operations) requires close verification.

5.4.5.6. The inspection team may adopt the additional and other plan for areas of inspection based on the need of particular inspection for the required purpose.

5.5 CONCLUDING SESSION:-

5.5.1 The inspection shall conclude with a final session between inspectors and firm's representatives. The final session shall cover (at least)

5.5.2. A detailed listing of the findings and deficiencies found by the inspectors during the course of their inspection;

5.5.3. Issues of non-compliance observed during inspections shall be noted, discussed with firm representatives and handed over a copy of the same.

5.6. REPORTING AND SUBMISSION: -

The report of the inspection shall be prepared as per checklists provided for guidance in this document. The checklist for inspection of manufacturing units is a general example and need to be adopted as per specific need of the inspection and the products, e.g. for inspection of LVPs, Biological Products other than Vaccines and for issuance of COPPs. As the said checklist is primarily prepared on the basis of provisions of Schedule M of the D & C Rules, it is imperative to adopt it as per the current applicable WHO GMP Guidelines in case of inspection for issuance of COPPs.

The report of Inspection shall be completed in all respects as per the checklist and submitted to the Controlling Authority for review, comments and for further necessary action as early as possible.

6.0. RECORDS:-

Annexure-A- Inspection Plan
Annexure-M- Checklist for inspections of manufacturing units as per schedule M of Drugs and Cosmetics Rules
Annexure-N- Format for 'Inspection Report for drugs'
Annexure-O- Inspection Checklist for Blood Centre
Annexure-P- Inspection Checklist for Medical Devices Manufacturing Unit
Annexure Q-Checklist for inspection of approved Testing Laboratories.
Annexure-R Inspection Format for inspection of Public Testing Laboratories.

7.0 ABBREVIATION(S)

D & C ACT & RULE- DRUGS & COSMETICS ACT 1940 & RULES 1945
CDSCO – Central Drug Standard Control Organisation
CLAA-Central Licence Approving Authority
SLA – State Licensing Authority
OSE- On Site Evaluation
DML-Drug Manufacturing Licence
COPP – Certificate of Pharmaceutical Product
TDA- Technical Data Associate
RM/PM- Raw Material/Packaging Material
WHO TRS – World Health Organisation, Technical Report Series
NCB-National Competitive Bidding
ICB- International Competitive Bidding.
HVAC- Heating Ventilation & Air Conditioning System.
ETP- Effluent Treatment Plant

Note: - When the application is made for 'Site Certification' as prescribed in WHO TRS 908, similar procedure as mentioned above for inspection shall be adopted if all the categories of the products licensed for manufacturing on the premises / section applied for, fulfils the WHO GMP requirements with respect to stability, process validation, analytical method validation etc.

		TITLE		Division Name	Technical
		Screening of applications for COPPs, CLAA Items & Approved Testing Laboratories		Document No.	SOP/002
				Revision No.	00
				Effective Date	
				Page No.	
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 OBJECTIVE:

To lay down the procedure for scrutiny of the documents submitted along with the application in respect of grant/ revalidation of COPP & CLAA items and Public Testing Laboratories.

2.0 **SCOPE:**

This procedure is applicable for screening of the documents submitted by the Pharmaceutical companies at respective CDSCO, Zonal and Sub-zonal Offices.

3.0 RESPONSIBILITIES:

3.1. For Scrutnization & Preparation of checklist and draft - Should be done by STA/TA/ADI/DI/TDA at CDSCO.

3.2. For review, correction & approval of checklist and draft - Should be done by Technical Head of the Department.

4.0 DEFINITION(S):

COPP:– Certificate issued by the international drug regulatory authority in accordance with the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in international commerce.

5.0 PROCEDURE:

5.1 All Zonal/ Sub Zonal Office is required to display the documents (in case non availability of online plat form) required for submission of application.

5.2 Receive the documents in the CD/ SUGAM/ NSWS and physically (hard copy). Trace the file and attach the received application with CD in the corresponding file.

5.3 Scrutinize the content of CD/ Checklist of SGAM/NSWS as per respective annexures.

5.4 After scrutinization, prepare the checklist with details of documents submitted in the CD.

5.5 In case of online system like SUGAM/ NSWS comment is required to provided with all checklist points.

5.6 A draft should be prepared according to the observations listed in the checklist in case of application in CD/ Hard copy.

5.7 In case of online system the query raise is forwarded to head of office for further issue to the applicant and SLA.

5.8 After preparation of Checklist and/or draft, it should be sent to the Technical head for review/ correction.

5.9 The query may be communication to applicant and SLA through email/ online platform in case of SUGAM/ NSWS or through post.

5.10 After dispatch, it should be attached to the corresponding file.

5.11 Application is required to scrutinized and inspection may be planned as per time line provided in this guidance document.

6.0 Records:-

Annexure B- Document Required for Grant/ Revalidation of COPPs

Annexure C- Checklist for screening: the document for submission of application for issue of COPP (WHO-GMP) for Drugs

Annexure D- Documents Required for Grant/ Renewal of Blood Center License

Annexure E- Checklist for screening the documents (Blood Centre)

Annexure F- Documents required for Grant/retention of License for Vaccines

Annexure G- Checklist for the documents required for Grant/Retention of License for Vaccines

Annexure H-Checklist (Through SUGAM Portal) of documents required for the grant of manufacturing license or loan license for Medical Devices and In-vitro diagnostic (IVD) medical device

Annexure K- Document's required for grant/retention of manufacturing license in Form 28-D/Form 28-DA (LVP/r-DNA/Sera etc):

Annexure L Checklist for screening the document's required for grant/retention of manufacturing license in Form 28-D/Form 28-DA (LVP/r-DNA/Sera etc)

7.0 ABBREVIATION(S)

CDSCO – Central Drug Standard Control Organisation
CoPP – Certificate of Pharmaceutical Product
LVP- : Large Volume Parentral
OSD – Oral Solid Dosage
SLA – State Licensing Authority
WHO TRS – World Health Organisation, Technical Report Series
DI- Drugs Inspector
ADI- Assistant Drugs Inspector
NSWS-National Single Window System

Annexure: A

GENERAL SHECDULE OF INSPECTION PLAN

To be adopted for 2-5 Days as per requirements)

Day	Topic	Points to be covered	Average Time (May be adjusted accordingly)
First day	Opening Meet	Introduction Describe Purpose of Inspection Firm's presentation Preliminary review of • SMF • Layout Plan	9.00 AM-10.30 AM
	Tea		
	Site Evaluation Tour		
	Raw Material & Packing Material Receipt area & Store	• Material Receiving Bay • De-dusting procedure • Assessment of Vendors' qualification • Procedure for receipt of materials • Quarantine/under test/Approved/ rejected Area • Sampling Area & procedure • Dispensing Area /booth • Storage Condition • Stock Register & Physical Verification of raw materials along with distribution process	10.30 AM -1.30 PM
	Lunch Break		1:30 PM to 2:00 PM
	Production area	• Change Rooms • Gowning Procedure • Processing area	2:00 PM to 5:30PM

		• Air Filtration with Pressure • Internal Finishing of Core • Balancing • Environmental Monitoring • System • Production Layout & Men • Material Movement • Drainage system & Service • Lines • Equipments placement, • Cleaning/ sanitization &MOC • Tools & Change Part Storage	
Second Day		• IPQC • Bulk Quarantine • Primary Packing • Secondary Packing	09:00 AM to 1:30 PM
	QC Area, HVAC System, Water System Loop Evaluation	General requirements • Ware housing area • Production area • Ancillary areas • Quality control area • Water and compressed air system • HVAC System • Personnel • Health, clothing, sanitation of workers Manufacturing operation and controls • Sanitation in manufacturing premises • Raw materials • Equipment Documentation and records • Master formula records • Packaging records • Batch packaging records • Batch processing records • Distribution records • APQR • Statistical data AMV records • Audit trail • Labels and other printed material	

		• Quality Management system • Internal Quality review, • Quality risk Management, • Pharmaceutical Quality system, • Approved vendor list, • Good Practices in Production and Quality control • self-Inspection • Quality assurance • Quality control system Specification • SOP's and STP's • Reference samples • Reprocessing and recoveries • Validation and process validation • Product recalls Complaints and adverse reactions • Site master file	
	Lunch Break		1:30 PM to 2:00 PM
	Documents evaluation (contd.)	Verification of 1 or 2 specific batch manufacturing record along with supporting documents.	2:00 PM to 5:30 PM
Third Day	Report Preparation	As per the specified check list.	9:00 AM to 2:00 PM
	Lunch Break		2:00 PM to 2:30PM
	Concluding Session	Discussion with the management representative regarding non-compliance observations noted during the inspection and shares the observations with them.	2:30 PM to 5:30PM

Note: Depending on the Complexity of the categories of application and product applied for Grant/Renewal of License and WHO-GMP (COPP) and procedure adopted above inspection plan may be extended/relaxed after obtaining necessary direction for such modification from the zonal head

Annexure: B

DOCUMENT REQUIRED FOR GRANT/ REVALIDATION OF COPPs

1. Application with covering letter on company's letter head duly signed and stamped by Authorized signatory indicating the name and designation of the authorized signatory along with the name and address of the firm with the following:
2. Intent of application

   i) Whether the application is submitted for the first time

   ii) Whether the application is submitted for re-issue

   iii) Whether the application is submitted for additional product
3. Index with page Nos
4. Address of facility where the drug substances (APIs)/ Drug products (Formulation) are to be manufactured
5. List of product/APIs applied for issuance of COPPs (WHO-GMP)
6. Product approval issued by State Licensing Authority.
7. List of SOPs and STPs
8. Stability Data (3 batches,6 Months) Consolidated
9. Accelerated
10. Real time
11. Process validation for 3 batches of each applied API/Formulation
12. Export data of last 2 years in case of revalidation
13. Product summery sheet
14. Last inspection date
15. Copy of License issued to all APIs/ Formulations approved by SLA (License copy)
16. List of Technical staff with their qualification, experience and approval by SLA.
17. Copy of WHO-GMP & COPPs certificate issued as per WHO guidelines
18. Site Master file (as specified under WHO TRS 996)
19. Manufacturing layout
20. Schematic diagram of water system specifying circulation loop and MOC

21. Schematic diagram of HVAC system specifying terminal filter configuration

22. List of equipment and Instrument

23. List of major changes after last inspection

24. Analytical method validation for all applied products
25. Detail as per sheet attached:-

Annexure: C

CHECKLIST FOR SCREENING: THE DOCUMENT FOR SUBMISSION OF APPLICATION FOR ISSUE OF COPP (WHO-GMP) FOR DRUGS

Name and Address of the firm:

Date of receipt of Application:

S.NO.	Parameter	Status	Page Nos.	Remarks
Part-A (Product related documents)				
1	Application with covering letter on company's letter head duly signed and stamped by Authorized signatory indicating the name and designation of the authorized signatory along with the name and address of the firm with the following:	Yes /No		
	Intent of application	Yes/No		
	i) Whether the application is submitted for the first time	Yes/No/NA		
	ii) Whether the application is submitted for re-issue	Yes/No/NA		
	iii) Whether the application is submitted for additional product	Yes/No/NA		
	Index with page Nos	Yes/No		
	Address of facility where the drug substances (APIs)/ Drug products (Formulation) are to be manufactured	Yes/No		
	List of product/APIs applied for issuance of COPPs (WHO-GMP)	Yes/No		
2	List of SOPs and STPs	Yes/No		
3	Stability Data (3 batches,6 Months) Consolidated	Yes/No		
	Accelerated	Adequate/		

		inadequate		
	Real time	Adequate/ inadequate		
4	Process validation for 3 batches of each applied API/Formulation	Yes/No		
5	Export data of last 2 years in case of revalidation	Yes/No		
6	Product summery sheet	Yes/No		
7	Last inspection date	Yes/No		
Part-B (Site Related Document)				
8	Copy of License issued to all APIs/ Formulations approved by SLA (License copy)	Yes/No		
9	List of Technical staff with their qualification, experience and approval by SLA.	Yes/No		
10	Copy of WHO-GMP & COPPs certificate issued as per WHO guidelines	Yes/No		
11	Site Master file (as specified under WHO TRS 996)	Yes/No		
	Manufacturing layout	Yes/no		
	Schematic diagram of water system specifying circulation loop and MOC	Yes/No		
	Schematic diagram of HVAC system specifying terminal filter configuration	Yes /No		
12	List of equipment and Instrument	Yes/No		
13	List of major changes after last inspection	Yes/No		
14	Analytical method validation for all applied products	Yes/No		

Submitted by:

Name:

Designation:

Opinion: On security of the submitted document vide Letter No. …….

Dated……..the aforesaid document are submitted/ yet to be submitted.

Scrutinized by:	Verified By:
Name:	Name:
Designation:	Designation:

ANNEXURE: D

DOCUMENTS REQUIRED FOR GRANT/ RENEWAL OF BLOOD CENTER LICENSE

1. Covering letter
2. Copy of License/Last Renewal Certificate
3. A plan of Premises
4. List of equipment & machinery
5. Memorandum of association/constitution ofthe firm (List of Directors)
6. Attested copies of certificates of competent technical staff (as per Drugs & Cosmetic Actand Rules 1945)
7. Documents relating to ownership or tenancyof the premises
8. Whether inspection carried out
9. NOC from SBTC where applicable
10. Registration Certificate of charitable trust(ifapplicable)
11. Copy of Labels
12. List of SOPS
13. Self-declaration of technical person
14. Self-declaration of directors
15. Any Other Document
16. Agreement for Biomedical WasteManagement
17. License fee receipt/Challan form
18. Form 27C

ANNEXURE: E

Checklist for screening the documents (Blood Centre)

Name of the firm: M/s

Date of receipt of application: ----------

Subject: Grant / Renewal of license for the preparation of Whole Human Blood/ Components/ Aphaeresis

S. No.	Documents	Status	Remark
1	Covering letter		
2	Copy of License/Last Renewal Certificate	Yes/No	
3	A plan of Premises	Yes/No	
4	List of equipment & machinery	Yes/No	
5	Memorandum of association/constitution ofthe firm (List of Directors)	Yes/No	
6	Attested copies of certificates of competent technical staff (as per Drugs & Cosmetic Actand Rules 1945)	Yes/No	
7	Documents relating to ownership or tenancyof the premises	Yes/No	
8	Whether inspection carried out	Yes/No	
9	NOC from SBTC where applicable	Yes/No	
10	Registration Certificate of charitable trust(ifapplicable)	Yes/No	
11	Copy of Labels	Yes/No	
12	List of SOPS	Yes/No	
13	Self-declaration of technical person	Yes/No	
14	Self-declaration of directors	Yes/No	
15	Any Other Document	Yes/No	
16	Agreement for Biomedical WasteManagement	Yes/No	
17	License fee receipt/Challan form	Yes/No	
18	Form 27C	Yes/No	

Submitted by:

Name:

Designation:

Opinion: On security of the submitted document vide Letter No. …….

Dated……..the aforesaid document are submitted/ yet to be submitted.

Scrutinized by: Verified By:

Name: Name:

Designation: Designation:

Annexure: F

Documents required for Grant/retention of License for Vaccines

1. Covering letter address to appropriate authority
2. Application in prescribed legal Form (i.e. Form 27-D- in case of grant of license/Form 27-DA- in case of grant of loan license)
3. Copy of Challan/ Proof of submission of application fees Paid.
4. Copy of Site Master file (as specified under current effective WHO TRS)
5. Copy of Manufacturing License available with the Firm
6. (In case of Retention)
7. Specific Power of Attorney in Favour of Authorized Signatory for Submitting Application On Behalf Of The Company.
8. Constitution details of the firm with supporting documents
9. List of Directors, Partners, Trustees, along with AOA and MOA submitted to ROC, LLP, Registered Partnership deed, Trust deed, etc. (As applicable)
10. Self-attested copies of documents pertaining to the possession, ownership or tenancy of the premises such as, Register ownership /rent /lease/allotment letter /Possession Letter, Tax Receipt, (Documents should be Registered with appropriate Authority)
11. Consent from the State Pollution Control Board to establish & consent to operate the manufacturing site.
12. NOC issued by Department of Industrial Safety & Health.
13. Permissions from CPCSEA for operation of animal house used for testing , If any
14. Plan layout of the premises Approved by the Licensing Authority.
15. Plan layout of premises shall consists :

i) General Layout

ii) Material & Personal movement layout

iii) HVAC Area classification and Pressure differential layout for

16. for critical Mfg. & QC areas - Floor wise/ Block wise
17. iv) Location of Equipment's in Mfg. & Location of Instruments in QC areas- Floor wise/ Block wise
18. v) Pass Box positioning in critical area.
19. Section wise List of machinery and equipment to be employed for manufacture and testing
20. List of Competent Technical Staff appointed for manufacturing with their qualification, Registration, Experience, previous FDA Approvals, Etc.
21. Appointment/Acceptance Letter of Competent Technical staff of manufacturing Section.
22. List of Competent Technical Staff appointed for testing with their qualification, Registration, Experience, previous FDA Approvals, Etc.

23. Appointment/Acceptance Letter of Competent Technical staff of Testing Section.
24. Details of water used to including quality of water at site, Details of Water generation Systems (Purified Water & WFI) used for water generation at the site. Schematic diagram of Water system.
25. Water Generation and circulation system Installation and validation Reports/ Certificate
26. Details of HVAC system used for maintaining Classified Area (including schematic diagram of classified area and HVAC system). AHU Installation and Validation Reports/Certificate
27. List of SOPs and STPs
28. Washing arrangements for the components and equipment's used for manufacturing.
29. List of utilities used at side with Equipment I D and Capacity of equipment's used for generation
30. In case of loan license copy of agreement between the loan licensee or contract giver and the manufacturing facility provider or contract acceptor defining responsibilities of each party, covering the outsourced activities, the products or operations to which they are related.
31. Source of drug substance along with current regulatory approval status with copy of Form CT-19/CT-22, 45A/46A/ drug substance for (as applicable, if obtained)
32. Copy of permission issued by DCG(I) to manufacture new drug formulation in Form CT-23 OR in FORM 46 (as applicable)
33. Master Manufacturing Formula
34. Manufacturing process flow chart
35. Manufacturing Procedure/draft Batch Manufacturing Record (BMR)
36. Certificate of Analysis of the drug substance
37. Detailed information on Procurement and Characterization of Master Cell Bank
38. Detailed information (SOPs and reports) w.r.t on preparation, qualification and usage of Working Cell Bank
39. Method of Analysis for Drug Substance and Finished product
40. Analytical method validation report for methods used for analysis of Drug Substance.
41. Analytical method validation report for methods used for analysis of Finished product
42. Certificate of Analysis of three consecutive batches by manufacturer and Certificate of Analysis of at least three batches tested by CDL, Kasauli
43. Process validation report for applied product.
44. Stability study report as per requirements mentioning batch size and Container Closure system (should be presented in tabular form with details of Batch No, Batch size, Container Size, Fill volume, Date of Manufacturing, Date of initiation and Container Closure system details etc.).
45. Permissions taken for manufacturing of Process validation and Stability study batches, If any
46. i.e. Copy of permission issued by DCG(I) to manufacture new drug or investigational new drug for examination, test and analysis Form CT-11 OR valid Test license in in Form 29 (as applicable).

47. Form 10 Issued by CDSCO wherever required, if applicable.
48. Specimen Package Insert & Labels of Products licensed /applied.
49. Undertaking in Form 51 that the applied drug brand doesn't bear name of similar brand names of any drug in the country.
50. Details of inspections performed at site by regulatory authorities after grant/retention of license.
51. For licensed product :- Recall statement for last five years, if any?.
52. For licensed product :- List of major changes done after last inspection if any?.
53. For licensed product :- List of major complaints received after last inspection, if any?.
54. For licensed product :- List of NSQ reported by government analyst in last five years, if any?.
55. For licensed product :- Details of actions taken by regulatory authorities (suspension/cancellation of product permissions, Recall imposed by regulatory authorities) in last five years, if any?.
56. Post Approval changes if any

Annexure: G

Checklist for the documents required for Grant/Retention of License for Vaccines

Sr. No.	Particulars of Documents	Status (Yes/No)	Remark
Part A – Firm/facility related documents			
1.	Covering letter address to appropriate authority		
2.	Application in prescribed legal Form (i.e. Form 27-D- in case of grant of license/Form 27-DA- in case of grant of loan license)		
3.	Copy of Challan/ Proof of submission of application fees Paid.		
4.	Copy of Site Master file (as specified under current effective WHO TRS)		
5.	Copy of Manufacturing License available with the Firm (In case of Retention)		
6.	Specific Power of Attorney in Favour of Authorized Signatory for Submitting Application On Behalf Of The Company.		
7.	Constitution details of the firm with supporting documents		
8.	List of Directors, Partners, Trustees, along with AOA and MOA submitted to ROC, LLP, Registered Partnership deed, Trust deed, etc. (As applicable)		
9.	Self-attested copies of documents pertaining to the possession, ownership or tenancy of the premises such as, Register ownership /rent /lease/allotment letter /Possession Letter, Tax Receipt, (Documents should be Registered with appropriate Authority)		
10.	Consent from the State Pollution Control Board to establish & consent to operate the manufacturing site.		
11.	NOC issued by Department of Industrial Safety & Health.		
12.	Permissions from CPCSEA for operation of animal house used for testing , If any		
13.	Plan layout of the premises Approved by the Licensing		

Sr. No.	Particulars of Documents	Status (Yes/No)	Remark
	Authority. Plan layout of premises shall consists : i) General Layout ii) Material & Personal movement layout iii) HVAC Area classification and Pressure differential layout for for critical Mfg. & QC areas - Floor wise/ Block wise iv) Location of Equipment's in Mfg. & Location of Instruments in QC areas- Floor wise/ Block wise v) Pass Box positioning in critical area.		
14.	Section wise List of machinery and equipment to be employed for manufacture and testing		
15.	List of Competent Technical Staff appointed for manufacturing with their qualification, Registration, Experience, previous FDA Approvals, Etc.		
16.	Appointment/Acceptance Letter of Competent Technical staff of manufacturing Section.		
17.	List of Competent Technical Staff appointed for testing with their qualification, Registration, Experience, previous FDA Approvals, Etc.		
18.	Appointment/Acceptance Letter of Competent Technical staff of Testing Section.		
19.	Details of water used to including quality of water at site, Details of Water generation Systems (Purified Water & WFI) used for water generation at the site. Schematic diagram of Water system. Water Generation and circulation system Installation and validation Reports/ Certificate		
20.	Details of HVAC system used for maintaining Classified Area (including schematic diagram of classified area and HVAC system). AHU Installation and Validation Reports/Certificate		
21.	List of SOPs and STPs		
22.	Washing arrangements for the components and equipment's used for manufacturing.		
23.	List of utilities used at side with Equipment I D and Capacity of equipment's used for generation		

Sr. No.	Particulars of Documents	Status (Yes/No)	Remark
24.	In case of loan license copy of agreement between the loan licensee or contract giver and the manufacturing facility provider or contract acceptor defining responsibilities of each party, covering the outsourced activities, the products or operations to which they are related.		

Sr. No.	Particulars of Documents	Status (Yes/No)	Remark
Part B - Product specific documents/Details			
25.	Source of drug substance along with current regulatory approval status with copy of Form CT-19/CT-22, 45A/46A/ drug substance for (as applicable, if obtained)		
26.	Copy of permission issued by DCG(I) to manufacture new drug formulation in Form CT-23 OR in FORM 46 (as applicable)		
27.	Master Manufacturing Formula		
28.	Manufacturing process flow chart		
29.	Manufacturing Procedure/draft Batch Manufacturing Record (BMR)		
30.	Certificate of Analysis of the drug substance		
31.	Detailed information on Procurement and Characterization of Master Cell Bank		
32.	Detailed information (SOPs and reports) w.r.t on		

Sr. No.	Particulars of Documents	Status (Yes/No)	Remark
	preparation, qualification and usage of Working Cell Bank		
33.	Method of Analysis for Drug Substance and Finished product		
34.	Analytical method validation report for methods used for analysis of Drug Substance.		
35.	Analytical method validation report for methods used for analysis of Finished product		
36.	Certificate of Analysis of three consecutive batches by manufacturer and Certificate of Analysis of at least three batches tested by CDL, Kasuli		
37.	Process validation report for applied product.		
38.	Stability study report as per requirements mentioning batch size and Container Closure system (should be presented in tabular form with details of Batch No, Batch size, Container Size, Fill volume, Date of Manufacturing, Date of initiation and Container Closure system details etc.).		
39.	Permissions taken for manufacturing of Process validation and Stability study batches, If any i.e. Copy of permission issued by DCG(I) to manufacture new drug or investigational new drug for examination, test and analysis Form CT-11 OR valid Test license in in		

Sr. No.	Particulars of Documents	Status (Yes/No)	Remark
	Form 29 (as applicable).		
40.	Form 10 Issued by CDSCO wherever required, if applicable.		
41.	Specimen Package Insert & Labels of Products licensed /applied.		
42.	Undertaking in Form 51 that the applied drug brand doesn't bear name of similar brand names of any drug in the country.		
43.	Details of inspections performed at site by regulatory authorities after grant/retention of license.		
44.	For licensed product :- Recall statement for last five years, if any?.		
45.	For licensed product :- List of major changes done after last inspection if any?.		
46.	For licensed product :- List of major complaints received after last inspection, if any?.		
47.	For licensed product :- List of NSQ reported by government analyst in last five years, if any?.		
48.	For licensed product :- Details of actions taken by regulatory authorities (suspension/cancellation of product permissions, Recall imposed by regulatory authorities) in last five years, if any?.		
49.	Post Approval Change if any		

Annexure-H

Checklist of documents required for the grant of manufacturing license or loan license for Medical Devices and In-vitro diagnostic (IVD) medical device

PART I- Medical Devices

(a) Checklist for the grant of manufacturing license in Form MD-9 for Class C & Class D Medical Devices

Form Type:	**Fresh (Form MD-7)**	Status (Yes/No)	Remark
Section no.	Checklist Name		
1.0	Covering Letter		
2.0	Application (Form MD-7)		
3.0	Fee Challan		
4.0	Details of the constitution of the firm along with the relevant documents		
5.0	The Establishment /Site ownership /Tenancy Agreement		
6.0	**Plant Master file as per Appedix I of Fourth Schedule of MDR, 2017**		
6.1	General Information of the facility		
6.2	Personnel- Organisation chart		
6.3	Personnel -Qualification, Experience and responsibilities		
6.4	Premises and Facilities		
6.5	Plant Layout of premise with indication of scale		
6.6	List of equipments and instruments used for manufacturing and testing		
6.7	Sanitation		
6.8	Production		
6.9	Quality Assurance		
6.10.	Storage		
6.11	Documentation		
7.0	**Quality Management System Requirements**		

7.1	Undertaking from the manufacturer stating that the manufacturing site is in compliance with the provisions of the Fifth Schedule of MDR, 2017		
7.2	Quality Manual		
7.3	Control of Documents		
7.4	Control of Records		
7.5	Management Responsibility		
7.6	Resource management		
7.7	Control of production and service provision		
7.8	Internal Audit System		
7.9	Control of nonconfomting product		
7.10	Corrective Action and Preventive Action		
7.11	Table the areas showing the environmental requirement for Medical Devices as per Annexure A of Fifth Schedule of MDR, 2017.		
8.0	**Device Master file in the line of Appendix II of Fourth Schedule of MDR, 2017**		
8.1	Executive Summary		
8.2	Descriptive information of the device		
8.3	Justification for the Medical Device Grouping		
8.4	Product Specification, including variants and accessories		
8.5	Substantial equivalence with reference to the predicate device or previous generations of the device		
8.6	Labelling information (Labels, Instruction for Use, etc)		
8.7	Device Design and Manufacturing Information		
8.8	Essential Principles checklist for demonstrating conformity to the Safety and Performance of the Medical Device		
8.9	Risk analysis and control summary		
8.1	Verification and validation of the medical device		
8.11	Biocompatibility validation data (if applicable)		

8.12	Medicinal substances data (if device contains Drug)		
8.13	Biological Safety (if applicable)		
8.14	Sterilization Validation data (if applicable)		
8.15	Software verification and validation (if software used)		
8.16	Animal studies – Preclinical data (if any)		
8.17	Stability study data (Real-time and Accelerated conditions)		
8.18	Clinical evidence (if any)		
8.19	Post Marketing Surveillance data (Vigilance reporting)		
8.20	Batch Release Certificates or Certificate of Analysis for minimum 3 consecutive batches/ Software version release certificate		
9.0	Any other additional documents		
10.0	Test License obtained in Form MD-13 (if any)		
11.0	Copy of Permission in Form MD-27 (incase of Medical device which does not have Predicate medical device)		

(b) Checklist for the grant of manufacturing license in Form MD-9 for additional Class C & Class D Medical Devices

Form Type	**Endorsement (Form MD-7)**	Status (Yes/No)	Remark
Section no.	**Checklist Name**		
1.0	Covering Letter		
2.0	Application (Form MD-7)		
3.0	Fee Challan		
4	Copy of manufacturing license obtained under MDR-2017		
5.0	**Plant Master file as per Appendix I of Fourth Schedule of Medical Devices Rules, 2017**		
5.1	Undertaking from the manufacturer stating that there is no major change in the Plant master file		
6.0	**Quality Management System Requirements**		
6.1	Undertaking from the manufacturer stating that the manufacturing site is in compliance with the provisions of the Fifth Schedule of Medical Devices Rules, 2017 for manufacturing of applied product		
6.2	Table the areas showing the environmental requirement for applied product as per Annexure A of Fifth Schedule of Medical Devices Rules, 2017.		
7.0	**Device Master file in the line of Appendix II of Forth Schedule of Medical Devices Rules, 2017**		
7.1	Executive Summary		
7.2	Descriptive information of the device		
7.3	Justification for the Medical Device Grouping		
7.4	Product Specification, including variants and accessories		
7.5	Substantial equivalence with reference to the predicate device or previous generations of the device		

7.6	Labelling information (Labels, Instruction for Use, etc)		
7.7	Device Design and Manufacturing Information		
7.8	Essential Principles checklist for demonstrating conformity to the Safety and Performance of the Medical Device		
7.9	Risk analysis and control summary		
7.10	Verification and validation of the medical device		
7.11	Biocompatibility validation data (if applicable)		
7.12	Medicinal substances data (if device contains Drug)		
7.13	Biological Safety (if applicable)		
7.14	Sterilization Validation data (if applicable)		
7.15	Software verification and validation (if software used)		
7.16	Animal studies – Preclinical data (if any)		
7.17	Stability study data (Real-time and Accelerated conditions)		
7.18	Clinical evidence (if any)		
7.19	Post Marketing Surveillance data (Vigilance reporting)		
7.20	Batch Release Certificates or Certificate of Analysis for minimum 3 consecutive batches/ Software version release certificate		
8.0	Any other additional documents		
9.0	Test License obtained in Form MD-13 (if any)		
10	Copy of Permission in Form MD-27 (incase of Medical device which does not have Predicate medical device)		

(c) Checklist for the retention of manufacturing license granted in Form MD-9 for Class C & Class D Medical Devices

Form Type:	**Form MD-9 - Retention**	Status (Yes/No)	Remark
Section no.	**Checklist Name**		
1.0	Covering letter		
2.0	Duly Signed Retention Form		
3.0	Fee Challan		
4.0	Copy of the existing manufacturing licence or its retention (if obtained)		
5.0	Copy of endorsement(s) to the existing manufacturing license		
6.0	List of the device(s) deleted from the existing manufacturing license along with the reason		
7.0	Detailed breakup of the fees deposited in terms of site, risk class of the device and Medical device grouping etc.		
8.0	Undertaking from manufacturer stating that there is no change in the Constitution of the Firm.		
9.0	An undertaking from the manufacturer stating that there is no major change(s) in the existing Device Master File (DMF) and Plant Master File (PMF)		
10.0	Qualification, experience and responsibilities of current competent Technical staff.		
11.0	Post marketing surveillance data (Vigilance reporting) during last 5 yrs (details of complaints, recall (if any), CAPA taken, etc), duly authenticated by the manufacturer.		
12.0	Any other additional documents.		
13.0	Copy of the manufacturing license obtained under MDR-2017 or its retention (if obtained)		
14.0	Post Approval Changes taken due to change in name and/or address of the firm, product details (if any)		

(d) Checklist for the grant of loan license for manufacturing in Form MD-10 for Class C & Class D Medical Devices

Form Type:	**Fresh (Form MD-8)**	Status (Yes/No)	Remark
Section no.	Checklist Name		
1.0	Covering Letter		
2.0	Application (Form MD-8)		
3.0	Fee Challan		
4.0	Details of the constitution of the firm along with the relevant documents		
5.0	The Establishment /Site ownership /Tenacy Agreement		
6.0	Agreement between the applicant and the manufacturer whose manufacturing site is to be utilized for the manufacturing of applied device(s)		
7.0	Copy of manufacturing license of the manufacturer showing that the their facility is licensed for manufacturing of the same device (s)		
8.0	**Plant Master File requirements:**		
8.1	Undertaking from the manufacturer (parent firm) stating that there is no major changes in the Plant Master File		
9.0	**Quality Management System Requirements:**		
9.1	Undertaking signed by the manufacturer stating that the manufacturing site is in compliance with the provisions of the Fifth Schedule of MDR, 2017 for manufacturing of applied devices		
10.0	**Information on the Device Master File from the Manufacturer:**		
10.1	Undertaking from the manufacturer (parent firm) stating that the Device Master File of the approved product applies for the proposed product		
10.2	Executive Summary of the applied devices		

10.3	Descriptive information of the applied device		
10.4	Justification for the Medical Device Grouping		
10.5	Product Specification, including variants and accessories of the applied devices		
10.6	Labelling Details (Labels and Instruction for Use)		
10.7	Essential Principles checklist for demonstrating conformity to the Safety and Performance of the Medical Device		
10.8	Risk analysis and control summary		
10.9	Biocompatibility validation data (if applicable)		
10.10	Sterilization Validation data (if applicable)		
10.11	Stability study data (Real-time and Accelerated conditions)		
10.12	Post Marketing Surveillance data (Vigilance reporting)		
10.13	Batch Release Certificates or Certificate of Analysis for minimum 3 consecutive batches/ Software version release certificate of the approved product		
11.00	Any other additional documents		

(e) Checklist for the grant of loan license for manufacturing in Form MD-10 for additional Class C & Class D Medical Devices

Form Type:	**Endorsement to Loan license (Form MD-8)**	Status (Yes/No)	Remark
Section no.	Checklist Name		
1.0	Covering Letter		
2.0	Application (Form MD-8)		
3.0	Fee Challan		
4.0	Agreement between the applicant and the manufacturer whose manufacturing site is to be utilized for the manufacturing of applied device(s)		
5.0	Copy of manufacturing license of the manufacturer showing that the their facility is licensed for manufacturing of the same device (s)		
6.0	**Plant Master File requirements:**		
6.1	Undertaking from the manufacturer (parent firm) stating that there is no major changes in the Plant Master File		
7.0	**Quality Management System Requirements:**		
7.1	Undertaking signed by the manufacturer stating that the manufacturing site is in compliance with the provisions of the Fifth Schedule of MDR, 2017 for manufacturing of applied devices		
7.2	**Information on the Device Master File from the Manufacturer:**		
7.3	Undertaking from the manufacturer (parent firm) stating that the Device Master File of the approved product applies for the proposed product		
7.4	Executive Summary of the applied devices		
7.5	Descriptive information of the applied device		

7.6	Justification for the Medical Device Grouping		
7.7	Product Specification, including variants and accessories of the applied devices		
7.8	Labelling Details (Labels and Instruction for Use)		
7.9	Essential Principles checklist for demonstrating conformity to the Safety and Performance of the Medical Device		
7.10	Risk analysis and control summary		
7.11	Biocompatibility validation data (if applicable)		
7.12	Sterilization Validation data (if applicable)		
7.13	Stability study data (Real-time and Accelerated conditions)		
7.14	Post Marketing Surveillance data (Vigilance reporting)		
7.15	Batch Release Certificates or Certificate of Analysis for minimum 3 consecutive batches/ Software version release certificate of the approved product		
8.0	Any other additional documents		

(f) Checklist for the retention of loan license granted for manufacturing in Form MD-10 for Class C & Class D Medical Devices

Form Type:	**Checklist for Form MD-10 - Retention**	Status (Yes/No)	Remark
Sr no	**Title**		
1.0	Covering letter		
2.0	Duly Signed Retention Form		
3.0	Fee Challan		
4.0	Copy of the existing manufacturing licence or its retention (if obtained) of the loan licensee		
5.0	Copy of endorsement(s) to the existing manufacturing license		
6.0	Copy of the existing manufacturing licence or its retention (if obtained) of the parent firm		
7.0	List of the device(s) deleted from the existing manufacturing license along with the reason		
8.0	Detailed breakup of the fees deposited in terms of site, risk class of the device and Medical device grouping etc.		
9.0	Undertaking from manufacturer (loan licensee) stating that there is no change in the Constitution of the Firm.		
10.0	An undertaking from the manufacturer (parent firm) stating that there is no major change(s) in the existing Device Master File (DMF) and Plant Master File (PMF)		
11.0	Qualification, experience and responsibilities of current competent Technical staff.		
12.0	Post marketing surveillance data (Vigilance reporting) during last 5 yrs (details of complaints, recall (if any), CAPA taken, etc), duly authenticated by the manufacturer.		
13.0	Any other additional documents.		
15.0	Post Approval Changes taken due to change in name and/or address of the firm, product details (if any)		

PART II- In-vitro diagnostic Medical Devices

(a) Checklist for the grant of manufacturing license in Form MD-9 for Class C & Class D In-vitro diagnostic Medical Devices

Form Type:	**Fresh (Form MD-7)**	Status (Yes/No)	Remark
Section no.	Checklist Name		
1.0	Covering Letter		
2.0	Constitution Details of manufacturer,		
2.1	Part 1,		
2.2	Part 2,		
3.0	Site or plant master file as specified in Appendix I of Fourth Schedule of MDR 2017.		
3.1	Part – 1 Plant Layout of premise with indication of scale		
3.2	Part – 2 Organisation chart showing the arrangements for key personnel		
3.3	Part – 3 Qualification, Experience and responsibilities of key Technical Persons		
3.4	Part – 4 List of Equipment and Instruments		
3.5	Part – 5 Contract Activities if any		
4.0	**Quality Management System**		
4.1	Part – 1 Quality Management System as per Fifth Schedule of Medical devices Rules, 2017		
4.2	Part – 2 Quality Manual		
4.3	Part – 3 Quality Policy		
4.4	Part – 4 Control of Documents		
4.5	Part – 5 Control of Records		
4.6	Part – 6 Management Responsibility		
4.7	Part – 7 Internal Audit System		
4.8	Part – 8 Preventive and Corrective Action		
4.9	Part – 9 Procedure for identifying training needs and ensure that all persons are trained to adequately		

Form Type:	Fresh (Form MD-7)	Status (Yes/No)	Remark
	perform their assigned responsibilities.		
4.10	Part – 10 Table the areas showing the environmental requirement for Medical Devices as per Annexure A of Fifth Schedule of Medical devices Rules, 2017.		
5.0	Undertaking signed by the manufacturer stating that the manufacturing site is in compliance with the provisions of the Fifth Schedule of MDR 2017		
6.0	**Regulatory certificates**		
6.1	copy of latest inspection or audit report carried out by Notified bodies or National Regulatory Authority or Competent Authority within last 3 years (if any)		
6.2	Copy of NOC from Department of Animal Husbandry, Ministry of Agriculture, In Case of Veterinary IVD Kits (if available)		
6.3	Copy of NOC from Bhabha Atomic Research Centre (BARC), Mumbai, In case Radio Immuno Assay Kits (if available)		
6.4	Valid copy of Quality Management System certificate (ISO:13485) certificate issued by the competent authority (if any)		
6.5	Copy of Test licence obtained for testing and generation of quality control data, if any		
6.6	Self-attested copy of valid Whole sale licence or manufacturing licence if any		
7.0	**Device Master File for In Vitro Diagnostic Medical Devices as per Appendix – III of Part III of Fourth Schedule of Medical devices Rules, 2017**		
7.1	Part – 1 Executive Summary		
7.2	Part-2 Regulatory status of the similar device in India (approved or new in vitro diagnostic medical device).		
7.3	Part-3 Description and specification, including variants and accessories of the in vitro diagnostic medical device		

Form Type:	Fresh (Form MD-7)	Status (Yes/No)	Remark
7.4	Part – 4 Essential principles checklist for demonstrating conformity to the essential principles of safety and performance of the in vitro medical device		
7.5	Part – 5 Risk analysis and control summary		
7.6	Part – 6 Device Design and Manufacturing Information		
7.7	Part-7 Product validation and verification		
7.8	Part-8 Analytical studies, Specimen type, Analytical performance characteristics, Analytical sensitivity, Analytical Specificity, Metrological traceability of calibrator and control material values, Measuring range of assay, Definition of assay		
7.9	Part – 9 Claimed Shelf life - stability study report for at least 3 lots including the protocol, acceptance criteria, testing intervals and conclusion.		
7.10	Part-10 In use stability study report for 1 lot including the protocol, acceptance criteria, testing intervals and conclusion for		
7.11	Part-11 Shipping stability study report for 1 lot including the protocol, acceptance criteria, testing intervals and conclusion for Part-11 Shipping stability study report for 1 lot including the protocol, acceptance criteria, testing intervals and conclusion for		
7.12	Part-12 Clinical Evidence		
7.13	Part-13 Product Insert, Pack size, Label		
7.14	Part-14 Specimen batch test report for at least consecutive 3 batches showing specification of each testing parameter		
7.15	Part-15 Specific evaluation report, if done by any laboratory in India, showing the sensitivity and specificity of the in vitro diagnostic medical device		
7.16	Part-16 Copy of performance evaluation report issued by the central medical device testing laboratory or medical device testing laboratory		

Form Type:	**Fresh (Form MD-7)**	Status (Yes/No)	Remark
	registered under sub-rule (3) of rule 83 of MDR 2017 for three batches		
7.17	Part-17 Post Market Surveillance Data		
7.18	Part-18-Others		
8.0	Fee Challan		
9.0	Legal Form		

(b) Checklist for the grant of manufacturing license in Form MD-9 for additional Class C & Class D In-vitro diagnostic Medical Devices

Form Type:	**Endorsement (Form MD-7)**	Status (Yes/No)	Remark
Section no.	Checklist Name		
1.0	Covering Letter		
2.0	Constitution Details of Manufacturer,		
2.1	Part 1,		
2.2	Part 2,		
3.0	**Site or plant master file as specified in Appendix I of Fourth Schedule of MDR 2017.**		
3.1	Part – 1 Plant Layout of premise with indication of scale		
3.2	Part – 2 Organisation chart showing the arrangements for key personnel		
3.3	Part – 3 Qualification, Experience and responsibilities of key Technical Persons		
3.4	Part – 4 List of Equipment and Instruments		
3.5	Part – 5 Contract Activities if any		
4.0	**Quality Management System**		
4.1	Part – 1 Quality Management System as per Fifth Schedule of Medical devices Rules, 2017		
4.2	Part – 2 Quality Manual		
4.3	Part – 3 Quality Policy		
4.4	Part – 4 Control of Documents		
4.5	Part – 5 Control of Records		
4.6	Part – 6 Management Responsibility		
4.7	Part – 7 Internal Audit System		
4.8	Part – 8 Preventive and Corrective Action		
4.9	Part – 9 Procedure for identifying training needs and ensure that all persons are trained to adequately perform their assigned responsibilities.		
4.10	Part – 10 Table the areas showing the environmental requirement for Medical Devices as per Annexure A of Fifth Schedule of Medical devices Rules, 2017.		
5.0	Undertaking signed by the manufacturer stating that the manufacturing site is in compliance with the provisions of the Fifth Schedule of MDR 2017		

6.0	**Regulatory certificates**		
6.1	Copy of latest inspection or audit report carried out by Notified bodies or National Regulatory Authority or Competent Authority within last 3 years .(if any)		
6.2	copy of NOC from Department of Animal Husbandry, Ministry of Agriculture, In Case of Veterinary IVD Kits (if available)		
6.3	copy of NOC from Bhabha Atomic Research Centre (BARC), Mumbai, In case Radio Immuno Assay Kits (if available)		
6.4	valid copy of Quality Management System certificate (ISO:13485) certificate issued by the competent authority .(if any)		
6.5	Copy of Test licence obtained for testing and generation of quality control data, if any		
6.6	Self-attested copy of valid Whole sale licence or manufacturing licence if any		
7.0	**Device Master File for In Vitro Diagnostic Medical Devices as per Appendix – III of Part III of Fourth Schedule of Medical devices Rules, 2017**		
7.1	Part – 1 Executive Summary		
7.2	Part-2 Regulatory status of the similar device in India (approved or new in vitro diagnostic medical device).		
7.3	Part-3 Description and specification, including variants and accessories of the in vitro diagnostic medical device		
7.4	Part – 4 Essential principles checklist for demonstrating conformity to the essential principles of safety and performance of the in vitro medical device		
7.5	Part – 5 Risk analysis and control summary		
7.6	Part – 6 Device Design and Manufacturing Information		
7.7	Part-7 Product validation and verification		
7.8	Part-8 Analytical studies, Specimen type, Analytical performance characteristics, Analytical		

	sensitivity, Analytical Specificity, Metrological traceability of calibrator and control material values, Measuring range of assay, Definition of assay		
7.9	Part – 9 Claimed Shelf life - stability study report for at least 3 lots including the protocol, acceptance criteria, testing intervals and conclusion.		
7.10	Part-10 In use stability study report for 1 lot including the protocol, acceptance criteria, testing intervals and conclusion		
7.11	Part-11 Shipping stability study report for 1 lot including the protocol, acceptance criteria, testing intervals and conclusion for Part-11 Shipping stability study report for 1 lot including the protocol, acceptance criteria, testing intervals and conclusion		
7.12	Part-12 Clinical Evidence		
7.13	Part-13 Product Insert, Pack size, Label		
7.14	Part-14 Specimen batch test report for atleast consecutive 3 batches showing specification of each testing parameter		
7.15	Part-15 Specific evaluation report, if done by any laboratory in India, showing the sensitivity and specificity of the in vitro diagnostic medical device		
7.16	Part-16 Copy of performance evaluation report issued by the central medical device testing laboratory or medical device testing laboratory registered under sub-rule (3) of rule 83 of MDR 2017 for three batches		
7.17	Part-17 Post Market Surveillance Data		
7.18	Part-18-Others		
8.0	Fee Challan		
9.0	Legal Form		

(c) Checklist for the retention of manufacturing license granted in Form MD-9 for Class C & Class D In-vitro diagnostic Medical Devices

Form Type:	**Retention of Form MD-9**	Status (Yes/No)	Remark
Section no.	Checklist Name		
1.0	Covering letter with purpose of application		
2.0	Undertaking duly signed and stamped with designation from manufacturer that there is no change in the Constitution of the Firm.		
3.0	Duly signed Undertaking and stamped with designation from manufacturer stating that there is no change in Plant Master File & Device Master File.		
4.0	Qualification, experience and responsibilities of current competent technical staff.		
5.0	Post Marketing Surveillance data (Details of Sales, complaints, Recall, CAPA if any).		
6.0	Any other additional documents.		
7.0	Copy of existing manufacturing license (MD-5/MD-6/MD-9/MD-10) for which retention is applied.		
8.0	Post Approval Change Applications (If Any)		
9.0	Retention Fee Challan along with late fees (if any).		
10.0	Duly Signed Retention Form		

(d) Checklist for the grant of loan license for manufacturing in Form MD-10 for Class C & Class D In-vitro diagnostic Medical Devices

Form Type:	Fresh (Form MD-8)	Status (Yes/No)	Remark
Section no.	Checklist Name		
1.0	Covering Letter		
1.1	Constitution of the Firm		
1.2	The Establishment /Site ownership / Tenancy Agreement		
2.0	Copy of Duly notarized valid copies of Quality Certificate in respect manufacturing site(s), if any		
2.1	Copy of Certificate supporting quality management system (ISO: 13485), if any		
3.0	Plant Master file from the Manufacturer as specified in Appedix 1 of Forth Schedule of Medical Devices Rules		
3.1	Part – 1 Plant Layout of premise with indication of scale		
3.2	Part – 2 Organisation chart showing the arrangements for key personnel		
3.3	Part – 3 Qualification, Experience and responsibilities of key Technical Persons		
3.4	Part – 4 List of Equipment and Instruments		
3.5	Part – 5 Contract Activities if any		
4.0	Quality Management System		
4.1	Part – 1 Quality Management System as per Fifth Schedule of Medical devices Rules, 2017		
4.2	Part – 2 Quality Manual		
4.3	Part – 3 Quality Policy		
4.4	Part – 4 Control of Documents		
4.5	Part – 5 Control of Records		
4.6	Part – 6 Management Responsibility		

4.7	Part – 7 Internal Audit System		
4.8	Part – 8 Preventive and Corrective Action		
4.9	Part – 9 Procedure for identifying training needs and ensure that all persons are trained to adequately perform their assigned responsibilities.		
4.10	Part – 10 Table the areas showing the environmental requirement for Medical Devices as per Annexure A of Fifth Schedule of Medical devices Rules, 2017.		
5.0	Device Master file from the Manufacturer as specified in Appendix II (only for Medical Devices) of Forth Schedule of Medical Device Rules. Note: In case of Class A devices, Appendix II is not required.		
5.1	Part 1		
5.2	Part 2. Reference to predicate or previous generations of the device		
5.3	Part – 3 Label, Product Insert and Pack Size		
5.4	Part – 4 Device Design and Manufacturing process with flow chart		
5.5	Part – 5 Essential principles checklist for demonstrating conformity to the essential principles of safety and performance of the in vitro medical device		
5.6	Part – 6 Risk analysis and control summary		
5.7	Part – 7 Analytical validation data for Accuracy, Reproducibility, sensitivity and specificity		
5.8	Part – 8 Stability (Claimed shelf life, In use Stability and Shipping Stability study report)		
5.9	Part – 9 Clinical Evidence data		
5.10	Part – 10 Post marketing surveillance data		
5.11	Part – 11 Copy of three batches performance evaluation report issued by the central medical device testing		
5.12	Part – 12 Specific evaluation report, if done by any laboratory in India, showing the sensitivity and specificity of the in vitro diagnostic medical device (if available)		

5.13	Part – 13 Copy of NOC from Department of Animal Husbandry, Ministry of Agriculture, In Case of Veterinary IVD Kits (if applicable)		
5.14	Part – 14 Copy of NOC from Bhabha Atomic Research Centre (BARC), Mumbai, In case Radio Immuno Assay Kits (if applicable)		
6.0	Performance Evaluation Report of IVDs only		
7.0	Test License obtained for testing and generation of quality control data		
8.0	Undertaking signed stating that the manufacturing site is in compliance with provision of Fifth schedule		
9.0	Fee Challan		
10.0	Legal Form		

(e) Checklist for the grant of loan license for manufacturing in Form MD-10 for additional Class C & Class D In-vitro diagnostic Medical Devices

Form Type:	**Endorsement (Form MD-8)**	**Status (Yes/No)**	**Remark**
Section no.	Checklist Name		
1.0	Covering Letter		
1.1	Constitution of the Firm		
1.2	The Establishment /Site ownership /Tenacy Agreement		
2.0	Copy of Duly notarized valid copies of Quality Certificate in respect manufacturing site(s), if any		
2.1	Copy of Certificate supporting quality management system (ISO: 13485), if any		
3.0	Plant Master file from the Manufacturer as specified in Appedix 1 of Forth Schedule of Medical Devices Rules		
3.1	Part – 1 Plant Layout of premise with indication of scale		
3.2	Part – 2 Organisation chart showing the arrangements for key personnel		
3.3	Part – 3 Qualification, Experience and responsibilities of key Technical Persons		
3.4	Part – 4 List of Equipment and Instruments		
3.5	Part – 5 Contract Activities if any		
4.0	Quality Management System		
4.1	Part – 1 Quality Management System as per Fifth Schedule of Medical devices Rules, 2017		
4.2	Part – 2 Quality Manual		
4.3	Part – 3 Quality Policy		
4.4	Part – 4 Control of Documents		
4.5	Part – 5 Control of Records		

4.6	Part – 6 Management Responsibility		
4.7	Part – 7 Internal Audit System		
4.8	Part – 8 Preventive and Corrective Action		
4.9	Part – 9 Procedure for identifying training needs and ensure that all persons are trained to adequately perform their assigned responsibilities.		
4.10	Part – 10 Table the areas showing the environmental requirement for Medical Devices as per Annexure A of Fifth Schedule of Medical devices Rules, 2017.		
5.0	Device Master file from the Manufacturer as specified in Appendix II (only for Medical Devices) of Forth Schedule of Medical Device Rules. Note: In case of Class A devices, Appendix II is not required.		
5.1	Part 1		
5.2	Part 2. Reference to predicate or previous generations of the device		
5.3	Part – 3 Label, Product Insert and Pack Size		
5.4	Part – 4 Device Design and Manufacturing process with flow chart		
5.5	Part – 5 Essential principles checklist for demonstrating conformity to the essential principles of safety and performance of the in vitro medical device		
5.6	Part – 6 Risk analysis and control summary		
5.7	Part – 7 Analytical validation data for Accuracy, Reproducibility, sensitivity and specificity		
5.8	Part – 8 Stability (Claimed shelf life, In use Stability and Shipping Stability study report)		
5.9	Part – 9 Clinical Evidence data		
5.10	Part – 10 Post marketing surveillance data		

5.11	Part – 11 Copy of three batches performance evaluation report issued by the central medical device testing		
5.12	Part – 12 Specific evaluation report, if done by any laboratory in India, showing the sensitivity and specificity of the in vitro diagnostic medical device (if available)		
5.13	Part – 13 Copy of NOC from Department of Animal Husbandry, Ministry of Agriculture, In Case of Veterinary IVD Kits (if applicable)		
5.14	Part – 14 Copy of NOC from Bhabha Atomic Research Centre (BARC), Mumbai, In case Radio Immuno Assay Kits (if applicable)		
6.0	Performance Evaluation Report of IVDs only		
7.0	Test License obtained for testing and generation of quality control data		
8.0	Undertaking signed stating that the manufacturing site is in compliance with provision of Fifth schedule		
9.0	Fee Challan		
10.0	Legal Form		

(f) Checklist for the retention of loan license granted for manufacturing in Form MD-10 for Class C & Class D In-vitro diagnostic Medical Devices

Section no.	Checklist Name	Status (Yes/No)	Remark
1.0	Covering letter with purpose of application		
2.0	Undertaking duly signed and stamped with designation from manufacturer that there is no change in the Constitution of the Firm.		
3.0	Duly signed Undertaking and stamped with designation from manufacturer stating that there is no change in Plant Master File & Device Master File.		
4.0	Qualification, experience and responsibilities of current competent Technical staff.		
5.0	Post Marketing Surveillance data (Details of Sales, complaints,Recall, CAPA if any).		
6.0	Any other additional documents.		
7.0	Copy of existing manufacturing license (MD-5/MD-6/MD-9/MD-10) for which retention is applied.		
8.0	Post Approval Change Applications (If Any)		
9.0	Retention Fee Challan along with late fees (if any).		
10.0	Duly Signed Retention Form		

Annexure: I

Documents required for Approval for carrying out tests on drugs / cosmetics and raw materials used in their manufacture on behalf of licensees for manufacture for sale of drugs / cosmetics.

1. Documents
2. Application from Laboratories
3. License Fees (Treasury Receipt)
4. Form 36/ Form COS- 22
5. List of SOPs and STPs
6. List of equipment and Instrument
7. List of technical staff, their qualification, experience and approval status
8. List of media for microbiology
9. List of reference standard
10. CPCSEA approval for animal house, if applicable
11. Laboratory layout
12. HVAC system for microbiological section, if applicable, in the testing Laboratory
13. NOC from Pollution Control Board for handling Bio-medical Laboratory waste
14. Contact details

Annexure J

Checklist for the documents required for Approval for carrying out tests on drugs / cosmetics and raw materials used in their manufacture on behalf of licensees for manufacture for sale of drugs / cosmetics.

S.No.	Documents	**Status (Yes/No)**	**Remark**
1	Application from Laboratories		
2	License Fees (Treasury Receipt)		
3	Form 36/ Form COS- 22		
4	List of SOPs and STPs		
5	List of equipment and Instrument		
6	List of technical staff, their qualification, experience and approval status		
7	List of media for microbiology		
8	List of reference standard		
9	CPCSEA approval for animal house, if applicable		
10	Laboratory layout		
11	HVAC system for microbiological section, if applicable, in the testing Laboratory		
12	NOC from Pollution Control Board for handling Bio-medical Laboratory waste		
13	Contact details		

Annexure K

Documents required for grant/retention of manufacturing license in Form 28-D/Form 28-DA (LVP/r-DNA/Sera etc):

1. Covering letter
2. Specific Power of Attorney in favour of authorized signatory for submitting application on behalf of the company
3. Site Plan and layout of the building with the name, address, scale, measurements of the area as per Schedule –M Requirement
4. Self-attested copies of documents pertaining to the possession of premises such as, Register ownership /rent /lease/allotment letter /Possession Letter, Tax Receipt, (Documents should be Registered with appropriate Authority)
5. Consent to establish from State pollution control Board.
6. List of Directors, Partners, Trustees, along with ROC Copy Registered Partnership deed, Trust deed
7. List of Competent Technical Staff with their qualification, Registration, Experience, previous FDA Approvals, Etc.
8. Appointment/Acceptance Letter of Competent Technical staff of manufacturing Section.
9. Appointment/Acceptance Letter of Competent Technical staff of Testing Section.
10. Section wise List of plant and Machineries
11. NOC of department of industrial safety & Health
12. HVAC installation and validation Certificate
13. Water System installation and validation Certificate
14. Site Master File (as specified in current WHO TRS)
15. Constitution details of firms
16. List of SOPs/STPs
17. Self-declaration of technical person
18. Self-declaration of Directors
19. **Part B - Product specific details**
20. Copy of valid Test license in Form 29/CT-11

21. Source of drug substance along with current regulatory status with copy of Form 46A/45A/CT-19/CT-22. (if obtained)
22. Certificate of Analysis of the drug substance
23. Master Manufacturing Formula
24. Manufacturing Procedure/draft BMR
25. Product Development report with Excipient compatibility and forced degradation study (if applicable)
26. Process validation report of three batches
27. Finished product specification including impurity profile
28. Finished Product Method of Analysis
29. Finished product Analytical method validation report
30. Finished Product Certificate of Analysis for three consecutive batches/three validation batches
31. Stability study report as per requirements mentioning batch size. (should be presented in tabular form with details of Batch No, Batch size, Date of Manufacturing, Date of initiation, Packaging details)
32. Comparative Dissolution Release Profile with the Approved formulation (in case of oral dosage form)
33. Comparative evaluation of pharmaceutical equivalence with international brand(s) or approved Indian brands, if applicable
34. Draft specimen of the label and carton & package insert
35. Bio Equivalence protocol and report, if applicable
36. Justification on Bio equivalence study waiver, if requested
37. Details of the approval of the New Drug in the country. In case of new drugs, copy of approval of new drug from CLAs in favour of the applicant in Form 46/CT-23 (if available).
38. Form 10 Issued by CDSCO wherever required, if applicable
39. Form 51 Undertaking
40. Challan of Fees Paid To Be Upload
41. Any Other Document
42. Application in prescribed legal form (e.g. Form 27-D/Form 27-DA)

Note:

1. For obtaining permission for additional items on approved category, the applicant will be required to submit details as mentioned at serial no. 19 to 41 only.

2. If applicant is submitting, not applicable (NA) against any above-mentioned documents, the same needs to be justified adequately.

Annexure: L

Checklist for screening the document's required for grant/retention of manufacturing license in Form 28-D/Form 28-DA (LVP/r-DNA/Sera etc)

S.No.	Documents	Status	Remark
	Part A – Firm/facility related details		
01	Covering letter		
02	Specific Power of Attorney in favour of authorized signatory for submitting application on behalf of the company		
03	Site Plan and layout of the building with the name, address, scale, measurements of the area as per Schedule –M Requirement		
04	Self-attested copies of documents pertaining to the possession of premises such as, Register ownership /rent /lease/allotment letter /Possession Letter, Tax Receipt, (Documents should be Registered with appropriate Authority)		
05	Consent to establish from State pollution control Board.		
06	List of Directors, Partners, Trustees, along with ROC Copy Registered Partnership deed, Trust deed		
07	List of Competent Technical Staff with their qualification, Registration, Experience, previous FDA Approvals, Etc.		
08	Appointment/Acceptance Letter of Competent Technical staff of manufacturing Section.		
09	Appointment/Acceptance Letter of Competent Technical staff of Testing Section.		
10	Section wise List of plant and Machineries		

11	NOC of department of industrial safety & Health		
12	HVAC installation and validation Certificate		
13	Water System installation and validation Certificate		
14	Site Master File (as specified in current WHO TRS)		
15	Constitution details of firms		
16	List of SOPs/STPs		
17	Self-declaration of technical person		
18	Self-declaration of Directors		
	Part B - Product specific details		
19	Copy of valid Test license in Form 29/CT-11		
20	Source of drug substance along with current regulatory status with copy of Form 46A/45A/CT-19/CT-22. (if obtained)		
21	Certificate of Analysis of the drug substance		
22	Master Manufacturing Formula		
23	Manufacturing Procedure/draft BMR		
24	Product Development report with Excipient compatibility and forced degradation study (if applicable)		
25	Process validation report of three batches		
26	Finished product specification including impurity profile		
27	Finished Product Method of Analysis		
28	Finished product Analytical method validation report		

29	Finished Product Certificate of Analysis for three consecutive batches/three validation batches		
30	Stability study report as per requirements mentioning batch size. (should be presented in tabular form with details of Batch No, Batch size, Date of Manufacturing, Date of initiation, Packaging details)		
31	Comparative Dissolution Release Profile with the Approved formulation (in case of oral dosage form)		
32	Comparative evaluation of pharmaceutical equivalence with international brand(s) or approved Indian brands, if applicable		
33	Draft specimen of the label and carton & package insert		
34	Bio Equivalence protocol and report, if applicable		
35	Justification on Bio equivalence study waiver, if requested		
36	Details of the approval of the New Drug in the country. In case of new drugs, copy of approval of new drug from CLAs in favour of the applicant in Form 46/CT-23 (if available).		
37	Form 10 Issued by CDSCO wherever required, if applicable		
38	Form 51 Undertaking		
39	Challan of Fees Paid To Be Upload		
40	Any Other Document		
41	Application in prescribed legal form (e.g. Form 27-D/Form 27-DA)		

Note:

3. For obtaining permission for additional items on approved category, the applicant will be required to submit details as mentioned at serial no. 19 to 41 only.

4. If applicant is submitting, not applicable (NA) against any above-mentioned documents, the same needs to be justified adequately.

Submitted by:

Name:

Designation:

FOR OFFICE USE ONLY

Opinion: On security of the submitted document vide Letter No. …….

Dated……..the aforesaid document are submitted/ yet to be submitted.

Scrutinized by: Verified By:

Name: Name:

Designation: Designation:

Annexure M

Checklist for inspections of manufacturing units as per Schedule M of Drugs and Cosmetics Rules

GUIDANCE INSPECTION CHECKLIST FOR GRANT OF MANUFACTURING LICENCES
GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS
(MAIN PRINCIPLES AS PER PART I OF SCHEDULE M)

GENERAL INFORMATION	
Name of the manufacturing unit	
Address of the manufacturing unit	
Constitution of the firm	
List of Directors/Partners/Proprietor	
State/ Union Territory	
Categories of drugs permitted to be manufactured (e.g. Solid Oral Dosage Forms (Beta Lactams/Non Beta Lactams) /Liquid Orals/Semi-solids/Sex Hormones/ Cytotoxics etc.	
Date of Inspection	
Name and Designation of the Inspecting team members	
Number of manufacturing blocks	
Number of Technical Personnel in Manufacturing	
Number of Technical Personnel in QA	
Number of Technical Personnel in QC	
Number of Technical Personnel in Microbiology	
Number of Technical Personnel from other Department	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART I OF SHEDULE M (MAIN PRINCIPLES AS PER PART I OF SCHEDULE M)

Sr. No.	Sch. M Ref.	Particulars	Observations
1.0 Pharmaceutical Quality System (PQS)			
1	1.2	Whether the roles and responsibilities of senior management and other authorities are defined, communicated and implemented throughout the organization.	
2	1.4	Whether the Good Manufacturing Practices are applied to the life-cycle stages, from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing, until the product discontinuation.	
3	1.4	Whether all parts of the product quality system are adequately resourced and maintained, including being provided with sufficient competent personnel, suitable premises, equipment and facilities.	
4	1.5	The product quality system appropriate to manufacture of pharmaceutical products shall ensure:-	
	(a)	product realisation is achieved by designing, qualifying, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;	
	(b)	product and process knowledge is managed throughout all lifecycle stages	
	(c)	pharmaceutical products are designed and developed in a way that takes into account, the requirements of GMP and other GXPs such as those of Good Laboratory Practices (GLP) and Good Clinical Practices (GCP);	
	(d)	production and quality control operations shall be clearly specified in a written form and GMP requirements are adopted;	
	(e)	managerial responsibilities are clearly specified in the job descriptions;	
	(f)	arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is the correct material from the approved supply chain;	
	(g)	all necessary controls on starting materials, intermediate products, and bulk products and other in- process controls, calibrations and validations are carried out;	

	(h)	the finished product is correctly processed and checked, according to the defined procedures;	
	(i)	authorised persons have certified that each production batch has been produced and controlled in accordance with the requirements of the licence and other applicable regulations relevant to the production, control and release of pharmaceutical products;	
	(j)	processes are in place to ensure the management of outsourced activities;	
	(k)	satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf-life;	
	(l)	there is a procedure for self-inspection or quality audit that regularly appraises the effectiveness and applicability of the product quality system;	
	(m)	product and processes are monitored and the results taken into account in batch release, in the investigation of deviations and, with a view to taking preventive action to avoid potential deviation so occurring in the future;	
	(n)	Arrangements are in place for the prospective evaluation and approval of planned changes and their approval prior to their implementation, taking into account regulatory notification and approval where required. After implementation of any change, an evaluation is undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;	
	(o)	regular reviews of the quality of pharmaceutical products are conducted with the objective of verifying the consistency of the process and identifying where there is a need for improvement;	
	(p)	a state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;	
	(q)	continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge	
	(r)	there is a system for QRM	
	(s)	Deviations, suspected product defects and other problems are reported, investigated and recorded. An appropriate level of	

		root cause analysis is applied during such investigations. The most likely root causes shall be identified and appropriate corrective and preventive actions shall be identified and taken. The effectiveness of corrective and preventive actions shall be monitored	
5.	1.6.	Whether the periodic management reviews are conducted with the involvement of senior management of the operation of the product quality system to identify opportunities for continual improvement of products, processes and the system itself.	
6.	1.6.	What is the frequency for the periodic management reviews (Unless otherwise justified, such reviews shall be conducted at least annually)	
7.	1.7	Whether the product quality system is well defined and documented.	
8.	1.7	Whether a quality manual or an equivalent documentation is available and it contains a description of the quality management system including management responsibilities.	
2.0 Quality Risk Management (QRM):			
9.	2.1	Whether the firm has well defined Quality Risk Management to assess, control, communication and review the risks to the quality of the medicinal product.	
10.	2.2	Whether the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;	
2.3 Product quality review			
11.	2.3.1	Whether the firm has well defined procedure/SOP for Product quality review	
12.	2.3.1	Whether the firm has conducted Regular, periodic or rolling quality reviews of all pharmaceutical products,	
13.	2.3.1	Check that Product quality reviews are conducted for products for domestic consumption as well as for products for export also.	
14.	2.3.1	Whether such reviews are conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.	
15.	2.3.2.	What is frequency for conducting the Product quality review(Product quality review shall be conducted and documented annually, taking into account previous reviews. Ensure that the Product quality review reports includes the parameters as per Para 2.3.2 of schedule M.)	

16.	2.3.3.	Whether the manufacturer has evaluated the results of the review and an assessment is made as to whether corrective and preventive actions or any revalidation needs to be undertaken.	
17.	2.3.3.	Whether the corrective and preventive actions arising out of PQR are completed in a timely and effective manner and according to the documented procedures.	
18.	2.3.3.	Check whether the firm has procedures for the on-going management and review of the actions arising out of PQR and Check whether effectiveness of these procedures is verified during self-inspection of by the firm.	
19.	2.3.3	Whether technical agreement is in place between the various parties that defines their respective responsibilities in producing the quality review.	
20.	2.3.3	Whether the authorized person responsible for final batch certification ensures that the quality review is performed in a timely manner and is accurate. Verify how it is ensured.	
3.0 Good manufacturing practices (GMP) for pharmaceutical products			
21	3.1(1)	Whether all manufacturing processes are clearly defined, systematically reviewed for associated risks and are capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications.	
22	3.1(2)	Whether qualification of equipment's and process validations are performed for all equipment's and processes as, applicable, and re-qualifications/ process validations are repeated as and when applicable	
23	3.1(3)	Whether the manufacturer has provided necessary resources as per Para 3.1(3) of Schedule M.	
24	3.1(4)	Whether the instructions and procedures are written in clear and unambiguous language.	
25	3.1(6)	Whether the records are made (manually or by recording instruments or by both) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected	
26	3.1(6)	Whether the significant deviations (if any) are fully recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive actions are implemented	
27	3.1(7) & 17.3.10 .15	Whether the records covering manufacture and distribution (to enable the complete history of a batch to be traced/ to facilitate the recall) are retained in a comprehensible and accessible form;	
28	3.1(8)	Whether the storage and distribution of the products is done properly to minimizes risk to the product quality, if any	

29	3.1(9)	Whether manufacturer is having a system to recall batch of product from sale or supply. (if required)	
4.0 Sanitation and hygiene:			
30	4	Specify the sanitation and hygiene process employed by firm in every aspect of the manufacture of drugs. Whether the scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection and any other source of contamination to the product.	
5.0 Qualification and Validation			
31	5.1	Whether the manufacturer has identified the qualification and validation work is required to prove that the critical aspects of their particular operations are controlled.	
32	5.2	Whether the manufacturer has well defined validation master plan and key elements of a qualification and validation programmed are clearly defined and documented in a validation master plan	
33	5.3.	Whether required qualifications and validation(DQ, IQ, OQ & PQ are performed for the premises, supporting utilities, equipment and processes	
34	5.3.	Whether [process validations (PV) / performance qualification (PQ) are performed to ensure that specific process consistently produce a product meeting its predetermined specifications and quality attributes.	
35	5.4.	Whether changes in aspect of operation(including significant changes to the premises, facilities, equipment or processes) which may affect the quality of the product, directly or indirectly, are qualified and validated, as and when required.	
36	5.5	Whether the firm is having on-going Qualification/validation programmed to follow their first implementation/outcome of a periodic review.	
37	5.6.	Whether the commitment to maintain continued validation status is stated in firm's quality manual or validation master plan.	
38	5.7.	Whether the responsibility for performing validation is clearly defined.	
39	5.8.	Whether the Validation studies are conducted in accordance with predefined and approved protocols.	
40	5.9	Whether written reports summarizing the results recorded and the conclusions reached are available	
41	5.10.	Whether the Processes and procedures are established on the basis of the results of the validation performed.	
42	5.11.	Whether the firm has performed validation of analytical test methods, automated systems and cleaning procedures.	
6.0 Complaints and adverse reaction:			

43	6.1	Whether the firm is having SOP for review and investigations product complaints. Whether all the complaints/other information concerning potentially defective products are carefully reviewed according to the written procedures and corrective actions are implemented accordingly?	
44	6.2	Whether the firm has designated person responsible for handling the complaints and deciding the measures to be taken. Whether sufficient supporting staff is available to assist him or her.	
45	6.2	If this person is different from the authorized person (responsible for final batch certification), then how the latter is made aware of any complaint, investigation or recall.	
46	6.3.	Whether the firm has written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.	
47	6.5	Verify that the person responsible for Quality Control (QC) is involved in the review of such investigations.	
48	6.6.	In case, If a product defect is identified or suspected in a batch. Then check if consideration is given to check other batches in order to determine whether they are also affected.	
49	6.7	Whether the firm is taking necessary/appropriate follow-up action (including product recall, if required), after investigation and evaluation of the complaint.	
50	6.8.	Whether all decisions made and measures taken as a result of a complaint are recorded and referenced to the corresponding batch records.	
51	6.9.	Whether complaint records are regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.	
52	6.10.	Whether firm informs the licensing authorities, if they are considering action following the faulty manufacture, product deterioration, a suspect product or any other serious quality problems with a product.	
53	6.11.	Whether the firm have a pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the adverse drug reactions emerging from the use of drugs manufactured or marketed by the firm.	
7.0 Product recalls:			
54	7.2	Whether authorized person responsible for the execution and coordination of recalls. He or she shall have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency	
55	7.3	Whether Recall operations are capable of being initiated at the required level in the distribution chain.	

56	7.4	Whether recalled products are stored in secure segregated area.	
57	7.5.	Whether the firm informs the licensing authorities about any intention to recall the product because it is, or is suspected of being, defective.	
58	7.6	Whether distribution records shall be readily available to the authorized person, and they shall contain sufficient information on wholesalers and directly supplied customers to permit an effective recall.	
59	7.7	Whether progress of the recall process are monitored and recorded. (Records shall include the disposition of the product. A final report shall be issued, including reconciliation between the delivered and recovered quantities of the products.)	
60	7.8	Whether effectiveness of the arrangements for recall shall be tested and evaluated from time to time.	
61	7.9.	Whether prompt and effective product recall system is devised for timely information of all concerned stockists, wholesalers, suppliers, up to the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard	
Change Control			
62	8.1	Whether the firm has well defined and established formal change control system to evaluate all changes that may affect the production and control of the product.	
63	8.2	Whether the written change control procedures covers the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software etc.	
64	8.3	Whether proposals for relevant changes to GMP are drafted, reviewed and approved by the appropriate organizational unit and reviewed and approved by the quality unit.	
65	8.4.	Whether the potential impact of the proposed change on the quality of the intermediate or Active Pharmaceutical Ingredient (API) or finished product is evaluated.	
		Whether classification procedure is available for determining the level of testing, validation and documentation needed to justify changes to a validated process.	
66	8.6	After the change has been implemented , whether firm is having procedure to evaluate the first batch produced or tested under the change,	
9.0 Production under loan licence or contract and contract analysis and other activities:			
9.3 Loan licensee or contract giver			

67	9.3.1.	Whether the product quality system of the loan licensee or contract includes the control and review of any outsourced activities.	
68	9.3.2.	Whether the loan licensee/contract giver has provided the manufacturing facility provider or contract acceptor all the information necessary to carry out the contracted operations correctly in accordance with the licence / other legal requirements	
69	9.3.3.	Whether the loan licensee/contract giver reviews/assess the records and results related to the outsourced activities	
70	9.3.3.	Verify the mechanism/process implemented by the contract giver to ensure that all the products and materials delivered by the manufacturing facility provider/ contract acceptor have been processed in accordance with good manufacturing practices and the licence;	
71	9.3.3.	Verify the mechanism/process implemented by the contract giver to ensure that all the products and materials delivered by the manufacturing facility provider are complying with their specifications and that the product has been released by the authorised person in accordance with good manufacturing practices and the licence.	
72	9.3.4.	Verify the mechanism/process implemented by the loan licensee or contract giver to monitor and review the performance of the manufacturing facility provider or contract acceptor.	
9.4.Manufacturing facility provider or contract acceptor			
73	9.4.1.	Whether the manufacturing facility provider or contract acceptor have adequate premises, equipment, knowledge, experience and competent personnel to satisfactorily carry out the work ordered by the loan licensee or contract giver.	
74	9.4.2	Ensure that the manufacturing facility provider/contract acceptor has not passed to a third party any of the work entrusted to him or her under the contract without the loan licensee or contract giver's prior evaluation and approval of the arrangements.	
9.5.Contract			
75	9.5.1	Whether a written contract between the loan licensee or contract giver and the manufacturing facility provider or contract acceptor is available.	
76	9.5.2.	Whether the contract clearly states that the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the licence.	

77	9.5.5.	Whether the contract clearly describes who is responsible for contracted activities e.g., knowledge management, technology transfer, supply chain, sub-contracting, testing and releasing materials and undertaking production and quality control, including in-process controls, and who has responsibility for sampling and analysis..	
78	9.5.5.	In the case of contract analysis, ensure whether the contract states whether the manufacturing facility provider or contract acceptor shall take samples at the premises of the manufacturer or not.	
79	9.5.6.	Ensure whether the manufacturing, analytical and distribution records and reference samples are to be kept by, or be available to, the loan licensee or contract giver.	
80	9.5.7	Ensure whether the contract clearly describes the handling of starting materials, intermediate, bulk and finished products, if they are rejected.	
81	9.5.7	Ensure whether the contract clearly describes the procedure to be followed if the contract analysis shows that the tested product must be rejected.	
10. Self-inspection, quality audits and suppliers' audits and approval:			
82	10.3.	Verify if Self-inspections are conducted by a self-inspection team consisting of experts in their respective fields who are familiar with GMP.	
83	10.4	Frequency of self-inspection- Whether the firm has defined the frequency for self-inspections in SOP., The frequency shall be at least once in a year	
84	10.5.	Verify that Self-inspection report is prepared after completion of a self-inspection. Verify that the report include the followings, - (a) self-inspection results; (b) evaluation and conclusions; and (c) recommended corrective actions	
85	10.6	Whether the firm has an effective follow-up programmed for Self-inspection findings Whether the company management evaluates both the self-inspection report and the corrective actions as necessary ?.	
10.7.Quality audit-			
86	10.7	Whether the firm conducts Quality audit for examination and assessment of all or part of a quality system with the specific purpose of improving it	
10.8. Suppliers' audits and approval			
87	10.8.1	Whether the firm has written procedure for approval of suppliers	

88	10.8.2	Before suppliers are approved and included in the approved suppliers' list or specifications, they shall be evaluated. The evaluation shall take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it shall determine the supplier's ability to conform with good manufacturing practices standards.	
11 Personnel:			
89	11.1	Whether the firm has well established and maintained system of Quality Assurance (QA) to ensure the correct manufacture and control of pharmaceutical products and active ingredients.	
90	11.1	Whether the firm has appointed sufficient numbers of qualified personnel's to carry out all the tasks for which the manufacturer is responsible.	
91	11.2	Whether responsibilities of all individuals are clearly defined and understood by the persons concerned and recorded	
92	11.2.4	Whether the firm has taken adequate measures to prevent entry of unauthorised people from entering production, storage and QC areas.	
11.3. Key personnel			
93	11.3.1.	Whether the key posts {heads of production, the heads of quality units (QA and QC functions) and the authorised person} are occupied by full-time personnel's	
94	11.3.1.	Whether the heads of production and quality units shall be independent of each other.	
95	11.3.2.	Whether the Key personnel responsible for supervising the production and quality units for pharmaceutical products possess the qualifications and experience as specified under the rules.	
96	11.3.4.	Whether the responsibilities of head of production are defined and includes responsibilities as per Para 11.3.4 of schedule M	
97	11.3.5.	Whether the responsibilities of quality units are defined and includes responsibilities as per Para 11.3.5 of schedule M	
98	11.3.6.	Whether the firm has designated authorised person responsible for release of finished product for sale or supply.	
99	11.3.7.	Whether the assessment of production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product and an examination of the finished pack is done before release of finished products	
100	11.3.8.	How firm ensures that no batch of product is to be released for sale or supply prior to certification by the authorised persons	

101	11.3.9	Whether the authorised person responsible for approving a batch for release ensure that the requirements as per Para are met 11.3.9 of Schedule M.	
11.4. Training			
102	11.4.1.	Whether the firm is having approved written programmed for all personnel working manufacturing areas and in control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required	
103	11.4.1.	Whether the trainings are conducted as per the training program	
104	11.4.2.	Whether the training program includes Besides basic training on the theory and practice of good manufacturing practices,	
105	11.4.2.	Whether the training is given to newly recruited personnel's appropriate to the duties assigned to them	
106	11.4.2.	Whether Continuous training is given, and its practical effectiveness is assessed periodically.	
107	11.4.2.	Whether Training records are maintained and available as per training program	
108	11.4.3.	Whether specific training is given to personnel's involved in handling of hazardous, highly active, toxic, infectious or sensitising materials and persons working in clean areas.	
109	11.4.5	Whether the visitors or untrained personnel are given information about relevant procedures (particularly about personal hygiene) and the prescribed protective clothing. Whether they are closely supervised by company personnel's (Visitors or untrained personnel shall preferably not be taken into the production and quality control areas.)	
110	11.4.6.	Whether the consultants and contract staff used by firm are qualified for the services they are providing. Whether Evidences/training records for the same are available with firm	
11.5. Personal hygiene			
111	11.5.1.	Whether firm is performing health check-ups of all personnel's, prior to and during employment, as appropriate.	
112	11.5.1.	Whether firm is performing periodic eye check-ups for the personnel conducting visual inspections.	
113	11.5.2.	Specify whether SOPs for personal hygiene is available? and whether all personnel's are trained in the practices of personal hygiene	
114	11.5.3.	Ensure that persons showing apparent illness or open lesions that may adversely affect the quality of products are not allowed to participate in manufacturing activity.	

115	11.5.5.	Ensure that operators are not touching to the starting materials, primary packaging materials, intermediate or bulk products with bare hands.	
116	11.5.6.	Whether firm has provided clean gowns to the personnel's (including appropriate hair covering) working at site to ensure protection of the product from contamination, appropriate to the duties they performing	
117	11.5.6.	Whether the firm is reusing clothes/gowns. If so whether they are stored in a separate closed container until properly laundered and, if necessary, disinfected or sterilised.	
118	11.5.8.	Ensure that personal hygiene procedures, including the wearing of protective clothing, are applied to all persons entering production areas, whether they are temporary or full-time employees or non -employees, e.g., contractors' employees, visitors, senior managers and inspectors	
12. Premises			
119	12	Whether the Premises conform to the conditions as laid down in the Factories Act, 1948 (63 of 1948)	
120	12.2.1.	Whether the layout , design & constructed of premises is done to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt and in general, any adverse effect on the quality of products	
121	12.2.2.	Whether sufficient measures taken to avoid cross-contamination and facilitate cleaning for the operations where dust is generated (e.g., during sampling, weighing, mixing and processing operations or packaging of powder)	
122	12.2.3.	Whether the Premises is situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.	
123	12.2.4	Whether the Premises used for the manufacture of finished products is designed and constructed to facilitate cleaning and sanitation	
124	12.2.6	Whether the SOPs for cleaning and disinfection of the Premises are available and records for the same are maintained.	
125	12.2.7.	Whether the Electrical supply, lighting, temperature, humidity and ventilation is appropriately maintained to ensure quality of pharmaceutical products during their manufacture and storage or the accurate functioning of equipment.	
126	12.2.8.	Whether the design, installation, qualification and maintenance records of the Heating, Ventilation, Air Conditioning (HVAC) systems are available	

127	12.2.9	Whether the Premises are designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals..Whether the firm is having procedures for rodent and pest control	
128	12.2.10.	Whether the Premises are designed to ensure the logical flow of materials and personnel	
12.3 Ancillary areas			
129	12.3.1	Ensure that the Rest and refreshment are separated from the manufacturing and control areas.	
130	12.3.2.	Ensure that the facilities for changing and storing clothes and for washing and toilet purposes shall be easily accessible and appropriate for the number of users	
131	12.3.2.	Ensure that the toilets are not directly communicate/connected with production or storage areas	
132	12.3.3.	Ensure that the Maintenance workshops, if possible be separated from production areas. Whenever parts and tools are stored in the production area, Ensure that they shall kept in Whenever parts and tools are stored in the production area, Ensure that they shall kept in rooms or lockers reserved for that use.	
133	12.3.4.	Ensure that the Animal houses are well isolated from other areas, with separate entrance (animal access) and air-handling facilities.	
12.4. Storage areas			
134	12.4.1.	Whether adequate storage areas have been allocated for orderly storage of the various categories of materials and products (e.g. starting and packaging materials, intermediates, bulk and finished products, products in quarantine and released, rejected, returned or recalled products) with proper separation and segregation	
135	12.4.2.	Ensure that the storage areas shall are designed or adapted to ensure good storage conditions. Ensure that the storage areas are clean, dry, sufficiently lit and maintained within acceptable temperature limits. Ensure that special storage conditions (e.g., temperature, humidity) are provided, if required and they are controlled, monitored and recorded as appropriate.	
136	12.4.3.	Whether the firm has provided separate Receiving and dispatch bays	
137	12.4.3.	Whether the Receiving and dispatch bays are designed to protect the materials and products from the weather.	
138	12.4.3.	Whether the receiving area is designed and equipped to for cleaning of containers of incoming materials, if necessary,	
139	14.4	Whether all incoming materials are quarantined immediately after receipt.	

140	12.4.4	Ensure that if quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access must be restricted to authorized personnel. Specify If firm is using any system in replacement the physical quarantine. If so, ensure that system used by firm is giving equivalent security.	
141	12.4.5.	Whether Segregation is provided for the storage of rejected, recalled or returned materials or products.	
142	12.4.6.	Whether the safe and secure areas are provided for storage of the Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion etc.	
143	12.4.7.	Whether the Printed packaging materials are stored in safe and secure storage areas	
144	12.4.7.	Whether the firm have SOPs for sampling of Printed packaging materials and Whether necessary provisions are made for sampling of Printed packaging materials	
145	12.4.8	Whether separate sampling area provided for starting materials. If sampling is performed in the storage area, Ensure that it is conducted in such a way so as to prevent contamination or cross-contamination	
12.5. Weighing areas			
146	12.5.	Whether separate weighing areas are provided for weighing of starting materials and the estimation of yield by weighing	
147	12.5.	Whether weighing areas specifically designed for that use (for example with provisions for dust control).	
12.6. Production areas			
148	12.6.1.	Specify whether the whole facility is separated and dedicated for manufacturing of the pharmaceutical products and is not utilized for any other non-pharmaceutical products	
149	12.6.1.	Specify whether dedicated and self-contained facilities are provided for the production of particular pharmaceutical products, such as highly sensitising materials (e.g., penicillins) or biological preparations (e.g., live microorganisms).	
150	12.6.1.	Ensure that production of highly active products, such as some antibiotics, hormones, cytotoxic substances and non-pharmaceutical products shall not be conducted in the same facilities. (Note :-In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made.	
151	12.6.2.	Ensure that there is no criss-cross flow of materials and men?	

152	12.6.3.	Whether adequate the working and in-process storage space is provided for orderly and logical positioning of equipment and storage of materials so as to minimise the risk contamination of different pharmaceutical products or their components OR to avoid cross-contamination	
153	12.6.4.	Whether facility (wherever starting and primary packaging materials and intermediate or bulk products are exposed) is designed and maintained in away the interior surfaces (walls, floors and ceilings) are smooth and free from cracks and open joints, dose not sheds the particulate matter and permit easy and effective cleaning and, if necessary, disinfection.	
154	12.6.5.	Whether the Pipework, light fittings, ventilation points and other services designed and sited to avoid the creation of recesses that are difficult to clean.	
155	12.6.6	Specify whether the Drains are of adequate size and designed and equipped to prevent back-flow	
156	12.6.7.	Whether the Production areas are effectively ventilated and equipped with air-control/air filtration facilities to prevent contamination and cross-contamination and to control temperature and humidity appropriate to the products handled/operations undertaken.	
157	12.6.7.	Whether the adequate filtration systems are provided to ensure that the hazardous contaminates (e.g. cytotoxic drugs) are not exposed /released into the external environment.	
158	12.6.8	Whether the premises for the packaging is designed and laid to avoid mix ups, contamination or cross-contamination.	
159	12.6.9.	Whether the Production areas are well lit. Check particularly for areas where visual online controls are carried out.	
12.7. Quality Control (QC) areas			
160	12.7.1.	Ensure and specify whether the QC laboratory is separated from production areas.	
161	12.7.1.	Ensure and specify whether the area for biological, microbiological or radioisotope test methods is separated from each other.	
162	12.7.2.	Ensure that QC laboratory is designed to suit the operations to be carried out in them and sufficient space is provided to avoid mix ups and cross-contamination.	
163	12.7.2.	Ensure that adequate suitable storage space is provided for samples, reference standards (if necessary, with cooling), solvents, reagents and records etc.	
164	12.7.3.	Ensure that construction materials of laboratories/working platforms is suitable for the work undertaking	
165	12.7.3.	Ensure that sufficient ventilation and arrangement's for prevention of fumes are provided	

166	12.7.3.	Ensure and specify whether separate air supply is provided to laboratories and production areas.	
167	12.7.3.	Ensure and specify whether separate air-handling units and other provisions are provided for biological, microbiological and radioisotope laboratories.	
168	12.7.4.	Ensure that separate room are provided for the instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors or where it is necessary to isolate the instruments.	
13. Equipment:			
169	13.1.	Ensure that the equipment is designed and installed to minimize the risk of errors and to permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt.	
170	13.3.	Verify whether the fixed pipework are clearly labeled to indicate the contents and where applicable the direction of flow.	
171	13.5.	Verify whether the Balances and other measuring equipment of an appropriate range and precision are available for production and control operations	
172	13.5.	Verify whether the balances and other measuring equipment are calibrated according to a fixed schedule	-
173	13.6.	Whether the firm is having a fixed schedule for cleaning of production equipment's and records for cleaning are maintained	
174	13.7.	Ensure that Laboratory equipment and instruments are suited to the testing procedures undertaken.	
175	13.9.	Ensure that the parts of the production equipment that come into contact with the product are reactive, additive or absorptive to an extent that would affect the quality of the product.	
176	13.10.	Ensure that the defective equipment is removed from production and QC areas OR are clearly labelled as defective and do not use (If this is not possible to remove form area)	
177	13.12	Whether firm is using validated cleaning procedures for cleaning of Non-dedicated equipment g used for production of different pharmaceutical products.	
178	13.13	Whether firm is having current drawing of critical equipment and support systems.	
14. Materials:			
179	14.3.	Ensure that no materials used for operations such as cleaning, lubrication of equipment and pest control shall come into direct contact with the product. Where possible, such materials shall be of a suitable grade (e.g., food grade) to minimize health risks.	

180	14.4	Whether all incoming materials and finished products are quarantined immediately after receipt or processing, until they are released for further use or distribution.	
181	14.5.	Whether firm has established storage conditions for materials and products and Whether materials/products are stored under the appropriate conditions as established by firm OR as per the manufacturers recommendation.	
182	14.5.	Whether firm has stored all materials and products and in an orderly fashion, to permit batch segregation and stock rotation by a first-expire, first-out rule.	
183	14.6	Whether firm is using validated water systems for treatment of water drawn from own or any other source to render it potable in accordance with the standards specified by the Bureau of Indian Standards or Local Municipality, as the case may be, so as to produce purified water conforming to Pharmacopoeial specification.	
184	14.6	Whether firm is using Purified Water for all the manufacturing operations (Note;-potable water may be used washing and cleaning operations).	
185	14.6	Whether Water is stored in tanks, which do not adversely affect quality of water and ensure freedom from microbiological growth.	
186	14.6	Whether the tanks used for storage of water are cleaned periodically.	
187	14.6	Whether the firm has performed design, installation and operation of pharmaceutical water systems	
188	14.7	Whether trained personnel's are involved in the purchase of starting materials.	
189	14.9.	Whether each consignment, at a minimum, the containers is checked at least for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.	
190	14.10.	Whether all containers of incoming materials are cleaned where necessary and labeled, if required, with the prescribed information.	
191	14.10.	Where additional labels are attached to containers, ensure that the original information is not lost.	
192	14.12	Ensure that If one delivery of material is made up of different batches then each batch must be considered as separate for sampling, testing and release.	
193	14.13	Whether starting materials in the storage areas are appropriately labeled.	
		Whether labels bear at least the following information, namely:—	
		(a) the designated name of the product and the internal code reference where applicable;	

		(b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;	
		(c) the status of the contents (e.g., in quarantine, on test, released, rejected, returned or recalled); and	
		(d) Where appropriate, an expiry date or a date beyond which retesting is necessary.	
		(Note :- When fully validated computerized storage systems are used, all of the above information need not to be mentioned on the label)	
194	14.14. & 14.147	How firm ensures that only raw materials which have been released by the QC Department and which is within their shelf life is used for processing.	
195	14.15.	Ensure that for raw materials other than APIs, if released by QC Department for use in manufacturing without any specific batch testing, then it shall be based on vendor approval and statistical data analysis of earlier test results of such material for release.	
196	14.16.	Whether the firm has appropriate procedures or measures to ensure the identity of the contents of each container of starting material (API).	
	14.16.	Ensure that the bulk containers from which samples have been drawn are identified/labeled accordingly.	
197	14.18.	Whether the firm has written procedures for dispensing of starting materials to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers and Whether firm has designated for dispensing activity	
198	14.19	Whether the firm has written procedures to verify that each dispensed material and its weight or volume is independently checked and recorded.	
199	14.20.	Ensure that the Materials dispensed for each batch of the final product is kept together and conspicuously labeled	
200	14.21.	Ensure that the firm is following similar procedures for the purchase, handling and control of primary and printed packaging materials as that of starting materials.	
201	14.22.	Ensure that the printed packaging materials are stored in secure conditions so as to avoid the possibility of unauthorized access.	
202	14.22.	Ensure that cut labels (leftover Roll feed labels) and other loose printed materials is stored and transported in separate closed containers to avoid mix ups.	
203	14.22.	Whether the firm has written procedures for issuance of Packaging materials and Whether materials are issued only designated and trained personnel’s	

204	14.23.	Ensure that each delivery or batch of printed or primary packaging material is given a specific reference number or identification mark.	
205	14.24.	Whether the firm has written procedures for destruction of Out-dated or obsolete primary packaging material or printed packaging material and whether its disposal record is maintained.	
206	14.25	Whether the firm has written procedures for verification all products and packaging delivered to the packaging department for verification of quantity, identity and conformity with the packaging instructions.	
207	14.26	Whether the containers and closures used for intended use comply with the pharmacopoeial requirements.	
208	14.26	Whether the firm has specifications and validated test methods and cleaning procedure and sterilization procedure, (wherever indicated)for containers and closures used	
		Whether the firm has to ensured that containers and closures used are not reactive, additive, absorptive, or leach to an extent that significantly affects the quality or purity of the drug..	
209	14.26	Ensure that firm is not suing second hand or used containers and closures	
210	14.26.1.	Whenever bottles are being used, check if the written schedule of cleaning of bottles is laid down and followed.	
		Where bottles are not dried after washing, ensure that they are rinsed with purified water or water for injection, as the case may be	
211	14.26.3.	Whether Packaging materials used by firm for packaging of pharmaceutical products complies with the requirements prescribed in Indian Pharmacopoeia (IP)	
212	14.27.	Whether Intermediate and bulk products are stored under appropriate conditions	
213	14.28.	Ensure that if Intermediate and bulk products are purchased then on receipt it is handled as if they were starting materials.	
214	14.29.	Ensure that finished products are held in quarantine until their final release and after which they are stored as usable stock under conditions established by the firm	

215	14.32.	a) Verify the procedures followed by firm for reworking or recovery of rejected products. Ensure that such incidents are exceptional and permitted only if the quality of the final product is not affected and if the specifications are met. b) Whether it is done in accordance with a defined and authorized procedure after evaluation of the risks involved c) Whether records are kept for reworking or recovery	
216	14.32.	Ensure whether a new batch number is given to reworked batch.	
217	14.33.	a) Verify whether the firm is having procedure/practices for recovery i.e. introduction of all or part of earlier batches (only if conforming to the required quality standards) into a batch of the same product at a defined stage of manufacture. b)Ensure such activities are done only with the prior approval of the authorized personnel and only if batches conforming to the required quality standards are utilized c)Whether the firm has maintained record of recovery.	
218	14.34.	Ensure that whether the need for additional testing on the finished product that has been reprocessed reworked or into which a recovered product has been incorporated is considered by the QC Department.	
219	14.35.	Ensure that products returned from the market are destroyed unless it is certain that their quality is satisfactory.	
220	14.39.	Verify, whether the firm is applying both positive and negative controls to verify the suitability of culture media each time they are prepared and used. Ensure whether the size of the inoculum used in positive controls is appropriate to the sensitivity required?	
15. Reference Standards:			
221	15.1.	Ensure that firm is using official reference standards (whenever exist).	
222	15.2.	Ensure that firm is procuring Indian Pharmacopoeia reference standards from Indian Pharmacopoeia Commission.	
223	15.3.	Ensure that Official reference standards are used for the purpose described in the appropriate monograph.	
224	15.4.	Ensure whether the **reference standards** prepared by the manufacturer are tested, released and stored in the same way as official standards.	
225	15.4.	Ensure whether the **reference standards** are stored in a secure area under the responsibility of a designated person.	
226	15.5.	Ensure whether the firm is reforming appropriate tests and checks at regular intervals for secondary or working standards established by the firm to ensure standardization	

227	15.6.	Ensure whether reference standards are properly labeled and the label or accompanying document or both contains least the following information, as appropriate.	
		(a) name of the material;	
		(b) batch or lot number Or control number;	
		(c) date of preparation/date of manufacture	
		(d) shelf-life & expiry date	
		(e) potency or concentration	
		(f) Storage conditions.	
		g) date of opening of closure (date when opened first time)	
228	15.7	Ensure whether the firm has standardized all in-house working standards or secondary standards against an official reference standard, when available, initially and at regular intervals thereafter.	
16. Waste materials:			
229	16.1.	Whether the firm has made necessary provisions for the proper and safe storage of waste materials waiting disposal.	
		Ensure whether the Toxic substances and flammable materials are stored in suitably designed, separate, enclosed cupboards.	
230	16.2.	Ensure whether the waste material is disposed of safely and in a sanitary manner at regular and frequent intervals.	
231	16.3.	Ensure whether the disposal of sewage and effluents (solid, liquid and gas) from the manufacturing area conforms to the requirements of the guidelines issued by the Environmental Pollution Control Board. (Verify NOC/Consent obtained by firm from State Pollution control board in this regard.)	
232	16.4.	Ensure whether the bio-medical waste is destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 2016.	
262.	16.5.	Ensure that the Rodenticides, insecticides, fumigating agents and sanitizing materials used by firm are not coming in contact with process equipment, starting materials, packaging materials, in-process materials or finished products Or does not contaminate them	
17. Documentation			
233	17.2.2.	Ensure that documents are approved, signed and dated by the responsible persons.	
		Ensure that No document are changed without authorization and approval.	
234	17.2.4.	Whether firm regularly reviews the documents and whether firm has a system in place to prevent inadvertent use of the superseded version. Superseded documents shall be retained for a specific period of time	

235	17.2.5	Where documents require the entry of data, these entries shall be clear, legible and indelible. Sufficient space shall be provided for such entries	
236	17.2.6	Any alteration made to a document shall be signed and dated; the alteration shall be done in such a way so as to permit the reading of the original information. Where appropriate, the reason for the alteration shall be recorded.	
237	17.2.7	Records shall be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records shall be retained for at least one year after the expiry date of the finished product.	
238	17.2.8	If documentation is handled by electronic data-processing methods, then, verify that only authorized persons are able to enter or modify data in the computer system, and there is a record of changes and deletions; access is restricted by passwords or other means and the entry of critical data is independently checked.	
239	17.2.8	If Batch records are stored electronically then, verify that the same are protected by back-up transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means.	
240	17.2.9	Whether the firm has prepared the site master file as per the Appendix-I to the Part I of schedule M	
17.3. Documents Required			
17.3.1. Labels[1]			
241	17.3.1.1.	Whether the firm has procedure/Sops for labeling of containers, equipment or premises.	
17.3.2. Specifications and testing procedures			
242	17.3.2.1.	Whether the firm has validated all testing procedures in the context of available facilities and equipment's before they are adopted for routine testing	
243	17.3.2.2	Whether the firm has written, authorized and dated specifications for tests conducted on starting/packaging materials, intermediate or bulk products (where appropriate) and for finished products.	
244	17.3.2.2	Whether the firm has written, authorized and dated specifications for water, solvents and reagents (e.g., acids and bases) used in production.	
245	17.3.2.3	Ensure that each specification is approved, signed and dated and maintained by the QC or QA units.	
246	17.3.2.4	Ensure that firm has procedure for periodic revisions of the specifications to comply with new editions of the Indian pharmacopoeia or other official pharmacopoeia.	

247	17.3.2.5.	Ensure that official Pharmacopoeias, reference standards, reference spectra and other reference materials are available in the QC laboratory.	
17.3.3 Specifications for starting and packaging materials[1]			
248	17.3.3.1 and 17.3.3.2	Ensure that specifications for starting, primary and printed packaging materials are having information as per Para 17.3.3.1 and 107.3.3.2 of schedule M	
249	17.3.3.3.	What is procedure adopted by firm to ensure that the Packaging material is conforming to the specifications and are compatible with the material or with the drugs or both it contains.	
250	17.3.3.3.	Ensure that the packaging materials are examined for compliance with the specification and for defects as well as for the correctness of identity markings.	
251	17.3.3.4.	Ensure whether the documents describing testing procedures/Specifications states the required frequency for re-assaying each starting material (as determined by its stability)	
17.3.4. Specifications for intermediate and bulk products-			
252	17.3.4.	Whether the firm has written, authorized and dated specifications for tests conducted on intermediate and bulk products	
17.3.5 Specifications for finished products-			
253	17.3.5	Check whether the specifications for finished products is having information as per 17.3.5 of schedule M	
17.3.6. Master formula records[1]			
254	17.3.6.1.	Check whether the firm have authorized master formula for each product and batch size to be manufactured.	
255	17.3.6.2.	Check whether the master formula is having information as per 17.3.6.2. of Schedule M	
17.3.7.Packaging instructions			
256	17.3.7.	Check whether the firm have authorized packaging instructions for each product, pack size and type.	
257	17.3.7.	Check whether the authorized packaging instructions is having information as per 17.3.7.of Schedule M.	
17.3.8. Batch processing records			
258	17.3.8.1.	Ensure whether the firm has kept a batch processing record for each batch processed.	
259	17.3.8.3.	Check whether the batch processing record is having information as per 17.3.8.3 of Schedule M.	
260	17.3.8.2	Specify whether before starting any processing, the firm is having procedure to check that the equipment and work station are clear of previous products, documents, or materials not required for the planned process and that the equipment is clean and suitable for use.	

17.3.9. Batch packaging records[1]			
261	17.3.9.1	Ensure whether the firm has kept a batch packaging record for each batch processed. Check whether the batch packaging record is having information as per 17.3.9.3 of Schedule M.	
262	17.3.9.2	Specify whether before starting any packaging operation, the firm is having procedure to check that the equipment and work station are clear of previous products, documents, or materials not required for the planed packaging operation and that the equipment is clean and suitable for use.	
17.3.10. Standard operating procedures and records:			
263	17.3.10.1.	Verify whether the firm is having Standard Operating Procedures (SOPs) and associated records for	
		a) equipment assembly and validation;	
		(b) analytical apparatus and calibration;	
		(c) maintenance, cleaning and sanitization;	
		(d) personnel matters including qualifications, training, clothing and hygiene;	
		(e) environmental monitoring; (f) pest control;	
		(g) complaints;	
		(h) recalls and	
		(i) Returns.	
264	17.3.10.3	Verify whether the firm has maintained records of the receipts as per Para 17.3.10.3 of schedule M	
265	17.3.10.4.	Verify whether the firm has SOPs for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials	
266	17.3.10.5.	Verify whether the firm has SOPs for use, calibration, cleaning and maintenance etc. of each instrument and piece of equipment.	
267	17.3.10.6	Verify whether the firm has SOPs for sampling specifying the persons authorized to take samples.	
268	17.3.10.8.	Verify whether the firm has SOPs for batch (lot) numbering system to ensure that each batch of intermediate, bulk or finished product is identified with a specific batch number.	
269	17.3.10.13	Verify whether the Analysis records maintained are as per Para 17.3.10.13 of schedule M	
270	17.3.10.14.	Verify whether the firm has SOPs /Written procedures for release and rejection for materials and products and	
		Verify whether the SOPs specifies that Batch of finished product shall be released by authorized person for sale	
	18. Good practices in production:		
271	18.2.1.	Whether the firm has written procedures for handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution.	

272	18.2.2	Ensure, if deviations occur, they shall be in accordance with an approved procedure.	
273	18.2.4	Check that Operations on different products are not carried out simultaneously or consecutively in the same room or area unless there is no risk of mix up or cross-contamination.	
274	18.2.5	Check that during processing all materials, bulk containers, equipment , the processing rooms and packaging lines being used, are labeled /identified with an indication of the product or material being processed, its strength (as applicable) and the batch number.	
275	18.2.6.	Check that Access to production premises is restricted to authorized personnel's only	
18.3. Prevention of cross-contamination and bacterial contamination during production			
276	18.3.1.	Check that when dry materials and products are used in production, special precautions are taken to prevent the generation and dissemination of dust. Verify that Provision are made for proper air control (e.g., supply and extraction of air of suitable quality)	
277	18.3.3	Whether the firm has taken adequate measures to avoid risk Contamination of a starting material or of a product by another material or product (a mentioned in Para 18.3.3 of schedule M)	
278	18.3.4.	Whether the effectiveness of the Measures taken to prevent cross-contamination is reviewed periodically according to SOPs.	
279	18.3.5	Whether firm performs the periodic monitoring (e.g. microbiological and particulate matter, as appropriate) of the Production areas where susceptible products are processed.	
18.4.Processing operations			
280	18.4.2.	Whether firm performs the necessary in-process controls and environmental controls and whether records for the same are available .	
281	18.4.4	Whether time limits for storage of process materials and equipment, after cleaning and before use, are stated and based on relevant data	
282	18.4.8.	Whether the Pipes used for conveying distilled /deionized water and, where appropriate, other water pipes are sanitized and stored according to written procedures. Whether the action limits for microbiological contamination are defined and the procedures are available for measures to be taken in case limit exceeds the action limits.	

283	18.4.9.	a) Whether, measuring, weighing, recording and control equipment and instruments are serviced and calibrated at pre-specified intervals and records maintained. b) Whether analytical instruments are checked daily or prior to use for performing analytical tests. c) Whether date of calibration and servicing and the date when recalibration is due shall is clearly indicated on a label attached to the instrument.	
18.5.**Packaging operations:**			
284	18.5.2.	Whether, line clearance is performed before packaging operations are begun, according to an appropriate procedure and checklist and is recorded.	
285	18.5.3.	Whether the product name and batch number of the product being handled is displayed at each packaging station or line.	
286	18.5.5	Whether the firm is **performing checks** at regular intervals for correctness of performance of any printing operation (e.g., of code numbers or expiry dates) done separately or in the course of the packaging and whether record for the same is maintained	
287	18.5.6.	Whether the firm is performing checks at regular intervals to ensure that any electronic code readers, label counters or similar devices are operating correctly.	
288	18.5.7.	Verify that the Printed and embossed information on packaging materials is distinct and resistant to fading or erasing.	
289	18.5.8.1	Verify whether the regular online checks/controls performed by firm during packaging includes at list following minimum checks on the product	
		(a) the general appearance of the packages;	
		(b) whether the packages are complete;	
		(c) whether the correct products and packaging materials are used;	
		(d) whether any overprinting is correct; and	
		(e) the correct functioning of line monitors	
290	18.5.8.2.	How firm ensures that Samples taken away from the packaging line is returned back?	
291	18.5.9.	Whether firm is having procedure for re-packing of products that have been involved in an unusual event during packaging and whether such products are reintroduced into the process only after special inspection, investigation and app approval by the authorized personnel.	
292	18.5.10.	Whether, any significant /unusual discrepancies observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced are investigated, satisfactorily accounted for and recorded before release	

293	18.5.11.	Whether the firm has documented procedure for destruction of the unused batch-coded packaging materials left upon completion of a packaging operation, and the whether the destruction record is maintained.	
294	18.5.11.	Whether firm has documented procedure for checks to be performed before returning unused materials/un-coded printed materials back to the stock and whether the record for the same is maintained.	
295	18.5.12.	Whether the firm has procedure to review production records as part of the approval process of batch release before transfer to the authorized person.	
19. Good practices in quality control			
296	19.3.	Whether firm has QC function independent of other Departments and under the authority of a person with appropriate qualifications and experience.	
297	19.3.	Whether firm has provided Adequate resources and arrangements as per Para 19.3 for effectively and reliable functioning of the QC section	
298	19.3 (b)	Whether the samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by the methods and personnel approved by the QC Department;	
299	Sch-L1	Ensure that analytical instruments are housed in dust-free environment and whenever required, conditions of temperature and humidity are maintained and periodic checks on temperature and humidity are made and records are maintained	
300	Sch-L1	a) Whether firm have Standard Operating Procedures for the operation, maintenance and calibration of instruments used in QC.	
	4(d)	b) Whether calibration schedule for analytical instruments is available?	
	7(c)	c) Whether the analytical instruments requiring calibration are calibrated at regular intervals and records of such calibration or maintenance are maintained.	
		d) Whether logbooks maintained for proper documentation of calibration results.	
301	Sch-L1	Ensure whether the equipment's such as burettes, pipettes, volumetric flasks, weight boxes, thermometers, etc., are calibrated are before acceptance for use	
	4 (h)	Specify which grade of glassware is used in assay procedures and whether they are certified/calibrated. Verify the certificates and calibration records.	
302	Sch-L1- 4 (k)	Whether maintenance of equipment's for services like electricity, gas, water, steam, and compressed gas is handled by competent person	

303	Sch-L1-4 (i)	Whether Autoclaves used in laboratory meets the requirements described for operations, safety and validation procedures and the validation is carried out by the laboratory and records are maintained	
304	Sch-L1-5 (b)	Whether all reagents and solutions, stock solutions and of standard solutions used the laboratory are properly labeled	
305	Sch-L1-6 (b) (iv)	Whether adequate first aid kit and fire fighting equipment's are provided in the laboratory is located at the right places and the staff is familiar and trained for fire fighting equipment.	
306	Sch-L1-6 (b) (vi)	Whether the staff is trained in the first aid techniques, emergency care and use of antidotes	
307	Sch-L1-6 (c) (i)(ii)	Whether require safety equipment is provided in laboratory (e.g. water showers are installed at appropriate places in the laboratory and required safety precautions are taken (e.g. use of rubber suction bulbs for manual pipettes and siphons)	
Sch-L1 (Para 9.0) Microbiological Cultures:-			
308	Sch-L1-9 (a)	Whether laboratory is having SOPs for preparation/maintenance of microbial culture and sub-culture prepared by the laboratories.	
309	Sch-L1-9 (a) & 9 (b)	Whether laboratory is having SOPs for destruction of cultures that have become non-viable or mutant. Whether proper procedures are followed (autoclaving) to destroy these cultures.	
310	Sch-L1-9	a) Verify passages levels up to which cultures are prepared and used (Preferably not more than five passages may be prepared).	
		b) Verify the laboratories performs standard biochemical tests on the sub-culture as given in literature to ensure their viability	
		c) Ensure that all activities in a aseptic area are conducted by authorized person.	
	Sch-L1 9-15) :-Raw data:-		
311	Sch-L1-15(a) & 16 (C)	Verify whether laboratory has archived the raw data of testing activities undertaking	
312	Sch-L1-15(b)	Ensure that if data is ratified /corrected then it is done by single line shall strike through the data being changed and the correct information is recorded along with the old data and the reason of change. Analyst making change is identified by his signature with date.	
313	Sch-L1-15(b)	Ensure that if data is ratified/corrected for automated data collection system, then the person responsible is identified at the time of data output. Ensure that if the original entry is saved and the system has audit trial for all the data.	

	Sch-L1-15(b)	Ensure that if the original entry is saved and the system has audit trial for all the data.	
314	Sch-L1-15(c)	Whether Data integrity and security is maintained and the data is not accessible to any unauthorized person	
	16. Storage and archival.-		
315	Sch-L1-16 (c) & (d)	Whether, data /records are archived in suitable environment to prevent modification, damage, or deterioration and/or loss. Whether, original documents are stored to ensure their security and confidentiality,	
316	Sch-L1-16 (f)	If data is stored in only optical disc, the life of disc shall be longer than the storage time	
317	Sch-L1-16 (g)	Ensure that firm has archived photocopy of the thermal paper along with original record for the raw data on thermal paper that might fade away with time;	
318	Sch-L1-16 (h)	Whether the firm has prescribed time limit (retention period) up to which laboratory records are retained.	
19.6. Control of starting materials and intermediate, bulk and finished products			
319	19.6.1.	Whether the firm has written test procedure for all tests performed for each material or product. Whether the test results are checked by the supervisor before the material or product is released or rejected.	
320	19.6.2	Whether the samples taken by the firm are representative of the batches of material from which they are taken and they are taken in accordance with the approved written procedure.	
321	19.6.6.	Whether the sample container bears a label indicating	
		(a) the name of the sampled material;	
		(b) the batch or lot number;	
		(c) the number of the container from which the sample has been taken;	
		(d) the number of the sample;	
		(e) the signature of the person who has taken the sample; and	
		(f) the date of sampling.	
322	19.6.7	Whether the firm has written procedure for investigation of Out-of-specification results obtained during testing of materials or products and whether investigation records are maintained.	
19.7. Test requirements			
323	19.7.2	Whether an identity test is conducted on a sample from each container of starting material.	

324	19.7.3.	Ensure whether each batch (lot) of printed packaging materials is examined following its receipt.	
325	19.7.5.	Whether, in-process control records are maintained and form part of the batch records.	
19.8. **Batch record review:**			
326	19.8.1.	Whether Quality Control records are reviewed as part of the approval process of batch release before transfer to the authorized person.	
19.8.2. Retention samples			
327	19.8.2.	Whether Retention samples from each batch of finished product are kept for at least one year after the expiry date.	
328	19.8.2.	Check whether retention sample of finished products are kept in their final packaging and stored under the recommended conditions.	
329	19.8.2.	Check whether samples of active starting materials are retained for at least one year beyond the expiry date of the corresponding finished product.	
330	19.8.2.	Check whether quantity of the Retention samples of materials and products are sufficient to permit at least two full re-examinations.	
19.9. Stability studies			
331	9.9.1.	Check whether the stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products is established by the QC department of firm.	
332	19.9.2.	Check whether the expiry dates and shelf-life specifications are established on the basis of the stability tests related to storage conditions.	
333	19.9.3	Whether the firm has developed and implemented programmed for on-going stability determination. (on-going stability determination programmed shall be developed and implemented as per elements mentioned din Para 19.9.3 of schedule M.)	
334	19.9.4.	Check whether the firm is performing stability study after any significant changes in processes, equipment or packaging materials.	
20. Computerized systems:			
335	20.1	Check whether the firm has validated all GMP-related computerized systems considering the diversity, complexity and criticality of the computerized application. (If an existing system was not validated at the time of installation then verify, if a retrospective validation is conducted and appropriate documentation is available)	

336	20.4.	Check whether the Computerized systems have sufficient controls to prevent unauthorized access or changes to data. {There shall be controls to prevent omissions in data (e.g., the system being turned off and data not captured). There shall be a record of any data change made, the previous entry, the person who made the change and when the change was made}.	
337	20.5.	Check whether the written procedures are available for the operation and maintenance of the computerized systems.	
338	20.6	Where critical data are being entered manually, Check whether the firm has an additional check on the accuracy of the data entered.	
339	20.7.	Check whether the Incidents related to computerized systems that could affect the quality of products or the reliability of records or test results are recorded and investigated.	
340	20.8.	Check whether the Changes to the computerized system are made according to a change procedure and records are maintained for all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system.	
341	20.9	Check whether the firm has provided a back-up system to ensure that there is no permanent loss of records due to system breakdown or failure.	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART II OF SCHEDULE M GMP INSPECTION OF STERILE PRODUCTS, PARENTERAL PREPARATIONS (SMALL VOLUME INJECTABLES AND LARGE VOLUME PARENTERALS) AND STERILE OPHTHALMIC PREPARATIONS

Note.-Good Manufacturing Practices for pharmaceutical products:- Main principles as given in Part I shall be complied with, mutatis mutandis, for the manufacture of sterile products, parenteral preparations (small volume injectables and large volume parenterals) and sterile ophthalmic preparations. In addition to these requirements, the following specific requirements shall also be followed,

Sr.No.	Sch M Ref.	Particulars	Observation
1. General considerations:-			
1	1.1.	The whether required clean areas provided for production of sterile preparations and entry is through airlocks for personnel or for equipment and materials or both?	
2	1.1.	Whether clean areas are maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.	
3	1.2.	Whether various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilisation are carried out in separate areas within the clean area.	
2. Quality control:-			
4	2.1	Ensure that the sterility test method is validated for the product concerned.	
	2.3	Ensure that the Pharmacopoeial methods are used for the validation and performance of the sterility test. (Note that the sterility test applied to the finished product is regarded as the last in a series of control measures by which sterility is assured, Ensure that firm has implemented sufficient measures to ensure sterility of product.)	
5	2.2	Ensure whether the samples taken for sterility are representative of the whole of the batch and in particular, includes samples taken from parts of the batch considered to be most at risk of contamination, for example- (i) For aseptically filled products samples shall include containers filled at the beginning and end of the batch and after any significant interruption of work; (ii) For products that have been heat sterilised in their final containers, consideration shall be given to taking samples from that part of the load that is potentially the coolest.	
6	2.3.	Ensure whether that firm has performed sufficient validation to assure sterility of the finished product i.e. validation of the sterilisation cycle in the case of terminally sterilised products and “media simulation” or “media fill” runs for aseptically processed products	

7	2.3.	Ensure whether Batch processing records and environmental monitoring records (for aseptic processing), are examined in conjunction with the results of the sterility tests for taking decision on release of the batch	
8	2.3.	Ensure whether special attention is paid to the validation and the monitoring of the entire manufacturing process, in those cases where parametric release has been authorized in place of sterility testing.	
9	2.4.	Ensure that for injectable products firm is performing test for endotoxins for the water for injection, the intermediate (if appropriate) and for finished products. Ensure whether test methods used are established pharmacopoeial method and validated for each type of product.	
10	2.4.	Ensure that for large-volume parenterals monitoring of water or intermediates for endotoxins is always be done, in addition to any tests required by an approved monograph for the finished product.	
11	2.4.	Whether the cause of the failure is investigated and necessary action shall be taken in case above sample fails in endotoxins test.	
12	2.5.	Check whether firm is using rapid microbiological methods in replacement the traditional microbiological methods for monitoring of microbiological quality of water, environment monitoring or bio burden etc. If so, ensure that the methods used are appropriately validated and a comparative assessment of the proposed rapid method is performed against the pharmacopoeial method.	
3. Sanitisation :			
13	3.1	Whether the firm has approved written programme for cleaning/sanitation of clean areas and ensure whether they are cleaned as per defined frequency	
14	3.3.	Whether the effectiveness of cleaning and disinfectant procedure is demonstrated/validated.	
15	3.1	Whether the disinfectants are used for cleaning/sanitation. If so, ensure that more than one type of disinfectants are employed.	
16	3.1	Whether monitoring is done regularly to detect contamination or the presence of an organism against which the cleaning procedure is ineffective.	
17	3.1	Whether Interactions between different cleaning materials are validated.	
18	3.2.	Whether appropriate cleaning validation is carried out to ensure disinfectant residuals can be detected and removed by the cleaning process.	
19	3.2.	Ensure whether the disinfectants and detergents are monitored for microbial contamination. Ensure whether the Disinfectants and detergents used in Grade A and B areas are sterilized before use.	

20	3.3.	Ensure whether the disinfectant programme includes a sporicidal agent.	
21	3.4.	Whether there are any inaccessible places , if so what is procedure followed (e.g. Fumigation) for reducing microbial contamination in inaccessible places	
4. Manufacture of sterile preparations:-			
22	4.1.	Whether Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Whether Each manufacturing operation are conducted in appropriate clean area in appropriate level of environmental cleanliness in the operational state to minimize the risk of particulate or microbial contamination of the product or materials being handled	
23	4.3	Ensure that manufacture of sterile pharmaceutical preparations is performed classified areas specified in Para 4.3 of part II e.g. **Grade A**: The local zone for high-risk operations, e.g., filling and making aseptic connections. Grade A conditions are achieved by using unidirectional airflow work station which provides air speed of 0.36-0.54 m/s (guidance value) at a defined test position 15-30 cm below terminal filter or air distributor system. The velocity at working level shall not be less than 0.36 m/s. The uniformity and effectiveness of unidirectional airflow shall be demonstrated by undertaking airflow visualisation tests. **Grade B**: In aseptic preparation and filling, this is the background environment for the Grade A zone. **Grades C and D**: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e., aseptic connection with aseptic connectors and operations in a closed system). A unidirectional airflow and lower velocities may be used in closed isolators and glove boxes.	
24	4.4.	Whether the number of air changes for grade B, C and D air grades are appropriate for the size of the room and the equipment and personnel present in it.	
25	4.5.	Whether High-efficiency particulate air (HEPA) filters are subjected to an installed filter leakage test in accordance with ISO standards at a recommended interval of every six months (not exceeding twelve month)	
26	4.5	Ensure that the aerosol selected for HEPA leak testing shall not support microbial growth and shall be composed of a sufficient number or mass of particles.	
27	4.5	Whether HEPA filter patching is allowed at filter the filter manufacturer and in situ operation provided that the patch sizes and procedures followed the recommendations of ISO standards.	
28	4.6	Whether clean rooms and clean air devises classifies in accordance with ISO standards.	

29	4.6.1.	Whether area Classification "at rest" and "in opration" are clearly defined and ensure that the maximum permitted airborne particle concentration for each Grade is as per Table 1 of Para 4.6.1 of Part II of Schedule M	
31	4.6.2	Ensure that for classification purposes in Grade A zones, a minimum sample volume of $1m^3$ shall be taken per sample location	
32	4.6.2	For classification purposes ISO standards methodology defines both the minimum number of sample locations and the sample size based on the class. limit of the largest particle size considered and the method of evaluation of the data collected. The sample volume shall be determined according to ISO standards. However, for lower grades (Grade C in operation and Grade D at rest) the sample volume per location shall be at least two litres and the sample time per location shall be not less than one minute.	
33	4.6.3	Ensure that Portable particle counters with a short length of sample tubing shall be used for classification purposes to avoid the loss of particles ≥ 5.0 μm	
34	4.6.3.	Whether Isokinetic sample heads/Probes are used in unidirectional airflow systems.	
35	4.6.4.	Whether firm has demonstrated "In operation" classification during normal operations, simulated operations or during media fills	
36	4.7.	Whether firm has written procedure and programme for routine monitoring of clean rooms and clean-air devices while in operation and Whether the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms or clean-air devices or both.	
37	4.7.1.	a) Whether firm is performing particle monitoring for Grade A zones covering the full duration of critical processing, including equipment assembly (except where justified by contaminants in the process that would damage the particle counter or present a hazard, for example, live organisms and radiological hazards.) b) Ensure whether in such cases monitoring during routine equipment set-up operations is undertaken before exposure to the risk. c) Ensure whether monitoring during simulated operations is performed.	
38	4.7.1.	Whether Grade A zone are monitored at a frequency and sample size such that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. Verify the procedures adopted by firm for handling of exertions in particle count	
39	4.7.2	Ensure that similar system be used for Grade B zones, although the sample frequency may be decreased. The importance of the particle monitoring system shall be determined by the effectiveness of the segregation between the adjacent Grade A and B zones.	

40	4.7.2.	Whether The Grade B zone are monitored at a frequency and with a sample size such that changes in levels of contamination and any deterioration of the system would be captured and alarms triggered if alert limits are exceeded.	
41	4.7.3	Ensure that the length of tubing and the radii of any bends in the tubing are considered in the context of particle losses in the tubing whenever remote sampling systems are used.	
42	4.7.5.	whether "at rest" state is achieved in the absence of the operating personnel after a short "clean-up" or "recovery" period of about 15–20 minutes (guidance value), after completion of the operations.	
43	4.7.5.	Whether Grade A "in operation" is maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment.	
44	4.7.5.	Verify whether firm has performed "clean-up" or "recovery" test as per the ISO standards.	
45	4.7.6.	Verify whether firm written procedures and schedule/programme for monitored of airborne particles and microbial contamination. Ensure whether airborne particles are monitored periodically "in operation" at critical locations.	
46	4.7.6	Ensure that Locations and sample sizes shall be determined based on an assessment of the process and contamination risk.	
47	4.7.7.	Verify whether monitoring of Grade C and D areas in operation is performed in accordance with the principles of QRM. The requirements and alert or action limits will depend on the nature of the operations carried out, but the recommended "clean-up period" shall be attained.	
48	4.7.8.	Verify whether environmental conditions such as temperature and relative humidity is maintained depend on the product and nature of the operations carried out and whether these parameters are monitored. Ensure that temperature and relative humidity shall not interfere with defined cleanliness standards.	
49	4.8.	Verify whether firm has written procedures and programme for monitoring of microbiological cleanliness of Grades A to D in-operation, Specify monitoring methods (settle plates, volumetric air and surface sampling i.e. swabs and contact plates) used for monitoring during aseptic operations. Whether results from monitoring are considered while reviewing batch documentation for finished product release. Whether surfaces and personnel are monitored after critical operations. Whether additional microbiological monitoring is also required outside production operations e.g. after validation of systems, cleaning and sanitisation.	

50	4.9	a) Specify whether firm has established appropriate alert and action limits for the results of particulate and microbiological monitoring. b) Specify whether firm is performing trends analysis for microbiological monitoring is performed or not.	
51	4.1	c) Specify whether firm is having SOPs for performing investigation in case action limits are exceeded or a trend is identified in the alert limits. d) Whether appropriate corrective actions are taken after investigations	
52	4.11	Ensure that the area Grades specified in this Part shall be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g., aseptic media fills or others types of process simulations) are used to establish processing hold times and a maximum fill duration.	
53	4.11	Ensure that the determination of an appropriate process area environment and a time limit shall be based on the microbial contamination (bioburden) found.	
54	4.11	Whether firm has establish processing hold times and a maximum fill duration time based on aseptic media fills or others types of process simulations/validations	
4.11.1 Terminally sterilised product			
55	4.11.1.1.	Specify the Grade of clean room in which components and products are prepared (Note components and products shall be prepared least a Grade D zone to ensure low microbial bio burden and particulate counts prior to filtration and sterilization) Specify where the product is at unusual risk of microbial contamination (e.g., because it actively supports microbial growth, must be held for a long period before sterilization, or is necessarily processed mainly in open vessels), If so the preparation shall generally be done in a Grade C zone.	
56	4.11.1.2.	Specify the Grade of clean room in which filling of products for terminal sterilisation is done Ensure that it is done in at least a Grade C environment.	
57	4.11.1.3	Where the product is at unusual risk of contamination from the environment (e.g., because the filling operation is slow, the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling shall be done in a Grade A zone with at least a Grade C background.	
58	4.11.1.4.	Ensure that preparation and filling of ointments, creams, suspensions and emulsions is done in a Grade C zone before terminal sterilization.	
4.11.2 Aseptic preparation :			
59	4.11.2.1	Ensure whether Components after are handled in at least Grade D zone	

60	4.11.2.1	Ensure whether handling of sterile starting materials and components is undertaken in a Grade A zone with Grade B background (unless subjected to sterilisation or filtration through a microorganism-retaining filter later in the process)	
61	4.11.2.2.	a) Ensure whether preparation of solutions which are to be sterile-filtered during the process is undertaken in Grade C zone (if closed system is used, then use of Grade D zone is acceptable). b) Ensure whether the preparation of materials and products (If not sterile-filtered therefore an aseptic manipulation) is undertaken in Grade A zone with Grade B background.	
62	4.11.2.3	Ensure whether handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, is undertaken in Grade A zone with Grade B background.	
63	4.11.2.4.	Ensure whether transfer of partially closed containers (as used in freeze-drying, before stoppering is completed) is undertaken either in Grade A zone with Grade B background or in sealed transfer trays in Grade B zone.	
64	4.11.2.5.	Ensure whether preparation and filling of sterile ointments, creams, suspensions and emulsions shall be undertaken in Grade A zone with Grade B background in condition when the product is exposed and is not subsequently filtered.	
5. Processing :			
65	5.1.	Whether necessary precautions are taken to minimise contamination during all processing stages, including the stages before sterilization	
66	5.2.	a) Ensure that preparations containing live micro-organisms are not made in areas used for the processing of other pharmaceutical products. b) Ensure that area used for filling of containers of live micro-organisms is not used for filling other pharmaceutical products. (However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live micro-organisms, the use of multi-product facilities may be justifiable)	
67	5.3.	Ensure whether validation of aseptic processing is done using a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium shall be based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium	
68	5.4.	Ensure whether the process simulation test imitates as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.	
69	5.5.	Whether the Process simulation are performed by running three consecutive satisfactory simulation tests.	
70	5.5.	Whether the process simulation are repeated at defined intervals and after any significant modification to the HVAC system, equipment or process.	
71	5.5.	Whether all activities and interventions known to occur during normal production as well as in the worst-case situations are incorporated in Process simulation tests	

72	5.5.	Whether the process simulation tests are representative of each shift and shift changeover to address any time-related and operational features.	
73	5.6.	Whether number of containers used for media fills are sufficient to enable a valid evaluation. For small batches the number of containers for media fills shall at least equal to the size of the product batch. Whether acceptance criteria is meeting as per Para 5.6. of Part II of schedule M	
74	5.6.	Whether acceptance criteria for process simulation is meeting as mentioned below The target shall be zero growth and the following shall apply: (a) when filling fewer than 5000 units, no contaminated units shall be detected; (b) when filling 5000–10000 units (i) one contaminated unit shall result in an investigation, including consideration of a repeat media fill; (ii) two contaminated units are considered cause for revalidation following investigation; c) when filling more than 10000 units – (i) One contaminated unit shall result in an investigation; (ii) Two contaminated units are considered cause for revalidation following investigation.	
75	5.7.	Whether intermittent incidents of microbial contamination in media fill run that may be indicative of low-level contamination are investigated. Whether Investigation of gross failures includes the potential impact on the sterility assurance of batches manufactured since the last successful media fill.	
76	5.8	Ensure that care shall be taken to ensure that any validation does not compromise the processes	
77	5.9.	Whether water sources, water-treatment equipment and treated water are monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use Whether records of the results monitoring and of any action taken is maintained	
78	5.1	Ensure that Activities in clean areas, especially when aseptic operations are in progress, shall be kept to a minimum and the movement of personnel shall be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity. As far as possible, personnel shall be excluded from Grade A zones	
79	5.10.	Ensure that ambient temperature and humidity is not uncomfortably high because of the nature of the garments worn and to reduce the risk of contamination liberated from the personnel.	
80	5.11.	Ensure that presence of containers and materials liable to generate fibers is minimized in clean areas and avoided completely when aseptic work is in progress.	

81	5.12	Whether components, bulk-product containers and equipment are handled after the final cleaning process in such a way so as to ensure that they are not re-contaminated.	
82	5.12	Whether the stage of processing of components as well as the bulk-product containers and equipment is properly identified.	
83	5.13.	Ensure whether the interval between the washing and drying and the sterilisation of components, bulk-product containers and equipment, as well as between sterilisation is short as possible and subject to a time limit appropriate to the validated storage conditions.	
84	5.14.	Ensure whether the time between the start of the preparation of a solution and its sterilisation or filtration through a bacteria-retaining filter is as short as possible and whether maximum permissible time is set for each product that takes into account its composition and the prescribed method of storage.	
85	5.15.	Ensure whether gases used to purge a solution or blanket a product are passed through a sterilising filter.	
86	5.16.	Whether bio burden of each batch of aseptically filled products and terminally sterilised products is monitored before sterilisation. Whether working limits for bio burden before sterilisation are defined.	
87	5.16.	Whether bio burden monitored at suitable scheduled intervals where overkill sterilisation parameters are set for terminally sterilised products.	
88	5.16.	For parametric release systems, whether bio burden is performed on each batch and considered as an in-process test.	
89	5.17.	Whether components, bulk-product containers, equipment and any other articles required in a clean area where aseptic work is in progress are sterilised and wherever possible passed into the area through double ended sterilisers sealed into the wall. (Other procedures that prevent the introduction of contamination may be acceptable in some circumstances).	
90	5.18.	Ensure whether the efficacy of any new processing procedure is validated and the validation is repeated at regular intervals thereafter or when any significant change is made in the process or equipment.	
6. Sterilisation :			
91	6.3.	Whether bio burden of starting materials is monitored before sterilisation. Whether specifications includes requirements for microbiological quality when the need for this has been indicated by monitoring.	
92	6.4.	Whether sterilisation processes are validated. (Particular attention shall be paid when the adopted sterilisation method is used for a preparation that is not a simple aqueous or oily solution, for example, colloidal suspensions).	

93	6.5.	Whether suitability of sterilization process for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed is demonstrated by physical measurements and by biological indicators, where appropriate	
94	6.5.	Whether validity of the **validated sterilization process** is verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records shall be kept of the results	
95	6.7.	a) Whether biological indicators are stored and used according to the manufacturer's instructions and their quality checked by positive controls. b) Whether strict precautions are taken to avoid any transfer of microbial contamination from them.	
96	6.8.	Whether clear means are implemented for differentiating products that have not been sterilized from those which are not sterilized.	
97	6.8.	Whether each basket, tray, or other carrier of products or components is clearly labeled with the name of the material, its batch number and an indication of whether or not it has been sterilized.	
98	6.8	Whether Indicators such as autoclave tape are used where appropriate to indicate whether or not a batch (or sub-batch) has passed through a sterilization process.	
99	6.9.	Whether validated loading patterns are established for all sterilization processes.	
100	6.10.	Whether sterilization records for each sterilization run is available and they are approved as part of the batch-release procedure	
6.11.1 Terminal Sterilization :			
Heat Sterilization			
101	6.11.1.1.	Whether each heat-sterilization cycle is recorded by means of appropriate equipment of suitable accuracy and precision, e.g., on a time or temperature chart with a suitably large scale. a) Whether temperature is recorded by a probe situated at the coolest part of the load or loaded chamber, this point having been determined during the validation; b) Whether temperature is checked against a second independent temperature probe located at the same position. c) Whether Sterilization records are available for each sterilization run and are approved as part of the batch release procedure. d) Ensure that Chemical or biological indicators are used but shall not take the place of physical controls	
102	6.11.1.2.	Whether sufficient time is allowed for the whole of the load to reach the required temperature before measurement of the sterilising time is started. Whether This is determined for each type of load to be processed.	

103	6.11.1.3.	Whether precautions are taken to avoid contamination of a sterilised load during cooling after the high-temperature phase of a heat sterilisation cycle,	
104	6.11.1.3.	Whether cooling fluid or gases coming in contact with the product are sterilised.	
105	6.11.1.4.	a) Ensure that Both temperature and pressure is used to monitor the process. b) Whether control instrumentation is independent of monitoring instrumentation and recording charts. c) Where automated control and monitoring systems are used for these applications whether they are validated to ensure that critical process requirements are met d) Whether System and cycle faults are registered by the system and observed by the operator. e) Ensure whether reading of the independent temperature indicator is routinely checked against the reading on the chart recorder during the sterilisation period. f) For sterilisers fitted with a drain at the bottom of the chamber, whether temperature at this position is recorded throughout the sterilisation period. g) Whether regular leak tests are conducted on the chamber when a vacuum phase is part of the cycle.	
106	6.11.1.5.	Whether the items to be sterilised, other than products in sealed containers, are wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilisation. (Specially designed autoclavable stainless steel containers, that allow steam to enter and air to leave, can also be used)	
107	6.11.1.5.	How firm ensured that all parts of the load is contact with water or saturated steam at the required temperature for the required time.	
108	6.11.1.6.	Whether steam used for sterilisation is tested regularly for suitable quality chemical, microbiological and endotoxin analysis of condensate and physical examination of steam (such as dryness, superheat and non-condensable gases) and does not contain additives at a level that could cause contamination of the product or equipment.	
109	6.11.1.7.	a) Ensure whether air supplied for sterilisation by dry heat cycle is passed through a microorganism-retaining filter (e.g., a HEPA filter). b) Ensure whether challenge tests using endotoxins are conducted as part of the validation. Where such sterilization by dry heat is intended to remove pyrogens	
Sterilization by radiation :			
110	6.11.1.8.	Whether the absence of deleterious effects on the product has been confirmed experimentally for use of sterilisation by radiation.	

111	6.11.1 .8.	Ensure that ultraviolet irradiation is not used for terminal sterilisation as is not an acceptable method for terminal sterilisation.	
112	6.11.1 .9.	If sterilisation by radiation is done by an outside contractor, Whether manufacturer has ensured that the requirements of paragraph 6.8 are met and that the sterilisation process is validated	
113	6.11.1 .10.	a) Whether the radiation dose is measured during the sterilisation procedure b) The dosimeters used for this purpose is independent of the dose rate and provides a quantitative measurement of the dose received by the product itself. c) Whether dosimeters are inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber. d) Where plastic dosimeters are used ensure whether they are used within the time-limit of their calibration e) Whether Dosimeter is read/recorded shortly after exposure to radiation f) Whether radiation-sensitive colour discs are used to differentiate between packages that have been subjected to irradiation and those that have not subjected to irradiation g) Whether information above obtained about radiation constitute the part of the batch record.	
114	6.11.1 .11.	Whether Validation procedures ensures that consideration is given to the effects of variations in the density of the packages	
115	6.11.1 .12.	Whether material-handling procedures are in place to prevent any mix-up of irradiated and non-irradiated materials.	
116	6.11.1 .12.	Whether each package carries a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment	
117	6.11.1 .13.	Whether total radiation dose is administered within a predetermined period	
118	6.11.1 .14.	Ensure that sterilisation by gases and fumigant is used for finished products only where there is no suitable alternative.	
119	6.11.1 .15.	a) Whether firm has demonstrated during process validation, that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned. b) Ensure whether these limits are incorporated in the specifications	
120	6.11.1 .16	Ensure that Direct contact between gas and microorganisms is essential; precautions shall, therefore, be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.	

121	6.11.1 .17.	Whether firm has defined humidity and temperature required for the sterilisation process before exposure to the gas.	
122	6.11.1 .18.	Whether each sterilisation cycle shall be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. Whether the information thus obtained forms part of the batch record	
123	6.11.1 .19.	Whether biological indicators are stored and used according to the manufacturer's instructions and their performance checked by positive controls.	
124	6.11.1 .20.	a) Whether for each sterilization cycle, records made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration is maintained b) Whether the pressure and temperature are recorded on a chart throughout the cycle. c) Whether the records forms part of the batch record	
125	6.11.1 .21	a) Whether after sterilisation, the load is stored in a controlled manner in ventilated conditions to allow concentration of residual gas and reaction products to fall to their prescribed levels. b) Whether this process is validated	
6.11.2. Aseptic processing and sterilisation by filtration:-			
126	6.11.2 .2.	Whether operating conditions are maintained to prevent microbial contamination.	
127	6.11.2 .3	Whether careful attention is given to the following in order to maintain the sterility of the components and the product during aseptic processing:- (a) the environment; (b) personnel; (c) critical surfaces; (d) container or closure sterilisation and transfer procedures; (e) the maximum holding period of the product before filling into the final container; and (f) the sterilising filter.	
128	6.11.2 .5.	a) Whether firm is having practice of performing a double-filter layer or second filtration through a further sterilised microorganism-retaining filter immediately prior to filling. b) Ensure that the final sterile filtration is carried out as close as possible to the filling point. (Note Owing to the potential additional risks of the filtration method as compared with other sterilisation processes, a double-filter layer or second filtration through a further sterilised microorganism-retaining filter immediately prior to **filling may be advisable.)**	
129	6.11.2 .6	Ensure that the fiber-shedding characteristics of filters are minimal (virtually zero). (Asbestos-containing filters shall not be used under any circumstances).	

130	6.11.2.7	Whether integrity of the sterilised filter is verified before use and is confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test.	
131	6.11.2.7.	Whether the time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter is determined during validation and any significant difference from these during routine manufacturing are noted and investigated.	
132	6.11.2.7.	Whether results of integrity test of filter are included in the batch record.	
133	6.11.2.7.	Whether, integrity of critical gas and air vent filters is confirmed after use. Whether firm is having SOPs for , integrity test of these filters and whether frequency for integrity test is defined	
134	6.11.2.7	Whether integrity of other filters is confirmed at appropriate intervals	
135	6.11.2.8.	Ensure that same filter is not used for more than one working day unless such use has been validated.	
136	6.11.2.9.	Ensure that the filters used do not affect the product either by removing ingredients from it or by releasing substances into it.	
6.11.3. Isolator technology			
137	6.11.3.2.	Whether sufficient controls/procedures are in place for transfer of materials into and out of the isolators to avoid contamination.	
138	6.11.3.3.	Whether background air environment/ classification of isolators is designed and controlled considering the design of the isolator and its application.	
139	6.11.3.3.	Whether background air environment/ classification of isolators used for aseptic processing it marinated at least as Grade D.	
140	6.11.3.4.	Whether Isolators are introduced only after appropriate validation. Whether all critical factors of isolator technology, for example, the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity are into account while validation	
141	6.11.3.5.	Whether monitoring of Isolators is done routinely and Whether frequent leak testing of the isolator and the glove or sleeve system is defined.	
6.11.4. Blow, Fill-Seal technology :			
142	6.11.4.1.	a) Ensure whether Blow, Fill-Seal equipment used for aseptic production is fitted with an effective Grade A air shower and is installed in at least a Grade C zone, provided that Grade A or B clothing is used. b) Ensure whether environment comply with the viable and non-viable limits at rest and the viable limit only when in operation. c) Ensure whether Blow, Fill Seal equipment used for the production of terminally sterilised is installed in at least a Grade D zone.	

143	6.11.4 .2.	Whether firm has assured followings for Blow, Fill-Seal technology (a) equipment design and qualification; (b) validation and reproducibility of cleaning-in-place and sterilisation-in-place; (c) background clean room environment in which the equipment is located; (d) operator training and clothing; and (e) Interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.	
7. Personnel :			
144	7.1.	How firm ensures that minimum number of personnel required are present in clean areas; particularly important during aseptic processes.	
145	7.2.	Whether all personnel's (including those concerned with cleaning and maintenance) employed in such areas have received initial and regular training in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology.	
146	7.2.	What precautions are taken if outside staff who have not received such training (e.g., building or maintenance contractors) need to be brought in, Whether instruction are given to them and Whether they are supervised	
147	7.3.	Ensure that staff that have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process is not entering in sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.	
148	7.4.	Whether high standards of personal hygiene and cleanliness are followed in the manufacture of sterile preparations	
149	7.4.	Whether personnel's involved in the manufacture of sterile preparations are instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; and Whether periodic health checks for such conditions are desirable	
150	7.5.	Whether changing and washing is done following a written procedure designed to minimize the contamination of clean-area clothing or the carry-through of contaminants to clean areas	
151	7.5.	Whether the clothing and its quality is appropriate for the process and the grade of the working area. clothing Whether clothing is worn in such a way so as to protect the product from contamination.	
152	7.6.	Ensure that Outdoor clothing is not brought into changing rooms leading to Grade B and C rooms.	

153	7.6.	Whether clean sterile (sterilised or adequately sanitized) protective garments are provided at each work session for every worker in a Grade A or B area,	
154	7.6.	Whether gloves are regularly disinfected during operations.	
155	7.6.	Whether the masks and gloves are changed at least every working session.	
156	7.6.	Whether operators working in Grade A and B zone are wearing sanitised goggles	
157	7.7.	Ensure that wrist-watches, cosmetics and jewellery are not worn in clean areas.	
158	7.8.	Ensure whether clothing required for each grade is as follows: **(i) Grade D:** The hair and, where relevant, beard and moustache shall be covered. Protective clothing and appropriate shoes or overshoes shall be worn. Appropriate measures shall be taken to avoid any contamination from outside the clean area. **(ii) Grade C:** The hair and, where relevant, beard and moustache shall be covered. A one-piece jumpsuit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes shall be worn. The clothing shall shed virtually no fibers or particulate matter. **(iii) Grades A and B:** Entry of personnel into Grade A zone shall be minimized. Headgear shall totally enclose the hair and, where relevant, beard and moustache. A one-piece jumpsuit, gathered at the wrists and with a high neck, shall be worn. The headgear shall be tucked into the neck of the suit. A facemask shall be worn to prevent the shedding of droplets. Sterilized, non-powdered gloves of appropriate material and sterilized or disinfected footwear shall be worn. Trouser bottoms shall be tucked inside the footwear and garment sleeves into the gloves. The protective clothing shall shed virtually no fibers or particulate matter and shall retain particles shed by the body.	
159	7.9.	a) Whether clothing used in clean areas is laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. b) Whether separate laundry facilities for such clothing (Separate laundry facilities for such clothing are desirable) c) Washing and sterilisation operations are done following standard operating procedures.	
8. Premises:			
160	8.1.	Whether all premises is designed (as far as possible) to avoid the unnecessary entry of supervisory or control personnel. Whether Grade A and B zone are designed so that all operations can be observed from outside.	
161	8.2.	Whether all exposed surfaces in clean areas are be smooth, impervious and unbroken to minimise the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.	

162	8.3.	a) Ensure that there are no unclean able recesses and a minimum of projecting ledges, shelves, cupboards and equipment are there reduce the accumulation of dust and to facilitate cleaning,. b) Doors shall be carefully designed to avoid unclean able recesses (Sliding doors may be undesirable for this reason). c) Ensure whether swing doors opens to the high pressure side and be provided with self-closers	
163	8.4.	Whether the False ceilings is sealed to prevent contamination from the void space above them.	
164	8.5.	Whether the Pipes and ducts and other utilities are installed in a way that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Whether Sanitary pipes and fittings are used (threaded pipe connections shall be avoided)	
165	8.6.	a) Whether sinks and drains are avoided wherever possible? b) Whether Sinks and drains are excluded from Grade A and B zone where aseptic operations are carried out and shall be avoided wherever possible. c) Where installed, whether they are designed, located and maintained so as to minimise the risks of microbial contamination; they shall be fitted with effective, easily cleanable traps and with air breaks to prevent backflow. d) Whether floor channels are open and easily cleanable and are connected to drains outside the area in a manner that prevents the ingress of microbial contaminants.	
166	8.7.	Whether changing rooms are designed as airlocks and used to provide physical separation of the different stages of changing to minimise microbial and particulate contamination of protective clothing.	
167	8.7.	Whether changing rooms are flushed effectively with filtered air.	
168	8.7.	Whether the final stage of the changing room, in the at rest state, is the same Grade as the zone into which it leads. (The use of separate changing rooms for entering and leaving clean areas is sometimes desirable)	
169	8.7.	Whether hand washing facilities are provided only in the first stage of the changing rooms. (In general hand washing facilities shall be provided only in the first stage of the changing rooms.	
170	8.7.	Ensure that there shall not be a change of more than one Grade between airlocks or passages and changing rooms, i.e., a Grade D passage can lead to a Grade C airlock, which leads to a Grade B changing room, which leads to a Grade B clean room.	
171	8.7.	Whether Changing rooms are of a sufficient size to allow for ease of changing.	
172	8.7.	Whether Changing rooms are equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room	

173	8.8.	Ensure that Airlock doors are not opened simultaneously. Whether interlocking system and a visual or audible or both warning system are operated to prevent the opening of more than one door at a time.	
174	8.9.	a) Whether filtered air supply is used to maintain a positive pressure and the airflow relative to surrounding areas of a lower Grade under all operational conditions; it shall flush the area effectively. b)Whether adjacent rooms of different Grades have a pressure differential of approximately 10 to 15 Pascal (guidance value). (The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products.)	
175	8.9.	Whether the decontamination of the facilities and the treatment of air leaving a clean area is done as necessary for some operations	
176	8.10.	Whether firm has demonstrated that airflow patterns do not present a contamination risk; Whether, care is taken to ensure that particles from a particle generating person, operation or machine are not conveyed to a zone of higher product risk.	
177	8.11.	Whether a warning system is operated to indicate failure in the air supply.	
178	8.11.	Whether Indicators of pressure differentials are fitted between areas where this difference is important, and whether the pressure differentials are regularly recorded and failure alarmed.	
179	8.12.	Whether consideration is given to restricting unnecessary access to critical filling areas e.g., Grade A filling zones, by means of a physical barrier.	
9. Equipment:			
180	9.1	Ensure that a conveyor belt is not passing through a partition between a Grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilised (e.g., in a sterilising tunnel).	
181	9.2.	Whether equipment used for processing sterile products are chosen so that it can be effectively sterilised by steam or dry heat or other methods, whenever possible,	
182	9.3.	Whether equipment fittings and services are designed and installed (as far as possible) so that operations, maintenance and repairs can be carried out outside the clean area.	
183	9.3.	Whether equipment that has to be taken apart for maintenance are re-sterilised after complete reassembly, wherever possible.	
184	9.4	Ensure that when equipment maintenance is carried out within a clean area, clean instruments and tools are used and the area is cleaned and disinfected again, where appropriate, before processing recommences,	

185	9.5	Whether all equipment such as sterilisers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems are subjected to validation and planned maintenance; Whether their return to use is approved	
9.6. Water-treatment plants and distribution systems			
186	9.6.	Whether water-treatment plants and distribution systems are designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality	
187	9.6.	Ensure that water-treatment plants and distribution systems are not operated beyond their designed capacity.	
188	9.6.	Whether consideration is given to include a testing programme in the maintenance of a water system.	
189	9.6.	Whether water for injection is produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g., by constant circulation at a temperature above 70 °C or not more than 4 °C	
10. Finishing of sterile products:-			
190	10.1.	Whether containers are closed by appropriately validated methods.	
191	10.1.	a) Whether containers closed by fusion, e.g., glass or plastic ampoules, are subjected to 100 percent integrity testing. b) Whether samples of other containers are checked for integrity according to appropriate procedures	
192	10.2.	Whether crimping of the cap is, performed as soon as possible after stopper insertion.	
193	10.3.	Ensure whether the equipment (used for crimping) is located at a separate station equipped with adequate air extraction. (the equipment used to crimp vial caps can generate large quantities of non-viable particulates)	
194	10.4.	a) Whether Vial capping is undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. b) Where latter approach is adopted, ensure that vials are protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials are e protected with a Grade A air supply until the cap has been crimped.	
195	10.5.	a) Ensure whether vials with missing or displaced stoppers are rejected prior to capping b) Ensure whether appropriate technology is be used to prevent direct contact with the vials and to minimise microbial contamination, where human intervention is required at the capping station,.	
196	10.7.	Whether containers sealed under vacuum are tested for maintenance of that vacuum after an appropriate, predetermined period.	

197	10.8.	Whether filled containers of parenteral products are inspected individually for extraneous contamination or other defects.	
198	10.8.	When inspection is carried out visually, Whether is done under suitable and controlled conditions of illumination and background.	
199	10.8.	Whether operators doing the inspection have passed regular eyesight checks, using personal corrective lenses (e.g., spectacles or contact lenses) as required,	
200	10.8.	Whether operators doing the inspection are allowed frequent breaks from inspection	
201	10.8.	Ensure that where other methods of inspection are used, the process are validated	
202	10.8.	Whether the performance of the equipment (used for inspection) is checked at intervals. And Whether results are recorded.	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART III OF SCHEDULE M GMP INSPECTION OF FOR MANUFACTURING OF PHARMACEUTICAL PRODUCTS CONTAINING HAZARDOUS SUBSTANCES SUCH AS SEX HORMONES, STEROIDS (ANABOLIC, ANDROGENIC) OR CYTOTOXIC SUBSTANCES AS PER PART- PART III OF SCHEDULE-M

Note.- Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part I Schedule shall be complied with, mutatis mutandis, for the manufacture of hazardous substances such as certain sex hormones, steroids (anabolic, androgenic) or cytotoxic substances. In addition to these requirements,

Sr.No.	Sch M Reference	Particulars	Observation
1.0 Introduction:-			
1	1.2.	Whether the production of products containing hazardous substances (Sex Hormones, Steroids (Anabolic, Androgenic) Or Cytotoxic Substances) is conducted in separate, dedicated, self-contained facilities. (These self-contained facilities may be in the same building as another facility but shall be separated by a physical barrier and have e.g., separate entrances, staff facilities and air handling systems). Whether the extent of the separation from adjacent facilities and sharing of common services is determined by risk assessment.	
2	1.4.	Whether the firm has provided following control measures for effective operation of a facility.	
		(a) Appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and product protection;	
		(b) Manufacturing process controls including adherence to SOPs;	
		(c) Appropriately designed Environmental Controls Systems (ECS) or HVAC; (d) extraction systems;	
		(e) Personal Protective Equipment (PPE);	
		(f) Appropriate de-gowning and decontamination procedures;	
		(g) Industrial hygiene (monitoring staff exposure levels);	
		(h) Medical surveillance (monitoring staff exposure levels); and	
		(i) Administrative controls.	
2. Risk assessment:-			
3	2.1.	a) Whether risk assessments is carried out to determine the potential hazards of all products to operators and to the environment.	
		b) Whether risk assessments covers phases of the product production and control cycles, from manufacture of the API to distribution of the finished product,.	

		c) Whether risk assessments applicable to the environment includes airborne contamination as well as liquid effluent contamination.	
	2.2.	Whether the design and operation of the facility is done considering the risk assessment determining that the products or materials being handled pose a risk to the operators or to the public or to the environment,	
	2.4.	Whether the risk assessment has take into account occupational health and safety requirements for OELs in the work environment	
4. Personal Protection Equipment and breathing air systems:-			
4	4.1.	Whether the fundamental design principle for a facility and its production equipment is to provide product containment and operator protection.	
5	4.1.	Whether , operator protection are provided, in case of the facility and equipment design is not providing adequate product containment,	
6	4.1.	Whether, PPEs are available for handling of a spillage or non-routine incident could cause a hazardous situation.	
7	4.1.	In case of the facility and equipment design is not providing adequate product containment, whether it is specified in the material safety data sheet, operators are protected from exposure with an appropriate method, such as by wearing-	
		(a) Flash-spun, high-density polyethylene fiber material suits or impervious washable protective suits. Integral hoods may be required depending on the respirator type used;	
		(b) Flash-spun, high-density polyethylene fiber material shoes, lower leg covers or cleanable boots;	
		(c) Suitable single-use, disposable gloves. Double gloves shall be worn where direct active contact with the product cannot be avoided. Gloves shall be taped or sealed on to the protective suit sleeves; and	
		(d) Respirator eye and face protection with associated breathing air systems.	
8	4.2.	Where breathing air systems are used, ensure whether these are provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility.	
	4.2.	Whether personnel are appropriately trained and assessed in the use of breathing air systems, before they enter the area.	
	4.2.	Whether the breathing air systems comprises a protective face mask, which forms an integral part of a protective suit.	
9	4.2.	Whether breathing air systems is as per any of the systems described below-	

		(a) A central air supply system which connects to the operator's facemask by means of flexible hoses and quick coupling sockets, also called an Airline Respirator (AR). The air connection shall incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply shall be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high pressure fan or an air compressor. If an air compressor is used, it shall be of the oil-free type or have suitable oil removal filters fitted;	
		(b) A Self-Contained Breathing Apparatus (SCBA) or Powered Air Purifying Respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;	
		(c) For zones with lower contamination levels, a half-mask High Efficiency Particulate Air filter (HEPA) cartridge respirator of N95-type paper filter mask may be acceptable.	
10	4.3.	Whether the selection of the respirator type is based on the relationship between the accepted OEL and the respirator certified Protection Factor (PF).	
11	4.4.	Whether the air supplies are filtered through a final filter, which is HEPA filter rated as an H13 filter according to European norms.	
12	4.4.	Ensure whether the supply of breathing air into the face masks or protective suit or both results in the interior of the mask and suit being at a positive pressure relative to the facility environment.	
13	4.5.	Whether Central breathing air supply systems have a one hundred percent back-up system in the event of the main system failing. (This could be in the form of a gas bottle system with at least five minutes supply. Change over from the normal supply to the back-up supply shall be automatic).	
14	4.5.	Whether the system have a monitoring system and send alarm signals to a permanently manned location in the following situations, namely:-	
		(i) failure of main air supply;	
		(ii) temperature out of specification (OOS);	
		(iii) humidity OOS;	
		(iv) carbon dioxide (CO2) OOS;	
		(v) carbon monoxide (CO) OOS; and	
		(vi) sulfur dioxide (SO2) OOS.	
15	4.6	Whether the breathing air is filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications of ISO standards and European norms.	

16	4.7.	a) Where air is delivered through a central system the piping, Ensure that it does not causes any contamination to be liberated into the air stream.	
		b) Ensure whether the final filters are as close as possible to the operator connection points.	
		c) Ensure whether operator hose connection to the air supply is a dedicated connection specific to the breathing air system to avoid inadvertent connection to a different gas system.	
5. Environmental protection:-			
17	5.1. & 5.3	a) Ensure that neither the product nor its residues is allowed to escape into the atmosphere or to be discharged directly to normal drainage systems. b) Whether the external atmosphere and the public in the vicinity of the facility are protected from possible harm from hazardous substances. c)Whether the effluent is treated before being discharged to a municipal drain, If liquid effluent poses a safety or contamination risk,	
18	5.4.	Whether exhaust air filtration ensures environmental protection	
6. Facility layout:-			
19	6.1.	Whether the premises is designed and constructed to prevent the ingress or egress of contaminants.	
		Whether, attention is paid to the level of containment provided by the equipment while drawing up the facility design,	
20	6.2.	Whether the link between the interior and exterior of the premises is through airlocks [Personnel Airlock (PAL), Material Airlock (MAL)], changing rooms, pass boxes, pass-through hatches, decontamination devices, etc.	
21	6.2.	Whether these entry and exit doors for materials and personnel have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.	
22	6.3.	Whether the changing rooms have an arrangement with a step-over- bench.	
23	6.3.	Whether the changing facilities on the exit side incorporates showers for the operators	
24	6.4.	Whether the premises are laid out and designed so as to facilitate the required pressure cascades and containment	
25	6.5.	Whether the premises and equipment are appropriately designed and installed to facilitate cleaning and decontamination	

26	6.6.	Whether the manufacturing site and buildings are described in sufficient detail by means of plans and written explanations to ensure that the designation and conditions of use of all the rooms are correctly shown.	
27	6.7.	Whether the flow of people and products is clearly marked on the layouts and plans.	
28	6.10.	Whether the facility is a well-sealed structure with no air leakage through ceilings, cracks or service areas	
29	6.11.	Whether the areas of the facility where exposed product presents a risk are maintained at a negative air pressure relative to adjacent area.	
7. Air-handling systems :-			
30	7.1.	Whether the HVAC systems are appropriately designed, installed and maintained to ensure protection of product, personnel and the environment.	
31	7.2. (i)	Ensure that there is no direct venting of air to the outside;	
32	7.2. (ii)	a) Whether air-conditioning or ventilation results in a negative pressure relative to the outside.	
		b) Ensure whether air pressure is such that there is no uncontrolled flow of air between the work area and the external environment;	
33	7.2. (iii)	a) Whether appropriate air pressure alarm systems are provided to warn of any pressure cascade reversal or loss of design pressure status.	
		b) Whether appropriate design, alert and action limits are in place.	
		c) Whether system redundancies are in place to respond appropriately to pressure cascade failure;	
34	7.2. (iv)	Whether the starting and stopping of the supply and exhaust air fan is synchronized so that the premises remain at a negative pressure during start-up and shut-down;	
35	7.2. (vi)	Whether visual indication of the status of room pressures is provided in each room;	
36	7.2. (vii)	Whether Air is exhausted to the outside through HEPA filters and not re-circulated except to the same area, and provided that a further HEPA filtration stage is applied to the return air.	
37	7.2.(ix)	a) Whether exhaust air or return air is filtered through a safe-change or bag- in-bag-out filter housing.	
		b) Whether the filter housing contains pre-filters and HEPA filters and whether both of which are removable with the safe bagging system.	
38	7.2. (x)	Whether changing rooms are supplied with air filtered to the same standard as that for the work area they serve;	

39	7.2. (xi)	a) Whether airlocks, pass-through hatches, etc., have supply and extract air to provide the necessary air pressure cascade and containment.	
		b) Whether the final, or containment perimeter, airlock or pass[1]through hatch bordering on an external or non-good manufacturing practices area is at a positive pressure relative to the environment, to prevent the ingress of contaminants to the facility;	
40		If the operators' garments are contaminated with dust, whether the operators leaving the containment area pass through a decontamination system e.g., air showers or a mist shower system, to assist with removing or controlling dust particles on their garments and whether operators follow this route before de-gowning to use the ablutions or canteen facilities.	
		c) Whether all garments leaving the facility for laundering are safely bagged.	
		d) Whether appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities are in place.	
41	7.3.	Whether the appropriate measures are taken to prevent airflow from the primary packing area (through the conveyor "mouse hole") to the secondary packing area, If required, (Note.- This could be overcome by having a pass-through chamber over the "mouse hole" which is maintained at a negative pressure to both primary and secondary packing. This principle can be applied to other situations where containment from two sides is required.)	
42	7.4.	Whether the HEPA filters in the supply air system are terminally mounted (where possible), to provide protection against back-flow cross-contamination in the event of failure in the supply airflow.	
43	7.5	Specify whether firm is using biosafety cabinets, isolation systems or glove boxes as a means for containment and operator protection. (Note :-In some cases consideration can be given to the use of biosafety cabinets, isolation systems or glove boxes	
44	7.6.	Whether a system description including schematic drawings detailing the filters and their specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications is available with firm.	
45	7.8	Whether Consideration is given to providing an emergency power supply, e.g., diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.	

46	7.9.	Whether the principles of airflow direction, air filtration standards, temperature, humidity and related parameters are ensured and the filtration is consistent with the zone concepts and product protection required	
8. Air-Handling Units (AHU):-			
47	8.1.	Whether the decision to use return air or re-circulated air is made on the basis of a risk assessment.	
48	8.2.	Where a full fresh-air or single-pass system is used, use of an energy recovery wheel could be considered.	
		In such condition ensure that there is no potential for air leakage between the supply air and exhaust air as it passes through the wheel and the relative pressures between supply and exhaust air systems is such that the exhaust-air system operates at a lower pressure than the supply system.	
49	8.3.	Whether the risk management principles are applied to address the potential of cross-contamination where energy wheels are used.	
50	8.4.	If return air is to be re-circulated, Whether it is passed through a safe change filtration system before being introduced back into the supply AHU. (In such the return air fan could form part of the AHU; however, the safe change filter shall be a dedicated unit)	
51	8.5	a) Whether the starting and stopping of the supply and exhaust air fans and associated system ventilation fans is synchronised such that the premises retain their design pressure and flow relationships during start[1]up and shut-down.	
		b) Whether processing stops when the fans are not running.	
		c) Ensure whether that this fan interlock sequence applies if any fan fails, to ensure that there is no airflow reversal in the system	
9. Safe change filter housings:-			
52	9.1.	Whether safe change or bag-in-bag-out filter housings are suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed.	
53	9.1.	Whether the Safe change filter bypass arrangement is provided .	
54	9.2.	a) Whether the final filters on the safe change unit are HEPA filters with at least an H13 classification according to European norms filter standards.	
		b) Whether air pre-filtration filters are provided for dusty return to prolong the life of the HEPA filters.	
		c) Ensure whether pre-filtration filters are also removable through the bag-in-bag out method.	

55	9.3.	Whether two banks of HEPA filters in series are provided to provide additional protection if the first filter fail, for exhaust systems where the discharge contaminant is considered particularly hazardous.	
56	9.4.	a) Whether all filter banks are provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters	
		b) Whether Connection to these gauges are of copper or stainless steel and not plastic tubing, which could perish causing a contamination hazard.	
		c) Whether the tube connections on the filter casing are provided with stopcocks, for safe removal or calibration of gauges.	
57	9.5	Whether monitoring of filters is done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.	
58	9.6.	Whether firm has installed computer based data monitoring systems to monitor filter condition. (Computer based data monitoring systems may be installed)	
59	9.7.	Whether the filter pressure gauges are marked with the clean filter resistance and the change-out filter resistance.	
60	9.8.	Whether firm has performed installed filter leakage tests in accordance with ISO standards and Whether access ports (downstream) are provided for performing installed filter leakage tests.	
61	9.9.	Whether the exhaust air fan on a safe change filter system are located after the filters so that the filter housing is maintained at a negative pressure (Alternatively, an independent booster fan system can be used, with appropriate shut-off dampers).	
62	9.11.	Whether exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, are passed through safe change filter housings before being exhausted to the atmosphere.	
63	9.12.	Whether all exhaust points outside the building are located as far as possible from air entry points and exit points are at a high level to minimise the possibility of re-entrainment of exhaust air.	
64	9.13	a) Where excessively dust-laden air is handled, whether a dust collector or bag house is considered with the dust collector being located in an enclosed room maintained at a negative pressure.	

		b) Whether Access control, maintenance staff, PPE and breathing air systems are provided to protect the operators during removal of dust from the collector bins.	
65	9.14.	a) Whether portable vacuum cleaners and portable dust collectors are fitted with H13 HEPA filters.	
		b) Whether these types of units are emptied and cleaned in a room which is under negative pressure relative to the environment.	
		c) Whether Personnel are provided with suitable PPE.	
66	9.15.	Whether records of the safe disposal of all contaminated filters and dust is kept.	
10. Personnel decontamination systems:-			
67	10.1.	Whether a means of preventing contaminants from leaving the facility on the garments of personnel are provided, If required, (This could be in the form of an air shower; mist shower, water shower or appropriate device).	
68	10.2.	a) Ensure whether an air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g., from the sides of the airlock) in order to dislodge dust particles. And whether Air extraction grilles (e.g., at low level) draws the air away and return it to the filtration system. b) Ensure whether air showers are used are correctly designed to effectively extract dust. whether Air filtration of the supply air and return or exhaust air complies with the same filtration standards as used in the manufacturing facility.	
69	10.3.	Whether flushing devices similar to air or mist showers are provided at material exits to assist with removing contaminants.	
70	10.4.	Whether wet mist or fog decontamination systems for operators are employed for deactivating contaminants on the operators' garments or causing contaminants to adhere to the garments so that they are not easily liberated.	
11. Effluent treatment:-			
71	11.1.	Whether liquid and solid waste effluent are handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.	
72	11.2.	Whether all effluent is disposed of in a safe manner and the means of disposal are documented.	
73	11.2.	Whether external contractors are used (if any) for effluent disposal have certification authorising them to handle and treat hazardous products.	
12. Maintenance:-			

74	12	Whether regular maintenance is carried out, to ensure that all parameters remain within specified tolerances to ensure the efficient and safe operation of a facility handling hazardous materials	
13. Qualification and validation:-			
75	13	Whether system qualification and validation are carried out.	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART IV OF SCHEDULE M MANUFACTURING OF BIOLOGICAL PRODUCTS	
A. General Information:	
Company information:	*Name of manufacturer*
Corporate address of manufacturer	*Corporate Address of the firm* *Phone No.: +91-* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Contact person, telephone number and email address:	*1) Name:* *Designation:* *Contact No.: +91-* *Email I.D:* *2) Name:* *Designation:* *Contact No.: +91-* *Email I.D:*
Constitution of firm:	*Public/Private Limited/ Partnership/others (Specify)*
Name of Directors:	*Name of directors*
Inspected site:	*Name & Address of the manufacturing site* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Manufacturing licence number and other regulatory accreditations:	1.
Product details	*Type of products manufactured or to be manufactured at premise*
Date(s) of inspection(s)	

Type and purpose of inspection:	*For example, Grant of manufacturing License, WHO-GMP inspection, initial, routine, follow-up, special*
Inspection Team:	*Name(s) and agency affiliations of lead inspector, inspector(s), accompanying experts and observers*
Number of manufacturing blocks	
Number of Technical Personnel in Manufacturing	
Number of Technical Personnel in Quality Control	
Number of Technical Personnel in Microbiology	
Number of Technical Personnel in Quality Assurance	

A. Inspection checklist:

Note:

1) Good Manufacturing Practices for pharmaceutical products: main principles as given in Part-I of Schedule-M shall be complied with, mutatis mutandis, for the manufacture of Biological Products. In addition to these requirements, the following specific requirements shall also be followed:
2) Comments should be descriptive without ambiguity and suitable reference of documents like SOPs, etc needs to be given and answer like "Yes" or "No" should be avoided.

Sr. No.	Reference	Particulars	Comments by firm/ inspection team
1.0 Principles and general considerations			
1.	1.3	Whether manufacturing procedures used by the firm includes:	
2.	a)	Growth of strains of microorganisms and eukaryotic cells;	
3.	b)	Extraction of substances from biological tissues, including human, animal and plant tissues, and fungi	
4.	c)	Recombinant DNA (rDNA) techniques;	
5.	d)	Hybridoma techniques; and	

6.	e)	Propagation of microorganisms in embryos or animals.	
7.	1.7	Whether firm has performed validation of specific and critical manufacturing steps such as virus removal or inactivation.	
2.0 Pharmaceutical quality system and quality risk management			
8.	2.1	Whether the Biological products are manufactured in accordance with the requirements of a pharmaceutical quality system (PQS) based on a life-cycle approach, Good Manufacturing Practices for Pharmaceutical Products: Main Principles which facilitates innovation and continual improvement, and also strengthens the link between pharmaceutical development and manufacturing activities.	
9.	2.2	Whether QRM principles are used to develop the control strategy across all manufacturing and control stages including materials sourcing and storage, personnel and materials flow, manufacture and packaging, quality control, quality assurance, storage and distribution activities.	
10.	2.2	Whether the PQS includes ongoing trend analysis and periodic review due to inherent variability of biological processes and starting materials and whether special attention paid to starting material controls, change control, trend analysis and deviation management in order to ensure production consistency.	
11.	2.2	Whether monitoring systems is designed so as to provide early detection of any unwanted or unanticipated factors that may affect the quality, safety and efficacy of the product.	
12.	2.2	Whether effectiveness of the control strategy in monitoring, reducing and managing risks are regularly reviewed and the systems updated as required taking into account scientific and technical progress.	
3.0 Personnel			
13.	3.1	Whether personnel responsible for production and control has an adequate background in relevant scientific disciplines such as microbiology, biology, biometry, chemistry, medicine, pharmacy,	

		pharmacology, virology, immunology, biotechnology and veterinary medicine, together with sufficient practical experience to enable them to perform their duties.	
14.	3.2	Whether health status of personnel has been taken into consideration as part of ensuring product safety.	
15.	3.2	Whether personnel engaged in production, maintenance, testing and animal care (and inspections) has been vaccinated with appropriate specific vaccines and have regular health checks.	
16.	3.2	Whether any changes in the health status of personnel which could adversely affect the quality of the product is precluded from working in the production area and appropriate records kept.	
17.	3.2	Whether scope and frequency of health monitoring is commensurate with the risk to the product and personnel.	
18.	3.3	Whether the risk of microbial and adventitious contamination and the nature of the target microorganisms and growth media routinely used is emphasized in training of cleaning and disinfection procedures, hygiene and microbiology.	
19.	3.4	Where restrictions on the movement of all personnel (including quality control, maintenance and cleaning staff) is defined on the basis of QRM principles to minimize the opportunity for cross-contamination.	
20.	3.4	Whether all personnel including those not routinely involved in the production operation (such as management, engineering staff and validation staff or auditors) are allow to pass from areas with exposure to live microorganisms, genetically modified microorganisms, animal tissue, toxins, venoms or animals to areas where other products (inactivated or sterile) or different organisms are handled. If such passage is unavoidable during a working day, then contamination control measures (for example, clearly defined decontamination measures such as a complete change of appropriate clothing and shoes, and showering if applicable) is followed by all	

		personnel visiting any such production area unless otherwise justified on the basis of QRM.	
21.	3.5	Whether personnel working in an animal facility are restricted from entering production areas where potential risks of cross-contamination exist.	
22.	3.6	Whether Staff assigned to the production of BCG products are working with other infectious agents or virulent strains of Mycobacterium tuberculosis or exposed to a known risk of tuberculosis infection.	
23.	3.6	Whether staff working in BCG are carefully monitored, with regular health checks that screen for tuberculosis infection.	
24.	3.7	Whether health checks are performed If personnel working in BCG manufacturing and in animal quarters need to be reassigned to other manufacturing units.	
4.0 Starting materials			
25.	4.1	Whether source, origin and suitability of active substances, starting materials (for example, cryo-protectants and feeder cells), buffers and media (for example, reagents, growth media, serum, enzymes, cytokines, growth factors and amino acids) and other components of the finished product are clearly defined and controlled according to the principles set out in Part-I of this Schedule-M.	
26.	4.2	Whether manufacturer is retaining information describing the source and quality of the biological materials used for at least 1 year after the expiry date of the finished products and according to regulations concerning biological products.	
27.	4.2	Whether manufacturer is retaining documents for longer periods which may provide useful information related to adverse events following immunization (AEFIs) and other investigations.	
28.	4.3	Whether all starting material suppliers (that is, manufacturers) are initially qualified on the basis of documented criteria and a risk-based approach.	

29.	4.3	Whether regular assessments of their status carried out, particularly to the identification and monitoring of any variability that may affect biological processes.	
30.	4.3	Whether there is provision of qualification of brokers, who could increase the risk of contamination by performing repackaging operations, when starting materials are sourced from them; an audit may form part of such qualification, as needed.	
31.	4.4	Whether an identity test, or equivalent, is performed on each batch of received starting materials prior to release and identification of all starting materials is in compliance with the requirements appropriate to the stage of manufacture.	
32.	4.4	Whether level of testing is commensurate with the qualification level of the supplier and the nature of the materials used. How many numbers of containers sampled in the case of starting material used to manufacture active substances and whether sampling is justified on the basis of QRM principles.	
33.	4.4	Whether each container of starting materials and intermediates used in formulation of finished products is sampled for identity testing in accordance with the main principles of GMP for pharmaceutical products unless reduced testing has been validated.	
34.	4.5	What measure are taken for sampling of incoming starting materials under appropriate conditions in order to prevent contamination and cross-contamination and to ensure that sampling process does not adversely affect the quality of the product.	
35.	4.6	Where the sampling of sterile starting materials is carried out by the manufacturer and what measures have been taken for sampling of sterile starting materials and what is criteria for release of such sterile materials.	
36.	4.7	What is the criteria for processing of starting materials before the test results are available where the necessary tests for approving starting materials take a significantly long time.	

		Whether there is justified documented procedure and records for usage of these materials.	
37.	4.8	Whether risk of contamination of starting materials during their passage along the supply chain is assessed, with particular emphasis on adventitious agents such as those causing TSEs.	
38.	4.8	Whether other materials that come into direct contact with manufacturing equipment and/or with potential product contact surfaces (such as filter media, growth media during aseptic process simulations and lubricants) is controlled.	
39.	4.8	Whether a quality risk assessment is performed to evaluate the potential for adventitious agents in biological starting materials.	
40.	4.9	Whether the sterilization of starting materials (where required) is carried out by heat, whenever possible. Where necessary, whether other appropriate validated methods may also be used for this purpose (such as irradiation and filtration).	
41.	4.10	Whether controls required for ensuring the quality of sterile starting materials and of the aseptic manufacturing process is based on the principles and guidance contained in the Part-II of Schedule-M.	
42.	4.11	Whether there is a written quality agreement between the responsible parties (if they are different commercial entities) for transport of critical materials, reference materials, active substances, human tissues and cells to the manufacturing site and transport activities are performed as per the written agreement.	
43.	4.11	Whether Manufacturing sites has documentary evidence of adherence to the specified storage and transport conditions, including cold chain requirements, if required.	
44.	4.11	Whether the required traceability starting at tissue establishments through to the recipients, and including the traceability of materials in contact with the cells or tissues is ensured, maintained and documented.	
5.0 Seed lots and cell banks			

45.	5.1	Whether recommendations set out in GMP for API is followed taking into consideration specific guidance for API manufactured by cell culture or fermentation.	
46.	5.2	Whether firm has maintained appropriate controls over sourcing, testing, transport and storage of human or animal cells when used as feeder cells in the manufacturing process.	
47.	5.3	Whether firm has system of master and working seed lots and/or cell banks in order to prevent the unwanted drift of genetic properties which might result from repeated subcultures or multiple generations, the production of biological products obtained by microbial culture, cell culture or propagation in embryos and animals.	
48.	5.4	Whether number of generations (expressed as passages or doublings) between the seed lot or cell bank and the finished product are defined as maximum and whether are consistent with the marketing authorization dossier and not to be exceeded.	
49.	5.5	Cell-based medicinal products are often generated from a cell stock obtained from a limited number of passages. In contrast with the two-tier system of MCBs and WCBs, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life-cycle of the product. Whether Cell stock changes are covered by a validation protocol and communicated to the NRA and whether are consistent with the marketing authorization dossier and not to be exceeded.	
50.	5.6	Whether establishment and handling of the MCBs and WCBs is performed under conditions which are demonstrably appropriate and include an appropriately controlled environment to protect the seed lot and the cell bank, and the personnel handling them.	
51.	5.6	Whether other living or infectious material (such as viruses, cell lines or microbial strains) are handled simultaneously in the same area or by the same	

		persons during the establishment of the seed lot and cell bank.	
52.	5.7	Whether firm has defined procedure for Quarantine and release of Master and Working cell banks/ seed lots and whether procedure is followed, including adequate characterization and testing for contaminants.	
53.	5.7	Whether full characterization testing of the MCB is done initially, including genetic identification.	
54.	5.7	Whether a new MCB (from a previous initial clone, MCB or WCB) is subjected to the same established testing as the original MCB, unless otherwise justified.	
55.	5.7	Whether viability, purity and other stability-indicating attributes of seed lots and cell banks are checked regularly according to justified criteria.	
56.	5.7	Whether evidence of the stability and recovery of the seed lots and banks is documented and records of evaluation of trend maintained.	
57.	5.8	Whether each storage container is adequately sealed, clearly labelled and kept at an appropriate temperature.	
58.	5.8	Whether a stock inventory is maintained.	
59.	5.8	Whether storage temperature is recorded continuously and, where applicable, the liquid nitrogen level is monitored.	
60.	5.8	Whether records of any deviation from the set limits, and any corrective and preventive action taken are maintained.	
61.	5.8	Whether alarm system for deviation in temperature and nitrogen levels are available and records of deviation maintained.	
62.	5.9	Whether Seed lots and cell banks are stored and used in such a way as to minimize the risks of contamination or alteration (for example, stored in qualified ultra-low temperature freezers or liquid nitrogen storage containers).	
63.	5.9	Whether control measures for the storage of different seeds and/or cells or both in the same area or	

		equipment prevent mix-up and should take into account the infectious nature of the materials in order to prevent cross-contamination.	
64.	5.10	Whether MSLs, MCBs, and preferably also WSLs and WCBs, are stored in two or more controlled separate sites in order to minimize the risk of total loss due to natural disaster, equipment malfunction or human error and whether a contingency plan is in place	
65.	5.11	Whether storage and handling conditions for the cell or seed banks are defined.	
66.	5.11	Whether access to cell or seed bank is controlled and restricted to authorized personnel, and appropriate access records maintained.	
67.	5.11	Whether records of location, identity and inventory of individual containers of cell or seed bank are kept.	
68.	5.11	Whether once containers are removed from the seed lot/cell bank management system they are not returned to stock.	
6.0 Premises and equipment			
69.	6.1	Whether preparations containing live microorganisms or live viruses are manufactured and containers are filled in areas used for the processing of other pharmaceutical products.	
70.	6.1	When multi-product facilities are used for production of biological product, whether the manufacturer can demonstrate and validate effective containment and decontamination of the live microorganisms and viruses and measures such as campaign production, closed systems and/or disposable systems are considered and based on QRM principles.	
71.	6.2	Whether documented QRM is carried out for every additional product in a biological manufacturing multi-product facility, which may include a potency and toxicological evaluation based on crosscontamination risks and other factors are taken into account include facility or equipment design and use, personnel and material flows, microbiological controls, physicochemical characteristics of the active substance, process characteristics, cleaning processes	

		and analytical capabilities relative to the relevant limits established from product evaluation.	
72.	6.2	Whether the outcome of the QRM process is the basis for determining the necessity for premises and equipment to be dedicated to a particular product or product family, and the extent to which this shall be the case. This may include dedicating specific product contact parts.	
73.	6.3	Whether adequate decontamination and cleaning measures are implemented on the basis of QRM where Inactivated vaccines, antisera and other biological products including those made by rDNA techniques, toxoids and bacterial extracts, following inactivation, manufactured on the same premises.	
74.	6.4	Whether Cleaning and sanitisation take into account the fact that processes often include the handling of growth media and other growth-promoting agents.	
75.	6.4	Whether Validation studies are carried out to ensure the effectiveness of cleaning, sanitisation and disinfection, including elimination of residues of used agents.	
76.	6.4	Whether Environmental and personnel safety precautions are taken during the cleaning and sanitisation processes.	
77.	6.4	Whether the use of cleaning and sanitising agents not pose any major risk to the performance of equipment.	
78.	6.4	Whether the use of closed systems to improve asepsis and containment considered where practicable.	
79.	6.4	Whether, where open systems are utilised during processing (for example, during addition of growth supplements, media, buffers and gases, and during sampling and aseptic manipulations during the handling of live cells such as in cell-therapy products) control measures put in place to prevent contamination, mix-up and cross-contamination.	
80.	6.4	Whether logical and unidirectional flows of personnel, materials and processes, and the use of clean-in-place and sterilise-in-place systems, are considered wherever possible.	

81.	6.4	Whether, where sterile single-use systems such as bags and connectors are utilised, they are qualified with respect to suitability, extractables, leachables and integrity.	
82.	6.5	Whether approved starting materials that have to be measured or weighed for the production process (such as growth media, solutions and buffers) are kept in small stocks in the production area for a specified period of time according to defined criteria for the duration of manufacture of the batch or of the campaign at appropriate storage condition and controls are maintained during such temporary storage due to the variability of biological products, and of the corresponding manufacturing processes. Whether these materials are returned to the general stock.	
83.	6.5	Whether Materials used to formulate buffers, growth media and so on are weighed and made into a solution in a contained area using local protection (such as a classified weighing booth) and outside the aseptic processing areas in order to minimise particulate contamination of the later.	
84.	6.6	Whether, the mix-up of entry and exit of personnel is avoided through the use of separate changing rooms or through procedural controls in manufacturing facilities where Biosafety Risk Group 3 or 4 organisms are handled.	
7.0 Containment			
85.	7.1	Whether Airborne dissemination of live microorganisms and viruses used for the production process, including those from personnel, are avoided.	
86.	7.2	Whether adequate precautions are taken to avoid contamination of the drainage system with dangerous effluents and drainage systems are designed in such a way that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination.	
87.	7.2	Whether specific and validated decontamination systems are available for effluents when infectious or potentially infectious materials are used for production.	

88.	7.2	Whether regulations issued by the Central Government are complied with in order to minimise the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.	
89.	7.3	Whether dedicated production areas used for the handling of live cells capable of persistence in the manufacturing environment, for pathogenic organisms of Biosafety Risk Group 3 or 4 or for spore-forming organisms until the inactivation process is accomplished and verified.	
90.	7.3	Whether strictly dedicated facilities are utilised for each individual product of Bacillus anthracis, Clostridium tetani and Clostridium botulinum.	
91.	7.3	Whether only one product is processed at any one time in a facility or suite of facilities where campaign manufacture of spore-forming organisms occurs.	
92.	7.3.1	Whether use of any pathogenic organism above Biosafety Risk Group 3 allowed according to the biohazard classification of the organism, the risk assessment of the biological product and its emergency demand.	
93.	7.4	Whether production of BCG related product is taken place in a dedicated area and by means of dedicated equipment and utilities (such as HVAC systems) in order to minimise the hazard of cross-contamination.	
94.	7.5	What are the specific containment requirements applied to poliomyelitis vaccine to minimise poliovirus facility associated risk and for the safe production and quality control of inactivated poliomyelitis vaccine manufactured from wild polioviruses.	
95.	7.5	Whether measures and procedures necessary for containment of poliomyelitis vaccine (i.e., for protecting the environment and ensuring the safety of the operator) not conflict with those for ensuring product quality.	
96.	7.6	Whether air-handling systems is designed, constructed and maintained to minimise the risk of cross-	

		contamination between different manufacturing areas as required.	
97.	7.6	Whether the need for dedicated air handling units or single pass systems is based on QRM principles, taking into account the biohazard classification and containment requirements of the relevant organism, and process and equipment risks.	
98.	7.6	Whether air is not recirculated to any other area in the facility and exhausted through HEPA filters that are regularly checked for performance in the case of Biosafety Risk Group 3 organisms.	
99.	7.6	Whether a dedicated non-recirculating ventilation system and HEPA filtering of exhaust air is provided when handling Biosafety Risk Group 4 organisms.	
100.	7.7	Whether the Primary containment equipment is designed and initially qualified for integrity in order to ensure that the escape of biological agents or material into the immediate working area and outside environment is prevented.	
101.	7.7	Whether in line with relevant guidelines and quality risk management principles, periodical tests are performed to ensure that the Primary containment equipment is in proper working condition.	
102.	7.8	Whether activities associated with the handling of live biological agents (such as centrifugation and blending of products which can lead to aerosol formation) is contained in such a way so as to prevent contamination of other products or the egress of live agents into the working or outside environment or both.	
103.	7.8	Whether the viability of such live biological agents and their biohazard classification is taken into consideration as part of the management of such risks.	
104.	7.8	Whether firm has procedure for handling of accidental spillages, especially of live organisms.	
105.	7.8	Whether firm has validated decontamination measures for each organism or groups of related organisms.	
106.	7.8	Whether the decontamination process is validated with one representative strain, unless the strains vary significantly in their resistance to the decontaminating	

		agents used, where different strains of a single bacteria species or very similar viruses are involved.	
107.	7.9	Whether the areas where Biosafety Risk Group 3 or 4 organisms are handled have a negative air pressure relative to the environment.	
108.	7.9	Whether air-lock doors are interlocked to prevent from being opened simultaneously in the areas where Biosafety Risk Group 3 or 4 organisms are handled.	
109.	7.9	Whether Differential pressure alarms are provided in the areas where Biosafety Risk Group 3 or 4 organisms are handled wherever required and are validated and monitored.	
110.	7.10	Whether air vent filters are hydrophobic and subject to integrity testing at intervals determined by a QRM approach.	
111.	7.11	Whether the safe changing of filters is ensured or bagin-bag-out housings is employed, where the filtration of exhaust air is necessary.	
112.	7.11	Whether once removed, filters are decontaminated and properly destroyed.	
113.	7.11	Whether In addition to HEPA filtration other inactivation technologies such as heat inactivation and steam scavenging are considered for exhaust air to ensure effective inactivation of pathogenic organisms of Biosafety Risk Group 3 or 4.	
8.0 Clean rooms:			
114.	8.1	Whether firm has developed the environmental classification requirements for biological manufacturing processes to address the specific manufacturing processes involved in the production of biological products, and particularly vaccines, the environmental monitoring of clean rooms in vaccine manufacturing facilities.	
115.	8.2	Whether environmental monitoring programme is supplemented with methods to detect the presence of the specific microorganisms used for production (for example, recombinant yeast and toxin or polysaccharide producing bacteria).	

116.	8.2	Whether environmental monitoring programme includes detection of the produced organisms and adventitious agents of production organisms, especially when campaign manufacture is applied on the basis of QRM principles.	
9.0 Production			
117.	9.1	Whether particular attention is paid to the control strategy for ensuring that effective steps are in place for preventing or minimising the occurrence of unwanted bioburden, endotoxins, viruses of animal and human origin and associated metabolites since cultivation conditions, media and reagents are designed to promote the growth of cells or microbial organisms, typically in an axenic state.	
118.	9.2	Whether QRM process is the basis for implementing the technical and organisational measures required to control the risks of contamination and cross-contamination and these could include, though are not limited to:	
119.	i).	carrying out processing and filling in segregated areas	
120.	ii).	containing material transfer by means of an airlock and appropriate type of pass box with validated transfer procedures, clothing change and effective washing and decontamination of equipment;	
121.	iii).	recirculation of only treated (HEPA filtered) air;	
122.	iv).	acquiring knowledge of the key characteristics (for example, pathogenicity, detectability, persistence and susceptibility to inactivation) of all cells, organisms and any adventitious agents within the same facility;	
123.	v).	when considering the acceptability of concurrent work in cases where production is characterised by multiple small batches from different starting materials (for example, cell-based products) taking into account factors such as the health status of donors and the risk of total loss of a product from or for specific patients during development of the cross-contamination control strategy;	

124.	vi).	preventing the risk of live organisms and spores entering non-related areas or equipment by addressing all potential routes of cross-contamination (for example, through the HVAC system) through the use of single use components and closed systems;	
125.	vii).	conducting environmental monitoring specific to the microorganism being manufactured in adjacent areas while paying attention to cross-contamination risks arising from the use of certain monitoring equipment (used for airborne particle monitoring) in areas handling live or spore forming organisms or both; and	
126.	viii).	using campaign-based production.	
127.	9.3	Whether the inoculum preparation area is designed so as to effectively control the risk of contamination, and equipped with a biosafety hood for primary containment, when applicable.	
128.	9.4	Whether growth media is sterilised in- situ by heat or in-line microbial-retentive filters, If possible.	
129.	9.4	Whether additionally, in-line microbial-retentive filters are used for the routine addition of gases, media, acids, alkalis and so on to fermenters or bioreactors.	
130.	9.5	Whether data from continuous monitoring of certain production processes (fermentation) is formed part of the batch record.	
131.	9.5	Whether special consideration are given to parameters such as temperature, pH, pO2, CO2 and the rate of feed or carbon source with respect to growth of cells where continuous culture is used.	
132.	9.6	What measures are taken (for example, in relation to facility layout, unidirectional flow and equipment) to avoid the risk of recontamination of treated products by non-treated products in cases where a viral inactivation or removal process is performed.	
133.	9.7	Whether QRM principles are applied to devise the control strategy regarding equipment and components (for example, resins, matrices and cassettes) which are	

		used for purification purposes when used in campaign manufacture and in multi-product facilities.	
134.	9.7	Whether reuse of components at different stages of processing of one product is discouraged but, if performed, whether it is validated.	
135.	9.7	Whether acceptance criteria, operating conditions, regeneration methods, lifespan and sanitisation or sterilisation methods, cleaning process, and hold time between the use of reused components is defined and validated.	
136.	9.7	Whether firm is reusing the components for different products.	
137.	9.8	Whether appropriate measures are taken including product recall where adverse donor (human or animal) health information becomes available after procurement or processing or both, and this information relates to product quality, if applicable.	
138.	9.9	Whether firm is using Antibiotics during the early stages of production to help prevent inadvertent microbial contamination or to reduce the bioburden of living tissues and cells.	
139.	9.9	Whether use of antibiotics is well justified and whether they are cleared from the manufacturing process at the stage specified in the marketing authorisation.	
140.	9.9	Whether acceptable residual levels are defined and validated.	
141.	9.9	Whether Penicillin and other betalactam antibiotics are used at any stage of the process.	
142.	9.10	Whether a procedure is in place to address equipment or accessories failure or both (air vent filter failure) which include a product impact review.	
143.	9.10	Whether the Licensing Authority is notified and the need for a batch recall is considered, if equipment or accessories failure or both (air vent filter failure) are discovered following batch release.	
10.0 Campaign production			

144.	10.1	Whether the campaign changeover procedures, including sensitive techniques used for the determination of residues, are validated and proper cleaning acceptance criteria is defined on a toxicology basis of product residues from the last campaign, as applicable.	
145.	10.1	Whether equipment assigned to continued production or to campaign production of successive batches of the same intermediate product are cleaned at appropriate validated intervals to prevent build-up and carryover of contaminants (product degradants or objectionable levels of microorganisms).	
146.	10.2	Whether firm is performing campaign production for downstream operations of certain products (for example, pertussis or diphtheria vaccines), if yes, whether it is well justified.	
147.	10.2	Whether firm is performing finishing operations (formulation and filling) in dedicated facilities or using campaigns in the same facility and whether it depend on the specific characteristics of the biological product, on the characteristics of the other products (including any non-biological products), on the filling technologies used (single use closed systems).	
148.	10.3	Whether Campaign changeover involves intensive decontamination or sterilisation (if required) and cleaning of the equipment and manufacturing area and whether decontamination or sterilisation (if required) and cleaning includes all equipment and accessories used during production, as well as the facility itself. Whether following recommendations are considered, namely: -	
149.	i).	Whether waste is removed from the manufacturing area or sent to the bio-waste system in a safe manner;	
150.	ii).	Whether materials is transferred by a validated procedure; and	
151.	iii).	Whether Quality Unit confirms area clearance by inspection, and review the campaign changeover data (including monitoring results) prior to releasing the area for the next product.	

152.	10.4	Whether the corresponding diluent for the product is filled in the same facility in line with the defined campaign production strategy for finished product.	
153.	10.5	Whether the facility layout and the design of the premises and equipment permits effective cleaning and decontamination or sterilisation (if required) based on QRM principles and validated procedures following the production campaign, when campaign-based manufacturing is considered.	
11.0 Labelling			
154.	11.1	Whether the information provided on the inner label (also called the container label) and on the outer label (on the packaging) is readable and legible and as per the content approved by the Licensing Authority.	
155.	11.3	Whether the suitability of labels for low and ultra-low storage temperatures is verified, if applicable.	
156.	11.3	Whether the label is remain properly attached to the container under different storage conditions during the shelf-life of the product.	
157.	11.3	Whether the label and its adhesive have no adverse effect on the quality of the product caused by leaching, migration or other means.	
12.0 Validation			
158.	12.2.	Whether QRM approach is used to determine the scope and extent of validation.	
159.	12.3	Whether all critical biological processes (including inoculation, multiplication, fermentation, cell disruption, inactivation, purification, virus removal, removal of toxic and harmful additives, filtration, formulation and aseptic filling) are subjected, as applicable, to process validation.	
160.	12.3	Whether manufacturing control parameters to be validated includes specific addition sequences, mixing speeds, time and temperature controls, limits of light exposure and containment.	
161.	12.4	Whether critical processes are subject to monitoring and trending with the objective of assuring consistency and detecting any unexpected variability	

		after initial process validation studies have been finalised and routine production has begun.	
162.	12.4	Whether a system or systems for detecting unplanned departures from the process as designed is in place to ensure that the process remains in a state of control.	
163.	12.4	Whether collection and evaluation of information and data on the performance of the process allow for detection of undesired process variability and determine whether action taken to prevent, anticipate or correct problems so that the process remains under control.	
164.	12.5	Whether Cleaning validation is performed in order to confirm the effectiveness of cleaning procedures designed to remove biological substances, growth media, process reagents, cleaning agents, inactivation agents and so on.	
165.	12.6	Whether critical processes for inactivation or elimination of potentially harmful microorganisms of Biosafety Risk Group 2 or above, including genetically modified ones, are subject to validation.	
166.	12.7	Whether Process revalidation is triggered by a process change as part of the change control system.	
167.	12.7	Whether process revalidation is conducted at pre-determined regular intervals according to risk considerations due to the variability of processes, products and methods.	
168.	12.7	Whether firm is performing a detailed review of all changes, trends and deviations occurring within a defined time period for example, one year, based on the regular Product Quality Review (PQR) which may indicate a need for process revalidation.	
169.	12.8	Whether the integrity and specified hold times of containers used to store intermediate products are validated unless such intermediate products are freshly prepared and used immediately.	
13.0 Quality Control			
170.	13.1	Whether special consideration is given to the nature of the materials being sampled (for example, the need to avoid contamination, ensure biocontainment or cold	

		chain requirements) in order to ensure that the testing carried out is representative as part of quality control sampling and testing procedures for biological materials and products.	
171.	13.2.1	Whether Reference samples of biological starting materials are retained under the recommended storage conditions for at least one year beyond the expiry date of the corresponding finished product.	
172.	13.2.1	Whether Reference samples of other starting materials (other than solvents, gases and water) as well as intermediates for which critical parameters cannot be tested in the final product are retained for at least two years after the release of the product if their stability allows for this storage period. Certain starting materials such as components of growth media need not necessarily be retained.	
173.	13.2.2	Whether Retention samples of a finished product are stored in their final packaging at the recommended storage conditions for at least one year after the expiry date.	
14.0 Documentation (batch processing records)			
174.	14.1	Whether the processing records of regular production batches provides a complete account of the manufacturing activities of each batch of biological product showing that it has been produced, tested and dispensed into containers in accordance with the approved procedures.	
175.	14.1	Whether a batch processing record and a summary protocol is prepared for each batch for the purpose of lot release by the Licensing Authority in the case of vaccines.	
176.	14.2	Whether manufacturing batch records are retained for at least one year after the expiry date of the batch of the biological product and is readily retrievable for inspection by the Licensing Authority.	
177.	14.3	Whether starting materials has additional documentation on source, origin, supply chain, method of manufacture and controls applied in order to ensure an appropriate level of control, including the microbiological quality, if applicable.	

15.0 Use of animals			
178.	15.1	What type of animals are used for the manufacture or quality control of biological products and what type of special considerations are provided by the firm when animal facilities are present at a manufacturing site.	
179.	15.2	Whether live animals in the production area are avoided unless otherwise justified. However, Embryonated eggs are allowed in the production area, if applicable.	
180.	15.2	Whether particular care is taken to prevent contamination of the production area (for example, appropriate disinfection procedures shall be undertaken) if the extraction of tissues or organs from animals is required.	
181.	15.3	Whether areas used for performing tests involving animals or microorganisms are well separated from premises used for the manufacturing of products and have completely separate ventilation systems and separate staff.	
182.	15.3	Whether the separation of different animal species before and during testing is considered, as the necessary animal acclimatisation process, as part of the test requirements.	
183.	15.4	Whether in addition to monitoring compliance with TSE regulations and other adventitious agents that are of concern (including those causing zoonotic diseases and diseases in source animals) is also be monitored and recorded in line with specialist advice on establishing such programmes.	
184.	15.4	Whether the instances of ill health occurring in the source or donor animals is investigated with respect to their suitability and the suitability of in-contact animals, for continued use (for example, in manufacture, as sources of starting materials and for quality control and safety testing) and whether decisions are documented.	
185.	15.5	Whether a look-back procedure is in place in relation to the decision-making process used to evaluate the continued suitability of the biological active substance	

		or finished product in which animal sourced starting materials have been used or incorporated.	
186.	15.5	Whether decision making process includes the retesting of reference samples from previous collections from the same donor animal (where applicable) to establish the last negative donation.	
187.	15.5	Whether the withdrawal period of therapeutic agents used to treat source or donor animals is documented and taken into account when considering the removal of those animals from the programme for defined periods.	
188.	15.6	Whether particular care is taken to prevent and monitor infections in source or donor animals and whether measures taken covers sourcing, facilities, husbandry, biosafety procedures, testing regimes, control of bedding and feed materials, one hundred percent fresh air supply, appropriate design of the HVAC system, water supply and appropriate temperature and humidity conditions for the species being handled and it is of special relevance to Specific Pathogen-Free (SPF) animals where pharmacopoeial monograph requirements are met.	
189.	15.6	Whether housing and health monitoring is defined for other categories of animals (for example, healthy flocks or herds).	
190.	15.7	Whether traceability is maintained in the creation of such animals from the source animals for products manufactured from transgenic animals.	
191.	15.8	Whether firm has defined, monitored and recorded key criteria for different animal species and lines which may include the age, sex, weight and health status of the animals.	
192.	15.9	Whether animals, biological agents and tests carried out are appropriately identified to prevent any risk of mix-up and to control all identified hazards.	
193.	15.10	Whether facility layout ensures a unidirectional and segregated flow of healthy animals, inoculated animals and waste decontamination areas.	

194.	15.10	Whether Personnel and visitors are following a defined flow in order to avoid cross-contamination.	
16.0 Complaints			
195.	16.1	Whether the person responsible for handling complaints and deciding on the measures to be taken to deal with them have appropriate training or experience in the specific features of the quality control of biological products.	
196.	16.2	Whether firm has defined complaint which are related to product quality complaints and adverse reactions or events.	
197.	16.3	Whether the quality related complaints are recorded in detail and the causes thoroughly investigated (e.g., by comparison with the reference samples kept from the same batch) and whether there is defined written procedures for the action to be taken.	
198.	16.4	Whether reports of any adverse reaction or event is entered in a separate register and an investigation is conducted to find out whether the adverse reaction or event is due to a quality problem and whether such reactions or events have already been reported in the literature or whether it is a new observation.	
199.	16.4	Whether complaint records are reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed products.	
200.	16.4	Whether firm has system for safety monitoring of biological products through pharmacovigilance systems dealing with specific issues relating to adverse reactions and adverse events following treatment with biological products.	
201.	16.5	Whether the licensing authority is informed of any complaints leading to a recall or restriction on supply and the records are maintained and available for inspection.	
	17.0	**Product recalls**	

202.	17.0	Whether Recall and Rapid Alert System for Drugs (including Biological and Vaccine) is in place for the product recall.	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART V OF SCHEDULE M MANUFACTURING OF RADIOPHARMACEUTICAL PRODUCTS	
General Information:	
Company information:	*Name of manufacturer*
Corporate address of manufacturer	*Corporate Address of the firm* *Phone No.: +91-* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Contact person, telephone number and email address:	*3) Name:* *Designation:* *Contact No.: +91-* *Email I.D:* *4) Name:* *Designation:* *Contact No.: +91-* *Email I.D:*
Constitution of firm:	*Public/Private Limited/ Partnership/others (Specify)*
Name of Directors:	*Name of directors*
Inspected site:	*Name & Address of the manufacturing site* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Manufacturing licence number and other regulatory accreditations:	2.
Product details	*Type of products manufactured or to be manufactured at premise*
Date(s) of inspection(s)	
Type and purpose of inspection:	*For example, Grant of manufacturing License, WHO-GMP inspection, initial, routine, follow-up, special*
Inspection Team:	*Name(s) and agency affiliations of lead inspector, inspector(s), accompanying experts and observers*
Number of manufacturing blocks	
Number of Technical Personnel in Manufacturing	
Number of Technical Personnel in Quality Control	
Number of Technical Personnel in Microbiology	
Number of Technical Personnel in Quality Assurance	

A. Inspection checklist:

Note:

1) Good Manufacturing Practices for pharmaceutical products: main principles as given in Part-I of Schedule-M shall be complied for the manufacture of Radiopharmaceuticals Products. In addition to these requirements, the following specific requirements shall also be followed:
2) Comments should be descriptive without ambiguity and suitable reference of documents like SOPs, etc needs to be given and answer like "Yes" or "No" should be avoided.

Sr.No.	Reference	Particulars	Comments by firm/ inspection team
1.0 Principles			
1.	1	Whether Radiopharmaceuticals are manufactured in accordance with the basic principles of GMP.	
2.0 Personnel:			
2.	2.1	Whether manufacturing establishment, whether a hospital radiopharmacy, centralised radio-pharmacy, nuclear centre or institution, industrial manufacturer or Positron Emission Tomography (PET) Centre and its personnel shall be under the control of a person who has a proven record of academic achievement together with a demonstrated level of practical expertise and experience in radio-pharmacy and radiation hygiene with supporting academic and technical personnel having the necessary post graduate or technical training and experience appropriate to their functions.	
3.	2.2	Whether the personnel working in radioactive, clean and aseptic areas is selected with care to ensure that they can be relied on to observe the appropriate codes of practice and are not subject to any disease or condition that can compromise the integrity of the product.	
4.	2.2	Whether health checks on personnel are requested before employment and periodically thereafter.	
5.	2.2	Whether there is defined criteria for temporary exclusion of the person from further radiation exposure if any changes in personal health status (e.g., in haematology) observed.	
6.	2.3	Whether minimum number of personnel required are present in clean and aseptic areas when work is in progress.	
7.	2.3	Whether access to clean and aseptic areas when work is in progress is restricted during the preparation of radiopharmaceuticals, kits or sterile set-ups.	
8.	2.3	Whether inspection and control procedures are conducted from outside these areas as far as possible	
9.	2.4	Whether during the working day, personnel are passing between radioactive and non-radioactive areas only if the safety rules of radiation control (health physics control) are followed.	

10.	2.5	Whether release of a batch is approved only by an authorised person or a person with academic qualifications officially registered as a suitably qualified person, and with appropriate experience in the manufacture of radiopharmaceuticals.	
11.	2.6	Whether personnel are trained in GMP, the safe handling of radioactive materials and radiation safety procedures to ensure the safe manufacture of radiopharmaceuticals and whether they are receiving periodic courses and training to keep abreast of the latest developments in their fields.	
12.	2.7	Whether training records are maintained and periodic assessments of the effectiveness of training programmes are made.	
13.	2.8	Whether all personnel engaged in production, maintenance and testing follow the relevant guidelines for handling radioactive products and monitored for possible contamination or irradiation exposure or both.	
	3.0	**Premises and equipment**	
14.	3.1	Whether buildings are located, designed, constructed, adapted and maintained to suit the operations to be carried out within them.	
15.	3.1	Whether the laboratories for the handling of radioactive materials is specially designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility.	
16.	3.1	Whether interior surfaces (walls, floors and ceilings) are smooth, impervious and free from cracks and not shedding matter and permit easy cleaning and decontamination.	
17.	3.1	Whether drains are avoided wherever possible and, unless essential, and excluded from aseptic areas.	
18.	3.2	Whether specific disposal systems is sued for radioactive effluents and these systems is effectively and carefully maintained to prevent contamination and exposure of personnel to the radioactive waste both within and outside the facility.	
19.	3.3	Whether sinks are excluded from aseptic areas.	
20.	3.3	Whether any sink installed in other clean areas is made of suitable material and regularly sanitised.	
21.	3.3	Whether adequate precautions are taken to avoid contamination of the drainage system with radioactive effluents.	
22.	3.4	Whether lighting, heating, ventilation and, if necessary, air-conditioning is designed to maintain a satisfactory temperature and relative humidity to ensure the comfort of personnel working in protective clothing.	

23.	3.4	Whether buildings are in a good state of repair and condition of the buildings is reviewed regularly and repairs carried out when and where necessary.	
24.	3.4	What precaution are taken to ensure that building repair or maintenance operations do not compromise the products.	
25.	3.4	Whether premises is provided with sufficient space for the operations to be carried out, allowing an efficient flow of work and effective communication and supervision.	
26.	3.4	Whether all buildings and rooms are clean, sanitary and free from radioactive contamination.	
27.	3.5	Whether ventilation of radiopharmaceutical production facilities meets the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity.	
28.	3.5	Whether suitable pressure and airflow patterns is maintained by appropriate isolation or enveloping methods.	
29.	3.5	Whether Air handling systems for both radioactive and non-radioactive areas are fitted with alarms so that the working personnel in the laboratory are warned of any failure of these systems.	
30.	3.6	Whether dedicated facilities and equipment are used for the manufacture of any radiopharmaceutical product derived from human blood or plasma.	
31.	3.6	Whether autoclaves used in production areas for radiopharmaceuticals is placed behind a lead shield to minimise the radiation exposure of the operators and such autoclaves are checked for contamination immediately after use to minimise the possibility of cross-contamination by radioactivity of the products in the next autoclave cycles	
32.	3.7	Whether all containers of radiopharmaceutical substances, regardless of the stage of manufacture, are identified by securely attached labels.	
33.	3.7	Whether cross-contamination is prevented by the adoption of some or all of the following measures, namely:	
34.	i).	processing and filling in segregated areas;	
35.	ii).	avoiding the manufacture of different products at the same time, unless they are effectively segregated;	
36.	iii).	containing material transfer by means of airlocks, air extraction, changing clothes and careful washing and decontamination of equipment	
37.	iv).	protecting against the risks of contamination caused by recirculation of untreated air or by accidental re-entry of extracted air;	
38.	v).	using “closed systems” of manufacture;	
39.	vi).	taking care to prevent aerosol formation; and	

40.	vii).	using sterilised containers.	
41.	3.8	Whether positive pressure areas are used to process sterile products.	
42.	3.8	Whether specifically designed areas maintained under negative pressures is used to handle any radioactivity.	
43.	3.8	Whether production of sterile radioactive products are carried out under negative pressure surrounded by a positive pressure zone ensuring that appropriate air quality requirements are met.	
44.	3.9	Whether Separate air-handling units are used for radioactive and non-radioactive areas.	
45.	3.9	Whether Air from operations involving radioactivity is exhausted through appropriate filters that are regularly checked for performance.	
46.	3.10	Pipework, valves and vent filters are properly designed to facilitate validated cleaning and decontamination.	
4.0 Production			
47.	4.1	Whether firm have SOPs for all operating procedures and are regularly reviewed and kept up to date for all manufacturing operations.	
48.	4.1	Whether all entries on batch records are initiated by the operator and independently checked by another operator or supervisor.	
49.	4.2	Whether specifications for starting materials includes details of their source, origin and (where applicable) method of manufacture and of the controls used to ensure their suitability for use.	
50.	4.2	Whether release of a finished product is conditional on satisfactory results being obtained in the tests on starting materials.	
51.	4.3	Whether validation of sterilisation methods is done and records maintained.	
52.	4.4	Whether equipment for chromatography is, in general, be dedicated to the preparation and purification of one or several products labelled with the same radionuclide to avoid radioactive cross-contamination and life span of columns is defined.	
53.	4.4	Whether care is taken in cleaning, sterilising and operating freeze-drying equipment used for the preparation of kits.	
54.	4.5	Whether a list of critical equipment is drawn up, including any equipment such as a balance, pyrogen oven, dose calibrator, sterilising filter, etc., and whether these devices is calibrated or tested at regular intervals and checked daily or before production is started and results of these tests are included in the daily production records.	

55.	4.6	Whether firm has provided specific equipment for radioactive measurements as well as radioactive reference standards.	
56.	4.6	Whether national central laboratories is contacted to calibrate the apparatus for the measurement of very short half-lives and where this is not possible, what alternative approaches, such as documented procedures, are used.	
57.	4.7	Whether freeze drying is carried out as an aseptic procedure in the case of labelling kits.	
58.	4.7	Whether an inert gas such as nitrogen, if used, which is used to fill vials, is filtered to remove possible microbial contamination.	
59.	4.8	Whether dispensing, packaging and transportation of radiopharmaceuticals is complying with the relevant provisions of the Atomic Energy Act 1962 and the rules made thereunder.	
5.0 Labelling:			
60.	5.1	Whether all products are clearly identified by labels, which remains permanently attached to the containers under all storage conditions.	
61.	5.1	Whether an area of the container is left uncovered to allow inspection of the contents.	
62.	5.1	Whether the label appears on package of final container, If the final container is not suitable for labelling.	
63.	5.2	Whether labels of radiopharmaceuticals comply with the requirements specified in Rule 96 of Drug Rules.	
64.	5.3	Whether label on the container shows:	
65.	a)	the name of the drug product or the product identification code or both;	
66.	b)	the name of the radionuclide	
67.	c)	the name of the manufacturer or the company and the person responsible for placing the drug on the market;	
68.	d)	the radioactivity per unit dose-	
69.	i).	for liquid preparations, the total radioactivity in the container, or the radioactive concentration per millilitre, at a stated date and, if necessary, hour, and the volume of liquid in the container;	
70.	ii).	for solid preparations, such as freeze-dried preparations, the total radioactivity at a stated date and, if necessary, hour;	
71.	iii).	for capsules, the radioactivity of each capsule at a stated date and, if necessary, hour, and the number of capsules in the container; and	
72.	iv).	where relevant, the international symbol for radioactivity	
73.	5.3	Whether the label on the package states:	
74.	a)	the qualitative and quantitative composition;	

75.	b)	the radioactive isotopes and the amount of radioactivity at the time of dispatch;	
76.	c)	the route of administration;	
77.	d)	the expiry date	
78.	e)	any special storage conditions; and	
79.	f)	mandatory information related to transport regulations for radioactive materials.	
80.	5.5	Whether the leaflet in the package contains the specific product information and indications for use. This information is especially important for preparation kits (cold kits), and shall include-	
81.	a)	the name of the product and a description of its use;	
82.	b)	the contents of the kit;	
83.	c)	the identification and quality requirements concerning the radio labelling materials that can be used to prepare the radiopharmaceutical, namely	
84.	i).	the directions for preparing the radiopharmaceutical, including the range of activity and the volume, together with a statement of the storage requirements for the prepared radiopharmaceutical;	
85.	ii).	a statement of the shelf-life of the prepared radio pharmaceutical;	
86.	iii).	the indications and contraindications (pregnancy, children, drug reactions, etc.) in respect of the prepared radiopharmaceutical	
87.	iv).	warnings and precautions in respect of the components and the prepared radiopharmaceutical, including radiation safety aspects;	
88.	v).	where applicable, the pharmacology and toxicology of the prepared radiopharmaceutical, including the route of elimination and the effective half-life;	
89.	vi).	the radiation dose that a patient will receive from the prepared radiopharmaceutical;	
90.	vii).	the precautions to be taken by users and patients during the preparation and administration of the product and the special precautions for the disposal of the container and any unconsumed portions;	
91.	viii).	a statement of the recommended use of the prepared radio-pharmaceutical and the recommended dosage;	
92.	ix).	a statement of the route of administration of the prepared radiopharmaceutical; and	
93.	x).	if appropriate, for particular kits (i.e., those subject to variability beyond the recommended limits), the methods and specifications needed to check radiochemical purity	
6.0 Production and distribution records			

94.	6.1	Whether the processing records of regular production batches provide a complete account of the manufacturing history of each batch of a radiopharmaceutical, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the written procedures.	
95.	6.2	Whether separate records for the receipt, storage, use and disposal of radioactive materials are maintained in accordance with the relevant provisions of the Atomic Energy Act 1962 and the rules made thereunder.	
96.	6.3	Whether firm has maintained distribution records.	
97.	6.3	What measures has been taken by the firm to prevent use rather than an actual return since the return of radioactive products is not practical.	
7.0 Quality assurance and quality control			
98.	7.1	Whether implementation of and compliance with the quality assurance of Radiopharmaceuticals is maintained by the firm as Radiopharmaceuticals are nearly always used before all quality control testing (e.g., tests for sterility, endotoxin, radionuclidic purity, etc.) has been completed.	
99.	7.2	Whether the Quality assurance or quality control or both have the following principal responsibilities, namely:	
100.	a)	the preparation of detailed instructions for each test and analysis;	
101.	b)	ensuring the adequate identification and segregation of test samples to avoid mix-ups and cross-contamination;	
102.	c)	ensuring that environmental monitoring and equipment and process validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;	
103.	d)	the release or rejection of starting materials and intermediate products	
104.	e)	the release or rejection of packaging and labelling materials;	
105.	f)	the release or rejection of each batch of finished preparation;	
106.	g)	the evaluation of the adequacy of the conditions under which the starting materials, intermediate products and finished radiopharmaceutical preparations are stored;	
107.	h)	the evaluation of the quality and stability of the finished products and, when necessary, of the starting materials and intermediate products;	
108.	i)	the establishment of expiry dates on the basis of the validity period related to specified storage conditions;	
109.	j)	the establishment and revision of the control procedures and specifications;	
110.	k)	assuming the responsibility for retaining samples of radiopharmaceutical products; and	

111.	l)	assuming the responsibility for keeping adequate records of the distribution of the radiopharmaceutical products.	
112.	7.3	Whether quality assurance and quality control duties are organised in separate groups, whenever the size of the establishment permits.	
113.	7.3	Whether Quality assurance includes the monitoring and validation of the production process.	
114.	7.4	Whether manufacturer's quality control laboratory is separated from the production area.	
115.	7.4	Whether control laboratory is designed, equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, the preparation of records and the performance of the necessary tests.	
116.	7.5	Whether firm is releasing starting materials only basis of certificates issued by the supplier of these materials without performing all qualitative and quantitative tests mentioned in the specifications for the starting materials, if yes, whether following is ensured that:	
117.	a)	there is a history of reliable production	
118.	b)	the producer or supplier is regularly audited; and	
119.	c)	at least one specific identity test is conducted by the manufacturer of the finished radiopharmaceutical	
120.	7.6	Whether samples of the intermediate and final products are retained in sufficient amounts and under appropriate storage conditions to allow repeated testing or verification of a batch control.	
121.	7.6	Whether these samples are kept for an appropriate period in accordance with the shelf-lives of the radioactive components concerned. However, this may sometimes not be applicable, e.g., for radiopharmaceuticals with a short half-life.	
122.	7.7	Whether firm has defined sampling procedures for the purposes of sampling and whether it consist of type of controls being applied, and the nature of the material being sampled (e.g., a small batch size or its radioactive content or both).	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART VI OF SCHEDULE M SPECIFIC REQUIREMENTS FOR PHYTOPHARMACEUTICALS

Sr. No	Reference	Particulars	Observations
1. General considerations: -			
1	1.1.	Whether Phytopharmaceuticals are prepared from materials of plant origin? Whether the procedures and techniques used in the manufacture and quality control of phytopharmaceuticals are different from those employed for conventional pharmaceutical products?	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART VI OF SCHEDULE M SPECIFIC REQUIREMENTS FOR PHYTOPHARMACEUTICALS

Sr. No	Reference	Particulars	Observations
2.	1.2.	To GMPs in the manufacture of Phytopharmaceuticals is an essential tool to assure their quality?	
2. Quality assurance in the manufacture of Phytopharmaceuticals: -			
3.	2.1	Whether, an appropriate quality assurance system shall be applied in the manufacture of phytopharmaceuticals ?	
3. Good manufacturing practice for Phytopharmaceuticals:			
4	3.1	The first critical step of their production where the application of GMP starts shall be clearly designated. This is of particular importance for those products which consist solely of comminuted or powdered plant materials.	
4. Sanitation and hygiene:-			
5	4.1	Whether plant materials contain microbiological contaminants?	
6.	4.2	Whether Water supply to the manufacturing unit shall be monitored to ensure consistency of quality?	
7.	4.3	To check a high standard of hygiene in the manufacturing area. Clearly marked waste bins shall be available, emptied and cleaned as needed, on daily basis	
5.Qualification and validation:-			
8	**5.1**	To check consistency of quality, efficacy and safety between batches.	
9	**5.2**	To check critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted (e.g., retrospective, prospective or concurrent) and the number of process runs.	
10.	**5.3**	Whether a formal change control system shall be established to evaluate the potential effects of any changes on the quality of the Phytopharmaceuticals, particularly content of the active ingredients?	
6. Complaints: -			
11	6.1	Whether the person responsible for handling complaints and deciding on the measures has taken appropriate training or experience in the specific features of the quality control of Phytopharmaceuticals?	
12	6.2	Whether it is a product quality complaints or adverse reactions/ events?	
13.	6.3	Whether complaint may be caused by problems such as faulty manufacture, product defects or deterioration, particular to Phytopharmaceuticals, adulteration of the plant material.	
14	6.4	Whether the adverse reaction or event is due to quality problem and whether such reactions or events have already been reported in the literature or whether it is a new observation?	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART VI OF SCHEDULE M SPECIFIC REQUIREMENTS FOR PHYTOPHARMACEUTICALS

Sr. No	Reference	Particulars	Observations
15.	6.5	Whether the licensing authority shall be kept informed of any complaints leading to a recall or restriction on supply and the records shall be made available for inspection?	
7: Product recalls			
16	7.1	Whether the products has recalled in prompt and effective manner up to the retailers level.	
8: Contract production and analysis:-			
17	**8.1**	Whether the contract partner shall have adequate premises and equipment for the production of Phytopharmaceuticals according to GMP?	
9 Self-inspection			
18	**9.1**	Whether any member of the self-inspection team shall possess a thorough knowledge of Phytopharmaceuticals.	
10 Personnel:-			
19	10.1	Whether the Personnel dealing with the production and quality control of Phytopharmaceuticals has taken adequate qualifications and training in the specific issues relevant to Phytopharmaceuticals.	
11 **Training:-**			
20.	11.1	Whether the personnel has taken adequate training in appropriate fields such as pharmaceutical technology,taxonomic botany, phytochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of Phytopharmaceuticals).	
21.	11.2	Whether Training records shall be maintained and periodic assessments of the effectiveness of training programmes shall be made.	
12 Personal hygiene:-			
22	12.1	Whether Written procedures listing the basic hygiene requirements shall be made available?	
23	12.2	Whether They has worn suitable gloves, caps, masks, work suits and shoes throughout the whole procedure from plant processing to product manufacture?	
13 Premises:-			
24.	**13.1**	**Storage areas-**	
25.	**13.1.1**	Whether the areas shall be well labeled and materials stored in such a way so as to avoid any risk of cross-contamination? Whether area shall be identified for the quarantine of all incoming plant materials?	
26.	**13.1.2**	Whether Incoming fresh plant materials stored between 2 °C and 8 °C, whereas frozen materials stored below ‑18 °C.	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART VI OF SCHEDULE M SPECIFIC REQUIREMENTS FOR PHYTOPHARMACEUTICALS

Sr. No	Reference	Particulars	Observations
27.	**13.2**	**Production areas-**	
28.	**13.2.1**	To Check cross-contamination and air-handling systems to achieve the desired differential pressure and net airflow.	
14 Equipment:-			
29.	**14.1**	Whether Vacuum or wet-cleaning methods are preferred. If wet-cleaning is done, the equipment shall be dried Immediately after cleaning to prevent the growth of microorganisms.	
15 Materials:-			
30.	**15.1**	Whether only permitted substances shall be used for fumigation and allowable limits for their residues together with specifications for the apparatus used shall be set?	
16 Reference samples and standards:-			
31.	**16.1**	Whether all reference standards shall be stored under appropriate Conditions to prevent degradation. Their expiry or revalidation date or both shall be determined and indicated.	
17. Documentation:-			
32.	**17.1**	Whether he general principles for documentation are as per Part I.	
18 Specifications:-			
33.	**18.1**	Whether, the selection of seeds, conditions of cultivation and harvesting of Phytopharmaceuticals & Their characterization are both comprehensive and relevant ?	
34.	**18.1.1.**	**Plant materials**:-	
35.	18.1.1.1	Whether source of the plant, method of cultivation, dates and conditions of harvesting, collection procedures, collection area, and brand, quantity and date of pesticide application, as per the WHO Guidelines on good agricultural and collection practices.	
36.	18.1.1.2	Whether the whole plant or only a part is used?	
37.	**18.1.2**	Whether a reference sample shall be available for identification purposes?	
38.	**18.1.3**	Whether limit test such as dry residue of liquids, ash value water-soluble extractives, moisture or water content and loss on drying has conducted	
39.	**18.1.4**	Whether Tests for toxic metals and for likely contaminants, foreign materials and adulterants has conducted	
40.	**18.1.5**	Is Tests for fungal, microbiological contamination, fumigant residues, mycotoxins, pest-infestations, radioactivity are found in acceptable limits?	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART VI OF SCHEDULE M SPECIFIC REQUIREMENTS FOR PHYTOPHARMACEUTICALS

Sr. No	Reference	Particulars	Observations
41.	**18.1.6**	If the plant material for processing does not comply with its quality specifications, the norms that apply for its rejection and to storage and disposal of the rejected plant material, has included?	
19 Finished phytopharmaceuticals:-			
42.	19.1	Whether Tests for microbiological contamination and tests for other toxicants have conducted?	
43.	19.2	Whether uniformity of weight disintegration time, hardness and friability example, uncoated tablets, viscosity, consistency and dissolution (tablets or capsules) has conducted.	
44.	19.3	Whether other specifications as per the general monograph under the Indian Pharmacopeia for the applicable dosage forms has complied	
45.	**20**	**Processing instructions**	
46.	20.1	Whether The drying conditions chosen shall be appropriate to the type of plant material processed?	
47.	20.2	Whether Steps in the processes of blending and adjustment to reach defined contents of pharmacologically active constituents has clearly documented.	
21 Good practices in production:-			
48	21.1	Whether steps in their production are clearly defined for quality, safety and efficacy of complex products of biological origin such as Phytopharmaceuticals?	
49.	21.2	Whether collection or cultivation or harvesting of medicinal plants has follow other relevant guidance;	
50.	21.3	Whether phytopharmaceutical extracts are used and the principles of parameters under this Part shall apply to any production step following postharvest processing.	
22. Mixing of batches and blending-			
51	22.1	Whether the blending process shall be adequately controlled and documented and the blended batch has tested for conformity with established specifications where appropriate?	
52	22.2	Whether every batch incorporated into the blend have been manufactured using an established process and have been individually tested and found to meet with the appropriate specifications prior to blending	
53	22.3	Whether Validation has included testing of critical attributes (e.g., particle size distribution, bulk density and tap density) that may be affected by the blending process.	
23 Good practices in quality control:-			
54	**23.1**	**Stability studies-**	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART VI OF SCHEDULE M SPECIFIC REQUIREMENTS FOR PHYTOPHARMACEUTICALS

Sr. No	Reference	Particulars	Observations
55	23.1.1	Whether Stability data is support the shelf-life proposed for the finished products (guidance document reference)	
56	23.1.2.	Whether the shelf-life of finished products has determine, as per paragraph 18 (Specifications), i.e., moisture content, microbial contamination and general dosage form control tests.	
57	23.1.3.	Whether the stability of preservatives and stabilisers shall be monitored.	
58	23.1.4	Whether the first three commercial production batches shall be included in the stability monitoring programme to confirm the expiry date. .	
59	**23.2**	**Packaging materials and labeling-**	
60.	23.2.1	Whether all packaging materials, such as bottles and other materials shall be stored properly?	
61.	23.2.2.	Whether adequate information on the label (or the package insert) has mentioned?	
62.	23.2.3.	Whether the quantity of the plant material or phytopharmaceutical preparation shall be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity.	
63.	23.2.4.	To check, if any other substance is added during the manufacture of the phytopharmaceutical preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substances shall be described as such or as "other ingredients" and the genuine extract as the "active ingredient.	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART VII OF SCHEDULE M Specific requirements for the manufacture of investigational pharmaceutical products for clinical trials in humans			
Sr. No.	**Reference**	**Particulars**	**Observations**
General considerations:-			
1.	1.1.1	Whether there is consistency between and within batches of the investigational product	
2	1.1.2	Whether there is consistency between the investigational product and the future commercial product	
3	1.1.3	Specify the steps to protect subjects of clinical trials from poor-quality products resulting from manufacturing errors (omission of critical steps such as sterilisation, contamination and cross-contamination, mixups, wrong labelling, etc.) or from starting materials and components of inadequate quality	
4	1.1.4	Whether there is documentation of all changes in the manufacturing process	
5	1.2	Description of the selection of an appropriate dosage for clinical trials. While it is accepted that in early trials (Phase I or Phase II), the dosage form may be very different from the anticipated final formulation (e.g., a capsule instead of a tablet), in the pivotal Phase III studies, it shall be similar to the projected commercial presentation.	
6	1.3	Whether data is submitted to the Licensing Authorities to demonstrate that the final dosage form is equivalent, in terms of bioavailability and stability, to that used in the clinical trials in case of significant differences between the clinical and commercial dosage forms. Are Final manufacturing methods revalidated following changes in processes, scaling-up, transfer to other manufacturing sites, etc.	
7	1.4	Whether General considerations specifically addresses those practices that may be different for investigational products, which are usually not manufactured in accordance with a set routine and which may possibly be incompletely characterised during the initial stages of clinical development	
Quality assurance:			

8	2.1	Whether the Quality assurance of pharmaceutical products is as per defined in detail in Part I.	
9	2.2	Whether the quality of dosage forms in Phase III clinical studies shall be characterised and assured at the same level as for routinely manufactured products. Whether the quality assurance system, designed, established and verified by the manufacturer, has been described in writing, taking into account the GMP principles to the extent that they are applicable to the operations in question. This system shall also cover the interface between the manufacture and the trial site (e.g., shipment, storage, occasional additional labelling)	
Validation:			
10	3.1	Whether a highly effective quality assurance system maintained for the increased complexity in the manufacturing operations	
11	3.2	Whether there is any reduction in the degree of validation of sterilising equipment. Whether sterility is maintained during Filling and sealing, which is often done by hand. Is environmental monitoring done.	
Complaints:-			
12	4.1	Whether there is SOP for the conclusions of any investigation carried out in response to a complaint including discussion between the manufacturer and the sponsor (if different) or between the persons responsible for manufacture and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development, to determine the cause and to take any necessary corrective action.	
Recalls:			
13	5.1	Whether Recall procedures are prepared and understood by the sponsor, investigator and are monitored in addition to the persons responsible for recalls as described in the guide on GMP.	
Personnel:			
14	6.1	Whether staff involved are separately designated as responsible for production and quality control and person concerned with development, involved in production and quality control are instructed in the principles of GMP	
Premises and equipment:-			

15	7.1	How investigational products, different products are handled in the same premises and at the same time during the manufacturing to eliminate all risks of contamination, including cross-contamination. Is validated cleaning procedures followed to prevent cross-contamination and special attention paid to line clearance in order to avoid mix-ups.	
16	7.2	Is cleaning maintained and account taken of the solubility of the product and excipients in various cleaning agents, because the toxicity of the materials may not be fully known.	
Materials:			
17	8.1.1	The consistency of production may be influenced by the quality of the starting materials. Are starting materials physical, chemical and, when appropriate, microbiological properties defined, documented in their specifications, and controlled. Whether Existing compendial Standards taken into consideration and specifications for active ingredients are as comprehensive as possible, give the current state of knowledge. Specifications for both active and non-active ingredients are periodically reassessed or not.	
18	8.1.2	Whether detailed information on the quality of active and non-active ingredients, as well as of packaging materials are available so as to make it possible to recognise and as necessary, allow for any variation in production.	
19	8.1.3	Are Chemical and biological reference standards available for analytical purposes	
20	8.1.4	Are Reference standards from reputable sources being used, if available; otherwise the reference substances for the active ingredients prepared, tested and released as reference materials by the producer of the investigational pharmaceutical product or by the producer of the active ingredient used in the manufacture of that product	
21	8.1.5	Whether detailed information on reference products for clinical trials is in accordance with the New Drugs and Clinical Trial Rules, 2019.	
22	8.1.6	In studies in which an investigational product is compared with a marketed product, steps shall be taken to ensure the integrity and quality of the reference products (final dosage form, packaging materials, storage conditions, etc.). If significant changes are to be made in the product, data shall be available (e.g., on stability, comparative dissolution) that demonstrate that these changes do not influence the original quality characteristics of the product.	

Documentation:			
23	9.1	Whether specifications (for starting materials, primary packaging materials, intermediate and bulk products and finished products), master formulae and processing and packaging instructions have been changed frequently as a result of new experience in the development of an investigational product. Whether each new version has taken into account the latest data and include a reference to the previous version so that traceability is ensured. Is Rationale for changes stated and recorded.	
24	9.2	Whether batch processing and packaging records have been retained for at least two years after the termination or discontinuance of the clinical trial, or after the approval of the investigational product.	
25	9.3	Whether the sponsor has requested the processing or packaging of a certain number of units or their shipping which may only be given by the sponsor to the manufacturer of an investigational product in writing (transmitted by electronic means), precise enough to avoid any ambiguity and formally authorised, and refer to the approved product specification file.	
Product specification files:			
26	9.4.1	Whether product specification file or files contain the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and shipping. Whether product specification file or files indicate who has been designated or trained as the authorised person responsible for the release of batches. Is product specification file continuously updated while at the same time ensuring appropriate traceability to the previous versions	
Specifications:			
27	9.5.1	Whether during developing specifications, special attention has been paid to characteristics which affect the efficacy and safety of pharmaceutical products, namely- (a) the accuracy of the therapeutic or unitary dose, homogeneity, content uniformity; (b) the release of active ingredients from the dosage form: dissolution time, etc.; and (c) the estimated stability, if necessary, under accelerated conditions, the preliminary storage conditions and the shelf-life of the product.	

28	9.5.2	Is the package size suitable for the requirements of the trial.	
29	9.5.3	Whether Changes in Specifications as development of the product progresses, made in accordance are in accordance with a written procedure and clearly recorded. Are specifications based on all available scientific data, current state-of-the-art technology and the regulatory and pharmacopoeial requirements.	
Master formulae and processing instructions:			
30	9.6.1	Whether master formulae and processing instructions have been changed in the light of experience, Whether such changes have been made in accordance with a written procedure and clearly recorded for any possible repercussions on stability and above all on bioequivalence between batches of finished products.	
31	9.6.2	Whether there is clear and adequate written instructions and written records for every manufacturing operation or supply. Whether records maintained for the preparation of the final version of the documents to be used in routine manufacture	
Packaging instructions			
32		Whether the number of units to be packaged is specified before the start of the packaging operations. Is the number of units necessary for carrying out quality controls and the number of samples from each batch used in the clinical trial to be kept as a reference for further rechecking and control have been taken into account. Is reconciliation carried out at the end of the packaging and labelling process	
Labelling instructions			
33	9.8.1	Whether the information presented on labels included- (a) the name of the sponsor; (b) a statement "for clinical research use only"; (c) a trial reference number; (d) a batch number; (e) the patient identification number; (f) the storage conditions; and (g) the expiry date (month or year) or a retest date.	
34	9.8.2	Is Additional information displayed in accordance with the order (e.g., dosing instructions, treatment period and standard warnings). Whether the batch number provided separately when necessary for blinding purposes and a copy of each type of label kept in the batch packaging record.	

Processing and packaging batch records-			
35		Whether processing and packaging batch records kept in sufficient detail for the sequence of operations to be accurately traced. Are these contain any relevant remarks which increase existing knowledge of the product, allow improvements in the manufacturing operations and justify the procedures used.	
Coding (or randomisation) systems			
36	9.10.1	Whether procedures are established for the generation, distribution, handling and retention of any randomisation code used in packaging' investigational products.	
37	9.10.2	Is coding system being introduced to permit the proper identification of "blinded" products. Whether the code, together with the randomisation list permit proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation and without delay in an emergency situation of the identity of the actual treatment product received by individual subjects.	
Production:			
38	10.1	Whether products intended for use in clinical trials (late Phase II and Phase III studies) are as far as possible manufactured at a licensed facility, namely: (a) a pilot plant, primarily designed and used for process development; (b) a small-scale facility (sometimes called a "pharmacy") separate both from the company's pilot plant and from routine production (c) a larger-scale production line assembled to manufacture materials in larger batches, e.g., for late Phase III trials and first commercial batches; and (d) the normal production line used for licensed commercial batches, and sometimes for the production of investigational pharmaceutical products if the number, e.g., of ordered ampoules, tablets or other dosage forms, is large enough;	
39	10.1.1	Is there relation between the batch size for investigational pharmaceutical products manufactured in a pilot plant or small-scale facility to the planned full-size batches which may vary widely depending on the pilot plant or "pharmacy" batch size demanded and the capacity available in full-size production	

40	10.1.2	Whether the licensed facilities are of the first and second types. In case of facilities of the remaining types are subject to all GMP rules for pharmaceutical products.	
41	10.1.3	Whether administratively, the manufacturer has contract out the preparation of investigational products Or Technically, the licensed facility is of one of the above-mentioned types. The contract must then clearly state, inter alia, the use of the pharmaceutical products in clinical trials. Close cooperation between the contracting parties is essential	
Manufacturing operations:			
42	10.2.1	Whether provisional production parameters and in-process controls deduced from experience with analogous products and careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continuously to the experience gained in production.	
43	10.2.2	Whether assurance of sterility not less than for licensed products is provided for sterile investigational products. Are Cleaning procedures appropriately validated and designed in the light of the incomplete knowledge of the toxicity of the investigational product. Whether additional quality control testing done where processes such as mixing have not been validated.	
Packaging and labelling			
44	10.3.1	Whether in packaging and labelling of investigational products "blinded" labels are used than for licensed products. Are Supervisory procedures such as label reconciliation, line clearance, etc., and the independent checks by quality control staff being accordingly intensified	
45	10.3.2	Whether the packaging ensure that the investigational product remains in good condition during transport and storage at intermediate destinations. Is any opening of or tampering with the outer packaging during transport being readily discernible.	
46	10.4	**Blinding operations**- Whether preparation of "blinded" products, in-process control includes a check on the similarity in appearance and any other required characteristics of the different products being compared.	
Quality control:-			
47	11.1	Is test or analysis of materials and investigational products in compliance to Schedule L1.	

48	11.2	Whether Product release is carried out in two stages, before and after final packaging	
49	11.2.1	**Bulk product assessment-** Whether all relevant factors, including production conditions, the results of in-process testing, a review of manufacturing documentation and compliance with the product specification file and the order covered	
50	11.2.2	**Finished product assessment**- Whether in addition to the bulk product assessment, all relevant factors, including packaging conditions, the results of in-process testing, a review of packaging documentation and compliance with the product specification file and the order covered	
51	11.3	Whether quality control also be used to verify the similarity in appearance and other physical characteristics, odour and taste of "blinded" investigational products when required	
52	11.4	Whether samples of each batch of product being retained in the primary container used for the study or in a suitable bulk container for at least two years after the termination or completion of the relevant clinical trial. Is stability data available for the sample not stored in the pack used for the study to justify the shelf-life. Are properly stored retained sample e.g., API or drug substance, inprocess material, phase-I investigational drug) subsequently analysed for comparison can provide important links in reproducing comparable products	
Shipping, returns, and destruction:			
53	12.1	Whether the shipping, return and destruction of unused products has been carried out in accordance with the written procedures laid down in the protocol. Are the all unused products sent outside the manufacturing plant as far as possible, either returned to the manufacturer or destroyed in accordance with clearly defined instructions.	
Shipping			
54	12.2.1	Whether Investigational products have been shipped in accordance with the shipping orders given by the sponsor.	
55	12.2.2	Whether a shipment has been sent to an investigator after the following two-step release procedure and record of the same:- (i) the release of the product after quality control ("technical green light"); and (ii) the authorisation to use the product, given by the sponsor ("regulatory green light").	

56	12.2.3	Whether the sponsor has ensured that the shipment will be received and acknowledged by the correct addressee as stated in the protocol.	
57	12.2.4	Whether a detailed inventory of the shipments made by the manufacturer has been maintained and made particular mention of the addressee's identification	
Returns:			
58	12.3.1	Are the Investigational products returned under agreed conditions defined by the sponsor, specified in written procedures and approved by authorised staff members.	
59	12.3.2	Are the returned investigational products have been clearly identified and stored in a dedicated area. Whether Inventory records of returned medicinal products are kept. Whether the responsibilities of the investigator and the sponsor are dealt with in greater detail in the guidelines on GCP.	
Destruction			
60	12.4.1	Whether specified that the sponsor is responsible for the destruction of unused investigational products, which shall therefore not be destroyed by the manufacturer without prior authorisation by the sponsor. Whether destruction operations are carried out in accordance with the environmental safety requirements.	
61	12.4.2	Whether destruction operations have been recorded, documented and the records are kept by the sponsor.	
62	12.4.3	Whether manufacturer delivered a certificate of destruction or a receipt for destruction to the sponsor if requested to destroy products with identification of batches involved.	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART VIII OF SCHEDULE M MANUFACTURING OF ORAL SOLID DOSAGE FORMS (TABLETS AND CAPSULES)	
General Information:	
Company information:	*Name of manufacturer*
Corporate address of manufacturer	*Corporate Address of the firm* *Phone No.: +91-* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Contact person, telephone number and email address:	*5) Name:* *Designation:* *Contact No.: +91-* *Email I.D:* *6) Name:* *Designation:* *Contact No.: +91-* *Email I.D:*
Constitution of firm:	*Public/Private Limited/ Partnership/others (Specify)*
Name of Directors:	*Name of directors*
Inspected site:	*Name & Address of the manufacturing site* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Manufacturing licence number and other regulatory accreditations:	3.
Product details	*Type of products manufactured or to be manufactured at premise*
Date(s) of inspection(s)	
Type and purpose of inspection:	*For example, Grant of manufacturing License, WHO-GMP inspection, initial, routine, follow-up, special*
Inspection Team:	*Name(s) and agency affiliations of lead inspector, inspector(s), accompanying experts and observers*
Number of manufacturing blocks	
Number of Technical Personnel in Manufacturing	
Number of Technical Personnel in Quality Control	
Number of Technical Personnel in Microbiology	
Number of Technical Personnel in Quality Assurance	

B. Inspection checklist:

Note:

3) Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part-I shall be complied with, mutatis mutandis, for the manufacture of oral Solid Dosage Forms (Tablets and capsules). In addition to these requirements, the following specific requirements shall also be followed, namely

4) Comments should be descriptive without ambiguity and suitable reference of documents like SOPs, etc needs to be given and answer like "Yes" or "No" should be avoided.

INSPECTION CHECKLIST FOR GMP INSPECTION OF ORAL SOLID DOSAGE FORMS MANUFACTURING SITES (TABLETS AND CAPSULES) AS PER PART-VIII OF SCHEDULE-M

Sr. No.	Sch. M Ref.	Particulars	Observation
1 General:-			
1	1.1	Pls specify the areas of dust generation and mechanism involved in controlling the dust. Wherever required, enclosed dust control manufacturing systems shall be employed.	
2	1.2	Whether Effective air extraction systems, with discharge points situated to avoid contamination of other products and processes are provided. (Filters shall be installed to retain dust and to protect the factory and local environment)	
3	1.3	Ensure that Wooden equipment are not used. Whether metal detector is provided. Whether Screens, sieves, punches and dies is examined for wear and tear or for breakage before and after each use.	
4	1.4	Whether all ingredients of dry product are sifted before use unless the quality of the input material can be assured. Whether sifting is carried out at dedicated areas	
5	1.5	Whether environmental conditions of pressure differentials between rooms are regularly monitored and any deviation is brought to the immediate attention to the Production and Quality assurance departments.	
6	1.6	Whether Particular care is being taken to ensure that any vacuum, compressed air or air-extraction nozzles are kept clean and that there is no evidence of lubricants leaking into the product from any part of the equipment.	
7	1.7	Whether suitable measures are taken to ensure that dust cannot move from one cubicle to another, where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct Oral Solid Dosage (OSD) manufacturing site.	
8	1.9	Whether corridor is maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure	

9	1.10	Whether Highly potent products is manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.	
10	1.11	Whether the pressure cascade for each facility is individually assessed according to the product handled and level of protection required	
11	1.14	Whether the limits for the pressure differential between adjacent areas is such that there is no risk of overlap in the acceptable operating range, e.g., 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in the failure of the pressure cascade, where the first room is at the maximum pressure limit and the second room is at its minimum pressure limit.	
12	1.17	Whether the pressure control and monitoring devices used is calibrated and qualified	
13	1.17	Whether pressure control devices is linked to an alarm system set according to the levels determined by a risk analysis	
14	1.19, 1.20.	Whether, airlocks with suitable differential pressure cascade regimes (cascade/ sink/ bubble) are provided to limit cross-contamination	
15	1.21.	There shall be a method to indicate if both doors to airlocks are open at the same time, or alternatively these shall be interlocked. The determination of which doors shall be interlocked shall be the subject of a risk assessment study.	
16	1.22	If Central dust extraction systems are used, ensure that the same is interlocked with the appropriate air-handling systems, to ensure that they operate simultaneously.	
17	1.24	Whether dust extraction Systems are designed to prevent dust flowing back in the opposite direction in the event of component failure or airflow failure.	
18	1.25.	Whether, adequate room pressure differential indication are provided so that each critical room pressure can be traced back to ambient pressure, in order to determine the room actual absolute pressure. (Room pressure indication gauges shall have a range and graduation scale which enables the reading to accuracy, as appropriate) Whether, normal operating range, alert and action limits are defined and displayed at the point of indication.	
19	1.26	What type of measures like Material Pass-Through-Hatches (PTH) or Pass Boxes (PB) provided by firm for separating two different zones.	

20	1.27	Whether temperature and relative humidity is controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products and provide a comfortable environment for the operator, where necessary.	
21	PART XIII (3.4)	Whether the manufacture of effervescent and soluble tablets is carried out in air-conditioned and dehumidified areas.	
22	1.28	Whether Maximum and minimum room temperatures and relative humidity are appropriate and alert and action limits on temperatures and humidity are defined and monitored.	
23	1.30	Whether Cubicles or suites, in which products requiring low relative humidity are processed, have well sealed walls and ceilings and also separated from adjacent areas with higher relative humidity by means of suitable airlocks.	
24	1.35	Ensure that Air filters are not installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth.	
25	1.41	Whether Dust extraction ducting is designed with sufficient transfer velocity to ensure that dust is carried away and does not settle in the ducting and whether Periodic checks is performed to ensure that there is no build-up of the dust in the ducting.	
26	1.43	Whether Airflow direction is chosen to ensure that the operator does not contaminate the product and operator is not put at risk by the product.	
27	1.45	Whether firm has performed and maintained records of airflow visualisation smoke tests to show correct flushing of the rooms.	
28	1.46	Whether firm has provided additional steps, such as handling the products in glove boxes or using barrier isolator technology when dealing with particularly harmful products.	
29	1.47	Whether Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and is provided with adequate filtration to prevent contamination of the ambient air.	
30	1.51	Whether the dust-slurry is removed by a suitable means, e.g., a drainage system or waste removal contractor, when wet scrubbers are used.	
31	1.55	Whether fumes are removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers).	
32	1.59.	Ensure that there is no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.	

33	1.60.	In case use of recirculated air,Ensure that that HEPA filters are installed in the supply air stream to remove contaminants and thus, prevent cross-contamination (HEPA filters may not be required where the air handling system is serving a single product facility and there is evidence that cross-contamination would not be possible)	
34	1.63	Where HEPA filters are terminally mounted, ensure that they are not connected by flexible ducting	
35	1.64	Ensure that Air containing dust from highly toxic processes or solvents or flammable vapours is not recirculated to the HVAC system.	
36	1.65	Whether adequate airlocks, such as personnel airlocks (PAL), material airlocks (MAL), change rooms and passages are provided to protect passage between different cleanliness conditions and whether these have supply and extract air systems as appropriate.	
37	1.66	Whether areas such as airlocks, change rooms and passages, are designed so that the required pressure cascades can be achieved.	
38	1.67	Whether firm has prepared and maintained detailed diagrams depicting pressure cascades, air flow directions and flow routes for personnel and materials.	
39	1.68	Whether personnel and materials are moving from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone; if moving from a lower cleanliness zone to a higher cleanliness zone whether changing or decontamination procedures are followed.	
40	1.69	Whether classification of final change room (“at rest”) is same as that of classification of area into which it leads.	
2.0 Sifting, mixing and granulation			
41	2.10	Whether mixing, sifting and blending equipment are fitted with dust extractors or in a dedicated area for each operation unless operated as a closed system.	
42	2.20	Whether residues from sieving operations are examined periodically for evidence of the presence of unwanted materials.	
43	2.30	Whether critical operating parameters like time and temperature for each mixing, blending and drying operation are specified in a Master Formula, monitored during processing, and recorded in the batch records.	
44	2.40	Whether filter bags fitted to fluid-bed-drier are used for different products, without being washed in between use.	
45	2.40	Whether for certain highly potent or sensitising products, bags specific to one product only are used.	
46	2.40	Whether Air entering the drier is filtered.	
47	2.40	Whether steps are taken to prevent contamination of the site and local environment by dust in the air leaving the drier due to close positioning of the air-inlets and exhaust.	

48	2.50	Whether granulation and coating solutions are made, stored and used in a manner which minimises the risk of contamination or microbial growth.	
3.0 Compression (Tablets)			
50	3.10	Whether each tablet compressing machine is provided with effective dust control facilities to avoid cross contamination.	
51	3.10	Whether the compression machine is installed in separate cubicles unless the same product is being made on each machine or unless the compression machine itself provides its own enclosed air-controlled environment.	
52	3.20	Whether suitable physical, procedural and labelling arrangements are made to prevent mix up of materials, granules and tablets on compression machinery.	
53	3.30	Whether accurate and calibrated weighing equipment are readily available and used for in-process monitoring of tablet weight variation and whether used procedures are capable of detecting out of limits tablets.	
54	3.40	Whether sufficient individual tablets are examined at fixed intervals to ensure that a tablet from each compression station or from each compression point has been inspected for suitable Pharmacopoeial parameters like “appearance”, “weight variation”, “disintegration”, “hardness”, “friability” and “thickness” at commencement of each compression run and in case of multiple compression points in a compression machine and whether the results are recorded as part of the batch documentation.	
55	3.50	Whether Tablets are de-dusted, preferably by automatic device and monitored for the presence of foreign materials besides any other defects.	
56	3.60	Whether Tablets are collected into clean, labelled containers.	
57	3.70	Whether rejected or discarded tablets are isolated in identified containers and their quantity recorded in the Batch Manufacturing Record.	
58	3.80	Whether in-process controls are employed to ensure that the products remain within specification.	
59	3.80	Whether during compression, samples of tablets are taken at regular intervals of not greater than thirty minutes to ensure that they are being produced in compliance with specified in-process specification.	
4.0 Coating (Tablets)			
61	4.10	Whether air supplied to coating pans for drying purposes is filtered air and of suitable quality.	
62	4.10	Whether coating area is provided with suitable exhaust system and environmental control (temperature and humidity) measures.	

63	4.20	Whether coating solutions and suspensions are made afresh and used in a manner which minimise the risk of microbial growth and their preparation and use is documented and recorded.	
5.0 Filling of Hard Gelatin Capsule			
65	5.00	Whether empty capsules shells are stored under conditions which ensure their safety from the effects of excessive heat and moisture	
66	6.00	Printing (Tablets and Capsules)	
67	6.10	What measure have been taken to avoid product mix-up during any printing of tablets and capsules.	
68	6.10	Whether sufficient measure have been taken when different products or different batches of the same product are printed simultaneously and whether operations are adequately segregated.	
69	6.10	Whether edible grade colours and suitable printing ink is used for such printing.	
70	6.20	Whether tablets and capsules are approved by Quality Control After printing, before release for packaging or sale.	
7.0 Packaging (Strip and Blister)			
72	7.10	Whether all "rogue" tablets, capsules or foils from packaging operation are removed before a new packaging operation is commenced when using automatic tablet and capsule counting, strip and blister packaging equipment.	
73	7.10	Whether there is an independent recorded check of the equipment before a new batch of tablets or capsules is handled.	
74	7.20	Whether uncoated tablets are packed on equipment designed to minimise the risk of cross-contamination.	
75	7.20	Whether packaging of uncoated tablets is carried out in an isolated area when potent tablets or Beta lactum containing tablets are being packed.	
76	7.30	Whether the strips coming out of the machine are inspected for defects such as misprint, cuts on the foil, missing tablets and improper sealing.	
77	7.40	Whether integrity of individual packaging strips and blisters is subjected to vacuum test periodically to ensure leak proofness of each pocket strip and blister and records maintained.	
78	PART XIII (3)	Whether tablet production department are divided into following sections. (a) Mixing, Granulation and Drying section; (b) Tablet compression section; (c) Packaging section (strip or blister machine wherever required); and (d) Coating section (wherever required).	

79	PART XIII (3.1)	Whether the following electrically operated equipment are provided for the manufacture of compressed tablets and hypodermic tablets- **(a) Granulation-cum-Drying section-** (1) Disintegrator and sifter;(2) Powder mixer;(3) Mass mixer or Planetary mixer or Rapid mixer granulator; (4) Granulator wherever required; (5) Thermostatically controlled hot air oven with trays (preferably mounted on a trolley) or Fluid bed dryer; and (6) Weighing machines; **(b) Compression section-** (1) Tablet compression machine, single or multi punch or rotatory;(2) Punch and dies storage cabinets; (3) Tablet de-duster; (4) Tablet Inspection unit or belt; (5) Dissolution test apparatus wherever required; (6) In-process testing equipment like single pan electronic balance, hardness tester, friability and disintegration test apparatus; and (7) Air-conditioning and dehumidification arrangement (wherever necessary).	
		(c) Packaging section- (1) Strip or blister packaging machine; (2) Leak test apparatus (vacuum system); (3) Tablet counters (wherever applicable); and (4) Air-conditioning and dehumidification arrangement (wherever applicable). **Area-** A minimum area of sixty square meters for basic installation and twenty square meters for ancillary area is recommended for un-coated tablets **(d) Coating section-** (1) Jacketed kettle stainless steel container or any other appropriate material (steam, gas or electrically heated for preparing coating suspension); (2) Coating pan (Stainless steel); (3) Polishing pan (where applicable);(4) Exhaust system (including vacuum dust collector);(5) Air conditioning and Dehumidification Arrangement; and (6) Weighing machine.	
80	PART XIII (3.2)	Whether the firm has provided minimum additional area of thirty square meters for coating section for basic installation and ten square meters for ancillary area	
81	PART XIII (4)	Whether Oral powder manufacturing area provided with the following equipment and areas.- (1) Disintegrator;(2) Mixer (electrically operated);(3) Sifter;(4) Stainless steel vessels and scoops of suitable sizes;(5) Filling equipment; and (6) Weighing machine. Area- A minimum area of thirty square meters is provided to allow for the basic installations. Where the additional room is provided for blending	

82	PART XIII (4)	Whether Capsules production are provided with following equipment. (1) Mixing and blending equipment (electrically or power driven); (2) Capsule filling units; (3) Capsules counters (wherever applicable); (4) Weighing machine; (5) Disintegration test apparatus; and (6) Capsule polishing equipment. Area- Whether minimum area of twenty-five square meters for basic installation and ten square meters for ancillary area is provided.	

Note:

1. Manufacture of Hypodermic tablets shall be conducted under aseptic conditions and applicable part of schedule M shall be referred. 2. In the case of pessaries/Suppositories manufactured by granulation and compression, the requirements as indicated under "item 3 of Tablet" of PART XIII shall be provided.

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART IX OF SCHEDULE M I MANUFACTURING OF ORAL LIQUIDS (SYRUPS, ELIXIRS, EMULSIONS AND SUSPENSIONS)	
General Information:	
Company information:	*Name of manufacturer*
Corporate address of manufacturer	*Corporate Address of the firm* *Phone No.: +91-* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Contact person, telephone number and email address:	*7) Name:* *Designation:* *Contact No.: +91-* *Email I.D:* *8) Name:* *Designation:* *Contact No.: +91-* *Email I.D:*
Constitution of firm:	*Public/Private Limited/ Partnership/others (Specify)*
Name of Directors:	*Name of directors*
Inspected site:	*Name & Address of the manufacturing site* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Manufacturing licence number and other regulatory accreditations:	4.
Product details	*Type of products manufactured or to be manufactured at premise*
Date(s) of inspection(s)	
Type and purpose of inspection:	*For example, Grant of manufacturing License, WHO-GMP inspection, initial, routine, follow-up, special*
Inspection Team:	*Name(s) and agency affiliations of lead inspector, inspector(s), accompanying experts and observers*
Number of manufacturing blocks	
Number of Technical Personnel in Manufacturing	
Number of Technical Personnel in Quality Control	
Number of Technical Personnel in Microbiology	
Number of Technical Personnel in Quality Assurance	

A. Inspection checklist:

Note:

5) Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part-I shall be complied with, mutatis mutandis, for the manufacture of Syrups, Elixirs, Emulsions and Suspensions. In addition to these requirements, the following specific requirements shall also be followed, namely
6) Comments should be descriptive without ambiguity and suitable reference of documents like SOPs, etc needs to be given and answer like "Yes" or "No" should be avoided.

INSPECTION CHECKLIST FOR GMP INSPECTION OF ORAL LIQUIDS (SYRUPS, ELIXIRS, EMULSIONS AND SUSPENSIONS) AS PER PART-IX OF SCHEDULE-M			
Sr.No.	**Sch. M Reference**	**Particulars**	**Observation**
2.0 Building and Equipment			
1	2.2	Whether firm is using closed system for processing and transfer to protect the product from contamination.	
2	2.2	Whether the production areas is effectively ventilated with filtered air where the products or open clean containers are exposed.	
3	2.3	Whether the manufacturing area have entry through double door air-lock facility.	
4	2.3	Whether firm has provided provision of “fly catcher’ or ‘air curtain’ to prevent entry of flies.	
5	2.4	Whether drains are of adequate in size and have adequate traps, without open channels and prevent back flow. Whether drains are shallow to facilitate cleaning and disinfecting.	
6	2.5	Whether the production area is cleaned and sanitised at the end of every production process.	
7	2.6	Whether Tanks, containers, pipe work and pumps are designed and installed so that they can be easily cleaned and sanitised.	
8	2.6	Whether Equipment design prevents accumulation of residual microbial growth or cross-contamination.	
9	2.7	Whether stainless steel or any other appropriate material is being used for parts of equipment’s coming in direct contact with the products.	
10	2.8	Whether arrangements for cleaning of containers, closures and droppers are made with the help of suitable machines or devices equipped with high pressure air, water and steam jets.	
11	2.9	Whether the quality of materials received in bulk tankers is checked before they are transferred to bulk storage tanks.	
12	2.1	Whether care is taken when transferring materials via pipelines ensuring that they are delivered to their correct destination.	

13	2.11	Whether the furniture used is smooth, washable and made of stainless steel or any other appropriate material which is scratch proof, washable and smooth.	
3.0 Purified Water			
14	3.1	Whether the chemical and microbiological quality of purified water used is specified and monitored routinely. Whether the microbiological evaluation of purified water includes testing for absence of pathogens and not exceeding 100 cfu per ml.	
15	3.2	Whether there is any written procedure for operation and maintenance of the purified water system.	
16	3.2	When sanitising agens are used , whether flushing is done to ensure that the sanitising agent has been effectively removed after any chemical sanitisation of the water system.	
17	3.2	If, sanitising agens are used , whether flushing is done to ensure that the sanitising agent has been effectively removed after any chemical sanitisation of the water system.	
4.0 Manufacturing			
18	4.1	Whether manufacturing personnel wears non fiber shedding clothing to prevent contamination of the product, wherever required.	
19	4.2	Whether materials which likely to shed fiber like gunny bags, or wooden pallets are carried out into the area where products or cleaned containers are exposed.	
20	4.3	Whether firm has provided appropriate stirrer during filling to maintain the homogeneity of emulsion.	
21	4.3	Whether mixing and filling processes is specified and monitored.	
22	4.3	Whether special care is taken at the beginning of the filling process after stoppage due to any interruption and at the end of the process to ensure that the product is uniformly homogenous during the filling process.	
23	4.4	Whether the primary packaging area have an air supply which is filtered through level-3 filters [Production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g., EN779 G4 plus F8 plus EN1822 H13 filters) (for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable].	
24	4.4	Whether the temperature of the primary packaging area is maintained below 30°C.	
25	4.5	Whether maximum period of storage and storage conditions are specified in the Master Formula when the bulk product is not immediately packed and maximum period of storage time of a product in the bulk stage is validated.	

26	PART XIII (2)	The following equipments are provided. (1) Mixing and storage tanks preferably of Stainless steel or any other appropriate material; (2) Jacketed Kettle or Stainless steel tank (steam, gas or electrically heated); (3) Portable stirrer (Electrically operated); (4) A colloid mill or suitable emulsifier (Electrically operated); (5) Suitable filtration equipment (Electrically operated); (6) Semi-automatic or automatic bottle filling machine; (7) Pilfer proof cap sealing machine; (8) Water distillation unit or deionizer; and (9) Clarity testing inspection units.	
27	PART XIII (2)	Whether minimum area of thirty square meters for basic installation and ten square meters for ancillary area is provided.	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART X OF SCHEDULE M MANUFACTURING OF TOPICAL PRODUCTS i.e., EXTERNAL PREPARATIONS (CREAMS, OINTMENTS, PASTES, EMULSIONS, LOTIONS, SOLUTIONS, DUSTING POWDERS AND IDENTICAL PRODUCTS)	
General Information:	
Company information:	*Name of manufacturer*
Corporate address of manufacturer	*Corporate Address of the firm* *Phone No.: +91-* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Contact person, telephone number and email address:	*1) Name:* *Designation:* *Contact No.: +91-* *Email I.D:* *2) Name:* *Designation:* *Contact No.: +91-* *Email I.D:*
Constitution of firm:	*Public/Private Limited/ Partnership/others (Specify)*
Name of Directors:	*Name of directors*
Inspected site:	*Name & Address of the manufacturing site* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Manufacturing licence number and other regulatory accreditations:	
Product details	*Type of products manufactured or to be manufactured at premise*
Date(s) of inspection(s)	
Type and purpose of inspection:	*For example, Grant of manufacturing License, WHO-GMP inspection, initial, routine, follow-up, special*
Inspection Team:	*Name(s) and agency affiliations of lead inspector, inspector(s), accompanying experts and observers*

Number of manufacturing blocks	
Number of Technical Personnel in Manufacturing	
Number of Technical Personnel in Quality Control	
Number of Technical Personnel in Microbiology	
Number of Technical Personnel in Quality Assurance	

A. Inspection checklist:

Note:

7) Good Manufacturing Practices for pharmaceutical products: Main principles as given in Part-I shall be complied with, mutatis mutandis, for the manufacture of Topical Products i.e., External Preparations (Creams, Ointments, Pastes, Emulsions, Lotions, Solutions, Dusting powders and identical products used for external applications). In addition to these requirements, the following specific requirements shall also be followed, namely.

8) Comments should be descriptive without ambiguity and suitable reference of documents like SOPs, etc needs to be given and answer like "Yes" or "No" should be avoided.

INSPECTION CHECKLIST FOR GMP INSPECTION OF EXTERNAL PREPARATIONS (CREAMS, OINTMENTS, PASTES, EMULSIONS, LOTIONS, SOLUTIONS, DUSTING POWDERS AND IDENTICAL PRODUCTS) AS PER PART-X OF SCHEDULE-M			
Sr.No.	**Sch M Ref**	**Particulars**	**Observation**
1.	1	Whether entrance to the area where topical products are manufactured is through a suitable airlock.	
2.	1	Whether the insectocutors are installed outside the airlock.	
3.	2	Whether HVAC system is in place.Whether the air to this manufacturing area is filtered through suitable filters and air-conditioned.	
5.	3	Whether the area is fitted with an exhaust system of suitable capacity to effectively remove vapours, fumes, smoke or floating dust particles.	
6.	4	Whether equipment used is designed and maintained to prevent the product from being accidentally contaminated with any foreign matter or lubricant.	
7.	5	Whether suitable cleaning equipment and material is used in the process of cleaning or drying the process equipment or accessories used.	
8.	6	Whether water used in compounding is Purified Water IP.	
9.	7	Whether Powder are suitably sieved before use, whenever used.	
10.	8	Whether Heating of vehicles and a base like petroleum jelly is done in a separate mixing area in suitable stainless-steel vessels, using steam, gas, electricity, solar energy, etc.	
11.	9	Whether a separate packing section is provided for primary packaging of the products.	
12.		Whether Primary plus secondary plus tertiary filters (e.g., EN779 G4 plus F8 plus EN1822 H13 filters) (for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable) for production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists.	

13	PART XIII (1)	Whether the premises is equipped with folowing equipments. (1) Mixing and storage tanks preferably of stainless steel or any other appropriate material; (2) Jacketed Kettle stainless steel container (steam, gas or electrically heated); (3) Mixer (Electrically operated); (4) Planetary mixer; (5) A colloid mill or a suitable emulsifier; (6) A triple roller mill or an ointment mill; (7) Liquid filling equipment (Electrically operated); and (8) Jar or tube filling equipment.	
14	PART XIII (1)	Whether minimum area of thirty square meters for basic installation and ten square meters for ancillary area is provided.	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART XI OF SCHEDULE M Specific Requirement for Manufacture of Metered Dose Inhalers (MDI)

Sr. No.	Reference	Particulars	Observations
	2. General		
1		Whether the manufacturing of Metered-Dose-Inhalers is done under conditions which ensures minimum microbial and particulate contamination. Whether the quality of components and the bulk product is assured. Whether the uniformity of suspension is established where medicaments are in suspended state. Whether the manufacturing and filling are carried out in a closed system (as far as possible).	
	3. Building and Civil Works		
2	3.1	Whether the building is located on a solid foundation to reduce risk of cracking walls and floor due to the movement of equipment and machinery.	
3	3.2	Whether building surfaces are impervious, smooth and non-shedding. Whether the flooring is continuous and provided with a cover between the floor and the wall as well as between the wall and the ceiling. Whether ceiling is solid, continuous and proceeded a cone with the walls. Whether the Light fittings and air-grills are flushed with the ceiling. Whether all service lines requiring maintenance are accessible from outside the production area.	
4	3.3	Whether the manufacturing area is segregated into change rooms for personnel, container preparation area, bulk preparation and filling area, quarantine area and spray testing and packing areas.	
5	3.4	Whether the secondary change rooms are provided for operators to change from factory clothing to special departmental clothing before entering the manufacturing and filling area.	
6	3.5	Whether separate area is provided for de-cartooning of components before they are air washed	

7	3.6	Whether the propellants used for manufacture are delivered to the manufacturing area distribution system by filtering them through 2µ filters. Whether the bulk containers of propellants are stored, suitably identified, away from the manufacturing facilities.	
	4. Environmental conditions		
8	4.1	Whether the area where products or clean components are exposed is supplied with filtered air of Grade C and personnel entrance is through airlocks	
9	4.2	Whether the requirements of temperature and humidity in the manufacturing area is decided depending on the type of product and propellants handled in the facility. Whether other support areas have comfort levels of temperature and humidity.	
10	4.3	Where the difference in room pressure between the manufacturing area and the support areas is maintained and the differential pressure is maintained not less than 15 Pascals (0.06 inches or 1.5 mm water gauge)	
11	4.4	Whether there is a written schedule for the monitoring of environmental conditions. Whether the temperature and humidity are monitored daily	
12	4.5	Ensure the HVAC system is in place.	
	5. Garments		
13	5.1	Whether the garment provided to personnel in the manufacturing and filling section is suitable single piece garment made out of non-shedding, tight weave material. Whether the personnel in support areas wears clean factory uniforms.	
14	5.2	Ensure the gloves are made of suitable material having no interaction with the propellants used by the operators in the manufacturing and filling areas. (Preferably, disposable gloves should be used)	
15	5.3	Whether suitable department specific PPE like footwear and safety glasses are being used, wherever hazard exists.	
	6. Sanitation		

16	6.1	Whether there is a written procedure for the sanitation of the MDI manufacturing facility. Whether special care is taken to handle residues and rinses of propellants.	
17	6.2	Whether the use of water for cleaning is restricted and controlled. Whether suitable disinfectants are used for sanitizing the different areas. Whether the records of sanitation are maintained.	
	7. Equipment		
18	7.1	Whether the manufacturing equipment is a closed system. Whether the vessels and supply lines are of stainless steel.	
19	7.2	Whether suitable check weights, spray testing machines and labelling machines are provided in the department.	
20	7.3	Whether all the equipment is suitably calibrated and their performance is validated on receipt and thereafter periodically.	
	8. Manufacture		
21	8.1	Whether the specifications, sampling and testing of metering valves for aerosols are carried out. Whether the Quality Assurance system of the valve manufacturer is audited.	
22	8.2	Whether all propellants (e.g., liquid or gaseous propellants) are filtered to remove particles greater than 0.2µ. Whether an additional filtration is carried out immediately before filling (desirable)	
23	8.3	Whether an approved Master Formula Records for the manufacture of metered dose inhalers provided.	
24	8.4	Whether the primary packing material is appropriately cleaned by compressed air (suitably filtered through 0.2µ filter). Whether the humidity of the compressed air is controlled as applicable.	
25	8.5	Whether the valves are handled carefully and are kept in clean, closed containers in the filling room after de-cartooning.	
26	8.6	Whether the containers and valves are cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g., lubricants) or undue microbiological contaminants. Whether valves are kept in clean, closed containers after cleaning and precautions are taken not to introduce contamination during subsequent handling, e.g., taking samples.	

		Whether the containers provided to the filling line are in a clean condition or cleaned on line immediately before filling.	
27	8.7	Whether the bulk is kept stirred continuously for suspensions. Whether precautions are taken to ensure uniformity of suspensions at the point of fill throughout the filling process.	
28	8.8	Whether the In-process controls is done including periodical checking of weight of bulk formulation filled in the containers. Whether one hundred per cent check on weight is carried out in case of a two-shot-filling process (liquid filling followed by gaseous filling)	
29	8.9	Whether the controls after filling ensures the absence of undue leakage. Whether the leakage test is performed in a way which avoids microbial contamination or residual moisture.	
30	8.10	Whether the filled containers are quarantined for a suitable period established by the manufacturer to detect leaking containers prior to testing, labelling and packing.	
	9. Documentation		
31	In addition to the routine good manufacturing practices documentation, ensure whether manufacturing records show the following additional information		
	(1) temperature and humidity in the manufacturing area;		
	(2) periodic filled weights of the formulation;		
	(3) records of rejections during on line check weighing;		
	(4) records of rejection during spray testing		

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART XII OF SCHEDULE M SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENT

Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
2. Quality management:-			
1	**2.1**	Principles	
2	**2.1.1.**	Specify quality management system in the firm	
3	**2.1.2.**	Whether quality units that is independent of production and that fulfils both quality assurance (QA) and quality control (QC) responsibilities is established	
4	**2.1.3.**	Who is authorised to release intermediates and APIs	
5	**2.1.4.**	Specify the comprehensive quality assurance system maintained by the firm *Inter-alia* to cover deviation, reporting, investigation and change control	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART XII OF SCHEDULE M SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENT			
Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
6	**2.1.**	Whether Procedures is established for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g., quality related complaints, recalls and regulatory actions).	
2.2. Responsibilities of the quality units			
7	**2.2.1**	Whether individual the quality units is established and involved in all quality-related matters.	
8	**2.2.2**	Whether the quality units review and approve all appropriate quality related documents	
9	**2.2.3**	Whether the main responsibilities of the independent quality units are described in writing and shall include but not necessarily be limited to:—	
	(i)	Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;	
	(ii)	establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;	
	(iii)	reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;	
	(iv)	making sure that critical deviations are investigated and resolved;	
	(v)	approving all procedures impacting the quality of intermediates or APIs	
	(vi)	approving all procedures impacting the quality of intermediates or APIs	
	(vii)	making sure that internal audits (self-inspections) are performed;	
	(viii)	approving intermediate and API contract manufacturers;	
	(ix)	approving changes that potentially impact quality of intermediates or APIs;	
	(x)	reviewing and approving validation protocols and reports	
	(xi)	making sure that quality related complaints are investigated and resolved	
	(xii)	making sure that effective systems are used for maintaining and calibrating critical equipment;	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART XII OF SCHEDULE M SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENT			
Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
	(xiii)	making sure that materials are appropriately tested and the results are reported;	
	(xiv)	making sure that there are stability data to support retest or expiry dates and storage conditions on APIs or intermediates where appropriate; and	
	(xv)	performing product quality reviews as defined in paragraph 2.5	
2.3. Responsibility for production activities-			
10	**2.3**	Whether the responsibility for production activities are described in writing and include but not necessarily be limited to:-	
	(i)	preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;	
	(ii)	producing APIs and, when appropriate, intermediates according to pre-approved instructions;	
	(iii)	reviewing all production batch records and ensuring that these are completed and signed	
	(iv)	making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;	
	(v)	making sure that production facilities are clean and when appropriate disinfected	
	(vi)	making sure that the necessary calibrations are performed and records are kept	
	(vii)	making sure that the premises and equipment are maintained and records are kept;	
	(viii)	making sure that validation protocols and reports are reviewed and approved;	
	(ix)	evaluating proposed changes in product, process or equipment; and	
	(x)	making sure that new and when appropriate, modified facilities and equipment are qualified.	
2.4. Internal audits (self-inspection)-			
11	**2.4.1.**	Whether the firm has constituted a self inspection team supplemented with a quality audit procedure to evaluate	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART XII OF SCHEDULE M SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENT			
Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
		that GMP is being followed. If no. How internal audits are carried out.	
12	**2.4.2**	Whether Audit findings and corrective actions are documented and brought to the attention of the responsible management of the firm.	
2.5. Product quality review			
13	**2.5.1**	Verify quality reviews of APIs conducted and documented annually and which include at least a review of:—	
	(i)	critical in-process control and critical API test results;	
	(ii)	all batches that failed to meet established specifications;	
	(ii)	all critical deviations or non-conformances and related investigations;	
	(iv)	any changes carried out to the processes or analytical methods;	
	(v)	results of the stability monitoring programme;	
	(vi)	quality-related returns, complaints and recalls; and	
	(vii)	adequacy of corrective actions.	
3. Personnel			
3.1 Personnel qualifications			
14	**3.1.1.**	whether an adequate number of personnel qualified by appropriate education, training or experience to perform and supervise the manufacture of intermediates and APIs.	
15	**3.1.2**	Whether the responsibilities of all personnel engaged in the manufacture of intermediates and APIs are specified in writing.	
16	**3.1.3.**	Whether Training is regularly conducted by qualified individuals and cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employees' functions. Verify the training records.	
3.2. Personnel hygiene			
17	**3.2.1.**	Whether all personnel are trained to ensure high level of personal hygiene. Specify whether primary clean garments are provided for each personnel entering the factory premises. Whether proper uniforms and adequate facilities for personal cleanliness are provided. Pls specify nature and type of dress used by the personnel in various areas of operation.	

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Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
		How many dress/footwear have been provided to each personnel.	
18	**3.2.2.**	Whether Smoking, eating, drinking, chewing and the storage of food are restricted to certain designated areas separate from the manufacturing areas	
3.3. Consultants			
19	**3.3.1.**	Whether Consultants advising on the manufacture and control of intermediates or APIs have sufficient education, training and experience or any combination	
20	**3.3.2.**	Whether Records are maintained stating the name, address, qualifications and type of service provided by these consultants.	
4. Buildings and facilities			
21	**4.1**	**Design and construction**	
22	**4.1.1.**	How the building has been designed constructed and maintained to suit the manufacturing operations so as to produce drugs under hygienic conditions. *Pls specify nature of construction used in the facility in respect of its maintenance and hygienic conditions.*	
23	**4.1.2.**	Whether the building confirm to the conditions laid down in the Factories Act, 1948 *Pls attach valid factory certificate/ license issued by the competent authority.*	
24	**4.1.3.**	Specify how the premises used for manufacturing operations and testing purpose prevents contaminations and cross contamination is: a) Compatible with other drug manufacturing operations that may be carried out in the same or adjacent area. Pls specify any special criteria for the product manufacturered. e.g. temperature, humidity, air class requirements maintained for aseptic products, etc.	
25	**4.1.4.**	Whether the following are defined areas or other control systems for the following activities:	
	(i)	receipt, identification, sampling and quarantine of incoming materials, pending release or rejection;	
	(ii)	quarantine before release or rejection of intermediates and APIs	
	(iii)	sampling of intermediates and APIs;	
	(iv)	holding rejected materials before further disposition (e.g., return, reprocessing or destruction);	

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	(v)	storage of released materials;	
	(vi)	production operations;	
	(vii)	packaging and labelling operations; and	
	(viii)	laboratory operations.	
26	**4.1.6.**	Adequate, clean washing and toilet facilities shall be provided for personnel.	
27	**4.1.7.**	Whether Laboratory areas and operations are separated from production areas.	
4.2. Utilities			
28	**4.2.1.**	Whether all utilities (e.g., steam, gases, compressed air and heating, ventilation and air conditioning) are qualified and appropriately monitored and action shall be taken when limits are exceeded. Whether Drawings for these utility systems are available .	
29	**4.2.2.**	Whether these systems are designed and constructed to minimise risks of contamination and cross-contamination.	
30	**4.2.3.**	If air is recirculated to production areas, what are appropriate measures e taken to control risks of contamination and cross-contamination.	
31	**4.2.4.**	Whether Permanently installed pipework are appropriately identified.	
32	**4.2.5.**	What kind of Drains are provided to prevent back-siphonage,	
4.3. Water			
33	**4.3.1.**	Verify whether a current drawing of the water system showing all equipment in the system from inlet to the points of use is available.	
34	**4.3.2.**	Specify the Material of Construction (MOC) of the purified water storage tank and its pipe line.	
35	**4.3.3.**	Specify whether water system validation/qualification has been carried out as per protocol and reports have been prepared and maintained.	
36	**4.3.4**	Specify source of raw water and give details of treatment processes, sampling points, distribution and storage system for raw and purified water.	
37	**4.3.5.**	Verify whether the Raw Water holding tank was sanitised as per specified SOP.	
38	**4.3.6**	Specify whether the quality of potable water used for the preparation of purified water meets the requirement of Schedule M	

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39	**4.3.7**	Specify how water tanks are cleaned periodically and records maintained thereof.	
4.4. Containment			
40	**4.4.1.**	Whether separate dedicated and self-contained facilities have been provided for the production of sensitive pharmaceutical product like Penicillin, Biological preparation with like micro-organism, Beta lactam, Sex Hormones and Cytotoxic substances. If yes pls explain how and attach copy of plan of premises of each category of drug.	
41	**4.4.2.**	What appropriate measures are established and implemented to prevent crosscontamination,	
42	**4.4.3.**	How Handling and storage of these highly toxic non-pharmaceutical materials are separate from APIs.	
4.5. Lighting-			
43	**4.5.1**	What measures have been taken so that the production and dispensing areas are well lighted and effectively ventilated, with air control facilities. Pls specify the lux level maintained in various parts of the premise.	
4.6. Sewage and refuse-			
44	**4.6.1**	Sewage, refuse and other wastes (e.g., solids, liquids, or gaseous by- products from manufacturing) in and from buildings and the immediate surrounding area shall be disposed of in a safe, timely and sanitary manner. Containers and pipes for waste material shall be clearly identified.	
4.7. Sanitation and maintenance:—			
45	**4.7.1.**	How the building has been designed constructed and maintained to suit the manufacturing operations so as to produce drugs under hygienic conditions. Pls specify nature of construction used in the facility in respect of its maintenance and hygienic conditions.	
46	**4.7.2.**	Whether Written procedures are established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment and materials to be used in cleaning buildings and facilities	
47	**4.7.3**	Describe the pest, insects, birds and rodents control system followed in the premises. Attach copy of pest / rodent control schedule along with contract agreement if any.	

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5. Process equipment:-			
48	**5.1**	**Design and construction**	
49	**5.1.1**	Whether the equipments are designed aiming to minimize risk of error and permit effective cleaning in order to avoid cross contamination, build up of dust suitably located for its intended use, cleaning, sanitisation (where appropriate) and maintenance	
50	**5.1.2.**	Whether a set of current drawings are maintained for equipment and critical installations (e.g., instrumentation and utility systems)	
5.2. Equipment maintenance and cleaning			
51	**5.2.1.**	Whether Preventive Maintenance Schedule of the equipments is followed and records available?	
52	**5.2.2.**	Whether Written procedures are established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. These procedures shall include:-	
	(i)	assignment of responsibility for cleaning of equipment;	
	(ii)	cleaning schedules including where appropriate, sanitising schedules	
	(iii)	a complete description of the methods and materials including dilution of cleaning agents used to clean equipment;	
	(iv)	when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;	
	(v)	instructions for the removal or obliteration of previous batch identification;	
	(vi)	instructions for the protection of clean equipment from contamination prior to use	
	(vii)	inspection of equipment for cleanliness immediately before use, if practical; and	
	(viii)	establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate	
53	**5.2.3.**	Whether the equipments are designed with aiming to minimize risk of error and permit effective cleaning and	

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		maintenance in order to avoid cross contamination &build up of dust.	
54	**5.2.7.**	Whether all equipments bear with Status label (e.g. ID No.)	
5.3. Calibration			
55	**5.3.1.**	Whether written SOP/protocol are available for Control, weighing, measuring, monitoring and test equipment	
56	**5.3.2.**	Whether Equipment calibrations are performed using standards traceable to certified standards, if these exist	
57	**5.3.3.**	Records of these calibrations shall be maintained.	
5.4. Computerised systems			
58	**5.4.1.**	Whether GMP-related computerised systems are validated.	
59	**5.4.2.**	Whether Appropriate installation qualification and operational qualification are performed	
60	**5.4.3.**	Whether authorized persons with log in access has been designated.	
61	**5.4.4.**	Whether Written procedures are available for the operation and maintenance of computerised systems	
62	**5.4.5**	Whether additional check on the accuracy of the data entered is provided, Where critical data are being entered manually	
63	**5.4.6.**	Whether Changes to the computerised system are made according to a change procedure and are authorised, documented and tested	
64	**5.4.7.**	Whether A back-up system is provided	
6. Documentation and records:-			
65	**6.1**	Documentation system and specifications	
66	**6.1.1.**	Verify the documents prepared for requisite areas for warehouse, sampling dispensing operations, manufacturing areas, packing areas, finished goods storage areas, and Quality Control and Quality assurance areas.	
67	**6.1.2.**	Whether documents are approved signed and dated by authorized person?	
68	**6.1.3.**	Whether documents specify title, nature and purpose.	
69	**6.1.4.**	Whether documents are meeting the Schedule-'M' and Schedule-'U' requirements.	
70	**6.1.5.**	Verify the Master Formula and detailed operating procedures for proposed products are available?	
71	**6.1.6.**	If document is to be handled by electronic data processing, whether authorized persons with log in access has been designated.	

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6.2. Equipment cleaning and use record			
72	**6.2.1.**	Whether Records of major equipment use, cleaning, sanitisation and sterilisation and maintenance show the date, time (if appropriate), product and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.	
6.3. Records of raw materials, intermediates, API labelling and packaging materials			
73	**6.3.1.**	Whether Records of raw materials, intermediates, API labelling and packaging materials includes:-	
	(i)	the name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; the name of the supplier; the supplier's control numbers, if known, or other identification number; the number allocated on receipt; and the date of receipt;	
	(ii)	the results of any test or examination performed and the conclusions derived from this;	
	(iii)	records tracing the use of materials	
	(iv)	documentation of the examination and review of API labelling and packaging material for conformity with established specifications; and	
	(v)	the final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.	
74	**6.3.2.**	Whether Master (approved) labels are maintained for comparison to issued labels	
6.4. Master production instructions (master production and control records):			
75	**6.4.1**	How master formula records are prepared, authorized and controlled. Whether head of production, quality control and quality assurance unit endorse this documents. Whether master formula is batch size specific**.**	
76	**6.4.2.**	Master production instructions must include:-	
	(i)	the name of the intermediate or API being manufactured and an identifying document reference code, if applicable;	
	(ii)	a complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;	
	(iii)	an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of	

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		measure. Where the quantity is not fixed, the calculation for each batch size or rate of production shall be included. Variations to quantities shall be included where they are justified;	
	(iv)	the production location and major production equipment to be used;	
	(v)	the production location and major production equipment to be used;	
	(a)	sequences to be followed;	
	(b)	ranges of process parameters to be used;	
	(c)	sampling instructions and in-process controls with their acceptance criteria, where appropriat	
	(d)	time limits for completion of individual processing steps and the total process, where appropriate; and	
	(e)	expected yield ranges at appropriate phases of processing or time;	
	(vi)	where appropriate, special notations and precautions to be followed, or cross-references and	
	(vii)	the instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.	
6.5. Batch production records (batch production and control records)-			
77	**6.5.1.**	Whether Batch production records are prepared for each intermediate and API and also include complete information relating to the production and control of each batch.	
78	**6.5.2.**	Whether BPR are based on current master formula record. How BPR are designed to avoid transcription errors.	
79	**6.5.3.**	Documentation of completion of each significant step in the batch production records (batch production and control records) include-	
	(i)	dates and, when appropriate, times;	
	(ii)	identity of major equipment (e.g., reactors, driers and mills) used;	
	(iii)	specific identification of each batch, including weights, measures and batch numbers of raw materials,	

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		intermediates or any reprocessed materials used during manufacturing;	
	(iv)	actual results recorded for critical process parameters;	
	(v)	any sampling performed;	
	(vi)	signatures of the persons performing and directly supervising or checking each critical step in the operation;	
	(vii)	in-process and laboratory test results;	
	(viii)	actual yield at appropriate phases or times;	
	(ix)	description of packaging and label for intermediate or API;	
	(x)	representative label of API or intermediate, if made commercially available;	
	(xi)	any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation, if stored separately; and	
	(xii)	results of release testing.	
80	**6.5.4**	Whether Written procedures is established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications.	
6.6. Laboratory control records			
81	**6.6.1**	Whether Laboratory control records include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows-	
	(i)	a description of samples received for testing, including the name of the material or its source, batch number or other distinctive code, the date on which the sample was taken and where appropriate, the quantity and date the sample was received for testing;	
	(ii)	a statement of reference to each test method used;	
	(iii)	a statement of the weight or measure of sample used for each test as described by the method;	
	(iv)	data on or cross reference to the preparation and testing of reference standards, reagents and standard solutions;	
	(v)	a complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;	

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	(vi)	a record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors and equivalency factors;	
	(vii)	a statement of the test results and how they compare with established acceptance criteria;	
	(vii)	the signature of the person who performed each test and the dates the tests were performed; and	
	(ix)	the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness and compliance with established standards	
81	**6.6.2**	Complete records is maintained for-	
	(i)	any modifications to an established analytical method;	
	(ii)	periodic calibration of laboratory instruments, apparatus, gauges and recording devices	
	(iii)	all stability testing performed on APIs; and	
	(iv)	out of specification (OOS) investigations.	
6.7. Batch production record review			
82	**6.7.1.**	Whether a Written procedures is established and followed for the review and approval of batch production and laboratory control records including packaging and labelling	
83	**6.7.2.**	Please specify the mechanisms to ensure that Pharmaceuticals products are released for sale by authorization person. Whether there is check list for release of a batch. Please specify current SOP No. for batch release.	
84	**6.7.3.**	Specify the comprehensive quality assurance system maintained by the firm Inter-alia to cover deviation, reporting, investigation and change control.	
85	**6.7.4.**	What is procedure for release of intermediates,	
7. Materials management:-			
86	**7.1**	General controls	
87	**7.1.1.**	Whether SOPs for sampling, inspecting, testing of Raw Materials, Finish products, Packing Materials and for monitoring environmental conditions are available.	
88	**7.1.2.**	Whether incoming materials are purchased from approved sources.	
89	**7.1.3.**	What is the procedure for approving the source for incoming materials?	
7.2. Receipt and quarantine			

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90	**7.2.1.**	Please specify the procedures followed receiving and processing of in-coming materials (Starting materials and packing material).	
91	**7.2.2.**	Whether first in / first out or first expiry principal has been adopted.	
92	**7.2.3.**	Whether incoming materials are purchased from approved sources.	
	(i)	What is the procedure for approving the source for incoming materials?	
	(ii)	Whether the raw materials are directly purchased from the manufacturers.	
	(iii)	Whether list of approved vendors is available to the user.	
93	**7.2.4.**	How the containers from which samples have been drawn labeled.	
94	**7.2.5.**	Whether labels of raw material in the storage area have information like (a) designated name of the product and the internal code reference, where applicable, and analytical reference number; (b) manufacturer's name, address and batch number; (c) the status of the contents (e.g. quarantine, under test, released, approved, rejected); and (d) The manufacturing date, expiry date and re-test date.	
7.3. Sampling and testing of incoming production materials			
95	**7.3.1.**	Whether all the containers of each batch of starting materials is sampled for identification test.	
96	**7.3.2.**	Whether each batch of a consignment is considered for sampling, testing and release.	
97	**7.3.3.**	How hazardous or poisonous materials are stored and handled.	
98	**7.3.4.**	Pls specify sampling plan used. Which type of sampling tools are used and how they are cleaned, dried and maintained.	
99	**7.3.5.**	Whether separate sampling area for active Raw Materials and Excipients is provided and maintained. If yes, what is the control on entry of material and men into the sampling area. Whether reverse LAF have been provided for sampling. Whether log book for sampling booth maintained.	

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		If not what provision has been made for sampling so as to prevent contamination, cross contamination and mix-ups at a time of sampling.	
100	**7.3.6.**	How containers are cleaned before and after sampling. Who carries out the sampling? (Pls specify whether the sampling is carried out as per the current SOP).	
7.4. Storage			
101	**7.4.1.**	How Materials are handled and stored to prevent degradation, contamination and cross-contamination.	
102	**7.4.2.**	Whether separate areas are provided for under test, approved and rejected materials.	
7.5. Re-evaluation			
103	7.5.1	Whether Materials is re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).	
8. Production and in-process controls:-			
104	8.1	Production operation	
105	**8.1.1.**	Whether balances and other measuring equipments with appropriate range are available in the Raw Material stores & production areas and they are calibrated in accordance with SOP maintained. Specify the calibration schedule of the balances.	
106	**8.1.2.**	the container receiving the material shall be labelled with the following information	
	(i)	material name or item code;	
	(ii)	receiving or control number;	
	(iii)	weight or measure of material in the new container; and	
	(iiv)	re-evaluation or retest date, if appropriate.	
107	**8.1.3.**	Critical weighing, measuring or sub-dividing operations shall be witnessed or subjected to an equivalent control. Prior to use, production personnel shall verify that the materials are those specified in the batch record for the intended intermediate or API.	
108	**8.1.4.**	Other critical activities shall be witnessed or subjected to an equivalent control.	
109	**8.1.5.**	the amount of product obtained after different and critical stages of manufacture (yield), (comments or explanations for significant deviations from the expected yield limits shall be given,	

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110	**8.1.6.**	Any deviation shall be documented and explained. Any critical deviation shall be investigated.	
111	**8.1.7.**	Whether the processing status of major units of equipment indicated either on the individual units of equipment or by appropriate documentation, computer control systems or alternative means	
112	**8.1.8.**	Addition of any recovered or reprocessed material with reference to recovery or reprocessing stages.	
8.2. Time limits			
113	**8.2.1.**	Specify the time limits instruction in master production instruction to ensure quality of intermediates and APIs. Deviations shall be documented and evaluate	
8.3. In-process sampling and control			
114	**8.3.1.**	Batch record include a record of the in-process controls and the initials of the person(s) carrying them out,and the results obtained	
115	**8.3.2.**	Details of in-process controls with instructions for sampling and acceptance mention in respective SOP	
8.4. Blending batches of intermediates or APIs			
116	**8.4.1.**	Whether Blending processes is adequately controlled and documented and whether the blended batch is tested for conformance to established specifications, where appropriate.	
117	**8..4.2.**	Whether blending operation are validated to show homogeneity of the combined batch. Validation shall include testing of critical attributes (e.g., particle size distribution, bulk density and tap density) that may be affected by the blending process	
8.5. Contamination control			
118	**8.5.1.**	What control are taken if Residual materials carried over into successive batches of the same intermediate or API.	
119	**8.5.2.**	Specify the measures conducted in Production operations to prevent contamination of intermediates or APIs by other materials.	
120	**8.5.3.**	What are measure or Precautions take to avoid contamination when APIs are handled after purification.	
9. Packaging and identification labelling of APIs and intermediates:-			
121	**9.1**	General	
122	**9.1.1.**	Specify written procedures describing the receipt, identification, quarantine, sampling, examination, testing	

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		and release and handling of packaging and labelling materials.	
123	**9.1.2.**	Whether Packaging and labelling materials are conform to the established specifications.	
124	**9.1.3.**	Whether Records are maintained for each shipment of labels and packaging materials	
9.2. Packaging materials			
125	**9.2.1.**	Whether Containers provide adequate protection against deterioration or contamination of the intermediate or API	
126	**9.2.2.**	How Containers are clean	
127	**9.2.3.**	If containers are reused, how they are cleaned in accordance with documented procedures	
9.3. Label issuance and control			
128	**9.3.1.**	Whether Access to the label storage areas are limited to authorised personnel	
129	**9.3.2.**	Whether re-conciliation of used packaging materials is maintained. Whether unused packaging materials return to the store or destroyed.	
130	**9.3.3.**	How returned/unused packaging material like foils is controlled so as to prevent contamination and cross-contamination.	
131	**9.3.4.**	Whether Obsolete and out dated labels are destroyed	
132	**9.3.5.**	Whether Printing devices used to print labels for packaging operations are controlled	
133	**9.3.6.**	Whether the samples from the bulk are drawn tested, approved and released prior to packaging and labeling. How carryout the sampling.	
134	**9.3.7.**	Whether a printed label representative of those used are included in the batch production record.	
9.4. Packaging and labelling operations			
135	**9.4.1.**	Whether a documented procedures is designed to ensure that the correct packaging materials and labels are used	
136	**9.4.2.**	How printed packaging materials, product leaflets etc. are stored separately to avoid chances of mix-up.	
137	**9.4.3.**	Whether Labels used on containers of intermediates or APIs indicate the name or identifying code, the batch number of the product and the storage conditions	

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138	**9.4.4.**	If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, whether the name and address of the manufacturer, quantity of contents and special transport conditions and any special legal requirements are included on the label.	
139	**9.4.5.**	Whether Packaging and labelling facilities are inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed.	
140	**9.4.6.**	Whether Packaged and labelled intermediates or APIs are examined to ensure that containers and packages in the batch have the correct label.	
141	**9.4.7.**	Whether Intermediate or API containers that are transported outside the manufacturer's control are sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered	
10. Storage and distribution:-			
10.1		Warehousing procedures	
142	**10.1.1.**	Whether facilities are available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records shall be maintained of these conditions.	
143	**10.1.2.**	Whether separate areas are provided for under test, approved and rejected materials.	
10.2. Distribution procedures			
144	**10.2.1.**	How APIs and intermediates are released for distribution to third parties after they have been released by the quality units	
145	**10.2.2.**	How APIs and intermediates are transported so that does not adversely affect their quality. l	
146	**10.2.3.**	Whether Special transport or storage conditions for an API or intermediate are stated on the labe	
147	**10.2.4.**	Whether a system is in place by which the distribution of each batch of intermediate or API or both can be readily determined to permit its recall	
11. Laboratory controls:-			
148	**11.1**	**General controls**	

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Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
149	**11.1.1.**	Whether QC area is independent of production area.	
150	**11.1.2.**	Whether QC carries out its own: physico-chemical testing, biological testing, microbiological testing & sterility testing and Instrumental testing.	
152	**11.1.3.**	Whether appropriate specifications are established for APIs	
153	**11.1.4.**	How Laboratory controls followed and documented at the time of performance	
154	**11.1.5.**	How OOS result obtained and documented according to the procedure.	
155	**11.1.6.**	Whether Reagents and standard solutions prepared and labelled following written procedures. "Use by" dates shall be applied as appropriate for analytical reagents or standard solutions.	
156	**11.1.7.**	Please specify the procedures of preparation of working standard from the reference standards. Whether they are stored as per provision	
11.2. Testing of intermediates and APIs			
157	**11.2.1.**	Whether for each batch of intermediate and API, appropriate laboratory tests is conducted to determine conformance to the specifications.	
158	**11.2.2.**	Whether an impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process has established for each API.	
159	**11.2.3.**	Whether the impurity profile is compared at appropriate intervals with the impurity profile in the regulatory submission or compared with historical data in order to detect changes to the API resulting from modifications to raw materials, equipment operating parameters or the production process	
160	**11.2.4.**	Whether appropriate microbiological tests is conducted on each batch of intermediate and API where microbial quality is specified.	
11.3. Certificates of analysis			
161	**11.3.1.**	Whether authentic certificates of analysis is issued for each batch of intermediate or API on request	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART XII OF SCHEDULE M SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENT			
Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
162	**11.3.2.**	Whether COA bears Information: • the name of the intermediate or API, including where appropriate its grade, • the batch number and the date of release • For intermediates or APIs with an expiry date • For intermediates or APIs with a retest date,	
163	**11.3.3.**	Whether the certificate bear list of each test performed in accordance with compendial or customer requirements, including the acceptance limits and the numerical results obtained (if test results are numerical).	
164	**11.3.4.**	Whether certificates bear dated and signed by authorised personnel and show the name, address and telephone number of the original manufacturer.	
165	**11.3.5.**	How new certificates are issued in case of by or on behalf of repackers or reprocessors, agents or brokers,	
11.4. Stability monitoring of APIs			
166	**11.4.1.**	Please specify the procedures for carrying out the stability studies.	
167	**11.4.2.**	Under what condition stability studies of the products are tested. How many stability chambers have been provided?	
168	**11.4.3.**	How self-life is assigned to a product. Please give current stability protocol No. Whether records of stability studies are maintained. Please attach stability calendar of last year.	
11.5. Expiry and retest dating			
169	**11.5.1.**	Whether the expiry date assigned on the basis of stability study?	
11.6. Reserve or retention samples			
170	**11.6.1.**	Whether reserve sample for each batch has been retained and record it maintained for the same.	
12. Validation:-			
171	**12.1**	Specify the validation policy of the company.	
172	**12.1.1.**	Whether validation master plan has been prepared.	
173	**12.1.2.**	Whether the critical parameters and attributes been identified during the development stage or from historical data and the ranges necessary for the reproducible operation shall be defined which include	

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	(i)	defining the API in terms of its critical product attributes;	
	(ii)	identifying process parameters that could affect the critical quality attributes of the API; and	
	(iii)	determining the range for each critical process parameter expected to be used during routine manufacturing and process control	
12.2. Validation documentation			
174	**12.2.1.**	Whether a written validation protocol is established that specifies how validation of a particular process will be conducted. The protocol shall be reviewed and approved by the quality units and other designated units.	
175	**12.2.2.**	Please specify whether the critical processes validated prospectively, retrospectively or concurrently	
176	**12.2.3.**	Whether validation of following performed and documented: Analytical methods, production and assay equipment, sterile production process, non-sterile production processes, cleaning procedures, critical support systems (purified water, water for injections, air, vapor etc.) facilities.	
177	**12.2.4.**	Are criteria established to assess the changes originating a revalidation? Are trend analyses performed to assess the need to re-validate in order to assure the process and procedures continue to obtain the desired results?	
12.3. Qualification			
178	**12.3.1.**	Whether Qualification is carried out by conducting the following activities, individually or combined:-	
	(i)	Are equipment Design Qualification (DQ) documented verify that the proposed design of the facilities, equipment or systems is suitable for the intended purpose;	
	(ii)	Are the equipment installation qualification(IQ) protocols contains following: introduction, installation, description, responsibilities, performed tests/assays, qualification acceptance criteria, data recording and reporting?	
	(iii)	Whether the equipment operation qualification (OQ) protocols contains following: introduction, equipment description of the equipment operation steps (SOP's), Responsibilities, qualification acceptance criteria, data recording and reporting. Whether report contains summery, description of performed tests/assays, obtained	

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Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
		data tables, results, conclusion, revision and approval signatures.	
	(iv)	Whether equipment performance qualification (PQ) protocols contain followings: Introduction, responsibilities, performed assays, qualification acceptance criteria, data recording and reporting.	
12.4. Approaches to process validation			
179	**12.4.1.**	Whether Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes	
	(a)	Whether critical quality attributes and critical process parameters have been identified;	
	(b)	Whether appropriate in-process acceptance criteria and controls have been established;	
	(c)	Whether impurity profiles have been established for the existing API.	
12.5. Process validation programme			
180	**12.5.1.**	Whether the firm has process validation programme	
181	**12.5.2.**	Please specify whether the critical processes validated prospectively, retrospectively or concurrently	
182	**12.5.3.**	Whether process validation confirm that the impurity profile for each API is within the limits specified.	
12.6. Periodic review of validated systems			
183	**12.6.1**	Whether Systems and processes are periodically evaluated to verify that they are still operating in a valid manner.	
12.7. Cleaning validation			
184	**12.7.1.**	Is validation performed to confirm cleaning effectiveness?	
185	**12.7.2.**	Does the protocol define the selection criteria for products or groups of products subject to cleaning validation? Is data produced supporting the conclusion that residues were removed to an acceptable level.	
186	**12.7.3.**	Please specify whether the validation is implemented to verify cleaning of: Surfaces in contact with the product after a change in product, between shift batches	
187	**12.7.4.**	Whether the cleaning validation protocol include: Interval between the end of production and the beginning of the cleaning SOP's.	

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		Cleaning SOP to be used. Any monitoring equipment to be used. Number of consecutive cycles performed? Clearly defined sampling points.	
188	**12.7.5.**	Whether validation records include recovery study data, Analytical methods including detection limits, acceptance criteria, signatures of the quality assurance manager, employee in charge of cleaning and the verification from production and quality control.	
189	**12.7.6.**	Please specify whether the validation strategy include contamination risks, equipment storage time, the need to store equipment dry sterilize and free of Pyrogens if necessary?	
190	**12.7.7.**	Whether Cleaning procedures is monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible.	
12.8. Validation of analytical methods			
191	**12.8.1.**	Whether Analytical methods are validated unless the method employed is included in the relevant pharmacopoeia or other recognised standard reference.	
192	**12.8.2.**	WhetherMethods is validated which include consideration of characteristics included within the ICH guidelines on validation of analytical methods.	
193	**12.8.3.**	Whether Complete records is maintained of any modification of a validated analytical method.	
13. Change control:			
194	**13.1.**	Whether a formal change control system has been established to evaluate all changes that may affect the production and control of the intermediate or API	
195	**13.2.**	Whether written procedures cover the identification, documentation, appropriate review and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software	
196	**13.3.**	Any proposals for relevant changes to GMP will be drafted, reviewed and approved by the appropriate	

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART XII OF SCHEDULE M SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENT			
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		organisational units and reviewed and approved by the quality units	
197	**13.4.**	Whether the potential impact of the proposed change on the quality of the intermediate or API is evaluated.	
198	**13.5.**	When implementing approved changes, whether measures are taken to ensure that all documents affected by the changes are revised	
199	**13.6.**	After the change has been implemented, whether the first batch produced or tested under the change has been evaluated.	
200	**13.7.**	Whether the potential for critical changes to affect established retest or expiry dates is evaluated.	
14. Rejection and reuse of materials:-			
201	**14.1.**	**Whether** Intermediates and APIs which fails to meet established specifications has been identified as such and quarantined. Whether record is maintained for the final disposition of rejected materials	
14.2. Reprocessing			
202	**14.2.1.**	Specify the procedures for re-processing. Whether reprocessed batch is subjected to stability evaluation. Whether the recoveries are added into the subsequent batches. If yes specify the procedures.	
14.3. Reworking			
203	**14.3.1.**	Whether an investigation into the reason for non-conformance has been performed, before a decision is taken to rework batches that do not conform to the established standards or specifications	
204	**14.3.2.**	Whether batches that have been reworked has been subjected to appropriate evaluation, testing, stability testing if warranted and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.	

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Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
205	**14.3.3.**	Specify procedures that has provide for comparing the impurity profile of each reworked batch with batches manufactured by the established process. Where routine analytical methods are inadequate to characterise the reworked batch, additional methods shall be used.	
14.4. Recovery of materials and solvents			
206	**14.4.1.**	Whether approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use if Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates or the API is considered	
207	**14.4.2.**	Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or comingling with other approved materials.	
208	**14.4.3.**	Fresh and recovered solvents and reagents can be combined, if adequate testing has shown their suitability for all manufacturing processes in which they may be used.	
209	**14.4.4.**	Whether the use of recovered solvents, mother liquors and other recovered materials has been adequately documented.	
14.5. Returns			
210	**14.5.1.**	Whether Returned intermediates or APIs been identified as such and quarantined	
211	**14.5.2.**	If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, whether the returned intermediates or APIs been reprocessed, reworked or destroyed, as appropriate.	
212	**14.5.3.**	Whether Records of returned intermediates or APIs been maintained. For each return, documentation shall include-	
		(i) name and address of the consignee;	
		(ii) intermediate or API, batch number and quantity returned;	
		(iii) reasons for return; and	
		(iv) use or disposal of the returned intermediate or API.	
15. Complaints and recalls			

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART XII OF SCHEDULE M SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ACTIVE PHARMACEUTICAL INGREDIENT			
Sr. No.	**Reference as per sch. M**	**Particulars**	**Observations**
213	**15.1.**	Whether all quality-related complaints, either received orally or in writing, has been recorded and investigated according to the written procedure	
214	**15.2.**	Complaint records include-	
		(I) name and address of complainant;	
		(II) name (where appropriate title) and telephone number of person submitting the complaint;	
		(III) nature of the complaint (including name and batch number of the API)	
		(IV) date on which the complaint was received;	
		(V) action initially taken (including dates and identity of person taking the action);	
		(VI) any follow-up action taken;	
		(VII) response provided to the originator of the complaint (including date on which the response was sent); and	
		(VIII) final decision on intermediate or API batch or lot.	
215	**15.3.**	Whether Records of complaints retained in order to evaluate trends, product-related frequencies and severity with a view to taking additional, and if appropriate, immediate corrective action.	
216	**15.4.**	Whether there is written procedure that defines the circumstances under which a recall of an intermediate or API to be considered.	
217	**15.5.**	Whether the recall procedure has been designate which involved in evaluating the information, how a recall shall be initiated, who shall be informed about the recall and how the recalled material shall be treated	
218	**15.6.**	Whether the recalls has been informed to the Licencing Authorities.	
16. Contract manufacturers (including laboratories):-			
219	**16.1.**	Specify the measures taken for the prevention of cross-contamination and to maintaining traceability.	
220	**16.2.**	Whether contract giver has evaluated Contract manufacturers (including laboratories) to ensure GMP compliance of the specific operations taking place at the contract sites.	

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221	**16.3.**	Whether there is written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party	
222	**16.4.**	Whether the contract permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.	
223	**16.5.**	Where sub-contracting is allowed, whether the contract acceptor has not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements.	
224	**16.6.**	Whether manufacturing and laboratory records is being kept at the site where the activity takes place and be readily available.	
225	**16.7.**	Whether changes in the process, equipment, test methods, specifications or other contractual requirements has not be made unless the contract giver is informed and approves the changes	

PART XIII: Requirements for Plant and Equipment

Sr. No.	Reference	Particulars	Observations
	1. External Preparations		
1	1	Whether equipment recommended for the manufacture of 'External preparations', (i.e., Ointments, Emulsions, Lotions, Solutions, Pastes, Creams, Dusting Powders and such identical products used for external applications whichever is applicable) provided as mentioned below:	
	(1)	Mixing and storage tanks preferably of stainless steel or any other appropriate material	
	(2)	Jacketed Kettle stainless steel container (steam, gas or electrically heated)	
	(3)	Mixer (Electrically operated)	
	(4)	Planetary mixer	
	(5)	A colloid mill or a suitable emulsifier	
	(6)	A triple roller mill or an ointment mill	
	(7)	Liquid filling equipment (Electrically operated)	
	(8)	Jar or tube filling equipment	
	Area- Whether a minimum area of thirty square meters for basic installation and ten square meters for ancillary area is provided		
	2. Oral Liquid Preparations		
2	2	Whether equipment recommended for the manufacture of oral or internal use preparations, i.e., Syrups, Elixirs, Emulsions and Suspensions, whichever is applicable is provided as mentioned below:	
	(1)	Mixing and storage tanks preferably of Stainless steel or any other appropriate material	
	(2)	Jacketed Kettle or Stainless steel tank (steam, gas or electrically heated)	
	(3)	Portable stirrer (Electrically operated)	

	(4)	A colloid mill or suitable emulsifier (Electrically operated)	
	(5)	Suitable filtration equipment (Electrically operated)	
	(6)	Semi-automatic or automatic bottle filling machine;	
	(7)	Pilfer proof cap sealing machine	
	(8)	Water distillation unit or deionizer;	
	(9)	Clarity testing inspection units	
	Area- Whether a minimum area of thirty square meters for basic installation and ten square meters for ancillary area is provided		
	3. Tablets		
3	3	Whether the Tablet section is free from dust and floating particles and air-conditioned. Whether each tablet compression machine is in isolated into cubicles and connected to a vacuum dust collector or an exhaust system. Whether the tablet production department is divided into four distinct and separate sections as follows: (a) Mixing, Granulation and Drying section (b) Tablet Compression section (c) Packing section (Strip or blister machine wherever required), and (d) Coating section (wherever required)	
4	3.1	Whether electrically operated equipment for the manufacture of compressed tablets and hypodermic tablets provided Whether following equipment provided in various section as mentioned below:	
	(a)	**Granulation-cum-Drying section-** (1) Disintegrator and sifter (2) Powder mixer (3) Mass mixer or Planetary mixer or Rapid mixer granulator (4) Granulator wherever required	

		(5) Thermostatically controlled hot air oven with trays (preferably mounted on a trolley) or Fluid bed dryer (6) Weighing machines	
	(b)	**Compression section** (1) Tablet compression machine, single or multi punch or rotatory (2) Punch and dies storage cabinets (3) Tablet de-duster (4) Tablet Inspection unit or belt (5) Dissolution test apparatus wherever required (6) In-process testing equipment like single pan electronic balance, hardness tester, friability and disintegration test apparatus (7) Air-conditioning and dehumidification arrangement (wherever necessary)	
	(c)	**Packaging section** (1) Strip or blister packaging machine (2) Leak test apparatus (vacuum system) (3) Tablet counters (wherever applicable) (4) Air-conditioning and dehumidification arrangement (wherever applicable)	
	Area- Whether a minimum area of sixty square meters for basic installation and twenty square meters for ancillary area for un-coated tablets is provided.		
	(d)	**Coating section** (1) Jacketed kettle stainless steel container or any other appropriate material (steam, gas or electrically heated for preparing coating suspension) (2) Coating pan (Stainless steel) (3) Polishing pan (where applicable)	

		(4) Exhaust system (including vacuum dust collector) (5) Air conditioning and Dehumidification Arrangement (6) Weighing machine.	
5	3.2	Whether the coating section is made dust free with suitable exhaust system to remove excess powder and fumes resulting from solvent evaporation. Whether the coating section is air-conditioned and dehumidified, wherever considered necessary.	
		Area- Whether a minimum additional area of thirty square meters for coating section for basic installation and ten square meters for ancillary area is provided Whether a separate area and equipment for mixing, granulation, drying, tablet compression, coating and packing is provided for Penicillin group of drugs on the lines indicated above. Whether care is exercised to avoid cross-contamination in case of operations involving dust and floating particles.	
6	3.3	Whether a separate air-conditioned room is provided for the manufacture of Hypodermic tablets under aseptic conditions and the walls of which should be smooth and washable. Whether the granulation, compression and packing is carried out in this room.	
7	3.4	Whether the manufacture of effervescent and soluble tablets is be carried out in air-conditioned and dehumidified areas.	
	4. Powders		
8	4	Whether equipment recommended for the manufacture of powders provide as mentioned below:	
	(1)	Disintegrator;	
	(2)	Mixer (electrically operated	

	(3)	Sifter	
	(4)	Stainless steel vessels and scoops of suitable sizes	
	(5)	Filling equipment	
	(6)	Weighing machine.	
9	4	Whether a suitable exhaust system is provided in the case of operation involving floating particles of fine powder. Whether the workers are provided with suitable masks during operation.	
	Area- Whether a minimum area of thirty square meters is provided to allow for the basic installations. Whether an additional room is provided for the purpose of the actual blending is to be done on the premises.		
	5. Capsules		
10	5	Whether a separate enclosed area suitably air-conditioned and dehumidified with an airlock arrangement is provided for the manufacture of capsules.	
		Whether equipment recommended for filling Hard Gelatin Capsules is provided as mentioned below:	
	(1)	Mixing and blending equipment (electrically or power driven	
	(2)	Capsule filling units	
	(3)	Capsules counters (wherever applicable)	
	(4)	Weighing machine	
	(5)	Disintegration test apparatus	
	(6)	Capsule polishing equipment	
11	Whether separate equipment and filling and packaging areas is provided in penicillin and non-penicillin sections. Whether a suitable exhaust system is provided in case of operations involving floating particles of fine powder.		

	Whether manufacturing and filling is carried out in air-conditioned areas and the room is dehumidified.		
12	Area- Whether a minimum area of twenty-five square meters for basic installation and ten square meters for ancillary area each for penicillin and non-penicillin sections is provided.		
	6. Surgical dressing		
13	6	Whether equipment recommended for the manufacture of surgical dressings other than Absorbent Cotton Wool is provided as mentioned below:	
	(1)	Rolling machine	
	(2)	Trimming machine	
	(3)	Cutting equipment	
	(4)	Folding and pressing machine for gauze	
	(5)	Mixing tanks for processing medicated dressing	
	(6)	Hot air dry oven	
	(7)	Steam steriliser or dry heat steriliser or other suitable equipment	
	(8)	Work tables and benches for different operations	
	Area- Whether a minimum area of thirty square meters is provided to allow for the basic installations. Whether another room with a minimum area of thirty square meters is provided in case medicated dressings are to be manufactured.		
	7. Ophthalmic preparations		
14	7	Whether a separate enclosed area with air lock arrangement is provided.	
		Whether equipment recommended for manufacture under aseptic conditions of Eye Ointment, Eye lotions and other preparations for external use is provided as mentioned below:	
	(1)	Thermostatically controlled hot air ovens (preferably double ended)	

	(2)	Jacketed kettle or Stainless-steel tanks (steam, gas or electrically heated)	
	(3)	Mixing and storage tanks of stainless steel or Planetary mixer	
	(4)	Colloid mill or ointment mill	
	(5)	Tube filling and crimping equipment (semi-automatic or automatic filling machines)	
	(6)	Tube cleaning equipment (air jet type)	
	(7)	Tube washing and drying equipment, if required	
	(8)	Automatic vial washing machine	
	(9)	Vial drying oven	
	(10)	Rubber bung washing machine	
	(11)	Sintered glass funnel, Seitz filter or filter candle (preferably cartridge and membrane filters)	
	(12)	Liquid filling equipment (semi-automatic or automatic filling machines)	
	(13)	Autoclave (preferably ventilator autoclave)	
	(14)	Air-conditioning and dehumidification arrangement (preferably centrally air-conditioned and dehumidification system)	
	(15)	Laminar air flow units.	
	Area: 1. Whether a minimum area of twenty-five square meters for basic installation and ten square meters for ancillary area is provided. Whether manufacture and filling are carried out in air-conditioned areas under aseptic conditions. Whether the rooms shall be further dehumidified as considered necessary, if preparations containing antibiotics are manufactured. 2. Whether areas for formulations meant for external use and internal use are provided separately to avoid mix up.		
	8. Pessaries and Suppositories		
15	1	Whether equipment recommended for manufacture of Pessaries and Suppositories is provided as mentioned below:	

	(i)	Mixing and pouring equipment	
	(ii)	Moulding equipment	
	(iii)	Weighing machine	
	Area- Whether a minimum area of twenty square meters is provided to allow for the basic installation		
16	2	Whether in the case of pessaries manufactured by granulation and compression, the requirements as indicated under "item 3 of Tablet" are provided.	
	9. Inhalers and Vitrallae		
17	9	Whether equipment recommended for manufacture of Inhalers and Vitrallae provided as mentioned below:	
	(1)	Mixing equipment	
	(2)	Graduated delivery equipment for measurement of the medicament during filling	
	(3)	Sealing equipment	
	Area: Whether an area of minimum twenty square metres is provided for the basic installations.		
	10. Repacking of drugs and pharmaceutical chemicals		
18	10	Whether equipment is recommended for repacking of drugs and pharmaceuticals, chemicals provided as mentioned below:	
	(1)	Powder disintegrator	
	(2)	Powder sifter (Electrically operated)	
	(3)	Stainless steel scoops and vessels of suitable sizes	
	(4)	Weighing and measuring equipment	
	(5)	Filling equipment (semi-automatic or automatic machine)	
	(6)	Electric sealing machine	
	Area- Whether an area of minimum thirty square metres is provided for the basic installation.		

	Whether a suitable exhaust system is provided n case of operations involving floating particles of fine powder		
	11. Parenteral Preparations		
19	11.1	**Parenteral preparations in glass containers**	
	1	**Water management area**: (This includes water treatment and storage) Whether the equipment recommended is provided as mentioned below: (1) Reverse Osmosis (RO) or Electro-deionisation (EDI) water treatment unit (2) Distillation (multi column with heat exchangers) unit (3) Thermostatically controlled water storage tank (4) Transfer pumps (5) Service lines for carrying water into user areas through continuously circulating pipe work loop. The Material of Construction (MOC) for the storage tank and circulating pipe line shall be of SS-316 L Grade.	
	2	**Containers and closures preparation area**: (This includes washing and drying of ampoules, vials, bottles and closures) Whether the equipment recommended is provided as mentioned below: (1) Automatic rotary ampoule or vial or bottle washing machine having separate air, water, distilled water jets (2) Automatic closures washing machine (3) Storage equipment for ampoules, vials, bottles and closure (4) Dryer or sterilizer (double ended) (5) Dust proof storage cabinets (6) Stainless steel benches or stools	
	3	**Solution preparation area**: (This includes preparation and filtration of solution) Whether the equipment recommended is provided as mentioned below: (1) Automatic rotary ampoule or vial or bottle washing machine having separate air, water, distilled water jets (2) Automatic closures washing machine (3) Storage equipment for ampoules, vials, bottles and closure	

		(4) Dryer or steriliser (double ended) (5) Dust proof storage cabinets (6) Stainless steel benches or stools.	
	4	**Filling capping and sealing area**: (This includes filling and sealing of ampoules or filling, capping and sealing of vials and bottles) Whether the equipment recommended is provided as mentioned below: (1) Automatic ampoule or vial or bottle filling, sealing and capping machine under laminar air flow work station (2) Gas lines (Nitrogen, Oxygen and Carbon di-oxide), wherever required (3) Stainless steel benches or stools.	
	5	**Sterilization area:** Whether the equipment recommended is provided as mentioned below: (1) Steam steriliser (preferably with computer control for sterilisation cycle along with trolley sets for loading or unloading containers before and after sterilisation) (2) Hot Air steriliser (preferably double ended) (3) Pressure leak test apparatus.	
	6	**Quarantine area:** Whether the equipment recommended is provided as mentioned below: (1) Storage cabinets (2) Raised platforms or steel racks.	
	7	**Visual inspection area:** Whether the equipment recommended is provided as mentioned below: (1) Visual inspection units (preferably conveyor belt type and composite white and black assembly supported with illumination) (2) Stainless steel benches or stools	
	8	**Packaging area:** Whether the equipment recommended is provided as mentioned below: (1) Batch coding machine (preferably automatic) (2) Labeling unit (preferably conveyor belt type) (3) benches or stools	
	Area: (1) Whether a minimum area of one hundred and fifty square meters for the basic installation and an ancillary area of one hundred square meters for Small Volume Injectable are provided. Whether an area of one hundred and fifty square meters each for the basic installation and for ancillary area is provided for Large Volume Parenterals.		

	Whether these areas are partitioned into suitable enclosures with airlock arrangements. (2) Whether areas for formulations meant for external use and internal use are provided separately to avoid mix-up. (3) Whether packaging materials for large volume Parenteral shall have a minimum area of one hundred square meters.		
20	11.2	**Parenteral preparations in plastic containers by Form-Fill-Seal or Blow, Fill-Seal technology**	
	1	**Water management area:** Whether the equipment recommended is provided as mentioned below: (1) RO or Electro-deionisation (EDI) water treatment unit (2) Distillation unit (multi column with heat exchangers) (3) Thermostatically controlled water storage tank (4) Transfer pumps (5) Service lines for carrying water into user areas through continuously circulating pipe work loop. The Material of Construction (MOC) for the storage tank and circulating pipe line shall be of SS-316 L Grade.	
	2	**Solution preparation area:** Whether the equipment recommended is provided as mentioned below: (1) Solution preparation and storage tanks (2) Transfer pumps (3) Cartridge and membrane filters	
	3	**Container moulding-cum-filling and sealing area:** Whether the equipment recommended is provided as mentioned below: (1) Sterile Form-Fill-Seal machine (all operations in one station with built-in laminar air flow work station having integrated container output conveyor belt through pass box) (2) Arrangement for feeding plastic granules through feeding-cum-filling tank into the machine	
	4	**Sterilization area:** Whether the equipment recommended is provided as mentioned below:	

		Super heated steam steriliser (with computer control for sterilisation cycle along with trolley sets for loading or unloading containers for sterilisation).	
	5	**Quarantine area:** Whether the equipment recommended is provided as mentioned below: Adequate number of platforms or racks with storage system.	
	6	**Visual inspection area:** Whether the equipment recommended is provided as mentioned below: Adequate number of platforms or racks with storage system.	
	7	**Packaging area:** Whether the equipment recommended is provided as mentioned below: (1) Pressure leak test apparatus (pressure belt or rotating disc type) (2) Batch coding machine (preferably automatic) (3) Labeling unit (preferably conveyor belt type)	
	Area: (1) Whether a minimum area of two hundred and fifty square meters for the basic installation and an ancillary area of one hundred and fifty square meters for large volume parenteral preparations in plastic containers by Form-Fill-Seal technology is provided. Whether these areas are partitioned into suitable enclosures with air-lock arrangements. (2) Whether areas for formulations meant for external use and internal use are provided separately to avoid mix up. (3) Whether the packaging materials for large volume Parenteral have a minimum area of one-hundred square meters.		

Annexure N

Format for Inspection Report for drugs

Central Drugs Standard Control Organization
Directorate General of Health Services, Ministry of Health and Family Welfare,
Government of India
FDA Bhavan, ITO, Kotla Road, New Delhi -110002

Part-1	General Information
Manufacturer details:	
Company information	Name of manufacturer
Corporate address of manufacturer	Corporate Address of the firm Phone No.: +91- Fax No.: +91- Contact telephone no.: +91- E mail:
Contact person, telephone number and email address	Name: Designation: Contact No.: +91- Email I.D: Name: Designation: Contact No.: +91- Email I.D:
Constitution of firm	Public/Private Limited/ Partnership/others (Specify)
Name of Directors	Name of directors
Inspected site	Name & Address of the manufacturing site Fax No.: +91-

	Contact telephone no.: +91- E mail:
Manufacturing licence number and other regulatory accreditations	License No. ……. dated under Form-25 dated XX/YY/ZZZZ with validity from XX/YY/ZZZZ to XX/YY/ZZZZ. License No. ……dated under Form-28 dated XX/YY/ZZZZ with validity from XX/YY/ZZZZ to XX/YY/ZZZZ. License No. ……. dated under Form-28D dated XX/YY/ZZZZ with validity from XX/YY/ZZZZ to XX/YY/ZZZZ. WHO-GMP Certificate No. ……dated XX/YY/ZZZZ with validity from XX/YY/ZZZZ to XX/YY/ZZZZ. GLP Certificate No. ……. dated with validity from XX/YY/ZZZZ to XX/YY/ZZZZ.
Summary of activities performed at the site	*The firm is involved in manufacturing, testing and release of Active Pharmaceutical Ingredient(s) (APIs)/ Finished Pharmaceutical Products (FPPs) of non-betalactum/ Beta-lactum/ Biological Products (Vaccine, r-DNA products, Blood Products, etc.)/ Hormonal Products, Cytotoxic products, Metered Dose Inhalers, etc. category of products.* *Description of main activities (including, e.g. FPP(s) or API(s) manufactured and their reference/registration/active pharmaceutical ingredient master file (APIMF)/drug master file (DMF)/certificate of suitability to the monographs of the European Pharmacopoeia (CEP) numbers, as appropriate); other manufacturing activities carried out on the site (e.g. manufacture of cosmetics, research and development); use of outside scientific, analytical or other technical assistance in manufacture and quality control Brief description of the quality management system of the firm responsible for manufacture. Reference can be made to a site master file if one is available.*
Product details	*The firm is involved in manufacturing, testing and release of following type of dosage forms:* *(List down the type pf dosage forms manufactured by the firm. For example)* *<u>Non-Betalactum Products:</u>* *Active Pharmaceutical Ingredients* *Tablets*

	Capsule (Hard and Soft Gelatin Capsules) *External preparation (Cream, Ointment, Gels, Lotion, Dusting Powder, etc)* *Oral Liquid Dosage Forms (Solution, Suspension, etc.* *Small Volume Parenterals (Vial, Ampoule, Prefilled Syringe, etc.)* *Large Volume Parenterals* *<u>Betalactum Products:</u>* *Active Pharmaceutical Ingredients* *Tablets* *Capsule (Hard and Soft Gelatin Capsules)* *External preparation (Cream, Ointment, Gels, Lotion, Dusting Powder, etc)* *Oral Liquid Dosage Forms (Solution, Suspension, etc.* *Small Volume Parenterals (Vial, Ampoule, Prefilled Syringe, etc.)* *Large Volume Parenterals* *Other categories of products like Biological Products (Vaccine, r-DNA products, Blood Products, etc.), Hormonal Products, Cytotoxic products, Metered Dose Inhalers, etc.*
Inspection details	
Date of inspection	XX/YY/ZZZZ to XX/YY/ZZZZ
Type of inspection	For example, Routine/ Follow-up/ For-cause/ Grant/ renewal of CoPP as per WHO Certification Scheme
Purpose of inspection	With reference to firm's application no. Nil dated xx/yy/zzzz received vide diary No. xxxxx dated xx/yy/zzzz and further directives received from Deputy Drugs Controller (I), CDSCO Sub-zone, Rishikesh vide letter no. …… dated xx/yy/zzzz for joint inspection of the firm for renewal of COPP as WHO Certification Scheme/ grant of fresh manufacturing license/ routine inspection as per Central Inspection Plan/ compliance verification inspection of previous inspection dated…….
Inspection Team:	*<u>Official from CDSCO Zone/ Sub-zone, (Name of Zonal/ Sub-zonal office):</u>* *Sh. ……., Drugs Inspector*

	Sh. ……., Drugs Inspector *<u>Officials from State Licensing Authority, (Name of State):</u>* *Sh. ……., Drugs Inspector* *Sh. ……., Drugs Inspector* *<u>Subject Expert, if any (Name of Institution/ Organisation):</u>* *Sh. ……., Designation* *Sh. ……., Designation*
Competent Regulatory Authority:	*Central Drugs Standard Control Organisation (CDSCO), Name of Zonal/ Sub-zonal office) and State Licensing Authority, (Name of State)*
Introduction:	

	S. No.	Date of inspection	Inspecting authority	Purpose	Compliance status
History of previous inspections conducted by Indian or International Drugs Regulatory Authorities (Last three Years):		xx/yy/zzzz to xx/yy/zzzz	CDSCO and SLA, (name of State)	Follow-up of previous Routine Inspection	Complied
		xx/yy/zzzz to xx/yy/zzzz	CDSCO and SLA, (name of State)	Routine Inspection	Not Complied
Major change since previous inspection	List of major change carried out by the firm is enclosed as Annexure-B.				

Scope of inspection	To verify the tenets of GMP as per Schedule-M of Drugs & Cosmetics Rules/ WHO guidelines.			
Areas inspected	List of area inspected along with identification no. of area in tabular form for each dosage form enclosed as Annexure-C.			
Key persons met	S.No.	Name	Designation	Department

Part-2	Brief summary of the findings and recommendations (where applicable)
	Location and surroundings:
	The whole manufacturing site was found located in an eco-friendly environment and free from open sewage, drain public lavatory or any other activities which may contaminate the final product. The whole plant was found covering a total area of around XXX square meter of land and total constriction area of plant is XXX Square meter with the facilities include raw and packaging materials warehouses, dedicated and total segregated areas for manufacture of different category of products like XXXXXXXX, Utility Block and ETP. A well-equipped stability cell along with Quality Control and Research & Development laboratory consist of Formulation Development Laboratory and Analytical Development Laboratory was also found in place. No Toxic or Hazardous substances were found used / manufactured in the facility. The overall locations and surroundings were found fit and satisfactory for the manufacture of Pharmaceutical Dosage Formulations. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately,* if any.

	Pharmaceutical quality system:
	The firm has comprehensively designed and correctly implemented pharmaceutical quality system (PQS) incorporating GMP and QRM which consist of clearly defined roles, responsibilities, and authorities which are defined, communicated and implemented throughout the organization and has specified production and quality control operations in a written form, managerial responsibilities, vendor qualification criteria, controls on starting materials, intermediate products, bulk products, finished products, batch certification or release criteria, procedure for handling deviation and change controls, product quality reviews, etc. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately*, if any.
	Quality Risk Management:
	The firm has defined SOP/ protocol/ Report (……...revision no. XX dated xx/yy/zzzz) and has performed Quality Risk Assessment and maintained records. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately*, if any.
	Product Quality Review:
	The firm has well defined procedure (SOP No. ……, revision No. xx dated xx/yy/zzzz) for Product Quality Review (PQR) and PQR was conducted once in a year from January to December for each product to verify consistency of the existing process, appropriateness of current specifications for starting materials, finished product, etc. as defined in Schedule-M of Drug Rules and WHO guidelines. The inspection team has verified PQR of following products and same were found carried out as per the defined SOP. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately*, if any.
	Good Manufacturing Practices for Pharmaceutical Products:
	Briefly describe how the elements of GMP are implemented
	Sanitation and Hygiene:
	Describe procedures and records relating to sanitation and hygiene for personnel, premises, equipment, production materials, cleaning materials and others that could become a source of contamination
	Qualification and Validation:
	Describe policies, procedures, records and any other evidence for qualification and validation and how the validation status is monitored and maintained

	Complaints:
	Describe procedures, responsibilities and records for handling complaints, including extension of investigation to other batches, possibility of counterfeits, trending and consideration for recall and notification of competent authorities
	Product recalls:
	The firm has defined procedure (SOP No. …….revision No. …dated xx/yy/zzzz) for Recall of products from the market which were known or suspected to be defective. The firm has designated Head of Quality Assurance for execution and coordination of recalls and provided adequate staff to handle all aspects of the recalls with the appropriate degree of urgency. The firm has also defined procedure to inform Licensing Authorities about recall of any products in SOP. The firm has provided dedicated area for storage of recalled products in a secured segregated area which was located in …….. The inspection team has verified recall register/ logbook and verified records of distribution, communication made to wholesalers/ suppliers/ customers and progress records of recalled products. The firm has performed mock recall at defined frequency of ……every month/ year to verify the effectiveness of the arrangements for recall. As per the records available firm has maintained records of all recalled products and recalled was found performed in timely manner and records of distribution, recall and reconciliation were maintained by the firm. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately,* if any.
	Contract production, analysis and other activities:
	The firm has maintained written contract between the loan licensee or contract giver and the manufacturing facility provider or contract acceptor which clearly establishes the responsibilities of each party, covering the outsourced activities, the products or operations to which they are related, communication processes relating to the outsourced activities and any technical arrangements made in connection with it. The contract consists of all information as prescribed under Part-I of Schedule-M of Drug Rules. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately,* if any.
	Self-inspection and quality audits:
	The firm has defined procedure (SOP No. ……. revision No. …dated xx/yy/zzzz) for self-inspection which was carried out to evaluate the manufacturer's compliance with good manufacturing practices in all aspects of production and QC. The firm has defined items that are to be evaluated during the self-inspection, composition of self-inspection team, frequency of self-inspection, self-inspection planner for a year covering all areas, etc. The firm has performed

	self-inspection at a frequency of twice in a year and last self-inspection was found carried out in …….of year ……..for the……departments and records along with complete report of self-inspection was found maintained by the firm and all non-conformities noted in self-inspection were found closed effectively in timely manner by the firm. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately,* if any.
	Vendor/ Suppliers' audits and approval:
	The firm has defined procedure (SOP No. ……. revision No. …dated xx/yy/zzzz) for Vendor/ Suppliers' audits and as per the SOP all raw material including API, excipients and primary packaging materials were found procured from the approved vendors. which was carried out to evaluate the manufacturer's compliance with g*Suppliers' audits and approval: describe procedures for evaluation and approval of suppliers including applications of risk management principles, especially determining the need and frequency for on-site audits.* . Raw Materials, Primary Packaging Materials Vendors were qualified through audits and information of the site through Vendor Questionnaires as defined in SOP. Raw materials in the warehouse were randomly verified with the approved vendor list and found satisfactory
	Personnel:
	Describe availability of adequate numbers of sufficiently qualified and experienced personnel, clarity of their responsibilities, limits and reporting hierarchy. Qualifications, experience and responsibilities of key personnel (head of production, head(s) of the quality unit(s), authorized person) and procedures for delegation of their responsibilities
	Training:
	The firm has defined SOP (……, revision No. xx dated xx/yy/zzzz) for training of employees and firm has prepared and implemented a structured annual training program which covers various aspects of GMP, GDP, safety, hygiene, cleaning, risk analysis, job related activities, etc. for all employees and effectiveness of training was evaluated through questionaries. The training was found imparted by the experience person who have adequate qualification and experience of the respective field or area. The employees were imparted induction training during the joining and thereafter regular training were imparted to concerned person as per the training needs identified by the head of department. The inspection team has randomly reviewed training records of person working in warehouse, production, testing, quality assurance and firm has maintained training records of concerned persons along with training evaluation records.

	However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately, if any.
	Personal hygiene:
	A total of XXXX employees were found engaged in the plant and all employees were found trained on various aspects including hygienic requirements at the time of induction and at regular intervals thereafter. Training record of some of the employees were checked by the inspecting team and found satisfactory. All the technical personnel were found possessing proper academic background and competent enough to perform the duty assigned to them. The list of approved technical personnel is enclosed as Annexure-A. The firm has defined SOP (……revision XX dated xx/yy/zzzz) for medical examination of all the employees and as per the SOP medical examination was carried out annually by the Dr. *name, Qualification*, Registration Number *XXXXX* in the month of *XXXX* of year *xxxx*. The firm has provided two sets of aprons, caps and foot wares to the employees authorized to enter into the general areas and Non fiber shedding garments with full covering were found provided (two sets) to all employees authorized to enter in to the manufacturing area. Auto IPA dispenser was found provided at the entry point of the production area to sanitize hands. The firm has their own laundry system for cleaning and washing the used linen. The cleaning validation of the linen was found in place and the residual limit of the detergent was found maintained at the level of not more than *XXXX* ppb calculated on the basis of wash water analysis. The Rest room and cafeteria for employees were found well outside the manufacturing and no smoking, eating, drinking, chewing and related materials from production, laboratory and storage areas. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately*, if any.
	Premises:
	Description of the appropriateness of the location, design, construction and maintenance of premises to minimize errors, avoid cross-contamination, permit effective cleaning and maintenance; measures for dust control; specific measures for ancillary areas, storage areas, weighing areas, production areas and quality control areas; measures for appropriate segregation and restricted access; provisions for appropriate lighting, effective ventilation and air-control to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity
	Water System:

	The firm has maintained a pre-specified water system for generation of purified water and water for injection. *(Describe the process of generation of Purified water from the raw water).* The source of raw water is Bore wells which is further stored in overhead HDPE raw water storage tank and this water is passed from online dosing with of free chlorine using Sodium Hypochlorite solution and this water was passed though Multi Grade Filter, cartridge filter, RO system, EDI (Electro Deionization) and finally through ultra filtration and stored in a SS316L storage tank of capacity of *XXXX* KL and then circulated through stainless steel circulation loop into production area and microbiology. The firm has provided Water for injection (WFI) generation and distribution system for manufacturing facility of parenteral dosage form and WFI is generated through distillation plant and distributed to production and microbiology area though stainless-steel circulation loop. Water For Injection (WFI) is kept under continuous circulation through close distribution loop system to avoid stagnancy and was maintained at more than 80 $^{\circ}$C. The firm has provided online TOC in WFI return loop and also provided provisions of auto-dumping valve based on conductivity and TOC. The firm has also defined Alert and action limits for purified water and water for injection and sanitisation of purified and water for injection storage tanks were carried out at frequency of ……as defined in respective SOP. The inspection team has reviewed trends and testing records of purified water and water for injection. The chemical and microbiological analysis report of purified water and water for injection showed that the said water was complying with the specification limit of purified water and water for injection as defined in current India Pharmacopoeia. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately*, if any.
	Air Handling Unit:
	The firm has provided total number of *XXXX* independent Air Handling Units (AHUs) to control the Production areas and Warehousing Areas. Each process operation has its own AHU to control temperature, humidity and particulate matter. The internal corridors were found at a positive pressure in comparison with the adjacent production rooms (where Powder generated) to prevent cross as well as the extraneous contamination of the products. The firm has installed Magnehelic manometers to indicate the pressure differential found in all strategic places and firm has provided door interlocking with arrangement for audio-visual alarm when pressure gradient between different rooms deviate from the established limits.

	Each AHU was found fitted with 10-micron filters, chilled water stroke brine coil, Hot water coil, 5-micron filters and finally through 0.3-micron HEPA filters provided at terminal. Separate return air ducts were found provided in each room at a height of 30 cm from the floor and were fitted with 10-micron filters in the return grills. The HVAC system was found BMS (Building Management System) controlled. Dust extraction systems with proper hoods were found provided in granulation and compression areas. Temperature is maintained at comfort condition. Some of the records related to AHUs for supplying air for different areas like compression, etc. area was examined with respect to test for HEPA filter integrity test, particle count, humidity and temperature, air change rates, pressure balancing etc. by the inspecting team during inspection and found satisfactory. The firm has maintained SOP for environmental Monitoring (……. revision XX dated xx/yy/zzzz) and as per SOP environmental monitoring was found carried out by settle plate, active air sampling and non-viable particle count and inspecting team has verified the records of environmental monitoring records of some of critical area like ……and same were found satisfactory. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately*, if any.
	Equipment:
	Describe the adequacy of the numbers, type, location, design and construction, and maintenance of equipment to minimize errors, avoid cross-contamination, permit effective cleaning and maintenance; use, cleaning and maintenance procedures, records and logs; calibration of balances and other measuring instruments; status labelling
	Materials:
	Describe measures in place to select, store, approve and use materials (including water) of appropriate quality and how these measures cover starting materials, packaging materials, intermediate and bulk products, finished products, reagents, culture media and reference standards. Describe also the measures for the handling and control of rejected, recovered, reprocessed and reworked materials; recalled products; returned goods; and waste materials
	Documentation:
	Describe the comprehensiveness and adequacy of the documentation system in place (labels; specifications and testing procedures, starting, packaging materials, intermediate, bulk products and finished products; master formulas; packaging instructions; batch processing and packaging records; standard operating procedures (SOPs) and records) and how principles of good documentation and

	data management (attributable, legible, contemporaneous, original, accurate (ALCOA)) are institutionalized, implemented and maintained
	Good practices in production:
	Describe procedures, facilities and controls in place for production (processing and packaging); prevention of risk of mix-up, cross-contamination and bacterial contamination during production
	Good practices in quality control:
	Describe the extent of the organizational and functional independence of the quality control function and the adequacy of its resourcing. Describe the procedures, facilities, organization and documentation in place which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be compliant with the requirements. Describe the procedures for the control of starting materials and intermediate, bulk and finished products; test requirements; procedures and responsibilities for batch record review; procedures, records and facilities for initial and ongoing stability studies; policy, procedures, facilities and records for retention samples.
	Stability Studies:
	Describe about the arrangement made for stability testing of applied product.
	Media Simulation Studies: (For Sterile API/ Drug Product manufacturing facilities)
	The firm has maintained SOP no. XXXXX dated XXXX for Mediafill and defined frequency of media fill as every 6 months. The firm has executed last mediafill on *XXXXXX* vide protocol and report no. *XXXXXXX* dated xx/yy/zzzz for *ampoule filling line for 1 ml and 5 ml pack size* and as per the firm records there was no growth observed in media fill. *However, discrepancies observed during the inspection are recorded in Part-3 of this inspection report separately*, if any.
	Seed Lots and Cell Banks: (For Biological Product Manufacturing facility)
	Describe about the seed lot and Cell Bank system, subculturing process, Master and Working Seed/ Cell Bank systems, storage, etc.
	Use of animals: (For Biological Product Manufacturing facility)
	Describe about the location & premise and facility provided for animals, range of animals used for production and testing, ventilation system, monitoring, measure to prevent mix-up, decontamination procedures, etc.

<table>
<tr><td></td><td colspan="4">Other heading can be included by inspection team as per the facility/ product inspected.</td></tr>
<tr><td rowspan="5">Samples taken (if any):</td><td colspan="4">The inspection team has taken …….. samples of following API/ drugs products:</td></tr>
<tr><td>S.No.</td><td>Sample No.</td><td>Name of Product</td><td>Batch No.
Mfg. Date
Exp. Date</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Assessment of the site master file (if applicable):</td><td colspan="4">The firm has maintained Site Master File (……., revision No…. dated XX/YY/ZZZZ). The firm has included all parameters as described in Schedule-M of Drugs Rules and WHO Guidelines. However, discrepancies observed during the inspection in the Site Master File are recorded in Part-3 of this inspection report separately, if any.</td></tr>
<tr><td>Annexes attached:</td><td colspan="4">List of approved technical personnel enclosed as Annexure-A.

List of major change carried out by the firm is enclosed as Annexure-B

List of area inspected along with identification no. of area in tabular form for each dosage form enclosed as Annexure-C.</td></tr>
</table>

Part-3	List of deficiencies		
	S.No.	Deficiencies	References
Critical:			
Major:			

Other:			

Part-4	Outcome
Initial Conclusion:	*Statement regarding the GMP status, including informationon any restrictions in scope.* *The following guidance may be used to determine theoutcome of the inspection based on the nature andnumber of deficiencies observed:* • *other deficiencies only: operating at an acceptable levelof compliance with GMP guidelines;* • *other and a few (e.g. < 6) major deficiencies: decisionon level of compliance to be made after receipt and evaluation of CAPAs;* • *any critical or several (e.g. ≥ 6) major deficiencies: operating at an unacceptable level of compliance withGMP guidelines.*

Part-5	List of GMP guidelines referenced in the inspection
References:	1. Drugs & Cosmetics Act & Rules made there under. 2. WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principles, Annex 2 WHO Technical Report Series, No. 986. 3. Reference of other relevant guidelines used by inspection team during the inspection stating the title of the guidelines, the title of the publication and web address where the guidelines can be accessed.

Part-6	Assessment of company response, final conclusion, risk rating and next due date
Brief narrative on the adequacy of the	

company's response to issues to be addressed:	
Final conclusion:	*Final statement of GMP compliance, including information on any restrictions in scope*
Risk rating following the inspection	For example, low (L), medium (M), high (H), critical (C)
Date next inspection due (for planning purposes):	*The inspectorate may decide to include this information forinternal use only*
Name(s) & Signature(s) of inspection team with Date:	

Annexure O

INSPECTION CHECKLIST FOR BLOOD CENTERS

PART-I					
A).	**General information about the Blood Centre:**				
1.	**Name and Address of Blood Centre:**				
2.	**Telephone No.:** **Fax No.:** **E-mail:**				
3.	**License number with validity:**				
4.	**Date of Inspection:**				
5.	**Inspected By:**	1. 2. 3.			
6.	**Date and purpose of previous joint inspection:**				
7.	**Institution represented by (Name & Designation):**				
8.	**Name & designation of key person present during joint inspection**	1. 2. 3.			
9.	**Type of Institution (Please write whichever is applicable):**	**Government**	**Charitable Trust/ Voluntary Organization**	**Indian Red Cross**	**Hospital Based**
10.	**Constitution Details:**				
11.	**Purpose of inspection:**				
12.	**Approval from State or Union Territory Blood Transfusion Council (in case of Blood Centre run by Charitable Trust or Voluntary organization):**				
13.	**Applied Product(s):**	**Cellular blood components:** 1. Packed Red Blood Cells (PRBC) 2. Packed Red Blood Cells in additive solutions 3. Modified Packed Red Blood Cells ➢ Saline Washed Red Cells ➢ Leucodepleted Red Cells ➢ Irradiated Red Cells ➢ Frozen Packed Red Blood Cells			

		➢ Packed Red Cell Aliquot 4. Random donor platelet concentrates 5. Pooled platelets concentrate 6. Modified platelets concentrate ➢ Leucodepleted Platelet Concentrate ➢ Irradiated Platelets Concentrate ➢ Washed Platelet Concentrate ➢ Platelets Suspended in additive solution ➢ Cryo Preserved Platelet Concentrate 7. Granulocyte Concentrates ➢ Pooled Buffy Coat Derived ➢ Apheresis derived 8. Single Donor Apheresis Platelets 9. Single Donor Apheresis Granulocyte concentrate 10. Single Donor Apheresis Lymphocyte 11. Single Donor Apheresis Mononuclear Cells 12. Single Donor Apheresis Red Cells 13. Single Donor Apheresis Haematopoietic Stem Cells (Periphral Blood Stem Cells) **<u>Acellular blood components</u>:** 1. Fresh frozen plasma (FFP) 2. Concentrate of anti-haemophiliac factor 3. Cryo poor plasma 4. Liquid plasma 5. Thawed plasma 6. Recovered plasma 7. Single Donor Apheresis Plasma			
B).	**Details of Blood Collection, Distribution and discard (in case of renewal or routine inspection):**				
1.	**Total Blood Collection (In last three financial years)**	**Year**			
		Opening Balance			
		Camp Collection			
		Voluntary			
		Replacement			
		Total			
2.	**Distribution (In last three financial years)**	Used in own hospital			
		Issued to others			
3.	**Discard (In last three financial years)**	Expired			
		Hepatitis-B Reactive			
		Hepatitis-C Reactive			

		HIV Reactive			
		VDRL Positive			
		Malarial parasite positive			
		Low Volume			
		High Volume			
		Others			

C).	**Details of Technical staff:**			
1)	**Medical Officer:**			
	Name	**Qualification**	**Experience**	**Remarks**
i.				
2)	**Technical Supervisor:**			
	Name	**Qualification**	**Experience**	**Remarks**
i.				
3)	**Blood Centre Technicians:**			
	Name	**Qualification**	**Experience**	**Remarks**
i.				
ii.				
4)	**Registered Nurse:**			
	Name	**Qualification**	**Experience**	**Remarks**
i.				
5)	**Counselor or Medical Social Worker (where blood centre organizing blood donation camps):**			
	Name	**Qualification**	**Experience**	**Remarks**
i.				

D).	**Details of area provided for operation and preparation of blood components:**			
	Details of areas	**Approx. Actual size of rooms (Meter)**		**Air conditioned (Yes/No)**
		Dimensions (Length X Width)	**Area (m2)**	
1.	Registration and Medical Examination			
2.	Blood Collection (Air-conditioned)			
3.	Blood Component Preparation (Air-conditioned)			
4.	Blood Group Serology (Air-conditioned)			
5.	Laboratory for transmissible diseases (Air-conditioned)			

6.	Sterilization cum Washing			
7.	Refreshment cum rest room (Air-conditioned)			
8.	Store cum Record room			
9.	Counseling area with adequate privacy			
10.	Quality Control area with component preparation area			
11.	Apheresis room			
12.	Any other additional area provided (if any)			

PART-II		
A).	**General comments on facility, equipment, supplies & reagent provided by Blood Centre:**	
a)	**Location and Surroundings:**	**Comments**
1.	Whether blood Centre is located at a place which is away from open sewage, drain, public lavatory or similar unhygienic surroundings.	
2.	Whether Blood Centre has provided 100 square meter area for its operation.	
3.	Whether Blood Centre has provided additional 50 square meter area for preparation of blood components.	
4.	Whether Blood Centre has provided additional 10 square meter air-conditioned area for Apheresis/ therapeutic procedures.	
b)	**Building:**	
1.	Whether building(s) used for operation of a blood Centre and/or preparation of blood components is constructed in such a manner so as to permit the operation of the blood bank and preparation of blood components under hygienic conditions and avoid the entry of insects, rodents and flies.	
2.	Whether facility is well lighted, ventilated and screened (mesh), wherever necessary.	
3.	Whether walls and floors of the rooms, where collection of blood or preparation of blood components of blood products is carried out is smooth, washable and capable of being kept clean.	

4.	Whether drains are of adequate size and where connected directly to a sewer, is equipped with traps to prevent back siphonage.	
c)	**Health, clothing and sanitation of staff:**	
1.	Whether employees are free from contagious or infectious diseases and whether blood centre has defined procedure for medical examination and maintained records.	
2.	Whether employees are provided with clean overalls, headgear, foot-wears and gloves, wherever, required.	
3.	Whether adequate, clean and convenient hand washing and toilet facilities are provided by the blood centre.	
d)	**Maintenance:**	
1.	Whether premises is maintained in a clean and proper manner to ensure adequate cleaning and maintenance of proper operations.	
2.	What facilities are provided by blood centre for following: *(Please give provision made and reference no. of relevant SOPs, if any).*	
i.	To maintain privacy and thorough examination of individuals to determine their suitability as donors.	
ii.	For collection of blood from donors with minimal risk of contamination or exposure to activities and equipment unrelated to blood collection.	
iii.	For storage of blood or blood components pending completion of tests.	
iv.	Provision for quarantine, storage of blood and blood components in a designated location, pending repetition of those tests that initially give questionable serological results.	
v.	Provision for quarantine, storage, handling and disposal of products and reagents not suitable for use.	
vi.	Storage of finished products prior to distribution or issue.	
vii.	For proper conduction of all packaging, labeling and other finishing operations.	

viii.	For provision for safe and sanitary disposal of Blood and/or blood components not suitable for use, distribution or sale and for trash and items used during the collection, processing and compatibility testing of blood and/or blood components.	
e)	**Equipment:**	
1.	Whether equipment used in the collection, processing, testing, storage and sale/distribution of blood and its components are maintained in a clean and proper manner and so placed as to facilitate cleaning and maintenance.	
2.	Whether equipments are observed, standardised and calibrated on a regularly scheduled basis as described in the Standard Operating Procedures or Manual and operates in the manner for which it was designed so as to ensure compliance with the official requirements (the equipments) as stated in item E of Part XII-B of Drugs Rules for blood and its components. *(Write the SOP no. and verify whether records of calibration are maintained by the blood centre).*	
f)	**Supplies and Reagents:**	
1.	Whether all supplies and reagents used in the collection, processing, compatibility, testing, storage and distribution of blood and blood components are stored at proper temperature in a safe and hygienic place.	
2.	Whether all supplies coming in contact with blood and blood components intended for transfusion are sterile, pyrogen-free, and not interact with the product in such a manner as to have an adverse effect upon the safety, purity, potency or effectiveness of the product.	
3.	Whether supplies and reagents that do not bear an expiry date are stored in a manner that the oldest is used first.	
4.	Whether supplies and reagents are used in a manner consistent with instructions provided by the manufacturer.	

5.	Whether all final containers and closures for blood and blood components not intended for transfusion are clean and free of surface solids and other contaminants.	
6.	Whether each blood collecting container and its satellite container(s), if any, is examined visually for damage or evidence of contamination prior to its use and immediately after filling. Such examination includes inspection for breakage of seals, when indicated and abnormal discoloration.	
7.	Whether representative samples of each lot of the reagents and/or solutions are tested regularly on a scheduled basis as per frequency defined in item F of Part XII-B of Drugs Rules by methods described in the Standard Operating Procedures or Manual to determine their capacity to perform as required.	
g)	**Good Manufacturing Practices/Standard Operating Procedures:**	
1.	Whether blood centre has maintained Written SOPs which includes all steps to be followed in the collection, processing, compatibility testing, storage and sale or distribution of blood and/or preparation of blood components for homologous transfusion, autologous transfusion and further manufacturing purposes.	
2.	Whether blood centre has maintained SOP for following:	
i.	Criteria used to determine donor suitability as per the item H of Part XII-B of Drugs Rules.	
ii.	Methods of performing donor qualifying tests and measurements including minimum and maximum values for a test or procedure, when a factor in determining acceptability	
iii.	Solutions and methods used to prepare the site of phlebotomy so as to give maximum assurance of a sterile container of blood	
iv.	Method of accurately relating the product(s) to the donor	
v.	Blood collection procedure, including in-process precautions taken to measure	

	accurately the quantity of blood drawn from the donor;	
vi.	Methods of component preparation including, any time restrictions for specific steps in processing	
vii.	All tests and repeat tests performed on blood and blood components during processing	
viii.	Pre-transfusion testing, wherever applicable, including precautions to be taken to identify accurately the recipient blood components during processing	
ix.	Procedures of managing adverse reactions in donor and recipient reactions	
x.	Storage temperatures and methods of controlling storage temperatures for blood and its components and reagents	
xi.	Length of expiry dates, if any, assigned for all final products	
xii.	Criteria for determining whether returned blood is suitable for reissue	
xiii.	Procedures used for relating a unit of blood or blood component from the donor to its final disposal	
xiv.	Quality control procedures for supplies and reagents employed in blood collection, processing and re-transfusion testing	
xv.	Schedules and procedures for equipment maintenance and calibration	
xvi.	Labeling procedures to safeguard its mix-ups, receipt, issue, rejected and inhand	
xvii.	Procedures of plasmapheresis, plateletpheresis and leucapheresis if performed, including precautions to be taken to ensure re-infusion of donor's own cells	
xviii.	Procedures for preparing recovered (salvaged) plasma if performed, including details of separation, pooling, labeling, storage and distribution	
xix.	Whether all records pertinent to the lot or unit maintained pursuant to these regulations are reviewed before the release or distribution of a lot or unit of final product.	

xx.	Whether a thorough investigation, including the conclusions and follow-up, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specification is made and recorded.		
3.	Whether licensee utilise current Standard Operating Procedures, such as the manuals of the following organisations, so long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part, namely:		
i.	Directorate General of Health Services Manual		
ii.	Other Organisations or individual blood bank's manuals, subject to the approval of State licensing authority and Central Licence Approving Authority.		
4.	Whether SOPs are available to the personnel for use in the concerned areas.		
h)	**Records:**		
	Whether the licensee has maintained following records, namely:		
1.	**Blood Donor Record:**	**Yes/No/NA**	**Comments**
	Whether it consist of following information:		
i.	Serial number		
ii.	Date of bleeding		
iii.	Name, address and signature of donor with other particulars of age, weight, haemoglobin, blood grouping, blood pressure, medical examination, bag number		
iv.	Patient's detail for whom donated in case of replacement donation		
v.	Category of donation (voluntary/replacement)		
vi.	Deferral records and signature of Medical Officer Incharge		
2.	**Master Records for blood and its components:**	**Yes/No/NA**	**Comments**
	Whether it consist of following information:		
i.	Bag serial number		
ii.	Date of collection		
iii.	Date of expiry		
iv.	Quantity in ml		
v.	ABO/Rh Group		

vi.	Results for testing of HIV I and HIV II antibodies		
vii.	Malaria		
viii.	V.D.R.L.		
ix.	Hepatitis B surface antigen and Hepatitis C virus antibody		
x.	Irregular antibodies (if any)		
xi.	Name and address of the donor with particulars		
xii.	Utilization issue number		
xiii.	Components prepared or discarded		
xiv.	Signature of the Medical Officer Incharge		
3.	**Issue register*:***	**Yes/No/NA**	**Comments**
	Whether it consist of following information:		
i.	Serial number		
ii.	Date and time of issue		
iii.	Bag serial number		
iv.	ABO/Rh Group		
v.	Total quantity in ml		
vi.	Name and address of the recipient		
vii.	Group of recipients		
viii.	Unit/institution		
ix.	Details of cross-matching report		
x.	Indication for transfusion		
4.	**Records of components supplied:**	**Yes/No/NA**	**Comments**
	Whether it consist of following information:		
i.	Quantity supplied		
ii.	Compatibility report		
iii.	Details of recipient		
iv.	Signature of issuing person		
v.	Whether blood and/or its components are distributed on the prescription of a Registered Medical Practitioner and records of same are maintained.		
5.	**Records of A.C.D./C.P.D/CPD-A/SAGM bags*:***	**Yes/No/NA**	**Comments**
	Whether it consist of following information:		
i.	Details of manufacturer		
ii.	Batch number		
iii.	Date of supply		
iv.	Results of testing		
6.	**Register for diagnostic kits and reagents used*:***	**Yes/No/NA**	**Comments**
	Whether it consist of following information:		

i.	Name of the kits/reagents		
ii.	Details of batch number		
iii.	Date of expiry		
iv.	Date of use		
7.	Whether Blood Centre issue the cross-matching report of the blood to the patient together with the blood unit.		
8.	Whether blood centre has maintained Transfusion adverse reaction records.		
9.	Whether records of purchase, use and stock in hand of disposable needles, syringes, blood bags are maintained.		
10.	Whether said records are kept by the licensee for a period of five years.		
i)	**Labels*:***	**Yes/No/NA**	**Comments**
	Whether labels on every bag containing blood and/or component contains the following particulars, namely		
1.	Proper name of the product in a prominent place and in bold letters on the bag.		
2.	Name and address of the blood Centre		
3.	Licence number		
4.	Serial number		
5.	The date on which the blood is drawn and the date of expiry as prescribed under Schedule P to Drug Rules.		
6.	Which colour scheme is used for labels of following blood groups:		
i.	O: Blue		
ii.	A: Yellow		
iii.	B: Pink		
iv.	AB: White		
7.	The results of the tests of Hepatitis B surface antigen and Hepatitis C virus antibody, syphilis, freedom from HIV I and HIV II antibodies and malarial parasite.		
8.	The Rh group		
9.	Total volume of blood, the preparation of blood, nature and percentage of anti-coagulant.		
10.	Keep continuously temperature at 2 degree centigrade to 6 degree centigrade for whole human blood and/or components as contained under III of Part XIIB.		

11.	Disposable transfusion sets with filter shall be used in administration equipment.		
12.	Appropriate compatible cross matched blood without a typical antibody in recipient shall be used.		
13.	The contents of the bag shall not be used if there is any visible evidence of deterioration like haemolysis, clotting or discoloration.		
14.	The label shall indicate the appropriate donor classification like "Voluntary Donor" or "Replacement Donor" in no less prominence than the proper name.		
j)	**General Equipments, Instruments and special reagents*:***		
I.	**For blood collection room*:***	**Yes/No/NA**	**Comments**
1.	Donor beds, chairs and tables		
2.	Bedside table		
3.	Sphygmomanometer and Stethoscope		
4.	Recovery beds for donors		
5.	Refrigerators for storing separately tested blood		
6.	Refrigerators for storing separately untested blood		
7.	Whether temperature of refrigerator is maintainedbetween 2 to 6 degree centigrade and refrigerator is equipped with digital dial thermometer, recording thermograph and alarm device, with provision for continuous power supply.		
8.	Weighing devices for donor		
9.	Weighing devices for blood containers		
10.	Blood collection monitor		
11.	Tube stripper		
12.	Tube sealer		
13.	Biomedical waste containers (colour coded)		
14.	Lancet		
15.	Blood collection bag		
II.	**For haemoglobin determination*:***	**Yes/No/NA**	**Comments**
1.	Copper sulphate solution (specific gravity 1.053)		
2.	Sterile lancet and impregnated alcohol swabs		
3.	Capillary tube (1.3 x 1.4 x 96 mm or pasteur pipettes)		

4.	Rubber bulbs for capillary tubings		
5.	Sahli's haemoglobinometer/ Colorimeteric method		
III.	**For temperature and pulse determination*:***	**Yes/No/NA**	**Comments**
1.	Clinical thermometers		
2.	Watch (fitted with a seconds-hand) and a stop-watch)		
IV.	**Emergency equipments/items:**	**Yes/No/NA**	**Comments**
1.	Oxygen cylinder with mask, gauge and pressure regulator		
2.	5 % Glucose or Normal Saline		
3.	Disposable sterile syringes and needles of various sizes		
4.	Disposable sterile I.V. infusion sets		
5.	Ampoules of Adrenaline, Noradrenaline, Mephentin, Betamethasone or Dexamethasone, Metoclorpropamide injections		
6.	Aspirin		
V.	**Accessories:**	**Yes/No/NA**	**Comments**
1.	Blankets, emesis basins, haemostats, set clamps, sponge forceps, gauze, dressing jars, solution jars, waste cans		
2.	Medium cotton balls, 1.25 cm. adhesive tapes		
3.	Denatured spirit, Tincture iodine, green soap or liquid soap		
4.	Paper napkins or towels		
5.	Autoclave with temperature and pressure indicator		
6.	Incinerator		
7.	Stand-by generator		
VI.	**Laboratory equipment:**	**Yes/No/NA**	**Comments**
1.	Refrigerators for storing diagnostic kits and reagents maintaining a temperature between 4 to 6 degree centigrade (plus/minus 2 degree centigrade) with digital dial thermometer having provision for continuous power supply		
2.	Compound Microscope with low and high-power objectives		
3.	Table Centrifuge		
4.	Water bath having range between 37 degree centigrade to 56 degree centigrade		

5.	Rh viewing box in case of slide technique		
6.	Incubator with thermostatic control		
7.	Mechanical shakers for serological tests for Syphilis		
8.	Hand-lens for observing tests conducted in tubes		
9.	Serological graduated pipettes of various sizes		
10.	Pipettes (Pasteur)		
11.	Glass slides		
12.	Test tubes of various sizes/micrometer plates (U or V type)		
13.	Precipitating tubes 6 mm x 50 mm of different sizes and glass beakers of different sizes		
14.	Test tube racks of different specifications		
15.	Interval timer electric or spring wound		
16.	Equipment and materials for cleaning glass wares adequately		
17.	Insulated containers for transporting blood, between 2 degree centigrade to 10 degree centigrade temperatures to wards and hospitals.		
18.	Wash bottles		
19.	Filter papers		
20.	Dielectric tube sealer		
21.	Plain and EDTA vials		
22.	Chemical balance (wherever necessary)		
23.	ELISA reader with printer, washer and micropipettes		
VII.	**For blood containers:**	**Yes/No/NA**	**Comments**
1.	Whether disposable PVC blood bags are used (closed system) as per the specifications of IP/UPS/BP.		
2.	Whether anti-coagulant solutionsare sterile, pyrogen-free and of the following composition that will ensure satisfactory safety and efficacy of the whole blood and/or for all the separated blood components.		
3.	Whether anti-coagulant solutions are of a licensed manufacturer and the blood bags in which the said solutions are contained have a certificate of analysis of the said manufacturer		

VIII.	Special Reagents:	Yes/No/NA	Comments
1.	Standard blood grouping sera Anti A, Anti B and Anti D with known controls.		
2.	Rh typing sera in double quantity and each of different brand or if from the same supplier each supply shall be of different lot numbers.		
3.	Reagents for serological tests of syphilis and positive sera for controls.		
4.	Anti Human Globulin Serum (Coomb's serum)		
5.	Bovine Albumin 22 per cent Enzyme reagents for incomplete antibodies.		
6.	ELISA or Rapid RPHA test kits for Hepatitis and HIV I & II.		
	PART-III		
A).	**Blood Donation Camps:**		
a)	Whether blood donation camp is organised by: a) a licensed designated Regional Blood Transfusion Centre; or b) a licensed Government blood bank; or c) the Indian Red Cross Society d) a licensed blood bank run by registered voluntary or charitable organization recognized by State or Union territory Blood Transfusion Council; or e) a private hospital blood bank		
	Whether following requirements are fulfilled/ complied with for holding a blood donation camp:		
b)	**Premises, Personnel etc.:**		
1.	Whether premises under the blood donation camp have sufficient area and the location is hygienic so as to allow proper operation, maintenance and cleaning.		
2.	Whether all information regarding the personnel working, equipment used and facilities available at such a Camp are well documented and made available for inspection, if required, and ensuring:		
i.	Continuous and uninterrupted electrical supply for equipment used in the Camp.		
ii.	Adequate lighting for all the required activities		

iii.	Hand-washing facilities for staff;		
iv.	Reliable communication system to the central office of the Controller/ Organiser of the Camp		
v.	Furniture and equipment arranged within the available place		
vi.	Refreshment facilities for donors and staff		
vii.	Facilities for medical examination of the donors		
iii.	Proper disposal of waste		
c)	**Personnel for Out-door Blood Donation Camp:**	**Yes/No/NA**	**Comments**
1.	Whether following requirements are fulfilled/ complied to collect blood from 50 to 70 donors in about 3 hours or from 100 to 120 donors in 5 hours,		
a)	One Medical Officer and two nurses or phlebotomists for managing 6-8 donor tables		
b)	Two medico social workers		
c)	Three blood bank technicians		
d)	Two attendants		
e)	Vehicle having a capacity to seat 8-10 persons with provision for carriage of donation goods including facilities to conduct a blood donation camp.		
d)	**Equipments for Blood Donation Camp:**	**Yes/No/NA**	**Comments**
1.	BP apparatus		
2.	Stethoscope		
3.	Blood bags (single, double, triple, quadruple)		
4.	Donor questionnaire		
5.	Weighing device for donors		
6.	Weighing device for blood bags		
7.	Artery forceps, scissors		
8.	Stripper for blood tubing		
9.	Bed sheets, blankets/mattress		
10.	Lancets, swab stick/tooth picks		
11.	Glass slides		
12.	Portable Hb meter/copper sulphate		
13.	Test tube (big) and 12x100 mm (small)		
14.	Test tube stand		
15.	Anti-A, Anti-B and Anti-AB, Antisera and Anti-D		
16.	Test tube sealer film		

17.	Medicated adhesive tape		
18.	Plastic waste basket		
19.	Donor cards and refreshment for donors		
20.	Emergency Medical Kit		
21.	Insulated blood bag containers with provisions for storing between 2 degree centigrade to 10 degree centigrade		
22.	Dielectric sealer or portable tube sealer		
23.	Needle destroyer (wherever necessary)		
PART-IV			
A).	**Collection of Blood:**		
1.	Whether Blood donor counselling takes place before, during and after blood donation by trained blood donor counsellor.		
2.	Whether a donor questionnaire or registration form is provided and maintained by the blood centre.		
3.	Whether donor questionnaire or registration form used is in English and the local language, which would enable easy understanding by the donor.		
4.	Whether donor questionnaire or registration form includes basic information such as donor name, demographic details, address, etc., from the intended blood donor.		
5.	Whether each blood donor is assigned a unique donor identification number which is most critical in ensuring the traceability of blood in the blood transfusion chain from donor to the recipient.		
6.	How is sample tubes labeled.		
7.	Preparation of phlebotomy site		
8.	Whether whole blood is collected into an approved container with a single clean non-traumatic venepuncture that allows rapid flow.		
9.	Type of anti-coagulant used		
10.	Amount of anti-coagulant used		
	For 350 ml:		
	For 450 ml:		
	For 100 ml:		
	Amount of blood collected		

11.	315-385 ml	
	405-495 ml	
12.	How periodical mixing of Blood with the anticoagulant during collection is done.	
13.	Whether blood samples is collected in plain and EDTA vials for TTI screening and blood group confirmation after the completion of blood donation.	
14.	What is average draw time of whole blood.	5-10 minutes
15.	Whether Pediatric Bags is used by the blood centre.	
16.	How blood is issued to pediatric patients if pediatric bags is not used by the blood centre.	
17.	Whether educational and motivational materials are displayed as well as readily available to the donors in the waiting and refreshment area.	
18.	Whether blood bags are supplied in pouches and used within the shelf life prescribed by the manufacturer.	
19.	Whether blood bags are checked for a batch number, lot number and date of manufacture and expiry on the bag.	
20.	Whether Blood bags are transported and stored between 20-24ºC at all times before blood collection to maintain the integrity and sterility of the preservative solution.	
B).	**Testing of Blood Testing**	
1.	Whether whole blood collected, processed and supplied conforms to the standards laid down in the Indian Pharmacopoeia and other tests published, if any, by the Government.	
2.	Whether samples of every blood unit tested, before use, for freedom from HIV I and HIV II antibodies either from laboratories specified for the purpose by the Central Government or in his own laboratory and whether results of such testing are recorded on the label of the container.	
3.	Whether each blood unit is tested for freedom from Hepatitis B surface antigen, Hepatitis C virus antibody, VDRL and	

	malarial parasite and results of such testing are recorded on the label of the container.	
4.	Whether Blood samples of donors in pilot tube and the blood samples of the recipient are preserved for 7 days after issue.	
5.	Whether blood intended for transfusion is not frozen at any stage.	
6.	Whether Blood containers are not come directly in contact with ice at any stage.	
7.	Haemoglobin estimation method	
8.	Method for ABO grouping	
9.	Procedure for grouping	
10.	Method of pooled cell preparation	
11.	Whether Du test done on D-samples	
12.	Whether test for unexpected antibodies done	
13.	Whether Hepatitis test done Method used: Name of kit manufacturer:	
14.	Whether Syphilis test done Method used: Name of kit manufacturer:	
15.	Whether HIV test done Method used: Name of kit manufacturer:	
16.	Whether HCV test done Method used: Name of kit manufacturer:	
17.	Whether Malaria test done Method used: Name of kit manufacturer:	
18.	Whether Donor informed in case of +ve results	
19.	In case of HBsAg /HIV +ve results Donor debarred permanently	
20.	Are HBsAg/ HIV +ve donors followed up?	
21.	Method used for Cross matching	
C).	**Storage of blood:**	
22.	Whether Temperature recording graph preserved.	
23.	Whether Alarm system checks done at defined frequency.	
24.	Whether physical Verification of alarm at lower and higher limit of temperature done and what is the frequency.	

25.	How is blood transported outside blood centre.		
D).	**Processing of blood components from whole blood by a blood bank:**		
a)	**Accommodation:**		
1.	Whether 50 square meter area is provided as per requirements of part XIIB of Drugs Rules.		
b)	**Equipment:**	**Yes/No/NA**	**Comments**
1.	Air Conditioner		
2.	Laminar air flow bench		
3.	Suitable refrigerated centrifuge		
4.	Plasma expresser		
5.	Clipper and clips and or dielectric sealer		
6.	Weighing device		
7.	Dry rubber balancing material		
8.	Artery forceps, scissors		
9.	Refrigerator maintaining a temperature between 2 degree centigrade to 6 degree centigrade, a digital dial thermometer with recording thermograph and alarm device, with provision for continuous power supply		
10.	Platelet agitator with incubator		
11.	Deep freezers maintaining a temperature between minus 30 degree centigrade to minus 40 degree centigrade		
12.	Deep freezers maintaining a temperature minus 75 degree centigrade to minus 80 degree centigrade		
13.	Refrigerated water bath for plasma thawing		
14.	Insulated blood bag containers with provisions for storing at appropriate temperature for transport purposes.		
c)	**Personnel:**		
1.	Whether whole time competent technical staff meant for processing of Blood Components (that is Medical Officer, Technical Supervisor, Blood Bank Technician and Registered Nurse) as specified in Part XII-B of Drug Rules provided by the Blood Centre.		
d)	**Testing Facilities:**	**Comments**	
1.	Whether test for A, B, AB and O groups and Rli(D) grouping, Hepatitis B surface		

	antigen and Hepatitis C virus antibody, VDRL, HIV I and HIV II antibodies and malarial parasites is carried out for every blood unit before it is used for the preparation of blood components.	
E).	**Categories of Blood Components:**	
a)	**Concentrated Human Red Blood Corpuscles/ Packed Red Blood Cells:**	
1.	Whether SOP is available for preparation of Concentrated Human Red Blood Corpuscles.	
2.	Please specify the followings:	
i).	Source Material:	
ii).	Method:	
iii).	RCF:	
iv).	Speed:	
v).	Time:	
3.	Whether blood is obtained from donorwho meets the criteria for blood donation as specified in item H under Part XIIB of Drugs Rules.	
4.	Whether packed red blood cells confirmed to the standard of current version of Indian Pharmacopoeia.	
5.	How the Pilot tubes/samples are collected.	
6.	Whether Pilot tubes/samples are meeting following specifications:	
i).	Whether one or more pilot samples of either the original blood or of the Packed Red Blood Cells being processed are preserved with each unit of Packed Red Blood Cells which is issued	
ii).	How all pilot sample tubes are marked or identified so as to relate them to the donor of that Unit or Packed Red Blood Cells before they are filled.	
iii).	Whether all pilot sample tubes, accompanying a unit of Packed Red Blood Cells, are filled immediately after the blood is collected or at the time the final product is prepared and attached in a tamper-proof manner that conspicuously identify removal and re-attachment.	
7.	Whether pilot tube is attached in a tamper proof manner to the unit?	
8.	What is shelf life for Packed Red Blood	

	Cells:	
i).	Whole Human Blood stored in ACD Solution	
ii).	Whole Human Blood stored in CPDA-1 Solution	
iii).	Whole Human Blood stored in Additive solution (SAGM)	
iv).	Packed Red Blood Cells Frozen, if prepared	
v).	What is storage condition for PRBC.	
9.	Whether components are inspected immediately after separation of the plasma, during storage and again at the time of issue.	
10.	Whether products are issued if there is any abnormality in colour or physical appearance or any indication of microbial contamination.	
11.	Whether 1% of Packed Red Cells prepared are tested and 75 per cent of the units are conforming to following quality control criteria:	
i).	Volume:	
•	250 ml ± 10 % from 450 ml bag	
•	150 ml ± 10 % from 350 ml bag	
ii).	Haematocrit:	
•	65-70% when stored in CPDA-1 solution	
•	50-60% when stored in SAGM solution	
iii).	Culture shall be Sterile	
b)	**Platelets Concentrates*:***	
1.	Whether SOP is available for preparation of Platelets Concentrates.	
2.	Please specify the followings:	
i).	Source Material:	
ii).	Method:	
iii).	RCF:	
iv).	Speed:	
v).	Time:	
3.	Whether the whole Blood / source material is stored at 20 degree to 24 degree centigrade after collection, before processing to platelet concentrate.	
4.	Whether the temperature as close as possible to a range between 20 degree centigrade to 24 degree centigrade is	

	maintained during the transport when blood is transported from the venue of blood collection to the processing laboratory.	
5.	Whether Platelet Concentrates are separated within 6 hours after the time of collection whole blood/ source material and it is ensured.	
6.	Whether platelet concentrates are tested for:	
i).	Platelet Count:	
•	For 350 ml (Limit is NLT 3.5 x 10^{10})	
•	For 450 ml (Limit is NLT 4.5 x 10^{10})	
ii).	Whether 1% of total platelets prepared are tested and 75 per cent of the units are conforming to the defined platelet count.	
iii).	pH (Limit is NLT 6.0)	
iv).	Measurement of actual Plasma volume	
v).	Whether 1% of total platelets prepared are tested for sterility.	
vi).	Whether the tests for functional viability of the platelets is done by swirling movement before issue.	
7.	Whether final containers used for platelets are colourless and transparent to permit visual inspection of the contents.	
8.	How final container are marked or identified so as to relate it to the donor at the time of filing.	
9.	Whether platelet concentrates are stored under continuous agitation for a period of 5 days between 20 degree centigrade to 24 degree centigrade.	
10.	Whether compatible transfusion for the purpose of variable number of Red Blood Cells, A, B, AB and O grouping is done if the platelets concentrate is contaminated with red blood cells.	
11.	Whether the unit collected with a draw time beyond 10 and 12 minutes are used for preparing platelet concentrates from 350 and 450 ml blood bags, respectively.	
12.	**Preparation of Pooled Platelet Concentrate:**	
i).	What is method for preparation of pooled plate concentrate.	

ii).	How many units of random donor platelet are used for preparation of pooled plate concentrate.	
iii).	What is the platelet content in the pooled product (Limit is $\geqslant 2 \times 10^{11}$/ unit).	
c)	**Granulocyte Concentrates*:***	
1.	Whether SOP is available for preparation of Granulocyte Concentrates.	
2.	Please specify the followings:	
i).	Source Material:	
ii).	Method:	
iii).	RCF:	
iv).	Speed:	
v).	Time:	
3.	What is storage condition and maximum duration of storage of Granulocyte Concentrate.	
4.	What is the unit of granulocytes when prepared on cell separator (Limit is At least 1×10^{10}).	
5.	Whether Group specific tests/HLA test wherever required are carried out.	
d)	**Fresh Frozen Plasma *(FFP):***	
1.	Whether SOP is available for preparation of Fresh Frozen Plasma.	
2.	Please specify the followings:	
i).	Source Material:	
ii).	Method:	
iii).	RCF:	
iv).	Speed:	
v).	Time:	
3.	Whether deep freezers capable of maintaining temp between minus 75^0 C to 80^0 C is available for storage of FFP.	
4.	Whether deep freezers capable of maintaining temp between minus 30^0 C to 80^0 C is available for storage of FFP.	
5.	What is Lag time between collecting of blood and processing of FFP.	
6.	What is storage period and maximum duration of storage of FFP.	
7.	Whether quality control of FFP includes following:	
i).	Volume:	
•	For 350 ml bag: 180-220 ml	

•	For 450 ml bag: 220-300 ml	
ii).	Factor VIII: At least 70 IU	
8.	Whether excess and expired plasma is issued for fractionation to the licensed fractionation centre in the country and maintained records for justification in writing.	
9.	Whether the unit collected with a draw time beyond 13 and 15 minutes are used for preparing FFP from 350 and 450 ml of blood bags respectively.	
10.	Whether blood units subjected to fresh frozen plasma are transported in blood transport containers with ice or gel packs maintaining the temperature below 10ºC.	
e)	**Cryoprecipitate*:***	
1.	Whether SOP is available for preparation of Cryoprecipitate.	
2.	Please specify the followings:	
i).	Source Material:	
ii).	Method:	
iii).	RCF:	
iv).	Speed:	
v).	Time:	
3.	Whether thawing facilities (like Cryobath/ blood bank refrigerator/ cold room) for FFP and what is the temperature used for thawing.	
4.	Whether quality control of Cryoprecipitate includes following:	
i).	Volume: 15-20 ml	
ii).	Fibrinogen: at least 150 mg/bag	
iii).	Factor VIII: At least 70 IU	
iv).	Whether anti-hemophiliac factor activity of 1% of total cryoprecipitate prepared is tested of which 75% conform to specification.	
v).	What is the value of anti-hemophiliac factor activity of prepared cryoprecipitate (Limit is NLT 80/ bag).	NLT 80/ bag
5.	Whether blood units subjected cryoprecipitate preparation are transported in blood transport containers with ice or gel packs maintaining the temperature below 10ºC.	

f)	**Blood component separation by apheresis**		
I.	**Single Donor Platelets by Plateletpheresis:**		
1.	Whether an air-conditioned area of 10 square meters is provided for apheresis/ therapeutic procedures in the blood Centre.		
2.	Whether plateletpheresis donor fulfilling following specific requirements besides the general donor selection criteria for whole blood donors:		
	Name of the test	Acceptance criteria	**Comments**
i.	Donor weight	More than 50 Kg	
ii.	The interval between procedures	At least 48 hours	
iii.	A donor should not undergo the procedure	More than 2 times a week or 24 times a year	
iv.	Hemoglobin/Heamatocrit	>12.5 g/dl	
v.	Platelet count	More than 150,000/µl	
vi.	Serum protein	More than 6.0 g/dl	
vii.	pH	6 or higher	
viii.	WBC count	Within Normal Limits	
ix.	Differential count	Within Normal Limits	
3.	Whether apheresis platelet concentrate contains minimum 3 X 10^{11} platelets in 75% of the units tested amongst 1% of monthly production or 4 platelet concentrate per month, whichever is higher.		
4.	What is storage condition and duration of Single Donor Platelets.		
5.	Whether Donors who have taken aspirin-containing medication within 3 days/ 72 hours are deferred		
6.	**Equipments:**	**Yes/No/NA**	**Comments**
i.	Cell separator		
ii.	Dielectric tube sealer		
iii.	Oxygen cylinder with mask, gauge and pressure regulator		

iv.	5 per cent Glucose or Normal Saline		
v.	Disposable sterile syringes and needles of various sizes		
vi.	Disposable sterile I.V. infusion sets		
vii.	Ampoules of Adrenaline, Noradrenaline, Mephentin, Betamethasone or Dexamethasone, Metoclorpropamide injections		
viii.	Aspirin		
II.	**Single Donor Plasma by Plasmapheresis:**		
1.	Whether Plasmapheresis donor fulfilling following specific requirements besides the general donor selection criteria for whole blood donors:		
	Name of the test	Acceptance criteria	
i.	Donor Age	Between 18-50 years	
ii.	Weight	60 Kg or more	
iii.	Preferably donor should have given whole blood earlier	1 -2 times	
iv.	Total blood count	Within Normal Limits	
v.	Serum proteins	> 6.0 g/dl	
vi.	Platelet count	More than 150,000/µl	
vii.	Serum protein	More than 6.0 g/dl	
2.	What is the quantity of plasma separated from the blood of donor per sitting and once in fortnight	NMT 500 ml	
3.	What is the quantity of plasma separated from the blood of donor per month	NMT 1000 ml	
III.	**Therapeutic Plasmapheresis and Cytapheresis**		
1.	Whether Therapeutics apheresis activity is carried out in the blood centre attached to the hospital having apheresis facility.		
2.	Whether Therapeutics apheresis activity is carried out under the responsibility of Registered Medical Practitioner.		
3.	Whether consent of patient and records of which are maintained and signed by the Registered Medical Practitioner and Blood Bank Medical Officer.		
4.	Whether Therapeutics apheresis activity is		

	done at the written request of the patient's physician.		
5.	Whether the records of the Therapeutics apheresis activity is maintained.		
F).	**Storage of Blood Components:**		
	Blood Component	**Temperature**	**Duration/ Expiry Period**
1.	Whole Human Blood IP stored in ACD Solution	2^0C to 6^0C	21 days
2.	Whole Human Blood IP stored in CPDA-1 Solution	2^0C to 6^0C	35 days
3.	Concentrated Human Blood Corpuscles/ Packed Red Blood Cells stored in ACD Solution	2^0C to 6^0C	21 days
4.	Concentrated Human Blood Corpuscles/ Packed Red Blood Cells stored in CPDA-1 Solution	2^0C to 6^0C	35 days
5.	Concentrated Human Blood Corpuscles/ Packed Red Blood Cells stored in Additive Solution	2^0C to 6^0C	42 days
6.	Frozen Packed Red Blood Cells	-65^0C	10 years
7.	Platelets Concentrates	20^0C to 24^0C	5 days
8.	Granulocytes Concentrate	20^0C to 24^0C	24 Hour
9.	Fresh Frozen Plasma	-30^0C	NMT 1 Year
10.	Cryoprecipitate	-30^0C	NMT 1 year

PART-V

A).	**Non-conformances/ observations noted during the joint inspection:**	
S.No.	**Non-conformances/ observation Noted**	**Reference**
1.		
2.		
3.		
B).	**Recommendation/ Conclusion:**	
C).	**Signature and Designations of Inspection Team members:**	

(Name of Officer) **Designation**	**(Name of Officer)** **Designation**	**(Name of Officer)** **Subject Expert**

CDSCO Zonal/ Sub-zonal Office	State Licensing Authority	Name of Office

Enclosures:

1) List of Equipments/ instruments:

S.No.	Name of equipment	Equipment ID	Make	Last Calibration date
1.				
2.				
3.				
4.				
5.				

2) List of reagents:

S.No.	Name of Kit/ reagent/ Blood bag	Lot No.	Mfg. By	Use By date
1.				
2.				
3.				
4.				
5.				
6.				

Annexure - P

Inspection checklist for Medical Device Manufacturing Units

PART A - General Information of the firm

a. Date of inspection		
b. Name and Address (Regd. Office)		
c. Name and Address (Manufacturing site)		
d. Constitution of the Firm (Enclose copy of the constitution)		
e. Contact details of the firm		
f. Fax No./E-mail ID of the firm		
g. Purpose of Inspection		
h. Scope of Inspection		
i. Inspection Team Members		
j. **License No. of firm, if any** *(Enclose copy of the license)*		
k. Any Certificates/ approval held by the firm (NOC pollution control, Fire Dept. etc,)		
l. Categories of the Medical Devices manufactured/will be manufactured at the site (Clearly specify whether the firm manufacture devices containing drugs) *(Enclose list of items manufactured at site)*		
m. Production capacity categories wise per shift. *(Enclose list of items being manufactured at site)*		
n. Whether the firm is engaged in contract manufacturing / loan licensing. *If yes, details thereof.*		
o. Last two years turnover of the firm (overall of all units)		
Trade		

Govt. Supply		
Export (if any)		
Total (Rupees)		
p. Name of Key Personnel like Top management, site head, authorized personnel for manufacturing, quality control, quality assurance, Engineering, procurement, Regulatory affairs etc. *(Enclose organizational chart along with responsibility matrix of key personnel)*		

PART B - General Information of the Manufacturing premises

a) General Information of the facility	
b) Personnel- Organisation chart	
c) Personnel -Qualification, Experience and responsibilities	
d) Premises and Facilities	
e) Whether the Plant layout is approved by the competent authority (Enclose copy of the site plan)	
f) Plant Layout of premise with indication of scale	
g) List of equipments and instruments used for manufacturing and testing	
h) Sanitation	
i) Production	
j) Quality Assurance	
k) Storage	
l) Documentation	
m)Applicable Product standards and Process standards	

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
1. General requirements					
Scope					
Exclusions of clause with Justification					
4.1 General requirements					
Has the organization determined the sequence and interaction of process?					
4.2. Documentation requirements					
4.2.1. General					
4.2.1(a) Has the organisation have documented statements of Quality Policy and objectives?					
4.2.1(c) Does the organisation have documented procedures as required by the schedule. If so how many procedures?					
4.2.1(e) Does the organisation have records as required by the schedule. If so how many procedures?					
Has the organisation established and maintaining a file either containing or identifying documents defining product specifications and quality management system requirements					
Does the organisation have Plant Master File					
Does the organisation have Device Master File for applied devices					
Wherever documentation is handled by electronic data processing methods, does the organization have control over the access on such records?					
4.2.2. Has the organization established and maintained a Quality Manual?					
4.2.3Control of Documents					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
4.2.3(a)Are the documents reviewed and approved for adequacy prior to issue. Please provide the document numbers audited in all departments. Does the organization have Change control procedure to review and approve changes to the documents?					
4.2.3(d)Does the revision numbers of the documents available at the point of use is the same as it is in the Master document list. Please provide the document numbers audited in all departments.					
4.2.3(f)Has the organisation identified documents of external origin been identified and distribution controlled. If Yes provide the document number. Is there a mechanism to ensure that the latest version of the document is made available? Please describe					
4.2.3(g) Does the organisation have a process to withdraw and store the documents which have undergone undergoing revision changes. Please explain Does the manufacturer have a process to retain one copy of the obsolete documents. If so what is the retention period. Does it comply with the statutory requirements as defined in MDR					
4.2.4 Control of records Does the organisation have a documented procedure established to define the controls needed for the identification, storage, protection, retrieval, retention time and disposition of records. Please provide the document numbers, retention time and how records are disposed,					
5.Management responsibility					
5.1 Management commitment Is the Top management commitment evident in the organisation? If so give an example					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
5.2 Customer focus Is there an evidence to prove that customer requirements are determined and met? Please provide the record no and check randomly atleast five customer orders.					
5.3. Quality Policy a. Is the quality policy appropriate to the purpose of the manufacturing facility. If so provide justification b. How is the quality policy communicated to all the employees of the organisation. c. Is the suitability of quality Policy getting reviewed if so when and how many times the quality policy has been revised.					
Planning					
Quality objectives Is the quality objectives SMART (specific, measurable, achievable, realistic, and time-based) If so explain how					
5.4.2.Quality Management System Planning Has the Top management ensured planning of QMS is carried out inorder to meet the specified requirements ?					
5.5. Responsibility, Authority & Communication					
5.5.1. Responsibility & Authority Has the organisation established responsibilities and authorities and has documented and communicated throughout the organisation. If so how?					
5.5.2.Management Representative(MR) a. Has the Top management appointed a management representative? If so please provide the order number and date of appointment. b. Explain briefly the process of how MR report the performance of QMS to top management. What is the process of promoting awareness of regulatory and customer requirements throughout the organization					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
5.5.3.Internal Communication How is the effectiveness of the QMS communicated within the manufacturing organization					
5.6 Management Review					
5.6.1 General What is the interval period for the review of organziations QMS?					
5.6.2 Review Input Has the Management review considered all the mandatory requirements. If not what has been left out and the reason thereof					
5.6.3 Review Output Has the MRM output address all the requirements listed. If not which is not addressed and reason thereof Are the records from management reviews maintained?					
6.Resource Management					
6.1 Provision of Resources Has the resources required for the implementation of QMS been determined.					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
6.2 Human Resources 6.2.1 General: Has all personnel coming in to the contact with the product as well as those working on production equipment been tested for eye sight or for communicable diseases. If so indicate the testing requirements identified and the records of testing done. What is the frequency of medical checkup? 6.2.2 Competency, awareness and training Has the organisation determined the education and competency requirements for all the personnel performing work which affect the quality of the product? If so please provide the documents as well as record number. Who is responsible for it? Is there a periodic review of the competency requirement for each job? Is there a documented procedures for identifying training needs ? Is there a process of training and retraining of employees? Record number and please verify 5 operators training in Production and QC critical operations. Please indicate how effectiveness check is being done. Please indicate the employee numbers of those verified					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
6.3 Infrastructure Has the organisation identified and provided area required to do the process. If so please state the number of persons/sq meter of each process are. Is the area crowded? What is the number of employees /square meter allowed as per Factories rules. If clean room is available will the density affect the bioburden of the clean room. Has the clean room been validated with DQ, IQ, PQ and OQ and what is the routine revalidation frequency Has there been an increase in the bioburden of the clean room from the stipulated limit. If so what actions has been taken? Has the organisation identified the process equipment required for the process both hardware or software, Has the organisation identified supporting services like transport, which can affect the quality of the product. If so please explain. Has the organization established documented requirements for maintenance activities, including their frequency? Please provided document and records of such maintenance activities carried out.					
6.4. Work Environment					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
Has the organisation determined the work environment requirement for all the production Areas as per Annexure A of the Fifth Schedule of MDR-2017? Does the process require clean room? If yes whether the IQ,PQ, OQ has been conducted. Please provide the document/Work instruction and the record numbers. Has the same been done as per applicable Standards Is the clean room being maintained daily as per the requirement of applicable Standards? What are the parameters being monitored daily. How the organisation has fixed the acceptable limits. If the parameters goes above acceptable limits what actions are to be taken. Whether the same has been documented in work instructions/SOPs. Provide the document/record numbers verified Has the organisation stated the cleanliness and clothing requirement for each production areas. Has the same be trained and well understood by all those working in each production areas. Please record the document number as well as evidence to prove the understanding of employees. Is there a possibility of cross contamination in the production areas.					
7. Product Realization					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.1. Planning of product realization Has the organisation identified, implemented and established documented requirements for risk management as per applicable standard? Is the risk management process embedded in all stages of the product life cycle. If so provide evidence on how risk management is applied in design as well as Post Market surveillance process Has the records arising from risk management maintained?					
7.2. Customer related processes					
7.2.1 Determination of requirements related to the product Does the organisation determine the customers stated requirements before acceptance of the order. Check minimum of 05 orders randomly and verify the stated needs are met. List the order numbers verified. Are there requirements not stated by the customer but necessary for specified or intended use, where known. If so what is the mechanism to capture the same and review it before the acceptance of the order. Give two examples if this is applicable Has the organisation identified the statutory requirements like standards BIS etc.					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.2.2. Review of requirements related to the product. (a)Whether the product requirements are defined and documented? (b) contract or order requirements differing from those previously expressed are resolved? (c) the manufacturer has the ability to meet the defined requirements. (d) Whether records of the results of the review and actions arising from the customer requirement review are maintained?					
7.2.3. Customer Communication Does the organization have documented procedure for Complaint handling process? Has the organisation communicated the product information to the customer? Is there a process to ensure that the contracts are reviewed and ensured that the organisation is capable of delivering the product as required by the customer? If concessions need to be received has the organisation received it before the product is manufactured Is there a process for receiving customer feedback and customer complaints Does the organisation do investigation for causality assessments. Does the organisation trend the complaints received and take appropriate action. If so please provide the document number of the process as well as the record number. Please verify the action taken by the manufacturer based on trending. Has the organisation issued advisory notices based on the investigation on customer complaints?					
7.3. Design & Development Has the organisation excluded this process If so what is the justification					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.3.1. Design & Development Planning Does the organisation have a documented procedures for design and development? If so please provide the document number Has the organisation identified different design stages and respective review, verification and validation stages? If so please provide the document numbers Has the organisation identified the responsibilities and authorities for design and development? Please provide evidence. Is the planning output documented and maintained as the design stage progress and please provide the evidence. Is there a process to verify that the design planning out puts are verified before design output becomes specification? Are there any design transfer activities undertaken?					
7.3.2. Design & Development Inputs Does the organisation have process to capture the product requirements Has the organisation identified the product requirements in line with the intended use of the product? Is there any statutory or regulatory requirement needed for the product? Is there any other requirement for design and development Has the input to design taken account of output from design and safety requirements. Provide the records maintained for design and development inputs					
7.3.3. Design & Development Outputs Has the output of design provided in a form that enables verification against the design and development input? Does the product design output meets the intended use of the device? Provide the records maintained for design and development outputs					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.3.4. Design & Development review Please provide details of the planned stages of design review planned and demonstrated Has the review of design identified any issues? If so please provide details and necessary action taken to overcome the design related issues. Please provide the record number of the design review What is the composition of the functions involved in design review? Are specialist related to the relevant field of the product included in the design review team. Please provide records of the results of reviews.					
7.3.5. Design & Development verification Is there a process for design verification? What is the evidence provided Is there a record of verification of design and are maintained. If so please provide the record number					
7.3.6. Design & Development validation Is there a process to validate the result of the design process to ensure that the resultant product is capable of meeting the requirements and intended use? Are the validation of design performed under defined operating conditions? Please provide the batch/serial number of the initial lot of product produced for validation. Please provide the details of clinical evaluations / performance evaluations conducted Is there a software associated with the device? If so provide records of software validation as per applicable standards Please provide the details of risk analysis conducted and the record number of the risk analysis conducted					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.3.7. Control of design & development changes Are the design development changes identified and records maintained? If so please provide the record number and number of changes incorporated Is there a process evident incorporating the feedback from product use and reviewing the design based on feed back Is there a Design History File? If so please provide the file number Does the design history file demonstrate that the design development was done according to the design plan? Does the design history file provide details of the design development requirements					
7.4. Purchasing					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.4.1. Purchasing Process Has the organisation identified and established the specifications for the purchased product affecting the quality of the product / process and infrastructure. If so please provide the details of document establishing the approved specifications. Has the organization established documented procedures to ensure that purchased product conforms to specified purchase requirements. What is the process established by the organisation to define the approved specification Has the organisation outsourced any process affecting the quality of the product? If so what is the control the organisation have in controlling the outsourced process Is there a process of evaluation of the suppliers and what are the controls on the suppliers Is there a process to rate and re-evaluate the suppliers ability to supply the products supplied. What is the duration of the re-evaluation. Are records available on re-evaluation. What is the process to ensure that the product supplied conforms to the specification Is there an approved supplier list.					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.4.2. Purchasing information Does the purchase order clearly specify the specification of the product .and process equipment. Please check random five purchase orders. Equipment purchased and acceptance as well as installation record Does the organisation have qualified personnel to do the purchasing as well as the verification activities? If so please provide the record number Has the organisation maintained records of purchased product record and verification done? Please provide the record number Does the organisations laboratories have enough infrastructure to do testing of the purchased product					
7.4.3. Verification of Purchased product What is the process set up for verification of the purchased product? Please explain Does the organisation rely on the supplier test result? If so has the validation and verification of testing activity at suppliers end audited. Please provide record number. What is the arrangement for product release? Does the organisation use external test laboratories to do verification? If so what is the process of qualification. Are the laboratories used NABL certified. Please verify the qualification record of test laboratories Are the records of verification maintained? What is the duration? What is the rationale for fixing the time limit of maintaining?					
7.5. Production and service provision					
7.5.1. Control of production & service provision					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.5.1.1 General Requirements Has the organisation identified the controlled conditions required for the manufacture/service provision of the product based on the characteristics of the product? Is so please provide the conditions identified Is the product sterile or non-sterile If the product is sterile, does the manufacturer identified the clean room requirement as per applicable Standards Has the organisation developed documented requirements of the clean room and necessary work instruction for the day to day operation of clean room Does the organisation have necessary equipments to monitor the particulate count, pressure difference, number of air changes and bio burden of the work are. (wherever applicable) What is the bioburden limit fixed by the manufacturer and what's the basis. Is there any prescribed requirement specified as per the regulatory/standard reference. If so please provide the details. Are there any deviations from the fixed parameters? If so what is the rationale of the manufacturer to set this limit.(wherever applicable) What is the periodicity with which particle count, bioburden, flow rate and number of air changes being monitored . (wherever applicable)					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
Has the organisation conducted IQ and OQ for the clean room as per the IS/ISO standard . (wherever applicable) Does the organisation have defined procedure for cleaning of the clean room. Is there a process to rotate the use of anti-bacterial and fungal agents so that it doesn't develop resistance? (wherever applicable) Has the organisation validated the effect of cleaning and anti-bacterial/fungal agents to ascertain the effect of the same to the product Has the organisation conducted the validation of the cleanroom as per the procedures specified in applicable Standards What are the operation requirements in terms of particulate count, bio burden and number of air changes finalised as per the requirement of applicable Standards (wherever applicable) Does the manufacturer establish and maintain a record for each batch of medical device or IVDs?					
7.5.1.2 Control of Production and Service Provisions					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.5.1.2.1. Cleanliness of product and contamination control Does the organisation have procedures for cleaning the product? What is the process used for cleaning the product. If water is used for cleaning, what is the specification of water used? Does the organisation ensure that by cleaning process additional contamination is not added? If air is used for cleaning what are the measures the organisation has taken to ensure that the air used does not add contamination to the product like bioburden, oil etc If the product is moulded what is the process to ensure that the mould releasing agent is removed from the product before further processing. If the product is supplied non sterile at the point of use, does the instruction for use mention the preferred method of sterilisation. Has the organisation validated the cleaning process listed in the IFU before release of the product in the market					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.5.1.2.2. Installation activities Does the medical device manufactured need to be installed in the point of use by the manufacturer. If so does the organisation have documented requirements of installation activities and their acceptance criteria. Are the records of installation and verification performed by the manufacturer or its authorized agent maintained? If the medical device is a plug and play which can be installed by the user, does the instruction for use contain step by step process for installing the device and trouble shooting if applicable including pictorial diagram for the lay user. If applicable does the organisation have documented requirements for verification of installation activities either by the manufacturer or by its authorised agents, Has the organisation established servicing provisions for the device installed. Does the IFU provided have details of the contact for servicing activity? If the servicing is done by the third party, what is the process in place for to ensure that the servicing calls are answered in time and closed.					
What is the process of training of the servicing professional available? If the product is supplied pan India does the organisation have enough infrastructure to attend the servicing activity in time. Does the organisation have a validated service manual and whether the manual is constantly updated based on the unanticipated failure mode. If so please provide detail of one such failure mode included in the service manual after the product has been launched in the market					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.5.1.3 Particular requirements for sterile medical devices. Is the product supplied sterile? What is the method of sterilisation of the product. Does the packaging material meet the requirements of applicable Standards requirement. Please include the list of records provided by the manufacturer to demonstrate conformance. Has the organisation validated the sealing and assembly process as per applicable Standards. If so what are the list of documents available with the manufacturer Does the organisation routinely check the product bioburden of each batch. If so what is the limit fixed and what is the basis of it. Does the organisation have internal arrangements to do culturing of microbes so that routine clean room process control, product bioburden as well as the sterility can be tested. If the organisation is using contract testing laboratory, is the laboratory NABL certified and what are the process for qualifying the laboratory. Does the organisation have qualified/trained microbiology experts who will be able to do the testing.					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
If the product is sterilised by ETO has the sterilisation procedure been validated as per applicable Standards. List the documents and records available to demonstrate that validation has been completed as per the standard. If the sterilisation is ETO, and is done within the manufacturing setup has the organisation developed procedures for measuring the ETO exposure to the operators and what is the limit set by the organisation. What is the basis of setting this limit, Has the organisation validated the residual ETO available with the product. What are the precautions taken by the manufacturer to ensure that the ETO is not let out in the atmosphere and whether monitoring of the same is done on a routine basis If the ETO sterilisation is carried out by a contract steriliser, what are the controls in place to ensure sterilisation process is effective. In both the cases what is the sterility Assurance level expected out of the sterilisation process. Is the sterilisation is carried out by Gamma radiation Has the organisation ensured that the material of construction of the product will withstand the maximum dosage of the process					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
Is the sterilisation process being carried out based on the bioburden of the device or is it a fixed dosage. If it is the fixed dosage, what is the maximum dosage and the minimum dosage of the process. Has the organisation validated the radiation sterilisation as per applicable Standards and is following the routine control. Does each batch of sterilisation have a dosimetry report indicating the minimum and the maximum supplied dosage If biological indicators are used are the results being interpreted as per applicable Standards If the organisation uses steam sterilization has the sterilisation process been validated as per applicable standard. If any other means of sterilisation is used please indicate the applicable standard against which the process has been validated Is sterility test conducted prior to the release of product. If so please indicate the standard used . If parametric release is done is it done as per the applicable standard. Does the batch sterilisation records as well as release records available in the Device batch manufacturing records?					
7.5.2. Validation of processes for production and service provision:					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.5.2.1. Does the organization have procedures for validation of processes for the production and service provision? At what frequency the processes would be revalidated? Provide records of validation of critical production and QC processes Has the organization established documented procedures for the validation of the application of computer software for production and service provision that affect the ability of the product conform to specified requirements?					
7.5.3 Identification and Traceability					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.5.3.1 Identification Does the organisation have documented procedures for identification of the products throughout the process? Are the equipments/instruments used in the production and testing process identified with serial numbers which are traceable to the batch records? Does the organisation receive returned goods supplied? Are they identified clearly and stored separately without mixing with the normal production. Are the rejected goods in the raw material incoming area earmarked separately such that it do not mix with the accepted goods. Please provide evidence. What is the process available to segregate the in process wastage and in process rejected goods. Is it properly identified such that it donot mix up with accepted goods. Has the organisation identified service lines like water, air etc. Has the color coding done as per the Factories and Boilers guidelines. If so please provide details. Does the organisation bring in returned products and if so are they properly identified and separated from the regular production. Is there a documented procedure established for the same?					
7.5.3.2 Traceability					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
General. Does the organisation have documented procedures to demonstrate product traceability, If so please provide the document number. Also please provide the extent of product traceability is maintained and records thereof. Please provide the record number. Is there a numbering scheme to identify production lots/serial number? If product is sterile, is there a traceability maintained such that each production lot and respective sterilisation lot is clearly identified. Does the device batch record of each batch/ serial number clearly reflect the components used their respective unique acceptance number. Does the organisation maintain configuration management if so please provide the details.					
Particular requirements for active implantable medical devices and implantable medical devices Are the products manufactured by the organization active implantable medical devices and implantable medical devices ? Is yes, whether the Batch records include records of all components, materials and work environment conditions involved in the manufacturing processes? Does the agents or distributors of the device maintain records of the distribution of active implantable medical devices and implantable medical devices to allow traceability? Are the name and address of the shipping package consignee maintained?					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.5.3.3 Status identification Does the manufacturer identify the status of monitoring and measurement throughout the process. Please explain Does the organisation have status identification of the raw materials, in process, finished goods, rejected product and on hold? Please explain. What is the status identification mechanism available in the product QC testing area? Please explain Please explain how the status of health information data of the employees maintained and monitored. What action does the organisation take using it.					
7.5.4 Customer Property Does the organisation receive customer property ~~in processing of medical devices~~? If yes please provide details of the customer property. If the organisation receive customer property please answer the questions below. If no please go to the next clause. What is the process of verification of the customer property How are customer property identified How is the customer property stored and protected. If the customer property is damaged are found not meeting requirements during verification what is the process to inform the customer. Please provide supporting data.					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.5.5 Preservation of product Has the organisation conducted packaging validation as per applicable Standards Is the product given a claimed shelf life on the labelling information? If yes, provide the Stability study protocol for the products and records of accelerated stability study data, on-going real time data and Shipping/transport stability validation data. What is the storage condition prescribed and the scientific basis of it? Is there a special storage condition prescribed. How do the manufacturer ensure that all the storage condition prescribed is maintained till the point of use? Does the organisation audit the channel partners till the distributor level. What is the frequency of audit of the channel partner? Does the organisation ensure that the climatic conditions required for the storage is maintained throughout. What is the arrangement available to ensure that the storage conditions are maintained during transport? How are the transporters qualified? Provide the documented criteria. Does the organisation ensures that the trucks are inspected and documented on the ability to maintain the storage conditions? What is the arrangement for pest control in the finished product storage area?					
If aerosol spray is used has the organisation ensured that the same donot affect the safety of the patient. Check the records. If product labels are used within the sterile pouches for implantable, has the organisation checked the toxicity of the printing ink. If so please provide the details of the verification done to ensure that ink with lead content does not come in contact with the implantable product.					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
7.6 Control of monitoring & measuring devices Does the organisation have documented procedures for installing and putting the monitoring & measuring devices to use like Installation qualification, operation qualification and performance qualification? Please provide the document number. Has the organisation identified the monitoring and measuring equipment which will affect the quality of product? Please provide the record number of the annual maintenance and calibration calendar for the monitoring and measuring equipment identified. Does the monitoring and measuring equipment have identification labels indicating its operability as well as the calibration status? Please verify atleast five Monitoring and Measuring equipment and provide their equipment numbers. Please check whether the calibration of these equipment is done with standards traceable to applicable standards. If the organisation uses other calibration standards please provide the details of the same and the scientific reason as to why this standard is being used for calibration. Does the organisation have equipment which need to be calibrated before every use? If so please check randomly five readings whether the reading has been taken after calibration. Please provide the document number. If computer software are used please check whether there are records demonstrating that a verification has been done to ensure that the same has been verified before the use. Please provide the record numbers.					
8.Measurement, analysis & improvement					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
8.1. General Does the organisation have a feed back mechanism in all its process for improvement. What are the statistical tools used by the organisation to analyse the ability of their process and the product to meet the intended needs. What is the scientific rationale to choose each tool for the process it has been identified to be used. Does the organisation use control charts in their process Does the organisation ensures that the product meet the essential principles of safety and performance. Provide a copy of the EPSP checklist of product If the manufacturer uses any test procedures which are not listed in any of the standards. Has the procedure been validated. Please verify the record of validation including the protocol and the scientific rationale for the procedure. If the manufacturer is using its own specification please verify the scientific rationale used by the manufacturer to demonstrate conformance to essential principles. If only a part standard has been used please provide the rationale.					
8.2 Monitoring & Measurement					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
8.2.1. Feedback Has the manufacturer identified all the regulatory requirements applicable to the product as well as to the manufacturing unit. What is the mechanism available with the organisation to capture the new regulation in all the regions they are distributing the product. If new regulations are captured does the organisation do the gap analysis and based on gap analysis initiate action to comply with regulatory requirement. Has the organisation received the respective operating licences applicable to the product, process and personnel. Please verify the gaps identified and action taken in that regard to ensure that the product is compliant. What is the process in place to ensure that the quality system is in place and the QMS is effective Does the organisation have a documented procedure for a feedback mechanism to provide the organisation a early warning of quality problems and for input into corrective and preventive action processes so as to ensure that the organisation has met the customers and regulatory requirement. Is there a procedure for review of the product performance at a specified interval if so what is the interval and what is the documents number. After review of product performance is there a procedure to incorporate the risks identified in the product use and update the risk management file. Please check the last five review of the product and whether the results of the same has been included in the risk management and the file has been updated.					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
What are the mitigation action taken in Product/process based on the risk review and whether product design has been revised or process parameters have been revised. Please provide details. Has the organisation conducted a mock recall to understand the time lines taken to remove the product from the field. Has the results been reviewed and approved based on scientific rationale. Please provide details.					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
8.2.2. Internal audit Does the organisation have a planned internal audit schedule. Please provide the record number Does the organisation ensure that the audit is done by personnel who are independent of the area being audited. Has the organisation identified the qualification required for the auditors and please provide the record number of the qualification of auditors Before the audit happens is there a planning done by the auditors and are there records maintained Are the audit finding objective clearly indicating the evidences available which are conforming or not conforming to the Fifth Schedule of MDR-2017. Does the organisation have documented procedures to define the responsibilities of the auditor, how internal audit need to be conducted and how to followup need to be done to complete the investigation and corrective action. Is there a procedure to conduct investigation. What is the technique used to investigate the root cause What is the maximum time line specified for each activity investigation and closure of Non-conformances. Does the organization maintain records of Internal audit conducted?					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
8.2.3 Monitoring and measurement of Processes Who is responsible for monitoring the performance of each process. What is the procedure implemented for the same. What is the process in place to take correction and corrective action when process are not as per the requirements identified. Please provide examples to demonstrate that correction and corrective actions are taken Please check the level of understanding of the emplyees on correction, corrective action and preventive action					
8.2.4 Monitoring & measurement of product					
8.2.4.1 General Requirements What are the processes at which the product requirements coming out of the process is verified as per the defined requirements Is there a quality plan for the same What is the scientific rationale for the quality plan. Does the record of verification to the specified requirement included in the respective device batch record and the same is reviewed before release of the product					
8.2.4.2 Particular requirement for active implantable medical devices and implantable medical devices. Is the product an active implantable medical devices and implantable medical devices? Does the batch manufacturing record have the details of personnel performing any inspection or testing of the device. Are the training record for these personnel being maintained					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
8.3. Control of non conforming product Is there a procedure to handle product which do not conform to the requirement at the incoming stage, in process or at final release. Who are the personnel authorised to handle the non-conforming products. Has the organisation specified the qualification and experience required for personnel dealing with the non-conforming product Are there process available to take action to eliminate the nonconformity If the organisation has procedures to accept the nonconforming product under concession, what are the requirement to take a decision and who is authorised to take this decision. Please check the records of acceptance of nonconforming product with concession. What is the process implemented to verify the corrected product. Based on the feedback after delivery of product if product non-conformance is identified, what is the process implemented in dealing with the non conformity. If the product is taken back from the field for correction, is there a process to inform the regulator. Are there any Batch recall of the products distributed? If yes, records thereof Is there a process to authorise the work instruction as well as rework process with responsibilities and authority. Is there a work instruction for rework. Has the process been validated to ensure that rework do not affect the performance of the product. Please verify the respective records and document the record number					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
8.4. Analysis of data What is the documented procedure to collect and analyse data to demonstrate conformance of process and product Based on the analysis finding what is the process in place to ensure that action is taken to improve the product as well as process performance. Does the organisation do trending of the analysis data and take appropriate action. If a feed back is received to improve the performance of the product and process, what is the process in place to deliberate on the suggestion and take action to improve the product/process. Are there records available to indicate that the performance of the suppliers are analysed and appropriate action been taken to improve the performance. Please provide details of improvement done to a supplier.					
8.5. Improvement					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
8.5.1 General Does the organisation have documented procedures to issue advisory notices. If so what is the document number. Please follow a trail from the customer complaint ,investigation and the decision to issue advisory notice and verify whether it is as per the documented procedure. Has the organisation conducted and documented the investigation for all complaints received. What is the pathway prescribed on a complaint when no sample is received and how did the organisation validated the process of investigation when samples are not defective samples are not received. Check all the complaints and see if any complaint has not been investigated. If so whether the reason for not investigating the complaint has been recorded or not? What is the corrective action proposed when the investigation reveals that the root cause of complaint is not due to the quality of the product. Has different scenarios have been identified. Based on the customer complaint does the organisation analyse region wise, state wise, district wise and hospital wise if if so please provide an example of the analysis done.					

Fifth Schedule/ Clause reference	Observations to be noted by the inspecting team	Evaluation			Remarks
		Yes	No	NA	
8.5.2 Corrective Action Please explain the process identified and documented for corrective action. Mention the documented procedure number for the same. Please explain the procedure for root cause identification. Does the organisation uses any technique used for root cause analysis. Does the organisation identify action needed for the defect not to reoccur. Does the organisation have a procedure for reviewing the corrective action and verify that the recurrence has been arrested Has the organisation reviewed the corrective action for its effectiveness					
8.5.3. Preventive action What is the process identified and documented to identify the cause of a potential non conformance. What are the requirements identified for evaluating the need for action to prevent occurrence of nonconformities, What is the process for reviewing the preventive action and whether it is effective or not. Does the required personnel throughout the process able to clearly define the difference between the corrective action and preventive action.					

<u>Note:</u> Please record the objective evidence of the documented information

Summarized Observations:

<u>Recommendations:</u>

Signature of the inspection team members:

…..Name of the officer 1……

……Designation……..

…..Office……..

…..Name of the officer 2 ……

……Designation……..

…..Office……..

Annexure Q

CHECKLIST FOR INSPECTION OF PUBLIC TESTING LABORATORIES

01.	**General**		
1.1	Date of Inspection		
1.2	Name & address of the Laboratory:		
1.3	Telephone Number	**FaxNumber**	**E-mail id**
1.4	**Names and designation of the Inspection Team Members**		
	Name	**Designation**	
1.5	Constitution of the firm:		
1.6	(i) Approval Number and Date: -		
	NABL (if any)		
1.7	Name and designation of the Responsible Persons of Laboratory present during Inspection:		

	Name	**Designation**

1.8	Organization Structure of the Laboratory (Please attach annexure, if required)	
1.9	Name of Approved Staff with Qualification, Experience, and approval status.	
1.10	List of the provided equipment and Instruments	
1.11	Whether the management of the laboratory has prepared validation Master Plan/ Quality Manual to ensure that the laboratory carries out its testing, calibration, validation, and all other technical activities in such a way as to meet Good Laboratory Practices (GLP) requirements.	
1.12	Whether the laboratory has appointed Technical or Quality Manager if yes Specify the responsibilities of the same.	

S. No.	**Categories**	**Compliance Y/N/N.A.**	**Remark/Comments**
2.	Whether approval has been granted for carrying out testing on the following Categories of Drugs Items and Cosmetics		
2.1	Drugs other than those specified in Schedule C & C (1) including/excluding Homeopathic Medicine.		
2.1.1.	Crude Vegetable Drugs		
2.1.2.	Mechanical contraceptives (Schedule R) Contraceptives (sterility test only)		
2.1.3.	Surgical Dressings (Schedule F-II)		

2.1.4.	Drugs requiring using U.V./I.R. Or Chromatography		
2.1.5.	Disinfectants		
2.1.6.	Other Drugs (Indicate Category)		
(a)	Medicinal Gases		
(b)	Diagnostics		
(c)	Medical Devices		
2.2	Drugs other than those Specified in Schedule C&C(1)		
2.2.1.	Sera, Vaccines, Antigens, Toxins, Antitoxins, Toxoids, Bacteriophages & similar Immunological products		
2.2.2.	Antibiotics		
2.2.3.	Vitamins (excluding electrophoresis)		
2.2.4.	Parenteral Preparations		
2.2.5.	Sterilized Surgical Ligature/Suture.		
2.2.6.	Drug requiring the use of animals for their test.		
2.2.7.	Drugs requiring microbiological tests.		
2.2.8.	Drugs requiring using U.V./I.R. or Chromatography.		
2.2.9.	Other Drugs (Indicate Category)		
(a)	Diagnostics		
2.3.	Homeopathic Drugs		
2.4.	Cosmetics		
3.	**PERSONNEL**		

3.1	Name of the Person In-charge(s)		
3.2	Details of the Analysts appointed by the firm (attach List with qualification and experience)		
3.3	Indicate any change in the Person In-charge and Expert Staff		
3.4	Medical examination of Staff		
3.5	Record of Periodicity of Medical Examinations Available		
3.6	Is education/experience of Personnel adequate		
	Internal: External		
4.	**PERSONNEL SAFETY:**		
4.1	Are protective steps against likely damage to health due to occupational hazards being taken as follows:		
4.2	Is There Adequate Provision For water shower		
4.3	Is there washing shower provision for eye wash		
4.4	Is There An Exclusive Overhead water tank for shower		
4.5	Are First Aid Medical Facilities made available at appropriate point?		
4.6	Are Safety personal appliances like Safety gloves, glass face shields, gas masks and proactive clothing be made available to persons engaged in handling hazardous items.		

4.7	Are adequate numbers of fire extinguishers of appropriate type with their status labels installed at the required places and people trained in operating the extinguishers?		
4.8	Whether proper safety measures have been taken to protect staff handling Hazardous/contaminated articles.		
4.9	Are SOPs provided for safety of personal and for waste disposal		
5.	**PREMISES:**		
5.1	Are there any sourcesof pollution in the neighborhood of the building?		
5.2	Is there any open drain, blocked sewer or public lavatory nearby		
5.3	Site Plan Showing Area Allotted for each section.		
5.4	Is the plan lay out already approved by the Licensing Authority? Indicate any change in the approved premises.		
5.5	Are the premises have adequate space not only for equipment to carry out necessary test but also for samples tested/proposed in the laboratory and utilities like water, power, and gas;		
5.6	Is there any evidence of the entry of birds, rodents, and insects in the Laboratory? Specify the measure employed to prevent it.		
5.7	Is lighting and ventilation Adequate for work.		

5.8	Is the Air conditioning facility provided to control the temperature and relative humidity for testing conditions and storage of drug samples if required.		
5.9	Whether The drainage system facilitate proper maintenance and preventwater logging in the Laboratory.		
5.10	Whether workbenches are constructed with acid, alkali and solvent resistant material and are smooth and free from crevices		
6.	**ANIMAL HOUSE**		
	Animal House have the approval of the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA)		
6.1	Is the animal house separate from other activities.		
6.2	Is the animal house air conditioned.		
6.3	Are the animals kept in hygienic surroundings, specify the provision for clean corridor and dirty corridor.		
6.4	Are there proper arrangements for cleaning of animal house.		
6.5	Are there suitable arrangements for preparation of animal feed.		
6.6	Are there suitable arrangements for quarantining of animals		
6.7	Is there separate arrangement for housing the animals under Test?		
6.8	Are the sick animals isolated?		

6.9	Are the animals being periodically examined for their physical fitness by a veterinary doctor, are the records Available?		
	Whether any Standard Operating Procedure are available for breeding and care of animals, maintenance, cleaning, or sanitation with suitable schedule for cleaning of animal Cages, racks, floor and other equipment's.		
6.10	Is the firm complying with the requirements of the Prevention of Crudely to animal act 1960(59/of 1960) as amended from time to time.		
6.11	Whether proper arrangements for disposal of carcasses of animals in a manner as not to cause hazard to public health being followed.		
7.	**MICROBIOLOGICAL AREA**		
7.1	Is microbiological section separate from other activities (with proper airlock)		
7.2	Whether Sterile area properly designed kept it free from outside contaminations		
7.3	Sterile area is Provided With proper working table with absolute Aseptic conditions.		
7.4	Are LAF tables properly validated to class 100 requirements.		
7.5	Are proper SOPs provided for maintenance of sterile area.		

7.6	Whether Standard Operating Procedure for maintenance of microbial culture and sub- culture are available with the Laboratory.		
7.7	In case when cultures have become non-viable or mutant, proper procedures are followedto destroy these cultures by autoclaving under authorized personnel for biological testing. Preferably not more than five passages are prepared. Specify the SOP No.		
8	**Instruments required for testing of Drugs other than those specified in Schedule C & C1**		
8.1	**Crude Vegetable Drugs**		
	General glassware Balance (Analytical) Microscope Soxhlet Extractor Water Bath Refractometer Oven HotPlate TLCKit U.V. Chamber Any Other Specialized equipment		
8.2	**Mechanical Contraceptives (Schedule R)**		
	Leakage Tester		

	ii) Bursting col., pressure tester iii) Vernier Caliper iv) Micrometer v) Balance (Analytical) vi) Aging Oven vii) Equipments for package integrity test.		
8.3	**Surgical Dressing (Schedule F11)**		
	U.V.Cabinet Soxhletextractor Oven Scale Absorbency Tester Balance(Analytical) All Equipment Required For Sterility testing		
8.4	**Drug requiring Instrumental Analysis**		
	i) UV/VIS Spectrophotometer ii) I.R. Spectrophotometer a) Pellet Maker and holder b) Liquid Cell Holder ii) HPLC (Gradient/Isocretic) a) Required columns b) Type of detector iv) AAS v) HPTLC		

	vi) Fluorometer vii) Potentiometric Titrator viii) Flame Photometer ix) Balance (Analytical) x) Microscope xi) KF Titrator xii) Oven xiii) Furnace xiv) Waterbath xv) Fridge xvi) Dissolution Test Apparatus a) Basket type b) Paddle type xvii) Disintegration test apparatus xviii) Melting point apparatus xix) Refractometer xx) Polarimeter xxi) General Glassware xxii) Chemicals xxiii) Stop watch xxiv) Water Distillation plant xxv) Particle counter (Specially for LVPs) xxvi) Any other instrument required for specialized testing		
9.	**Drugs requiring use of Microbiological Testing**		
9.1	**General**		

	Cleanroom Laminar Flow Autoclave pH Meter Gas Burner Water Bath Incubator Filtration Unit Vacuum Pump BOD Incubator Refrigerator Balance (Analytical) Glasswares Centrifuge Microscope Other2 general equipment required for general day-to-day activity. Cultures		
9.2	Special requirements other than General for:		
(a)	Disinfectants		
	Platinum loop Proper Culture Stopwatch Ovenupto35^{o}C		
(b)	Antibiotics		

	Spectrophotometer Vernier Caliper/Zone Reader Proper Culture Borer Media		
(c)	Vitamins (excluding electrophoresis) Spectrophotometer Vernier Caliper/Zone Reader Vortex Mixer Culture Media Borer		
(d)	Sterility		
	Filtration Unit Vacuum Pump Media 0.45m Pore Filter Paper Sterile Sterile forceps, Scissors & Bone cutter, Surgical blade, Ampoule Cutter Sterile Gloves Face Masks Caps Sterile Garments		
(e)	Endotoxins		

	LAL Reagents Heating Block Sterile Test Tubes Vortexmixer Sterile Tips Pipettes (Pyrogen Free) Stopwatch LAL Water/Pyrogen Free Sterile distilled water		
(f)	Pyrogen		
	Animal House Pyrothermometer/Rectal thermometer Sterile Syringes, needles Pyrogen Free Glassware Pyrogen free Sodium Chloride Solution/Water Animal Holding Stands		
(g)	Sterilized surgical Sutures and Ligatures		
	Sterility testing facilities Tensile Strength Tester		
(h)	Sera Vaccines		
	Sterility testing facilities and Other specialized testing facilities required for Testing Sera vaccines		
(i)	Pharmacological Testing:		

	Operation Table Kymograph Water Bath Manometer Cannula Oxygen Cylinder Other equipment required for Pharmacological testing		
10.	**RECORD/DOCUMENTS**		
10.1	Whether The Details Of Sample booking are available		
10.2	Whether the details of Certificate & Reports are maintained		
10.3*	Whether the details Sample distribution are available		
10.4	Whether the documents list with retention period is available		
10.5	Whether the Chemist Raw data records are available		
10.6*	Whether equipment's details are recorded		
10.7*	Is GLP manual and SOP(s) are available and being followed?		
11.	**EQUIPMENT**		
11.1*	Whether logbooks of equipment are maintained?		
11.2*	Whether the equipment records are proper such as Name of equipments, Manufactures's name, Serial No.etc.(attach details)		
11.3*	Whether the condition of equipment is recorded when		

	received (new, used, reconditioned)		
11.4	Whether the instruction manual of all major equipment is available		
11.5	Whether the calibration records are properly maintained		
11.6	Whether the next calibration date is recorded		
11.7	Whether the details of damage malfunction, repair (if any) of major equipment recorded		
11.8	Whether SOPs for equipment use, maintenance preventive maintenance & calibration are available		
12.	**CERTIFICATE REPORTS**		
12.1	Whether test reports are issued on prescribed Form 39 containing the required information as prescribed (attached photocopy of Form 39)		
12.2	Whether description of sample received for testing are available including receipt identification		
12.3*	Whether statement of method used for each test is maintained and available		
12.4	Whether complete records of all raw data including graphs, charts etc. are available		
12.5	Whether records of all calculations performed are available. Check calculation on random basis.		

12.6	Whether statement of test results and how they compare with specification are available		
12.7	Whether initials or signature along with date of person performing each test are available in the records.		
12.8	Whether initials or signature along with date of second person showing that the records have been reviewed for accuracy, completeness and compliance with the specifications are available in the records.		
12.9	Whether records of preparation of laboratory reference standards, reagents and standard solution are available.		
12.10	**Standard Operating Procedures** Whether the SOPs are prepared by the laboratory as follows.		
	sample handling and accountability;		
	receipt identification, storage, mixing and method sampling of the test and control articles;		
	record keeping, reporting, storage and retrieval of data;		
	coding of different studies, handling of data including use of computerized data system;		
	operation of technical audit personnel in performing and reporting audits, inspections and final report reviews;		

	routine inspection of cleaning, maintenance, testing, calibration and standardization of instruments;		
	action to be taken in respect of equipment failure;		
	analytical data methods;		
	the raw data;		
	data handling and storage retrieval;		
	health and safety protection;		
	animal room preparations;		
	animal care;		
	storage and maintenance of microbial cultures;		
	maintenance of sterility room (i.e. constant maintenance and monitoring of Aseptic condition of sterility room);		
	use and storage of reference standards		
	procurement of stores and equipment;		
	monitoring of testing of samples;		
	method of retention of unexpended samples, their location, maintenance and disposal;		
	document control;		
	redressal of technical complaints;		
	housing-keeping;		
	corrective and preventing action;		

	working procedure (test methods);		
	calibration Manual; and		
	Training manual.		
	Handling out of Specification		
13.	**LABORATORY REAGENTS SOLUTION**		
13.1	Whether properly labeled along with concentration/titer and expiration date		
13.2	Whether proper storage facilities are available		
13.3	Whether Period For Reuse and Scientific basis for this period is available.		
13.4	Whether calibration certificates of weights from authorized agencies are available		
13.5	Whether the logbooks for standardization are maintained		
13.6	Whether standardization is within permissible limit (10% of stated value)		
14.	**REFERENCE/WORKING STANDARD**		
14.1	Whether list of available reference standards being maintained		
14.2	Whether lab has adequate arrangements for proper storage, security and labeling of reference standard and working standard		

14.3*	Whether the lab Maintain the records of procurement/source of references and(traceability)		
14.4*	Whether the lab maintains a record of preparation of working standard for daily Use.		
14.5	Whether the lab has written procedure for handling and storage of reference standards		
14.6	Are SOPs for testing of working standards available if so, records thereof		
15.	**SPECIFICATIONS/METHODS**		
15.1	Whether Analytical Method Validation records are available to cover important parameters like linearity, precision, accuracy etc. For in house methods other than the compendia methods		
15.2	Whether specification/standards are authentic and original		
15.3	Whether details of Drugs/Cosmetics reported not of standard quality forwarded to the respective Drug Controller and the Licensing Authority. Whether records maintained in this regard		
15.4	Whether standard reference books available (attach list)		
15.5	a) For how long the sample declared of standard quality Preserved		
	b) For how long the sample declared not of standard quality preserved.		

15.6	Whether the comparison is available that the in-house method is equivalent or superior, in case in-house method is used instead of compendial method		
15.7	Whether the record of study that noninterference of placebo has been confirmed, is available		
16.	**HANDLING & RETENTION**		
16.1	**SAMPLE**		
(a)	Whether samples are right from receiving till disposal are being handled properly		
(b)	After completion of test samples of standard quality and not of standard quality are being kept up to declared time in proper condition		
(c)	The retrieval of control sample is effective or not		
(d)	Average workload of testing during the year		
(e)	No. of samples received		
16.2	**RECORDS**		
(a)	Whether records in case of substance for which an expiry date is assigned are being retained for a period of two years from the expiry of such date. Whether in case of other substances such records are being maintained for six years.		
17	**DISPOSAL**		
17.1	**SAMPLE**		

(a)	Whether disposal of samples after retention period is proper and documented (Standard Quality and not of Standard Quality)		
(b)	Whether manner of disposal of carcasses of animals is proper and according to regulatory requirements.		
(c)	Whether adequate arrangements for disposal of sewage and effluent made		
17.2	**RECORDS**		
(a)	Whether disposal of records is being done in proper manner and with proper authorization.		

Annexure R

Inspection format for inspection of Public Testing Laboratories

Summary Report for Joint Inspection Report of M/s. XXXXXXXXXX

On the basis of the application on form 36 submitted by the authorized signatory of M/s.xxxxxxxxxxx vide letter no. XXXXXXXXXX dated and the letter Ref. No.XXXXX date XXXX received from the State Drug Controlling cum Licensing Authority, of XXXX and the subsequent instruction received from Dy. Drugs Controller (I), XXXX Zone, the undersigned officers jointly inspected the aforesaid testing facility for grant/renewal of approval for carrying out Analysis of drugs & pharmaceuticals by instrumental, chemical and microbiological tests on Form 37.

Following technical personnel were present throughout the inspection.

Name	Designation
1.	
2.	
3.	

The detailed observations about the infrastructure, technical personnel and other set up of the testing facility applied for instrumental, chemical and microbiological analysis of Drugs and pharmaceuticals or raw materials used in the manufacture there of on behalf of licensees for manufacture for sale of Drugs were noted and summarized in aforesaid checklist.

Following observations were made by the joint inspection team during the course of inspection.

Observations:

Conclusion & Recommendation: -

On the basis aforesaid inspection checklist and summarized observations, it may be concluded that M/s.XXXXXXXXXXXX found to have provided premises, technical staff, equipments, recording systems as per rule 150 C &E of Drugs & Cosmetics Rule.

In the view of above the inspecting team is of the opinion that the application furnished by the subject firm as per Form 36, for approval to carry out test on Drugs & pharmaceuticals or raw materials used in the manufacture thereof on behalf of 383 licensees for manufacture for sale of Drugs or raw material on Form-37 for following categories of Drugs by Chemical, Instrumental & Microbiological testing may be granted for the followings category of the drugs & Cosmetics:

Drugs other than those specified in schedule C & C(1) excluding Homeopathic Drugs

- Drugs requiring the use of ultraviolet spectroscopy or chromatography
- Disinfectants
- Cosmetics

b. Drugs specified in schedule C and C (1)

- Antibiotics
- Vitamins
- Parenteral preparations
- Drugs requiring the use of ultraviolet/IR spectroscopy or chromatography
- Drugs requiring microbiological tests.

Signatures of Inspection Team Members

Chapter-6

GUIDANCE DOCUMENTS FOR RISK BASED INSPECTION OF DRUG MANUFACTURING SITE

1. Introduction

- Ensuring the quality, safety, and efficacy of medicines is a critical aspect which contributes significantly to strengthening the assurance in public health systems including healthcare professionals and other stakeholders.
- Enforcement is one of the key components in the regulatory system to ensure that the safe, quality and efficacious drugs reach the patients.
- Schedule M to the Drugs Rules,1945 provides requirements for Good Manufacturing Practices (GMP) and requirements of plant and equipment for manufacture of drugs.
- It specifies in detail the requirements of premises, surroundings, personnel, sanitation, storage of raw materials, documentation and records, self- inspections and quality control systems and site master files etc.
- The manufacturer is required to comply with the requirements of Good Manufacturing Practices prescribed in Schedule M under the conditions of the licence so as to ensure that the drugs manufacturers in the country conform tothe standards prescribed for them.
- In the Indian context, the enforcement in drug regulation is designed as a control system in which the quality of the drugs manufactured are mainly monitored through random sampling, testing of the products and in case of quality failure, regulatory actions are taken through administrative measuresby way of suspension, cancellation or launching prosecution depending on thenature and criticality of the product quality failure.
- While, the Indian drug industry is spread out in the various States and Union Territories, the enforcement has been found to be of varying level among the states. Non-uniformity in the interpretation of the provisions of the law and
- their implementation, lack of adequate infrastructure and varying level of the competence of the regulatory officials have resulted in less than satisfactory performance in many States.
- Compliance to the Good Manufacturing Practices (GMP) is checked through

inspections that are undertaken predominantly in a routine manner. In contrastto this other well regulated country like the USA and the EU which follow a risk-based approach to inspections. They identify the facilities that need to be

inspected based on history of inspection, risk associated with the product and findings of past inspections. Such risk-based inspections result in optimizationof allocation of resources ensuring better quality products.

2. Background

- Risk Based Inspection is a methodology that is based upon the concept of rating manufacturing sites on the basis of an estimated risk that they maypose to patients, consumers, animals and users of medicines. The methodology also takes into account the risk to product quality.
- A risk based approach to inspection planning will improve the depth of GMP inspections and will allow effective implementation of the provisions of Schedule M of Drugs Rules 1945 for maintaining a high level of patient safety.
- Risk-based approach makes the best use of surveillance and enforcement resources.
- The principles of Quality Risk Management are employed while planning the risk-based inspection of the pharmaceutical manufacturing sites.

3. Objective

- The Central Drugs Standard Control Organization is responsible for laying down the standards of drugs, cosmetics, diagnostics and devices and enforcing the rules of Good Manufacturing Practice (GMP) in India for manufacturers of Finished Pharmaceuticals Products (FPP) and Active Pharmaceutical Ingredients (API).
- The objective of the drug regulation is to ensure safety, efficacy and quality of the drugs available in the country.
- The objective of this document is to provide uniform enforcement procedures for onsite inspections to evaluate compliance of the quality system and infrastructure with nationally & internationally accepted GMP Standards (based on the reference document as prescribed in the D & C Act & Rulesand WHO-GMP/TRS guidelines)

- The Competent Authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials or at the premises of manufacturing License Holders whenever it considers that there are grounds for suspecting non-compliance with the principles andguidelines of good manufacturing practice.
- A risk based approach to inspection planning will enable the frequency, depth

and breadth of inspections to be determined accordingly. This will allow flexible and effective administration and supervision whilst maintaining a high level of patient safety.

This document sets out a simple and flexible **Quality Risk Management tool** that may be used by GMP Pharmaceutical Inspectorates when planning the frequency and scope of GMP inspections. It is a methodology that is based upon the concept of rating manufacturing sites on the basis of an estimated risk that they may poseto patients, consumers, animals and users of medicines. The methodology also takes into account the risk to product quality.

4. Purpose:

- This document outlines recommendations for a risk based planning system according to which sites that fall under regulatory supervision are subject to inspection.
- It is intended that each GMP Pharmaceutical Inspectorate uses the document as the basis for developing and implementing its own annual Inspection programme.
- The purpose of this document is to provide a simple and qualitative Quality Risk Management tool that may be of use to GMP Pharmaceutical Inspectorates to priorities sites for inspections when planning the frequency and scope of GMP inspections.

5. **Scope**:

- The planning of routine GMP inspections of active substance and drug product manufacturers by the Competent Authorities;
- The planning of routine GMP inspections of Vaccines, New Drugs, Subsequent New drug etc. manufacturers by the Competent Authorities.
- Follow-up activities, such as assigning a new risk rating to the site following the receipt of new information about the site or its products. (Note: the typesof new information might include information on quality defects, product recalls, market surveillance test results, etc.
- The scope of this document does not extend to the planning of inspections at new manufacturers before any inspection has taken place.

- A useful rule of thumb to use is that the tool should not be applied to a site until the site has been granted a Manufacturing Authorisation and/or a GMP Certificate, as these actions indicate that the site will have been assessedfrom a compliance perspective.

6. Types of Inspection

A. Routine Inspection

a. Inspections for grant/renewal of licenses under CLAA Scheme.
b. Inspections for issuance / revalidation of COPPs as per WHO Certification Scheme for use in international commerce only.
c. Inspections for approval of Testing Laboratories.
d. Risk based inspections

B. Follow up inspection

a. Compliance verification inspection for verification of corrective &preventive actions.

7. Conduct During Inspection

- The inspectors are public servant within the meaning of Sec. 21 of IPC. Inspector shall act according to the procedures for handling of confidential information. All information observed or passed to the inspector is confidential and shall not be disclosed to anybody other than his controlling authority.
- Inspector shall neither carry with him any written or printed materials relatingto other units nor disclose any information relating to another company.
- The inspector's task is not only to point out deficiencies but also to provide guidance based on scientific evidence.

8. Steps in conduct of inspection

Identification of risk

There are two different kinds of risk –risk factor

A. An intrinsic risk: The intrinsic risk estimated for a site reflects the complexity of the site, its processes and products, the criticality of the products or services provided by the site including from a supply perspective as well as status of sample drawn and tested.

B. Compliance-related risk: The compliance-related risk reflects the GMP compliance status of the site immediately following the most recent routine inspection at the site.

The details of Quality Risk Management Tool for Risk Rating based on the intrinsic risk and compliance risk and Guidance on How to Score the Intrinsic Risk Factors is annexed as **Annexure I and II** respectively

9. Selection of Site for Risk Based Inspection:

a) ***Complexity*** refers to the complexity of the site, its manufacturing processes, and its products.
b) ***Criticality*** relates to how critical the availability of the products manufactured at the site is from a supply perspective, or how critical the services provided by the site.
c) ***Compliance*** reflects the compliance status of the site following the most recent routine inspection at the site. When this risk is being estimated, the classification and number of deficiencies identified at the last inspection are taken into account.

Following criteria should be applied for site selection for risk based inspection:

- The compliance history of the establishment;
- Complaints
- History of "Not of Standard Quality" drugs
- The record, history, and nature of recalls linked to the establishment;
- The inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment;
- The inspection frequency and history of the establishment;
- Whether the establishment has been inspected by a foreign government or anagency of a foreign government
- The level of competence demonstrated by staff at the site
- The major changes at the site since the last inspection
- The criticality of the products manufactured/wholesaled by the site, and the criticality of the analytical tests used by the site
- Any other criteria deemed necessary and appropriate

10. Planning of Inspection:

- The planning of the RBI will be done as per the risk criteria.
- The risk based inspection will be conducted in accordance with Risk Based Inspection checklist as per **Annexure III** and **IV**
- The Risk Based Inspection checklist encompasses of the GMP provisions ofthe Schedule M of the Drugs Rules, 1945 and WHO TRS.

A general schedule of Inspection is to be followed by the Inspection team.

- Receipt of File of the firm to the deputed inspection team member(s).
- A review should be made relating to the firm to be visited from thedocuments available in the office file. This may include: -

    - Drug Manufacturing License.
    - Product permission for the applied products.
    - Site Master File
    - Evaluation of: -

        i. Product records (process validation and stability studies),

        ii. Reports of adverse Drugs reaction,

        iii. Market complaint,

        iv. Product recall record,

        v. NSQ reports available in the office file,

        vi. Discrepancies pointed out in previous inspection reports.

Preparation of the day wise inspection plan (1-3 days)

Communication with the Local Authority for access to the site of inspection andregarding the Schedule of inspection.

11. Conduct of Inspection:

- There will be a preliminary tour of the site to allow the inspectors to get a general orientation of the site. It is recommended that the inspecting team start the plant tour as soon as possible after arrival. It is advisable to follow the inspection plan as per material flow.
- Over the course of the inspection the inspectors shall review all procedures,

production and laboratory records, validations and any other record or documentation relating to production and control of the production process.

- It is advisable to check the items that are specific to certain areas of the

facility, such as, Sampling /Dispensing of RM/PM, in process testing andworking documents at the point of operation.

- The inspection shall also include detailed tours of all production facilities,

laboratories, stores, utilities, the plant's record and documentation centre.The following

specific issues shall be investigated,

a) The suitability of the facility for its purpose, including the orderliness of itsLay-out for man and material movement, equipment and cleanliness;
b) The production equipment – its qualification/validation, calibration and

cleanliness, preventive maintenance, daily equipment usage logs. Whether production records are fully maintained and in real time.

c) Critical systems: HVAC, water system, filtered compressed air, drainage.ETP and any other relevant systems.

d) The documents such as master formulae, test specifications, Standard Operating Procedures, batch records (including protocols of analysis and documents relating to the control of printed material and labellingoperations) requires close verification.

- The inspection team may adopt the additional and other plan for areas of inspection based on the need of particular inspection for the required purpose.

12. Areas to be covered during inspection

To cover following areas as per SOP, Checklist benchmarks etc. provided in the Guidance document available on CDSCO website under Public notices vide F. No. DCG(I)/Misc/2016(60) dated 26-05-2016

1.	Building and premises
2.	Ancillary areas
3.	Security system
4.	Water & Compressed air system
5.	Disposal of waste(Ambient protection)
6.	Health, clothing and sanitation of workers
7.	Training
8.	Warehousing Area
9.	Raw Materials
10.	Production Area for Non Sterile preparation
11.	Air Handling Systems (HVAC
12.	Cleaning validation
13.	Manufacturing Operations and Controls:
14.	Precautions against mix-up and cross-contamination
15.	Sanitation in the Manufacturing areas:

16.	Equipment
17.	Production Area for Sterile Preparation
18.	Air Handling System (Central Air Conditioning)
19.	Environmental Monitoring
20.	Garments
21.	Sanitation
22.	Equipment
23.	Manufacturing Process

13. Findings:

How to write a Deficiencies / Non-compliance statements:

a) The non-compliance statement should include the requirement (R), evidence (E) and deficiency (D).

b) Example: (R) The relevant cleaning records and source data should be kept in cleaning validation reports; (E) the source of three samples taken for recovery testing during the process equipment validation was not traceable;

(D) cleaning validation reports did not include sufficient data.

c) Deficiencies/noncompliance statements should distinguish whether the defect lies in the system itself or in a failure to comply with the system.

For instance, when cleaning is found to be suboptimal, it is important to know whether the standard operating procedures (SOPs) are inadequate or lacking, or whether adequate written procedures exist but are not being followed by personnel.

d) Where more than one deficiency relates to the same basic quality system failure, the deficiencies should be grouped and listed as a single observation, under a heading that reflects the basic system failure.

e) Deficiencies should be reported with a focus on risk to patient health and/or need for corrective and preventive action (CAPA). Recommendations should relate to recommended regulatory action as appropriate.

f) Each deficiency should be classified as critical, major or other, according to the following definitions, which may be adapted according to the national or regional legal context.

The report should not include comments that could be construed as proposed specific solutions to issues raised.

14. Classification of Findings of Risk Based Inspection:

Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of another deficiency may be categorized as *major*.

A deficiency that was reported at a previous inspection and was not corrected may be reported with a higher classification.

One-off minor lapses or less significant issues are usually not formally reported, but are brought to the attention of the manufacturer during the inspection.

a) Critical deficiency

A critical deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to theuser.

Item/area/system/knowledge is missing or of such nature to warrant serious quality/compliance concerns.

b) Major deficiency

A major deficiency may be defined as a non-critical observation that:

a) has produced or may produce a product that does not comply with its condition of licence

b) indicates a major deviation from the GMP guidelines;

c) indicates a failure to carry out satisfactory procedures for release of batches;

d) indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;

e) consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

c) Other deficiency

A deficiency may be classified as other if it cannot be classified as either criticalor major, but indicates a departure from GMP. A deficiency may be other eitherbecause it is judged as minor or because there is insufficient information to classify it as major or critical.

15. Outcome of inspection:

Based on the number of the critical and major observations regulatory action like issuance of show cause notice or cancel a licence or suspend a licence for period as licensing authority thinks fit either wholly or in respect of any of the drugs or other actions as deemed fir under the provisions of D & C Act, 1940.

16. Action to be taken based on inspection findings:

a) When there is one or more critical or several major deficiencies (e.g.≥6):

i. The site is considered to be operating at an unacceptable level of compliance with Good Manufacturing Practices (GMP) guidelines.
ii. Administrative (Show cause notice followed by Stop production order, Cancellation of product permission, Cancellation of manufacturing license) and/or legal enforcement actions (prosecution) as necessary.
iii. Another inspection will normally be required.
iv. This action will continue till satisfactory resolution of the non compliance after joint verification by CDSCO& State.

b) When there are few major deficiencies (e.g.<6) and other deficiencies:

i. The site shall submit compliance report after rectification of deficiencies and the same shall be verified for determination of compliance to GMP. CAPAs forall deficiencies to include actions implemented and/or planned, timelines and documented evidence of completion, as appropriate.
ii. CAPAs are to be evaluated on paper and shall include an on-site inspectionfor verification of compliance submitted by the site.

c) When there are other deficiencies only:

i. The site is considered to be operating at an acceptable level of GMP compliance.
ii. The manufacture is expected to provide CAPAs. CAPAs for all deficiencies to include actions Implemented and/or planned, timelines and documented evidence of completion, as appropriate.
iii. CAPAs are to be evaluated on paper and followed up during the next routine inspection.

Annexures:

Annexure I- Quality Risk Management Tool for Risk Rating based on theintrinsic risk and compliance risk

Annexure II- Guidance on How to Score the Intrinsic Risk Factors**Annexure III**- Risk Based Inspection checklist cum Benchmark tool

References:

1. PICS document on "A Recommended Model for Risk-Based InspectionPlanning in The GMPEnvironment"
2. USFDA documents on "Understanding CDER's Risk-Based Site Selection Model"
3. WHO TRS 981, Annex 2 "WHO guidelines on quality risk management"

Annexure-I

Quality Risk Management Tool for Risk Rating based on the intrinsic risk andcompliance risk

A. The Intrinsic Risk Associated with the Site

Risk Factor	Risk Score	Matrix for Estimating the Intrinsic Risk
The Complexity of the site, its processes and products, is regarded as:	1 2 3 Circle one	
The Criticality of the products manufactured by the site, or the criticality of the analytical testing or other service offered provided by the site, is regarded as:	1 2 3 Circle one	

	Criticality		
Complexity	1	2	3
1	1 (Low)	2 (Low)	3 (Med)
2	2 (Low)	4 (Med)	6 (High)
3	3 (Med)	6 (High)	9 (High)

Use the above matrix and record the Intrinsic Risk associated with the site below:

Low ❑ Medium ❑ High ❑

B. The Compliance-related Risk based on the last Inspection

The **compliance risk** indicated by the most recent deficiency profile of the site is:	**Low ❑** **Medium ❑** **High ❑**	- No Major or Critical Deficiencies - 1 to 5 Major Deficiencies: *Number of Majors* = ____ - 1 or more Critical Deficiencies or more than 5 Majors *(Note: Customise as appropriate)*

C. The Risk-Rating assigned to the Site

Complete the matrix below by combining the Intrinsic risk score and the Compliance-related risk score to determine the **Risk Rating** for the site.

	Intrinsic Risk		
Compliance Risk	Low	Medium	High
Low	Risk Rating = A	Risk Rating = A	Risk Rating = B
Medium	Risk Rating = A	Risk Rating = B	Risk Rating = C
High	Risk Rating = B	Risk Rating = C	Risk Rating = C

The Risk Rating associated with this site is: A ❑ B ❑ C ❑

Annexure II

Guidance on How to Score the Intrinsic Risk Factors

No	Intrinsic Risk Factor & Scoring Mechanism
1	**Complexity:** This concerns the complexity of the site, its processes and its products. (Note: The Site Master File (if available) and the last GMP inspection report can be useful sources of information on which to assign the Complexity score.) There are three possible scores here, 1, 2 and 3. Sites with a low risk factor score in this area are known to have a low level of complexity in the design of the site, in its products and processes. When scoring this Risk Factor, it is useful to consider the following: General but useful indicators of **site complexity** are: • The size of the site – large sites are rated more complex than smaller sites • The number of different manufacturing or distribution processes that are in use at the site – larger numbers generally give rise to more complexity • The level of dedication of equipment and facilities (e.g. Air Handling Units) that is in place at the site – sites with a low level ofdedication are considered more complex than other sites • The number of staff at the site – larger numbers generally give riseto more complexity • The number of commercial markets/countries supplied by the site - larger numbers generally give rise to more complexity • The number of customers supplied by the site - larger numbers generally give rise to more complexity • If the site is a contract manufacturer or contract laboratory, the sitecan be regarded as being relatively complex General but useful indicators of **process complexity** are: • Sterile and aseptic manufacturing processes – these are always considered highly complex processes. • Parametric release activities – these are usually considered highlycomplex processes. • The number of critical steps that must be controlled within a process – generally, processes with a high number of critical stepscan be considered to be more complex processes. • The type of products manufactured – some product types such aslow concentration/high potency dosage forms and sustained released dosage forms can be more complex to manufacture than

	other types of products (such as immediate release tablets) and the complexity of their manufacturing process should be rated more highly here. • The number of unit operations in a non-sterile manufacturing process – larger numbers generally give rise to more complexity. • Repackaging activities - repackaging an already packaged batch can be considered a moderately to highly complex process. • The extent of reprocessing or reworking taking place at the site: these activities can add complexity to the process • Biological processes • The extent of subcontracting in use by the site - a significant use of contract manufacturers, off-site distribution sites or contract laboratories generally gives rise to complexity. • In case of importers, the complexity of importation, batch release and product distribution processes – sometimes the arrangements in place for importation can be quite complex. General but useful indicators of **product complexity** are: • The number of components that make up any one product pack -larger numbers of components in a pack generally give rise to more product complexity. For example, a pack of an injectable product may have 4 components within it (a lyophilised vial, a diluent vial, atransfer needle and a technical leaflet, whereas a pack of a tablet product may have just a blister strip and a patient information leaflet within it.) • Products requiring special storage and distribution: (e.g. cold chain products and short-shelf-life products such as radiopharmaceuticalscan be complex to manage.) Scoring Guideline: Assign a score of 1 to sites with a low overall level of Complexity Assign a score of 2 to sites with a moderate overall level ofComplexity Assign a score of 3 to sites with a high overall level ofComplexity Note: When assigning the overall complexity rating, the rating (1, 2or 3) which most reflects the various individual complexity ratings that were assigned to site, process and product complexity should be chosen. This is similar to taking an average of all of the individualcomplexity ratings that were assigned. In cases where there is insufficient information or knowledge aboutthe complexity associated with the site, its processes and products,a medium score of 2 should be assigned.
2	**Criticality:** This concerns how critical the availability of the products manufactured by the site are from a supply perspective, or how

	critical the services provided by the site are. An example of a criticalservice provided by a site may be an analytical testing service performed for several other companies. (Note: The Site Master File (if available) and the last GMP inspection report can be useful sources of information on which to assign the Criticality score.) There are three possible scores here, 1, 2 and 3.Scoring Guideline: Assign a high score (of 3) for the sites where "Not of Standard Quality" are more than 5 per year. Assign a high score (of 3) to sites that are known to manufacture essential products or that are known to be sites that provide an essential service that is not readily available elsewhere. • These may be sites that are the major or sole supplier of an essential product (such as an important vaccine, a critical blood product, etc.). Note: it is recognised that being the major or the sole supplier of anessential product does not present any risk to product quality; rather, it presents a risk to product availability. • The test methods (and related equipment) used by these sites cannot easily or readily be performed or used by other laboratories. • These may be sites that provide a contract manufacturing or testing service to a number of other manufacturers and a disruptionin such services would have a significant impact on product availability. Assign a low score (of 1) to sites that are known to manufactureonly non-essential products or that are known to be sites that donot provide an essential service. Assign a high score (of 1) for the sites where "Not of StandardQuality" are 0-3 per year • These may be sites that are not the sole supplier of any importantproducts (such as an important vaccine, a critical blood product, etc.). • The test methods (and related equipment) used by these sites arenot such that they cannot be readily performed or used by other laboratories. • These are not sites that provide a contract manufacturing or testingservice to many other manufacturers, where a disruption in such services would have a significant impact on product availability.

	Assign a medium score (of 2) to sites that are in between the abovetypes of sites. Assign a high score (of 2) for the sites where “Not of Standard Quality” are 3-5 per year Note: In cases where there is insufficient information or knowledgeabout the criticality associated with the site, a medium score of 2 should be assigned.

Annexure III

Inspection checklist for Risk Based Inspection (RBI) Cum Benchmarking

Name of the manufacturing unit	
Address	
Mfg. Lic. no.	
Validity of License.	
Constitution of the firm	
List of Directors/Partners/Proprietor	
License issuing authority	
Categories of drugs permitted to be manufactured	
Specify whether COPP has been issued to the firm	
Name and Designation of the Inspecting team members	
Site Specific Data	
No. of Products manufactured at site (during last year)	
No. of manufacturing blocks	
No. of Technical Personnel in Manufacturing	
No. of Technical Personnel in QA	
No. of Technical Personnel in QC	
No. of Technical Personnel in Microbiology	
No. of Technical Personnel from other Department	
No. of Technical Personnel in R&D	
No. Of technical personnel in Formulation development	
No. of Samples drawn by QC (during last year)	
No. of Samples declared OOS (during last year)	
No. of samples declared NSQ by Govt. Analyst (during last year). Collect reasons for such failures and annexe with this checklist	

Observations should be descriptive without ambiguity and answer like "Yes" or "No" should be avoided

CHECKLIST FOR GMP INSPECTION OF MANUFATURCING SITE AS PER PART I OF SHEDULE M (MAIN PRINCIPLES AS PER PART I OF SCHEDULE M)

Sr. No.	Sch M Ref.	Particulars	2	1	0	x	Observations
1.0 Pharmaceutical Quality System (PQS)							
1	1.2	Whether the roles and responsibilities of senior management and other authorities are defined, communicated and implemented throughout the organization.	NA	The roles and responsibilities of senior management and other authorities are defined in written and are properly communicated through communication matrix and implemented throughout the organization.	The roles and responsibilities of senior management and other authorities are not defined, not communicated and not implemented throughout the organization.		
2	1.4	Whether the Good Manufacturing Practices are applied to the life-cycle stages, from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing, until the product discontinuation.	Good Manufacturing Practices are applied to the life-cycle stages, from the manufacture of investigational medicinal products, technology transfer, and	The firm is following the principles of GMP to the life-cycle stages of products as applicable.	The firm is not following the principles of GMP in some stages.	The firm is not following the principles of GMP in any stage.	

			commercial manufacturing, until the product discontinuation.				
3	1.4	Whether all parts of the product quality system are adequately resourced and maintained, including being provided with sufficient competent personnel, suitable premises, equipment and facilities.	NA	Adequate and trained staff, premises, equipment's, facility and machinery are available	The firm is deficient/in adequate in skilled manpower, equipment, facility and machinery.	The firm has not provided facility for manufacturing of concerned dosage form.	
4	1.5	The product quality system appropriate to manufacture of pharmaceutical products shall ensure:-					
	(a)	product realisation is achieved by designing, qualifying, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;		The firm has taken the appropriate steps for product designing, qualifying, planning, implementing, maintaining and continuously improving a system like pre and post licensing, development, validation and critical control in process parameters are fixed. Further consistency is maintained by continuous review	No steps are taken by the firm.		

				(APQR) and trend analysis			
	(b)	product and process knowledge is managed throughout all lifecycle stages		The firm has maintained the record through out life cycle	No such approached has been made by the firm.		
	(c)	pharmaceutical products are designed and developed in a way that takes into account, the requirements of GMP and other GXPs such as those of Good Laboratory Practices (GLP) and Good Clinical Practices (GCP);		The firm has designed and developed the product taken in account of GXPs	No such activity has been performed.		
	(d)	production and quality control operations shall be clearly specified in a written form and GMP requirements are adopted;		All activity of Production and Quality control are in written and GMP followed.	GMP are lacking in all or some areas.		
	(e)	managerial responsibilities are clearly specified in the job descriptions;		Job description of all staff are available	Job descriptions are not available or job descriptions of some officials are not available.		
	(f)	arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is the correct material from the approved supply chain;		Vendor qualification are available for all starting and packing material. Further, regular verification of vendors are performed in define intervals	Vendor qualification are not verified in define interval.	No vendor qualificati on is performed.	

	(g)	all necessary controls on starting materials, intermediate products, and bulk products and other in- process controls, calibrations and validations are carried out;		The critical control parameter and all the steps are incorporated in Validation activity	Validation activity is inappropriate.		
	(h)	the finished product is correctly processed and checked, according to the defined procedures;		The Finished product is released after checking all required defined parameters	Finished product is released without proper checking		
	(i)	authorised persons have certified that each production batch has been produced and controlled in accordance with the requirements of the licence and other applicable regulations relevant to the production, control and release of pharmaceutical products;		The firm has proper checks to verify all control and regulatory requirement to release the batch which was documented and signed by authorized person.	No such checks area available		
	(j)	processes are in place to ensure the management of outsourced activities;		The outsourced activity are properly managed with MOU/ agreement and other written documents	Outsourced activity are not properly managed.		
	(k)	satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf-life;		The firm is following and verifying the Good Distribution practice	Good Distribution Practice is not maintained.		

	(l)	there is a procedure for self-inspection or quality audit that regularly appraises the effectiveness and applicability of the product quality system;		Self inspection is planned in define interval	Self inspection is not carried out		
	(m)	product and processes are monitored and the results taken into account in batch release, in the investigation of deviations and, with a view to taking preventive action to avoid potential deviation so occurring in the future;		The deviation are properly investigated and capture in APQR, further prevention action is taken for potential deviation in future.	No investigation carried out and investigation are inappropriate without root cause.		
	(n)	Arrangements are in place for the prospective evaluation and approval of planned changes and their approval prior to their implementation, taking into account regulatory notification and approval where required. After implementation of any change, an evaluation is undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;		The firm has process of change control and its approval including impact assessment on quality. Further Regulatory approval is taken wherever required for changes.	The firm has no process of change control and no regulatory approval is taken wherever is required.		
	(o)	Regular reviews of the quality of pharmaceutical products are conducted with the objective of verifying the consistency of the process and identifying where there is a need for improvement;		APQR is maintained by the firm	No APQR or some APQR is available.		

	(p)	a state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;		There is effective monitoring and control system is established	No such practice followed.		
	(q)	continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge		There is system of continual improvement and implemented	No system of continual improvement is established		
	(r)	there is a system for QRM		There is system if QRM	No QRM followed		
	(s)	Deviations, suspected product defects and other problems are reported, investigated and recorded. An appropriate level of root cause analysis is applied during such investigations. The most likely root causes shall be identified and appropriate corrective and preventive actions shall be identified and taken. The effectiveness of corrective and preventive actions shall be monitored		Deviation, out of specification, market compliant and NSQ are investigated and established root cause including the prevention action for future activity	No such activity is followed by the firm.		
5.	1.6.	Whether the periodic management reviews are conducted with the involvement of senior management of the operation of the product quality system to identify opportunities for continual improvement of products, processes and the system itself.	NA	The firm is having all written procedure for MRM and same is implemented. Senior Management is part of MRM.	The firm may have SOPs but not implemented.	NA	

6.	1.6.	What is the frequency for the periodic management reviews (Unless otherwise justified, such reviews shall be conducted at least annually)	NA	Frequency for the periodic management reviews is defined and followed.	Frequency for the periodic management reviews may defined but not followed.	NA	
7.	1.7	Whether the product quality system is well defined and documented.	NA	PQS is defined and documented.	PQS is not defined.		
8.	1.7	Whether a quality manual or an equivalent documentation is available and it contains a description of the quality management system including management responsibilities.	NA	quality manual or an equivalent documentation is available and it contains a description of the quality management system including management responsibilities	quality manual or an equivalent documentation is not available or deficient in requisite information.	NA	
2.0 Quality Risk Management (QRM):							
9.	2.1	Whether the firm has well defined Quality Risk Management to assess, control, communication and review the risks to the quality of the medicinal product.	NA	QRM is well defined	QRM is not well defined or there is no procedure for QRM.	NA	
10.	2.2	Whether the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;	NA	Risk was evaluated based on scientific knowledge, experience with the process	Criteria not defined in evaluation of risk or no procedure followed for risk evaluation.	NA	
2.3 Product quality review							
11.	2.3.1	Whether the firm has well defined procedure/SOP for Product quality review		Procedure/SOP for Product quality review available	Defined procedure/SOP for Product quality review are not available/are inadequate		

12.	2.3.1	Whether the firm has conducted Regular, periodic or rolling quality reviews of all pharmaceutical products,		Regular, periodic or rolling quality reviews of all pharmaceutical products has been conducted and trend are maintained,	No such activity performed or not performed for all products.		
13.	2.3.1	Check that Product quality reviews are conducted for products for domestic consumption as well as for products for export also.		PQR Conducted for both i.e. Products for domestic consumption as well as for products for export also.	PQR Not Conducted for either		
14.	2.3.1	Whether such reviews are conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.		PQR are conducted with trends and also identify product and process improvements.	PQR are deficient with respect to requirements		
15.	2.3.2.	What is frequency for conducting the Product quality review(Product quality review shall be conducted and documented annually, taking into account previous reviews. Ensure that the Product quality review reports includes the parameters as per Para 2.3.2 of schedule M.)		Product quality review are conducted and documented annually, taking into account previous reviews are prepared considering requirements per Para 2.3.2 of schedule M and further frequency is defined.	Product quality review frequency is not defined/followed/ PQR not meeting the requirements as per Para 2.3.2 of schedule M/ frequency is not defined.		

16.	2.3.3.	Whether the manufacturer has evaluated the results of the review and an assessment is made as to whether corrective and preventive actions or any revalidation needs to be undertaken.	The PQR results are properly and statistically analyzed considering all analytical parameters	The corrective and preventive actions or revalidation are undertaken as required	PQRs are not evaluated and Firm neither initiated nor undertaken corrective and preventive actions or revalidation , as required		
17.	2.3.3.	Whether the corrective and preventive actions arising out of PQR are completed in a timely and effective manner and according to the documented procedures.		Corrective and preventive actions are completed in a timely and effective manner and according to the documented procedures.	corrective and preventive actions arising out of PQR are not completed in a timely and effective manner and documented procedures are not available		
18.	2.3.3.	Check whether the firm has procedures for the on-going management and review of the actions arising out of PQR and Check whether effectiveness of these procedures is verified during self-inspection of by the firm.		Firm has procedures in place for on-going management and review of the actions arising out of PQR and effectiveness of these procedures is verified during self-inspection of by the firm.	Firm is not having procedures for on-going management and review of the actions arising out of PQR and effectiveness of these procedures is not verified during self-inspection . Or Procedures are available but inadequate		

19.	2.3.3	Whether technical agreement is in place between the various parties that defines their respective responsibilities in producing the quality review.		Technical agreement is in place with all contractual activity	Technical agreement is not in place with all contractual activity (specify the activity for which agreement is not available)		
20.	2.3.3	Whether the authorized person responsible for final batch certification ensures that the quality review is performed in a timely manner and is accurate. Verify how it is ensured.		Authorized person responsible for final batch certification.	Authorized person are available responsible for final batch certification but not ensuring that the quality review is performed in a timely manner and is accurate.		
3.0 Good manufacturing practices (GMP) for pharmaceutical products							
21	3.1 (1)	Whether all manufacturing processes are clearly defined, systematically reviewed for associated risks and are capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications.		Firm has written procedure/SOPs/Documents for all manufacturing processes and are clearly defined, reviewed for associated risks	Firm is not having written procedure/SOPs/Documents for all manufacturing processes OR procedures are inadequate		
22	3.1 (2)	Whether qualification of equipment's and process validations are performed for all equipment's and processes as, applicable, and re-qualifications/ process validations are repeated as and when applicable		Firm has performed qualification of equipment's and process validations are performed for processes as, applicable. Re-qualifications/ Re-validations criteria are	qualification of equipment's and process validations are performed are deficient. Re-qualifications / Re-validations criteria are not defined	Qualification of critical process equipment's and process validations are not performed which may have direct impact on	

				defined and implemented		product quality	
23	3.1 (3)	Whether the manufacturer has provided necessary resources as per Para 3.1(3) of Schedule M.		The manufacturer has provided necessary resources as per Para 3.1(3) of Schedule M.	Manufacturer has not /Inadequately provided necessary resources as per Para 3.1(3) of Schedule M		
24	3.1 (4)	Whether the instructions and procedures are written in clear and unambiguous language.	SOPs are availabl e and staff is trained for all SOPs	SOPs are available and well defined	SOPs are not available/Def icient		
25	3.1 (6)	Whether the records are made (manually or by recording instruments or by both) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected		Records of manufacturing activities showing all steps are available	Records of manufacturin g activities showing all steps are not available/Ina dequate		
26	3.1 (6)	Whether the significant deviations (if any) are fully recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive actions are implemented		Significant deviations (if any) are recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive	Significant deviations (if any) are not recorded/ inadequately handled.		

				actions are implemented			
27	3.1 (7) & 17. 3.1 0.1 5	Whether the records covering manufacture and distribution (to enable the complete history of a batch to be traced/ to facilitate the recall) are retained in a comprehensible and accessible form;		Records of manufacture and distribution are available and retained in a comprehensible and accessible form;	Records of manufacture and distribution are inadequate maintained		
28	3.1 (8)	Whether the storage and distribution of the products is done properly to minimizes risk to the product quality, if any		Products are stored and distributed properly as per required storage condition	Products are not stored and distributed properly as per required storage condition	Products are stored and distributed under extreme storage and unhygienic conditions which may risk to the product quality	
29	3.1 (9)	Whether manufacturer is having a system to recall batch of product from sale or supply. (if required)	The firm has recall system inline with internat ional availabl e guidelin es viz.. WHO,	Firm is effective system to recall batch of product from sale or supply	Firm is not having system to recall batch of product from sale or supply Or /system is inadequate	Firm was unable to perform the effective recall of impugned batch of drug as the case may be. (may be proven with examples of such cases)	
4.0 Sanitation and hygiene:							

30	4	Specify the sanitation and hygiene process employed by firm in every aspect of the manufacture of drugs. Whether the scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection and any other source of contamination to the product.		Procedures for sanitation and hygiene process are available and implemented. Sanitation and hygiene procedures covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection and any other source of contamination to the product.	Procedures for sanitation and hygiene process are not available OR inadequately implemented	Unhygienic practices (which may have impact on product quality) are observed in a core manufacturing area during inspection.	
5.0 Qualification and Validation							
31	5.1	Whether the manufacturer has identified the qualification and validation work is required to prove that the critical aspects of their particular operations are controlled.		Manufacturer is having procedure for qualification and validation work covering critical aspects of particular operation.	Manufacturer is not having procedure for qualification and validation work required. OR Procedures are inadequate.		
32	5.2	Whether the manufacturer has well defined validation master plan and key elements of a qualification and validation programmed are clearly defined and documented in a validation master plan		Manufacturer has well defined validation master plan and key elements of a qualification and validation programmed are clearly defined and documented.	Validation master plan is not available Or Inadequate		

33	5.3.	Whether required qualifications and validation(DQ, IQ, OQ & PQ are performed for the premises, supporting utilities, equipment and processes		Firm has performed qualifications (DQ, IQ, OQ & PQ) for the premises, supporting utilities, equipment	Qualifications (DQ, IQ, OQ & PQ) for the premises, supporting utilities, equipment		
34	5.3.	Whether [process validations (PV) / performance qualification (PQ) are performed to ensure that specific process consistently produce a product meeting its predetermined specifications and quality attributes.		Process validations (PV) / performance qualification (PQ) are performed to ensure that specific process consistently produce a product meeting its predetermined specifications and quality attributes.	Process validations (PV) / performance qualification (PQ) are performed but are inadequate	Process validations (PV) / performance qualification (PQ) are not performed.	
35	5.4.	Whether changes in aspect of operation(including significant changes to the premises, facilities, equipment or processes) which may affect the quality of the product, directly or indirectly, are qualified and validated, as and when required.		Changes are well documented, evaluated and processed.	Changes are inadequately documented, evaluated and processed.	Significant changes to the premises, facilities, equipment or processes which may affect the quality of the product are not documented and evaluated.	
36	5.5	Whether the firm is having on-going Qualification/validation programmed to follow their first implementation/outcome of a periodic review.		On-going Qualification/validation programmed available	On-going Qualification/ validation programmed not available		

37	5.6.	Whether the commitment to maintain continued validation status is stated in firm's quality manual or validation master plan.		Available in QM/VMP	Not Available in QM/VMP		
38	5.7.	Whether the responsibility for performing validation is clearly defined.		Responsibility for performing validation is clearly defined.	Responsibility for performing validation is not clearly defined.		
39	5.8.	Whether the Validation studies are conducted in accordance with predefined and approved protocols.		Predefined protocols available.	Predefined protocols not available.		
40	5.9	Whether written reports summarizing the results recorded and the conclusions reached are available		Reports summarizing the results are available.	Reports summarizing the results are not available.		
41	5.10.	Whether the Processes and procedures are established on the basis of the results of the validation performed.		Processes and procedures are established on the basis of validation performed.	Processes and procedures are not established on the basis of validation performed.		
42	5.11.	Whether the firm has performed validation of analytical test methods, automated systems and cleaning procedures.		Firm has performed validation of analytical test methods, automated systems and cleaning procedures.	Firm has inadequately (not covered all critical control parameters) performed validation of analytical test methods, automated systems and cleaning procedures.	Firm has not performed validation of analytical test methods, automated systems and cleaning procedures. (which may have impact on product quality).	
6.0 Complaints and adverse reaction:							

43	6.1	Whether the firm is having SOP for review and investigations product complaints. Whether all the complaints/other information concerning potentially defective products are carefully reviewed according to the written procedures and corrective actions are implemented accordingly?		SOP for review and investigations product complaints available and Market complaints are effectively investigated and appropriate measures (CAPA) are taken in respect of the defective products to prevent recurrence.	SOP for review and investigations product complaints not available./Market complaints are not recorded Or inadequately processed. Appropriate measures (CAPA) are not taken in respect of the defective products to prevent recurrence.		
44	6.2	Whether the firm has designated person responsible for handling the complaints and deciding the measures to be taken. Whether sufficient supporting staff is available to assist him or her.		Firm has designated person responsible for handling the complaints and sufficient supporting staff is available to assist him or her.	Firm has NOT designated person responsible for handling the complaints and sufficient supporting staff is NOT available to assist him or her.		
45	6.2	If this person is different from the authorized person (responsible for final batch certification), then how the latter is made aware of any complaint, investigation or recall.		Procure for communication for procedure is well defined and established	Procure for communication for procedure is not available Or inadequate defined.		
46	6.3.	Whether the firm has written procedures describing the action to be taken, including the need to consider a recall, in the case of a		Firm has written procedures for market complaint describing the action to be	Firm has written procedures for market complaint are not available		

		complaint concerning a possible product defect.		taken, including the need to consider a recall,	OR inadequate		
47	6.5	Verify that the person responsible for Quality Control (QC) is involved in the review of such investigations.		Person responsible for Quality Control (QC) is involved in complaint investigations.	Person responsible for Quality Control (QC) is not involved in complaint investigations.		
48	6.6.	In case, If a product defect is identified or suspected in a batch. Then check if consideration is given to check other batches in order to determine whether they are also affected.		If a product defect is identified or suspected in a batch. Then consideration is given to check other batches in order to determine whether they are also affected.	If a product defect is identified or suspected in a batch. Then consideration not given to check other batches	If a product defect is identified or suspected in a batch then other batches are released without checks /outcome of investigations , as applicable	
49	6.7	Whether the firm is taking necessary/appropriate follow-up action (including product recall, if required), after investigation and evaluation of the complaint.		Necessary/appropriate follow-up action (including product recall, if required) are taken after investigation and evaluation of the complaint.	Firm has not adequate procedure and system	Necessary/ appropriate follow-up action w.r.t product recall is not taken after outcome of investigation and evaluation of the complaint, as and when required.	

50	6.8.	Whether all decisions made and measures taken as a result of a complaint are recorded and referenced to the corresponding batch records.		Complaint are recorded/referenced to corresponding batch record.	Complaint are not recorded/ referenced to corresponding batch record.		
51	6.9.	Whether complaint records are regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.	complaint records are regularly reviewed and statistically analyzed to made trends.	complaint records are regularly reviewed /documented and evaluated for reoccurrence.	No system is available for periodic review of complaints.		
52	6.10.	Whether firm informs the licensing authorities, if they are considering action following the faulty manufacture, product deterioration, a suspect product or any other serious quality problems with a product.		Procedure/records available	Procedure/records not available		
53	6.11.	Whether the firm have a pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the adverse drug reactions emerging from the use of drugs manufactured or marketed by the firm.	pharmacovigilance system in place and well defined. Data collected from market were analyzed and reported to concerned	Pharmacovigilance system in place and effective.	pharmacovigilance system/procedure is in place, but data inadequate.	No system in place	

			authority.				
7.0 Product recalls:							
54	7.2	Whether authorized person responsible for the execution and coordination of recalls. He or she shall have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency		The authorized and trained personnel along with adequate staff is provided	No designated/authorized personnel available or sufficient staff is not provided or staff is not adequately trained.		
55	7.3	Whether Recall operations are capable of being initiated at the required level in the distribution chain.	procedures are well established and tested for recall at each stage of distribution chain	Procedure are available and performed the mock recall from the end point of distribution.	No /inadequate Procedure. Mock recall not performed.		
56	7.4	Whether recalled products are stored in secure segregated area.		Recalled products are stored in secure segregated area.	Recalled products are not stored in secure segregated area.		
57	7.5.	Whether the firm informs the licensing authorities about any intention to recall the product because it is, or		Procedure/Records are available	Procedure/Records are not available		

		is suspected of being, defective.					
58	7.6	Whether distribution records shall be readily available to the authorized person, and they shall contain sufficient information on wholesalers and directly supplied customers to permit an effective recall.		Distribution records are readily available with requisite information	Distribution records are not readily available.		
59	7.7	Whether progress of the recall process are monitored and recorded. (Records shall include the disposition of the product. A final report shall be issued, including reconciliation between the delivered and recovered quantities of the products.)		Recall process are monitored and recorded. Reconciliation between the delivered and recovered quantities are available along with final disposition.	Recall process are not/inadequately monitored and recorded.	Reconciliation data not maintained /available	
60	7.8	Whether effectiveness of the arrangements for recall shall be tested and evaluated from time to time.		System is available to perform the mock recall and its effectiveness is evaluated from time to time.	No System is in place to perform the mock recall OR effectiveness is not evaluated from time to time(Mock recall not repeated).		
61	7.9.	Whether prompt and effective product recall system is devised for timely information of all concerned stockists, wholesalers, suppliers, up to the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard		Timelines are specified in SOP	Timelines are not specified in SOP		

Change Control							
62	8.1	Whether the firm has well defined and established formal change control system to evaluate all changes that may affect the production and control of the product.		SOP for change control available and implemented	SOP for change control are not available/inadequately implemented		
63	8.2	Whether the written change control procedures covers the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software etc.		Change control procedures covers the identification, documentation, appropriate review, and approval of changes.	Change control procedures are not available/ inadequate w.r.t review, evaluation and approval		
64	8.3	Whether proposals for relevant changes to GMP are drafted, reviewed and approved by the appropriate organizational unit and reviewed and approved by the quality unit.		Change controls are drafted, reviewed and approved by the appropriate organizational unit and are reviewed and approved by the quality unit.	Change controls are not drafted, reviewed and approved by the appropriate organizational unit and are reviewed and are not approved by the quality unit.		
65	8.4.	Whether the potential impact of the proposed change on the quality of the intermediate or Active Pharmaceutical Ingredient (API) or finished product is evaluated.		Potential impact of the proposed change on the quality of product is evaluated.	Potential impact of the proposed change on the quality of product is not/inadequately evaluated.		

		Whether classification procedure is available for determining the level of testing, validation and documentation needed to justify changes to a validated process.		Classification procedure is available for determining the level of testing, validation and documentation needed.	Classification procedure is not available/inadequately available for determining the level of testing, validation and documentation needed.		
66	8.6	After the change has been implemented , whether firm is having procedure to evaluate the first batch produced or tested under the change,		Firm is having procedure and first batch is evaluated or tested after change (for applicable changes controls)	Firm is not having /inadequate procedure	For critical changes , firm has not evaluated first batch for possible impact on product quality.	
9.0 Production under loan licence or contract and contract analysis and other activities:							
9.3 Loan licensee or contract giver							
67	9.3.1.	Whether the product quality system of the loan licensee or contract includes the control and review of any outsourced activities.		Product quality system of the loan licensee or contract includes the control and review of any outsourced activities	Do not have any such system.		
68	9.3.2.	Whether the loan licensee/contract giver has provided the manufacturing facility provider or contract acceptor all the information necessary to carry out the contracted operations correctly in accordance with the licence / other legal requirements		Such Information shared.	No such information shared.		
69	9.3.3.	Whether the loan licensee/contract giver reviews/assess the		Records and results are reviewed &	Records and results are not reviewed &		

		records and results related to the outsourced activities		assessed by loan licensee/contract giver.	assessed by loan licensee/contract giver.		
70	9.3.3.	Verify the mechanism/process implemented by the contract giver to ensure that all the products and materials delivered by the manufacturing facility provider/ contract acceptor have been processed in accordance with good manufacturing practices and the licence;		Verification carried out by the contract giver.	Verification not carried out by the contract giver.		
71	9.3.3.	Verify the mechanism/process implemented by the contract giver to ensure that all the products and materials delivered by the manufacturing facility provider are complying with their specifications and that the product has been released by the authorised person in accordance with good manufacturing practices and the licence.		control and check are available at contract giver end	contract giver has no provided any control and check and relied on manufacturing release.		
72	9.3.4.	Verify the mechanism/process implemented by the loan licensee or contract giver to monitor and review the performance of the manufacturing facility provider or contract acceptor.		The loan licencee or contract giver is performing inspection and review the performance of contract acceptor. Further, documents are prepared and maintained.	No check available at loan licensee and contract giver end.		
9.4.Manufacturing facility provider or contract acceptor							

73	9.4.1.	Whether the manufacturing facility provider or contract acceptor have adequate premises, equipment, knowledge, experience and competent personnel to satisfactorily carry out the work ordered by the loan licensee or contract giver.		The firm has provided the adequate facility & adequate staff.	The firm has not provided the adequate facility & adequate staff.		
74	9.4.2	Ensure that the manufacturing facility provider/contract acceptor has not passed to a third party any of the work entrusted to him or her under the contract without the loan licensee or contract giver's prior evaluation and approval of the arrangements.		No such activity conducted.	Further sub-contract is done without prior approval of contract giver.		
9.5.Contract							
75	9.5.1	Whether a written contract between the loan licensee or contract giver and the manufacturing facility provider or contract acceptor is available.		Available	Not available		
76	9.5.2.	Whether the contract clearly states that the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the licence.		Contract agreement covers all such requirements.	Contract agreement does not cover all requirements/ inadequate.		

77	9.5.5.	Whether the contract clearly describes who is responsible for contracted activities e.g., knowledge management, technology transfer, supply chain, sub-contracting, testing and releasing materials and undertaking production and quality control, including in-process controls, and who has responsibility for sampling and analysis..		Contract agreement defines all such requirements.	Contract agreement does not cover all requirements/ inadequate.		
78	9.5.5.	In the case of contract analysis, ensure whether the contract states whether the manufacturing facility provider or contract acceptor shall take samples at the premises of the manufacturer or not.		Contract agreement defines all such requirements.	Contract agreement does not cover all requirements/ inadequate.		
79	9.5.6.	Ensure whether the manufacturing, analytical and distribution records and reference samples are to be kept by, or be available to, the loan licensee or contract giver.		Manufacturing, analytical and distribution records and reference samples are kept /available to the loan licensee or contract giver.	Manufacturing, analytical and distribution records and reference samples are not kept /not accessible to the loan licensee or contract giver.		
80	9.5.7	Ensure whether the contract clearly describes the handling of starting materials, intermediate, bulk and finished products, if they are rejected.		Contract agreement defines such requirements.	Contract agreement does not cover such requirements/ inadequate.		
81	9.5.7	Ensure whether the contract clearly describes the procedure to be followed if the contract analysis shows		Contract agreement defines such requirements.	Contract agreement does not cover such		

		that the tested product must be rejected.			requirements/ inadequate.		
10. Self-inspection, quality audits and suppliers' audits and approval:							
82	10.3.	Verify if Self-inspections are conducted by a self-inspection team consisting of experts in their respective fields who are familiar with GMP.		Self-inspections are conducted by a team consisting of experts in their respective fields who are familiar with GMP.	Self-inspections are not conducted by a team/ or not consisting of experts in their respective fields.		
83	10.4	Frequency of self-inspection- Whether the firm has defined the frequency for self-inspections in SOP., The frequency shall be at least once in a year	Self inspection carried out more than twice in a year.	Frequency defined & meeting the requirement.	Frequency not defined/ not meeting the requirement.		
84	10.5.	Verify that Self-inspection report is prepared after completion of a self-inspection. Verify that the report include the followings, - (a) self-inspection results; (b) evaluation and conclusions; and (c) recommended corrective actions		Self-inspection report are available and contains required information.	Self-inspection report are not available/ not contained required information.		
85	10.6	Whether the firm has an effective follow-up programmed for Self-inspection findings Whether the company management evaluates both the self-inspection report and the corrective actions as necessary ?.		Follow up program for self inspection finding is available and self-inspection report and the corrective actions are reviewed by the company management.	No Follow up program for self inspection/self-inspection report and the corrective actions are not reviewed by the company management.		
10.7.Quality audit-							

86	10.7	Whether the firm conducts Quality audit for examination and assessment of all or part of a quality system with the specific purpose of improving it	Quality audit performed along with external experts & extended to all the part of quality system including supplier management.	NA	NA	NA	
10.8. Suppliers' audits and approval							
87	10.8.1	Whether the firm has written procedure for approval of suppliers		Procedure available	Procedure not available		
88	10.8.2	Before suppliers are approved and included in the approved suppliers' list or specifications, they shall be evaluated. The evaluation shall take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it shall determine the supplier's ability to conform with good manufacturing practices standards.		Approved supplier's list is available & prepared after evaluation of suppliers. Audits are conducted for APIs/ KSM.	Approved supplier's list is not prepared on the basis of evaluation of suppliers or no audit performed for APIs/ KSM.	Approved supplier's list is not available.	
11 Personnel:							
89	11.1	Whether the firm has well established and maintained system of Quality Assurance (QA) to ensure the correct manufacture and control of pharmaceutical		Separate/ independent QA deptt. Provided.	QA deptt. Provided but independent.	No such deptt. exist.	

		products and active ingredients.					
90	11.1	Whether the firm has appointed sufficient numbers of qualified personnel's to carry out all the tasks for which the manufacturer is responsible.		Sufficient competent staff is available.	Staff is not in line with the load of work.		
91	11.2	Whether responsibilities of all individuals are clearly defined and understood by the persons concerned and recorded		Responsibilities defined in the job description.	Responsibilities not defined in the job description.		
92	11.2.4	Whether the firm has taken adequate measures to prevent entry of unauthorised people from entering production, storage and QC areas.		Adequate measures provided to prevent entry of unauthorised people in said areas.	Adequate measures not taken to prevent entry of unauthorised people in said areas.		
11.3. Key personnel							
93	11.3.1.	Whether the key posts {heads of production, the heads of quality units (QA and QC functions) and the authorised person} are occupied by full-time personnel's		All the key personnel are full time employees.	Key personnel are not full time employees/ or appointed on contract basis.		
94	11.3.1.	Whether the heads of production and quality units shall be independent of each other.		Heads of the production and quality units are independent.	Heads of the production and quality units are not independent.		
95	11.3.2.	Whether the Key personnel responsible for supervising the production and quality units for pharmaceutical products possess the qualifications and experience as specified under the rules.		Key personnel responsible for supervising the production and quality units for pharmaceutical products possess the qualifications and experience	Key personnel responsible for supervising the production and quality units for pharmaceutical products does not		

				as specified under the rules.	possess the qualifications and experience as specified under the rules.		
96	11.3.4.	Whether the responsibilities of head of production are defined and includes responsibilities as per Para 11.3.4 of schedule M		Responsibilities of head of production are defined and meeting the requirements as per Para 11.3.4 of schedule M	Responsibilities of head of production are not defined and/ or not meeting the requirements as per Para 11.3.4 of schedule M		
97	11.3.5.	Whether the responsibilities of quality units are defined and includes responsibilities as per Para 11.3.5 of schedule M		Responsibilities of quality units are defined and meeting the requirements as per Para 11.3.5 of schedule M	Responsibilities of quality units are not defined and/ or not meeting the requirements as per Para 11.3.5 of schedule M		
98	11.3.6.	Whether the firm has designated authorised person responsible for release of finished product for sale or supply.		Authorized person designated for release of finished product for sale or supply.	Authorized person not designated for release of finished product for sale or supply.		
99	11.3.7.	Whether the assessment of production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product and an examination of the finished pack is done before release of finished products		Such assessment is done before release of finished products	Such assessment is not done before release of finished products OR adequate assessment done		

100	11.3.8.	How firm ensures that no batch of product is to be released for sale or supply prior to certification by the authorised persons		Procedure and controls available to ensures that no batch of product is to be released for sale or supply prior to certification by the authorized persons	Procedure and controls are not available to ensures that no batch of product is to be released for sale or supply prior to certification by the authorized persons		
101	11.3.9	Whether the authorised person responsible for approving a batch for release ensure that the requirements as per Para are met 11.3.9 of Schedule M.		Requirement as per Para 11.3.9 of Schedule M are reviewed by authorized person before batch release	Requirement as per Para 11.3.9 of Schedule M are inadequately reviewed by authorized person before batch release.	No such activity performed before batch release	
11.4.Training[1]							
102	11.4.1.	Whether the firm is having approved written programmed for all personnel working manufacturing areas and in control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required		Training programmed covering all the personnel available.	Training programmed covering all the personnel not available/inadequate.		
103	11.4.1.	Whether the trainings are conducted as per the training program		Trainings are conducted as per the training program.	Trainings are not conducted as per the training program/Inadequate.		
104	11.4.2.	Whether the training program includes Besides basic training on the theory and practice of good manufacturing practices,		Training program includes basic training on the theory and practice of good	Training program not covered basic training on the theory and practice of good		

				manufacturing practices.	manufacturing practices/Inadequate.		
105	11.4.2.	Whether the training is given to newly recruited personnel's appropriate to the duties assigned to them		Training is given to newly recruited personnel's appropriate to the duties to assigned to them.	Training is not given to newly recruited personnel's appropriate to the duties assigned to them/Inadequate,		
106	11.4.2.	Whether Continuous training is given, and its practical effectiveness is assessed periodically.		Continuous training is given, and its practical effectiveness is assessed periodically.	Continuous training is not given/training effectiveness is not assessed./Inadequate.		
107	11.4.2.	Whether Training records are maintained and available as per training program		Training records are maintained and available as per training program	Training records are not maintained as per training program.		
108	11.4.3.	Whether specific training is given to personnel's involved in handling of hazardous, highly active, toxic, infectious or sensitising materials and persons working in clean areas.		Specific training is provided for such activities.	Specific training is not provided for such activities.		
109	11.4.5	Whether the visitors or untrained personnel are given information about relevant procedures (particularly about personal hygiene) and the prescribed protective clothing. Whether they are closely supervised by company personnel's (Visitors or untrained personnel shall preferably not be taken		Procedure available for entry of Visitors/ untrained personnel	No procedure available/ procedure not followed.		

		into the production and quality control areas.)					
110	11.4.6.	Whether the consultants and contract staff used by firm are qualified for the services they are providing. Whether Evidences/training records for the same are available with firm		Consultants and contract staff used by firm are qualified for the services they are providing. Documents for the same are available	Consultants and contract staff used by firm are not qualified /inadequately qualified for the services they are providing.		
11.5. Personal hygiene[1]							
111	11.5.1.	Whether firm is performing health check-ups of all personnel's, prior to and during employment, as appropriate.		Firm is performing health check-ups of all personnel's, prior to and during employment, and records available	Firm is not performing health check-ups of all personnel's, prior to and during employment OR relevant records not available		
112	11.5.1.	Whether firm is performing periodic eye check-ups for the personnel conducting visual inspections.		Whether firm is performing periodic eye check-ups for the personnel conducting visual inspections.	Whether firm is not performing periodic eye check-ups for the personnel conducting visual inspections/ Documents are not signed by concerned doctor/ registration no. of doctor is not available.		
113	11.5.2.	Specify whether SOPs for personal hygiene is available? and whether all personnel's are trained in the practices of personal hygiene		SOPs for personal hygiene is available and personnel's are trained	SOPs for personal hygiene is not available/personnel's are not trained		

114	11.5.3.	Ensure that persons showing apparent illness or open lesions that may adversely affect the quality of products are not allowed to participate in manufacturing activity.		Procedure available	Procedure available		
115	11.5.5.	Ensure that operators are not touching to the starting materials, primary packaging materials, intermediate or bulk products with bare hands.		Procedures available and followed	Procedures not available/not followed. (such observations noted during inspection)		
116	11.5.6.	Whether firm has provided clean gowns to the personnel's (including appropriate hair covering) working at site to ensure protection of the product from contamination, appropriate to the duties they performing		Clothing appropriate to the duties performed is provided	Not provided/Inadequate		
117	11.5.6.	Whether the firm is reusing clothes/gowns. If so whether they are stored in a separate closed container until properly laundered and, if necessary, disinfected or sterilised.		Procedures available and followed	Procedures not available/not followed		
118	11.5.8.	Ensure that personal hygiene procedures, including the wearing of protective clothing, are applied to all persons entering production areas, whether they are temporary or full-time employees or non - employees, e.g., contractors' employees, visitors, senior managers and inspectors		Procedures available and followed	Procedures not available/not followed		
12. Premises							
119	12	Whether the Premises conform to the		Permission/NOC/Document	Permission/NOC/Documen		

		conditions as laid down in the Factories Act, 1948 (63 of 1948)		from concerned authority is available	t from concerned authority is not available		
120	12.2.1.	Whether the layout , design & constructed of premises is done to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt and in general, any adverse effect on the quality of products		Layout , design & constructed of premises is done to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt and in general, any adverse effect on the quality of products	Design of the premises and installation of equipment do not facilitate cleaning and decontamination. Cris cross flow of materials and men was observed within the manufacturing areas during inspection	Layout , design & constructed of premises is found to lead the unhygienic condition.	
121	12.2.2.	Whether sufficient measures taken to avoid cross-contamination and facilitate cleaning for the operations where dust is generated (e.g., during sampling, weighing, mixing and processing operations or packaging of powder)		Adequate measures provided.	Inadequate measure provided.		
122	12.2.3.	Whether the Premises is situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.		Situated in eco-friendly zone/ industrial area and not effected by other industries.	Situated in industrial area and obnoxious fumes, smoke is produced in the surroundings.		
123	12.2.4	Whether the Premises used for the manufacture of finished products is designed and constructed to facilitate cleaning and sanitation		Premises facilitate cleaning and sanitation.	Premises not facilitate cleaning and sanitation.		

124	12.2.6	Whether the SOPs for cleaning and disinfection of the Premises are available and records for the same are maintained.		SOPs for cleaning and disinfection of the Premises are available and records for the same are maintained.	SOPs for cleaning and disinfection of the Premises are not available /records for the same are not maintained/Inadequate.		
125	12.2.7.	Whether the Electrical supply, lighting, temperature, humidity and ventilation is appropriately maintained to ensure quality of pharmaceutical products during their manufacture and storage or the accurate functioning of equipment.		Electrical supply, lighting, temperature, humidity and ventilation is appropriately maintained to ensure quality of pharmaceutical products during their manufacture and storage or the accurate functioning of equipment.	Electrical supply, lighting, temperature, humidity and ventilation is inappropriately maintained		
126	12.2.8.	Whether the design, installation, qualification and maintenance records of the Heating, Ventilation, Air Conditioning (HVAC) systems are available		Design, installation, qualification and maintenance records of the Heating, Ventilation, Air Conditioning (HVAC) systems are available	Design, installation, qualification and maintenance records of the Heating, Ventilation, Air Conditioning (HVAC) systems are not available /Inadequate		
127	12.2.9	Whether the Premises are designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals..Whether the firm is having		Premises are designed and equipped to provide maximum protection against the entry of	Paste control measure are inadequate	No Paste control found carried out	

		procedures for rodent and pest control		insects, birds or other animals.. Adequate Paste control measure are available			
128	12.2.10.	Whether the Premises are designed to ensure the logical flow of materials and personnel		logical flow of materials and personnel observed	criss cross movement of materials /personnel observed		
12.3 Ancillary areas[1]							
129	12.3.1	Ensure that the Rest and refreshment are separated from the manufacturing and control areas.		Rest and refreshment are separated from the manufacturing and control areas.	Rest and refreshment are within the manufacturing and control areas.		
130	12.3.2.	Ensure that the facilities for changing and storing clothes and for washing and toilet purposes shall be easily accessible and appropriate for the number of users		Adequate in numbers	Inadequate in numbers		
131	12.3.2.	Ensure that the toilets are not directly communicate/connected with production or storage areas		Not directly communicate/connected with production or storage areas	Not directly connected , However de-gowning/gowning procedure not found followed before and after for use of toilets	Directly communicate/connected to core production /storage areas	
132	12.3.3.	Ensure that the Maintenance workshops, if possible be separated from production areas. Whenever parts and tools are stored in the production area, Ensure that they shall kept in Whenever parts and tools are stored in the production area, Ensure		Maintenance workshops are separated from production areas. OR separate rooms or lockers provided for storage of tools in production area.	Separate rooms or lockers are not provided for storage of tools in production area.		

		that they shall kept in rooms or lockers reserved for that use.					
133	12.3.4.	Ensure that the Animal houses are well isolated from other areas, with separate entrance (animal access) and air-handling facilities.		Animal houses are well isolated from other production areas.	Animal houses are not isolated from other production areas.		
12.4. Storage areas							
134	12.4.1.	Whether adequate storage areas have been allocated for orderly storage of the various categories of materials and products (e.g. starting and packaging materials, intermediates, bulk and finished products, products in quarantine and released, rejected, returned or recalled products) with proper separation and segregation		Proper and segregated storage area provided for each category	Inadequate storage area with the respect to production capacity/Segregated storage area not provided for various categories		
135	12.4.2.	Ensure that the storage areas shall are designed or adapted to ensure good storage conditions. Ensure that the storage areas are clean, dry, sufficiently lit and maintained within acceptable temperature limits. Ensure that special storage conditions (e.g., temperature, humidity) are provided, if required and they are controlled, monitored and recorded as appropriate.		The storage areas are clean, dry, sufficiently lit and maintained as per required storage conditions (e.g., temperature, humidity) and are monitored /recorded. Records are available	The storage areas Are inadequately maintained. OR monitoring records not available		
136	12.4.3.	Whether the firm has provided separate Receiving and dispatch bays		Separate Receiving and dispatch bays provided	Separate Receiving and dispatch bays not provided		

137	12.4.3.	Whether the Receiving and dispatch bays are designed to protect the materials and products from the weather.		Receiving and dispatch bays are covered properly and designed to protect the materials and products from the weather.	Receiving and dispatch bays are inadequate to protect the materials and products from the weather.		
138	12.4.3.	Whether the receiving area is designed and equipped to for cleaning of containers of incoming materials, if necessary,		Provision for cleaning of containers of incoming materials is provided	Provision for cleaning of containers of incoming materials not provided		
139	14.4	Whether all incoming materials are quarantined immediately after receipt.		Incoming materials are quarantined immediately after receipt. Procedure and provisions for the same are available	Incoming materials are not quarantined immediately after receipt.		
140	12.4.4	Ensure that if quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access must be restricted to authorized personnel. Specify If firm is using any system in replacement the physical quarantine. If so, ensure that system used by firm is giving equivalent security.		Separate areas with access control is provided for storage of quarantine materials OR equivalent alternative secure system is provided	No Separate areas provided for storage of quarantine materials OR access control is not provided		
141	12.4.5.	Whether Segregation is provided for the storage of rejected, recalled or returned materials or products.		Segregated area provided for the storage of rejected, recalled or returned materials or products.	Segregated area not provided for the storage of rejected, recalled or returned materials or products.		

142	12.4.6.	Whether the safe and secure areas are provided for storage of the Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion etc.		Safe and secure areas are provided for storage of such materials.	Safe and secure areas are not provided		
143	12.4.7.	Whether the Printed packaging materials are stored in safe and secure storage areas		Printed packaging materials are stored in safe and secure storage areas	Printed packaging materials are not stored in safe and secure storage areas		
144	12.4.7.	Whether the firm have SOPs for sampling of Printed packaging materials and Whether necessary provisions are made for sampling of Printed packaging materials		SOPs and necessary provisions are available for sampling of Printed packaging materials	SOPs /necessary provisions are not available for sampling of Printed packaging materials		
145	12.4.8	Whether separate sampling area provided for starting materials. If sampling is performed in the storage area, Ensure that it is conducted in such a way so as to prevent contamination or cross-contamination		Sampling area provided with control measures.	Separate sampling area provided for starting materials. However inadequate control measures to prevent contamination/cross-contamination. OR sampling is conducted in storage areas without adequate control to prevent contamination/cross-contamination.	Sampling area not provided and Sampling is conducted in an open environment/ conducted in such a way there is evidence of contamination/cross-contamination.	
12.5. Weighing areas							

146	12.5.	Whether separate weighing areas are provided for weighing of starting materials and the estimation of yield by weighing		Separate weighing areas provided	Separate weighing areas not provided		
147	12.5.	Whether weighing areas specifically designed for that use (for example with provisions for dust control).		Dust control measures provided wherever required.	Dust control measures not provided.		
12.6. Production areas							
148	12.6.1.	Specify whether the whole facility is separated and dedicated for manufacturing of the pharmaceutical products and is not utilized for any other non-pharmaceutical products	The whole facility was found separated, dedicated and is not a part of any other non-drug facility. Even no other category of drugs like sex hormones, beta lactam, cyto-toxic, spore forming are manufactured in the same campus	the whole facility was found separated, dedicated and is not a part of any other non-drug facility.	Non drug items like nutraceuticals, Cosmetics was found manufactured along with general drug item	1) The manufacturing facilities for potent drugs such as sex hormones, beta-lactam and cytotoxic are common with general drugs. 2) Some of the critical areas of manufacturing are exposed directly with the environment	

149	12.6.1.	Specify whether dedicated and self-contained facilities are provided for the production of particular pharmaceutical products, such as highly sensitising materials (e.g., penicillins) or biological preparations (e.g., live microorganisms).	Dedicated and self contained facility provided and separate manufacturing blocks present for each category of drugs	Dedicated and self-contained facilities are provided for production of highly sensitising materials (e.g., penicillin) or biological preparations (e.g., live microorganisms). Having common building with separate entries and separate storage/utility area f	Dedicated and self-contained facilities are provided with inadequate measures to prevent cross contamination	Dedicated facilities not provided for sensitizing materials (e.g., penicillin) or biological preparations (e.g., live microorganisms)	
150	12.6.1.	Ensure that production of highly active products, such as some antibiotics, hormones, cytotoxic substances and non-pharmaceutical products shall not be conducted in the same facilities. (Note :-In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made.	Production of highly active products conducted in dedicated and self contained facilities.	Production of highly active products is not conducted in the same facilities OR adequate precautions and necessary validations are conducted in case of campaign manufacturing	Production of highly active products is not conducted in the same facilities OR inadequate precautions/ measures taken.	Neither dedicated facilities nor any measures taken to avoid contamination/cross contamination	
151	12.6.2.	Ensure that there is no criss-cross flow of materials and men?		There is no criss-cross flow of materials and men	There is criss-cross flow of materials and men		
152	12.6.3.	Whether adequate the working and in-process storage space is provided for orderly and logical positioning of equipment and storage		Adequate working and in-process storage space is provided for logical	Working and in-process storage space provided by firm is inadequate.		

		of materials so as to minimise the risk contamination of different pharmaceutical products or their components OR to avoid cross-contamination		positioning of equipment and of materials.			
153	12.6.4.	Whether facility (wherever starting and primary packaging materials and intermediate or bulk products are exposed) is designed and maintained in away the interior surfaces (walls, floors and ceilings) are smooth and free from cracks and open joints, dose not sheds the particulate matter and permit easy and effective cleaning and, if necessary, disinfection.		The wall floor and ceiling of core areas are smooth, and free from cracks and open joints, dose not sheds the particulate matter and permit easy and effective cleaning and disinfection.	The wall floor and ceiling of core areas are not smooth, and having cracks /open joints, have risk to sheds the particulate matter and dose not permit easy and effective cleaning and disinfection.		
154	12.6.5.	Whether the Pipework, light fittings, ventilation points and other services designed and sited to avoid the creation of recesses that are difficult to clean.		Rework, light fittings, ventilation points are concealed and are easy to clean.	Rework, light fittings, ventilation points are not concealed and dusty		
155	12.6.6	Specify whether the Drains are of adequate size and designed and equipped to prevent back-flow		GMP Drains provided	GMP Drains not provided	NA	
156	12.6.7.	Whether the Production areas are effectively ventilated and equipped with air-control/air filtration facilities to prevent contamination and cross-contamination and to control temperature and humidity appropriate to the products	Production areas are effectively ventilated and temperature and humidity is	Production areas are effectively ventilated and temperature and humidity is maintained appropriate to the products handled/operations undertaken.	Production areas are effectively ventilated, However, temperature and humidity is not Monitored /Not in within limit	Air filtration facilities not provided to prevent contamination and cross-contamination	

		handled/operations undertaken.	monitored using BMS system				
157	12.6.7.	Whether the adequate filtration systems are provided to ensure that the hazardous contaminates (e.g. cytotoxic drugs) are not exposed /released into the external environment.		Adequate filtration systems are provided in supply and return/exhaust including scrubber	Adequate filtration systems are provided but not monitored/Inadequate measures	Filtration systems are not provided and hazardous contaminates (e.g. cytotoxic drugs) are exposed /released into the external environment.	
158	12.6.8	Whether the premises for the packaging is designed and laid to avoid mix ups, contamination or cross-contamination.		Packaging lines are physically segregated to avoid mix ups, contamination or cross-contamination.	Packaging of different products is going on without physically segregated lines but with procedural controls.		
159	12.6.9.	Whether the Production areas are well lit. Check particularly for areas where visual online controls are carried out.	400-500 lux in the processing area 300-400 lux in ancillary areas 200-300 lux in storage area More then 500 lux in	400-500 lux in the processing area 300-400 lux in ancillary areas 200-300 lux in storage area More then 500 lux in inspection areas	Less then 500 lux in inspection areas Less then 400 lux in processing area		

			inspection areas For photo sensitive products monochromatic light is used				
12.7. Quality Control (QC) areas[1]							
160	12.7.1.	Ensure and specify whether the QC laboratory is separated from production areas.		QC laboratory is separated from production areas.	QC laboratory is not separated from production areas.		
161	12.7.1.	Ensure and specify whether the area for biological, microbiological or radioisotope test methods is separated from each other.		Area for biological, microbiological or radioisotope test methods is separated from each other	area for biological, microbiological is not separated from each other		
162	12.7.2.	Ensure that QC laboratory is designed to suit the operations to be carried out in them and sufficient space is provided to avoid mix ups and cross-contamination.		Sufficient space is provided to avoid mix ups and cross-contamination.	Sufficient space is not provided		
163	12.7.2.	Ensure that adequate suitable storage space is provided for samples, reference standards (if necessary, with cooling), solvents, reagents and records etc.		Adequate storage space is provided . Reference standards /Samples/Solvents found stored in controlled storage conditions	Inadequate storage space and materials are not stored in controlled storage condition		
164	12.7.3.	Ensure that construction materials of laboratories/working		RCC Structure is provided and smooth, acid and alkali	Construction materials of laboratories/ working		

		platforms is suitable for the work undertaking		resistant and vibration free working platform is provided.	platforms is not suitable for the work undertaking		
165	12.7.3.	Ensure that sufficient ventilation and arrangement's for prevention of fumes are provided		Sufficient ventilation and fuming hood is provided	No such provisions available		
166	12.7.3.	Ensure and specify whether separate air supply is provided to laboratories and production areas.		Separate air supply (AHU) is provided to laboratories and production areas.	Air supply (AHU) of laboratories and production areas is common.		
167	12.7.3.	Ensure and specify whether separate air-handling units and other provisions are provided for biological, microbiological and radioisotope laboratories.		Separate air-handling units provided for each section	Common air-handling units provided		
168	12.7.4.	Ensure that separate room are provided for the instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors or where it is necessary to isolate the instruments.		Instruments operational requirements are taken into consideration while installing /using instruments.	Instruments operational requirements are not taken into consideration		
13. Equipment:							
169	13.1.	Ensure that the equipment is designed and installed to minimize the risk of errors and to permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt.		Equipment are well designed and installed to get proper cleaning.	Equipment are not cleaned properly.		
170	13.3.	Verify whether the fixed pipework are clearly labeled to indicate the contents and where		Pipework are clearly labeled to indicate the contents and	Pipework are not labeled		

		applicable the direction of flow.		the direction of flow.			
171	13.5.	Verify whether the Balances and other measuring equipment of an appropriate range and precision are available for production and control operations		Balances and other measuring equipment used are of appropriate range and precision	Balances and other measuring equipment used are not having required operational range/precision		
172	13.5.	Verify whether the balances and other measuring equipment are calibrated according to a fixed schedule		Balances and other measuring equipment are calibrated according to a fixed schedule, covering appropriate working range	Schedule for calibration of balances and other measuring equipment is not available OR Calibration not done as per schedule		-
173	13.6.	Whether the firm is having a fixed schedule for cleaning of production equipment's and records for cleaning are maintained		Cleaning schedule and records for cleaning are available	Cleaning schedule and records as per schedule are not available		
174	13.7.	Ensure that Laboratory equipment and instruments are suited to the testing procedures undertaken.		Laboratory equipment and instruments are suitable to the testing undertaken.	Laboratory equipment and instruments are not suitable for testing undertaken.		
175	13.9.	Ensure that the parts of the production equipment that come into contact with the product are reactive, additive or absorptive to an extent that would affect the quality of the product.		Material of construction is suitable for products manufactured using equipment	Material of construction is not suitable for products manufactured using equipment		
176	13.10.	Ensure that the defective equipment is removed from production and QC		Defective equipment are removed from	Defective equipment without		

		areas OR are clearly labelled as defective and do not use (If this is not possible to remove form area)		production and QC areas/clearly labeled.	justification found production /QC areas		
177	13.12	Whether firm is using validated cleaning procedures for cleaning of Non-dedicated equipment g used for production of different pharmaceutical products.		cleaning validation performed and reports available	cleaning validation not performed/Inadequate		
178	13.13	Whether firm is having current drawing of critical equipment and support systems.		Current drawing of critical equipment and support systems is available	Current drawing of critical equipment and support systems is not available		
14. Materials:							
179	14.3.	Ensure that no materials used for operations such as cleaning, lubrication of equipment and pest control shall come into direct contact with the product. Where possible, such materials shall be of a suitable grade (e.g., food grade) to minimize health risks.		The firm has provided the separate area for storage of material used for cleaning, pest control, etc. then starting & packing material for the product and food grade lubricant is used.	The material are not stored separately and there is no evidence of food grade lubricant.		
180	14.4	Whether all incoming materials and finished products are quarantined immediately after receipt or processing, until they are released for further use or distribution.		Incoming material & finished product are quarantine immediately after receipt before release.	No quarantine area is provided.		
181	14.5.	Whether firm has established storage conditions for materials and products and Whether		The materials are stored as per the required condition.	Materials are not stored properly.		

		materials/products are stored under the appropriate conditions as established by firm OR as per the manufacturers recommendation.					
182	14.5.	Whether firm has stored all materials and products and in an orderly fashion, to permit batch segregation and stock rotation by a first-expire, first-out rule.		The firm has maintained the FEFO system.	FEFO system is not maintained.		
183	14.6	Whether firm is using validated water systems for treatment of water drawn from own or any other source to render it potable in accordance with the standards specified by the Bureau of Indian Standards or Local Municipality, as the case may be, so as to produce purified water conforming to Pharmacopoeial specification.		Water is system is validated with all phases. Source of the water is tested/ monitored as per specification of BIS/ local municipality/ pharmacopoeia.	Validation of water system is inadequate/ Source of the water is not tested/ monitored as per specification of BIS/ local municipality/ pharmacopoeia.	No validation of water system.	
184	14.6	Whether firm is using Purified Water for all the manufacturing operations (Note;- potable water may be used washing and cleaning operations).		Purified Water is used for all the manufacturing operations & records of testing are available.	Records of testing of Purified Water used for manufacturing operations are not available.	Potable water is used for manufacturing operations.	
185	14.6	Whether Water is stored in tanks, which do not adversely affect quality of water and ensure freedom from microbiological growth.		MOC of the water tank is suitable for storage of water.	MOC of the water tank is not suitable for storage of water.		
186	14.6	Whether the tanks used for storage of water are cleaned periodically.		Water storage tanks are cleaned periodically and records are maintained.	Water storage tanks are not cleaned periodically/ records not maintained.	Purified Water storage tanks used for manufactu	

						ring operations are found in unhygienic condition.	
187	14.6	Whether the firm has performed design, installation and operation of pharmaceutical water systems		Following treatment processes are in the water purification system for PW: —Raw water storage —Sodium hypochlorite dosing —Multimedia filtration —Softener —Soft water storage tank —cartridge filter 150 micron —SMBS dosing, —ADH dosing (for anti scaling), —Auto pH correction (using NAOH), Mixed Bed — PW storage tank and IQ/ OQ/ PQ are available.	Following treatment processes are in the water purification system for PW: —Raw water storage —Sodium hypochlorite dosing — Sand and Charcoal filter —Softener —Ion exchange treatment — PW storage tank and IQ/ OQ/ PQ are not available.	Potable water was found outsourced without any records/validation regarding any further treatment and/or analysis before use.	
188	14.7	Whether trained personnel's are involved in the purchase of starting materials.		Personnel are trained & competent.	Personnel are not trained & competent/ training records are not available.		
189	14.9.	Whether each consignment, at a minimum, the containers is checked at least for integrity of		Damage & integrity of containers/ bags are checked	Damage & integrity of containers/ bags are not checked		

		package and seal and for correspondence between the order, the delivery note, and the supplier's labels.		including relevant documents during the receipt of the material.	including relevant documents during the receipt of the material.		
190	14. 10.	Whether all containers of incoming materials are cleaned where necessary and labeled, if required, with the prescribed information.		Incoming materials are cleaned where necessary and labeled.	Incoming materials are not cleaned & labeled.		
191	14. 10.	Where additional labels are attached to containers, ensure that the original information is not lost.		Labels are properly pasted without loosing the original information.	Labels are pasted which hides the original information.		
192	14. 12	Ensure that If one delivery of material is made up of different batches then each batch must be considered as separate for sampling, testing and release.		It was observed that each batch of a consignment is considered for sampling, testing and release.	No such system was found followed		
193	14. 13	Whether starting materials in the storage areas are appropriately labeled.		All relevant information was found available on the labels.	All relevant information was found not available on the labels./Inadequate		
		Whether labels bear at least the following information, namely:—					
		(a) the designated name of the product and the internal code reference where applicable;					
		(b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;					
		(c) the status of the contents (e.g., in quarantine, on test, released, rejected, returned or recalled); and					

		(d) Where appropriate, an expiry date or a date beyond which retesting is necessary. (Note :- When fully validated computerized storage systems are used, all of the above information need not to be mentioned on the label)					
194	14.14. & 14.147	How firm ensures that only raw materials which have been released by the QC Department and which is within their shelf life is used for processing.		Procedure/System found in place.	Procedure/System found in place.		
195	14.15.	Ensure that for raw materials other than APIs, if released by QC Department for use in manufacturing without any specific batch testing, then it shall be based on vendor approval and statistical data analysis of earlier test results of such material for release.		The Raw materials (other than APIs), if released without testing are based on vendor approval and statistical data analysis of earlier test results of such material for release.	The Raw materials (other than APIs) are released without testing and vendor approval and statistical data analysis found inadequate.	The Raw materials (other than APIs) are released without vendor approval or without statistical data analysis or without testing.	
196	14.16.	Whether the firm has appropriate procedures or measures to ensure the identity of the contents of each container of starting material (API).		Procedure and records available.	Procedure/records not available /Inadequate.		
	14.16.	Ensure that the bulk containers from which samples have been drawn are identified/labeled accordingly.		Procedure for Identification/labeling of Containers from which samples have been drawn is available and followed.	Procedure for Identification /labeling of Containers from which samples have been drawn is not available/not followed.		

197	14. 18.	Whether the firm has written procedures for dispensing of starting materials to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers and Whether firm has designated for dispensing activity		Procedure available to ensure correct materials are accurately weighed into clean and properly labeled containers. Dispensing carried out by designated, and trained personnel.	Procedure not available/not followed/Inadequate. Designated personnel not assigned for dispensing activity.		
198	14. 19	Whether the firm has written procedures to verify that each dispensed material and its weight or volume is independently checked and recorded.		Procedure and records available.	Procedure not available/ not followed.		
199	14. 20.	Ensure that the Materials dispensed for each batch of the final product is kept together and conspicuously labeled		Procedure available and followed	Procedure not available/ not followed		
200	14. 21.	Ensure that the firm is following similar procedures for the purchase, handling and control of primary and printed packaging materials as that of starting materials.		Procedures for the purchase, handling and control of primary and printed packaging materials are similar as that of starting materials.	Procedures for the purchase, handling and control of primary and printed packaging materials are not similar/inadequate.		
201	14. 22.	Ensure that the printed packaging materials are stored in secure conditions so as to avoid the possibility of unauthorized access.		Printed packaging materials are stored in secure conditions.	Printed packaging materials are not stored in secure conditions and accessible to unauthorized personnel.		

202	14.22.	Ensure that cut labels (leftover Roll feed labels) and other loose printed materials is stored and transported in separate closed containers to avoid mix ups.		Procedure and provisions for transfer/storage of leftover labels and loose printed materials are available to avoid mix ups.	Procedure and provisions for transfer/storage of leftover labels and loose printed materials are inadequate.		
203	14.22.	Whether the firm has written procedures for issuance of Packaging materials and Whether materials are issued only designated and trained personnel's		Procedure available for issuance of Packaging materials. Dispensing carried out by designated, and trained personnel.	Procedure not available/not followed/ Inadequate. Designated personnel not assigned for dispensing activity.		
204	14.23.	Ensure that each delivery or batch of printed or primary packaging material is given a specific reference number or identification mark.		Each delivery or batch of printed or primary packaging material is given a specific reference number or identification mark.	Procedure not available/Inadequate.		
205	14.24.	Whether the firm has written procedures for destruction of Out-dated or obsolete primary packaging material or printed packaging material and whether its disposal record is maintained.		Procedure and records available.	Procedure/records not available/ Inadequate.		
206	14.25	Whether the firm has written procedures for verification all products and packaging delivered to the packaging department for verification of quantity, identity and conformity with the packaging instructions.		Procedure and records available.	Procedure/records not available/ Inadequate.		

207	14.26	Whether the containers and closures used for intended use comply with the pharmacopoeial requirements.		Containers and closures used are comply with the pharmacopoeial requirements.	Containers and closures used are not comply with the pharmacopoeial requirements.		
208	14.26	Whether the firm has specifications and validated test methods and cleaning procedure and sterilization procedure, (wherever indicated)for containers and closures used		Specification including test records and validated procedure available.	Specification / test records/validated procedure not available/Inadequate.		
		Whether the firm has to ensured that containers and closures used are not reactive, additive, absorptive, or leach to an extent that significantly affects the quality or purity of the drug..		Leachability & Extractability test performed (as applicable)	Leachability & Extractability test not performed.		
209	14.26	Ensure that firm is not suing second hand or used containers and closures		Second hand or used containers and closures not used.	NA	Recycled /second hand containers and closures are used for primary packaging.	
210	14.26.1.	Whenever bottles are being used, check if the written schedule of cleaning of bottles is laid down and followed.		Procedure and Cleaning schedule available.	Procedure /Cleaning schedule not available.		
		Where bottles are not dried after washing, ensure that they are rinsed with purified water or water for injection, as the case may be		Bottle are washed with purified water or water for injection as the case may be.	Bottle are not washed/dried as per requirements	Final cycle of washing is with potable water	

211	14.26.3.	Whether Packaging materials used by firm for packaging of pharmaceutical products complies with the requirements prescribed in Indian Pharmacopoeia (IP)		Packaging materials used are meeting the Pharmacopoeial requirements	Packaging materials used are not tested /not meeting the Pharmacopoeial requirements		
212	14.27.	Whether Intermediate and bulk products are stored under appropriate conditions		Storage conditions maintained and monitored	Storage conditions not maintained/Not Monitored		
213	14.28.	Ensure that if Intermediate and bulk products are purchased then on receipt it is handled as if they were starting materials.		Procedures for the purchase, handling and control of Intermediate and bulk products are similar as that of starting materials.	Procedures for the purchase, handling and control of Intermediate and bulk products are not similar/inadequate.		
214	14.29.	Ensure that finished products are held in quarantine until their final release and after which they are stored as usable stock under conditions established by the firm		Finished products are quarantine until their final release and storage conditions are maintained and monitored	Finished products are not quarantine until their final release /storage conditions are not maintained/not monitored		
215	14.32.	a) Verify the procedures followed by firm for reworking or recovery of rejected products. Ensure that such incidents are exceptional and permitted only if the quality of the final product is not affected and if the specifications are met. b) Whether it is done in accordance with a defined and authorized procedure after		Procedures followed and records maintained are adequate	Procedures/records not maintained/Inadequate		

		evaluation of the risks involved c) Whether records are kept for reworking or recovery					
216	14.32.	Ensure whether a new batch number is given to reworked batch.		New batch number is given to reworked batch.	New batch number is not given to reworked batch.		
217	14.33.	a) Verify whether the firm is having procedure/practices for recovery i.e. introduction of all or part of earlier batches (only if conforming to the required quality standards) into a batch of the same product at a defined stage of manufacture. b)Ensure such activities are done only with the prior approval of the authorized personnel and only if batches conforming to the required quality standards are utilized c)Whether the firm has maintained record of recovery.		Procedures followed and records maintained are adequate	Procedures/records not maintained/Inadequate		
218	14.34.	Ensure that whether the need for additional testing on the finished product that has been reprocessed reworked or into which a recovered product has been incorporated is considered by the QC Department.		Procedures followed and records maintained are adequate	Procedures/records not maintained/Inadequate		
219	14.35.	Ensure that products returned from the market are destroyed unless it is certain that their quality is satisfactory.		Procedure and records available are adequate	Procedure and records are not maintained/Inadequate		

220	14.39.	Verify, whether the firm is applying both positive and negative controls to verify the suitability of culture media each time they are prepared and used. Ensure whether the size of the inoculum used in positive controls is appropriate to the sensitivity required?		Procedure to check the Suitability of culture media are available and positive and negative control are used and record maintained.	Procedure not available/positive and negative control are not used/record not maintained.		
15. Reference Standards:							
221	15.1.	Ensure that firm is using official reference standards (whenever exist).		Firm is using official reference standards (whenever exist).	Firm is not using official reference standards (whenever exist)		
222	15.2.	Ensure that firm is procuring Indian Pharmacopoeia reference standards from Indian Pharmacopoeia Commission.		Indian Pharmacopoeia reference standards are procured from Indian Pharmacopoeia Commission.	Indian Pharmacopoeia reference standards are not procured from Indian Pharmacopoeia Commission. Records of purchase not available		
223	15.3.	Ensure that Official reference standards are used for the purpose described in the appropriate monograph.		Official reference standards are used for the purpose as described in the appropriate monograph.	Official reference standards are not as described in the appropriate monograph.		
224	15.4.	Ensure whether the **reference standards** prepared by the manufacturer are tested, released and stored in the same way as official standards.		Tested, released and stored as per the requirements	Not Tested/released / stored as per the requirements		
225	15.4.	Ensure whether the **reference standards** are stored in a secure area under the		Stored in a secure area under designated person.	Not Stored in a secure area under /designated		

		responsibility of a designated person.			person not assigned.		
226	15.5.	Ensure whether the firm is reforming appropriate tests and checks at regular intervals for secondary or working standards established by the firm to ensure standardization		Procedure and standardization records are available	Procedure and standardization records are not available		
227	15.6.	Ensure whether reference standards are properly labeled and the label or accompanying document or both contains least the following information, as appropriate.		Label available with such details	Inadequate labeling system		
		(a) name of the material;					
		(b) batch or lot number Or control number;					
		(c) date of preparation/date of manufacture					
		(d) shelf-life & expiry date					
		(e) potency or concentration					
		(f) Storage conditions.					
		g) date of opening of closure (date when opened first time)					
228	15.7	Ensure whether the firm has standardized all in-house working standards or secondary standards against an official reference standard, when available, initially and at regular intervals thereafter.		Procedure and standardization records are available	Procedure and standardization records are not available		
16. Waste materials:							
229	16.1.	Whether the firm has made necessary provisions for the proper and safe storage of waste materials waiting disposal.		Necessary arrangement available with documents	Necessary arrangement not available/Inadequate		

		Ensure whether the Toxic substances and flammable materials are stored in suitably designed, separate, enclosed cupboards.		Necessary arrangement available with documents	Necessary arrangement not available/Inadequate		
230	16.2.	Ensure whether the waste material is disposed of safely and in a sanitary manner at regular and frequent intervals.		Procedure and records available	Procedure and records are not available/Inadequate		
231	16.3.	Ensure whether the disposal of sewage and effluents (solid, liquid and gas) from the manufacturing area conforms to the requirements of the guidelines issued by the Environmental Pollution Control Board. (Verify NOC/Consent obtained by firm from State Pollution control board in this regard.)		Procedure and records available. NOC/Consent obtained by firm from State Pollution control board.	Procedure and records are not available/Inadequate		
232	16.4.	Ensure whether the bio-medical waste is destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 2016.		Provisions of the Bio-Medical Waste (Management and Handling) Rules, 2016 followed.	Provisions of the Bio-Medical Waste (Management and Handling) Rules, 2016 not followed.		
262.	16.5.	Ensure that the Rodenticides, insecticides, fumigating agents and sanitizing materials used by firm are not coming in contact with process equipment, starting materials, packaging materials, in-process materials or finished products Or does not contaminate them		Required control and procedures available.	Required control and procedures not available.		
17. Documentation							

233	17.2.2.	Ensure that documents are approved, signed and dated by the responsible persons.		Documents are approved, signed and dated by the responsible persons.	Procedure not available/Inadequate.		
		Ensure that No document are changed without authorization and approval.		Procedure and records available	Procedure/records are not available		
234	17.2.4.	Whether firm regularly reviews the documents and whether firm has a system in place to prevent inadvertent use of the superseded version. Superseded documents shall be retained for a specific period of time		Procedure and records available	Procedure/records are not available		
235	17.2.5	Where documents require the entry of data, these entries shall be clear, legible and indelible. Sufficient space shall be provided for such entries		Data are legible & contemporaneous.	Data are found overnighted and not contemporaneous.		
236	17.2.6	Any alteration made to a document shall be signed and dated; the alteration shall be done in such a way so as to permit the reading of the original information. Where appropriate, the reason for the alteration shall be recorded.		Meet the requirement	Does not meet the requirement		
237	17.2.7	Records shall be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records shall be retained for at least one year after the expiry		Records are available for 1 year	Records are not available for 1 year.		

		date of the finished product.					
238	17.2.8	If documentation is handled by electronic data-processing methods, then, verify that only authorized persons are able to enter or modify data in the computer system, and there is a record of changes and deletions; access is restricted by passwords or other means and the entry of critical data is independently checked.		Authorized personnel is available for changes and changes are recorded.	The firm is not following such procedure.		
239	17.2.8	If Batch records are stored electronically then, verify that the same are protected by back-up transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means.		Backup available (Pls specify the type of backup)	Backup not available		
240	17.2.9	Whether the firm has prepared the site master file as per the Appendix-I to the Part I of schedule M		SMF available.	SMF is inadequate.		
17.3. Documents Required							
17.3.1. Labels[1]							
241	17.3.1.1.	Whether the firm has procedure/Sops for labeling of containers, equipment or premises.		SOP available	SOP not available		
17.3.2. Specifications and testing procedures							

242	17.3.2.1.	Whether the firm has validated all testing procedures in the context of available facilities and equipment's before they are adopted for routine testing		Following Characteristics were found considered during validation of analytical methods: — Specificity — Linearity — Range — Accuracy — Precision — Detection Limit — Quantification Limit — Robustness. —Solution Stability/Filter Study	Following Characteristics were found not considered during validation of analytical methods: — Specificity — Linearity — Range — Accuracy — Precision — Detection Limit — Quantification Limit — Robustness. —Solution Stability/Filter Study		
243	17.3.2.2	Whether the firm has written, authorized and dated specifications for tests conducted on starting/packaging materials, intermediate or bulk products (where appropriate) and for finished products.		Specifications available	Specifications not available/ inadequate		
244	17.3.2.2	Whether the firm has written, authorized and dated specifications for water, solvents and reagents (e.g., acids and bases) used in production.		Specifications available	Specifications not available/ inadequate		
245	17.3.2.3	Ensure that each specification is approved, signed and dated and maintained by the QC or QA units.		Specification approved by QC/ QA	Specification not approved		
246	17.3.2.4	Ensure that firm has procedure for periodic revisions of the specifications to comply with new editions of the Indian pharmacopoeia		Periodic revision in place	No procedure for periodic revision.		

		or other official pharmacopoeia.					
247	17.3.2.5.	Ensure that official Pharmacopoeias, reference standards, reference spectra and other reference materials are available in the QC laboratory.		Reference books and reference standard available.	Reference books and reference standard not available.		
17.3.3 Specifications for starting and packaging materials[1]							
248	17.3.3.1 and 17.3.3.2	Ensure that specifications for starting, primary and printed packaging materials are having information as per Para 17.3.3.1 and 107.3.3.2 of schedule M		Specification including all information	Inadequate specification		
249	17.3.3.3.	What is procedure adopted by firm to ensure that the Packaging material is conforming to the specifications and are compatible with the material or with the drugs or both it contains.		Pancaking material testing procedure are available.	Pancaking material testing procedure are not available.		
250	17.3.3.3.	Ensure that the packaging materials are examined for compliance with the specification and for defects as well as for the correctness of identity markings.		Packing material test records are available.	Packing material test records are not available.		
251	17.3.3.4.	Ensure whether the documents describing testing procedures/Specifications states the required frequency for re-assaying each starting material (as determined by its stability)		Documents for mentioning the frequency for re-test is available.	Frequency for re-test is not available.		
17.3.4. Specifications for intermediate and bulk products-							
252	17.3.4.	Whether the firm has written, authorized and dated specifications for tests conducted on		Specification is available	Specification is not available		

		intermediate and bulk products					
17.3.5 Specifications for finished products-							
253	17.3.5	Check whether the specifications for finished products is having information as per 17.3.5 of schedule M		Specification is available	Specification is inadequate		
17.3.6. Master formula records[1]							
254	17.3.6.1.	Check whether the firm have authorized master formula for each product and batch size to be manufactured.		Master formula for each product and batch size to be manufactured is available with required information.	Master formula for each product and batch size to be manufactured is not available/Inadequate		
255	17.3.6.2.	Check whether the master formula is having information as per 17.3.6.2. of Schedule M					
17.3.7.Packaging instructions							
256	17.3.7.	Check whether the firm have authorized packaging instructions for each product, pack size and type.		Packaging instruction for each product, pack size and type is available with required information	Packaging instruction for each product, pack size and type is not available/Inadequate.	0	
257	17.3.7.	Check whether the authorized packaging instructions is having information as per 17.3.7.of Schedule M.					
17.3.8. Batch processing records							
258	17.3.8.1.	Ensure whether the firm has kept a batch processing record for each batch processed.		BMR for each product is available with required information.	BMR for each product is not available/Inadequate.		
259	17.3.8.3.	Check whether the batch processing record is having information as per 17.3.8.3 of Schedule M.					
260	17.3.8.2	Specify whether before starting any processing, the firm is having procedure to check that the equipment and work station are clear of previous products,		Procedure for Line clearance is available.	Procedure for Line clearance is not available/Inadequate.		

		documents, or materials not required for the planned process and that the equipment is clean and suitable for use.					
17.3.9. Batch packaging records[1]							
261	17.3.9.1	Ensure whether the firm has kept a batch packaging record for each batch processed. Check whether the batch packaging record is having information as per 17.3.9.3 of Schedule M.		BPR for each product is available with required information	BPR for each product is not available/Inadequate.		
262	17.3.9.2	Specify whether before starting any packaging operation, the firm is having procedure to check that the equipment and work station are clear of previous products, documents, or materials not required for the planed packaging operation and that the equipment is clean and suitable for use.		Procedure for Line clearance is available.	Procedure for Line clearance is not available/Inadequate.		
17.3.10. Standard operating procedures and records:							
263	17.3.10.1.	Verify whether the firm is having Standard Operating Procedures (SOPs) and associated records for		SOPs available	SOPs not available/Inadequate		
		a) equipment assembly and validation;					
		(b) analytical apparatus and calibration;					
		(c) maintenance, cleaning and sanitization;					
		(d) personnel matters including qualifications, training, clothing and hygiene;					
		(e) environmental monitoring; (f) pest control;					

		(g) complaints;					
		(h) recalls and					
		(i) Returns.					
264	17.3.10.3	Verify whether the firm has maintained records of the receipts as per Para 17.3.10.3 of schedule M		Records available	Records not available		
265	17.3.10.4.	Verify whether the firm has SOPs for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials		SOPs available	SOPs not available/Inadequate		
266	17.3.10.5.	Verify whether the firm has SOPs for use, calibration, cleaning and maintenance etc. of each instrument and piece of equipment.		SOPs available	SOPs not available/Inadequate		
267	17.3.10.6	Verify whether the firm has SOPs for sampling specifying the persons authorized to take samples.		SOPs available	SOPs not available/Inadequate		
268	17.3.10.8.	Verify whether the firm has SOPs for batch (lot) numbering system to ensure that each batch of intermediate, bulk or finished product is identified with a specific batch number.		SOPs available	SOPs not available/Inadequate		
269	17.3.10.13	Verify whether the Analysis records maintained are as per Para 17.3.10.13 of schedule M		Records available	Records not available/Inadequate		
270	17.3.10.14.	Verify whether the firm has SOPs /Written procedures for release and rejection for materials and products and		SOPs available	SOPs not available/Inadequate		
		Verify whether the SOPs specifies that Batch of finished product shall be		SOPs available	SOPs not available/Inadequate		

		released by authorized person for sale					
	18. Good practices in production:						
271	18.2.1.	Whether the firm has written procedures for handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution.		SOPs available	SOPs not available/Inadequate		
272	18.2.2	Ensure, if deviations occur, they shall be in accordance with an approved procedure.		SOPs and deviations records are available	SOPs not available/deviations not recorded.		
273	18.2.4	Check that Operations on different products are not carried out simultaneously or consecutively in the same room or area unless there is no risk of mix up or cross-contamination.		One product processed at a time OR Risk assessment carried out for the processing of Different products simultaneously or consecutively in the same room.	NA	Different product are handled in same room/area without sufficient control to avoid mix up or cross-contamination.	
274	18.2.5	Check that during processing all materials, bulk containers, equipment , the processing rooms and packaging lines being used, are labeled /identified with an indication of the product or material being processed, its strength (as applicable) and the batch number.		Procedure for status labeling available	Procedure for status labeling not available/not followed/Inadequate.		
275	18.2.6.	Check that Access to production premises is restricted to authorized personnel's only	Biometric Access control provided	Only authorized person is allowed to enter in processing	No control measure are provided.		

				area. Procedural control are available.			
18.3. Prevention of cross-contamination and bacterial contamination during production							
276	18.3.1.	Check that when dry materials and products are used in production, special precautions are taken to prevent the generation and dissemination of dust. Verify that Provision are made for proper air control (e.g., supply and extraction of air of suitable quality)		Dust extraction system provided for dust control	Dust extraction system provided not provided for dust control.		
277	18.3.3	Whether the firm has taken adequate measures to avoid risk Contamination of a starting material or of a product by another material or product (a mentioned in Para 18.3.3 of schedule M)		Adequate measures followed to avoid risk of Contamination	Measures used to avoid risk Contamination are inadequate		
278	18.3.4.	Whether the effectiveness of the Measures taken to prevent cross-contamination is reviewed periodically according to SOPs.		Procedure available and Periodic risk assessment done	Periodic risk assessment not done / inadequate		
279	18.3.5	Whether firm performs the periodic monitoring (e.g. microbiological and particulate matter, as appropriate) of the Production areas where susceptible products are processed.		Periodic monitoring (e.g. microbiological and particulate matter, as appropriate) of the Production areas is done as per schedule	Periodic monitoring (e.g. microbiological and particulate matter, as appropriate) of the Production areas is not done/ inadequate		
18.4.Processing operations							

280	18.4.2.	Whether firm performs the necessary in-process controls and environmental controls and whether records for the same are available .		Procedure for in-process controls and environmental controls is available and records found maintained	Procedure for in-process controls and environmental controls is not available/inadequate and records not maintained /Inadequate		
281	18.4.4	Whether time limits for storage of process materials and equipment, after cleaning and before use, are stated and based on relevant data		Time limits found established based on hold time studies of equipment/Materials. Time limits found specified on status labels	Time limits not established based on hold time studies/Inadequate.		
282	18.4.8.	Whether the Pipes used for conveying distilled /deionized water and, where appropriate, other water pipes are sanitized and stored according to written procedures. Whether the action limits for microbiological contamination are defined and the procedures are available for measures to be taken in case limit exceeds the action limits.		Procedures for cleaning and sanitization of pipelinees used for conveying processing liquids available. Action limits for microbiological contamination and measures to be taken in case microbial limit exceeds the action limits are defined. Records are available	Procedures /records not available/Inadequate.		

283	18.4.9.	a) Whether, measuring, weighing, recording and control equipment and instruments are serviced and calibrated at pre-specified intervals and records maintained. b) Whether analytical instruments are checked daily or prior to use for performing analytical tests. c) Whether date of calibration and servicing and the date when recalibration is due shall is clearly indicated on a label attached to the instrument.		Schedule for calibration available and calibrations found conducted as per schedule. Calibration status found displayed on instrument	Schedule for calibration not available/Not Followed . Calibration status not displayed on instrument		
18.5.**Packaging operations:**							
284	18.5.2.	Whether, line clearance is performed before packaging operations are begun, according to an appropriate procedure and checklist and is recorded.		Procedure for line clearance is available and it is followed	Procedure for line clearance is not available/not followed		
285	18.5.3.	Whether the product name and batch number of the product being handled is displayed at each packaging station or line.		Status labels available	Status labels not available		
286	18.5.5	Whether the firm is **performing checks** at regular intervals for correctness of performance of any printing operation (e.g., of code numbers or expiry dates) done separately or in the course of the packaging and whether record for the same is maintained		In-process check are performed for printing operation and recorded	In-process check are not performed for printing operation /Not recorded		

287	18.5.6.	Whether the firm is performing checks at regular intervals to ensure that any electronic code readers, label counters or similar devices are operating correctly.		Performance/challenge tests are performed for electronic code readers, label counters or similar devices.	Performance/ challenge tests are not performed for electronic code readers, label counters or similar devices.		
288	18.5.7.	Verify that the Printed and embossed information on packaging materials is distinct and resistant to fading or erasing.		It is verified that printed and embossed information on packaging materials found distinct and resistant to fading or erasing	It is observed that printed and embossed information on packaging materials is not distinct	Required printed information are missing/fading.	
289	18.5.8.1	Verify whether the regular online checks/controls performed by firm during packaging includes at list following minimum checks on the product		Regular check are performed.	Regular check are not performed.		
		(a) the general appearance of the packages;					
		(b) whether the packages are complete;					
		(c) whether the correct products and packaging materials are used;					
		(d) whether any overprinting is correct; and					
		(e) the correct functioning of line monitors					
290	18.5.8.2.	How firm ensures that Samples taken away from the packaging line is returned back?		Samples are not returned back and records are maintained properly.	No records are found available.		

291	18.5.9.	Whether firm is having procedure for re-packing of products that have been involved in an unusual event during packaging and whether such products are reintroduced into the process only after special inspection, investigation and app approval by the authorized personnel.		Procedure are available and records are maintained.	Procedure /Records are not available.		
292	18.5.10.	Whether, any significant /unusual discrepancies observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced are investigated, satisfactorily accounted for and recorded before release		Procedure for the investigation available and records maintained.	Procedure for the investigation not available/Investigation not carried out before release.		
293	18.5.11.	Whether the firm has documented procedure for destruction of the unused batch-coded packaging materials left upon completion of a packaging operation, and the whether the destruction record is maintained.		Documented procedure available and records are maintained.	Documented procedure not available/records not maintained.		
294	18.5.11.	Whether firm has documented procedure for checks to be performed before returning unused materials/un-coded printed materials back to the stock and whether the record for the same is maintained.		Documented procedure available and records are maintained.	Documented procedure not available/records not maintained.		
295	18.5.12.	Whether the firm has procedure to review production records as part of the approval process of batch release		Documented procedure available and followed	Documented procedure not available/not followed		

		before transfer to the authorized person.					
19. Good practices in quality control							
296	19.3.	Whether firm has QC function independent of other Departments and under the authority of a person with appropriate qualifications and experience.		The quality control is in depended to the other department. The head is qualified and experienced enough.	The quality control is not in depended to the other department. The head is not qualified and experienced to supervise/ perform duties. .		
297	19.3.	Whether firm has provided Adequate resources and arrangements as per Para 19.3 for effectively and reliable functioning of the QC section		Resources and arrangements are adequate	Resources and arrangements are not adequate		
298	19.3 (b)	Whether the samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by the methods and personnel approved by the QC Department;		Procedure for sampling are available and sampling carried out by personnel approved by the QC Department	Procedure for sampling not available and personnel conducting is not approved by the QC Department		
299	Sch-L1	Ensure that analytical instruments are housed in dust-free environment and whenever required, conditions of temperature and humidity are maintained and periodic checks on temperature and humidity are made and records are maintained		Analytical instruments are housed in dust-free environment and temperature and humidity are maintained and periodic checks on temperature and humidity are made and records are maintained.	Analytical instruments are not housed in dust-free environment/ temperature and humidity are not maintained/Records for temperature and humidity are not maintained.		

300	Sch-L1	a) Whether firm have Standard Operating Procedures for the operation, maintenance and calibration of instruments used in QC.		SOP available	SOP not available		Added
	4(d)	b) Whether calibration schedule for analytical instruments is available?		calibration schedule for analytical instruments is available	calibration schedule for analytical instruments is not available		
	7(c)	c) Whether the analytical instruments requiring calibration are calibrated at regular intervals and records of such calibration or maintenance are maintained.		Analytical instruments requiring calibration are calibrated at regular intervals and records of such calibration or maintenance are available.	Analytical instruments requiring calibration are not calibrated at regular intervals and records of calibration/maintenance are not available.		
		d) Whether logbooks maintained for proper documentation of calibration results.		Logbook maintained for usage and calibration.	Logbook not maintained for usage and calibration.		
301	Sch-L1	Ensure whether the equipment's such as burettes, pipettes, volumetric flasks, weight boxes, thermometers, etc., are calibrated are before acceptance for use		Equipment's such as burettes, pipettes, volumetric flasks, weight boxes, thermometers, etc., are calibrated before for use	No records are found available.		
	4 (h)	Specify which grade of glassware is used in assay procedures and whether they are certified/calibrated. Verify the certificates and calibration records.		Certificates and calibration records available	Certificates /calibration records not available		

302	Sch-L1-4 (k)	Whether maintenance of equipment's for services like electricity, gas, water, steam, and compressed gas is handled by competent person		Qualified and trained personnel available	Qualified and trained personnel not available		
303	Sch-L1-4 (i)	Whether Autoclaves used in laboratory meets the requirements described for operations, safety and validation procedures and the validation is carried out by the laboratory and records are maintained		Procedure for operations, safety and validation are available and validation records are maintained	Procedure for operations, safety and validation are not available/validation records are not maintained.		
304	Sch-L1-5 (b)	Whether all reagents and solutions, stock solutions and of standard solutions used the laboratory are properly labeled		Al reagents and solutions, stock solutions and of standard solutions used the laboratory are labeled properly.	All reagents and solutions, stock solutions and of standard solutions used the laboratory are not labeled properly./Inadequate.		
305	Sch-L1-6 (b) (iv)	Whether adequate first aid kit and fire fighting equipment's are provided in the laboratory is located at the right places and the staff is familiar and trained for fire fighting equipment.		First aid kit and fire fighting equipment's are provided in the laboratory are located at the right places and staff is trained for fire fighting equipment.	First aid kit / fire fighting equipment's are not provided in the laboratory/ not located at the right places/staff is not trained for fire fighting equipment.		
306	Sch-L1-6 (b) (vi)	Whether the staff is trained in the first aid techniques, emergency care and use of antidotes		Staff is trained in the first aid techniques, emergency care and use of antidotes	Staff is not trained		

307	Sch-L1-6 (c)(i)(ii)	Whether require safety equipment is provided in laboratory (e.g. water showers are installed at appropriate places in the laboratory and required safety precautions are taken (e.g. use of rubber suction bulbs for manual pipettes and siphons)		Safety equipment is provided in laboratory and required safety precautions are taken.	Safety equipment are not provided in laboratory and required safety precautions are not taken/Inadequate.		
Sch-L1 (Para 9.0) Microbiological Cultures:-							
308	Sch-L1-9 (a)	Whether laboratory is having SOPs for preparation/maintenance of microbial culture and sub-culture prepared by the laboratories.		SOPs for preparation/maintenance of microbial culture and sub-culture are available and records maintained.	SOPs for preparation/ maintenance of microbial culture/sub-culture are not available/records not maintained.		
309	Sch-L1-9 (a) & 9 (b)	Whether laboratory is having SOPs for destruction of cultures that have become non-viable or mutant. Whether proper procedures are followed (autoclaving) to destroy these cultures.		SOPs for destruction of cultures is available and records are maintained.	SOPs for destruction of cultures is not available and records are not maintained.		
310	Sch-L1-9	a) Verify passages levels up to which cultures are prepared and used (Preferably not more than five passages may be prepared).		Procedure available and records maintained.	Procedure not available and records not maintained.		
		b) Verify the laboratories performs standard biochemical tests on the sub-culture as given in literature to ensure their viability					
		c) Ensure that all activities in a aseptic area are conducted by authorized person.		Authorized personnel are designated to conduct the activities in a aseptic area.	Authorized personnel are not designated to conduct the activities in a aseptic area.		

	Sch-L1 915) :-Raw data:-						
311	Sch-L1-15(a) & 16 (C)	Verify whether laboratory has archived the raw data of testing activities undertaking		Procedure for archival of Raw data are available.	Procedure for archival of Raw data are not available.		
312	Sch-L1-15(b)	Ensure that if data is ratified /corrected then it is done by single line shall strike through the data being changed and the correct information is recorded along with the old data and the reason of change. Analyst making change is identified by his signature with date.		Procedure for ratification/correction are available.	Procedure for ratification/correction are not available.		
313	Sch-L1-15(b)	Ensure that if data is ratified/corrected for automated data collection system, then the person responsible is identified at the time of data output. Ensure that if the original entry is saved and the system has audit trial for all the data.		Procedure for ratification/correction of for automated data collection system.	Procedure for ratification/correction of for automated data collection system re not available./Inadequate.		
	Sch-L1-15(b)	Ensure that if the original entry is saved and the system has audit trial for all the data.		Automated system has audit trial for all the data.	Automated system are not having audit trial.		
314	Sch-L1-15(c)	Whether Data integrity and security is maintained and the data is not accessible to any unauthorized person		Data integrity and security is maintained and the data is not accessible to any unauthorized person	Data security is maintained is inadequate and the data is accessible unauthorized personnel	1) Data is not recorded on a contemporary basis/Records are not made at the time of actual activity. 2) Records	

						are completed later on arbitrarily. 3) Falsification of data is observed.	
	16. Storage and archival.-						
315	Sch-L1-16 (c) & (d)	Whether, data /records are archived in suitable environment to prevent modification, damage, or deterioration and/or loss. Whether, original documents are stored to ensure their security and confidentiality,		Firm has provided suitable measures for archival of data /records to prevent modification, damage, or deterioration and/or loss	Measures for archival of data /records are inadequate		
316	Sch-L1-16 (f)	If data is stored in only optical disc, the life of disc shall be longer than the storage time		Life of disc used is longer than the storage time of records	Life of disc used is less than the storage time of records		
317	Sch-L1-16 (g)	Ensure that firm has archived photocopy of the thermal paper along with original record for the raw data on thermal paper that might fade away with time;		Photocopy of the thermal paper along with original record for the raw data on thermal paper is maintained	Photocopy not maintained for the records on thermal paper that might fade away with time		
318	Sch-L1-16 (h)	Whether the firm has prescribed time limit (retention period) up to which laboratory records are retained.		Firm has prescribed time limit (retention period) for laboratory records and records are found maintained up to retention period.	Firm has not prescribed time limit (retention period) for laboratory records.		
19.6. Control of starting materials and intermediate, bulk and finished products							

319	19.6.1.	Whether the firm has written test procedure for all tests performed for each material or product. Whether the test results are checked by the supervisor before the material or product is released or rejected.		Written test procedure available and test results are checked by the supervisor before the material or product is released or rejected.	Written test procedures not available OR test results are not checked by the supervisor before the material or product is released or rejected.		
320	19.6.2	Whether the samples taken by the firm are representative of the batches of material from which they are taken and they are taken in accordance with the approved written procedure.		Written sampling procedure available and followed. Sample taken is representative of the batches/material	Written sampling procedure not available/not followed. Sample taken is not representative of the batches/material		
321	19.6.6.	Whether the sample container bears a label indicating (a) the name of the sampled material; (b) the batch or lot number; (c) the number of the container from which the sample has been taken; (d) the number of the sample; (e) the signature of the person who has taken the sample; and (f) the date of sampling.		Sample container are labeled with required information	Sample containers are not labeled with required information		
322	19.6.7	Whether the firm has written procedure for investigation of Out-of-specification results obtained during testing of materials or products and whether investigation records are maintained.		Firm have written procedure for investigation of Out-of-specification results and investigation records are maintained	Firm do not have written procedure for investigation of Out-of-specification results / investigation are not conducted/In		

				including rout cause analysis.	adequate Investigations		
19.7. Test requirements							
323	19.7.2	Whether an identity test is conducted on a sample from each container of starting material.		Firm is performing identity test on a sample from each container of starting material.	Firm is not performing identity test on a sample from each container of starting material.		
324	19.7.3.	Ensure whether each batch (lot) of printed packaging materials is examined following its receipt.		Each batch (lot) of printed packaging materials is examined after receipt.	Each batch (lot) of printed packaging materials is not examined after receipt.		
325	19.7.5.	Whether, in-process control records are maintained and form part of the batch records.		In-process control records are maintained in batch records.	In-process control records are not maintained in batch records.		
19.8. **Batch record review:**							
326	19.8.1.	Whether Quality Control records are reviewed as part of the approval process of batch release before transfer to the authorized person.		Quality Control records are reviewed by authorized person.	Quality Control records are not reviewed /Review not done by authorized person.		
19.8.2. Retention samples							
327	19.8.2.	Whether Retention samples from each batch of finished product are kept for at least one year after the expiry date.		Retention samples from each batch of finished product are kept and maintained one year after the expiry date.	Retention samples not taken from each batch of finished product OR not are kept up to one year after the expiry date.		

328	19.8.2.	Check whether retention sample of finished products are kept in their final packaging and stored under the recommended conditions.		Retention sample of finished products found kept in their final packaging and are stored under the recommended conditions.	Retention sample of finished products are not kept in their final packaging OR recommended storage conditions not maintained.		
329	19.8.2.	Check whether samples of active starting materials are retained for at least one year beyond the expiry date of the corresponding finished product.		Retention samples of active starting materials are retained for at least one year beyond the expiry date of the corresponding finished product.	Retention samples of active starting materials are not retained OR retained for less duration.		
330	19.8.2.	Check whether quantity of the Retention samples of materials and products are sufficient to permit at least two full re-examinations.		Quantity of Retention samples is sufficient to permit at least two full re-examinations.	Quantity of Retention samples is is inadequate		
19.9. Stability studies							
331	9.9.1.	Check whether the stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products is established by the QC department of firm.		Stability found performed as per schedule and is meeting the requirements	Stability initiated/completed but is inadequate/Not as per schedule	Stability not performed / initiated for marketed product.	
332	19.9.2.	Check whether the expiry dates and shelf-life specifications are established on the basis of the stability tests related to storage conditions.		Expiry dates /shelf-life specifications found established on the basis of the stability tests	Expiry dates /shelf-life specifications are not found established on the basis of the stability tests		

333	19.9.3	Whether the firm has developed and implemented programmed for on-going stability determination. (on-going stability determination programmed shall be developed and implemented as per elements mentioned din Para 19.9.3 of schedule M.)		On-going stability study programmed available and followed	On-going stability study programmed not available /Not followed		
334	19.9.4.	Check whether the firm is performing stability study after any significant changes in processes, equipment or packaging materials.		Stability studies found conducted after any significant changes in processes, equipment or packaging materials.	Stability studies not conducted after significant changes in processes, equipment or packaging materials.		
20. Computerized systems:							
335	20.1	Check whether the firm has validated all GMP-related computerized systems considering the diversity, complexity and criticality of the computerized application. (If an existing system was not validated at the time of installation then verify, if a retrospective validation is conducted and appropriate documentation is available)		Computerized systems found validated	Computerized systems are not validated		
336	20.4.	Check whether the Computerized systems have sufficient controls to prevent unauthorized access or changes to data. {There shall be controls to prevent omissions in data (e.g., the system being turned off and data not		Computerized systems are managed by password to prevent unauthorized access or changes to data. Controls available to	Computerized systems are not access controlled OR Controls not available to prevent prevent omissions in data OR		

		captured). There shall be a record of any data change made, the previous entry, the person who made the change and when the change was made}.		prevent prevent omissions in data and record of any data change made is maintained	record of any data change made is not maintained		
337	20.5.	Check whether the written procedures are available for the operation and maintenance of the computerized systems.		Written procedures for the operation and maintenance of the computerized systems Are available .	Written procedures not available for the operation and maintenance of the computerized systems .		
338	20.6	Where critical data are being entered manually, Check whether the firm has an additional check on the accuracy of the data entered.		Accuracy of the data entered is re-checked where critical data entered manually	Procedure not available to recheck accuracy of the data entered where critical data entered manually		
339	20.7.	Check whether the Incidents related to computerized systems that could affect the quality of products or the reliability of records or test results are recorded and investigated.		Incidents related to computerized systems are recorded and investigated.	Incidents related to computerized systems are not recorded/investigated.		
340	20.8.	Check whether the Changes to the computerized system are made according to a change procedure and records are maintained for all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system.		Changes to the computerized system are made according to a change procedure and records are maintained	Procedures nota available for making changes to the computerized system OR records not maintained		

341	20.9	Check whether the firm has provided a back-up system to ensure that there is no permanent loss of records due to system breakdown or failure.		back-up system available	back-up system not available		

INSPECTION CHECKLIST FOR GMP INSPECTION OF STERILE PRODUCTS, PARENTERAL PREPARATIONS (SMALL VOLUME INJECTABLES AND LARGE VOLUME PARENTERALS) AND STERILE OPHTHALMIC PREPARATIONS AS PER Part II OF SCHEDULE M							
Sr .No.	**Sch M Ref.**	**Particulars**	**2**	**1**	**0**	**X**	**Observation**
1. General considerations:-							
1	1.1.	The whether required clean areas provided for production of sterile preparations and entry is through airlocks for personnel or for equipment and materials or both?	NA	Cleans areas provided for production of sterile preparation. Airlocks provided for entry of personnel and pass boxes provided for entry of material.	No clean areas provided for production of sterile preparation. Entry of personnel and material is through same airlock'	There is neither clean areas provided nor airlocks provided for entry of personnel and material	
2	1.1.	Whether clean areas are maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.	NA	Cleaning procedures are in place for clean area. Clean rooms supplied with HEPA filtered air	Inadequate cleaning procedure for clean area. Clean rooms supplied with HEPA filters	Neither cleaning procedure is in place nor clean rooms provided with HEPA filtered air.	
3	1.2.	Whether various operations of component preparation (such as those involving containers and closures), product preparation,	NA	Manufacturing area clearly separated into following areas : 1. Component washing area. 2. Component preparation and autoclave loading area. 3. Autoclave unloading area. 4. Blending area.	Manufacturing area not clearly separated into following areas : 1. Component washing area. 2. Component	NA	

		filling and sterilisation are carried out in separate areas within the clean area.		5. Material staging area. 6. Filling area.	preparation and autoclave loading area. 3. Autoclave unloading area. 4. Blending area. 5. Material staging area. 6. Filling area.		
2. Quality control:-							
4	2.1	Ensure that the sterility test method is validated for the product concerned.	NA	Sterility test method validation is in place for the product concerned.	Sterility test method validation not in place for the product concerned.	NA	
	2.3	Ensure that the Pharmacopoeial methods are used for the validation and performance of the sterility test. (Note that the sterility test applied to the finished product is regarded as the last in a series of control measures by which sterility is assured, Ensure that firm has implemented sufficient measures to ensure	NA	Pharmacopoeal methods used for validation and performance.	Pharmacopoeal methods not used for validation and performance.	NA	

		sterility of product.)					
5	2.2	Ensure whether the samples taken for sterility are representativ e of the whole of the batch and in particular, includes samples taken from parts of the batch considered to be most at risk of contaminatio n, for example- (i) For aseptically filled products samples shall include containers filled at the beginning and end of the batch and after any significant interruption of work; (ii) For products that have been heat sterilised in their final containers, consideration shall be given to taking samples from that part of	NA	Sterility samples taken from Initial, middle, end of batch and after any significant interruption of work	Sterility samples not taken from Initial, middle, end of batch and after any significant interruption of work	NA	

		the load that is potentially the coolest.					
6	2.3.	Ensure whether that firm has performed sufficient validation to assure sterility of the finished product i.e. validation of the sterilisation cycle in the case of terminally sterilised products and "media simulation" or "media fill" runs for aseptically processed products	NA	Validation of Sterilisation cycle in the case of terminally sterilised products and "media simulation" or "media fill" runs for aseptically processed products performed. Protocol and reports are maintained with complete raw data.	Validation is in adequate and not cover all critical control parameters/ protocol and reports are not available with complete raw data	Validation not performed/ deviated from time line but manufacturing activity performed without impact analysis.	
7	2.3.	Ensure whether Batch processing records and environmenta l monitoring records (for aseptic processing), are examined in conjunction with the results of the sterility tests for taking decision on release of the batch	NA	BMR and BPR are available with environmental monitoring record and examined during the batch releas activity with the result of sterility.	The record are not conducted and not taken into account during batch release.		

8	2.3.	Ensure whether special attention is paid to the validation and the monitoring of the entire manufacturing process, in those cases where parametric release has been authorized in place of sterility testing.	NA	Firm has conducted validation and monitoring of the entire manufacturing process, in those cases where parametric release is performed	validation/ monitoring not performed	Batches are released to market without testing, validation and monitoring as required.	
9	2.4.	Ensure that for injectable products firm is performing test for endotoxins for the water for injection, the intermediate (if appropriate) and for finished products. Ensure whether test methods used are established pharmacopoeial method and validated for each type of product.	NA	Test for endotoxins for water for injection, the intermediate (if appropriate) and for finished products is performed as per established pharmacopoeial method validated for each type of product.	Test for endotoxins for water for injection, the intermediate (if appropriate) and for finished products is performed but methods are not validate/Inadequate documentation	Test for endotoxins not conducted for finished products.	

10	2.4.	Ensure that for large-volume parenterals monitoring of water or intermediates for endotoxins is always be done, in addition to any tests required by an approved monograph for the finished product.	NA	Monitoring of water or intermediates for endotoxins is conducted	Procedure used for monitoring of water or intermediates for endotoxins is inadequate/Records not maintained.	Test for endotoxins not conducted for finished products.	
11	2.4.	Whether the cause of the failure is investigated and necessary action shall be taken in case above sample fails in endotoxins test.	NA	Root cause analysis conducted for endotoxin failure and adequate CAPA undertaken.	Root cause analysis not conducted/Inadequate. Effective CAPA not implemented.		
12	2.5.	Check whether firm is using rapid microbiological methods in replacement the traditional microbiological methods for monitoring of microbiological quality of water, environment monitoring or bio burden etc.	NA	Rapid methods used are appropriately validated and a comparative assessment of rapid method is performed against the pharmacopoeial method	Rapid methods used are not appropriately validated /comparative assessment is not performed.		

		If so, ensure that the methods used are appropriately validated and a comparative assessment of the proposed rapid method is performed against the pharmacopoeial method.					
3. Sanitisation :							
13	3.1	Whether the firm has approved written programme for cleaning/sanitation of clean areas and ensure whether they are cleaned as per defined frequency	NA	Specified SOP for cleaning procedure of the manufacturing areas was found in place along with defined frequency and followed. Records found maintained in this regard.	Neither any SOP nor any records for cleaning procedure of the manufacturing areas was found in place.	NA	
14	3.3.	Whether the effectiveness of cleaning and disinfectant procedure is demonstrated /validated.	NA	Effectiveness of cleaning and disinfectant procedure is demonstrated	Effectiveness of cleaning and disinfectant procedure not demonstrated	NA	
15	3.1	Whether the disinfectants are used for cleaning/sanitation. If so, ensure that more than one type of disinfectants are employed.	NA	More than one disinfectants used on rotational basis for cleaning / sanitization	one disinfectant used for cleaning / sanitization	NA	

16	3.1	Whether monitoring is done regularly to detect contaminatio n or the presence of an organism against which the cleaning procedure is ineffective.	NA	Periodic microbial monitoring is performed to detect contamination	Periodic microbial monitoring not performed	NA	
17	3.1	Whether Interactions between different cleaning materials are validated.	NA	Interaction between cleaning materials are validated	Interaction between cleaning materials are not validated	NA	
18	3.2.	Whether appropriate cleaning validation is carried out to ensure disinfectant residuals can be detected and removed by the cleaning process.	NA	Cleaning validation performed to ensure disinfectant residuals can be detected and removed by the cleaning process.	Cleaning validation not performed to ensure disinfectant residuals can be detected and removed by the cleaning process.	NA	
19	3.2.	Ensure whether the disinfectants and detergents are monitored for microbial contaminatio n. Ensure whether the Disinfectants and detergents used in Grade A and B areas are	Disinfe ctants and deterge nts are monitor ed for microbi al contami nation; dilution s are in previou sly cleaned contain ers and	Disinfectant solutions are sterilized by membrane filtration or any other suitable method(if available) and is stored in the sterile containers.	Sterilized disinfectants are not stored in sterile containers. The sterilization procedure is not properly followed (i.e. selection of suitable sterilization grade filter or any other ineffective sterilization	NA	

		sterilized before use.	are only be stored for defined periods unless sterilized. Disinfectants and detergents used in Grade A and B areas are sterilized before use.		procedure is adopted). The sterilization records not effectively maintained etc.		
20	3.3.	Ensure whether the disinfectant programme includes a sporicidal agent.	NA	Sporicidal agent included in disinfectant programme	Sporicidal agent not included in disinfectant programme	NA	
21	3.4.	Whether there are any inaccessible places , if so what is procedure followed (e.g. Fumigation) for reducing microbial contamination in inaccessible places	There are no in accessible places in clean rooms	In accessible area are there in clean rooms and detailed procedure for sanitisation of the inaccessible area mentioned in cleaning SOP.	In accessible area are there in clean rooms and no procedure for sanitisation of the inaccessible area mentioned in cleaning SOP.	NA	
4. Manufacture of sterile preparations:-							

22	4.1.	Whether Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Whether Each manufacturing operation are conducted in appropriate clean area in appropriate level of environmental cleanliness in the operational state to minimize the risk of particulate or microbial contamination of the product or materials being handled	NA	Manufacturing area clearly separated into following areas : 1. Component washing area. 2. Component preparation and autoclave loading area. 3. Autoclave unloading area. 4. Blending area. 5. Material staging area. 6. Filling area.	Manufacturing area not clearly separated into following areas : 1. Component washing area. 2. Component preparation and autoclave loading area. 3. Autoclave unloading area. 4. Blending area. 5. Material staging area. 6. Filling area.	NA	
23	4.3	Ensure that manufacture of sterile pharmaceutical preparations is performed classified areas specified in Para 4.3 of part II e.g. **Grade A**: The local	NA	Following classification defined with respect to operation performed, Grade A - Filling Grade B - Background for Grade A for aseptic filling. Grade C - Manufacturing, component	Following classification not defined with respect to operation performed, Grade A - Filling Grade B - Background for Grade A for aseptic filling. Grade C -	NA	

		zone for high-risk operations, e.g., filling and making aseptic connections. Grade A conditions are achieved by using unidirectional airflow work station which provides air speed of 0.36-0.54 m/s (guidance value) at a defined test position 15-30 cm below terminal filter or air distributor system. The velocity at working level shall not be less than 0.36 m/s. The uniformity and effectiveness of unidirectional airflow shall be demonstrated by undertaking airflow visualisation tests. **Grade B**: In aseptic preparation and filling, this is the background		preparation, autoclave loading. Grade D - Washing area	Manufacturing, component preparation, autoclave loading. Grade D - Washing area		

		environment for the Grade A zone. **Grades C and D**: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e., aseptic connection with aseptic connectors and operations in a closed system). A unidirectiona l airflow and lower velocities may be used in closed isolators and glove boxes.					
24	4.4.	Whether the number of air changes for grade B, C and D air grades are appropriate for the size of the room and the equipment and personnel present in it.	NA	Number of air changes in Grade A/B and Grade C,D areas was found NLT 20	No records could be produced in this regard	NA	

25	4.5.	Whether High-efficiency particulate air (HEPA) filters are subjected to an installed filter leakage test in accordance with ISO standards at a recommended interval of every six months (not exceeding twelve month)	NA	HEPA filter leakage testing performed at every six months frequency.	No records could be produced in this regard	NA	
26	4.5	Ensure that the aerosol selected for HEPA leak testing shall not support microbial growth and shall be composed of a sufficient number or mass of particles.	NA	Aerosol selected for HEPA leak testing not support microbial growth and composed of a sufficient number or mass of particles	No records could be produced in this regard	NA	
27	4.5	Whether HEPA filter patching is allowed at filter the filter manufacturer and in situ operation provided that the patch sizes and procedures followed the recommendations of ISO standards.	NA	Procedure for patching of HEPA filter defined in procedure as per ISO standards	Procedure for patching of HEPA filter not defined in procedure as per ISO standards	NA	

28	4.6	Whether clean rooms and clean air devises classifies in accordance with ISO standards.	NA	Clean room classification complies with ISO standards	Clean room classification not complies with ISO standards	NA	
29	4.6.1.	Whether area Classification "at rest" and "in opration" are clearly defined and ensure that the maximum permitted airborne particle concentration for each Grade is as per Table 1 of Para 4.6.1 of Part II of Schedule M	NA	Area classification (at rest and in operations) is defined and meets the requirements.	Area classification (at rest and in operations) are not compiling to the limits.	Area classification (at rest and in operations) are not defined/not maintained.	
31	4.6.2	Ensure that for classification purposes in Grade A zones, a minimum sample volume of $1m^3$ shall be taken per sample location	NA	Sample volume for Grade A zones is more than 1m3	Sample volume for Grade A zones is less than 1m3	NA	
32	4.6.2	For classification purposes ISO standards methodology defines both the minimum number of sample locations and the sample size based on	NA	Sample volume and sample locations considered as per ISO standards	Sample volume and sample locations not considered as per ISO standards	NA	

		the class. limit of the largest particle size considered and the method of evaluation of the data collected. The sample volume shall be determined according to ISO standards. However, for lower grades (Grade C in operation and Grade D at rest) the sample volume per location shall be at least two litres and the sample time per location shall be not less than one minute.					
33	4.6.3	Ensure that Portable particle counters with a short length of sample tubing shall be used for classification purposes to avoid the loss of particles ≥ 5.0 µm	NA	Portable particle counters with a short length of sample tubing used.	Portable particle counters with a long length of sample tubing used.	NA	
34	4.6.3.	Whether Isokinetic sample heads/Probes	NA	Isokinetic sample heads/Probes are used in	Isokinetic sample heads/Probes are not used	NA	

		are used in unidirectional airflow systems.		unidirectional airflow systems	in unidirectional airflow systems		
35	4.6.4.	Whether firm has demonstrated "In operation" classification during normal operations, simulated operations or during media fills	NA	firm has demonstrated "In operation" classification during normal operations, simulated operations or during media fills	firm has not demonstrated "In operation" classification during normal operations, simulated operations or during media fills	NA	
36	4.7.	Whether firm has written procedure and programme for routine monitoring of clean rooms and clean-air devices while in operation and Whether the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms or clean-air devices or both.	NA	Procedure for routine monitoring of clean rooms and clean air devices is in place. Selection of routine monitoring location is based on risk analysis.	Procedure for routine monitoring of clean rooms and clean air devices not in place. Selection of routine monitoring location is not based on risk analysis.	NA	

37	4.7.1.	a) Whether firm is performing particle monitoring for Grade A zones covering the full duration of critical processing, including equipment assembly (except where justified by contaminants in the process that would damage the particle counter or present a hazard, for example, live organisms and radiological hazards.) b) Ensure whether in such cases monitoring during routine equipment set-up operations is undertaken before exposure to the risk. c) Ensure whether monitoring during simulated operations is performed.	NA	Particle monitoring of Grade A performed throughout the critical processing including equipment assembly.	Particle monitoring of Grade A not performed throughout the critical processing including equipment assembly.	NA	

38	4.7.1.	Whether Grade A zone are monitored at a frequency and sample size such that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. Verify the procedures adopted by firm for handling of exertions in particle count	NA	Rationale / justification for selection of particle monitoring location is in place. Procedure for handling of particle excursions is in place.	Neither Rationale / justification for selection of particle monitoring location nor procedure for handling of particle excursions is in place.	NA	
39	4.7.2	Ensure that similar system be used for Grade B zones, although the sample frequency may be decreased. The importance of the particle monitoring system shall be determined by the effectiveness of the segregation between the adjacent	NA	Rationale / justification for selection of particle monitoring location is in place. Procedure for handling of particle excursions is in place.	Neither Rationale / justification for selection of particle monitoring location nor procedure for handling of particle excursions is in place.	NA	

		Grade A and B zones.					
40	4.7.2.	Whether The Grade B zone are monitored at a frequency and with a sample size such that changes in levels of contamination and any deterioration of the system would be captured and alarms triggered if alert limits are exceeded.	NA	Rationale / justification for selection of particle monitoring location is in place. Procedure for handling of particle excursions is in place.	Neither Rationale / justification for selection of particle monitoring location nor procedure for handling of particle excursions is in place.	NA	
41	4.7.3	Ensure that the length of tubing and the radii of any bends in the tubing are considered in the context of particle losses in the tubing whenever remote sampling systems are used.	NA	Sampling tube of remote sampling system is short without bends	Sampling tube of remote sampling system is long with bends and radii of bend is not appropriate.	NA	
42	4.7.5.	whether “at rest” state is achieved in the absence of the operating personnel after a short “clean-up” or “recovery”		Recovery time of B & C zone was found less than 20 minutes and records are maintained.	Recovery time is not complying with requirements /Records not maintained.	NA	

		period of about 15–20 minutes (guidance value), after completion of the operations.					
43	4.7.5.	Whether Grade A "in operation" is maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment.		Particle count of Grade A area monitored at appropriate location (wherever the product or open container is exposed to the environment) during operation and records are maintained.	Particle count of Grade A area is monitored however the location of sampling is not appropriate.	Particle count of Grade A area is not monitored during critical operation.	
44	4.7.5.	Verify whether firm has performed "clean-up" or "recovery" test as per the ISO standards.	NA	firm has performed "clean-up" or "recovery" test as per the ISO standards.	firm has not performed "clean-up" or "recovery" test as per the ISO standards.	NA	
45	4.7.6.	Verify whether firm written procedures and schedule/programme for monitored of airborne particles and microbial contamination. Ensure whether airborne particles are monitored	NA	Firm written procedures and schedule/programme for monitoring of airborne particles and microbial contamination is in place and critical locations monitored periodically during operation.	Firm written procedures and schedule/programme for monitoring of airborne particles and microbial contamination is not in place and critical locations not monitored periodically during operation.	NA	

		periodically "in operation" at critical locations.					
46	4.7.6	Ensure that Locations and sample sizes shall be determined based on an assessment of the process and contaminatio n risk.	NA	Sampling location and sample size determined based on assessment of process and contamination risk.	Sampling location and sample size not determined based on assessment of process and contaminatio n risk.	NA	
47	4.7.7 .	Verify whether monitoring of Grade C and D areas in operation is performed in accordance with the principles of QRM. The requirements and alert or action limits will depend on the nature of the operations carried out, but the recommende d "clean-up period" shall be attained.	NA	Monitoring of Grade C & D performed accordance with QRM principles. Alert and action limits are established considering clean-up period.	Monitoring of Grade C & D not performed accordance with QRM principles. Alert and action limits are not established considering clean-up period.	NA	

48	4.7.8.	Verify whether environmental conditions such as temperature and relative humidity is maintained depend on the product and nature of the operations carried out and whether these parameters are monitored. Ensure that temperature and relative humidity shall not interfere with defined cleanliness standards.	NA	Environmental conditions such as temperature and relative humidity is maintained depend on the product and nature of the operations carried out	Environmental conditions such as temperature and relative humidity is not maintained depend on the product and nature of the operations carried out	NA	
49	4.8.	Verify whether firm has written procedures and programme for monitoring of microbiological cleanliness of Grades A to D in-operation, Specify monitoring methods (settle plates, volumetric air and surface sampling i.e.	NA	Firm has written procedures and programme for monitoring of microbiological cleanliness of Grades A to D in-operation which includes monitoring methods used for monitoring during aseptic operation. Results of monitoring considered while reviewing batch documentation for finished product release.	Firm has not written procedures and programmed for monitoring of microbiological cleanliness of Grades A to D in-operation which includes monitoring methods used for monitoring during aseptic	NA	

		swabs and contact plates) used for monitoring during aseptic operations. Whether results from monitoring are considered while reviewing batch documentation for finished product release. Whether surfaces and personnel are monitored after critical operations. Whether additional microbiological monitoring is also required outside production operations e.g. after validation of systems, cleaning and sanitisation		Surfaces and personnel are monitored after critical operations. Additional monitoring performed outside production operation	operation. Results of monitoring not considered while reviewing batch documentation for finished product release. Surfaces and personnel are not monitored after critical operations. Additional monitoring not performed outside production operation		
50	4.9	a) Specify whether firm has established appropriate alert and action limits for the results of particulate and microbiologi	NA	Alerts and action limits for particulate and microbiological monitoring results are established and trend analysis of results is performed.	Neither alerts and action limits for particulate and microbiological monitoring results are established	NA	

		cal monitoring. b) Specify whether firm is performing trends analysis for microbiologi cal monitoring is performed or not.			nor trend analysis of results is performed.		
51	4.1	c) Specify whether firm is having SOPs for performing investigation in case action limits are exceeded or a trend is identified in the alert limits. d) Whether appropriate corrective actions are taken after investigation s	NA	Firm is having SOPs for performing investigation in case action limits are exceeded or a trend is identified in the alert limits and corrective action taken after investigations	Firm is not having SOPs for performing investigation in case action limits are exceeded or a trend is identified in the alert limits and corrective action taken after investigation s	NA	
52	4.11	Ensure that the area Grades specified in this Part shall be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g., aseptic media	NA	Validation runs i.e. media fill or others types of process simulations are used to establish processing hold times and a maximum fill duration.	Validation runs i.e. media fill or others types of process simulations are not used to establish processing hold times and a maximum fill duration.	NA	

		fills or others types of process simulations) are used to establish processing hold times and a maximum fill duration.					
53	4.11	Ensure that the determination of an appropriate process area environment and a time limit shall be based on the microbial contamination (bioburden) found.	NA	Determination of an appropriate process area environment and a time limit is based on the microbial contamination (bioburden) found.	Determination of an appropriate process area environment and a time limit is not based on the microbial contamination (bioburden) found.	NA	
54	4.11	Whether firm has establish processing hold times and a maximum fill duration time based on aseptic media fills or others types of process simulations/validations	NA	Firm has establish processing hold times and a maximum fill duration time based on aseptic media fills or others types of process simulations/validations	Firm has not establish processing hold times and a maximum fill duration time based on aseptic media fills or others types of process simulations/ validations	NA	
4.11.1 Terminally sterilised product							

55	4.11.1.1.	Specify the Grade of clean room in which components and products are prepared (Note components and products shall be prepared least a Grade D zone to ensure low microbial bio burden and particulate counts prior to filtration and sterilization) Specify where the product is at unusual risk of microbial contaminatio n (e.g., because it actively supports microbial growth, must be held for a long period before sterilization, or is necessarily processed mainly in open vessels), If so the preparation shall generally be done in a Grade C zone.	NA	Component preparation for sterilization is performed in Grade C and product manufacturing is performed in Grade C	Component preparation for sterilization is not performed in Grade C and product manufacturi ng is not performed in Grade C	NA	

56	4.11.1.2.	Specify the Grade of clean room in which filling of products for terminal sterilisation is done Ensure that it is done in at least a Grade C environment.	NA	Filling area of terminally sterilized product done in Grade C	Filling area of terminally sterilized product not done in Grade C	NA	
57	4.11.1.3	Where the product is at unusual risk of contamination from the environment (e.g., because the filling operation is slow, the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling shall be done in a Grade A zone with at least a Grade C background.	NA	Filling of terminally sterilized product is done in Grade A with Grade C background	Filling of terminally sterilized product is not done in Grade A with Grade C background	NA	
58	4.11.1.4.	Ensure that preparation and filling of ointments, creams, suspensions and emulsions is done in a Grade C zone before	NA	Preparation and filling of ointments, creams, suspensions and emulsions is done in a Grade C zone before terminal sterilization	Preparation and filling of ointments, creams, suspensions and emulsions is not done in a Grade C zone before	NA	

		terminal sterilization.			terminal sterilization		
4.11.2 Aseptic preparation :							
59	4.11.2.1	Ensure whether Components after are handled in at least Grade D zone	NA	Components after are handled in Grade D	Components after are handled in lower than Grade D	NA	
60	4.11.2.1	Ensure whether handling of sterile starting materials and components is undertaken in a Grade A zone with Grade B background (unless subjected to sterilisation or filtration through a microorganism-retaining filter later in the process)	NA	Handling of sterile starting materials and components is undertaken in a Grade A zone with Grade B background	Handling of sterile starting materials and components is not undertaken in a Grade A zone with Grade B background	NA	
61	4.11.2.2.	a) Ensure whether preparation of solutions which are to be sterile-filtered during the process is undertaken in Grade C zone (if closed system is used, then	NA	Preparation of solutions which are to be sterile-filtered during the process is undertaken in Grade C zone. Preparation of materials and products (If not sterile-filtered therefore an aseptic	Preparation of solutions which are to be sterile-filtered during the process not undertaken in Grade C zone. Preparation of materials and products	NA	

		use of Grade D zone is acceptable). b) Ensure whether the preparation of materials and products (If not sterile-filtered therefore an aseptic manipulation) is undertaken in Grade A zone with Grade B background.		manipulation) is undertaken in Grade A zone with Grade B background	(If not sterile-filtered therefore an aseptic manipulation) is not undertaken in Grade A zone with Grade B background		
62	4.11.2.3	Ensure whether handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, is undertaken in Grade A zone with Grade B background.	NA	Handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, is undertaken in Grade A zone with Grade B background	Handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, is not undertaken in Grade A zone with Grade B background	NA	
63	4.11.2.4.	Ensure whether transfer of partially closed containers (as used in freeze-drying, before stoppering is completed) is undertaken either in	NA	transfer of partially closed containers (as used in freeze-drying, before stoppering is completed) is undertaken either in Grade A zone with Grade B background or in sealed transfer trays in Grade B zone.	transfer of partially closed containers (as used in freeze-drying, before stoppering is completed) is undertaken neither in Grade A	NA	

		Grade A zone with Grade B background or in sealed transfer trays in Grade B zone.			zone with Grade B background nor in sealed transfer trays in Grade B zone.		
64	4.11.2.5.	Ensure whether preparation and filling of sterile ointments, creams, suspensions and emulsions shall be undertaken in Grade A zone with Grade B background in condition when the product is exposed and is not subsequently filtered.	NA	Preparation and filling of sterile ointments, creams, suspensions and emulsions is undertaken in Grade A zone with Grade B background in condition when the product is exposed and is not subsequently filtered	Preparation and filling of sterile ointments, creams, suspensions and emulsions is not undertaken in Grade A zone with Grade B background in condition when the product is exposed and is not subsequently filtered	NA	
5. Processing :							
65	5.1.	Whether necessary precautions are taken to minimise contaminatio n during all processing stages, including the stages before sterilization	NA	Precautions are taken to minimize contamination during all processing stages, including the stages before sterilization	Precautions are not taken to minimize contaminatio n during all processing stages, including the stages before sterilization	NA	

66	5.2.	a) Ensure that preparations containing live micro-organisms are not made in areas used for the processing of other pharmaceutical products. b) Ensure that area used for filling of containers of live micro-organisms is not used for filling other pharmaceutical products. (However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live micro-organisms, the use of multi-product facilities may be justifiable)	NA	The whole facility was found separated, dedicated for other pharmaceutical products and is not a part of any other facility wherein preparations containing live micro-organisms are handled.	Other pharmaceutical products was found manufactured along with preparations containing live micro-organisms	NA	

67	5.3.	Ensure whether validation of aseptic processing is done using a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium shall be based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium	NA	Selection of the nutrient medium is done based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium	Selection of the nutrient medium is not done based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium	NA	
68	5.4.	Ensure whether the process simulation test imitates as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.	NA	Process simulation test imitates as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.	Process simulation test not imitates as closely as possible the routine aseptic manufacturing steps except where the activity may lead to any potential microbial contamination.	NA	
69	5.5.	Whether the Process simulation are performed by	NA	Process simulation are performed by running three consecutive	Process simulation are performed by running	NA	

		running three consecutive satisfactory simulation tests.		satisfactory simulation tests.	less than three satisfactory simulation tests.		
70	5.5.	Whether the process simulation are repeated at defined intervals and after any significant modification to the HVAC system, equipment or process.	NA	Process simulation are repeated at defined intervals and after any significant modification to the HVAC system, equipment or process.	Process simulation are not repeated at defined intervals and after any significant modification to the HVAC system, equipment or process.	NA	
71	5.5.	Whether all activities and interventions known to occur during normal production as well as in the worst-case situations are incorporated in Process simulation tests	NA	all activities and interventions known to occur during normal production as well as in the worst-case situations are incorporated in Process simulation tests	all activities and interventions known to occur during normal production as well as in the worst-case situations are not incorporated in Process simulation tests	NA	
72	5.5.	Whether the process simulation tests are representativ e of each shift and shift changeover to address any time-related and operational features.	NA	Process simulation tests covers each shift and shift changeover to address any time-related and operational features.	Process simulation tests not covers each shift and shift changeover to address any time-related and operational features.	NA	

73	5.6.	Whether number of containers used for media fills are sufficient to enable a valid evaluation. For small batches the number of containers for media fills shall at least equal to the size of the product batch. Whether acceptance criteria is meeting as per Para 5.6. of Part II of schedule M	NA	Media fill batch size selection criteria is meeting as per Para 5.6 of Part II of schedule M	Media fill batch size selection criteria is not meeting Para 5.6 of Part II of schedule M	NA	
74	5.6.	Whether acceptance criteria for process simulation is meeting as mentioned below The target shall be zero growth and the following shall apply: (a) when filling fewer than 5000 units, no contaminated units shall be detected; (b) when filling 5000–10000 units (i) one contaminated	NA	Acceptance criteria for process simulation is meeting as per Para 5.6 of Part II of schedule M	Acceptance criteria for process simulation is not meeting as per Para 5.6 of Part II of schedule M	NA	

		unit shall result in an investigation, including consideration of a repeat media fill; (ii) two contaminated units are considered cause for revalidation following investigation; c) when filling more than 10000 units – (i) One contaminated unit shall result in an investigation; (ii) Two contaminated units are considered cause for revalidation following investigation.					
75	5.7.	Whether intermittent incidents of microbial contaminatio n in media fill run that may be indicative of low-level contaminatio n are investigated. Whether Investigation of gross failures includes the potential	NA	Microbial excursions during media fill simulations are investigated. In case of gross failure, potential impact on sterility of batches produced from last successful media fill is evaluated.	Microbial excursions during media fill simulations are not investigated. In case of gross failure, potential impact on sterility of batches produced from last successful media fill is	NA	

		impact on the sterility assurance of batches manufactured since the last successful media fill.			not evaluated.		
76	5.8	Ensure that care shall be taken to ensure that any validation does not compromise the processes	NA	Validation does not compromise the processes	Validation compromise the processes	NA	
77	5.9.	Whether water sources, water-treatment equipment and treated water are monitored regularly for chemicals, biological contaminatio n and contaminatio n with endotoxins to ensure that the water complies with the specifications appropriate to its use Whether records of the results monitoring and of any action taken is maintained	NA	Water sampling for chemical & microbial testing is performed as per schedule. Trend analysis of water results is performed and required action is taken wherever applicable.	Water sampling for chemical & microbial testing is not performed as per schedule. Neither trend analysis of water results is performed and nor required action is taken wherever applicable.	NA	

78	5.1	Ensure that Activities in clean areas, especially when aseptic operations are in progress, shall be kept to a minimum and the movement of personnel shall be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity. As far as possible, personnel shall be excluded from Grade A zones	NA	Defined number of persons allowed in aseptic area during operation. No human intervention in Grade A during batch processing activity	Limit for number of persons allowed in aseptic area during operation not followed and not mentioned in procedure. Direct human intervention in Grade A during batch processing activity	NA	
79	5.10.	Ensure that ambient temperature and humidity is not uncomfortably high because of the nature of the garments worn and to reduce the risk of contamination liberated from the personnel.	NA	Relative humidity and temperature is controlled and monitored	Relative humidity and temperature is not controlled and monitored	NA	

80	5.11.	Ensure that presence of containers and materials liable to generate fibers is minimized in clean areas and avoided completely when aseptic work is in progress.	NA	Non fiber / particle generating materials used in clean area during aseptic work	Fiber / particle generating materials used in clean area during aseptic work	NA	
81	5.12	Whether components, bulk-product containers and equipment are handled after the final cleaning process in such a way so as to ensure that they are not re-contaminated .	NA	Controls are in place to avoid contamination of cleaned material during handling.	Controls are not in place to avoid contaminatio n of cleaned material during handling.	NA	
82	5.12	Whether the stage of processing of components as well as the bulk-product containers and equipment is properly identified.	NA	Status labels mentioning stage of processing of components as well as the bulk-product containers and equipment in place	Status labels mentioning stage of processing of components as well as the bulk-product containers and equipment not in place	NA	
83	5.13.	Ensure whether the interval between the washing and drying and the	NA	Hold time after cleaning and sterilization for containers and equipment is established.	Hold time after cleaning and sterilization for containers and	NA	

		sterilisation of components, bulk-product containers and equipment, as well as between sterilisation is short as possible and subject to a time limit appropriate to the validated storage conditions.			equipment is not established.		
84	5.14.	Ensure whether the time between the start of the preparation of a solution and its sterilisation or filtration through a bacteria-retaining filter is as short as possible and whether maximum permissible time is set for each product that takes into account its composition and the prescribed method of storage.	NA	Hold time for bulk solution before and after filtration is established.	Hold time for bulk solution before and after filtration is not established.	NA	

85	5.15.	Ensure whether gases used to purge a solution or blanket a product are passed through a sterilising filter.	NA	Filtered gases used for purging solution	Non filtered gases used for purging solution	NA	
86	5.16.	Whether bio burden of each batch of aseptically filled products and terminally sterilised products is monitored before sterilisation. Whether working limits for bio burden before sterilisation are defined.	NA	Bio burden of each batch of aseptically filled products and terminally sterilized products is monitored before sterilization and limits for bio burden before sterilization are defined.	Bio burden not monitored for each batch/ Bio burden of each batch monitored but limit are not defined.		
87	5.16.	Whether bio burden monitored at suitable scheduled intervals where overkill sterilisation parameters are set for terminally sterilised products.	NA	Frequency for monitoring of bio burden for terminally sterilized product is available and records are maintained.	Frequency for monitoring of bio burden for terminally sterilized product is not available/ not carried out /records are maintained.		
88	5.16.	For parametric release systems, whether bio burden is performed on	NA	Bio burden is performed on each batch as an in-process test.	Bio burden is not performed on each batch as an in-process test.		

		each batch and considered as an in-process test.					
89	5.17.	Whether components, bulk-product containers, equipment and any other articles required in a clean area where aseptic work is in progress are sterilised and wherever possible passed into the area through double ended sterilisers sealed into the wall. (Other procedures that prevent the introduction of contaminatio n may be acceptable in some circumstance s).	NA	Adequate procedure and control are available	Procedure/co ntrol are inadequate.		
90	5.18.	Ensure whether the efficacy of any new processing procedure is validated and the validation is repeated at regular	NA	Procedure used are validated and revalidation carried out at defined frequency and after any significant changes.	Procedure used are not adequately validated/ revalidation not carried out at defined frequency.	Critical procedure used are not validated/ Revalidation not carried out after significant changes.	

		intervals thereafter or when any significant change is made in the process or equipment.					
6. Sterilisation :							
91	6.3.	Whether bio burden of starting materials is monitored before sterilisation. Whether specifications includes requirements for microbiologi cal quality when the need for this has been indicated by monitoring.		Procedure and records are available	Procedure and records are not available /Inadequate.		
92	6.4.	Whether sterilisation processes are validated. (Particular attention shall be paid when the adopted sterilisation method is used for a preparation that is not a simple aqueous or oily solution, for example, colloidal suspensions).		Sterilization processes are validated.	Sterilization processes are inadequately validated.	Sterilization processes are not validated.	

93	6.5.	Whether suitability of sterilization process for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed is demonstrated by physical measurements and by biological indicators, where appropriate		Sterilization method is validated with predefined load patterns. Physical measurement (temperature, pressure) and biological indicators are used (where appropriate) during validation.	Sterilization method is not adequately validated.	Non validated sterilization method is used.	
94	6.5.	Whether validity of the **validated sterilization process** is verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records shall be kept of the results		sterilization process is re-validated at least annually and after significant modifications and records found maintained.	sterilization process is not re-validated annually/after significant modifications/records not maintained/Inadequate.		

95	6.7.	a) Whether biological indicators are stored and used according to the manufacturer's instructions and their quality checked by positive controls. b) Whether strict precautions are taken to avoid any transfer of microbial contamination from them.		Procedures and records available	Procedures/records are inadequate		
96	6.8.	Whether clear means are implemented for differentiating products that have not been sterilized from those which are not sterilized.		Physical segregation/Procedures and status labeling is available	Procedures/ status labeling is inadequate	Sterilized and non sterilized product found stored at same place without any segregation	
97	6.8.	Whether each basket, tray, or other carrier of products or components is clearly labeled with the name of the material, its batch number and an indication of whether or		Appropriate status labeling is available	status labeling is inadequate		

		not it has been sterilized.					
98	6.8	Whether Indicators such as autoclave tape are used where appropriate to indicate whether or not a batch (or sub-batch) has passed through a sterilization process.		Autoclave tape are used where appropriate	Autoclave tape are not used		
99	6.9.	Whether validated loading patterns are established for all sterilization processes.		All load patterns are validated	Validation does not covers all load patterns /Inadequate validations performed.	Sterilizations performed are not as per validated load pattern	
100	6.10.	Whether sterilization records for each sterilization run is available and they are approved as part of the batch-release procedure		Sterilization records for each sterilization run is available and they are reviewed as part of the batch-release	Sterilization records not available for each sterilization run / they are not reviewed as part of the batch-release OR Thermographs/sterilization records are not legible		
6.11.1 Terminal Sterilization :							
Heat Sterilization							

101	6.11.1.1.	Whether each heat-sterilization cycle is recorded by means of appropriate equipment of suitable accuracy and precision, e.g., on a time or temperature chart with a suitably large scale. a) Whether temperature is recorded by a probe situated at the coolest part of the load or loaded chamber, this point having been determined during the validation; b) Whether temperature is checked against a second independent temperature probe located at the same position. c) Whether Sterilization records are available for each sterilization run and are approved as part of the		a) Records of each sterilization cycle are available and are reviewed suitably. b) Temperature recording probe is found situated at the coolest part as determined during the validation; c) Chemical or biological indicators are used wherever appropriate d) Physical parameters (temperature/pressure) monitored for each cycle. e) Sterilisation records are reviewed as part of the batch release procedure.	Control Measures implemented /Records maintained are inadequate	No record available about sterilisation cycles used for product sterilisation.	

		batch release procedure. d) Ensure that Chemical or biological indicators are used but shall not take the place of physical controls					
102	6.11.1.2.	Whether sufficient time is allowed for the whole of the load to reach the required temperature before measurement of the sterilising time is started. Whether This is determined for each type of load to be processed.		Equilibrium time for each load is determined & verified during validation	Equilibrium time for each load is determined & verified during validation		
103	6.11.1.3.	Whether precautions are taken to avoid contaminatio n of a sterilised load during cooling after the high-temperature phase of a heat sterilisation cycle,		Controls are in place to avoid contamination of sterilized loads during cooling phase after sterilization phase.	Controls are not in place to avoid contaminatio n of sterilized loads during cooling phase after sterilization phase.		

104	6.11.1.3.	Whether cooling fluid or gases coming in contact with the product are sterilised.		cooling fluid or gases coming in contact with the product are sterilised by filtration or suitable method.	cooling fluid or gases coming in contact with the product are not sterilised.		
105	6.11.1.4.	a) Ensure that Both temperature and pressure is used to monitor the process. b) Whether control instrumentation is independent of monitoring instrumentation and recording charts. c) Where automated control and monitoring systems are used for these applications whether they are validated to ensure that critical process requirements are met d) Whether System and cycle faults are registered by the system and observed by the operator. e) Ensure whether reading of		Following controls available with respect to autoclave, 1. Both temperature and pressure used to monitor the sterilization process. 2. control instrumentation is independent of monitoring instrumentation and recording charts. 3. Where automated control and monitoring systems are used for these applications whether they are validated to ensure that critical process requirements are met. 4. System and cycle faults are recorded and observed by operator. 5. Reading of the independent temperature indicator is routinely checked against the reading on	Following controls not available with respect to autoclave/Inadequate, 1. Both temperature and pressure used to monitor the sterilization process. 2. control instrumentation is independent of monitoring instrumentation and recording charts. 3. Where automated control and monitoring systems are used for these applications whether they are validated to ensure that critical process requirements are met. 4. System and cycle faults are	No records available for sterilization cycle used for terminal sterilization of product.	

		the independent temperature indicator is routinely checked against the reading on the chart recorder during the sterilisation period. f) For sterilisers fitted with a drain at the bottom of the chamber, whether temperature at this position is recorded throughout the sterilisation period. g) Whether regular leak tests are conducted on the chamber when a vacuum phase is part of the cycle.		the chart recorder during the sterilization period. 6.Sterilisers fitted with a drain at the bottom of the chamber, whether temperature at this position is recorded throughout the sterilization period. 7. Regular leak tests are conducted on the chamber when a vacuum phase is part of the cycle	recorded and observed by operator. 5. Reading of the independent temperature indicator is routinely checked against the reading on the chart recorder during the sterilization period. 6.Sterilisers fitted with a drain at the bottom of the chamber, whether temperature at this position is recorded throughout the sterilization period. 7. Regular leak tests are conducted on the chamber when a vacuum phase is part of the cycle		

106	6.11.1.5.	Whether the items to be sterilised, other than products in sealed containers, are wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilisation. (Specially designed autoclavable stainless steel containers, that allow steam to enter and air to leave, can also be used)		Suitable wrapping material / containers is used that allows the removal of air and the penetration of steam but prevents recontamination after sterilisation.	Suitable Wrapping material / containers not used.		
107	6.11.1.5.	How firm ensured that all parts of the load is contact with water or saturated steam at the required temperature for the required time.		Sufficient probes are provided to record the temperature of different parts of load	Insufficient number of probes /location of probes is inadequate		
108	6.11.1.6.	Whether steam used for sterilisation is tested regularly for suitable quality chemical, microbiologi		Steam quality is checked periodically for followings. 1. Chemical, microbial and endotoxin level. 2. Physical tests such as dryness, superheat and	Steam quality is not checked for followings/Frequency not specified/followed 1. Chemical, microbial and		

		cal and endotoxin analysis of condensate and physical examination of steam (such as dryness, superheat and non-condensable gases) and does not contain additives at a level that could cause contaminatio n of the product or equipment.		non condensable gases.	endotoxin level. 2. Physical tests such as dryness, superheat and non condensable gases.		
10 9	6.11. 1.7.	a) Ensure whether air supplied for sterilisation by dry heat cycle is passed through a microorganis m-retaining filter (e.g., a HEPA filter). b) Ensure whether challenge tests using endotoxins are conducted as part of the validation. Where such sterilization by dry heat is intended to remove pyrogens		HEPA filters used in sterilizer. Endotoxin challenge test is performed during validation	HEPA filters not used for sterilizer. Endotoxin challenge test is not performed during validation		
Sterilization by radiation :							

110	6.11.1.8.	Whether the absence of deleterious effects on the product has been confirmed experimentally for use of sterilisation by radiation.		The absence of deleterious effects on the product has been confirmed experimentally for use of sterilisation by radiation.	The absence of deleterious effects on the product has not been confirmed experimentally for use of sterilisation by radiation.		
111	6.11.1.8.	Ensure that ultraviolet irradiation is not used for terminal sterilisation as is not an acceptable method for terminal sterilisation.		Ultraviolet irradiation is not used for terminal sterilisation as is not an acceptable method for terminal sterilisation.	NA	Ultraviolet irradiation is used for terminal sterilisation.	
112	6.11.1.9.	If sterilisation by radiation is done by an outside contractor, Whether manufacturer has ensured that the requirements of paragraph 6.8 are met and that the sterilisation process is validated		Procedure and records are available	Procedure/records are not available		

113	6.11.1.10.	a) Whether the radiation dose is measured during the sterilisation procedure b) The dosimeters used for this purpose is independent of the dose rate and provides a quantitative measurement of the dose received by the product itself. c) Whether dosimeters are inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber. d) Where plastic dosimeters are used ensure whether they are used within the time-limit of their calibration e) Whether Dosimeter is read/recorded shortly after exposure to radiation		Following controls are in place to ensure sterilization, a) Radiation dose is measured during the sterilisation procedure b) The dosimeters used for this purpose is independent of the dose rate and provides a quantitative measurement of the dose received by the product itself. c) Dosimeters are inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber. d) Plastic dosimeters are used ensure whether they are used within the time-limit of their calibration e) Dosimeter is read/recorded shortly after exposure to radiation f) Radiation-sensitive colour discs are used to differentiate between packages that have been subjected to	Controls are inadequate/Records not maintained/Inadequate.	Radiation dose is not measured during the sterilisation procedure/Radiation dose is inadequate.	

		f) Whether radiation-sensitive colour discs are used to differentiate between packages that have been subjected to irradiation and those that have not subjected to irradiation g) Whether information above obtained about radiation constitute the part of the batch record.		irradiation and those that have not g) Information above obtained about radiation constitute the part of the batch record.			
114	6.11.1.11.	Whether Validation procedures ensures that consideration is given to the effects of variations in the density of the packages		Validation procedures ensures that consideration is given to the effects of variations in the density of the packages	Validation procedures not ensures that consideration is given to the effects of variations in the density of the packages		
115	6.11.1.12.	Whether material-handling procedures are in place to prevent any mix-up of irradiated and non-irradiated materials.		Material-handling procedures are in place to prevent any mix-up of irradiated and non-irradiated materials.	Material-handling procedures are not in place to prevent any mix-up of irradiated and non-irradiated materials.		

116	6.11.1.12.	Whether each package carries a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment		radiation-sensitive indicators are used for each package	radiation-sensitive indicators are not used for each package		
117	6.11.1.13.	Whether total radiation dose is administered within a predetermined period		Total radiation dose is administered within a predetermined period	Total radiation dose is not administered within a predetermined period		
118	6.11.1.14.	Ensure that sterilisation by gases and fumigant is used for finished products only where there is no suitable alternative.		Sterilisation by gases and fumigant is used for finished products only where there is no suitable alternative.	Sterilisation by gases and fumigant is used for finished products even after availability of suitable alternative.		
119	6.11.1.15.	a) Whether firm has demonstrated during process validation, that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are to reduce any residual gas and reaction products to defined		Firm has demonstrated during process validation, that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material concerned and these limits are	Firm has not demonstrated during process validation, that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are to reduce any residual gas and reaction products to defined		

		acceptable limits for the type of product or material concerned. b) Ensure whether these limits are incorporated in the specifications		incorporated in the specifications.	acceptable limits for the type of product or material concerned and these limits are not incorporated in the specification s.		
120	6.11.1.16	Ensure that Direct contact between gas and microorganisms is essential; precautions shall, therefore, be taken to avoid the presence of organisms likely to be enclosed in materials such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.		location of material during gaseous sterilization is defined during initial validation.	location of material during gaseous sterilization is not defined during initial validation.		
121	6.11.1.17.	Whether firm has defined humidity and temperature required for the sterilisation process before exposure to the gas.		Firm has defined humidity and temperature required for the sterilisation process before exposure to the gas.	Firm has not defined humidity and temperature required for the sterilisation process before exposure to the gas.		

122	6.11.1.18.	Whether each sterilisation cycle shall be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. Whether the information thus obtained forms part of the batch record		Each sterilisation cycle is monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load and information thus obtained forms part of the batch record	Each sterilisation cycle is not monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load and information thus obtained forms part of the batch record		
123	6.11.1.19.	Whether biological indicators are stored and used according to the manufacturer ’s instructions and their performance checked by positive controls.		Biological indicators are stored and used according to the manufacturer’s instructions and their performance checked by positive controls.	Biological indicators neither stored and used according to the manufacture r’s instructions nor their performance checked by positive controls.		
124	6.11.1.20.	a) Whether for each sterilization cycle, records made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and		Adequate procedure are available and required records are maintained	procedure/re cords are inadequate		

		of the gas concentration is maintained b) Whether the pressure and temperature are recorded on a chart throughout the cycle. c) Whether the records forms part of the batch record					
125	6.11.1.21	a) Whether after sterilisation, the load is stored in a controlled manner in ventilated conditions to allow concentration of residual gas and reaction products to fall to their prescribed levels. b) Whether this process is validated		a)Limit for residual gas is established through validation. b) Procedures available to control concentration of residual gas to acceptable level	a) Limit for residual gas are not established through validation .b) Procedures not available to control concentration of residual gas to acceptable level/Inadequate procedures		
6.11.2. Aseptic processing and sterilisation by filtration:-							
126	6.11.2.2.	Whether operating conditions are maintained to prevent microbial contamination.		Operating conditions are maintained to prevent microbial contamination	Operating conditions are not maintained to prevent microbial contamination		

127	6.11.2.3	Whether careful attention is given to the following in order to maintain the sterility of the components and the product during aseptic processing:- (a) the environment; (b) personnel; (c) critical surfaces; (d) container or closure sterilisation and transfer procedures; (e) the maximum holding period of the product before filling into the final container; and (f) the sterilising filter.		Careful attention is given to the following in order to maintain the sterility of the components and the product during aseptic processing:- (a) the environment; (b) personnel; (c) critical surfaces; (d) container or closure sterilisation and transfer procedures; (e) the maximum holding period of the product before filling into the final container; and (f) the sterilising filter.	Careful attention is not given to the following in order to maintain the sterility of the components and the product during aseptic processing:- (a) the environment ; (b) personnel; (c) critical surfaces; (d) container or closure sterilisation and transfer procedures; (e) the maximum holding period of the product before filling into the final container; and (f) the sterilising filter.		
128	6.11.2.5.	a) Whether firm is having practice of performing a double-filter layer or second filtration through a further sterilised		Firm is having practice of second filtration through a further sterilised microorganism-retaining filter immediately prior to filling and final sterile filtration is carried out as	Firm is having practice of second filtration , However, final sterile filtration is not carried out as close as possible		

		microorganism-retaining filter immediately prior to filling. b) Ensure that the final sterile filtration is carried out as close as possible to the filling point. (Note Owing to the potential additional risks of the filtration method as compared with other sterilisation processes, a double-filter layer or second filtration through a further sterilised microorganism-retaining filter immediately prior to filling may be advisable.)		close as possible to the filling point.	to the filling point.		
129	6.11.2.6	Ensure that the fiber-shedding characteristics of filters are minimal (virtually zero). (Asbestos-containing		The filters used are non fiber-shedding	NA	Asbestos-containing filters are used .The filters used are fibre-sheddin	

		filters shall not be used under any circumstances).					
130	6.11.2.7	Whether integrity of the sterilised filter is verified before use and is confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test.		Integrity of the sterilised filter is verified before use and is confirmed immediately after use.	Records maintained are inadequate	Integrity of the sterilised filter is not verified before use and immediately after use.	
131	6.11.2.7.	Whether the time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter is determined during validation and any significant difference from these during routine manufacturing are noted and investigated.		The time taken to filter a known volume of bulk solution is determined during validation and any significant difference from these during routine manufacturing are noted and investigated.	The time taken to filter a known volume of bulk solution not validated/Not Monitored/significant difference during routine manufacturing are not investigated.		

132	6.11.2.7.	Whether results of integrity test of filter are included in the batch record.		Results of integrity test of filter are included in the batch record.	Results of integrity test of filter are not included in the batch record. Records/Printouts maintained are not legible.		
133	6.11.2.7.	Whether, integrity of critical gas and air vent filters is confirmed after use. Whether firm is having SOPs for , integrity test of these filters and whether frequency for integrity test is defined		Firm is having SOPs for , integrity test of these filters and frequency for integrity test is defined. Integrity of critical gas and air vent filters is confirmed after use.	Firm is not having SOPs for , integrity test of these filters and frequency for integrity test is defined. Integrity of critical gas and air vent filters is not confirmed after use.	Firm is not performing integrity test of critical gas and air vent filters wherein, air/gases are coming in direct contact with sterile product.	
134	6.11.2.7	Whether integrity of other filters is confirmed at appropriate intervals		Integrity of other filters is confirmed at appropriate intervals	Integrity of other filters is not confirmed at appropriate intervals		
135	6.11.2.8.	Ensure that same filter is not used for more than one working day unless such use has been validated.		The filter is not used for more than one working day/ If used, such use has been validated.	The filter is used for more than one working day and such use has not been validated.		
136	6.11.2.9.	Ensure that the filters used do not affect the product either by removing ingredients		The filters used do not affect the product either by removing ingredients from it or by releasing substances into it.	NA	The filters used affect the product by releasing substances into it.	

		from it or by releasing substances into it.					
6.11.3. Isolator technology							
137	6.11.3.2.	Whether sufficient controls/procedures are in place for transfer of materials into and out of the isolators to avoid contamination.		Sufficient controls/procedures are in place for transfer of materials into and out of the isolators to avoid contamination.	controls/procedures are not in place for transfer of materials into and out of the isolators to avoid contamination/controls/procedures are inadequate		
138	6.11.3.3.	Whether background air environment/ classification of isolators is designed and controlled considering the design of the isolator and its application.		Background air environment/ classification of isolators is designed and controlled considering the design of the isolator and its application.	Background air environment / classification of isolators is not designed and controlled considering the design of the isolator and its application.		
139	6.11.3.3.	Whether background air environment/ classification of isolators used for aseptic processing it marinated at least as Grade D.		Background air environment/ classification of isolators is at least Grade D.	Background air environment / classification of isolators is not complies to Grade D.		
140	6.11.3.4.	Whether Isolators are introduced only after appropriate validation. Whether all		Isolator Validation includes following 1. All critical factors of isolator	Isolator validations are inadequate w.r.t parameters considered/R		

		critical factors of isolator technology, for example, the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity are into account while validation		technology such as the quality of the air inside and outside (background) the isolator, sanitisation of the isolator. 2. The transfer process. 3. Isolator integrity.	ecords and frequency is not adequate		
141	6.11.3.5.	Whether monitoring of Isolators is done routinely and Whether frequent leak testing of the isolator and the glove or sleeve system is defined.		Isolators leak testing and gloves leak testing is performed routinely at defined intervals	Isolators leak testing and gloves leak testing is performed but frequency is not defined/Inadequate records	Isolators leak testing and gloves leak testing is not performed	
6.11.4. Blow, Fill-Seal technology :							
142	6.11.4.1.	a) Ensure whether Blow, Fill-Seal equipment used for aseptic production is fitted with an effective Grade A air shower and is installed in at least a Grade C zone, provided that Grade A or B clothing is		Blow, Fill-Seal equipment used for aseptic production includes following considerations, 1. Equipment is fitted with an effective Grade A air shower. 2. Equipment is installed in at least a Grade C zone, provided that Grade A or B clothing is used.	1) Qualifications performed are inadequate. 2) Frequency for monitoring of viable and non viable count is inadequate/Records are not maintained. 3) Suitable garments are not used.	Equipment is not fitted with Grade A air shower.	

		used. b) Ensure whether environment comply with the viable and non-viable limits at rest and the viable limit only when in operation. c) Ensure whether Blow, Fill Seal equipment used for the production of terminally sterilised is installed in at least a Grade D zone.		3. Environment comply with the viable and non-viable limits at rest and the viable limit when in operation.			
143	6.11.4.2.	Whether firm has assured followings for Blow, Fill-Seal technology (a) equipment design and qualification; (b) validation and reproducibility of cleaning-in-place and sterilisation-in-place; (c) background clean room environment in which the equipment is located; (d) operator		Firm has assured followings for Blow, Fill-Seal technology (a) equipment design and qualification; (b) validation and reproducibility of cleaning-in-place and sterilization-in-place; (c) background clean room environment in which the equipment is located; (d) operator training and clothing; and (e) Interventions in the critical zone of the equipment	Firm has not adequately assured followings for Blow, Fill-Seal technology (a) equipment design and qualification ; (b) validation and reproducibility of cleaning-in-place and sterilization-in-place; (c) background clean room environment in which the	Validation of sterilization-in-place is not conducted for aseptic processing	

		training and clothing; and (e) Interventions in the critical zone of the equipment including any aseptic assembly prior to the commencem ent of filling.		including any aseptic assembly prior to the commencement of filling.	equipment is located; (d) operator training and clothing; and (e) Interventions in the critical zone of the equipment including any aseptic assembly prior to the commencem ent of filling.		
7. Personnel :							
144	7.1.	How firm ensures that minimum number of personnel required are present in clean areas; particularly important during aseptic processes.		Number of personnel allowed in clean areas during aseptic processes are defined in procedure and same is simulated during routine media fill	Number of personnel allowed in clean areas during aseptic processes is not defined / not established through media fill/Number of personnel present not matching with established number.		
145	7.2.	Whether all personnel's (including those concerned with cleaning and maintenance) employed in such areas have received initial and regular training in disciplines		All personnel's (including those concerned with cleaning and maintenance) employed in clean areas have received initial and regular training in disciplines relevant to the correct manufacture of sterile products,	Personnel's are not trained and regular retraining are conducted/R ecords are not maintained.		

		relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology.		including hygiene and the basic elements of microbiology.			
146	7.2.	What precautions are taken if outside staff who have not received such training (e.g., building or maintenance contractors) need to be brought in, Whether instruction are given to them and Whether they are supervised		Procedure for entry of outside staff /Personnel/Vendors (e.g., building or maintenance contractors) is in place.	Procedure for entry of outside staff /Personnel/Vendors (e.g., building or maintenance contractors) is not available.		
147	7.3.	Ensure that staff that have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process is not entering in sterile-		Staff engaged in the processing of animal-tissue materials or of cultures of microorganisms are not allowed to enter in sterile-product areas.	Staff engaged in the processing of animal-tissue materials or of cultures of microorganisms are allowed to enter in sterile-product areas./Such observations		

		product areas unless rigorous and clearly defined decontamination procedures have been followed.			noticed during inspection.		
148	7.4.	Whether high standards of personal hygiene and cleanliness are followed in the manufacture of sterile preparations		Personal hygiene and cleanliness are followed in the manufacture of sterile preparations.	Personal hygiene and cleanliness are not adequate		
149	7.4.	Whether personnel's involved in the manufacture of sterile preparations are instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants ; and Whether periodic health checks for such conditions are desirable		Procedure for self deceleration of medical conditions is available and periodic health check-up conducted.	Procedure for self deceleration of medical conditions is not available		

150	7.5.	Whether changing and washing is done following a written procedure designed to minimize the contaminatio n of clean-area clothing or the carry-through of contaminants to clean areas		Changing and washing is done following a written procedure designed to minimize the contamination of clean-area clothing or the carry-through of contaminants to clean areas	Changing and washing is not done as per written procedure		
151	7.5.	Whether the clothing and its quality is appropriate for the process and the grade of the working area. clothing Whether clothing is worn in such a way so as to protect the product from contaminatio n		The clothing and its quality is appropriate for the process and the grade of the working area. clothing is worn in such a way so as to protect the product from contamination.	The clothing and its quality is not appropriate for the process and the grade of the working area. clothing is not worn in such a way so as to protect the product from contaminatio n.		
152	7.6.	Ensure that Outdoor clothing is not brought into changing rooms leading to Grade B and C rooms.		Outdoor clothing is not brought into changing rooms leading to Grade B and C rooms.	Outdoor clothing is brought into changing rooms leading to Grade B and C rooms.		
153	7.6.	Whether clean sterile (sterilised or adequately sanitized) protective garments are provided at each work		Clean sterile (sterilised or adequately sanitized) protective garments are provided at each work session for every worker in a	Clean sterile (sterilised or adequately sanitized) protective garments are not provided at each work session for	Firm has not provided sterile garments for aseptic process operations.	

		session for every worker in a Grade A or B area,		Grade A or B area,	every worker in a Grade A or B area.,		
154	7.6.	Whether gloves are regularly disinfected during operations.		Gloves are regularly disinfected during operations.	Gloves are not regularly disinfected during operations.		
155	7.6.	Whether the masks and gloves are changed at least every working session.		The masks and gloves are changed at least every working session. SOPs for the same are available.	The masks and gloves are not changed at every working session.		
156	7.6.	Whether operators working in Grade A and B zone are wearing sanitised goggles		Operators working in Grade A and B zone are wearing sanitised goggles	Operators working in Grade A and B zone are not wearing sanitised goggles		
157	7.7.	Ensure that wrist-watches, cosmetics and jewellery are not worn in clean areas.		Wrist-watches, cosmetics and jewellery are not worn in clean areas.	Wrist-watches, cosmetics and jewellery are worn in clean areas.		
158	7.8.	Ensure whether clothing required for each grade is as follows: **(i) Grade D:** The hair and, where relevant, beard and moustache shall be covered.		Required clothing as required for the Class/Grade of clean areas is provided	clothing provided is inadequate.		

		Protective clothing and appropriate shoes or overshoes shall be worn. Appropriate measures shall be taken to avoid any contaminatio n from outside the clean area. **(ii) Grade C:** The hair and, where relevant, beard and moustache shall be covered. A one-piece jumpsuit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes shall be worn. The clothing shall shed virtually no fibers or particulate matter. **(iii) Grades A and B:** Entry of personnel into Grade A zone shall be minimized. Headgear shall totally enclose the hair and,					

		where relevant, beard and moustache. A one-piece jumpsuit, gathered at the wrists and with a high neck, shall be worn. The headgear shall be tucked into the neck of the suit. A facemask shall be worn to prevent the shedding of droplets. Sterilized, non-powdered gloves of appropriate material and sterilized or disinfected footwear shall be worn. Trouser bottoms shall be tucked inside the footwear and garment sleeves into the gloves. The protective clothing shall shed virtually no fibers or particulate matter and shall retain particles shed by the body.					

159	7.9.	a) Whether clothing used in clean areas is laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. b) Whether separate laundry facilities for such clothing (Separate laundry facilities for such clothing are desirable) c) Washing and sterilisation operations are done following standard operating procedures.		a) Adequate procedure for washing and sterilisation of garments is available. b) Separate laundry facilities provided for washing of garments c) Washing and sterilization operations are done following standard operating procedures. d) Records for sterilization of garments is maintained	a) Written procedure are not available for washing and sterilization operations. b) Records for sterilization of garments is not maintained		
8. Premises:							
160	8.1.	Whether all premises is designed (as far as possible) to avoid the unnecessary entry of supervisory or control personnel. Whether Grade A and B zone are designed so that all operations can be		a) All premises is designed (as far as possible) to avoid the unnecessary entry of personnel. b) Grade A and B zone are designed so that all operations can be observed from outside.	a) All premises is not designed to avoid the unnecessary entry personnel. B) Provision are not made in order to observe the Grade A and B zone from outside.		

		observed from outside.					
161	8.2.	Whether all exposed surfaces in clean areas are be smooth, impervious and unbroken to minimise the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.		All exposed surfaces in clean areas are be smooth, impervious and unbroken to minimise the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.	All exposed surfaces in clean areas are not rough, permeable and broken		
162	8.3.	a) Ensure that there are no unclean able recesses and a minimum of projecting ledges, shelves, cupboards and equipment are there reduce the accumulation of dust and to facilitate cleaning,. b) Doors shall be carefully designed to avoid unclean able recesses		Premises designed to facilitate easy cleaning	Premises design do not facilitate cleaning		

		(Sliding doors may be undesirable for this reason). c) Ensure whether swing doors opens to the high pressure side and be provided with self-closers					
163	8.4.	Whether the False ceilings is sealed to prevent contamination from the void space above them.		False ceilings is sealed to prevent contamination from the void space above them.	leakage/void space/leakage observed.		
164	8.5.	Whether the Pipes and ducts and other utilities are installed in a way that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Whether Sanitary pipes and fittings are used (threaded pipe connections shall be avoided)		Pipes and ducts and other utilities are installed in a way that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings are used.	Pipes and ducts and other utilities are installed in a way that they do create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings are not used.		

165	8.6.	a) Whether sinks and drains are avoided wherever possible? b) Whether Sinks and drains are excluded from Grade A and B zone where aseptic operations are carried out and shall be avoided wherever possible. c) Where installed, whether they are designed, located and maintained so as to minimise the risks of microbial contaminatio n; they shall be fitted with effective, easily cleanable traps and with air breaks to prevent backflow. d) Whether floor channels are open and easily cleanable and are connected to drains outside the area in a manner that		Following controls available with respect to drains and sinks, 1. Sinks and drains are not present in Grade A and B zone where aseptic operations are carried out. 2. Drains are designed, located and maintained so as to minimise the risks of microbial contamination; 3. Drains are fitted with effective, easily cleanable traps and with air breaks to prevent backflow. 4.Floor channels are open and easily cleanable and are connected to drains outside the area in a manner that prevents the ingress of microbial contaminants. 5) Records for cleaning/sanitisat ion of drains available	1). Sinks/drains are present in Grade A and B zone where aseptic operations are carried out. 2) Records for cleaning/sani tisation of drains not available 3) Drains present is grade C/D area are not of suitable design as per requirements		

		prevents the ingress of microbial contaminant.					
166	8.7.	Whether changing rooms are designed as airlocks and used to provide physical separation of the different stages of changing to minimise microbial and particulate contamination of protective clothing.		Changing rooms are designed properly and provides physical separation of the different stages of changing	Changing rooms are not adequately designed/physical separation not provided at different stages of changing		
167	8.7.	Whether changing rooms are flushed effectively with filtered air.		Changing rooms are flushed with filtered air.	Changing rooms are not flushed with filtered air.		
168	8.7.	Whether the final stage of the changing room, in the at rest state, is the same Grade as the zone into which it leads. (The use of separate changing rooms for entering and leaving clean areas is sometimes desirable)		Last change room (in the at rest state), is of the same Grade as the zone into which it leads. The separate changing rooms for entering and leaving clean areas is in place.	Last change room (in the at rest state), is not of the same Grade as the zone into which it leads.		

169	8.7.	Whether hand washing facilities are provided only in the first stage of the changing rooms. (In general hand washing facilities shall be provided only in the first stage of the changing rooms.		Hand washing facilities are provided only in the first stage of the changing rooms.	Hand washing facilities are not provided.		
170	8.7.	Ensure that there shall not be a change of more than one Grade between airlocks or passages and changing rooms, i.e., a Grade D passage can lead to a Grade C airlock, which leads to a Grade B changing room, which leads to a Grade B clean room.		There is no change of more than one Grade between airlocks or passages and changing rooms.	There is change of more than one Grade between airlocks or passages and changing rooms.		
171	8.7.	Whether Changing rooms are of a sufficient size to allow for ease of changing.		Changing rooms are of a sufficient size to allow for ease of changing.	Changing rooms are not sufficient size to allow for ease of changing.		

172	8.7.	Whether Changing rooms are equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room		Changing rooms are equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room	Changing rooms are not equipped with adequate sized mirrors.		
173	8.8.	Ensure that Airlock doors are not opened simultaneously. Whether interlocking system and a visual or audible or both warning system are operated to prevent the opening of more than one door at a time.		Door interlock system available /Airlock doors can not be opened simultaneously.	Airlock doors can be opened simultaneously.		

174	8.9.	a) Whether filtered air supply is used to maintain a positive pressure and the airflow relative to surrounding areas of a lower Grade under all operational conditions; it shall flush the area effectively. b)Whether adjacent rooms of different Grades have a pressure differential of approximately 10 to 15 Pascal (guidance value). (The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial		a) Filtered air supply is used to maintain a positive pressure and the airflow relative to surrounding areas of a lower Grade under all operational conditions; b) Adjacent rooms of different Grades have a pressure differential of approximately 10 to 15 Pascal.	a) Filtered air supply is not used to maintain a positive pressure and the airflow relative to surrounding areas of a lower Grade under all operational conditions; b) Adjacent rooms of different Grades not have a pressure differential of approximately 10 to 15 Pascal.		

		materials or products.)					
175	8.9.	Whether the decontamination of the facilities and the treatment of air leaving a clean area is done as necessary for some operations		Decontamination of the facilities and the treatment of air leaving a clean area is done (wherever required).	Decontamination of the facilities and the treatment of air leaving a clean area is not done wherever required.		
176	8.10.	Whether firm has demonstrated that airflow patterns do not present a contamination risk; Whether, care is taken to ensure that particles from a particle generating person, operation or machine are not conveyed to a zone of		1. Airflow patterns study conducted to demonstrate that airflow do not present a contamination risk and particle generating person, operation or machine are not conveyed to a zone of higher product risk is demonstrated.	Air flow pattern study not conducted OR Not done adequately OR records are not maintained OR No evidences to establish the flow pattern		

		higher product risk.					
177	8.11.	Whether a warning system is operated to indicate failure in the air supply.		Warning system is present to indicate failure in the air supply.	Warning system is not in place to indicate failure in the air supply.		
178	8.11.	Whether Indicators of pressure differentials are fitted between areas where this difference is important, and whether the pressure differentials are regularly recorded and failure alarmed.		Indicators of pressure differentials are fitted between areas where this difference is important, and the pressure differentials are regularly recorded and failure alarmed.	Indicators of pressure differentials are not fitted between areas and the pressure differentials are not regularly recorded and failure not alarmed.		
179	8.12.	Whether consideration is given to restricting unnecessary access to critical filling areas e.g., Grade A filling zones, by means of a physical barrier.		Physical barriers is in place to restricting unnecessary access to critical filling areas e.g., Grade A filling zones.	Physical barriers is not in place to restricting unnecessary access to critical filling areas e.g., Grade A filling zones.		
9. Equipment:							

180	9.1	Ensure that a conveyor belt is not passing through a partition between a Grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilised (e.g., in a sterilising tunnel).		No conveyor belt is passing through a partition between a Grade A or B clean area and a processing area of lower air cleanliness.	Conveyor belt is passing through a partition between a Grade A or B clean area and a processing area of lower air cleanliness.		
181	9.2.	Whether equipment used for processing sterile products are chosen so that it can be effectively sterilised by steam or dry heat or other methods, whenever possible,		Equipment used for processing sterile products are selected considering that it can be effectively sterilised by steam or dry heat or other methods, whenever possible,	Equipment used for processing sterile products can not be effectively sterilised by steam or dry heat or other methods, whenever possible,		
182	9.3.	Whether equipment fittings and services are designed and installed (as far as possible) so that operations, maintenance and repairs can be carried out outside the clean area.		Equipment fittings and services are designed and installed (as far as possible) so that operations, maintenance and repairs can be carried out outside the clean area.	Equipment fittings and services are designed and installed in such way that operations, maintenance and repairs can not be carried out outside the clean area.		

183	9.3.	Whether equipment that has to be taken apart for maintenance are re-sterilised after complete reassembly, wherever possible.		Equipment taken apart for maintenance are re-sterilised after complete reassembly, wherever possible.	Equipment taken apart for maintenance are not re-sterilised after complete reassembly, wherever required		
184	9.4	Ensure that when equipment maintenance is carried out within a clean area, clean instruments and tools are used and the area is cleaned and disinfected again, where appropriate, before processing recommences ,		clean instruments /tools are used for equipment maintenance in clean area, and the area is cleaned and disinfected again after maintenance activity.	clean instruments /tools are not used for equipment maintenance in clean area/The area is not cleaned and disinfected again after maintenance activity.		
185	9.5	Whether all equipment such as sterilisers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems are subjected to validation and planned maintenance;		All equipment such as sterilisers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems are subjected to validation and planned maintenance.	All equipment are not subjected to validation/planned maintenance.		

		Whether their return to use is approved					
9.6. Water-treatment plants and distribution systems							
186	9.6.	Whether water-treatment plants and distribution systems are designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality		Water-treatment plants and distribution systems are designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality	Water-treatment plants and distribution systems are not suitably designed/constructed/maintained		
187	9.6.	Ensure that water-treatment plants and distribution systems are not operated beyond their designed capacity.		Water-treatment plants and distribution systems are not operated beyond their designed capacity.	Water-treatment plants and distribution systems are operated beyond their designed capacity.		
188	9.6.	Whether consideration is given to include a testing programme in the maintenance of a water system.		Testing programme after maintenance of a water system is available	Testing programme after maintenance of a water system is not available		

189	9.6.	Whether water for injection is produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g., by constant circulation at a temperature above 70 °C or not more than 4 °C		Water for injection is produced, stored and distributed in a manner which prevents the growth of microorganisms. Constant recirculation at temperature above 70 degree Celsius is maintained	Water for injection is not produced, stored and distributed in a manner which prevents the growth of microorganisms./recirculation at temperature above 70 degree Celsius is not maintained for WFI Loop		
10. Finishing of sterile products:-							
190	10.1.	Whether containers are closed by appropriately validated methods.		Procedure used for closing of Containers is validated	Procedure used for closing of Containers is not validated		
191	10.1.	a) Whether containers closed by fusion, e.g., glass or plastic ampoules, are subjected to 100 percent integrity testing. b) Whether samples of other containers are checked for integrity according to appropriate procedures		1a) Containers closed by fusion(e.g., glass or plastic ampoules) are subjected to 100 percent integrity testing. b)Samples of other containers are checked for integrity according to appropriate procedures	a) Containers closed by fusion (e.g., glass or plastic ampoules) are not subjected to 100 percent integrity testing. b) Procedure for integrity testing not available/Procedures are inadequate.		

192	10.2.	Whether crimping of the cap is, performed as soon as possible after stopper insertion.		Crimping of the cap is, performed as soon as possible after stopper insertion.	Crimping of the cap is not performed immediate after stopper insertion.		
193	10.3.	Ensure whether the equipment (used for crimping) is located at a separate station equipped with adequate air extraction. (the equipment used to crimp vial caps can generate large quantities of non-viable particulates)		The equipment (used for crimping) is located at a separate station and is equipped with adequate air extraction.	The equipment (used for crimping) is not located at a separate station /Not equipped with adequate air extraction.		
194	10.4.	a) Whether Vial capping is undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. b) Where latter approach is adopted, ensure that vials are protected by Grade A conditions up to the point of leaving the aseptic		a) Vial capping/Sealing is undertaken as an aseptic process using sterilised caps b) When clean process outside the aseptic core is used vials are protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials are protected with a Grade A air supply until	Provisions made and procedures adopted for Vial capping/Seal ing are inadequate		

		processing area, and thereafter stoppered vials are e protected with a Grade A air supply until the cap has been crimped.		the cap has been crimped.			
195	10.5.	a) Ensure whether vials with missing or displaced stoppers are rejected prior to capping b) Ensure whether appropriate technology is be used to prevent direct contact with the vials and to minimise microbial contaminatio n, where human intervention is required at the capping station,.		a) Vials with missing / displaced stoppers are rejected prior to capping b) No human intervention at capping station,.	a) Vials with missing /displaced stoppers are not rejected prior to capping b) Direct human intervention at capping station,.		
196	10.7.	Whether containers sealed under vacuum are tested for maintenance of that vacuum after an appropriate, predetermine d period.		Containers sealed under vacuum are tested for maintenance of that vacuum after an appropriate/ predetermined period.	Containers sealed under vacuum are not tested for maintenance of vacuum.		

197	10.8.	Whether filled containers of parenteral products are inspected individually for extraneous contaminatio n or other defects.		Procedures available for inspection. Filled containers of parenteral products are inspected individually for extraneous contamination or other defects.	Procedures used for inspection is inadequate. Filled containers of parenteral products are not inspected individually for extraneous contaminatio n or other defects.		
198	10.8.	When inspection is carried out visually, Whether is done under suitable and controlled conditions of illumination and background.		Inspection is carried out visually, under suitable and controlled conditions of illumination and background.	conditions of illumination /background is not adequate for inspection activity.		
199	10.8.	Whether operators doing the inspection have passed regular eyesight checks, using personal corrective lenses (e.g., spectacles or contact lenses) as required,		Regular eyesight checks conducted for operators doing the inspection.	Operators doing the inspection have not passed regular eyesight checks./Repe at eyesight checks not conducted.		
200	10.8.	Whether operators doing the inspection are allowed frequent breaks from inspection		Operators doing the inspection are allowed frequent breaks from inspection	Operators doing the inspection are not allowed frequent breaks from inspection		

201	10.8.	Ensure that where other methods of inspection are used, the process are validated		methods used (other than visual inspection) for inspection are used are validated	methods used (other than visual inspection) for inspection are not validated		
202	10.8.	Whether the performance of the equipment (used for inspection) is checked at intervals. And Whether results are recorded.		The performance of the equipment (used for inspection) is checked at intervals and results of the same are recorded.	The performance of the equipment (used for inspection) is not checked at intervals./Records not available		

INSPECTION CHECKLIST FOR GMP INSPECTION OF FOR MANUFACTURING OF PHARMACEUTICAL PRODUCTS CONTAINING HAZARDOUS SUBSTANCES SUCH AS SEX HORMONES, STEROIDS (ANABOLIC, ANDROGENIC) OR CYTOTOXIC SUBSTANCES AS PER PART- PART III OF SCHEDULE-M							
Sr. No.	**Sch M Reference**	**Particulars**	**2**	**1**	**0**	**X**	**Observation**
1.0 Introduction:-							
1	1.2.	Whether the production of products containing hazardous substances (Sex Hormones, Steroids (Anabolic, Androgenic) Or Cytotoxic Substances) is conducted in separate, dedicated, self-contained facilities. (These self-contained facilities may be in the same building as another facility but shall be separated by a physical barrier and have e.g., separate entrances, staff facilities and air handling systems). Whether the extent of the separation from adjacent facilities and	Separate, self-contained facility with dedicated building and staff provided for production of products containing hazardous substances.	Self-contained facilities separated by a physical barrier with separate entrance, air handling systems and dedicated staff facilities is provided. Firm has performed risk assessment for sharing common services	Self-contained facilities separated by a physical barrier. However, staff facilities are common. Risk assessment not performed for sharing common services	Hazardous substances (Sex Hormones, Steroids (Anabolic, Androgenic) Or Cytotoxic Substances) were found manufactured in a same facility used for manufacture of other products.	

		sharing of common services is determined by risk assessment.					
2	1.4.	Whether the firm has provided following control measures for effective operation of a facility.		Required control measures are available.(Kindly specify the control measures implemented by the firm)	control measures are inadequate	No control measures in place	
		(a) Appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and product protection;					
		(b) Manufacturing process controls including adherence to SOPs;					
		(c) Appropriately designed Environmental Controls Systems (ECS) or HVAC; (d)					

		extraction systems;					
		(e) Personal Protective Equipment (PPE);					
		(f) Appropriate de-gowning and decontamination procedures;					
		(g) Industrial hygiene (monitoring staff exposure levels);					
		(h) Medical surveillance (monitoring staff exposure levels); and					
		(i) Administrative controls.					
2. Risk assessment:-							
3	2.1.	a) Whether risk assessments is carried out to determine the potential hazards of all products to operators and to the environment.		Comprehensive risk assessments is carried out covering all points	Risk assessments conducted by firm is inadequate	No risk assessment conducted to define adequacy of control measures	
		b) Whether risk assessments covers phases of the product production and control cycles, from manufacture of the API to distribution of					

		the finished product,.					
		c) Whether risk assessments applicable to the environment includes airborne contamination as well as liquid effluent contamination .					
	2.2.	Whether the design and operation of the facility is done considering the risk assessment determining that the products or materials being handled pose a risk to the operators or to the public or to the environment,					
	2.4.	Whether the risk assessment has take into account occupational health and safety requirements for OELs in the work environment					
4. Personal Protection Equipment and breathing air systems:-							

4	4.1.	Whether the fundamental design principle for a facility and its production equipment is to provide product containment and operator protection.		Design of the facility and production equipment are well design to provide product containment and protection to operator.	Design of the facility and production equipment are not well design to provide product containment and protection to operator and no other control measures are adopted.		
5	4.1.	Whether , operator protection are provided, in case of the facility and equipment design is not providing adequate product containment,					
6	4.1.	Whether, PPEs are available for handling of a spillage or non-routine incident could cause a hazardous situation.		PPEs are available	PPEs are not available		
7	4.1.	In case of the facility and equipment design is not providing adequate product containment, whether it is specified in the material safety data sheet, operators are protected		Appropriate methods are available and effective implemented	Appropriate methods are not available/ inadequate	There is risk to harm the operator observed.	

		from exposure with an appropriate method, such as by wearing-					
		(a) Flash-spun, high-density polyethylene fiber material suits or impervious washable protective suits. Integral hoods may be required depending on the respirator type used;					
		(b) Flash-spun, high-density polyethylene fiber material shoes, lower leg covers or cleanable boots;					
		(c) Suitable single-use, disposable gloves. Double gloves shall be worn where direct active contact with the product cannot be avoided. Gloves shall be taped or sealed on to the protective suit sleeves; and					
		(d) Respirator eye and face					

		protection with associated breathing air systems.					
8	4.2.	Where breathing air systems are used, ensure whether these are provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility.		Breathing system are provided with safe breathing air	In appropriate breathing system.	Breathing system are not available	
	4.2.	Whether personnel are appropriately trained and assessed in the use of breathing air systems, before they enter the area.		The person are trained for handling the breathing system	The person are not trained.		
	4.2.	Whether the breathing air systems comprises a protective face mask, which forms an integral part of a protective suit.		Face mask was found provided with breathing system	face mask was not provided with breathing system/ face mask with breathing system is not an integral part of protective suite.		
9	4.2.	Whether breathing air systems is as per any of the systems described below-		Breathing air systems provided are adequate considering the	Breathing air systems provided are inadequate considering the products handled	Breathing system are not available	

		(a) A central air supply system which connects to the operator's facemask by means of flexible hoses and quick coupling sockets, also called an Airline Respirator (AR). The air connection shall incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply shall be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high pressure fan or an air compressor. If an air compressor is used, it shall be of the oil-free type or have suitable oil removal filters fitted;		products handled			

		(b) A Self-Contained Breathing Apparatus (SCBA) or Powered Air Purifying Respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;					
		(c) For zones with lower contamination levels, a half-mask High Efficiency Particulate Air filter (HEPA) cartridge respirator of N95-type paper filter mask may be acceptable.					

10	4.3.	Whether the selection of the respirator type is based on the relationship between the accepted OEL and the respirator certified Protection Factor (PF).		Respirator are selected based on accepted OEL and certification for Protection Factor (PF) is available	OEL not considered while selecting respirator and/ OR certification not available		
11	4.4.	Whether the air supplies are filtered through a final filter, which is HEPA filter rated as an H13 filter according to European norms.		Air supplies are filtered through a final filter, which is HEPA / H13	Air supplies are filtered through a final filter, which is HEPA / H13 , However, monitoring (leak test frequency) is inadequate.	Air supplies are filtered through a final filter, which is HEPA / H13	
12	4.4.	Ensure whether the supply of breathing air into the face masks or protective suit or both results in the interior of the mask and suit being at a positive pressure relative to the facility environment.		The design of protective suite is appropriate and suits was found at positive pressure.	The design of protective suite is not appropriate and suits was found at positive pressure.		
13	4.5.	Whether Central breathing air supply systems have a one hundred percent back-up system in the event of the main system		backup system provided for continuous working and change over in automatic.	No backup system provided/ backup system is provided for definite time frame/ changeover is not automatic.		

		failing. (This could be in the form of a gas bottle system with at least five minutes supply. Change over from the normal supply to the back-up supply shall be automatic).					
14	4.5.	Whether the system have a monitoring system and send alarm signals to a permanently manned location in the following situations, namely:-		The system is monitored and having alarm system in on of any situation	no monitoring and alarm system exists.		
		(i) failure of main air supply;					
		(ii) temperature out of specification (OOS);					
		(iii) humidity OOS;					
		(iv) carbon dioxide (CO2) OOS;					
		(v) carbon monoxide (CO) OOS; and					
		(vi) sulfur dioxide (SO2) OOS.					

15	4.6	Whether the breathing air is filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications of ISO standards and European norms.		Series of filters are provided as per requirement of ISO standard or European norms	ISO standard or European norms are not followed		
16	4.7.	a) Where air is delivered through a central system the piping, Ensure that it does not causes any contamination to be liberated into the air stream.	Piping of central air system is made-up of SS and easy to clean. No accumulation of dust observed.	Piping of central air system is made-up of material which is easy to clean and will not be able to cause contamination.	Piping is formed dirty and not easy to clean.		
		b) Ensure whether the final filters are as close as possible to the operator connection points.		Final filter is close to operator	final filter not found close/ inappropriate		
		c) Ensure whether operator hose connection to the air supply is a dedicated connection specific to the breathing air system to		System in place	system not found adequate.		

		avoid inadvertent connection to a different gas system.					
5. Environmental protection:-							
17	5.1. & 5.3	a) Ensure that neither the product nor its residues is allowed to escape into the atmosphere or to be discharged directly to normal drainage systems. b) Whether the external atmosphere and the public in the vicinity of the facility are protected from possible harm from hazardous substances. c)Whether the effluent is treated before being discharged to a municipal drain, If liquid effluent poses a safety or contamination risk,		The firm has provided the effective exhaust system and ETP.	The exhaust system and ETP is not effective. .	No system provided to protect the enjoinment.	
18	5.4.	Whether exhaust air filtration ensures environmental protection		Exhaust air filtration systems are adequately designed and	Exhaust air filtration systems inadequately designed/maintained n		

				maintained to ensure environmental protection			
6. Facility layout:-							
19	6.1.	Whether the premises is designed and constructed to prevent the ingress or egress of contaminants.		Facility is designed/ constructed and maintained to prevent the contaminants.	Facility is poorly design.		
		Whether, attention is paid to the level of containment provided by the equipment while drawing up the facility design,		The firm has taken all the necessary measures during qualification/ validation while installing the equipment inline with design of facility.	The firm has not taken any adequate measures.		
20	6.2.	Whether the link between the interior and exterior of the premises is through airlocks [Personnel Airlock (PAL), Material Airlock (MAL)], changing rooms, pass boxes, pass-through hatches, decontaminati		Interior and exterior of the premises is linked through suitable airlocks [Personnel Airlock (PAL), Material Airlock (MAL)], changing rooms, pass boxes, pass-	Controls provided (Airlocks, changing rooms, pass boxes, pass-through hatches, decontamination devices etc.) are inadequate		

		on devices, etc.		through hatches, decontamination devices, etc.			
21	6.2.	Whether these entry and exit doors for materials and personnel have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.		Entry and exit doors for materials and personnel have an interlock mechanism /other appropriate system to prevent the opening of more than one door at a time.	Entry and exit doors for materials and personnel do not have an interlock mechanism / appropriate system to prevent the opening of more than one door at a time.		
22	6.3.	Whether the changing rooms have an arrangement with a step-over- bench.		Cross/step-over-benches are provided in hanging rooms	Cross/step-over-benches are not provided in hanging rooms/Inadequate		
23	6.3.	Whether the changing facilities on the exit side incorporates showers for the operators		Exit change rooms provided with showers and procedures are in place for use of shower	Exit change rooms are not having provision of showers / procedures are inadequate		
24	6.4.	Whether the premises are laid out and designed so as to facilitate the required pressure		Required pressure cascades and containment is maintained	Required pressure cascades / containment is in adequate.		

		cascades and containment		as per the requirement considering the products handled			
25	6.5.	Whether the premises and equipment are appropriately designed and installed to facilitate cleaning and decontamination		Premises and equipment are appropriately designed and installed to facilitate cleaning and decontamination	Premises and equipment do not facilitate effective cleaning /decontamination		
26	6.6.	Whether the manufacturing site and buildings are described in sufficient detail by means of plans and written explanations to ensure that the designation and conditions of use of all the rooms are correctly shown.		Detailed layout plans are available	Detailed layout plans not available/are inadequate.		
27	6.7.	Whether the flow of people and products is clearly marked on the layouts and plans.		Layout plan for man and material movement is available and it is adequate.	Layout plan for man and material movement is not available/inadequate.		

28	6.10.	Whether the facility is a well-sealed structure with no air leakage through ceilings, cracks or service areas		Facility is well-sealed structure with no air leakage through ceilings, cracks or service areas	Air found leaking through facility		
29	6.11.	Whether the areas of the facility where exposed product presents a risk are maintained at a negative air pressure relative to adjacent area.		Areas where product is exposed is maintained at a negative air pressure relative to the adjacent area and differential pressure is monitored	Areas where product is exposed is not maintained at a negative air pressure relative to the adjacent area.		
7. Air-handling systems :-							
30	7.1.	Whether the HVAC systems are appropriately designed, installed and maintained to ensure protection of product, personnel and the environment.		HVAC system are provided with required filters units with coiling and heating coil system.	HVAC system is not appropriate to provided ambient temperature and filter system for stopping cross contamination.	HVAC system not provided	
31	7.2. (i)	Ensure that there is no direct venting of air to the outside;		No direct venting of air to the outside.	Direct venting of air to the outside.		
32	7.2. (ii)	a) Whether air-conditioning or ventilation		Areas where product is exposed is	Areas where product is exposed is not maintained at a		

		results in a negative pressure relative to the outside.		maintained at a negative air pressure relative to the adjacent area and differential pressure is monitored	negative air pressure relative to the adjacent area.		
		b) Ensure whether air pressure is such that there is no uncontrolled flow of air between the work area and the external environment;		Requisite pressure differential is maintained and monitored.	Requisite pressure differential is not maintained /monitored.		
33	7.2. (iii)	a) Whether appropriate air pressure alarm systems are provided to warn of any pressure cascade reversal or loss of design pressure status.		Air pressure alarm systems are provided	Air pressure alarm systems are not provided		
		b) Whether appropriate design, alert and action limits are in place.		Alert and action limits are in place.	Alert and action limits are not in place.		
		c) Whether system redundancies are in place to respond appropriately to pressure cascade failure;		System found in place.	System not found in place.		

34	7.2. (iv)	Whether the starting and stopping of the supply and exhaust air fan is synchronized so that the premises remain at a negative pressure during start-up and shut-down;		Facility, procedure and records are available	Facility/Procedure/records are not available/Inadequate.		
35	7.2. (vi)	Whether visual indication of the status of room pressures is provided in each room;		Pressure differential Indicators are provided for each room.	Pressure differential Indicators are not provided/Inadequate.		
36	7.2. (vii)	Whether Air is exhausted to the outside through HEPA filters and not re-circulated except to the same area, and provided that a further HEPA filtration stage is applied to the return air.	Single-pass air-handling systems with no recirculation are provided,	a) HEPA filter provided for exhaust of air to the outside b) In case of recirculation system, return air is passed though HEPA filter and re-circulated to the same area.	a) HEPA filter provided for exhaust of air to the outside; however monitoring is inadequate. b) In case of recirculation system, return air is not passed though HEPA filter before recirculate in same area.	a) HEPA filter are not provided for exhaust of air to the outside b) In case of recirculation system, return air from critical processing area is recirculate to other areas	
37	7.2.(ix)	a) Whether exhaust air or return air is filtered through a safe-change or bag- in-bag-out filter housing.		safe-change or bag- in-bag-out filter provided.	safe-change or bag- in-bag-out filter not provided.		

		b) Whether the filter housing contains pre-filters and HEPA filters and whether both of which are removable with the safe bagging system.					
38	7.2. (x)	Whether changing rooms are supplied with air filtered to the same standard as that for the work area they serve;		Changing rooms are supplied with air filtered to the same standard as that for the work area they serve;	Changing rooms are not supplied with air filtered to the same standard as that for the work area they serve;		
39	7.2. (xi)	a) Whether airlocks, pass-through hatches, etc., have supply and extract air to provide the necessary air pressure cascade and containment.		Provision made to maintained necessary air pressure cascade and containment.	Provision made are inadequate.		
		b) Whether the final, or containment perimeter, airlock or pass[1]through hatch bordering on an external or non-good manufacturing practices area is at a positive pressure relative to the environment, to prevent the		Change room/air lock connecting to external or non-GMP area is at a positive pressure relative to the environment to prevent the ingress of contamina	Change room/air lock connecting to external or non-GMP area is not at a positive pressure relative to the environment.		

		ingress of contaminants to the facility;		nts to the facility;			
40		If the operators' garments are contaminated with dust, whether the operators leaving the containment area pass through a decontaminati on system e.g., air showers or a mist shower system, to assist with removing or controlling dust particles on their garments and whether operators follow this route before de-gowning to use the ablutions or canteen facilities.		Decontami nation system e.g., air showers or a mist shower system is provided and followed.	Decontamination system e.g., air showers or a mist shower system is not provided/ Inadequate.		
		c) Whether all garments leaving the facility for laundering are safely bagged.		Procedure available	Procedure not available/Inadeq uate		
		d) Whether appropriate means for protecting laundry staff		Procedure available	Procedure not available/Inadeq uate		

		and prevention of contamination of other garments from non-hazardous facilities are in place.					
41	7.3.	Whether the appropriate measures are taken to prevent airflow from the primary packing area (through the conveyor "mouse hole") to the secondary packing area, If required, (Note.- This could be overcome by having a pass-through chamber over the "mouse hole" which is maintained at a negative pressure to both primary and secondary packing. This principle can be applied to other situations where containment from two sides is required.)		Adequate measures are provided to prevent airflow from the primary packing area (through the conveyor "mouse hole") to the secondary packing area.	Adequate measures are provided to prevent airflow from the primary packing area (through the conveyor "mouse hole") to the secondary packing area.		

42	7.4.	Whether the HEPA filters in the supply air system are terminally mounted (where possible), to provide protection against back-flow cross-contamination in the event of failure in the supply airflow.		HEPA filters in the supply air system are terminally mounted in critical area.	HEPA filters in the supply air system are not terminally mounted in critical area.		
43	7.5	Specify whether firm is using biosafety cabinets, isolation systems or glove boxes as a means for containment and operator protection. (Note :-In some cases consideration can be given to the use of biosafety cabinets, isolation systems or glove boxes		The firm has provided biosafety cabinets/ isolation systems / glove boxes/ any other suitable measure and control for containment and operator protection. (Please specify control measure provided by the firm).	Control measures for containment and operator protection are inadequate.		
44	7.6.	Whether a system description including schematic drawings detailing the filters and their		Requisite records/documents available.	Requisite records/documents not available/Inadequate.		

		specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications is available with firm.					
45	7.8	Whether Consideration is given to providing an emergency power supply, e.g., diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.		Suitable power backup system provided.	Suitable power backup system not provided/Inadequate.		
46	7.9.	Whether the principles of airflow direction, air filtration standards, temperature, humidity and related parameters are ensured and the filtration is consistent with the zone concepts and product protection required		All parameters are ensured during the validation and periodically monitored.	All parameters are not considered during the validation and not monitored periodically/Inadequate.		
8. Air-Handling Units (AHU):-							
47	8.1.	Whether the decision to use return air or re-circulated air		Risk assessment is performed	Risk assessment is not performed/Inadequate		

		is made on the basis of a risk assessment.					
48	8.2.	Where a full fresh-air or single-pass system is used, use of an energy recovery wheel could be considered.		Suitable mechanism available.	Suitable mechanism not available/Inadequate		
		In such condition ensure that there is no potential for air leakage between the supply air and exhaust air as it passes through the wheel and the relative pressures between supply and exhaust air systems is such that the exhaust-air system operates at a lower pressure than the supply system.					
49	8.3.	Whether the risk management principles are applied to address the potential of cross-contamination where energy wheels are used.		Risk assessment is performed	Risk assessment is not performed/Inadequate		

50	8.4.	If return air is to be re-circulated, Whether it is passed through a safe change filtration system before being introduced back into the supply AHU. (In such the return air fan could form part of the AHU; however, the safe change filter shall be a dedicated unit)		Adequate safe change filtration system provided.	Safe change filtration system not provided/Inadequate.		
51	8.5	a) Whether the starting and stopping of the supply and exhaust air fans and associated system ventilation fans is synchronised such that the premises retain their design pressure and flow relationships during start[1]up and shut-down.		System found in place.	System found not in place/Inadequate.		
		b) Whether processing stops when the fans are not running.					

		c) Ensure whether that this fan interlock sequence applies if any fan fails, to ensure that there is no airflow reversal in the system					
9. Safe change filter housings:-							
52	9.1.	Whether safe change or bag-in-bag-out filter housings are suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed.		safe change or bag-in-bag-out filter system adequately designed and maintained.	safe change or bag-in-bag-out filter system are in adequately designed/maintained.		
53	9.1.	Whether the Safe change filter bypass arrangement is provided .					
54	9.2.	a) Whether the final filters on the safe change unit are HEPA filters with at least an H13 classification according to European norms filter standards.					
		b) Whether air pre-filtration filters are					

		provided for dusty return to prolong the life of the HEPA filters.					
		c) Ensure whether pre-filtration filters are also removable through the bag-in-bag out method.					
55	9.3.	Whether two banks of HEPA filters in series are provided to provide additional protection if the first filter fail, for exhaust systems where the discharge contaminant is considered particularly hazardous.		Two banks of HEPA filters in series are provided for exhaust systems where the discharge contaminant is considered particularly hazardous.	Two banks of HEPA filters in series are not provided for exhaust systems where the discharge contaminant is hazardous.		
56	9.4.	a) Whether all filter banks are provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters		Filter banks are provided with pressure differential indication gauges.	Filter banks are not provided with pressure differential indication gauges.		
		b) Whether Connection to these gauges are of copper or stainless steel and not plastic tubing, which could		Connection to these gauges are of copper or stainless steel	Connection to these gauges are made up of plastic tubing.		

		perish causing a contamination hazard.					
		c) Whether the tube connections on the filter casing are provided with stopcocks, for safe removal or calibration of gauges.		Tube connections on the filter casing are provided with stopcocks, for safe removal or calibration of gauges.	Tube connections on the filter casing are not provided with stopcocks.		
57	9.5	Whether monitoring of filters is done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.		Monitoring of filters is done at regular intervals	Monitoring of filters is not done at regular intervals/Inadequate.		
58	9.6.	Whether firm has installed computer based data monitoring systems to monitor filter condition. (Computer based data monitoring systems may be installed)		System are adequate (if installed)	NA	NA	

59	9.7.	Whether the filter pressure gauges are marked with the clean filter resistance and the change-out filter resistance.		Pressure limits and marking is provided.	Pressure limits and marking is not provided/Inadequate.		
60	9.8.	Whether firm has performed installed filter leakage tests in accordance with ISO standards and Whether access ports (downstream) are provided for performing installed filter leakage tests.		Filter leakage tests are performed in accordance with ISO standards and records are available.	Filter leakage tests are not performed in accordance with ISO standards/records are not available/Inadequate.		
61	9.9.	Whether the exhaust air fan on a safe change filter system are located after the filters so that the filter housing is maintained at a negative pressure (Alternatively, an independent booster fan system can be used, with appropriate shut-off dampers).		Requisite system in place.	Requisite system is not in place/Inadequate.		

62	9.11.	Whether exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, are passed through safe change filter housings before being exhausted to the atmosphere.		Requisite system in place.	Requisite system is not in place/Inadequate.		
63	9.12.	Whether all exhaust points outside the building are located as far as possible from air entry points and exit points are at a high level to minimise the possibility of re-entrainment of exhaust air.		Exhaust points adequately designed and maintained.	Exhaust points not adequately designed/ maintained.		
64	9.13	a) Where excessively dust-laden air is handled, whether a dust collector or bag house is considered with the dust collector being located in an enclosed room maintained at		Dust collector found located in an enclosed room maintained at a negative pressure	Room used for placing dust collector is not maintained at a negative pressure		

		a negative pressure.					
		b) Whether Access control, maintenance staff, PPE and breathing air systems are provided to protect the operators during removal of dust from the collector bins.		Required Access control, maintenance staff, PPE and breathing air systems are provided to protect the operators during removal of dust from the collector bins.	Provision made are inadequate.		
65	9.14.	a) Whether portable vacuum cleaners and portable dust collectors are fitted with H13 HEPA filters.		portable vacuum cleaners /portable dust collectors are fitted with H13 HEPA filters.	Portable vacuum cleaners /portable dust collectors are not fitted with H13 HEPA filters.		
		b) Whether these types of units are emptied and cleaned in a room which is under negative pressure relative to the environment.		Such equipment are emptied cleaned in a room which is under negative pressure relative to the environment.	Room is not maintained at negative pressure relative to the environment.		

		c) Whether Personnel are provided with suitable PPE.		Personnel are provided with suitable PPE.	Personnel are not provided with suitable PPE.		
66	9.15.	Whether records of the safe disposal of all contaminated filters and dust is kept.		Records of the safe disposal of all contaminated filters and dust is maintained.	Records of the safe disposal of contaminated filters and dust is not maintained.		
10. Personnel decontamination systems:-							
67	10.1.	Whether a means of preventing contaminants from leaving the facility on the garments of personnel are provided, If required, (This could be in the form of an air shower; mist shower, water shower or appropriate device).		Air shower; mist shower, water shower or appropriate device is provided at exit of facility for preventing contamination the garments of personnel	appropriate devices not provided at exit of facility for preventing contamination the garments of personnel/Devices provided are inadequate		

68	10.2.	a) Ensure whether an air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g., from the sides of the airlock) in order to dislodge dust particles. And whether Air extraction grilles (e.g., at low level) draws the air away and return it to the filtration system. b) Ensure whether air showers are used are correctly designed to effectively extract dust. whether Air filtration of the supply air and return or exhaust air complies with the same filtration standards as used in the manufacturing facility.		Adequate designed air shower systems provided as per requirements	Air shower systems provided are inadequate		
69	10.3.	Whether flushing devices similar to air or mist showers are provided at material exits		Adequate flushing devices are provided at material exits to assist with removing	flushing devices are not provided at material exits /Inadequate devices provided		

		to assist with removing contaminants.		contaminants.			
70	10.4.	Whether wet mist or fog decontamination systems for operators are employed for deactivating contaminants on the operators' garments or causing contaminants to adhere to the garments so that they are not easily liberated.		Adequate systems available for decontamination of used the garments	Systems available for decontamination of used the garments are inadequate.		
11. Effluent treatment:-							
71	11.1.	Whether liquid and solid waste effluent are handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.		Effective effluent treatment plant is present along with established procedures and maintained all the record including risk assessment.	procedures are not well define and in adequate for ETP	No ETP Plant is available	
72	11.2.	Whether all effluent is disposed of in a safe manner and the means of disposal are documented.		Disposal of all type of effluent is recorded and documented properly	Documentation is not available/ inadequate		
73	11.2.	Whether external contractors are used (if any) for		Agreement and certification is available	agreement/ certification is not available		

		effluent disposal have certification authorising them to handle and treat hazardous products.					
12. Maintenance:-							
74	12	Whether regular maintenance is carried out, to ensure that all parameters remain within specified tolerances to ensure the efficient and safe operation of a facility handling hazardous materials		Preventive Manitenance schedule are established and followed	Preventive Maintenance schedule are not available		
13. Qualification and validation:-							
75	13	Whether system qualification and validation are carried out.		All the system are qualified and validate	Qualification and validation performed are inadequate.	Qualification and validation are not performed for critical process equipment/processes	

INSPECTION CHECKLIST FOR GMP INSPECTION OF ORAL SOLID DOSAGE FORMS MANUFACTURING SITES (TABLETS AND CAPSULES) AS PER PART-VIII OF SCHEDULE-M

Sr. No.	Sch. M Ref.	Particulars	2	1	0	X	Observation
	1	**General:-**					
1	1.1	Pls specify the areas of dust generation and mechanism involved in controlling the dust. Wherever required, enclosed dust control manufacturing systems shall be employed.		Enclosed dust control manufacturing systems provided OR Dust collectors were found installed in granulation, coating, compression and powder filling area to control the dust generated during manufacturing.	Dust control mechanism provided by the firm is inadequate.		
2	1.2	Whether Effective air extraction systems, with discharge points situated to avoid contamination of other products and processes are provided. (Filters shall be installed to retain dust and to protect the factory and local environment)		Air extraction systems with suitable discharge points which prevent contamination of other products and processes are provided.	Air extraction systems provided by the firm is inadequate. Filters are not installed to retain dust.		

				Suitable filters are installed to retain dust.			
3	1.3	Ensure that Wooden equipment are not used. Whether metal detector is provided. Whether Screens, sieves, punches and dies is examined for wear and tear or for breakage before and after each use.		1)Wooden equipment are not used. 2) Metal detector is provided. 3) The Screens, sieves, punches and dies are examined for wear and tear or for breakage before and after each use and records maintained.	2) Metal detectors are not provided/In adequate 3) The Screens, sieves, punches and dies are not examined for wear and tear or for breakage before and after each use/records not maintained.	1) Wooden equipment are used	
4	1.4	Whether all ingredients of dry product are sifted before use unless the quality of the input material can be assured. Whether sifting is carried out at dedicated areas		Procedure for sifting available (if required) and dedicated area provided for sifting.	Procedure for sifting not available/dedicated area provided for sifting.		
5	1.5	Whether environmental conditions of pressure differentials between rooms are regularly monitored and any deviation is brought to the immediate attention to the Production and Quality assurance departments.		Environmental conditions of pressure differentials between rooms are regularly monitored and	Environmental conditions of pressure differentials between rooms are not regularly monitored		

				records are maintained. Procedure for deviation reporting available and records are maintained	and records are not maintained /procedure for deviation reporting is not available		
6	1.6	Whether Particular care is being taken to ensure that any vacuum, compressed air or air-extraction nozzles are kept clean and that there is no evidence of lubricants leaking into the product from any part of the equipment.		Procedure for cleaning and maintenance are available and no lubricants was found leaking into the product from any part of the equipment.	Procedure for cleaning and maintenance of vacuum, compressed air or air-extraction nozzles are not available /inadequate.	There is evidence of non food grade lubricants leaking into the product from part of the equipment	
7	1.7	Whether suitable measures are taken to ensure that dust cannot move from one cubicle to another, where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct Oral Solid Dosage (OSD) manufacturing site.	Only one product is handles at time.	Different products are manufactured at the same time, in different areas or cubicles with sufficient control measures	Different products are manufactured at the same time, in different areas or cubicles with inadequate control measures	Different products are manufactured at the same time in same areas / cubicles without sufficient control measures and there is possibility /evidence of mix-up and cross-contamination	

8	1.9	Whether corridor is maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure		Pressure differential is maintained as per requirement to avoided the cross contamination.	Pressure differential of Corridor/cubicles is inadequately maintained considering operations performed OR records are not maintained		
9	1.10	Whether Highly potent products is manufactured under a pressure cascade regime that is negative relative to atmospheric pressure.		Negative pressure cascade regime is maintained for manufacturing of highly potent products and records are maintained.	Pressure cascade regime maintained for manufacturing of highly potent products is inadequate/ Records are not maintained.	Required negative Pressure cascade regime is maintained for manufacturing of highly potent products.	
10	1.11	Whether the pressure cascade for each facility is individually assessed according to the product handled and level of protection required	The pressure cascade for each facility shall be individually assessed according to the product handled and level of protection required.	Pressure cascade Is maintained considering the products manufactured and records are maintained.	Pressure cascade Is maintained considering the products manufactured and records are maintained.		

11	1.14	Whether the limits for the pressure differential between adjacent areas is such that there is no risk of overlap in the acceptable operating range, e.g., 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in the failure of the pressure cascade, where the first room is at the maximum pressure limit and the second room is at its minimum pressure limit.	Pressure differential between adjacent areas is well defined and monitored using BMS with alarm system	Pressure differential between adjacent areas is well defined and monitored	Pressure differential between adjacent areas inadequate/ Not monitored		
12	1.17	Whether the pressure control and monitoring devices used is calibrated and qualified		Devices used for control and monitoring of pressure are calibrated and records are maintained.	Devices used for control and monitoring of pressure are not calibrated /records not maintained.		
13	1.17	Whether pressure control devices is linked to an alarm system set according to the levels determined by a risk analysis		Pressure control devices are linked to an alarm system set according to the levels determined by a risk analysis	Pressure control devices are not linked to an alarm system /risk analysis not done		
14	1.19, 1.20.	Whether, airlocks with suitable differential pressure cascade regimes (cascade/sink/ bubble) are provided to limit cross-contamination		Airlocks with suitable differential pressure regimes are provided	Differential pressure regimes is not adequate (considering products handled)		

15	1.21.	There shall be a method to indicate if both doors to airlocks are open at the same time, or alternatively these shall be interlocked. The determination of which doors shall be interlocked shall be the subject of a risk assessment study.		Door are interlocked OR method to indicate if both doors to airlocks are open at the same time is provided	Door are not interlocked OR method to indicate if both doors to airlocks are open at the same time is not provided		
16	1.22	If Central dust extraction systems are used, ensure that the same is interlocked with the appropriate air-handling systems, to ensure that they operate simultaneously.		Central dust extraction systems used are interlocked with the appropriate air-handling systems, to ensure that they operate simultaneously.	Central dust extraction systems used are not interlocked with the appropriate air-handling systems		
17	1.24	Whether dust extraction Systems are designed to prevent dust flowing back in the opposite direction in the event of component failure or airflow failure.		Dust extraction Systems are designed to prevent dust flowing back in the opposite direction in the event of component failure or airflow failure & Records demonstrating the same is available	Dust extraction Systems are not designed to prevent dust flowing back in the opposite direction in the event of component failure or airflow failure.		

18	1.25.	Whether, adequate room pressure differential indication are provided so that each critical room pressure can be traced back to ambient pressure, in order to determine the room actual absolute pressure. (Room pressure indication gauges shall have a range and graduation scale which enables the reading to accuracy, as appropriate) Whether, normal operating range, alert and action limits are defined and displayed at the point of indication.		Room pressure indication gauges of appropriate range and graduation scale are provided. Normal operating range, alert and action limits of room pressure differential are defined and displayed. Monitoring records are available	Room pressure indication gauges are not installed/ are not of appropriate range and graduation. Normal operating range, alert and action limits of room pressure differential are not defined displayed at the point of indication. Monitoring records are not available /Inadequate		
19	1.26	What type of measures like Material Pass-Through-Hatches (PTH) or Pass Boxes (PB) provided by firm for separating two different zones.		Dynamic Pass Boxes are provided between the room of different classes. Static pass boxes are used between the rooms of same class.	The firm has not provide the dynamic pass box between rooms of different classes	The firm has provided the single door hatch for transfer of material.	

20	1.27	Whether temperature and relative humidity is controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products and provide a comfortable environment for the operator, where necessary.		Temperature and relative humidity is controlled as per the requirements and it is monitored and records maintained	Temperature and relative humidity is not controlled/ monitored/records not maintained		
21	PART XIII (3.4)	Whether the manufacture of effervescent and soluble tablets is carried out in air-conditioned and dehumidified areas.		Air-conditioned and dehumidifier provided in a way to minimize the risk for contamination from dehumidifier air. Temperature and relative humidity is controlled, monitored and records maintained	Air-conditioned and dehumidifier not provided/Temperature and relative humidity is not controlled/ monitored/records not maintained/ dehumidifier may be a source of contamination.		
22	1.28	Whether Maximum and minimum room temperatures and relative humidity are appropriate and alert and action limits on temperatures and humidity are defined and monitored.		Maximum and minimum room temperatures and relative humidity are appropriate. Alert and action limits for	Maximum and minimum room temperatures and relative humidity found out of specified limits. Alert and action limits are		

				temperatures and humidity are defined and monitored.	defined OR temperatures and relative humidity monitored.		
23	1.30	Whether Cubicles or suites, in which products requiring low relative humidity are processed, have well sealed walls and ceilings and also separated from adjacent areas with higher relative humidity by means of suitable airlocks.		Required measures /controls are available for area where products requiring low relative humidity are processed,	Controls ensures for handling of products requiring low relative humidity are inadequate		
24	1.35	Ensure that Air filters are not installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth.		Air filters are not installed immediately downstream of humidifiers	Air filters shall are installed immediately downstream of humidifiers		
25	1.41	Whether Dust extraction ducting is designed with sufficient transfer velocity to ensure that dust is carried away and does not settle in the ducting and whether Periodic checks is performed to ensure that there is no build-up of the dust in the ducting.		Dust extraction ducting is designed to ensure that dust is carried away and does not settle in the ducting and Periodic checks are performed to ensure that there is no build-up of the dust in the	Dust extraction system is adequate/ Periodic checks are not performed to ensure that there is no build-up of the dust in the ducting/Records of clening are not maintained		

				ducting/Records of cleaning are maintained			
26	1.43	Whether Airflow direction is chosen to ensure that the operator does not contaminate the product and operator is not put at risk by the product.		Airflow direction is appropriate to ensure that the operator does not contaminate the product and operator is not put at risk by the product.	Airflow direction is inappropriate to ensure that the operator does not contaminate the product and operator is not put at risk by the product.		
27	1.45	Whether firm has performed and maintained records of airflow visualisation smoke tests to show correct flushing of the rooms.		Airflow visualisation smoke tests are performed are records are maintained	Airflow visualisation smoke tests are not performed.		
28	1.46	Whether firm has provided additional steps, such as handling the products in glove boxes or using barrier isolator technology when dealing with particularly harmful products.		Firm has provided additional protections such as handling the products in glove boxes/ using barrier isolator technology while dealing with particularl	Firm has not provided additional protections such as handling the products in glove boxes/ using barrier isolator technology for handling of harmful products.		

				y harmful products.			
29	1.47	Whether Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and is provided with adequate filtration to prevent contamination of the ambient air.		Exhaust air discharge points for exhaust air from dust extraction systems are provided with adequate filtration to prevent contamination of the ambient air.	Exhaust air discharge points for exhaust air from dust extraction systems are not provided with adequate filtration to prevent contamination of the ambient air.		
30	1.51	Whether the dust-slurry is removed by a suitable means, e.g., a drainage system or waste removal contractor, when wet scrubbers are used.		Procedure for handling of waste/ dust-slurry from scrubbers is available and records for cleaning are maintained	Procedure for handling of waste/ dust-slurry from scrubbers is not available and records for cleaning are not maintained		
31	1.55	Whether fumes are removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers).		Wet scrubbers /dry chemical scrubbers (deep-bed scrubbers) are available , wherever required	wet scrubbers /dry chemical scrubbers (deep-bed scrubbers) are not provided for removal of		

					obnoxious fumes		
32	1.59.	Ensure that there is no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.	No recirculation of air, All systems are once through mode	Sufficient precautions are taken to ensure that there is no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.	Precautions are taken are inadequate		
33	1.60.	In case use of recirculated air,Ensure that that HEPA filters are installed in the supply air stream to remove contaminants and thus, prevent cross-contamination (HEPA filters may not be required where the air handling system is serving a single product facility and there is evidence that cross-contamination would not be possible)		HEPA filters are installed in the supply air stream for recirculation air systems	HEPA filters are not installed in the supply air stream for recirculation air systems		
34	1.63	Where HEPA filters are terminally mounted, ensure that they are not connected by flexible ducting		Terminally mounted HEPA filters are not connected by flexible ducting	Terminally mounted HEPA filters are connected by flexible ducting		

35	1.64	Ensure that Air containing dust from highly toxic processes or solvents or flammable vapours is not recirculated to the HVAC system.		Once through air circulation system is provided for handling of the air containing dust from highly toxic processes or solvents or flammable vapours.	Air containing dust from highly toxic processes or solvents or flammable vapours is recirculated to the HVAC system.		
36	1.65	Whether adequate airlocks, such as personnel airlocks (PAL), material airlocks (MAL), change rooms and passages are provided to protect passage between different cleanliness conditions and whether these have supply and extract air systems as appropriate.		Adequate airlocks with supply and extract air systems are provided to protect passage between different cleanliness conditions	Adequate airlocks are not provided to protect passage between different cleanliness conditions		
37	1.66	Whether areas such as airlocks, change rooms and passages, are designed so that the required pressure cascades can be achieved.		Airlocks, change rooms and passages, are having required pressure cascades and same is monitored	Airlocks, change rooms and passages, are not having required pressure cascades and same is not monitored		
38	1.67	Whether firm has prepared and maintained detailed diagrams depicting pressure cascades, air flow directions and flow routes for personnel and materials.		Firm has prepared and maintained detailed diagrams depicting pressure	Firm has not prepared/maintained detailed diagrams depicting pressure cascades, air		

				cascades, air flow directions and flow routes for personnel and materials.	flow directions and flow routes for personnel and materials.		
39	1.68	Whether personnel and materials are moving from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone; if moving from a lower cleanliness zone to a higher cleanliness zone whether changing or decontamination procedures are followed.		Procedure available for moving of personnel and materials from a lower cleanliness zone to a higher cleanliness zone with provision for changing or decontamination.	Procedure not available/Inadequate.		
40	1.69	Whether classification of final change room ("at rest") is same as that of classification of area into which it leads.		classification of final change room ("at rest") is same as that of classification of area into which it leads.	classification of final change room ("at rest") is not same as that of classification of area into which it leads.		
2.0 Sifting, mixing and granulation							
41	2.10	Whether mixing, sifting and blending equipment are fitted with dust extractors or in a dedicated area for each operation unless operated as a closed system.		mixing, sifting and blending operation carried out in closed system/ dedicated area/equipment fitted	mixing, sifting and blending operation not carried out in dedicated area and equipment not fitted		

				with dust extractor.	with dust extractor.		
42	2.20	Whether residues from sieving operations are examined periodically for evidence of the presence of unwanted materials.		Procedure and records are available	Procedure and records are not available		
43	2.30	Whether critical operating parameters like time and temperature for each mixing, blending and drying operation are specified in a Master Formula, monitored during processing, and recorded in the batch records.		Critical operating parameters monitored during processing and recorded in the batch records.	Critical operating parameters not monitored/ not recorded in the batch records./Inadequate.		
44	2.40	Whether filter bags fitted to fluid-bed-drier are used for different products, without being washed in between use.		Dedicated Filter bags provided for each product / Filter bag are used for different products are washed in between use and cleaning procedure is validated.	Dedicated Filter bags not provided for each product and Filter bag are used for different products without being washed in between use/Cleaning procedure for washing of filter bag is not validated.		
45	2.40	Whether for certain highly potent or sensitising products, bags specific to one product only are used.		Dedicated Filter bags provided for each highly potent or sensitising products.	Dedicated Filter bags are not provided for highly potent or sensitising products.		

46	2.40	Whether Air entering the drier is filtered.		Drier are fitted with air filter.	Drier are not fitted with air filter.		
47	2.40	Whether steps are taken to prevent contamination of the site and local environment by dust in the air leaving the drier due to close positioning of the air-inlets and exhaust.		Procedure and controls are available.	Procedure and controls are not available/Inadequate.		
48	2.50	Whether granulation and coating solutions are made, stored and used in a manner which minimises the risk of contamination or microbial growth.		Procedure and controls are available.	Procedure and controls are not available/Inadequate.		
3.0 Compression (Tablets)							
50	3.10	Whether each tablet compressing machine is provided with effective dust control facilities to avoid cross contamination.		Effective dust control system provided.	Effective dust control system not provided/Inadequate.		
51	3.10	Whether the compression machine is installed in separate cubicles unless the same product is being made on each machine or unless the compression machine itself provides its own enclosed air-controlled environment.		Compression machine is installed in separate cubicles/Same product is handled on each machine/Compression machine with enclosed air-controlled environment provided.	NA	Compression machines are installed in same cubical and different products are handled at a time.	
52	3.20	Whether suitable physical, procedural and labelling arrangements are made to prevent mix up of materials, granules and tablets on compression machinery.		Procedure and controls measures are adequate.	Procedure and controls measures not provided/Inadequate.		

53	3.30	Whether accurate and calibrated weighing equipment are readily available and used for in-process monitoring of tablet weight variation and whether used procedures are capable of detecting out of limits tablets.		Calibrated weighing equipment is available for in-process monitoring of tablet weight variation. Procedures used are capable of detecting out of limits tablets.	Weighing equipment is not available/Not calibrated/Procedures used are Inadequate.		
54	3.40	Whether sufficient individual tablets are examined at fixed intervals to ensure that a tablet from each compression station or from each compression point has been inspected for suitable Pharmacopoeial parameters like "appearance", "weight variation", "disintegration", "hardness", "friability" and "thickness" at commencement of each compression run and in case of multiple compression points in a compression machine and whether the results are recorded as part of the batch documentation.		Procedure and records are available.	Procedure and records are not available/Inadequate.		
55	3.50	Whether Tablets are de-dusted, preferably by automatic device and monitored for the presence of foreign materials besides any other defects.		Tablets Deduster available/ Tablets are Dedusted. Procedure for the inspection/ monitoring of Tablets for presence of foreign	Tablets are not Dedusted/Inadequate. Procedure for the inspection/ monitoring of Tablets for presence of foreign materials and other		

				materials and other defects is available and records are maintained.	defects is not available/records are not maintained.		
56	3.60	Whether Tablets are collected into clean, labelled containers.		Tablets are collected into clean, labeled containers.	Tablets are not collected into clean, labeled containers/Inadequate.		
57	3.70	Whether rejected or discarded tablets are isolated in identified containers and their quantity recorded in the Batch Manufacturing Record.		Rejected/discarded tablets stored in identified containers and their quantity found recorded in BMR.	Rejected/discarded tablets are not stored in identified containers /their quantity not found recorded in BMR		
58	3.80	Whether in-process controls are employed to ensure that the products remain within specification.		Procedure for in-process controls are employed to ensure that the products remain within specification.			
59	3.80	Whether during compression, samples of tablets are taken at regular intervals of not greater than thirty minutes to ensure that they are being produced in compliance with specified in-process specification.		In-process specifications available and In-process testing done at frequency not more than thirty minutes	In-process specifications not available /Frequency of In-process testing done at frequency more than thirty minutes	IPQC lab not available / IPQC tests not conducted	

4.0 Coating (Tablets)							
61	4.10	Whether air supplied to coating pans for drying purposes is filtered air and of suitable quality.		Filtered air of suitable quality is supplied to coating pans.	Air supplied to coating pans is not filtered/not of suitable quality		
62	4.10	Whether coating area is provided with suitable exhaust system and environmental control (temperature and humidity) measures.		Coating area is having suitable exhaust system and environmental conditions (temperature and humidity) are controlled and monitored	Coating area is not having suitable exhaust system / environmental conditions (temperature and humidity) are not controlled/ monitored		
63	4.20	Whether coating solutions and suspensions are made afresh and used in a manner which minimise the risk of microbial growth and their preparation and use is documented and recorded.		Procedure and controls are available.	Procedure and controls are not available/Inadequate.		
5.0 Filling of Hard Gelatin Capsule							
65	5.00	Whether empty capsules shells are stored under conditions which ensure their safety from the effects of excessive heat and moisture		Empty capsules shells are stored under required environmental conditions and records available	Empty capsules shells are stored under under required environmental conditions /monitoring records not available		
66	6.00	Printing (Tablets and Capsules)					
67	6.10	What measure have been taken to avoid product mix-up during any printing of tablets and capsules.		Measure taken to avoid product mix-up	Measure taken to avoid product mix-up		

				during printing of tablets /capsules are adequate.	during printing of tablets /capsules are inadequate.		
68	6.10	Whether sufficient measure have been taken when different products or different batches of the same product are printed simultaneously and whether operations are adequately segregated.		Printing operations are segregated / sufficient measure are taken when different products or different batches of the same product are printed simultaneously	Adequate segregation/ controls not provided OR Measure taken are inadequate.		
69	6.10	Whether edible grade colours and suitable printing ink is used for such printing.		Edible grade colours used for printing	NA	Non-edible grade colours are used for printing	
70	6.20	Whether tablets and capsules are approved by Quality Control After printing, before release for packaging or sale.		Tablets /capsules are approved by Quality Control after printing/Records maintained	Tablets /capsules are not approved by Quality Control /Records not maintained		
7.0 Packaging (Strip and Blister)							
72	7.10	Whether all "rogue" tablets, capsules or foils from packaging operation are removed before a new packaging operation is commenced when using automatic tablet and		Procedures and records are available	Procedures and records not available /Inadequate		

		capsule counting, strip and blister packaging equipment.					
73	7.10	Whether there is an independent recorded check of the equipment before a new batch of tablets or capsules is handled.		Procedures and records are available	Procedures and records not available /Inadequate		
74	7.20	Whether uncoated tablets are packed on equipment designed to minimise the risk of cross-contamination.		Equipment /Procedure and controls used are adequate	Equipment/ Procedure and controls used are not adequate		
75	7.20	Whether packaging of uncoated tablets is carried out in an isolated area when potent tablets or Beta lactum containing tablets are being packed.		Packaging of uncoated tablets of potent tablets or Beta lactum containing tablets is performed in an isolated areas	Packaging of uncoated tablets of potent tablets or Beta lactum containing tablets is not performed in an isolated areas		
76	7.30	Whether the strips coming out of the machine are inspected for defects such as misprint, cuts on the foil, missing tablets and improper sealing.		Procedures and records are available	Procedures and records not available /Inadequate		
77	7.40	Whether integrity of individual packaging strips and blisters is subjected to vacuum test periodically to ensure leak proofness of each pocket strip and blister and records maintained.		Integrity of packaging strips and blisters is checked periodically and records maintained.	Integrity of packaging strips and blisters is not checked periodically /Inadequate procedure used/records not maintained.		

78	PART XIII (3)	Whether tablet production department are divided into following sections. (a) Mixing, Granulation and Drying section; (b) Tablet compression section; (c) Packaging section (strip or blister machine wherever required); and (d) Coating section (wherever required).		Tablets manufacturing are is divided in to requisite sections	No such segregation is found		
79	PART XIII (3.1)	Whether the following electrically operated equipment are provided for the manufacture of compressed tablets and hypodermic tablets- **(a) Granulation-cum-Drying section-** (1) Disintegrator and sifter;(2) Powder mixer;(3) Mass mixer or Planetary mixer or Rapid mixer granulator; (4) Granulator wherever required; (5) Thermostatically controlled hot air oven with trays (preferably mounted on a trolley) or Fluid bed dryer; and (6) Weighing machines; **(b) Compression section-** (1) Tablet compression machine, single or multi punch or rotatory;(2) Punch and dies storage cabinets; (3) Tablet de-duster; (4) Tablet Inspection unit or belt; (5) Dissolution test apparatus wherever required; (6) In-process testing equipment like single pan electronic balance, hardness tester, friability and disintegration test apparatus; and (7) Air-conditioning and dehumidification arrangement (wherever necessary).		The firm has provided requisite equipment and area.	The firm has not provided requisite equipment and area/Inadequate.		

		(c) Packaging section- (1) Strip or blister packaging machine; (2) Leak test apparatus (vacuum system); (3) Tablet counters (wherever applicable); and (4) Air-conditioning and dehumidification arrangement (wherever applicable). **Area-** A minimum area of sixty square meters for basic installation and twenty square meters for ancillary area is recommended for un-coated tablets **(d) Coating section-** (1) Jacketed kettle stainless steel container or any other appropriate material (steam, gas or electrically heated for preparing coating suspension); (2) Coating pan (Stainless steel); (3) Polishing pan (where applicable);(4) Exhaust system (including vacuum dust collector);(5) Air conditioning and Dehumidification Arrangement; and (6) Weighing machine.					
80	PART XIII (3.2)	Whether the firm has provided minimum additional area of thirty square meters for coating section for basic installation and ten square meters for ancillary area		Requisite are is provided.	Requisite area is not provided/Inadequate.		

81	PART XIII (4)	Whether Oral powder manufacturing area provided with the following equipment and areas.- (1) Disintegrator;(2) Mixer (electrically operated);(3) Sifter;(4) Stainless steel vessels and scoops of suitable sizes;(5) Filling equipment; and (6) Weighing machine. Area- A minimum area of thirty square meters is provided to allow for the basic installations. Where the additional room is provided for blending		The firm has provided requisite equipment and area.	The firm has not provided requisite equipment and area/Inadequate.		
82	PART XIII (4)	Whether Capsules production are provided with following equipment. (1) Mixing and blending equipment (electrically or power driven); (2) Capsule filling units; (3) Capsules counters (wherever applicable); (4) Weighing machine; (5) Disintegration test apparatus; and (6) Capsule polishing equipment. Area- Whether minimum area of twenty-five square meters for basic installation and ten square meters for ancillary area is provided.		The firm has provided requisite equipment and area.	The firm has not provided requisite equipment and area/Inadequate.		

Note: 1. Manufacture of Hypodermic tablets shall be conducted under aseptic conditions and applicable part of schedule M shall be referred. 2. In the case of pessaries/Suppositories manufactured by granulation and compression, the requirements as indicated under "item 3 of Tablet" of PART XIII shall be provided.

INSPECTION CHECKLIST FOR GMP INSPECTION OF ORAL LIQUIDS (SYRUPS, ELIXIRS, EMULSIONS AND SUSPENSIONS) AS PER PART-IX OF SCHEDULE-M

Sr. No.	**Sch. M Reference**	**Particulars**	**2**	**1**	**0**	**X**	**Observation**
2.0 Building and Equipment							
1	2.2	Whether firm is using closed system for processing and transfer to protect the product from contamination.		The firm has provided the closed system for processing and transfer of drugs.	Systems provided for product transfer/manufacture are inadequate	The firm is manufacturing and transferring the material in open environment.	
2	2.2	Whether the production areas is effectively ventilated with filtered air where the products or open clean containers are exposed.		Filtered air provided where the products or open clean containers are exposed.	Facility provided for providing clean air is inadequate.	Filtered air is not provided	
3	2.3	Whether the manufacturing area have entry through double door air-lock facility.		Double door air-lock provided for entry in to manufacturing area.	Double door air-lock not provided for entry in to manufacturing area/ no filtered air provided in double airlock system		
4	2.3	Whether firm has provided provision of “fly catcher’ or ‘air curtain’ to prevent entry of flies.		“fly catcher’ or ‘air curtain’ are provided.	“fly catcher’ or ‘air curtain’ are not provided/Inadequate.		

5	2.4	Whether drains are of adequate in size and have adequate traps, without open channels and prevent back flow. Whether drains are shallow to facilitate cleaning and disinfecting.		Adequate number of GMP Drains provided. Procedure and records for cleaning and disinfection of drains are available.	GMP Drains not provided/Inadequate. Procedure/records for cleaning/disinfection of drains are not available.		
6	2.5	Whether the production area is cleaned and sanitised at the end of every production process.		Procedure and records are available.	The area is not found clean. Procedure/records are not available/Inadequate.		
7	2.6	Whether Tanks, containers, pipe work and pumps are designed and installed so that they can be easily cleaned and sanitised.		Tanks, containers, pipe work and pumps are designed and installed in a way to facilitate cleaning and sanitization. Records for the cleaning available.	Tanks, containers, pipe work and pumps are not designed/ installed to facilitate cleaning and sanitization/ Records for the cleaning not available.		
8	2.6	Whether Equipment design prevents accumulation of residual microbial growth or cross-contamination.		Equipment designed and installed in a way to prevents accumulation of residual microbial growth or cross-	There are difficult to clean part in equipment which may leads to accumulation of residual microbial growth or cross-		

				contamination. Further, The firm has find hard to clean area.	contamination.		
9	2.7	Whether stainless steel or any other appropriate material is being used for parts of equipment's coming in direct contact with the products.		MOC of contact part is of SS 316L/SS316 or any other appropriate material with proper justification.	MOC of contact part is not made up SS316 or 316 L OR proper justification not available for using other material	The material of construction of the equipment is not suitable for product handled. e.g., found rusted, cracked, leaking etc.	
10	2.8	Whether arrangements for cleaning of containers, closures and droppers are made with the help of suitable machines or devices equipped with high pressure air, water and steam jets.		Suitable machines/ devices provided for cleaning of containers, closures and droppers etc. Procedure and records for the cleaning are available. Cleaning procedure employed are validated.	Machines/devices provided are inadequate. Procedure/records for the cleaning are not available. Cleaning procedure employed are not validated.		
11	2.9	Whether the quality of materials received in bulk tankers is checked before they are transferred to bulk storage tanks.		Procedure and records are available.	Procedure/records are not available/Inadequate.		

12	2.1	Whether care is taken when transferring materials via pipelines ensuring that they are delivered to their correct destination.		Procedure and records are available.	Procedure/records are not available/Inadequate.		
13	2.11	Whether the furniture used is smooth, washable and made of stainless steel or any other appropriate material which is scratch proof, washable and smooth.		Furniture used is smooth, washable and made of stainless steel or any other appropriate material which is scratch proof, washable and smooth.	Furniture made of material which sheds the particles.		
3.0 Purified Water							
14	3.1	Whether the chemical and microbiological quality of purified water used is specified and monitored routinely. Whether the microbiological evaluation of purified water includes testing for absence of pathogens and not exceeding 100 cfu per ml.		Quality of purified water meets the requirement of IP/BP/USP & Schedule M and records found maintained	Testing frequency/ records are inadequate.	Purified water used for the manufacturing without testing/ Data in respect of its quality is falsified.	
15	3.2	Whether there is any written procedure for operation and maintenance of the purified water system.		Procedure and records are available.	Procedure/records are not available/Inadequate.	Purified water system is ill maintained and found in unhygienic condition	
16	3.2	When sanitising agens are used , whether flushing is done to ensure that the sanitising agent has been effectively removed after		Adequate control available and sanitizatio	Control are inadequate / sanitization records are	No control available to avoid microbial	

		any chemical sanitisation of the water system.		n records are maintaine d	not maintained	proliferati on.	
17	3.2	If, sanitising agens are used , whether flushing is done to ensure that the sanitising agent has been effectively removed after any chemical sanitisation of the water system.		Procedure and records are available.	Procedure /records are not available/In adequate.		
4.0 Manufacturing							
18	4.1	Whether manufacturing personnel wears non fiber shedding clothing to prevent contamination of the product, wherever required.		Non fiber shedding clothing is provided for personnel entering in manufactu ring area.	Inadequate clothing provided is entering in manufacturi ng area.		
19	4.2	Whether materials which likely to shed fiber like gunny bags, or wooden pallets are carried out into the area where products or cleaned containers are exposed.		Materials that may shed fiber are not taken Into the area where products or cleaned containers are exposed.	Materials that may shed fiber are taken Into the area where products or cleaned containers are exposed.		
20	4.3	Whether firm has provided appropriate stirrer during filling to maintain the homogeneity of emulsion.		Stirrer provided to maintain the homogene ity of emulsion during filling .	Stirrer not provided/Us ed to maintain the homogeneit y of emulsion during filling .		
21	4.3	Whether mixing and filling processes is specified and monitored.		Mixing and filling processes is specified /monitored and	Mixing and filling processes not specified /not monitored/		

				records maintained	records not maintained		
22	4.3	Whether special care is taken at the beginning of the filling process after stoppage due to any interruption and at the end of the process to ensure that the product is uniformly homogenous during the filling process.		Procedure available ensuring uniformity of emulsion during the filling process.	Adequate procedure not for available ensuring uniformity of emulsion during the filling process.		
23	4.4	Whether the primary packaging area have an air supply which is filtered through level-3 filters [Production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g., EN779 G4 plus F8 plus EN1822 H13 filters) (for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable].		Primary packaging area is having air supply filtered through level-3 filters	Air supplied to Primary packaging area is not filtered through level-3 filters		
24	4.4	Whether the temperature of the primary packaging area is maintained below 30°C.		Temperature of the primary packaging area is maintained below 30°C and records available.	Temperature of the primary packaging area is not maintained below 30°C/ Records not available.		
25	4.5	Whether maximum period of storage and storage conditions are specified in the Master Formula when the bulk product is not immediately packed and maximum period of storage time of a product in the bulk stage is validated.		Hold time of bulk is validated and storage conditions and acceptable hold time	Hold time of bulk is not validated / storage conditions acceptable hold time is not specified/H		

				is mentioned. bulk is used within validated time/Records are maintained.	old time not monitored while using bulk.		
26	PART XIII (2)	The following equipments are provided. (1) Mixing and storage tanks preferably of Stainless steel or any other appropriate material; (2) Jacketed Kettle or Stainless steel tank (steam, gas or electrically heated); (3) Portable stirrer (Electrically operated); (4) A colloid mill or suitable emulsifier (Electrically operated); (5) Suitable filtration equipment (Electrically operated); (6) Semi-automatic or automatic bottle filling machine; (7) Pilfer proof cap sealing machine; (8) Water distillation unit or deionizer; and (9) Clarity testing inspection units.		Requisite equipments are provided.	Requisite equipments are not provided/Inadequate.		
27	PART XIII (2)	Whether minimum area of thirty square meters for basic installation and ten square meters for ancillary area is provided.		Requisite area is provided	Requisite area is not provided/Inadequate		

INSPECTION CHECKLIST FOR GMP INSPECTION OF EXTERNAL PREPARATIONS (CREAMS, OINTMENTS, PASTES, EMULSIONS, LOTIONS, SOLUTIONS, DUSTING POWDERS AND IDENTICAL PRODUCTS) AS PER PART-X OF SCHEDULE-M

Sr. No.	Sch M Reference	Particulars	2	1	0	X	Observation
1.	1	Whether entrance to the area where topical products are manufactured is through a suitable airlock.		Double door air-lock provided for entry in to manufacturing area.	Double door air-lock not provided for entry in to manufacturing area.		
2.	1	Whether the insectocutors are installed outside the airlock.		insectocutors are installed at the entrance.	insectocutors are not provided.		
3.	2	Whether HVAC system is in place.Whether the air to this manufacturing area is filtered through suitable filters and air-conditioned.		HVAC system with suitable air filter and air conditon is available.	HVAC system with suitable air filter not provided/required temperature condtion not maintained.		
5.	3	Whether the area is fitted with an exhaust system of suitable capacity to effectively remove vapours, fumes, smoke or floating dust particles.		Suitable Exhaust sytem is provided	Suitable Exhaust sytem is not provided		
6.	4	Whether equipment used is designed and maintained to prevent the product from being accidentally contaminated with any foreign matter or lubricant.		Equipments are found suitable for intended use.	Equipments are not found suitable for intended use/Inadequatelty maintained.		
7.	5	Whether suitable cleaning equipment and material is used in the process of cleaning or drying the process equipment or accessories used.		Cleaning validation performed.	Cleaning validation not performed.		

8.	6	Whether water used in compounding is Purified Water IP.		Purified water used	Potable water used.		
9.	7	Whether Powder are suitably sieved before use, whenever used.		Procedure and records are available	Procedure/records are not available		
10.	8	Whether Heating of vehicles and a base like petroleum jelly is done in a separate mixing area in suitable stainless-steel vessels, using steam, gas, electricity, solar energy, etc.		Procedure performed in separate vessels made up of SS316/SS316L.	Separate vessels are not provided/ Vessels are not made up of SS316/SS316L.		
11.	9	Whether a separate packing section is provided for primary packaging of the products.		Separate packing section is provided for primary packaging of the products.	Separate packing section is not provided for primary packaging of the products.		
12.		Whether Primary plus secondary plus tertiary filters (e.g., EN779 G4 plus F8 plus EN1822 H13 filters) (for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable) for production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists.		For recirculation system- EN779 G4 plus F8 plus EN1822 H13 filters are provided and for fresh air system- G4 and F8 or F9 filters are proived.	Requisite filter are not provided.		
13	PART XIII (1)	Whether the premises is equipped with folowing equipments. (1) Mixing and storage tanks preferably of stainless steel or any other appropriate material; (2) Jacketed Kettle		Requisite equipments are provided.	Requisite equipments are not provided/Inadequate.		

		stainless steel container (steam, gas or electrically heated); (3) Mixer (Electrically operated); (4) Planetary mixer; (5) A colloid mill or a suitable emulsifier; (6) A triple roller mill or an ointment mill; (7) Liquid filling equipment (Electrically operated); and (8) Jar or tube filling equipment.					
14	PART XIII (1)	Whether minimum area of thirty square meters for basic installation and ten square meters for ancillary area is provided.		Requisite area is provided	Requisite area is not provided/Inadequate		

List of Observations/Deficiencies:

1) Critical:

1.1:

1.2:

2) Major:

2.1:

2.2:

3) Others:

3.1:

3.2:

3.3:

Concluding Remarks:

Name and Signatures of the Inspecting officials:

Chapter-7

Guidance document for issuance of Test License

Guidance Document

Introduction

Requirement for the submission of an application for issuance of:

1. Permission for the manufacture of unapproved/approved New Drugs in Form-29 for the purpose of examination, test & analysis for drugs other than Biologicals/Medical Devices/Diagnostic Kits.
2. License to import old approved drugs for the purpose of examination, test & analysis and BABE studies in healthy human subjects.
3. License to import new/unapproved drugs for the purpose of examination, test & analysis

Purpose

This guideline will corroborate various commonly found aspect of granting licence in Form – 29 for the manufacture of specific quantities of drugs under the provisions made in Chapter VIII of New Drugs and Clinical Trial Rules, 2019. A manufacturer can obtain license in Form – 29 from the concerned State Drug Department, under whose jurisdiction the manufacturing facility lies for the manufacture of any drug in small quantities for the purpose of examinations, test or analysis only, if the person proposing to manufacture a drug for the purpose of examination, test or analysis does not hold a license in Form – 25 or Form – 28 in respect of such drugs he shall, before commencing such manufacture, obtain a license in Form – 29.

Application for license to import old/approved drugs for the purpose of examination, test & analysis has to be made as per Rule 34 of Drugs and Cosmetic Rules, 1945 and license to import new/unapproved drugs for the purpose of examination, test & analysis under the provisions made in Chapter IX of New Drugs and Clinical Trial Rules, 2019.

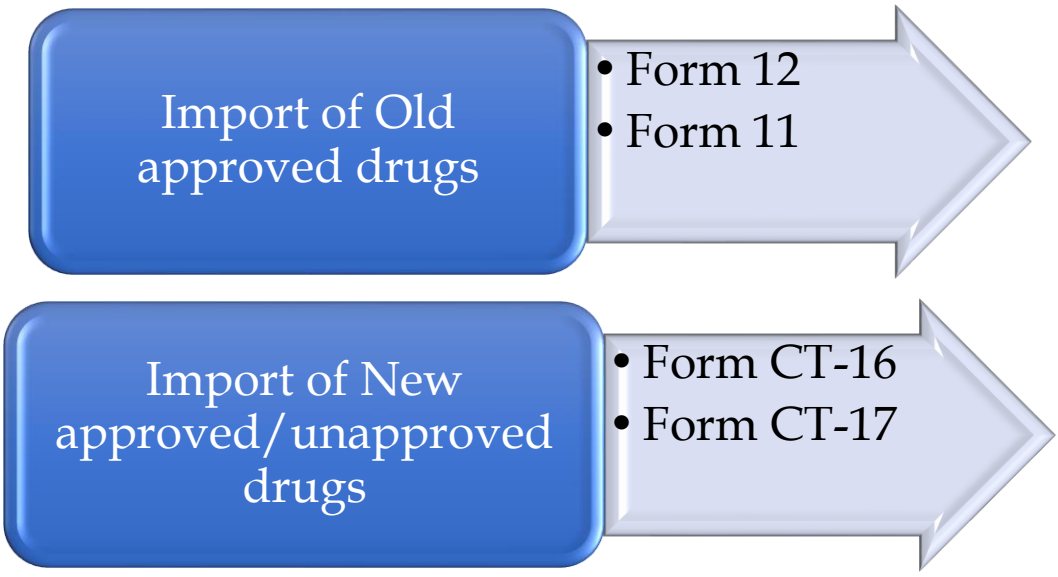
Scope

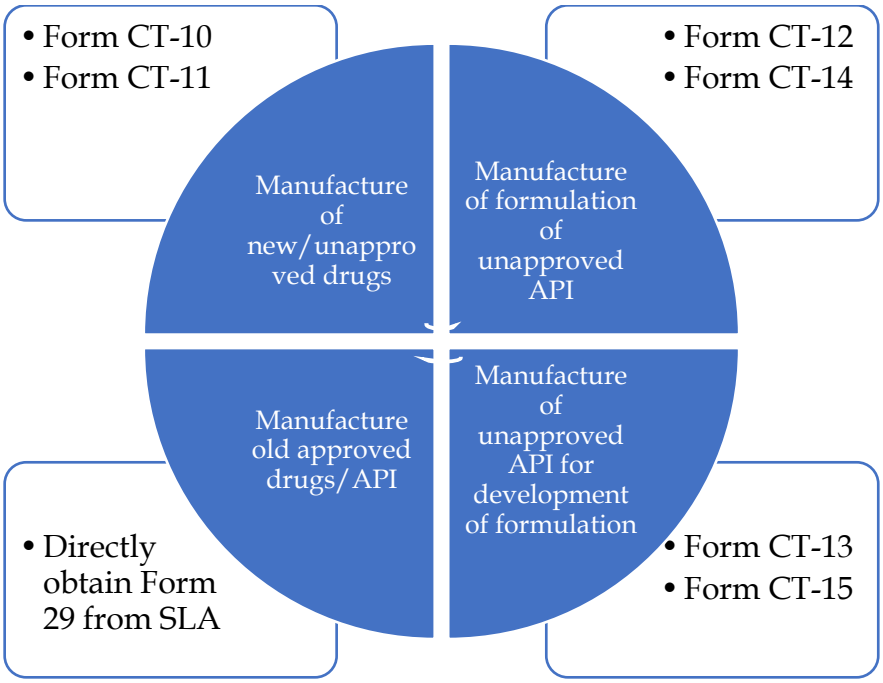
This document is applicable only for the applications for obtaining permission from Zonal/Sub-Zonal offices for Form – 29 manufacturing licence from State Licensing Authority for drugs excluding Biological/Medical Devices/Diagnostic Kits and license to import old approved/unapproved/new drugs for the purpose of examination, test & analysis as mentioned below:

Forms under Test License:

Sr. No.	Application Form	License/ Permission Form	Purpose

1	Form 12	Form 11	Import of old approved drugs for the purpose of examination, test & analysis and BABE studies in healthy human subjects.
2	Form CT-16	Form CT-17	Import of new/unapproved drugs for the purpose of examination, test & analysis
3	Form CT-10	Form CT-11	Manufacture of new/unapproved drugs for the purpose of examination, test & analysis
4	Form CT-12	Form CT-14	Manufacture of formulation of unapproved API for the purpose of examination, test & analysis
5	Form CT-13	Form CT-15	Manufacture of unapproved API for the purpose of examination, test & analysis





Jurisdiction:

Organization chart may be updated as per current set up as new zonal/subzonal offices have been created and power has been delegated to process/approve Test License to these new offices

State	**Name of zone/subzone**
Maharashtra	West Zone 2
Daman Diu/Dadra Nagar Haveli and Chattisgarh	West Zone 1
Madhya Pradesh	Subzone Indore
Goa	Subzone Goa
Gujarat	Ahmedabad Zone
Rajasthan, Uttar Pradesh and N.C.T. of Delhi	North Zone
Karnataka	Bangalore Zone
Andaman and Nicobar Island, Bihar, Jharkhand, Orissa, Sikkim, & West Bengal	East Zone
Kerala, Pondicherry, Lakshadweep and Tamil Nadu.	South Zone
Telangana	Hyderabad Zone

Haryana, Punjab, Himachal Pradesh, Union Territory of Chandigarh.	Baddi Zone
Uttarakhand	Subzone Rishikesh
Andhra Pradesh	Subzone Vishakhapatnam
Jammu and Ladakh	Subzone Jammu & Kashmir
Assam, Tripura, Nagaland, Mizoram, Meghalaya, Manipur and Arunachal Pradesh	Subzone Guwahati

Procedure:

An applicant may submit an application online on NSWS (National Single Window System) for import or manufacture of drugs for the purpose of examination, test & analysis in the respective Form as mentioned above to the respective zonal/subzonal office.

Flow of application on NSWS

Nodal officer (Level 1) [ADC(I)]
(Receipt of application and transfer to RO)

⇓

Reviewing officer (Level 2) [DI/TO/ADI/TDA]
(Scrutiny of application as per checklist and forward to NO/LA)

⇓

Nodal officer (Level 3) [ADC(I)]
(Scrutiny of application as per checklist and forward to LA)

⇓

Licensing Authority (Level 4) [ADC(I)/DDC(I)]
(Approval/Query/Rejection)

Important Points for consideration:

1. Reviewing officer will scrutinize the application as per the checklist and check for approval status of the drug through CDSCO website.
2. Reviewing officer shall ensure that the draft permission copy generated must be as per the details submitted by the applicant and make necessary changes in draft permission

copy for inclusion of strength, quantity, indication so that correct copy of permission can be generated at the LA level.

3. LA may again verify draft permission copy before digital signature of final permission.

Checklist

Form -12 (Testing & analysis)	
	APPLICATION FOR GRANT OF LICENCE TO IMPORT DRUGS FOR EXAMINATION, TEST AND ANALYSIS
Item No	Checklist Item
1	Covering letter of firm
2	Self attested by Head of the institution proprietor or director of the company or firm (with authority letter) Copies of Manufacturing Licences in Form-25/28/29 issued by SLA or Copy of Form 37 issued by SLA and/or DSIR approval in case of formulations and/or copy of BA/BE approved centre
3	Self attested copy of detailed utilization break up for each drug indicating the nature of tests and quantity required for each test duly signed and stamped by competent authority for bulk drugs and finished formulation for R&D purposes
4	Whenever appreciably large quantities of drugs are required to be imported then Justification for import and utilization breakup of the proposed quantities of drugs with reference to the detailed test parameter batch manufacturing plan in accordance with official regulatory documents/guidelines circulated by the National Drug regulatory authority of the country is where the study data would required to be submitted
5	Undertaking by competent authority that the drugs imported under test Licence would be used for Test & Analysis only should be enclosed
6	Detailed information regarding import of same drug during last 3 years along with certificate of destruction of unused drug from the Competent Regulatory Authority
7	In case of Narcotic and Psychotropic drugs, the relevant Schedule of the NDPS Act 1985 under which the drug falls is to be indicated
8	Technical literature or package inserts or brief technical write up of drugs
9	Upload duly signed Form-12 (non-mandatory* on NSWS)
10	TR-6 Challan of Fees paid (non-mandatory* on NSWS)

Form-12 (BA/BE)	
	APPLICATION FOR GRANT OF LICENCE TO IMPORT DRUGS FOR EXAMINATION, TEST AND ANALYSIS
Item No.	Checklist Item
1	Covering letter of firm
2	Regulatory status of the Drug in India indicating strength & dosage
3	The study protocols, Informed Consent Form (ICF) or Patient Information Sheet (PIS) along with audio-visual recording system as per Schedule Y guidelines; & copy of approval of protocol from the IEC, if available.
4	The study synopsis
5	Justification of Quantity
6	Upload duly signed Form-12 (non-mandatory* on NSWS)
7	TR-6 Challan of Fees paid (non-mandatory* on NSWS)

Form CT-10	
	APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS
Item No	Checklist Item
1	Covering letter of firm
2	Self attested by Head of the institution proprietor or director of the company or firm (with authority letter) Copies of Manufacturing Licences in Form-25/28/28D or loan license issued by SLA or DSIR approval in case of R&D
3	Self attested copy of detailed utilization break up for each drug indicating the nature of tests and quantity required for each test duly signed and stamped by competent authority for bulk drugs and finished formulation for R&D purposes
4	Upload status of new drug (API and its formulation) approved in India or in other countries
5	Proposed SOP for manufacturing

6	Proposed SOP for analysis /testing
7	List of manufacturing equipments
8	List of analytical instrument/facility
9	Proposed specification and STP
10	Source and specification of active raw material for formulation
11	In case of Narcotic and Psychotropic drugs, the relevant Schedule of the NDPS Act 1985 under which the drug falls is to be indicated
12	Upload duly signed Form CT-10 (non-mandatory* on NSWS)
13	TR-6 Challan of Fees paid (non-mandatory* on NSWS)

Form CT -12	
	APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE FORMULATION OF UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS
Item No	Checklist Item
1	Covering letter of firm
2	Self attested by Head of the institution proprietor or director of the company or firm (with authority letter) Copies of Manufacturing Licences in Form-25/28/28D or loan license issued by SLA or DSIR approval in case of R&D
3	Self attested copy of detailed utilization break up for each drug indicating the nature of tests and quantity required for each test duly signed and stamped by competent authority for bulk drugs and finished formulation for R&D purposes
4	Proposed SOP for manufacturing
5	Proposed SOP for analysis /testing
6	List of manufacturing equipments
7	List of analytical instrument/facility
8	List of technical staff for manufacturing and testing
9	Proposed specification and STP

10	Source and specification of active raw material for formulation
11	Notarized legal undertaking in Annexure I & II (attached)
12	In case of Narcotic and Psychotropic drugs, the relevant Schedule of the NDPS Act 1985 under which the drug falls is to be indicated
13	Technical literature or package inserts or brief technical write up of drugs
14	Copy of Form CT-15
15	Upload duly signed Form CT-12 (non-mandatory* on NSWS)
16	TR-6 Challan of Fees paid (non-mandatory* on NSWS)

Form CT-13	
	APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR DEVELOPMENT OF FORMULATION FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS
Item No	Checklist Item
1	Covering letter of firm
2	Self attested by Head of the institution proprietor or director of the company or firm (with authority letter) Copies of Manufacturing Licences in Form-25/28/28D or loan license issued by SLA or DSIR approval in case of R&D
3	Self attested copy of detailed utilization break up for each drug indicating the nature of tests and quantity required for each test duly signed and stamped by competent authority for bulk drugs and finished formulation for R&D purposes
4	Upload status of new drug (API)
5	Technical literature or brief technical write up of drugs manufacturing i.e. reaction scheme, source and specification of KSM etc.
6	Proposed SOP for manufacturing
7	Proposed SOP for analysis /testing
8	List of manufacturing equipments
9	List of analytical instrument/facility
10	List of technical staff for manufacturing and testing

11	Proposed specification and STP
12	GMP status of the manufacturing site (API)
13	Name and address of manufacturing site of formulation
14	Notarized legal undertaking in Annexure I
15	In case of Narcotic and Psychotropic drugs, the relevant Schedule of the NDPS Act 1985 under which the drug falls is to be indicated
16	Upload duly signed Form CT-13 (non-mandatory* on NSWS)
17	TR-6 Challan of Fees paid (non-mandatory* on NSWS)

Form CT-16	
	APPLICATION FOR GRANT OF LICENCE TO IMPORT NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS
Item No	Checklist Item
1	Covering letter of firm
2	Self attested by Head of the institution proprietor or director of the company or firm (with authority letter) Copies of Manufacturing Licences in Form-25/28/29 issued by SLA or Copy of Form 37 issued by SLA and/or DSIR approval in case of formulations and/or copy of BA/BE approved centre
3	Self attested copy of detailed utilization break up for each drug indicating the nature of tests and quantity required for each test duly signed and stamped by competent authority for bulk drugs and finished formulation for R&D purposes
4	Whenever appreciably large quantities of drugs are required to be imported then Justification for import and utilization breakup of the proposed quantities of drugs with reference to the detailed test parameter batch manufacturing plan in accordance with official regulatory documents/guidelines circulated by the National Drug regulatory authority of the country is where the study data would required to be submitted
5	Undertaking by competent authority that the drugs imported under test Licence would be used for Test & Analysis only should be enclosed if not manufactured under GMP conditions
6	Detailed information regarding import of same drug during last 3 years along with certificate of destruction of unused drug from the Competent Regulatory Authority

7	In case of Narcotic and Psychotropic drugs, the relevant Schedule of the NDPS Act 1985 under which the drug falls is to be indicated
8	Technical literature or package inserts or brief technical write up of drugs
9	Upload duly signed Form CT-16 (non-mandatory* on NSWS)
10	TR-6 Challan of Fees paid (non-mandatory* on NSWS)

(* Non-mandatory means that there is provision on NSWS for the preview of legal form and payment separately even if not submitted under the checklist)

Chapter-8

Guidance Document on common submission format for issuance of No Objection Certificate for export of Unapproved/Approved New drugs/Banned drugs.

INTRODUCTION

A manufacturer holding valid license copy in Form -25 and Form- 28 can obtain No Objection Certificate from Zonal offices of Central Drugs Standard Control Organization (CDSCO) for export purpose only for Approved / Unapproved New drug / Banned drug in India.

PURPOSE

Requirement for the common submission format for issuance of No Objection Certificate for export of unapproved/approved new drugs/Banned drugs from India. This document made as per guidelines issued by Ministry of Health and Family Welfare for Export purpose and Rule 94 of the Drugs and Cosmetic Act, 1940.

SCOPE

This document is applicable for the manufacturer to obtain No Objection certificate Zonal offices of Central Drugs Standard Control Organisation (CDSCO) for export purpose

PROCEDURE

Requirement for Common submission Format for issuance of No Objection Certificate for export of unapproved / approved new drugs / Banned drugs from India

The Following documents are required to be submitted on SUGAM portal in the following manner and order for issue of the No Objection Certificate for export of drugs from India: -

1. Covering Letter: - The covering letter is an important part of the application and should clearly specify the intent of the application. The list of documents that are being submitted (Index with page no‘s) as well as any other important and relevant information may be provided in the covering letter. The covering letter mentioning list of products to be exported clearly indicating name of the drug, dosage form, composition and strength pack size along with quantity and country to be exported duly signed and stamped by the authorized signatory, indicating the name & designation of the authorized signatory along with the name and address of the firm. Each application should be made by the manufacturer only.

2. Purchase Order: -

a. Order from the foreign buyer either in the name of manufacturer or in the name of trader mentioning list of products to be exported clearly indicating name of the drug, dosage form, composition and strength pack size duly signed by the competent authority with specific destination point of the importing country. In case

of purchase order in the name of trader further a letter from the trader in the name of manufacturer is required to be submitted along with the application

b. It should be signed by the competent authority/person with a valid purchase order no. and recent date not more than 6 month prior to the application made by the firm.

3. Manufacturing License: - License issued by the State Licensing Authority should be enclosed along with each application for the required location to manufacture the drug for export purpose.

4. Performa Invoice: - a. A copy of Performa invoice from the importing country should accompany with application for import of unapproved Active Pharmaceutical Ingredients, used in the drug formulation. b. A copy of Performa invoice duly signed by the competent authority should be addressed to the manufacturer mentioning the required quantity of the bulk drug.

5. Registration Certificate: -

a. For the export of drugs which are banned in India by Central government, which coming under list of drugs prohibited for manufacture and sale through gazette notifications under section 26a of drugs & cosmetics act 1940 by the ministry of health and family welfare.

b. A copy of registration certificate from the specific importing country along with composition and strength of the drug should accompany with the application

c. Registration certificate should be provided in the name of manufacturer.

While processing such applications the following conditions shall be taken into consideration:

1. The application shall provide copy of valid export order and NOC will be issued on a case by case basis against each such order.

2. The applicant shall identify the premises where the drug will be manufactured for export. 3. The applicant should mention whether the batch to be exported has undergone Quality control testing or shall be tested at the destined site.

4. The applicant shall ensure that the drug(s) manufactured on the basis of ―NOC given as per (1) above its exported and that no part of it is diverted for domestic sale in India.

5. The applicant shall make available for inspection of the appropriate authorities, on completion of the export orders, information regarding each consignment dispatched, remaining stock of drug and related raw materials and intermediates in hand.

6. The applicant shall ensure physical destruction of all un exported quantity of drugs. This should be included as a condition of manufacturing license issued to the applicant by the State licensing authority.

7. The applicant shall ensure that the drug for which NOC has been given shall cease to be manufactured or exported if the drug is prohibited in future in the country or in the importing country.

Checklist for issuance of No Objection Certificate for export of unapproved / approved new drugs / Banned drugs from India (API):

1. Covering Letter on the company(s) letter head duly signed and stamped by the Authorized signatory.
2. Copy of valid Export Order/Purchase Order/Performa invoice (received by the Formulation Manufacturer along with PO/Performa Invoice issued by Formulation Manufacturer to API Manufacturer for supply of API) Duly self-attested (not more than 6 months old).
3. Copy of Manufacturing License held by the applicant firm along with neutral code permission as applicable.
4. Proposed Label (Primary and Secondary) with QR Code.
5. Undertaking (on non-judicial stamp paper) as per Annexure-1 from the Manufacturer of API/Bulk Drug.
6. Reconciliation details for the same API/Bulk Drug for the quantities permitted earlier for Specific Quantity Export.
7. List of Export NOC details issued by SLA since 2018 in a tabular column along with permission/NOC copies (In case data is not readily available, applicant may submit undertaking to submit the data within 90 days of the First Application).
8. In case of Drugs covered under NDPS Act, Applicant to submit undertaking that they will obtain NOC from Narcotic Commissioner of India, Central Bureau of Narcotics, Gwalior.
9. Upload Export NOC Form.

Checklist for issuance of No Objection Certificate for export of unapproved / approved new drugs / Banned drugs from India (Formulations):

1. Covering Letter on the Company's letter head duly signed and stamped by the Authorized signatory.
2. Copy of valid Export Order/purchase Order/Performa invoice (received from Overseas Buyer along with PO/Performa Invoice issued by Trader, if so) duly self-attested (not more than 6 months old).
3. Copy of Manufacturing License held by the applicant firm along with neutral code permission as applicable.
4. Proposed Label & IFU (as per Importing Country requirements)
5. Justification/Calculation regarding quantity of Unapproved/Banned / New API/Bulk Drug requirement.
6. Undertaking (on non-judicial stamp paper) as per Annexure- II from Formulation manufacturer.
7. Reconciliation details for the same Formulations for the quantities permitted earlier for Specific Quantity Export.
8. List of Export NOC details issued by SLA since 2018 in a tabular column along with permission/NOC copies (in case data is not readily available applicant may submitted undertaking to submit the data within 90 days of the first application).
9. In case of Drugs covered under NDPS act, applicant to submit undertaking that they will obtain NOC from Narcotic Commissioner of India Central Bureau of Narcotics, Gwalior.
10. Upload Export NOC Form.

Chapter-9

Guidance for issuance of license for drugs to be imported for personal Use

	TITLE	Office Name	CDSCO, Zonal Offices.
	Procedure for processing of application for grant of permission for import of small quantities of drugs for personal use in Form-12B by online Sugam Portal	SOP No.	QMS/TEC/016
		Revision No.	00
		Effective Date	
		Page No.	667 of 1103

Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation	DDC(I)	Designation	DDC(I)	Designation	DCG(I)
Sign		Sign		Sign	
Date		Date		Date	

1.0 Purpose

To lay down a standard Procedure for processing of application for grant of permission for import of small quantities of drugs for personal use in Form-12 B by online Sugam Portal.

2.0 Scope

This document is applicable for the applications received through online SUGAM portal from patients for grant of permission for import of small quantities of drugs for personal use in Form-12B as per rule 36 of Drugs and Cosmetics Acts and Rules 1945.

3.0 Definitions & Abbreviations

3.1	SUGAM	e-portal of CDSCO for online application submission, processing and grant of permissions
3.2	LA	Licensing Authority
3.3	DCG(I)	Drugs Controller General (India)
3.4	DDC (I)	Deputy Drug Controller(India)

3.5	ADC (I)	Assistant Drug Controller(India)
3.6	SOP	Standard Operating Procedure
3.7	CDSCO	Central Drugs standard control organization

4.0 Responsibility:

4.1. ADC(I) at Port Offices will be responsible for approval/ rejection of application for Form12B in online Sugam portal.

5.0 Accountability

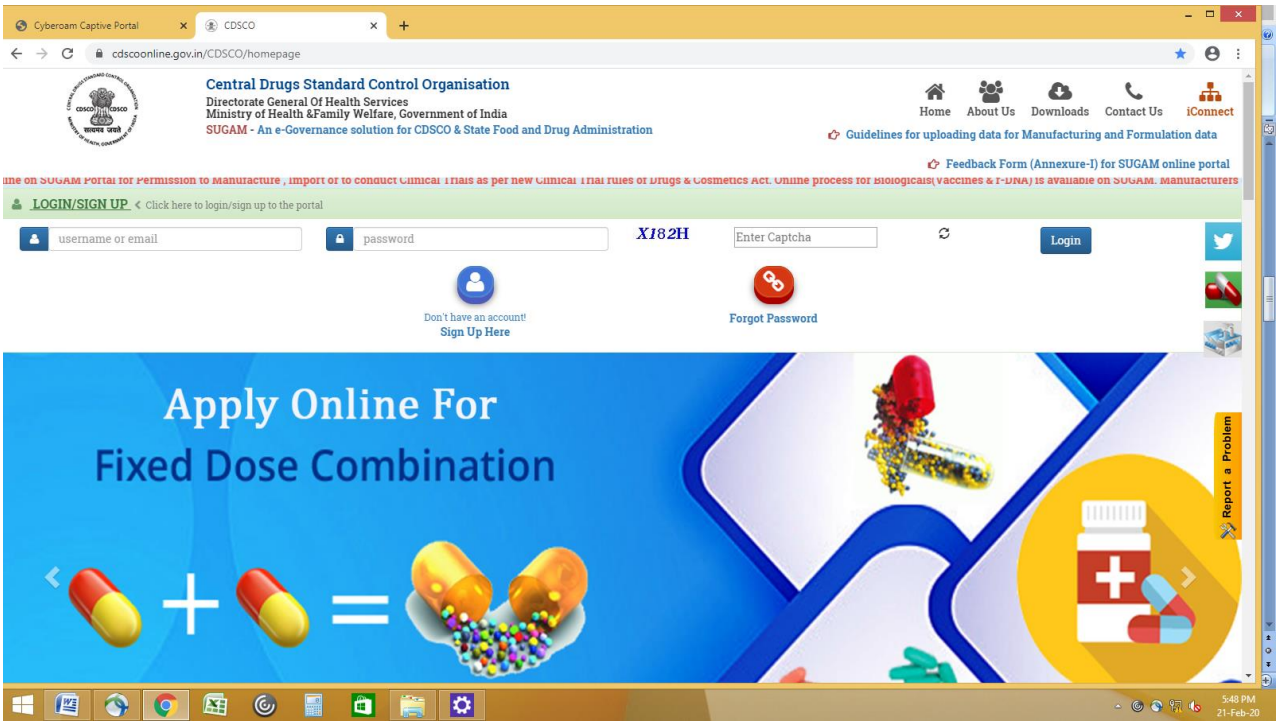
Asstt. Drugs Controller (India), CDSCO, Port Office.

Procedure

6.1. Login Process

In this process, operator has to enter the User ID and password in the respective login screen. As shown below:

Step 1: Enter **User ID** and **Password** then click on **Login** button after successful Login menu screen will appear.

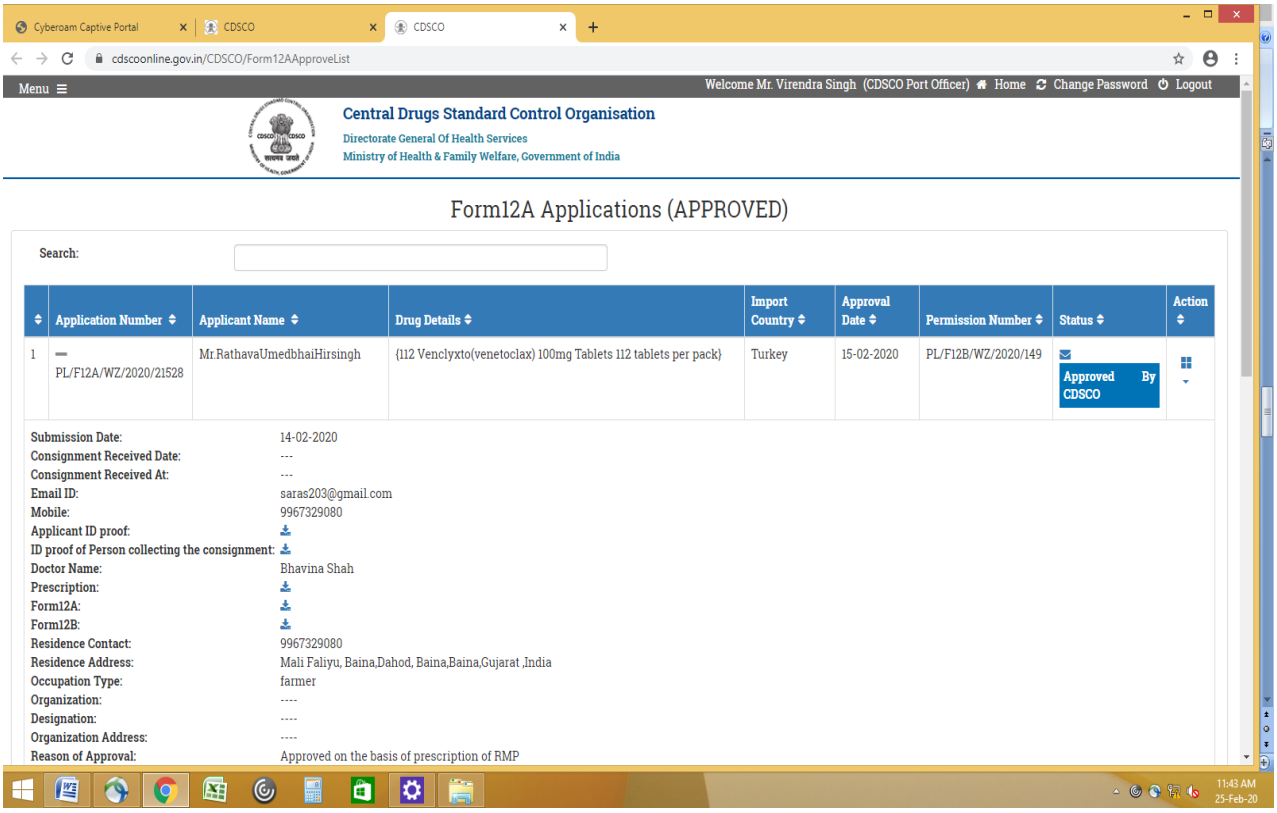


6.2. Review Documents

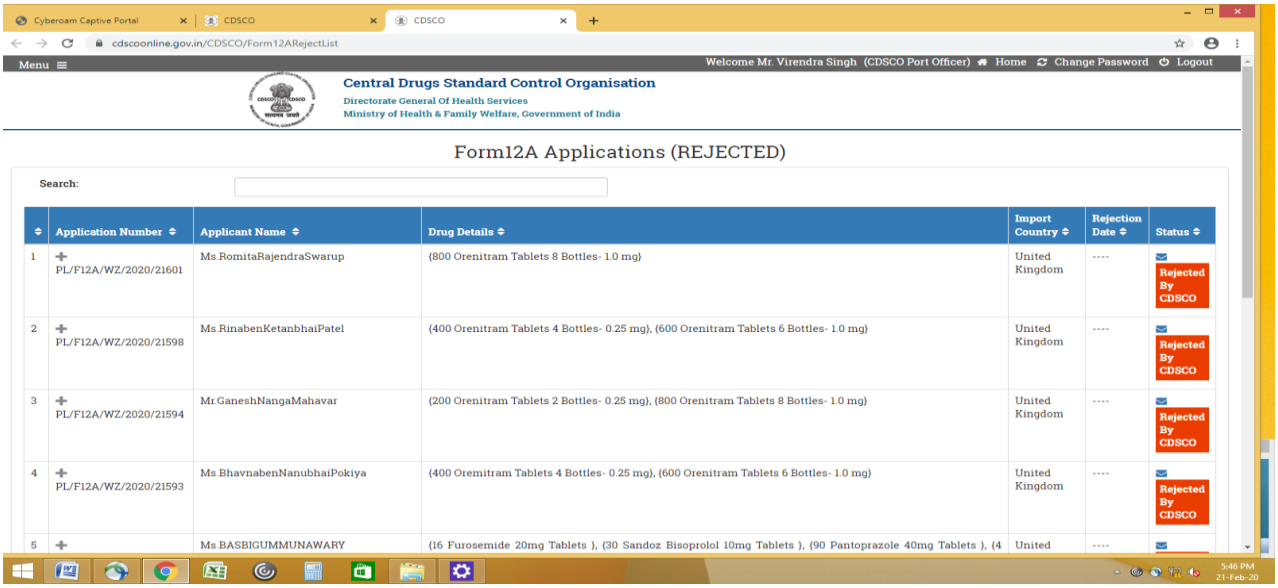
Step-1: Nodal Officer/ADCI of concerned port office shall mark the application to RO and RO shall be scrutinized the application as per documents available on SUGAM portal.

Step-2: If the document find in order than select decision '**Approved'** and click

Step-3: Licensing Authority shall approve the Personal License and download Form12B. Than upload digital/manual sign of Licensing Authority and put remark of approval.



Step-4: If the document find not in order than select decision **Rejected** and click the put remark of rejection.



6.3. Timeline for Disposal

The timeline for issuance of permission/rejection of Form-12**B** is **7** working days from the date of submission of application by the firm.

6.4. Maintenance of database:

The records of the application in Form-12B made to CDSCO, zonal office/Concerned Port office for grant of permission for import of small quantities of drugs for personal use is maintained in online server of the 'CDAC' and same can be retrieved anytime from the Sugam portal at Licensing Authority level.

6.0 Records

Annexure/Format no.	Title
Annexure-1	Format of Form-12A
Annexure-2	Format of Form-12B

7.0 References

Doc. No.	Title
1	The Drugs and Cosmetics Rules, 1945.
2	CDSCO Guidance Document on grant of Personal License in Form 12 B

Chapter-10

Written Confirmation

	TITLE	Division Name	International Cell
	Procedure for receipt, review, and processing of online application for issuance of "Written Confirmation Certificate" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46b(2)(b) of EU Directives No. 2001/83/EC, at Zonal/Sub-Zonal offices of CDSCO	Document No.	INC-WCC-001
		Revision No.	00
		Effective Date	
		Page No.	671 of 1103

Prepared By		Checked By		Approved By		Authorized By	
Name		Name		Name		Name	
Designation		Designation		Designation		Designation	
Sign		Sign		Sign		Sign	
Date		Date		Date		Date	

Background

European Union has mandated through Directives No.2001/83/EC dated 08.06.2011 that every consignment of Active Pharmaceutical Ingredient (API) from non-EU/non-listed countries must be supported by a "Written Confirmation Certificate" issued by the Competent Authority of that country, stating that the consignment conforms to standards of Good Manufacturing Practices (GMP) as laid down in the EU guidelines or equivalent thereof. Accordingly, Ministry of Health and Family Welfare vide OM No.X.11035/43/2012-DFQC dated 12.11.2012 has nominated Central Drugs Standard Control Organization (CDSCO) as competent authority for the purpose of issuance of the certificate as mandated under EU Directives, which has made effective from 02.07.2013. The standards applicable for issuance of a "Written Confirmation Certificate "for active substances exported to the EU for medicinal products for human use in accordance with Article 46b(2)(b) of EU Directive No.2001/83/EC and the requirements as per "Good Manufacturing Practices guide for Active Pharmaceutical Ingredients- ICH Harmonized Triplicate Guideline, ICH Q7" and various provision of the Drugs and Cosmetics Act, 1940 and Rules thereunder. The Drugs Controller General (India) issues "Written Confirmation Certificate" upon

recommendation from the concerned zonal/sub-zonal offices of CDSCO and subsequent review at CDSCO-HQ.

1.0 Purpose

To lay down a procedure for review, and processing of online application made through SUGAM portal (https://cdscoonline.gov.in) for issue of "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46b(2)(b) of Directives No. 2001/83/EC, by zonal/sub-zonal offices of CDSCO.

2.0 Scope

This document is applicable for zonal/sub-zonal offices of CDSCO to review and process the application including inspection, and forward the application along with inspection reports and clear recommendation letter through SUGAM portal to CDSCO (HQ).

3.0 Responsibility:

Sr. No.	Designation as per SUGAM Portal	Responsibility
3.1	NO-Nodal officer	1. Receipt and allocation of application in the SUGAM portal to 'RO' 2. Review and forward the application to DDA
3.2	RO-Reviewing officer (s)	1. Review of application 2. Conduct of inspection 3. Compliance verification 4. Submission of inspection/compliance verification report to NO/DDA
3.3	DDA- Deputy Decision Authority	1. Planning of inspection 2. Review of application and inspection/compliance verification report 3. Issuance of Recommendation Letter 4. Forwarding the file to CDSCO-HQ. 5. Overall implementation and regular monitoring of compliance of the SOP.

4.0 Accountability

Concerned Head of Zonal/Sub-Zonal offices of CDSCO.

5.0 Procedure (Flow chart attached as **Annexure-1**)

5.1 Receipt and allocation of application by NO: - Application made by the applicant for issue of "Written Confirmation" is received in the 'NO' portal and allocated to RO for review and further processing of the application.

5.2 Review of application at RO level:-

5.2.1 Review of the application as per the checklist(**Annexure-2)** of the SUGAM portal for its completeness

5.2.2 Communicating deficiencies or non-compliances (if any) to the applicant through the DDA

5.2.3 Review of the responses submitted by the applicant

5.2.4 Forwarding the review comments to NO for further review and processing

5.3 Review of application at NO level:-

5.3.1 Review of the assessment points noted by RO

5.3.2 Forwarding the application to DDA

5.4 Review of application at DDA level:-

5.4.1 Review of the assessment points noted by RO/NO

5.4.2 Planning and conduct of inspection **(Annexure-3)**

5.4.3 Uploading the inspection report along with recommendation letter in the portal

5.4.4 Forwarding the application to CDSCO-HQ, if satisfactory

5.4.5 Communicating administrative orders or regulatory actions to the applicant (if any)

5.4.6 Verification of the compliance

5.5 Timelines:-

- Review of Online application and planning for inspection: 15 working days
- Conduct of Inspection after review of application: 15 working days
- Report submission by Inspection Team after inspection 03 working days
- Recommendation and forwarding of online application by DDA to DA for consideration for issuance of WCC 07 days

6.0 Annexures

Annexure/Format No.	Title
Annexure-1	Flow chart for receipt and process of online application
Annexure-2	Application checklist
Annexure-3	Planning and conduct of inspection

7.0 References

Doc. No.	Title
1	GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU
2	WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No. 957, 2010
3	Good Manufacturing Practice guide for Active Pharmaceutical Ingredients stated as per ICH Q7 of ICH Harmonised Triplicate Guideline

8.0 Abbreviation

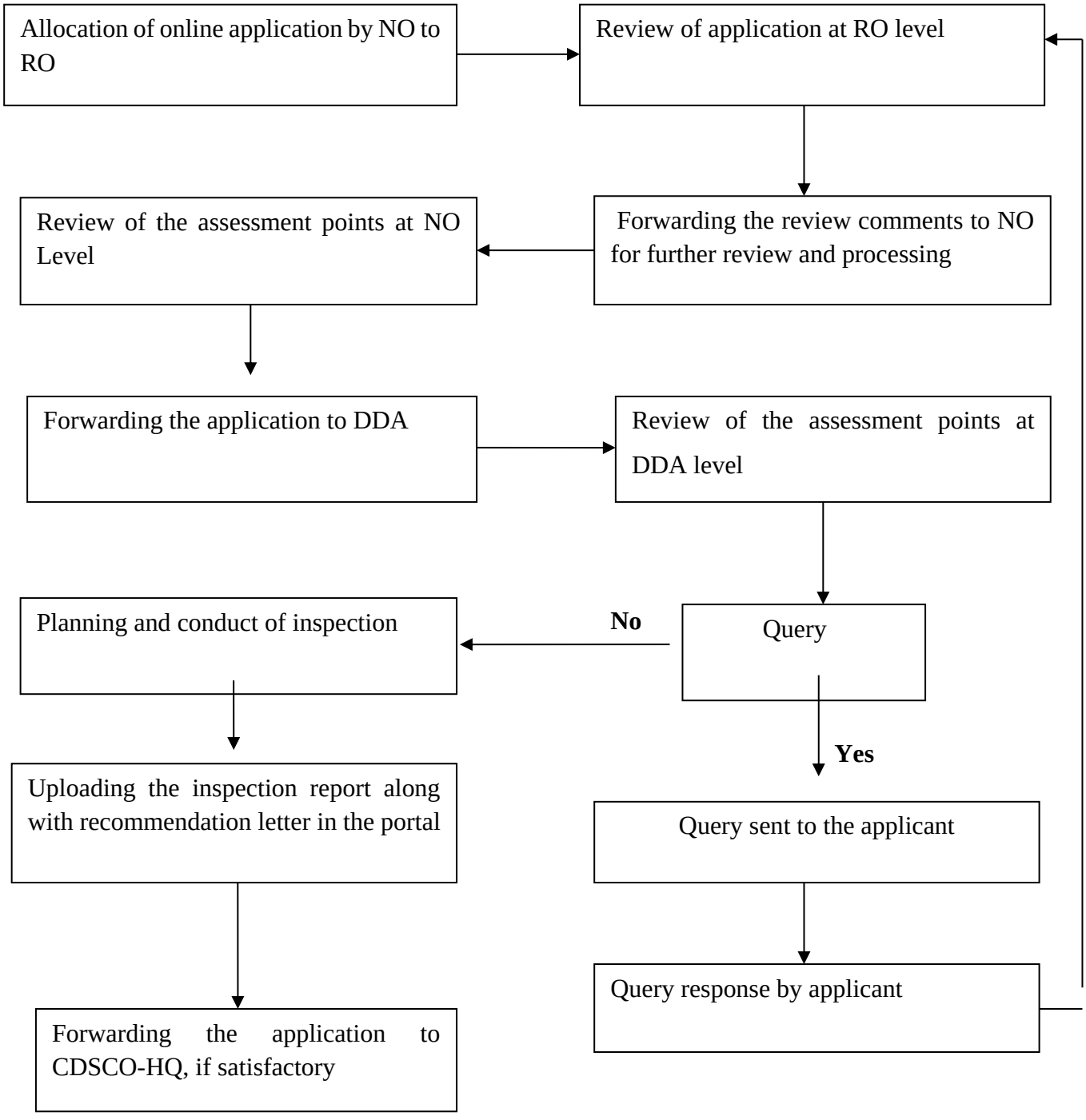
Acronym	Full Form
EC	European Commission
EU	European Union
WCC	Written Confirmation Certificate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
WHO	World Health Organization
CDSCO-HQ	Central Drugs Standard Control Organization-Headquarter
GMP	Good Manufacturing Practices
API	Active Pharmaceutical Ingredient

9.0 Revision History

Revision No.	Reason(s) for Revision
00	Implementation of New Format

Annexure-I of INC-WCC-001

Process flow chart for review and process of online applications for issuance of Written Confirmation at Zonal/Sub-Zonal Offices of CDSCO



Annexure-2 of INC-WCC-001
Checklist for documents to be submitted with application for grant/renewal of WCC

1. Covering Letter – The covering letter is an important part of the application and should clearly specify the intent of the application (whether the application is being submitted for the first time or for renewal or for the endorsement of additional products to an existing Written Confirmation Certificate). The covering letter should be duly signed and stamped by the authorized signatory, indicating the name & designation of the authorized signatory alongwith the name and address of the firm.
2. Site master file (as specified under WHO TRS 961, Annexure 14)
3. An Authorization letter in original issued by the Director/Company Secretary/Partner of the firm revealing the name & designation of the person authorized to sign (along with the name and address of the firm) on behalf of the firm.
4. Copy of GMP certificate issued as per WHO GMP, USFDA, EDQM, etc., if any
5. Copy of valid Manufacturing License
6. List of Products applied for Written Confirmation Certificate
7. Approved Product Permission by Licensing Authority
8. List of SOPs and STPs
9. List of Technical Staff, their Qualification, Experience and approval status & organogram
10. List of Equipment and Instruments
11. Manufacturing Plant Layout
12. Validation Master Plan
13. SOP for Good Distribution Practices followed by the firm
14. Legal undertaking stating that Inspection/ Investigation reports by Indian/overseas regulatory Authorities including Show Cause Notices/ Suspensions/ Cancellations if any shall be communicated to "Competent Authority" i.e. DCG(I), CDSCO within 03 working days.
15. Stability studies of 3 batches for minimum 06 months for accelerated and real time studies along with stability protocol and commitment
16. Process validation of three batches along with protocol and report
17. Certificate of Analysis(CoA) for latest three batches
18. Annual Product Review for last 3 years
19. Export data for last 3 years
20. Analytical Method Validation along with protocol and report. Method equivalency report in case of pharmacopeial drug substances
21. Market Complaint Review for last 3 years along with its SoP

22. Data of Impurity profiling including assessment report for Nitrosamine and Genotoxic Impurities

23. NSQ reports for last three years

24. Signed application for written confirmation

Annexure-3 of INC-WCC-001

Planning and conduct of inspection

1. **Planning of Inspection: -** Deputy Decision Authority (CDSCO, Zonal/Sub-Zonal Head) plans to conduct the inspection for issuance/endorsement/renewal of "Written Confirmation Certificate" based on the comments of Reviewing Officer and Nodal Officer.
2. **Waiving off the Inspection: -**

a) The first written confirmation issued to the manufacturing site shall be granted based on valid Certificate of Pharmaceutical Product (CoPP) issued as per WHO guidelines or US FDA or EDQM / TGA certificates (not more than 24 months old). If the company does not have any of these then inspection shall be conducted.

5.10 Those firms which are inspected within two years by the officers of CDSCO and found to comply with requirements of Article 46b(2)(b) of Directives No. 2001/83/EC:- GMP requirements as per directive 2001/83/EC or WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per WHO Technical report Series (TRS) No. 957 of 2010 (Annex-2), or Good Manufacturing Practice guide for Active Pharmaceutical Ingredients stated as per ICH Q7 of ICH Harmonised Triplicate Guideline.

5.11 **Duration of inspection**: - Two to four days depending upon the scope of inspection and products applied.

5.12 **Inspection Team**

4.1 Composition of the team

- One or two Drugs Inspectors from concerned zonal/sub zonal office.
- One QC expert from CDTL/RDTL/CDL may be included, if required

4.2 Responsibility of the Inspection Team

- To conduct a GMP inspection and to prepare an inspection report

5.13 **Guidelines to be followed for inspection:-**

5.1 Inspections carried out as per GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU, or WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per WHO Technical report Series (TRS) No. 957 of 2010 (Annex-2), or Good Manufacturing Practice guide for Active Pharmaceutical Ingredients stated as per ICH Q7 of ICH Harmonised Triplicate Guideline or as per various provisions of the Drugs and Cosmetics Act, 1940 and rules there under**.**

5.2 Systematic inspection carried out by taking rounds, interviewing the personnel, observing the activities and looking into relevant documents. The deficiencies should be discussed with the company personnel during the course of inspection for better understanding.

5.14 Writing of Inspection Report

6.1 Inspection report prepared by CDSCO team giving the details of name of manufacturer, names of inspectors, date of inspection, purpose of inspection and observations made during the inspection along with the recommendations.

6.2 Inspection report contains the deficiencies pointed out at the time of inspection which may be listed serially.

6.3 The deficiencies written clearly without ambiguity and may be classified as Critical, Major or Minor as per EU Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU, or WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series (TRS), No. 957, 2010, or Good Manufacturing Practice guide for Active Pharmaceutical Ingredients of ICH Harmonised Triplicate Guideline stated as per ICH Q7 or the Drugs and Cosmetics Act, 1940 and rules there under.

6.4 Categorize the deficiencies as critical or major or minor under the criteria as given below**:-**

CRITICAL DEFICIENCY	A deficiency which has a direct impact on quality of the product and which could result injurious to the patient or animal. Some of these defects are evidences of potential contamination and cross contamination issues, mix-up issues, falsification of data etc.
MAJOR DEFICIENCY	A non-critical deficiency that may have an impact on the quality of the product and adversely affect the quality of the product. Some these defects are evidences of non-compliances of GMP of non-critical norms, failure to carry out satisfactory procedures for release of batches etc.
MINOR DEFICIENCY	A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice

6.5 Recommendations given on the basis of purpose of inspection and level of GMP compliance and needs to be signed by Inspection team.

6.6 The report forwarded to the concerned Head of Zonal/Sub-Zonal Office of CDSCO for further necessary action.

5.15 Procedure after submission of inspection report

7.1 If deficiencies are pointed out for compliance, it is to be communicated to the firm for compliance by Zonal/Sub-Zonal Head of CDSCO. The concerned Zonal/Sub-Zonal Drugs Inspector is responsible for verification of compliance, once the compliance report is submitted by the firm.

7.2 If deficiencies are pointed out and application is rejected, it needs to be informed to the applicant with reasons.

5.16 Regulatory action:-On the basis of review of criticalities of deficiencies regulatory action needs to be taken like:

8.1 Notice need to be issued to the manufacturer stating that why such an order should not be passed and ask the manufacturer to reply within ten days of receipt of the copy of the order by the Concerned Zonal/Sub-Zonal office and a copy of the same sent to the office of DCGI.

8.2 Then based on the reply, if required, a suitable action may be recommended to SLA. For any violation under the Drugs & Cosmetics Act and Rules the "Written Confirmation' for active substances exported to the EU for medicinal products for human use, in accordance with Article 46b (2) (b) of Directives No. 2001/83/EC issued by the Competent Authority may be suspended or cancelled and a copy of the same shall be sent to the office of DCGI.

8.3 Manufacturer, if complies with the deficiencies and inform to the Competent Authority, the compliance report and document need to be scrutinized and on the basis of compliance report further inspection may be carried out.

8.4 Forwarding of application:-Inspection report, compliance verification report along with clear recommendation letter of Head of Zonal/Sub Zonal office of CDSCO attached in the dropdown section of the concerned SUGAM online application and the said online application forwarded to Licensing Authority for further necessary action.

GMP CHECKLIST

(Based on WHO Good Manufacturing Practices (GMP) for active pharmaceutical ingredients stated as per Annex 2- WHO Technical report Series(TRS), No. 957, 2010; Good Manufacturing Practice guide for Active Pharmaceutical Ingredients ICH Harmonised Triplicate Guideline stated as per ICH Q7; and GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU)

1	***Location and surroundings:***	**Self appraisal to be filled by the manufacturer along with all details (yes or no type reply will not be acceptable)**	**Observations to be noted by the inspecting team at the time of inspection**	**Remarks**
1.1	How factory building is situated and controlled to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any other factory which produces disagreeable or obnoxious, odors, fumes, excessive soot, dust, and smoke, chemical or biological emissions. *Pls specify industries / establishments adjoining manufacturing site.*			
2	**Building and premises: -**			
2.1	How the building has been designed constructed and maintained to suit the manufacturing operations so as to produce drugs under hygienic conditions. *Pls specify nature of construction used in the facility in respect of its maintenance and hygienic conditions.*			
2.2	Whether the building confirm to the conditions laid down in the Factories Act, 1948 *Pls attach valid factory certificate/ license issued by the competent authority.*			
2.3	Specify how the premises used for manufacturing operations and testing purpose prevents contaminations and cross contamination is: a) Compatible with other drug manufacturing operations that may			

	be carried out in the same or adjacent area. Pls specify any special criteria for the product manufacturered. e.g. temperature, humidity, air class requirements maintained for aseptic products, etc.			
2.4	b) Whether adequate working space is provided to allow orderly and logical placement of equipment, materials and movement of personnel so as to avoid risk of mix-up between different categories of drugs and to avoid possibility of the contamination by suitable mechanism. Pls specify space left around the machines. Pls attach equipment lay out, men and material movement, waste movement if applicable.			
2.5	c) Describe the pest, insects, birds and rodents control system followed in the premises. Attach copy of pest / rodent control schedule along with contract agreement if any.			
2.6	d) What measures have been taken to make Interior surface of (walls, floors, and ceilings) smooth and free from cracks, and to permit easy cleaning *Specify material of construction and finish for walls, ceiling, floor, coving etc. i.e. whether Epoxy or PU coated, kota / granite stone with epoxy sealed joints, solid / GI / gypsum / cal. Silicate board ceiling with epoxy, PU or any other pre-fabricated panel (GRP, powder coated SS or Aluminum etc.) paint.*			
2.7	e) What measures have been taken so that the production and dispensing areas are well lighted and effectively ventilated, with air control facilities. Pls specify the lux level maintained in various parts of the premise.			
2.8	Pls specify the air handling system used in various areas like stores, production, packing, QC areas etc.			

2.9	f) Specify drainage system which prevents back flow and entry of insects and rodents into the premises. Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage *(pls specify number and location of drains installed)*			
2.10	Containment area: Any production activities (including weighing, milling or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.			
3	**Water system: -**			
3.1	Whether the unit has validated system for treatment of water drawn from own or any other source to render it potable in accordance with standards specified by BIS or local municipal norms. Pls specify source of raw water and give details of treatment processes, sampling points, distribution and storage system for raw and purified water.			
3.2	How bio burden in purified water controlled / reduced.			
3.3	How water tank are cleaned periodically and records maintained thereof. How water distribution system is sanitized to control microbial contaminations.			
4	**Disposal of waste: -**			
4.1	Specify the system of disposal of sewage, and effluents (solid, liquid, and gas) from the manufacturing site. (Enclosed the copy of NOC obtained from State Pollution Control Board in this regard).			

4.2	Whether provision for disposal of bio-medical waste made as per the provisions of the Bio Medical Waste (Management and Handling) Rules 1996.			
5	***Warehousing Area: -***			
5.1	Whether adequate areas have been allocated for warehousing of Raw Materials, intermediates, Packaging Material, products in quarantine, finish products, rejected or returned products. How these areas marked or segregated. Please specify the total area provided for warehousing.			
5.2	How the warehousing areas being maintained to have good storage conditions. Are they clean and dry and maintained within acceptable temperature limits?			
5.3	Specify the storage arrangement provided for materials which sensitive to temperature, humidity and light and how the parameters are monitored. Is cold room or deep freezers required for storage of goods? If yes, how the temperature is monitored.			
5.4	Whether proper racks, bins and platforms have been provided for the storage.			
5.5	Whether receiving and dispatch bays are maintained to protect in coming and out going materials.			
5.6	How incoming materials are treated and cleaned before entry into the plant. Please specify the cleaning system for the outer surface of the container.			
5.7	How quarantined materials are segregated from other materials. How access to quarantined area is restricted.			

5.8	Whether separate sampling area for active Raw Materials and Excipients is provided and maintained. If yes, what is the control on entry of material and men into the sampling area. Whether reverse LAF have been provided for sampling. Whether log book for sampling booth maintained. If not what provision has been made for sampling so as to prevent contamination, cross contamination and mix-ups at a time of sampling.			
5.9	Specify the arrangements provided to sample the primary packaging materials foils, bottles, etc which are used as such.			
5.10	Pls specify sampling plan used. Which type of sampling tools are used and how they are cleaned, dried and maintained.			
5.11	How containers are cleaned before and after sampling. Who carries out the sampling? (Pls specify whether the sampling is carried out as per the current SOP).			
5.12	What precautions are taken during sampling of photosensitive, hygroscopic materials?			
5.13	What provisions have been made for segregated storage of rejected, recalled or returned materials or products. How is the access to these areas restricted.			
5.14	How highly hazardous, poisonous and explosive materials, narcotics, and psychotropic drugs are handled and stored. How these areas are safe and secure. Is there certification from competent authority for handling of explosives etc. If any. Pls attach the certificate issued by the competent authority.			
5.15	How printed secondary packaging materials are stored in safe, separate and secure manner.			

5.16	Specify the arrangement provided for dispensing of starting materials. What is the control on entry of material and men into the dispensing area? Whether reverse LAF have been provided for dispensing with back ground clean air supply. Whether pressure differential is maintained between the dispensing and adjacent areas.			
5.17	Which type of dispensing tools are used and how they are cleaned, dried and maintained. How containers are cleaned before and after dispensing. Who carries out the dispensing? (Pls specify whether the dispensing is carried out as per the current SOP).			
5.18	How and where sampling of sterile materials carried out.			
5.19	What steps are taken against spillage, breakage and leakage of containers?			
5.20	What provisions have been made to prevent the entry of rodents, insects, birds. Which substance is used for pest control and how it is handled. (Pls specify whether the pest control is carried out as per the SOP).			
5.21	Whether record of master labels is maintained for comparision to issued labels?			
6	***Production Area: -***			
6.1	Please specify the design of the manufacturing area which allow uni-flow and logical sequence of operations so as to prevent product contamination/ mix ups. Is there any criss cross of flow of materials and men. Specify the position of IPQC lab in the manufacturing area . Please specify whether non storage areas used for storage of any material.			

6.2	Whether separate dedicated and self-contained facilities have been provided for the production of sensitive pharmaceutical product like Penicillin, Biological preparation with like micro-organism, Beta lactam, Sex Hormones and Cytotoxic substances. If yes pls explain how and attach copy of plan of premises of each category of drug.			
6.3	Please specify the provisions of storage of dirty, washed and cleaned equipment parts, tool room, in process storage areas etc. Which provide sequential / logical manner so as to prevent contamination and cross contamination?			
6.4	Please specify how service lines like pipe work, electrical fittings, ventilation openings etc. are identified by colors for nature of supply and direction of the flow. Whether service lines in production areas are through service pendants. If not, how they are placed so as to avoid accumulation of dust.			
7	***Ancillary areas: -***			
7.1	Please specify the position of rest and refreshment rooms and mention whether they are separate and not leading directly to the manufacturing and warehouse areas.			
7.2	Are there general change rooms in plant? Are toilets, change room separate from mfg. Area? Pls specify number of washing station & toilets provided for number of users. Whether change facilities separated for both sexes. How many sets of protective garments provided for each personnel entering production area. Is there in house general laundry for garment washing / cleaning? If not how garments washing are carried out and monitored			

7.3	Whether maintenance workshop is separate and away from production.			
7.4	Whether animals for production or testing are housed in the facility if so whether areas housing animals are isolated from other areas. Please specify the provision of air conditioned and ventilation system for the animal house. How quarantined, under test and tested animals housed and controlled. How animal carcass are disposed of. Pls attach copy of CPCSEA.			
8	**Quality Control Area: -**			
8.1	Whether QC area is independent of production area. Whether QC carries out its own: □ physico-chemical testing, □ biological testing, □ microbiological testing & sterility testing and □ Instrumental testing. Whether firm is outsourcing testing. If yes names of the testing laboratories contacted or approved. Pls give list of test currently outsourced. In case of contractual testing what are the responsibilities of contract giver and contract acceptor. (Copy of the contract should be enclosed) Are there safety installation such as shower, eye washer, fire extinguisher etc in the laboratory. Is there separate area for humidity chambers for stability studies. How many humidity chambers have been provided. Pls attach stability calendar.			
8.2	Please specify the arrangement provided for handling and storage of test samples, retained samples, reference standards / cultures, reagents. Whether retained samples are stored for a period of 1 year after expiry or 3 years after distribution whichever is earlier?			

	Whether separate area for storage of reagents and glassware provided. Whether separate records room is provided.			
8.3	How hazardous or poisonous materials are stored and handled.			
8.4	How environmental conditions are met during the course of storage and testing of samples.			
8.5	Which grade of glassware are used in assay procedures.			
8.6	Whether separate AHU's are provided for biological, microbiological and radio iso-topes testing areas with HEPA filter arrangement.			
8.7	Whether separate areas provided for sterility testing within microbiology lab. Whether support areas are under AHU. Whether double door autoclave provided for sterilization of materials.			
8.8	Whether entry to the sterility area is through three air lock systems. What is the air class of these testing areas and whether pressure difference is maintained in these areas?			
8.9	Which types of workbenches are provided in these areas for testing? When was the last filter integrity tests performed on HEPA filters			
8.10	How waste (cultures etc) disposed of. Whether in case of antibiotic potency testing, statistical proof of the determination of potency and validity of the test carried out.			
9	***Personnel: -***			
9.1	Whether the manufacturing and testing of drugs is conducted under approved technical staff Names of Technical Staff alongwith qualification & experience For Manufacturing: - For Analysis:			

9.2	Please specify whether head of Q.C. is independent of manufacturing unit			
9.3	Name, qualification and experience of the personnel responsible for Quality Assurance function.			
9.4	Whether responsibilities for production and QC laid down and followed.			
9.5	Whether adequate number of personnel employed in direct proportion to the work load.			
9.6	What is the firm‟s policy on training of personnel at various levels?			
9.7	How is Periodic assessment of the training checked?			
10	***Health, clothing and sanitation of workers: -***			
10.1	Whether personnel handling Beta lactam antibiotics are tested for penicillin sensitivity before employment.			
10.2	Whether personnel involved in handling of sex hormones, cytotoxic and other portent drugs are periodically examined for adverse effect. (Pls specify whether the current SOP is followed or not).			
10.3	Whether all personnel prior to employment have undergone medical examination including eye examination and all free from Tuberculosis, skin and other communicable or contagious diseases			
10.4	Whether there is a SOP for medical examination.			
10.5	Pls give name and qualification of contracted medical officer for medical examination.			
10.6	Whether investigational reports, films of X rays etc. preserved. Whether records of such medical examination are maintained thereof			
10.7	Whether all personnel are trained to ensure high level of personal hygiene. Pls attach training calendar of last two years.			

10.8	Whether proper uniforms and adequate facilities for personal cleanliness are provided. Pls specify nature and type of dress used by the personnel in various areas of operation. How many dress/footwear have been provided to each personnel. Please specify whether cross over bench is in place in the change room and if so whether it rule out the possibility of entering dust particle to the clean side. Whether arrangements provided for cleaning of outside dust and dirt from foot Please specify whether hands are disinfected before entering the production area Whether for sterile garments in house clean laundry has been provided.			
11	***Manufacturing Operations and Controls: -***			
11.1	Whether the contents of all vessels and containers used in manufacture and storage is conspicuously labeled with the name of the products. Batch no, Batch Size, and stage of manufacture along with signature of technical staff.			
11.2	Whether the products not prepared under aseptic conditions are free from pathogens like Salmonella, Escherichia coli, Pyocyanea etc.			
11.3	If yes, pls give brief account of measures taken to assure freedom from pathogens.			
11.4	*Precautions against mix-up and cross-contamination: -*			
11.4.1	Whether proper AHU, pressure differential, segregation, status labeling have been provided to prevent mix-up and cross-contamination in manufacturing area			
11.4.2	Pls specify the areas of dust generation and mechanism involved in controlling the dust.			

11.4.3	Do all the areas have their own independent air locks separately for men and material entry.			
11.4.4	What criteria of pressure differential have been set for production v/s adjoining areas.			
11.4.5	Whether various operations are carried out in segregated areas.			
11.4.6	Whether processing of sensitive drugs like Beta lactum Antibiotics and Sex Hormones is done in segregated areas with independent AHU and proper pressure differentials alongwith demonstration of effective segregation of these areas with records.			
11.4.7	Please specify what measures has been taken to prevent contamination of products with Beta Lactum Antibiotics, Sex harmons and cyto toxic substances			
11.4.8	What measures has been taken to prevent mix-ups during various stages of production.			
11.4.9	Whether equipments use for production are labeled with their current status.			
11.4.10	What is the policy for the use of Recovery material?			
11.4.11	Whether packaging lines are independent and adequately segregated.			
11.4.12	How line clearance is performed. Whether records of line clearance is maintained according to appropriate checklist			
11.4.13	Whether separate coding area has been provided or online coding is performed How coding procedure is controlled.			
11.4.14	Please specify how temperature, humidity and air filtration are controlled in the areas where raw material and/or products are exposed and handled.			
11.4.15	How access of authorized persons to manufacturing areas including packaging is controlled.			

11.4.16	Whether separate gowning provision is follows before entering into the procedure.			
11.4.17	Whether segregated secured areas for recall or rejected materials or for such material which are to be processed or recovered are provided. Please specify the room No. of such areas in the plant.			
11.5	***Sanitation in the Manufacturing areas:-***			
11.5.1	Specify the cleaning procedure of the manufacturing areas. Whether cleaning procedure is validated. Please specify validation protocol No. of the same.			
11.5.2	Whether the manufacturing areas are used as the general thoroughfare and storage of materials not under process.			
11.5.3	Whether a routine sanitation program is in place. Please specify detailed account of sanitation proramme specific to various areas, equipment.			
11.5.3	Dose the location facilitate cleaning of equipment as well as the cleaning of the areas in which they are installed.			
11.5.4	Whether production area is adequately lit. If yes. Please give lux levels provided in production, visual inspect			
12	***Raw Materials: -***			
12.1	Whether the hard copies of records of Raw Materials are maintained.			
12.2	Please specify the procedures followed receiving and processing of in-coming materials (Starting materials and packing material).			
12.3	Whether first in / first out or first expiry principal has been adopted.			
12.4	How they are labeled and stored as per their status – Under Test, Approved and Rejected			
12.5	Whether incoming materials are purchased from approved sources.			

12.6	What is the procedure for approving the source for incoming materials.			
12.7	Whether the raw materials are directly purchased from the manufacturers.			
12.8	Whether list of approved vendors is available to the user.			
12.9	How damaged containers are identified recorded and segregated.			
12.10	How damaged containers are identified recorded and segregated.			
12.11	Whether all the containers of each batch of starting materials is sampled for identification test.			
12.12	Whether labels of raw material in the storage area have information like (a) designated name of the product and the internal code reference, where applicable, and analytical reference number; (b) manufacturer‘s name, address and batch number; (c) the status of the contents (e.g. quarantine, under test, released, approved, rejected); and (d) the manufacturing date, expiry date and re-test date.			
12.13	Whether separate areas are provided for under test, approved and rejected materials.			
12.14	How control on temperature and humidity conditions, wherever necessary, maintained in these storage areas.			
12.15	How the containers from which samples have been drawn labeled.			
12.16	Please specify the procedures by which it is ensured that the raw materials which has been released by the Quality Control Department and which are within their shelf life are going to be used in the product.			
12.17	How materials are stacked in the Stores i.e on Pallets, racks etc.			
13	***Equipment: -***			

13.1	Whether the equipments are designed aiming to minimize risk of error and permit effective cleaning in order to avoid cross contamination, build up of dust			
13.2	Whether all equipment are provided with log book.			
13.3	Please specify the procedures to clean the equipment after each batch production.			
13.4	Whether validity period for use after the cleaning of equipment is specified.			
13.5	Whether separate area is provided for storage of machine parts etc.			
13.6	Whether balances and other measuring equipments with appropriate range are available in the Raw Material stores & production areas and they are calibrated in accordance with SOP maintained. Specify the calibration schedule of the balances.			
13.7	Please specify material of construction of contact parts of the production equipments.			
13.8	Which types of lubricants are used in the equipment. Specify the quality and control reference No. of these lubricants.			
13.9	Specify the procedures to remove defective equipments from production areas.			
14	***Documentation and Records: -***			
14.1	How the documents are designed, prepared, reviewed and controlled to provide an audit trail. Whether documents are approved signed and dated by appropriate and authorized person. Whether documents are approved signed and dated by appropriate and authorized person. Whether documents specify title, nature and purpose. Whether documents are regularly reviewed and kept up to date. If yes. Please specify review period.			

	Please attached the list of documents maintained by the firm			
14.2	Whether the records are made at the time of each operation in such a way that all significant activities concerning to the production are traceable.			
14.3	Whether data is recorded by electronic data processing system or by other means. If by electronic data processing system then how access is controlled to enter, modify etc. the data.			
14.4	Whether master formula and detailed operating procedures are maintained as hard copy.			
14.5	Who is responsible for maintenance of these records.			
15	***Labels and Other Printed Materials:***			
15.1	Whether the printing is in bright colour and legible on labels and other printed materials.			
15.2	How printed labels (art work) are approved. Is there any SOP for this if yes please give current SOP No.			
15.3	Which colour coding system is used to indicate the status of a product and equipment.			
15.4	How printed packaging materials, product leaflets etc. are stored separately to avoid chances of mix-up.			
15.5	How labels cartons boxes circulars inserts and leaflets are controlled.			
15.6	Whether the samples from the bulk are drawn tested, approved and released prior to packaging and labeling. How carryout the sampling			
15.7	How records of receipt of all labeling and packaging materials are maintained.			
15.8	Whether re-conciliation of used packaging materials is maintained. Whether unused packaging materials return to the store or destroyed.			

15.9	How returned/unused packaging material like foils is controlled so as to prevent contamination and cross-contamination.			
15.10	How the labels of reference standard and culture maintained.			
16	***Quality Assurance: -***			
16.1	Specify the comprehensive quality assurance system maintained by the firm *Inter-alia* to cover deviation, reporting, investigation and change control. How the products are designed and developed in accordance with GMP.			
16.2	Please specify the arrangements provided to ensure that correct starting and packaging materials are used for manufacture.			
16.3	Please specify the mechanism by which all control like IP QC Calibration, Validation etc. are ensured.			
16.4	Please specify the mechanisms to ensure that the finished product has been correctly processed and checked in accordance with the established procedures.			
16.5	Please specify the mechanisms to ensure that Pharmaceuticals products are released for sale by authorization person.			
17	***Self Inspection and Quality Audit: -***			
17.1	Whether the firm has constituted a self inspection team supplemented with a quality audit procedure to evaluate that GMP is being followed. If no. How internal audits are carried out.			
17.2	What is the system of monitoring, evaluation of self inspection.			
17.3	How conclusion and recommended correcting actions are followed and adopted.			
17.4	What is the frequency of self-inspection.			
17.5	Is there any proforma for carrying out the self-inspection. Please indicate the date of last self-inspection.			
18	***Quality Control System: -***			

18.1	Please specify the details of quality control system of the unit.			
18.2	How the reference standards are stored, evaluated and maintained. Please provide list of reference standard and reference impurities procured from the authentic sources.			
18.3	Please specify the procedures of preparation of working standard from the reference standards.			
18.4	Whether SOPs for sampling, inspecting, testing of Raw Materials, Finish products, Packing Materials and for monitoring environmental conditions are available.			
18.5	Whether approved specifications for different materials, products, reagents, solvents including test of identity content, purity and quality available.			
18.6	How reference samples from each batch of the products are maintained.			
18.7	Who releases batch of the products for sale			
18.8	Whether there is check list for release of a batch. Please specify current SOP No. for batch release.			
18.9	Please specify the sampling procedures from various stages of production.			
18.10	How it is ensured that the sample collected are representative of the whole batch.			
18.11	Please specify the procedures for carrying out the stability studies.			
18.12	Under what condition stability studies of the products are tested. How many stability chambers have been provided.			
18.13	How self life is assigned to a product. Please give current stability protocol No.			
18.14	Whether records of stability studies are maintained.			
18.15	Please attach stability calendar of last year.			
18.16	How complaints are investigated.			
18.17	How instruments are calibrated and at which interval.			

18.18	How testing procedure validated before they are adopted for routine testing.			
18.19	Specify the validation procedure is responsible for validation of procedures.			
18.20	How validation procedures are documented (Please indicate various protocols/ recoding system applied during validation).			
18.21	Whether specifications for raw materials intermediates final products and packaging materials are available.			
18.22	Whether periodic revision of these specifications are carried out. Please specify No. of STPs being maintained by the firm.			
18.23	Which pharmacopoeias in original are available in the plant.			
19	***Specifications: -***			
19.1	Whether specification of raw material include. (a) the designated name and internal code reference; (b) reference, if any, to a pharmacopoeial monograph; (c) qualitative and quantitative requirements with acceptance limits; (d) name and address of manufacturer or supplier and original manufacturer of the material; (e) specimen of printed material; (f) directions for sampling and testing or reference to procedures; (g) storage conditions; and (h) Maximum period of storage before re-testing. Whether specification of finished product include (a) the designated name of the product and the code reference; (b) the formula or a reference to the formula and the pharmacopoeial reference; (c) directions for sampling and testing or a reference to procedures; (d) a description of the dosage form and package details;			

	(e) the qualitative and quantitative requirements, with the acceptance limits for release; (f) the storage conditions and precautions, where applicable, and (g) the shelf-life.			
19.2	Whether the container and closures meet the pharmacopial specifications. Whether second hand or used containers and closures used.			
20	**Master Formula Records: -**			
20.1	How master formula records are prepared, authorized and controlled.			
20.2	Whether head of production, quality control and quality assurance unit endorse this documents. Whether master formula is batch size specific.			
20.3	Whether all products have master formula containing. (a) the name of the product together with product reference code relating to its specifications; (b) the patent or proprietary name of the product along with the generic name, a description of the dosage form, strength, composition of the product and batch size; (c) name, quantity, and reference number of all the starting materials to be used. Mention shall be made of any substance that may „disappear" in the course of processing. (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable. (e) a statement of the processing location and the principal equipment to be used. (f) the methods, or reference to the methods, to be used for preparing the critical equipments including cleaning, assembling, calibrating, sterilizing; (g) detailed stepwise processing instructions and the time taken for each step;			

	(h) the instructions for in-process control with their limits; (i) the requirements for storage conditions of the products, including the container, labeling and special storage conditions where applicable; (j) any special precautions to be observed; (k) packing details and specimen labels.			
21	**Packaging Records: -**			
21.1	Whether authorized packaging instructions for each products, pack size and type are maintained and complied with. Whether following are included in the packaging instructions. (a) Name of the product; (b) the pack size expressed in terms of the weight or volume of the product in the final container; (d) complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types with the code or reference number relating to the specifications of each packaging material.; (e) reproduction of the relevant printed packaging materials and specimens indicating where batch number and expiry date of the product have been applied; (f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before the operations begin. (g) description of the packaging operation, including any significant subsidiary operations and equipment to be used; (h) details of in-process controls with instructions for sampling and acceptance; and (i) Re-conciliation after completion of the packing and labeling operation. (j) Whether line clearance records are part of batch packing records.			

22	***Batch Processing Records*** **(BPR)**			
22.1	Whether BPR are based on current master formula record.			
22.2	How BPR are designed to avoid transcription errors. Whether the Batch Processing Records for each product on the basis of currently approved master formula is being maintained. Whether following information are recorded in BPR (a) the name of the product, (b) the number of the batch being manufactured, (c) dates and time of commencement, significant intermediate stages and completion of production. (d) initials of the operator of different significant steps of production and where appropriate, of the person who checked each of these operations, (e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed, (f) any relevant processing operation or event and major equipment used, (g) a record of the in-process controls and the initials of the person(s) carrying them out,and the results obtained, (h) the amount of product obtained after different and critical stages of manufacture (yield), (i) comments or explanations for significant deviations from the expected yield limits shall be given, (j) notes on special problems including details, with signed authorization, for any deviation from the Master Formula, (k) Addition of any recovered or reprocessed material with reference to recovery or reprocessing stages. Specify the procedures for all the entries made in BPR‟s.			

	(l) Procedure for reprocessing and policy of the firm for adding of recovery.			
23	**Standard Operating Procedure and Records: -**			
	Whether SOPs and records are being maintained and complied for the following. SOP for receipt of in coming material (a) SOP for Internal labelling, quarantine, storage, packaging material and other materials (b) SOP for each instrument and Equipment (c) SOP for sampling (d) SOP for batch numbering (e) SOP for testing (f) SOP for equipment assembly and validation (g) SOP for Analytical apparatus and calibration (h) SOP for maintenance, cleaning and sanitation (i) SOP for training and hygiene for the personal (j) SOP for retaining reference Samples (k) SOP for handling, re-processing and recoveries (l) SOP for distribution of the product (m) SOP for warehousing of products. Whether applicable SOPs are available in each area where they are required. Whether recording formats are referred in SOP. Is there SOP for writing an SOP.			
24	**Reference Samples**			
24.1	Specify the procedures for collection of reference samples of active ingredients and finished formulations and how they are stored and maintained.			
25	**Reprocessing and Recoveries**			
25.1	Is appropriate Validation of recoveries and reprocessing done is being performed?			

26	**Distribution records**			
26.1	Whether pre dispatch inspections are carried out before release.			
26.2	Whether periodic audits of distribution center are carried out to access warehousing practices			
26.3	Whether distribution records are part of the batch record. If not how batch wise distribution record up to retail levels are maintained.			
26.4	Whether instruction for warehousing and stocking of products like LVPs, Heat sensitive etc are available in store.			
26.5	Whether Good Distribution Practices followed			
27	**Validation and Process Validation: -**			
27.1	Specify the validation policy of the company. Whether validation master plan has been prepared.			
27.2	Whether validation studies of processing, testing and cleaning procedures are conducted as per pre defined protocol.			
27.3	How records and conclusion of such validation studies are prepared and maintained.			
27.4	Whether master formula is based on approved process validation.			
27.5	Specify how significant changes to the manufacturing process equipments material etc are controlled.			
27.6	Whether DQ,IQ,OQ & PQ are in place for all major equipment and facility.			
27.7	Whether validation records of all utilities and major equipments are available.			
28	***Product Recalls: -***			
28.1	Specify the product recall system followed by the firm. How promptly recall operation at the level of each distribution channel up-to the retail level can be carried out. Whether there is a SOP for recall of products clearly defining			

	responsibility, procedure, reporting, re-conciliation etc.			
29	***Complaints and Adverse Reactions:***			
29.1	Specify the review system for complaints concerning the quality of products.			
29.2	How records of complaint maintained.			
29.3	Whether reports of serious complaints with comments and documents immediately sent to Licensing Authority			
29.4	Is there any criteria for action to be taken on the basis of nature of complaint.			
30	***Site Master file: -***			
30.1	Whether all the relevant information have been included in the site master file.			
30.2	Whether quality policy has been included in the site master file. Please attach the current version			
30.3	Is there a master plan (Master validation plan) covering:			
30.4	Resources and those responsible for its implementation.			
30.5	Identification of the systems and processes to be validated			
30.6	Documentation and standard operating procedures (SOPs), Work Instructions and Standards (applicable national and international standards)			
30.7	Validation list: facilities, processes (e.g. aseptic filling), products			
30.8	Key approval criteria			
30.9	Protocol format			
30.10	Each validation activity, including re-validation and reasonable unforeseen events (power failures, system crash and recovery, filter integrity failurer. Please attach validation calendar.			
30.11	Pls specify whether the critical processes validated Prospectively, retrospectively or concurrently.			
30.12	Whether validation of following performed and documented: Analytical methods, Production and assay equipment, Sterile production			

	processes, Non-sterile production processes, Cleaning procedures, Critical support systems (purified water, water for injections, air, vapor, etc.), Facilities			
30.13	Please list reasons considered important for validation or re-validation.			
30.14	In case electronic data processing systems are used, are these validated? Please specify whether periodical challenge tests performed on the system to verify reliability.			
30.15	Are the validation studies performed according to pre-defined protocols? Is a written report summarized, results and conclusions prepared and maintained? Is the validity of the critical processes and procedures established based on a validation study?			
30.16	Are criteria established to assess the changes originating a revalidation? Are trend analyses performed to assess the need to re-validate in order to assure the processes and procedures continue to obtain the desired results?			
31	**WATER SYSTEM** **PURIFIED WATER** **WATER FOR INJECTIONS**			
31.1	Please specify whether waster system qualification (IQ, OQ and PQ) has been carried out as per protocol and repots have been prepared and maintained.			
31.2	Whether IQ protocol include at least facility review, equipment specification vs. design, welding roughness testing on pipelines, absence of dead points / section in the pipelines, pipe and tank passivation, drawings, SOP for operations, cleaning, sanitation, maintenance and calibration of gadgets. Whether its report includes Conclusion / Summary, description of the performed assay, Data tables, Results, Conclusions, Protocol			

	reference, Revision and approval signatures.			
31.3	Whether OQ protocol include at least System production capacity (L/min), Flow type and water rate, Valve operation, Alarm system operation and Controls operation?			
31.4	Whether its report includes Conclusion / Summary, description of the performed assay, Data tables, Results, Conclusions, Protocol reference, Revision and approval signatures.			
31.5	Please specify the water whether Phase 1, Phase 2 and Phase 3 studies carried out in at PQ stages?			
31.5.1	Phase 1 : Whether the operations parameters, cleaning and sanitation procedures & frequencies defined. Whether daily sampling records for every pretreatment point and usage point for a period of 2 to 4 weeks maintained and SOP‘s prepared.			
31.5.2	PHASE 2 : Whether daily sampling records for every pretreatment point and usage point for a period of 4 to 5 weeks after Phase 1 maintained and reviewed.			
31.5.3	PHASE 3 : Whether weekly sampling records available of every usage point for a one-year period. In the case of water for injections systems, are the daily sampling records of at least one usage point available, with all the usage points sampled weekly? Whether results of these records summarized to show suitability. Are there personnel training records?			
32	**EQUIPMENT**			
32.1	Are the equipment installation Qualification (IQ) protocols contains followings: Introduction, Installation description, Responsibilities, Performed tests/assays, Qualification acceptance criteria and Data recording and reporting?			
32.2	Whether report contains Summary, Description of performed			

	tests/assays, Obtained data tables, Results, Conclusions, Installation diagrams, Revision and approval signatures.			
32.3	Whether the equipment operation qualification (OQ) protocols contains following: Introduction, Equipment description, Description of the equipment operation steps (SOP‘s), Responsibilities, Qualification acceptance criteria, Data recording and reporting. Whether report contains Summary, Description of performed tests/assays, Obtained data tables, Results, Conclusions, Revision and approval signatures.			
32.4	Whether equipment performance qualification (PQ) protocols contains followings: Introduction, Responsibilities, Performed assays, Qualification acceptance criteria, Data recording and reporting.			
32.5	Whether report contains Summary, Description of performed tests/assays, Obtained data tables, Results, Conclusions, Revision and approval signatures.			
32.6	Whether Preventive Maintenance Schedule of the equipments is followed and records available?			
33	**Analytical Method Validation**			
33.1	Please specify whether following Characteristics are considered during validation of analytical methods: — specificity — linearity — range — accuracy — precision — detection limit — quantitation limit — Robustness.			
33.2	Whether Paharmocopial methods are also validated. If yes, how.			
33.3	Whether system suitable testing is included in testing protocols e.g. HPLC, GC etc.			

33.4	Whether the procedure covers all aspects of impurity profiling required			
33.5	Whether procedure covers all aspects of Organic Volatile Impurities detection and quantification			
34	**CLEANING**			
34.1	Is a validation performed to confirm cleaning effectiveness?			
34.2	Does the protocol define the selection criteria for products or groups of products subject to cleaning validation?			
34.3	Is data produced supporting the conclusion that residues were removed to an acceptable level?			
34.4	Please specify whether the validation is implemented to verify cleaning of: Surfaces in contact with the product, After a change in product, Between shift batches.			
34.5	Please specify whether the Validation Strategy include contamination risks, equipment storage time, the need to store equipment dry and sterilize and free of pyrogens if necessary?			
34.6	Whether the cleaning Validation Protocol include: a. Interval between the end of production and the beginning of the cleaning SOP‘s. b. Cleaning SOP‘s to be used. c. Any monitoring equipment to be used. d. Number of consecutive cleaning cycles performed? e. Clearly defined sampling points.			
34.7	Whether Quality Control responsible of the sampling for cleaning verification?			
34.8	Whether personnel engaged in cleaning, sampling etc. trained.			
34.9	Please specify whether acceptance limits been set for cleaning verification and are based on following criteria: a. Visually clean.			

	b. 10 ppm in another product c. 0.1% of the therapeutic dose?			
34.10	Please specify whether detergent residues investigated and degradation products verified during validation.			
34.11	Whether validation records include Recovery study data, Analytical methods including Detection Limits and Quantification Limits, Acceptance Criteria, Signatures of the Quality Assurance Manager, employee in charge of cleaning and the verification from Production and Quality Control.			
35	**Air Handling System**			
35.1	Please specify whether following parameters have been qualified: — temperature — relative humidity — supply air quantities for all diffusers — return air or exhaust air quantities — room air change rates — room pressures (pressure differentials) — room airflow patterns — unidirectional flow velocities — containment system velocities —filter penetration tests (HEPA) — room particle counts — room clean-up rates — microbiological air and surface counts where appropriate — operation of de-dusting — warning/alarm systems where applicable.			
35.2	Whether strategic tests like Particle count, air pressure differential, air flow volume, air flow velocity etc. included in Air Handling System qualification.			
36	**Media fill test**			
36.1	Whether medial fill tests carried out twice in a year during normal working conditions.			
36.2	Pls give date of last such test.			
36.3	How many units are filled and tested.			

36.4	What is the criterion for qualification of this test?			
36.5	In case of failure of media fill test, what precautions or actions are taken.			
37	**Product Information**			
37.1	Name of product			
37.2	Whether validated master formula is available?			
37.3	Whether specific SOP for product processing is available?			
37.4	Comments on the above SOP			
37.5	Process Validation performed for the product covers all aspects and the approach is Risk Based			
37.6	No. of Batches Produced			
37.7	Stability studies (i) Accelerated (ii) Real Time (iii) Whether the expiry date assigned on the basis of stability study?			
37.8	Whether trend analysis was carried out and interpretation thereof?			
37.9	Whether Annual product review (APR) is carried out? Whether the following parameters considered in the Annual product review? 1 critical in-process control and critical API test results 2 all batches that failed to meet established specification(s) 3 all critical deviations or non-conformances and related investigations 4 any changes carried out to the processes or analytical methods 5 results of the stability monitoring programme 6 quality-related returns, complaints and recalls and adequacy of corrective actions			
37.10	Is there any complaint received for the product and If any, whether the investigation report along with ATR is maintained?			

	TITLE	Division Name	International Cell
	Procedure for review, and disposal of online application made through SUGAM portal for issuance of "Written Confirmation Certificate" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46b(2)(b) of Directives No. 2001/83/EC, by CDSCO-HQ	Document No.	INC-WCC-002
		Revision No.	00
		Effective Date	
		Page No.	713 of 1103

Prepared By		Checked By		Approved By		Authorized By	
Name		Name		Name		Name	
Designation		Designation		Designation		Designation	
Sign		Sign		Sign		Sign	
Date		Date		Date		Date	

1.0 Purpose

To lay down a procedure for review, and disposal of online application made through SUGAM portal (https://cdscoonline.gov.in) for issuance of "Written Confirmation Certificate" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46b(2)(b) of Directives No. 2001/83/EC, by CDSCO-HQ.

2.0 Scope

This document is applicable for International cell division and DCG (I) at CDSCO (HQ) to review the online application, inspection reports forwarded by CDSCO zonal and sub-zonal offices for issuance of "Written Confirmation Certificate' for active substances exported to the EU for medicinal products for human use, in accordance with Article 46b(2)(b) of Directives No. 2001/83/EC.

3.0 Responsibility:

Sr. No.	Designation as per SUGAM Portal	Responsibility
3.1	DA-Decision Authority International Cell at CDSCO (HQ)	3. Receipt and allocation of application in the SUGAM portal to 'RO'

		4. Review and forward the application to LA
3.2	RO-Review Officer International Cell at CDSCO (HQ)	Review and forward the application to SRO
3.3	SRO-Senior Review Officer International Cell at CDSCO (HQ)	Review and forward the application to DA
3.4	LA-Licensing Authority at CDCSO (HQ)	Review and issuance of "Written Confirmation Certificate"

4.0 Accountability

DA (Decision Authority) and LA (Licensing Authority) at CDSCO (HQ)

5.0 Procedure (Flow chart attached as **Annexure-I)**

5.17 Receipt and allocation of application by DA: - Application forwarded by Zonal/Sub-Zonal Office of CDSCO is received in DA portal at CDSCO (HQ) and allocated to RO for review and further processing of the application.

5.18 Review of application at RO level:-

5.18.1 Quality review of the application for ensuring uniformity

5.18.2 Communicating deficiencies or non-compliances (if any) to the applicant

5.18.3 Review of the responses submitted by the applicant

5.18.4 Forwarding the review comments to SRO

5.18.5 Communication with Zonal/Sub-Zonal Offices of CDSCO and the applicant through e-vartalap

5.19 Review of application at SRO level:-

5.19.1 Review of the assessment points noted by RO

5.19.2 Forwarding the application to DA

5.20 Review of application at DA level:-

5.20.1 Review of the assessment points noted by RO/SRO

5.20.2 Issuance of query to the applicant(if any)

5.20.3 Forwarding the application to Licensing Authority if satisfactory

5.21 Review of application at LA level:-

5.21.1 Review of the assessment points noted by RO/SRO/DA

5.21.2 Approval of application if found satisfactory

6.0 Timeline for disposal of "Written Confirmation" application:

- Review of Online application at RO Level 15 working days

- Review of Online application at SRO Level 05 Working days
- Review of Online application at DA Level 05 working days
- Review of Online application at LA Level 03 working days

6.0 Annexure

Annexure/Format No.	Title
Annexure-1	Procedure for receipt and process of online application

10.0 References

Doc. No.	Title
1	GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU
2.	CDSCO (HQ) circular no. F.No.7-5/2019/Misc/101 dated 09.09.2019
3.	CDSCO (HQ) circular no. F.No.7-5/2019/Misc/101 dated 04.03.2020
4.	Office Memorandum no. X.11035/43/2012-DFQC dated 12.11.2012
5.	CDSCO Circular no. 7-5/2019/Misc/01 dated 09.09.2019

11.0 Abbreviation

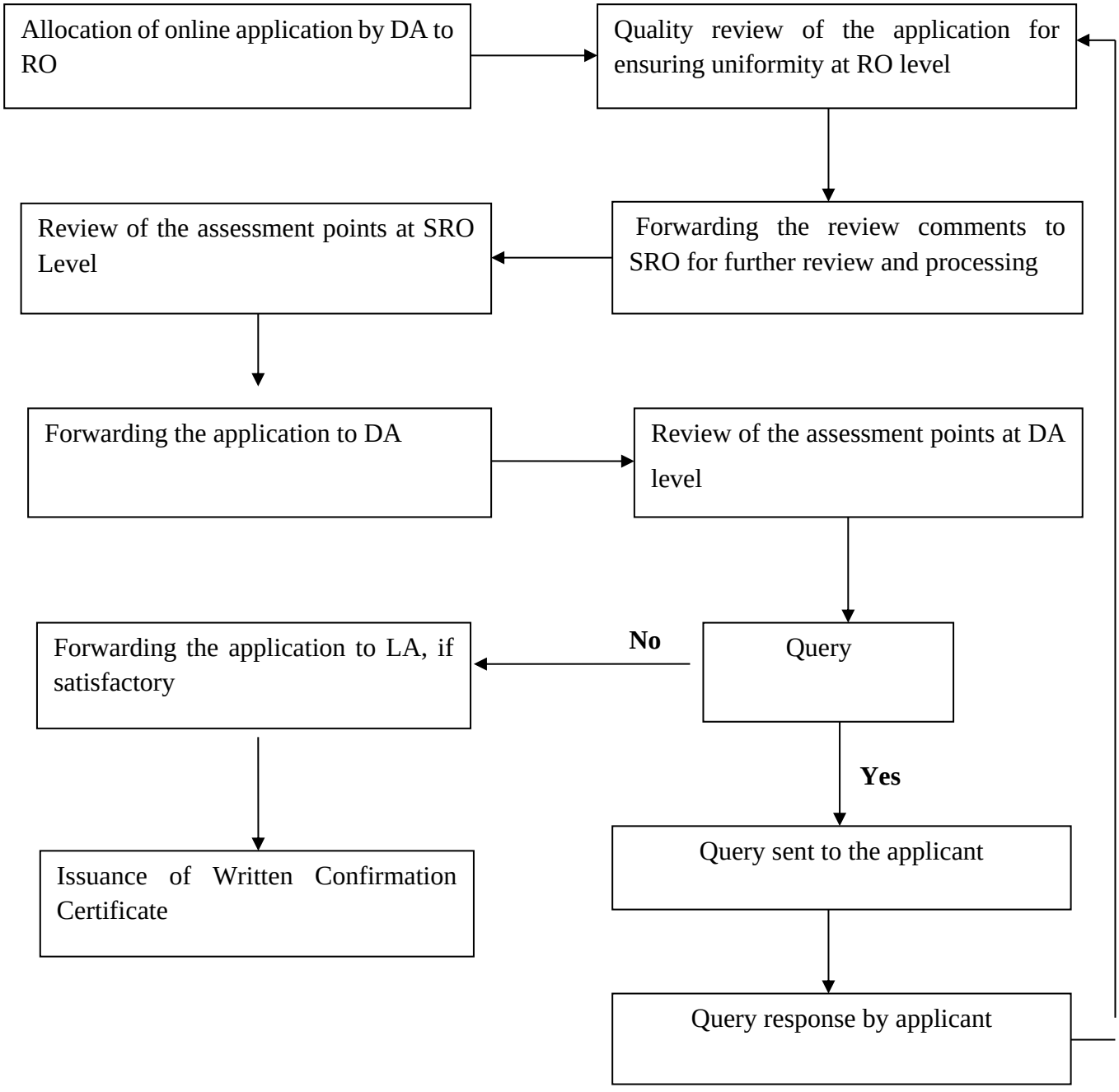
Acronym	Full Form
EC	European Commission
EU	European Union
WCC	Written Confirmation Certificate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
WHO	World Health Organization
CDSCO-HQ	Central Drugs Standard Control Organization-Headquarter
GMP	Good Manufacturing Practices
API	Active Pharmaceutical Ingredient

12.0 Revision History

Revision No.	Reason(s) for Revision
00	Implementation of New Format

Annexure-1 of INC-WCC-002

Process flow chart for review and process of online applications for issue of Written Confirmation Certificate at CDSCO (HQ)



	TITLE	Division Name	International Cell
	Procedure for forwarding Non-Compliance to EU	Document No.	INC-WCC-003
		Revision No.	00
		Effective Date	
		Page No.	718 of 1103

Prepared By		Checked By		Approved By		Authorized By	
Name		Name		Name		Name	
Designation		Designation		Designation		Designation	
Sign		Sign		Sign		Sign	
Date		Date		Date		Date	

1.0 Purpose

To lay down the procedure for forwarding Non-Compliances observed during review and inspection of the manufacturing premises to EU

2.0 Scope

This document is applicable to International cell& DCG(I) Office at CDSCO (HQ) for forwarding of Non-Compliances to EU for the manufacturers to whom "Written Confirmation" for active substances exported to the EU for medicinal products for human use, in accordance with Article 46b(2)(b) of Directives No. 2001/83/EC have already been issued.

3.0 Responsibility:

3.1	Heads of CDSCO Zonal and Sub Zonal Office	Forward the recommendation letter along with Inspection report/compliance verification report/Desktop Review report to CDSCO(HQ).
3.2	DCG(I) at CDCSO (HQ)	Forward the recommendation letter along with Inspection report/compliance verification report/Desktop Review report to Deputy Drugs Controller(India), International Cell(HQ)
3.3	Deputy Drugs Controller (India), International Cell at CDSCO (HQ)	Forward the recommendation letter along with Inspection report/compliance verification

		report/Desktop Review report to Assistant Drugs Controller(India), International Cell (HQ)
3.4	Drugs Inspector, International Cell at CDSCO (HQ)	Prepare summary of inspection findings.

4.0 Accountability

4.1 Drugs Controller General (India), CDSCO (HQ) and Deputy Drugs Controller(India), International Cell, HQ

5.0 **Procedure to be followed for forwarding Non-Compliance to EU**

5.1 Drugs Inspector of International Cell shall review recommendation letter pertaining to the WC application, inspection report, compliance verification inspection report / desk top review report forwarded through SUGAM WC online Portal by concerned heads of CDSCO, Zonal/subzonal Offices.

5.2 The Inspection findings at Active Pharmaceutical Ingredients manufacturing units carried out by any international Regulatory agencies like USFDA, UK-MHRA, PMDA etc., which have been circulated in digital media/news paper/news letter etc.,, shall also be considered for reporting to EU. The manufacturing unit to whom Written Confirmation Certificate has been already issued may be directed to submit the inspection findings of the inspections carried out by other regulatory agencies at their site.

5.3 The details of categories of Non-Compliances submitted in inspection report, compliance verification inspection report / desk top review report (if any for the observations noticed during the inspection) as well as inspection findings of other regulatory agencies shall be verified. If any, Critical and Major, Non-Compliances notified, details of Show Cause issued and any suitable action, if taken, shall be processed and forwarded to DCGI through ADC(I), DDC(I) and JDC(I) of International Cell for approval and to forward the Non-Compliances to EU.

5.4 Based on the DCGI approval, following information needs to be submitted to the EU:

1. Contact details of the notifying authority
2. Manufacturer name and address
3. Product-related information
4. Non-compliance issues

5.5 In case a “Written Confirmation” is suspended or cancelled, after successful compliance of Non Compliances observed during inspection by the firm the “Written Confirmation” shall be re-issued and same shall be informed to EU.

5.6 EU shall be informed by e-mail at qdefect@ema.europa.eu or by mail at the following address"Commission europeénne/EuropeseCommissie, Health and Consumers Directorate-General, 1049 Bruxelles/Brussel, BELGIQUE/BELGIË"

6.0 References

Doc. No.	Title
1	GMP requirements as per Directives No. 2001/83/EC latest amended vide Directive 2011/62/EU
2.	CDSCO (HQ) circular no. F.No.7-5/2019/Misc/101 dated 09.09.2019
3.	CDSCO (HQ) circular no. F.No.7-5/2019/Misc/101 dated 04.03.2020
4.	Office Memorandum no. X.11035/43/2012-DFQC dated 12.11.2012
5.	CDSCO Circular no. 7-5/2019/Misc/01 dated 09.09.2019

7.0 Abbreviation

Acronym	Full Form
EU	European Union
WCC	Written Confirmation Certificate
CDSCO (HQ)	Central Drugs Standard Control Organization, New Delhi
JDC(I)	Joint Drugs Controller(India)
DDC(I)	Deputy Drugs Controller (India)
ADC(I)	Assistant Drugs Controller (India)
DCGI	Drugs Controller General (India)
DI	Drugs Inspector

8.0 Revision History

Revision No.	Reason(s) for Revision
00	Implementation of New Format

Chapter- 11

Guidance Document for grant of permission for Drugs imported in Bulk for Non-Medicinal Use as per Rule 43 of Drugs and Cosmetics Rules 1945.

Introduction

This document provides guidance for the grant of permission for Drugs imported in Bulk for Non-Medicinal Use as per Rule 43 of Drugs and Cosmetics Rules 1945. The purpose of this guidance document is to ensure uniform implementation of Rule 43 of Drugs and Cosmetics Rule 1945 by CDSCO. It also specifies requirements to be fulfilled by the Importer for grant of such permissions. Efforts are also made to identify the list of drugs intended for Non- medicinal use with the help of stakeholders which can be amended from time to time.

The dual use permissions are usually requested by the manufacturer of bulk drug using one of the bulk drugs as starting material based on the approval of State Licensing Authorities. The dual use permission may also be sought by the other industries like food industries etc. which uses raw bulk substance in lower strength than approved as drug by this organization. Similarly, the Animal feed Industry makes application for the import of raw materials for the exclusive use as animal feed.

The list is enclosed with this guideline is only for reference purpose. The disposal of application is purely dependent on the intended use and its technical examination keeping in view the applicability of the status of drug.

The importers of dual use have a responsibility to undertake due diligence before making application for import of material for which following points may be important for consideration:

- The drugs already registered for import,
- Approval status of usages of imported item in the country (alone or in combination with other drugs),
- International status (e.g. in most of the countries multivitamins are not considered as drugs hence regulated differently)
- Technical survey through Martindale extra pharmacopeia etc.

The application for dual use import may be made well in advance before the actual import to facilitate technical review for consideration. The permission for dual use items will be granted by Dy. Drugs Controller (India) of the respective Zones.

For the purpose of this Guidance Document

1. “Drug” includes

(i) all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease

or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes;

(ii) Such substances (other than food) intended to affect the structure or any function of the human body or intended to be used for the destruction of [vermin] or insects which cause disease in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette;

(iii) All substances intended for use as components of a drug including empty gelatin capsules; and

(iv) Such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette, after consultation with the Board.

2. Rule 43 The drugs specified in Schedule D shall be exempt from the provisions of Chapter III of the Drugs and Cosmetics Act and of the Rules made there under to the extent, and subject to the conditions specified in that Schedule.

3. Schedule-D

Class of drugs	Extent and conditions of exemption
Substances not Intended for Medicinal Use excluding those intended to be used as drugs after further purification or rendering them sterile	All provisions of Chapter III of the Act and rules there under subject to the condition that if the substance is imported in bulk, the importer shall certify that the substance is imported for nonmedicinal uses, and if imported otherwise than in bulk, each container shall bear a label indicating that the substance is not intended for medicinal use or is of commercial quality.

Based on the intended use of the product, the drugs that are falling under Schedule-D of Drugs and Cosmetic Rules have been categorised into:

1. Drugs meant for Non- medicinal use.
2. Drugs meant for Animal feed supplement, Feed premix.
3. Drugs meant for further processing / conversion to other drug.

1. Drugs Meant for Non- Medicinal Use:

The following documents are required to be submitted for the items specified in **Table No. 1** to the Zonal Office for grant of necessary permission under Schedule - D, preferably before importing the consignment.

i. Covering letter- The applicant should submit covering letter by clearly specifying purpose of application, the drugs to be imported, the intended use of the drug, quantity to be imported, name and address of the manufacturer and list of documents that 398 are being enclosed (Index with page numbers). The covering letter should be duly signed and stamped by the Authorised Signatory, indicating name and Designation of the Authorised Signatory. The pages of the application should be numbered and should be accompanied with index.

ii. Legal Undertaking- The applicant has to submit Legal Undertaking on Rs. 100 stamp paper as per the proforma given under Annexure-I. (If the drug is imported by the actual User, Legal Undertaking as per the proforma provided in Annexure-II should be obtained from the Trader. The Trader has to retain such undertaking issued by the actual user for any inspection carried out by the regulators).

iii. A copy of valid Manufacturing Licence from Actual User for the products to be manufactured, issued by the Competent Authority wherein the imported drug will be used. iv. A copy of valid trade licence / Excise Registration Certificate from importer.

iv. A copy of letter (notarised) issued by the Competent Authority stating that the imported drug will be used in the manufacture of said finished product and not as an active principle. vi. A copy of Certificate of Analysis of the drug to be imported, issued by the manufacturer in the country of origin (not by exporter).

v. Detailed Technical Literature of the drug to be imported. viii. For subsequent permission, Reconciliation data of previously permitted quantity in addition to above details.

vi. For subsequent permission, Reconciliation data of previously permitted quantity in addition to above details.

Table No.: 1

S.NO	Drugs Names
1.	Aluminium Hydroxide
2.	Benzoyl peroxide
3.	Calcium Carbonate
4.	Cinchonine
5.	Citric acid
6.	Coumarin
7.	Cysteamine HCl
8.	Di calcium phosphate
9.	Diflorasone Base
10.	Disodium carbonate
11.	Disopyramide base

12.	Empty hard gelatine Capsules with TSE/BSE free certificate and GMP declaration of the manufacturing firm.
13.	Estrone
14.	Glycerine with pharmacopeial grade
15.	Guanidine hydrochloride
16.	Heavy Magnesium Carbonate
17.	Hesperidine
18.	Hydrogen Peroxide Pharmacopeial grade
19.	Isoxepac
20.	Magnesium hydroxide
21.	Magnesium oxide
22.	Magnesium Sulphate
23.	Mannitol (non for parenteral use)
24.	Mixed tocopherols 50%
25.	Monensin Sodium
26.	Simethicone Emulsion
27.	Triacetin
28.	Zinc Gluconate
29.	Manganese Sulphate
30.	Alpha Lipoic Acid
31.	Zinc Oxide
32.	Any Other Drug having Dual Use which may find suitable to be included in list.

2. Drugs meant for Animal feed supplement, Feed premix

Before grant of NOC for release of items stated in Table no.-2, the concerned Port Officer should verify / examine following documents-

i. Legal Undertaking- The applicant has to submit Legal Undertaking on Rs. 100 stamp paper as per the proforma given under Annexure I. (If the drug is imported by the actual User, Legal Undertaking as per the proforma provided in Annexure-II should be obtained from the Trader. The Trader has to retain such undertaking issued by the actual user for any inspection carried out by the regulators).
ii. Purchase order / Proforma invoice of the material to be imported.

iii. NOC from the Ministry of Animal Husbandry in favour of importer / manufacturers, if any.

iv. A copy of valid trade licence / Excise Registration Certificate from importer.

v. A copy of letter (notarised) issued by the Competent Authority stating that the imported drug will be used in the manufacture of said finished product and not as an active principle but as feed.

vi. A copy of Certificate of Analysis of the drug to be imported, issued by the manufacturer in the country of origin (not by exporter).

vii. Detailed Technical Literature of the item to be imported. 401 viii. For subsequent permission, Reconciliation data of previously permitted quantity in addition to above details.

Table No. - 2

List of the feed grade items which requires NOC from Port Office (CDSCO) for exclusive use in animal feed industry as an animal feed supplement, feed premix.

I. Amino Acids (granular)

i) L-Lysine Mono HCL 99% Feed grade
ii) L-Lysine Sulphate 65% Feed grade
iii) L-Lysine Sulphate 80% Feed Grade
iv) Methionine 90% Feed Grade
v) DL-Methionine 99% Feed grade
vi) L-Methionine 99% Feed Grade
vii) L-methionine 90%, Feed Grade
viii) L-Valine 98% Feed Grade
ix) L-Threonine Feed Grade
x) Methyl Hydroxy Analog 88% Feed Grade
xi) Methyl Hydroxy Analog Calcium salt 84% Feed Grade
xii) L-Threonine 98.5% Feed Grade
xiii) L-Tryptophan 98% Feed Grade
xiv) Isoleucine 98.5% by titration method or 90% by HPLC method-Feed Grade
xv) L- Lysine Monohydrochloride 98.5% Feed Grade (If genetically modified strain of bacteria is used to produce L-Lysine, its use shall be prohibited in view of possible presence of viable cells and DNA of the production strain in final product)
xvi) L- Lysine Sulphate 70% Feed Grade (If genetically modified strains of bacteria are used to produce L-Lysine, its use shall be prohibited in view of possible presence of viable cells and DNA of the production strain in final product)
xvii) L-arginine 98.5% Feed Grade (The product is also being sold as feed grade in exporting country and certificate to this effect should be accompanied with each consignment)
xviii) Coated Amino acids for dairy

II. Vitamin Premix

i. Vitamin AD3 Feed grade 1000:200
ii. Vitamin A Acetate 1000 Feed Grade
iii. Vitamin E 50% Feed grade
iv. Vitamin C coated 35% Feed Grade
v. Vitamin D3 0.5 miu/gm feed grade
vi. Vitamin B2 80% feed grade
vii. Biotin 2% & 10% Feed Grade
viii. Vitamin mineral Premix feed grade (as per formula)
ix. Choline chloride 50% & 60% on Corn Cob Feed Grade
x. Vitamin C 35% Monophosphate Feed Grade
xi. Vitamin B12 1% & 2% Feed Grade (As vitamin B12 is produced by fermentation by bacteria, it is necessary to ensure that the strain used for fermentation is safe and that there is

no presence of antibiotic resistance genes, the viable cells of the production strain or their DNA in the final product)

xii. 25 Hydroxy Vitamin D3 1.25% Feed Grade

III. Vitamins (May be used as feed additives / premixes in different compositions in animal feed manufacturing. However, the import of Active Pharmaceutical Ingredients (APIs) shall be as per the extant rules under the Drugs and Cosmetics Act, 1940)

i. Vitamin AD3
ii. Vitamin D
iii. Vitamin A
iv. Vitamin E
v. Vitamin K (MNB/MSB)
vi. Vitamin B1
vii. Vitamin B2
viii. VitaminB3 –Niacin
ix. Vitamin B5- Calpan
x. Vitamin B6
xi. Vitamin H - Biotin
xii. Vitamin B9- Folic Acid
xiii. Vitamin B 12
xiv. Vitamin C (L-ascorbic acid/ L-ascorbic acid Phosphate)
xv. Vitamin D 310

IV Chelate Minerals:-

Sr. No	Products	Remark
1	Glycinated Minerals	Composition varies with Manganese, Iron, Cobalt, Chromium, Selenium, Zinc, Copper, Iodine etc as glycinated blend or single mineral glycinate.
2	Proteinated Minerals	Composition varies with Manganese, Iron, Cobalt, Chromium, Selenium, Zinc, Copper, Iodine etc as Proteinated blend or single mineral Proteinate
3	Proteinated (Yeast based) Minerals	Composition varies with Manganese, Iron, Cobalt, Chromium, Selenium, Zinc, Copper, Iodine etc as Proteinated blend or single mineral Proteinate
4	Amino acid chelated minerals	Composition varies with Manganese, Iron, Cobalt, Chromium, Selenium, Zinc, Copper, Iodine etc with methionine or lysine based chelated blend or single amino acid chelate.

V Phosphates (Feed Grade)

i. Mono Calcium Phosphate (MCP) 22% Feed Grade

ii. Di Calcium Phosphate (DCP) 18% Feed Grade
iii. Sodium Hydrogen Phosphate 17% Feed Grade
iv. Mono Potassium Phosphate 26% Feed Grade
v. Di Potassium Phosphate 17% Feed Grade
vi. Cholesterol 95% Feed Grade

VI Enzymes (Feed Grade)

i. Phytase 5000 - 65000 FTU per gram Feed Grade
(The production strain (used to produce phytase) and its recombinant DNA should not be detected in products.)

VII Antibiotic / Antibacterial Feed Additives

i. Chlortetracycline (CTC) 15% Feed Grade
ii. Clopidol 25% Feed Grade
iii. Dichhlozuril 1% Feed Grade
iv. Tylosyn Phosphate 10% premix Feed Grade

VIII. Anticoccidiostats

i. Maduramycin 1% Feed grade (Use for broiler chicken only and withdrawal period of five-seven days should be given before disposal/slaughter)
ii. Salinomycin 12%
iii. Nicarbazine – upto 25% Feed Grade (Up to 25% can be used alone or in combination with Narasin (Feed Grade). However maximum dose of Nicarbazine should not exceed 125mg/kg of feed. Withdrawal period of 24 hours should be followed for use in poultry before slaughter.)
iv. Monensin Sodium 20% Premix Feed Grade Do not feed to laying chickens. Do not feed to chickens over 16 weeks of age. Do not allow horses, other equines, mature turkeys, or guinea fowl access to feed containing monensin.
v. Monensin Sodium 40% Feed Grade Do not feed to laying chickens. Do not feed to chickens over 16 weeks of age. Do not allow horses, other equines, mature turkeys, or guinea fowl access to feed containing monensin.
vi. Losolacid Sodium 15% Premix Feed Grade
vii. Decoquinate 6% Feed Grade
viii. Dinitolmide 25% Feed Grade (DOT)
ix. Clopidol 25% Feed Grade
x. Ethopabate 33% Feed Grade
xi. Halofuginione 6 % Feed Grade (Not to be fed to layers. In broilers withdrawal period of five days should be given before slaughter.)
xii. Narasin 10% (Feed Grade) (As per Codex Alimetarius Maximum residue limit (MRL) should not exceed 50 µg/kg iliver, fat, 15 µg/kg in muscles.)
xiii. Robenidine 10% Premix (Feed Grade) (MRL (mg/kg wet tissue) should not exceed 0.80 for liver, 0.35 for kidney, 0.20 for muscle and 1.30 for skin/fat)

IX. Medicated Feed Additive (Feed Grade)

S. No	Product	Remark
1	Flavophospholipol 4% & 8% Feed Grade	
2	Tiamulin Hydrogen Fumerate – 10% Feed Grade	Withdrawal period of 72 hours should be followed for use in poultry before slaughter.
3	Bamberomycin 4% and 8% - Feed Grade	Recommended at low dosages i.e. 1-2g/ton of feed in poultry
4	Lincomycin 11% - Feed Premix	As per Codex Alimetarius Maximum Residue Limit (MRL) should not exceed 100 µg/kg fat, 200 µg/kg in muscles, 500 µg/kg in liver and kidney.
5	Tiamulin 10% Feed Premix	Withdrawal period of 72 hours should be followed for use in poultry before slaughter
6	Virginiamycin 50% -Feed Grade	Withdrawal period of 5 days should be followed for use in poultry before slaughter.
7	Kitasamycin 8% feed premix	Withdrawal period of 7 days should be followed for use in poultry before slaughter.
8	Avilamycin 10% Feed Grade	As per Codex Alimetarius, Maximum residue limit (MRL) should not exceed 2000 µg/kg chicken fat/skin, and 300 µg/kg in liver.
9	Spectinomycin 2.2% feed premix	As per Codex Alimetarius Maximum residue limit (MRL) should not exceed 2000 µg/kg in liver, egg, fat, 500 µg/kg in kidney, 500 µg/kg in muscles
10	Combination of Lincomycin 2.2% (feed premix) and Spectinomycin (feed premix).	As mentioned earlier
11	Kitamycin 15% (Feed Grade)	Withdrawal period of 7 days should be followed for use in poultry before slaughter
12	Enramycin 8% Feed Grade	

X Probiotics (Feed Grade)

i. Bacillus amyoliquefaciens Feed Grade
ii. Probiotics Bacillus licheniforms feed grade
iii. Bacillus pumilus
iv. Dried Lactobacillus acidophilus fermentation product
v. Dried Enterococus faecius fermentation product

vi. Dried Lactobacillus plantarum fermentation product
vii. Enterococcus faecium feed grade

XI Minerals (Feed Grade)

i. Apocarotenoic ester Feed Grade
ii. Betacarotene 10% Feed Grade

XII Antioxidant

i. Propyl Gallate

XIII Exclusive Livestock Feed

i. Bypass Fat (triglyceride)

XIV Others (Feed Grade):-

S. No.	List of items used in food	
1.	Antioxidant Premix – Mixture of BHA, BHT & Ethoxiquin	
2.	Toxin Binders Feed Grade	
3.	Acidifiers Feed Grade – Mixture of organic acids	
4.	Inactivated Dry yeast (37-40% Protein) Feed Grade	
5.	Active Dry Yeast - Feed Grade	
6.	Yeast Cell Wall – for use in feed	
7.	Mannan-Oligosaccharides (MOS) & Fructo-oligosaccharides (FOS)	
8.	HSCAS - Hydrogen Sodium Calcium Amino Silicate for feed use.	
9.	Rumen protected/bypass amino acids – feed grade	
10.	Dried distillers grains with soluble (DDGS)	
11.	Cocktail enzymes – combination of enzymes for use in feed	
12.	Organic mineral mixtures – feed grade	
13.	Dried Bacillus subtilis fermentation products (Feed Grade)	
14.	Mould inhibitors feed grade Organic selenium feed grade	
15.	Organic trace minerals for feed	

16.	Dicalcium phosphate (feed grade) Tricalcium Phosphate (feed grade)	
17.	Nosiheptide 1% feed grade	
18.	Bacteriophage (Lytic & Temperate)	
19.	Yucca schidigera / Yucca plant extract	
20.	Pellet Binder	To be used in Cattle Feed, Poultry Feed and Aqua Feed
21.	Sodium Diformate	
22.	Potassium Diformate	
23.	Combination of fibre degrading enzymes (e.g. xylanase, betaglucanase, cellulase, betamannanase, amalyse, lipase, protease etc.)	
24.	Rumen Buffers	To be used in Cattle Feed
25.	Salt licks – Mineral supplement for cattle (Calcium, Phosphorus, Cobalt, Copper, Iodine, Manganese, Zinc)	
26.	Calcium salt of fatty acid (Oleic Acid, Palmitoleic Acid, Linolenic Acid)	
27.	Co-Enzyme Q 10 (Ubiquinone) 5% & 10% Premix (Feed Grade)	
28.	Calcium Butyrate coated (Feed Grade)	
29.	Sodium Butyrate Coated 30% (Feed Grade)	
30.	Bypass fats based on fatty acid FFA > 80%	
31.	Molasses Dried yeast – for animal feed	
32.	Selenium yeast Premix (Feed Grade)	
33.	Bacillus substilis Feed Grade	
34.	Algae based complimentary feed for fish (Azolla, Chlorella, Filamentous Algae)	
35.	Mixture of essential oil with plant extracts and spices (Thyme, Oregano, Rosemary, Thymol, Cinnamon)	
36.	Fumaric Acid	
37.	Saponine 2-2.5%	
38.	Calcium salts made from palm oil fatty acids, soya oil, sunflower oil and corn oil	
39.	Betaine HCL 93-98%	
40.	Deoiled Lecithin 90% on silicon Dioxide base	
41.	Betaine Anhydrous 96%	
42.	Bypass fat (fatty acid based)	

43.	Conjugated linolenic acid 10% Coated with bypass fat	
44.	Tributyrin 50%	

XIV Others (Feed Grade):-

i. Magnesium Sulphate (Anhydrous)

Feed grade Any other product included in the list of poultry/ Animal Feeds shall be included after approval from the Animal Husbandry Department.

NOTE:- Due to emergence of antimicrobial resistance in animal and human beings, henceforth, the following animal feed additives / feed supplements are not recommended for import into India:-

Category of Product	Name of the Product	Remarks
Antibiotic/ Antibacterial (Feed Grade)	Zinc Bacitracin	Earlier, these products were not recommended in the list issued on 13th August, 2020. It has been reviewed in the meeting dated 17th May, 2022 of subcommittee to 'assess and provide recommendations on submission of veterinary vaccines/biological/drugs for policy input' under the Expert Committee on Animal Health (ECAH).
	BMD – Bacitracin Methyl Disalicylate	
Anticoccidals (Feed Grade)	Any combination of Maduramycin and Nicarbazine	
	Maduramycin>1%	Reviewed in the meeting dated 17th May, 2022 of subcommittee to 'assess and provide recommendations on submission of veterinary vaccines/biological/drugs for policy input' under the Expert Committee on Animal Health (ECAH)

The Maximum Residue Limit / Tolerance limit of above recommended animal feed additives and feed supplements in the final article of food, wherever applicable, shall be as per the Food Safety and Standards (Contaminants, toxins and Residues) Second Amendment Regulations, 2018.

3. Drugs meant for further processing / conversion to other drug

For the import of any substance which attracts the definition of ―Drug as per the Drugs and Cosmetics Act 1940 for further processing / conversion to manufacture of other drugs, shall require NOC from Zonal Office for each consignment.

e.g.:- Erythromycin Thiocyanate for the manufacture of Erythromycin salts, Penicillin G Potassium for the manufacture of Penicillin drugs. Such permissions are considered for those manufactures which does not have manufacturing permission in the country for imported drug, however they got permission for manufacture of other drug using imported drug.

The following documents are required to be submitted to the Zonal Office for grant of necessary permission under Schedule- D, preferably before importing the consignment.

i. Covering letter- The applicant should submit covering letter by clearly specifying purpose of application, the drugs to be imported, quantity to be imported, name and address of the manufacturer and list of documents that are being enclosed (Index with page numbers). The covering letter should be duly signed and stamped by the Authorised Signatory, indicating name and Designation of the Authorised Signatory.

ii. A copy of Valid Drug Manufacturing Licence for the Drug to be manufactured, issued by the Drug Licensing Authority wherein the imported drug will be used.

iii. A copy of Master Formula Record of the product to be manufactured Signed and Stamped by the Authorised Signatory of the Firm.

iv. A copy of Certificate of Analysis of the drug to be imported, issued by the manufacturer.

v. Detailed Justification of the quantity of Drug to be imported.

vi. Brief Manufacturing Process including Flowchart wherein the imported product will be used.

vii. Detailed Technical Literature of the drug to be imported.

viii. For Subsequent permission, Reconciliation data of previously permitted quantity in addition to above details.

(The import of drug under dual use for purification or rendering it sterile will not be considered under dual use)

Table 3:

S. no.	Drugs meant for further processing/ conversion to other drugs	S.No	Drugs meant for further processing/ conversion to other drugs

1.	Aloe emodin	206.	Alkosel (prebiotics & probiotics
2.	Artemisinin	207.	Aminovilt Gold(Amino acid premix)
3.	Betamethasone base	208.	Ascorbic Acid
4.	Cyclocytidine HCL	209.	Availa Cu (chelated minerals)
5.	Erythromycin base	210.	Bectocell aqua (prebiotics & probiotics)
6.	Erythromycin Thiocyanate	211.	Betaine HCL 93-98%
7.	Flumethasone	212.	Betaine 96 %
8.	Fluorocytosine	213.	Biotin 2% & 10%
9.	5- Fluorouracil	214.	Btraxim Pro (Zinc & Magnesium)
10.	Fluticasone	215.	Carophyll Red 10%
11.	Hydrocortisone Base	216.	Carophyll yellow 10%
12.	L-arginine	217.	Cholesterol 95%
13.	L-phenyl alanine	218.	Choline Chloride 50% & 60%
14.	L-serine	219.	Dicalcium Phosphate 18%
15.	Penicillin G Potassium	220.	DL-Methionine 99%
16.	Piperazine Anhydrous	221.	Fibosel (prebiotics & probiotics)
17.	Prednisolone base	222.	Granulated Enzyme
18.	Riboflavin 80%	223.	Hydroxy Vitamin D3 0.5 mul/gm
19.	Salicylic acid	224.	Inositol
20.	Sirolimus	225.	L-Tryptophan 98%
21.	Sulphanillamide	226.	Levucell $B 20 (prebiotics & probiotics)
22.	Theophylline Crude	227.	Levucell SB10 ME Titan (prebiotics & probiotics)
23.	19-Nor-4-androsterone - 3,17-dione	228.	L-Lysine monohydrochloride 99%
24.	17 aplha hydroxy progesterone	229.	L-lysine sulphate 70%
25.	Acyclovir	230.	L-Threonine 98.5%

26.	Buprenorphine	231.	Lutavit B2 (Vitamin 82) 80%
27.	Chloramphenicol	232.	Lutavit B2 (Vitamin E)50%
28.	Dexamethasone	233.	Menadione Nicotinamide
29.	Mibemycin	234.	Methionine Analogue
30.	Morphine	235.	Monocalcium Phosphate 22%
31.	Oxytetracycline	236.	Phytase
32.	Thiamin Hydrochloride	237.	Propionic acid 42%
33.	Thiamine mononitrate	238.	Rovimix AD3 Vitamin A/D3 1000.200
34.	Tobramycin	239.	Rovimix 82 (Vitamin B2)
35.	Vancomycin Base	240.	Rovimix Calpan Vitamin B5
36.	36 Rovimix E5O (Vitamin E)	241.	Vitamin B1
37.	Saponine 2-2.5%	242.	Vitamin B12
38.	Tiamulin Hydrogen Fumarate 10%	243.	Vitamin K3
39.	Toxin Binders	244.	Xylanase, Beta-glucanase,cellulase, beta- mannase, amylase, lipsae protease
40.	Chlotetracycline 15%	245.	Monensin Sodium 20%
41.	Clopidol 25%	246.	Losolacid Sodium 15%
42.	Tylosin phophate 10%	247.	Nicarbazine 8%
43.	Maduramycin 1%	248.	Furazolidone
44.	Salinomycin 12%	249.	Ferric Oxide
45.	17-Alpha-1-methyl Testosterone	250.	Ferric Pyrophosphate
46.	2-Dimethylaminoethanol	251.	Ferrous Fumarate
47.	8-HydroxyQuinoline Sulphate	252.	Flavophospholidal
48.	Acerola Organic Powder	253.	Fructose syp
49.	Acid Cellulase Liquid	254.	Fungal hemi cellulase

50.	Acotiamide	255.	Ganciclovir
51.	Activated Carbon	256.	Gelatin
52.	Active Carbon	257.	Genu pectin LM 22CG LM-18CGYA D slow set
53.	Alendronic acid	258.	Gingko
54.	Alfacalcidol	259.	Gingko Biloba Extract, Aloe vera extract, Siberian Ganteng P.E
55.	Alfalfa Powder	260.	Glutamic acid
56.	Alginic Acid	261.	Glycerine
57.	Aloe Vera Gel	262.	Glycerol Formal Stabilized
58.	Alpha Amylase	263.	Glycine
59.	Alpha Tocopherol Acetate	264.	Glycocholic Acid
60.	Alumina Trihydrate	265.	Granulated Amigel
61.	Aluminium Chlorohydrate	266.	Grindamyl
62.	Aluminium Hydroxide	267.	Gualacol
63.	Aluminium Magnesium Hydroxide	268.	Guanidine
64.	Aluminium Oxide	269.	Guanidine Hydrochloride
65.	Aluminium Trihydrate	270.	Heme Iron polypeptide
66.	Amantadine	271.	Hide Glue
67.	Amino Pyridine	272.	HPMC Capsule
68.	Aminoguanide Bicarbonate	273.	hyacare Filler CL
69.	Ammonium Sulfate	274.	Hyaluronic Acid
70.	Amylase	275.	Hydrocortisone IP
71.	Anethole	276.	Hydrogen Fumarate
72.	Anhydrous Lactose NF	277.	Hydrogen Peroxide
73.	Anti-Irritant-Complex	278.	Hydroquinone
74.	Apple Herbasol Vinegar Extract	279.	Hydroxychloroquine

75.	Apremilast	280.	Hydroxypropyl Methylcellulose
76.	Arsenic Trioxide	281.	Hydroxyquinoline
77.	Ascorbic Acid	282.	Hypromellose
78.	Bakery Enzyme	283.	Hyroquinone
79.	Barium Sulphate	284.	lodine
80.	Beclamethasone	285.	ISO Eugenol
81.	Benzyl Alcohol	286.	Iso Propyl Alcohol
82.	Beta carotene 20%	287.	Isomalt
83.	Betain HCL	288.	L+Ascorbic Acid
84.	Betasitosterol	289.	Lactic Acid
85.	Blackberry Fruit Herbasol	290.	Lactobacillus
86.	Borax Pentahydrate	291.	Lactose monohydrate
87.	Boric Acid	292.	Lactrol
88.	Brimonidine	293.	L-Alpha-Glycerylphosphorycholine
89.	Caffeine	294.	L-Analine
90.	Calcite Minerals	295.	L-Arbinose
91.	Calcite Powder	296.	L-Arginine
92.	Calcium Acetate	297.	L-Ascorbate
93.	Calcium Ascorbate	298.	LAVA Cell
94.	Calcium Carbonate	299.	L-Carnitine base
95.	Calcium D Phosphate	300.	L-Carnosine
96.	Calcium D-Pantothenate	301.	L-Citruline
97.	Calcium Gluconate	302.	L-citruline L-malate
98.	Calcium Hydrogen Phosphate	303.	Lifwinu Bacillus
99.	Calcium Lactate	304.	Lipold
100	Calcium Propionate	305.	Lipoid PG

101	Calcium Saccharate	306.	Lithium Bromide Solution
102	Calcium Stearate	307.	Uthium Carbonate
103	Cannabidiol	308.	L-Lysine
104	Carbophyll	309.	L-Ornithine HCI
105	Carmustine	310.	Lovastatin
106	Carnitine	311.	L-Prolinamide
107	Castor Oil	312.	L-Proline
108	C-Cysteine	313.	L-Serine
109	Cellulase	314.	Magneisum Hydroxide
110	Charcoal Activated	315.	Magnesium Ascorbyl
111	Chemodeoxycholic acid	316.	Magnesium Carbonate
112	Chitosan	317.	Magnesium Chloridde
113	Chloride Solution	318.	Magnesium Oxide
114	Chlorobutanol	319.	Magnesium Stearate
115	Chlorpromazine Hydrochloride	320.	Magnesium Sulfate
116	Chlortetracycline	321.	Mannitol
117	Chlorzoxa 20me	322.	Mannose
118	Cholesterol	323.	Mehyl Salicylate
119	Choline Bitartrate	324.	Meltodextrin
120	Choline Chloride	325.	Methoxyphenol
121	Chondrotain Sulphate	326.	Methyl Butyrate
122	Cinchonine	327.	Methyl Cellulose
123	Citric acid monohydrate/Anhydrous	328.	Methyl Cholate
124	Climbazole	329.	Methyl Eugenol
125	Clove Leaf Oil	330.	Methyl Salicylater
126	Clove Oil	331.	Methylphenidate

127	Clove Rectified	332.	Methylprednisolone
128	Coated Calcite Powder	333.	Microcrystalline cellulose
129	Cresol	334.	Mixed Tocopheryl
130	Croscarmellose	335.	Mycophenolic acid
131	Crospovidone	336.	N-Acetyl-L-Cysteine
132	Crude Glycerine	337.	Natuzyme Enriched Enzyme
133	Crude Phenol	338.	Nisin
134	Cyanocabalamin	339.	O-phenol
135	Cyclizine Hydrochloride	340.	O Cresol
136	Cysteamine HCL	341.	Oleic Acid
137	D Xylose	342.	Opadry 20F180004
138	D-Calcium Pantothenate	343.	Ortho Chloro Toluene
139	D-chiro Inositol	344.	Oxybenzone
140	Dehydroepiandrosterone	345.	Paradichlorobenzene
141	Descote Ferrous Fumarate	346.	Pectinase
142	Developmental Thermostable Alpha	347.	phenothiazine
143	Dexpanthenol	348.	Phospholipon
144	Dextran	349.	Phosphonyl Methoxy Propyl
145	Dextromethorphan	350.	Pipperacillin acid
146	Dextrose Monohydrate	351.	Pnemocandin
147	D-Galactose	352.	Polyanionic Celts PAC LV
148	D Glucuronolactone	353.	Polysorbiete
149	Di Calcium Malate	354.	Potassium Carbonate
150	Dibenzoyl peronde	355.	Potassium Chloride
151	Di-Calcium Phosphate	356.	Potassium Hydrogen Carbonate
152	Diclazuril	357.	Potassium thioacetate

153	Dihydro Eugenol	358.	Povidone iodine
154	Dimethicone	359.	Prednisolone
155	Dimethyl Fumarate	360.	Procaine Hydrochloride
156	Diphenhydramine Hydrochloride	361.	Propanol
157	Daulfiram	362.	Propionic Acid
158	Disodium Hydrogen Phosphate	363.	Protamine Sulphate
159	DL Alpha Tocopherol	364.	Protamine Sulphate
160	DE Panthenol	365.	Pro-Taurine
161	DL-Alpha Tocopherol	366.	Pyridoxine Hydrochloride
162	D-Mannitol	367.	R-9-2-Phosphanomethoxypropyl Adenine
163	Docusate Sodium	368.	Rutin
164	Dompihen Bromide	369.	saccharin buse
165	Dopamine Hydrochloride	370.	S-Adenosyl-L-methionine Disulfate Tosylate
166	D-Panthenol	371.	Shikhimic Acid
167	D-Panthenytriacelate	372.	Simethicone Emulsion
168	D-Phenylalanine	373.	Sodium (L)-Lactate
169	D-Serine	374.	Sodium Alginate
170	Effersoda	375.	Sodium Ascorbate
171	EHG Capsules	376.	Sodium Benzoate
172	Emulsified Ferric Phosphate	377.	Sodium Bicarbonate
173	Encapsulated Benzoyl Peroxide	378.	Sodium Butyrare
174	Enzyme pepsin	379.	Sodium Carbonate
175	Estrone	380.	Sodium Chloride
176	Ethyl Panthenol	381.	Sodium Citrate
177	Eugenol	382.	Sodium CMC

178	Sucrose	383.	Sodium Fluoride
179	Sulfuric Acid	384.	Sodium Gluconate
180	Sulphadiazine	385.	Sodium Hyaluronate
181	Sunflower Lecithin	386.	Sodium Lactate
182	Superol K Glycerin	387.	Sodium L-Lactate
183	Taurine	388.	Sodium Monofluorophosphate
184	Tazobactum acid	389.	Sodium Percarbonte
185	Thiglycolic Acid	390.	Sodium Phenylbutyrate
186	Titanium Dioxide	391.	Sodium Phosphate
187	Triacetin	392.	Sodium Picosulfate
188	Trichloroisocyanuric acid	393.	Sodium Rifamycin
189	Triethanolamine	394.	Sodium Salicylate
190	Tripotassium Citrate	395.	Sodium Sulfate
191	Tris Buffer	396.	Sodium Thiosulfate
192	Tri-sodium citrate	397.	Sodium Thiosulpharma
193	Tri-Sodium Dihydrate	398.	Sodium Valproate
194	Tromethamine	399.	Sodium-L-Lactate
195	Trypsin Chymotrypsin	400.	Solifenacin Succinate
196	Ubidecarenane	401.	Sorbitol
197	Vinegar	402.	Soya Lecithin
198	Vitamin D3 oil	403.	Soya Phosphatidyl Choline
199	White Lotion	404.	Soya Phospholipids
200	Zinc Carbonate	405.	Soyabean Lecithin
201	Zinc Oxide	406.	Soyabean Oil
202	Zinc Pyrithione	407.	Stearic Acid
203	Zinc Stearate	408.	Streptomycin Sulphate

204	Zinc Sulfate	409.	ZinClear IM
205	Zink Citrate		

Annexure I

Legal Undertaking for the Import of Drugs as per provisions of Schedule D of Drugs and Cosmetic Rules 1945 to be submitted by the Actual Users to The Central Drugs Standard Control Organisation (CDSCO) Zonal office.

I/We.....S/o.....
having premises at .....aged about .....do hereby solemnly affirm state and undertake as under:

1. That I am the importer of..... (Name of the drug) from..... (Name and full address of the Manufacturer) of..... (Quantity) vide Bill of Entry No.....dated.....

2. That I undertake to use..... (Quantity) of above said drug for Non-Medicinal purpose/ as a pharma aid / as a drug intermediate to manufacture other drugs only. (delete whichever not applicable).

3. That I undertake to maintain books and records of transaction of above said drug for which NOC will be granted.

4. That I undertake to allow the Drug Inspectors from the CDSCO to inspect the books and records as well as the actual usage of (Name of the drug) as and when required.

5. I state that that consignment document like Certificate of Analysis, Bill of Entry, invoice etc. clearly mentions ―Not for Medicinal Use or ("for use as pharma aid").

6. That the bags/containers carrying (Name of the drug) along with other requirements of labelling and packaging also mentions – "Not For Medicinal Use" or ("for use as pharma aid").

DEPONANT VERIFICATION

Verified on this .....day of..... (Month & Year) that the contents of my above undertaking are true and that no part it is false and that nothing material has been concealed here from.

DEPONANT

Annexure II

Legal Undertaking for the import of Drugs as per provisions of Schedule D of Drugs and Cosmetic Rules 1945 to be submitted by the Importer/Trader to The Central Drugs Standard Control Organisation (CDSCO) Zonal Office.

I/We.....S/o.....
having premises at .....aged about .....do hereby solemnly affirm state and undertake as under:

1. That I am the importer/trader of..... (Name of the drug) from..... (Name and full address of the Manufacturer) of..... (Quantity) vide Bill of Entry / Purchase order no.....dated.....

2. That I undertake to sell..... (quantity) of above said drug for Non-Medicinal purpose / as a phrama aid / as a drug intermediate to manufacture other drugs only (delete whichever not applicable).

3. That I undertake to maintain books and records of transaction of above said drug for which NOC will be granted.

4. That I undertake to allow the Drug Inspectors from the CDSCO to inspect the books and records as well as the actual usage of said drug as and when required.

5. That the bags/containers of the said drug along with other requirements of labelling and packaging also mentions ―Not For Medicinal Use

6. That the data of my previous transaction is annexed with this undertaking (Optional in cases of subsequent transaction).

DEPONANT VERIFICATION

Verified on this .....day of..... (Month & Year) that the contents of my above undertaking are true and that no part it is false and that nothing material has been concealed here from.

DEPONANT

Important Points for consideration

- The application should be complete before submission to the authorities.
- Application for dual use clearance is advised to be made by the manufactures or its authorized agent or importer to the authorities well in time for technical review for consideration preferably before the actual import to avoid demurrages. It may be advised that a period of two months before the actual import will be effective for smooth clearance of consignment.
- The consignment label, bills, invoices etc. in respect of imported items should clearly have indelible marking for its intended use.
- The applicant for manufacture of a drug using imported drug must have Master Formula Record duly attested by the Licensing authority for import application.
- The import of drug under dual use for purification or rendering it sterile will not be considered under dual use.
- The import permission for dual use item can be considered to actual users for the period of one year.
- If application is made to the Port officer, it will be forwarded with remarks to the Zonal head of CDSCO for review and consideration preferably by e mail / fax. The NOC from Zonal Head via e mail / fax will be sufficient for release.
- The Zonal office will maintain data for such releases.

Chapter-12

ACTIVITIES OF THE PORT OFFICES

THE BROAD FUNCTIONS AND ACTIVITIES OF PORT OFFICES

All the port offices of central Drugs standard control organization (CDSCO) are under the control of Drugs Controller General (India). The CDSCO through the officers posted at the port, exercise control over drugs and cosmetics, which are imported / exported in the country. This control is exercise under chapter III of the Drugs & Cosmetics Act. The port officers function in an advisory capacity to the customs Authorities. Any action for contravention of section 10 of the Drugs and Cosmetics Act is resorted to by advising the Commissioner of Customs to take action under section 11 of Drugs & Cosmetics Act, read with relevant provisions of customs Act 1962.

All the port offices are headed by Assistant Drugs Controller (India) and assisted by Technical Officers/Drugs Inspectors along with some ministerial staff members. Following are the main activities of the port offices

Functions of Port Offices

(1) Scrutiny of the Bills of entry with a view to ensure that the imported drugs comply with the provisions of Chapter III of the Drugs & Cosmetic Act and Rules there under and Drugs and Magic Remedies (Objectionable Advertisements) Act and Rules & Narcotic Drugs and Psychotropic Substances Act(NDPS) & Rules there under and any other law for the time being in force.

(2) To check the shipping bills for export for compliance of Drugs & Cosmetics Act and keep control under Narcotic Drugs and Psychotropic Substances Act & Rules.

(3) In the case of Narcotic Drugs and Psychotropic Substances Act & Rules, a certificate issued by Narcotics commissioner must be checked for import/export and details furnished to Drugs Controller General (India) through the Deputy Drugs controller (India) of the respective Zones.

(4) To ensure that no New Drug is imported into the country unless its import permitted by the Central Licensing Authority under Chapter X and XI of (New Drugs and Clinical Trials Rules 2019).

(5) Small quantities of drugs (Approved/unapproved) to be imported for personal use is duly covered by License (Form 12-B) of Drugs Rules 1945.

(6) To ensure that no Medical Device is imported into the country unless its import is permitted by the Central Licensing Authority under Chapter V and VIII of Medical Devices Rules, 2017.

(7) Small quantities of Medical devices to imported for personal use is duly covered by License (MD-21) of Medical Devices Rules, 2017

(8) To ensure that no cosmetics is imported into the country unless its import permitted by the Central Licensing Authority under Chapter III and Chapter V of Cosmetics Rules, 2020.

(9) Maintenance of Statistical data regarding imports/export of all Drugs/Cosmetics/Medical devices and submit the same on monthly basis to the Deputy Drugs Controller (India) of the respective zones and to other authorities as and when required.

(10) Co-ordination with the Customs Authority – The Port Officers should be aware of the relevant portions of Customs Act and DGFT policies

(11) Import of raw materials under Duty Exemption Entitlement Certificate (DEEC)/ Advance licensing Scheme or 100% EOU cases, Re-imported raw materials, drugs, cosmetics, refurbished Medical devices, foreign trade, MOOWR scheme bonded warehouse items must be intimated to the concerned State Drugs Controller to examine proper post-import check with a copy marked to the DDC(I) of the concerned Zone.

(12) To bring into the notice of trade about any information (notice, circular etc.) as and when required.

(13) Preparation and forwarding of Quarterly and Annual Reports to DDC(I) of concerned Zonal Office

(14) Examination and recommendations for clearance of parcels/couriers through post for import and export of Drugs, Cosmetics and Medical devices.

(13) Coordination with the customs and other investigating agencies for the matters of violation of import/export under intimation to the DDC (I) of the concerned zone. Attending meetings with customs and trade e.g. Customs Clearance Facilitation Committee (CCFC) etc.

(14) To examine the re-import/re-export consignment as per the procedures.

(15) To draw samples from import/export and re-import consignment as per laid down procedures.

(16) To examine unclaimed/seized cargo when referred by customs and offer opinion as per procedure laid down.

(17) In case of Drugs, Cosmetics and Medical devices of Not of Standard quality/Spurious/Adulterated/Misbranded, to be informed to all the port offices directly with a copy marked to the Deputy Drugs Controller of the concerned zone.

Requirements for Import of Drugs, Cosmetics and Medical Devices

I. Drugs

1. All the Bulk Drugs, Finished Formulations and Manufacturing Site should be registered in India. The Registration Certificate in Form 41 and Import License in Form 10/10A to be obtained from Licensing Authority under the provisionsof the Drugs and Cosmetics Act 1940 and Rules made there under.

2. Registration certificate and Import license are not required for the drugs transitthrough India to foreign Countries and which are not required to be sold or distributed in India.

3. No registration certificate is required in respect of inactive bulk substances.

4. A Registration Certificate (Form 41), unless, it is sooner suspended or cancelled, shall be valid for a period of three years from the date of issue: provided that if the application for a fresh Registration Certificate is made ninemonths before the expiry of the existing certificate, the current registration certificate shall be deemed to continue in force until orders are passed on the application.

5. Small quantities of drugs the import of which is otherwise prohibited under Section 10 of the said Act may be imported for the purpose of examination, test or analysis under a license in Form 11.

6. Small quantities of new drugs, the import of which is otherwise prohibited under Section 10 of

the Act may be imported by a Govt. Hospital or Autonomous Medical Institution for the treatment of patients under a license inform 11-A.

7. A licence, unless, it is sooner suspended or cancelled, shall be valid for a period of three years from the date of its issue: Provided that if application for a fresh licence is made three months before the expiry of the existing licence the current licence shall be deemed to continue in force until orders are passed on the application.

II. Cosmetics

1. All the Cosmetic products should be registered in India and Registration Certificate in Form COS-2 in case of fresh registration and Form COS-4A in case of subsequent registration to be obtained from Licensing Authority underthe provisions of the New Cosmetics Rule 2020.

2. A registration certificate granted under Form COS-2 for import of Cosmetics shall remain valid in perpetuity, subject to payment of registration certificate retention fee as specified in the Third Schedule before completion of the period of five years from the date of its issue, unless, it is suspended or cancelled by the Licensing Authority.

If the licensee fails to pay the required registration certificate retention fee on or before the due date as referred to in sub-rule (1), the registration certificate holder shall, in addition to the registration certificate retention fee, be liable to pay a late fee calculated at the rate of two per cent. of the registration certificate retention fee for every month or part thereof within one hundred andeighty days and in the event of non-payment of such fee during that period, the registration certificate shall be deemed to have been cancelled

3. A registration certificate granted under Form COS- 4A for import of Cosmeticsin case of subsequent registration shall remain valid for a period of three years from the date of its issue, unless it is suspended or cancelled.

4. No cosmetic, the manufacture, sale or distribution of which is prohibited in the country of origin, shall be imported under the same name or under any other name except for the purpose of examination, test or analysis.

5. No cosmetics shall be imported unless the —" Use Before or use by date "shown on the label, wrapper or container of the cosmetic is later than six months from the date of import.

6. No cosmetic containing hexachlorophene shall be imported.

7. No cosmetic that has been tested on animals after the 12th day of November 2014 shall be imported into the country.

8. No cosmetic shall be imported unless it is packed and labelled in conformity with these rules and the label of imported cosmetics shall bear registration certificate number of the product and the name and address of the registrationcertificate holder for marketing the said product in India: Provided further that in cases where the imported cosmetics require India specific labelling, the same shall be allowed to be stickered on the unit pack atthe bonded warehouses.

9. Any person who intends to import a new cosmetic, shall apply to the Central Licensing Authority in Form COS- 12 along with requisite fee and the data on safety and effectiveness of cosmetic. If the Central Licensing Authority, after being satisfied that the cosmetic if permitted to be imported shall be

safe and effective for use in the country, may issue a prior permission in Form COS- 3, subject to the condition specified therein.

10. The prior permission obtained in Form COS- 3 shall be furnished along with the application for import under Chapter III of such new cosmetics. Methods of test or analysis to be employed for safety evaluation of new cosmetic shall be complied by manufacturer as specified in the IS 4011:2018 methods of test for safety evaluation of cosmetics, published by the Bureau of Indian Standards as amended from time to time.

III Medical Devices

1. All Medical devices and In-vitro diagnostic Medical devices should be registered in India and obtain Import License in Form MD-15 from Licensing Authority under the provisions of the Medical Devices Rule 2017.

2. A licence granted under Form MD-15 for import of Medical devices and In- vitro diagnostic medical devices shall remain valid in perpetuity, unless, it has been cancelled or surrendered, provided the authorised agent deposits the licence retention fee with the Central Licensing Authority as specified in the Second Schedule for each overseas manufacturing site and for each licenced medical device after completion of every five years from the date of its issue:

a. Provided that the Central Licensing Authority may permit to deposit the licence retention fee after due date but before expiry of ninety days with a late fee calculated at the rate of two per cent. per mensem:

b. Provided further that if the licencee fails to deposit the licence retentionfee within the above stipulated period, the licence shall be deemed to have been cancelled.

3. For import of Medical Device or In Vitro Diagnostic Medical Device for the purpose of test, evaluation, clinical investigations, etc. should obtain test licence in Form MD-17 from Central Licensing Authority. The medical device for which a test licence has been granted in Form MD-17, shall be used exclusively for purposes of clinical investigation, test, evaluation, demonstration or training, shall be conducted at a place specified in such test licence.

4. In cases where the Medical Device is required to be taken to any place other than the ones mentioned in the test licence, the Central Licensing Authority shall be informed in writing before doing so.

5. The medical devices including in vitro diagnostic medical device imported under Form MD -17 that are not used, may be permitted to be exported or destroyed under intimation to the Central Licensing Authority.

6. The import of small quantity of investigational medical device by Government hospital or statutory medical institution for treatment of patient, the import of which is not allowed, but approved in the country of origin, may be allowed to be imported by the Central Licensing Authority in Form MD-19 for treatment of a patient suffering from a life threatening disease or disease causing seriouspermanent disability or disease requiring therapy for unmet medical need.

7. Small quantity of medical device, the import of which is otherwise prohibited under section 10 of the Act, may be imported for personal use in Form MD-21 subject to the following conditions, namely,

- The medical device shall form part of a personal baggage of apassenger and be intended for the exclusive use of such passenger;

- The medical device shall be declared as personal baggage of the passenger to the customs authorities, if they so direct;
- The quantity of any single medical device so imported shall not exceed the quantity specified by the registered medical practitioner;
- The medical device has been prescribed by a registered medicalpractitioner; and
- The medical device so imported shall be accompanied with an invoice or a statement showing the name and quantity of medical

8. Residual shelf life (RSL) shall be based on shelf life of medical devices. It may be as per MDR Rules 2017, where shelf life of 90 days requires at least 40% RSL, shelf life in between 90 days to 365 days requires at least 50% RSL and shelf life more than 365days requires at least 60% RSL.

Check list for import of drugs, cosmetics and medical devices

(The documents required to be submitted by the importer and exporter should be displayed in the official notice board for perusal of the applicants and common public.)

1. The copy of Licences/Permissions/Certificates/other Authorizations issued by Licencing authority based on the category of items being imported.

2. If the drugs are imported under DEEC Scheme, Port Officer to verify for ITC Policy Circular No.9 dated 30.6.2003 and/or ITC Policy Circular No.15 dated 17.9.2003 endorsement on the DEEC License for giving benefit of exemption from Drug registration. Registration Certificate & Import License in Form 10 are exempted for DEEC/100% EOU as per DCGI circular dated 11.09.2003. The details of import to be informed to State DC/Zonal Officer immediately for post import check Copies of ITC Policy. Circulars are attached (Annexure:P-1 to P-2).

3. If the drugs are imported under 100% EOU/EPZ/SEZ and as are exempted from the condition of registration as per the above ITC Policy Circulars. To control misuse, as a precautionary measure an undertaking from the importer also to be taken and the details of import to be informed to the State Drug Controller / Zonal Officer / DCGI immediately for post import check.

4. If the drugs are imported under **import for export** policy, all the provisions of Chapter III of Act are exempted provided; the drugs are exported from the import shed itself without physically clearing the goods out of Customs area.

5. Patent and proprietary medicines shall be imported only in containers intended for retail sale. In case, a firm holds a manufacturing license can import such medicines in bulk for repacking against Rule 37 permission issued by DCGI under Drugs Rules 1945.

6. No drug having the shelf life of less than 60% is allowed for the import: provided that in exceptional cases the licensing authority may, for the reasons to be recorded in writing, allow the import of any drug having lesser shelf life period, but before the date of expiry as declared on the container of the drug

7. No drug, the manufacture, sale or distribution of which is prohibited in the country of origin shall be allowed to be imported under the same name or under any other name under any other name except for the purpose of examination, test or analysis.

8. All the drugs/cosmetics and medical devices imported in India are required to be stored at drug/product specific temperature conditions. All the drugs imported should comply to the standards as specified in the Second Schedule to the Act and Rules there under.

9. Drugs/cosmetics and medical devices which are under test and released by L/G shall be stored in licensed premises.

10. All the drugs/formulations imported into the India shall fulfil the labelling requirements as prescribed Part IX of Drugs Rules1945.

11. All the Cosmetics imported into the India shall fulfil the labelling requirements as prescribed Chapter VI of Cosmetics Rules 2020.

12. All the Medical devices imported into the India shall fulfil the labelling requirements as prescribed **Chapter VI of** Medical Devices Rules, 2017.

Documents to be scrutinized by Port Office for Import

Details of Bill of Entry shall be received in Port Office preferably through email by importer/CHA and then examined in ICEGATE.

Several items falling under different customs tariff heads have been mapped in SWIFT(Single Window Interface For Trade) and verified through ICEGATE (Indian Customs Electronic Data Interchange GATEway) by O/o ADC(I).

Following Documents are required to be scrutinized through ICEGATE system.

1. Bill of Entry

2. Self-Certified copy of Licences/Permissions/Certificates/other Authorizations issued by Licencing authority based on the category of items being imported.

3. Particulars of information in the Form of ADC import sheet **(Annexure: P-3)**

4. Self-certified Debit sheet for the licences/permissions mentioning the specific quantity to be imported.

4. Self-Certified copy of the licensed premises where Drugs, Cosmetics and Medical Devices are to be stored.

5. Self-Certified Certificate of analysis and Batch release Certificate of each batch.

6. Copy of invoice, packing list, certificate of country of origin (if necessary)

7. In case of Cosmetics, Declaration by the manufacturer that no animal is used for testing of cosmetics.

8. Other linked documents to be verified by the port office to ensure the authenticity of the consignments.

9. If goods are not directly supplied from the manufacturer, then the port officer may verify the authenticity of goods at manufacturer's end through e-mail or his authorized registered agent in India.

10. Letter of Guarantee wherever required.

11. Self-certified copy of labels and markings on the consignment.

12. Free sale certificate for Cosmetics at the country of origin.

13. If the consignment is not directly supplied from the manufacturer, then the port officer may verify the authenticity of goods thoroughly.

14. Undertaking by the importer that the consignment packaging is not damaged/broken/destroyed and the content of drug/cosmetic has not deteriorated**.(Annexure:P-4)**

15. For import of diagnostic kits/reagents for Research use only for academic research purpose, the applicant needs to submit an undertaking in this regard at the concerned port office of CDSCO stating that the imported products shall be used by the research institution for academic research purpose only and shall not be used for any in-vitro diagnostic/therapeutic purpose in diagnostic purpose in diagnostic labs/hospitals. Such products shall be labelled as "For research use only" **(Annexure:P-5)**

16. For import of non-drug/lab kits shipment related to clinical trial/clinical trial purposes, the sponsor/importer may submit an undertaking along with the copy of clinical trial/clinical research approval obtained by sponsor/importer, at the concerned port office of CDSCO stating that such imported items are being imported and will be used for clinical trial/clinical research purpose only and will not be diverted for any other purposes, as per applicable rules, based on which such import consignments may be cleared at the port of import**.(Annexure P-5)**

Examination of Bill of Entry

1. After scrutiny of the aforesaid documents and making the necessary entry in the records/computer, all Bills of Entry received in the office through ICEGATE must be disposed of preferably on same day with ADC(I) remarks. The Port officer should examine B/E and should decide at this stage whether:-

a) Labelling & marking need to be checked by the port officers and samples may be drawn (If the drug imported is in small container of 5 kg or less than the original container may be called for to check the markings/label). If the consignment is to be examined, location of the consignment shall be obtained from the custodian/Importer/CHA.

b) Samples are required to be sent for testing / analysis to the Government / Approved testing lab.

c) The consignment may be recommended for release.

2. If any discrepancies observed, same should be mentioned in ICEGATE while taking decision on release of consignment.

Inspection of Consignments and Drawing of Samples:

Intervention for inspection and sampling by port officers is only in the consignments where samples are required for testing as per defined risk based criteria issued by CDSCO vide order no. Import/Misc/89/2015-DC dated 07.03.2016**. (Annexure: P-7).**

- Random sampling of any one consignment in six months or of any oneconsignment in sequential 10 consignments, whichever is earlier is to bedone.

- Imported product & consignment, if from ICH countries (USA, EU, Australia, Japan, Canada) and being imported since last 5 years without any complaint/quality failure in testing of the samples drawn, the frequency of sampling is to be reduced to any one consignment in two years or to any one consignment in sequential 20 consignments, whichever is earlier.

- If the sample of any product has failed then, sampling has to be done on subsequent 5 consecutive consignments of the product.

- If the product is from a new source, it has to be sampled for testing.

- If the information/ evidences are received by Port officer of CDSCO/ Custom officer about doubtful quality of the product, it has to be sampled and tested.

(*Note: The above said Risk Based Criteria is applicable to drugs other than Human and Veterinary vaccines, which falls under high risk category. However, 100% samples are to be sent for testing for the itemslike Vaccines, Blood products, Critical Diagnostic Kits, Condoms and Re-Import case.*

Batch testing is being carried out at port offices of CDSCO only for the High Risk IVD reagents/kits (HIV, HBsAg, HCV and Blood Grouping reagents). Samples of imported consignment (100%) is drawn and sent to the Director-NIB, Noida for testing and the consignments of High Risk IVD reagents/kits (HIV, HBsAg, HCV and Blood Grouping reagents) should be released only after having complied with the prescribed specifications.

Other Medical devices are required to be sampled randomly and also on the basis of any complaint or quality failure.)

Further, the following points may also be considered for inspection andsampling:

1. There are no proper labels/markings or no markings on the containers or the markings are illegible.

2. Drugs/Medical Devices/Cosmetics imported from a supplier/manufacturer have been reported to be not of standard quality/spurious etc. at this port or any other port in India.

3. The price of the drug imported is abnormally low as compared with the previous imports.

4. Customs HS number on the invoice is not tallying with the declared item HS number.

5. On request from the Customs etc. based on certain information.

(Note: When sampling is to be done in case of expensive drugs, the minimum quantity required for test may be drawn and the duplicate and the unutilized sample may be returned to the importer later on his written request if everything is in order.)

Procedure for drawing of samples

1. Samples are drawn in duplicate.

2. Quantity required for test has been specified by the Director, CDL/ CRI/ CDTL/ NIB/NIV/NARI/NICD/IVRI etc. time to time.

3. Samples are drawn as far as possible under the direct supervision of a technical representative of the port office. Also, sampling should invariably be carried out in the presence of the importer's representative.

4. In case of drugs requiring special precautions due to their hygroscopic, thermo- labile nature etc., samples to be drawn invariably under proper conditions.

5. If the drug is sterile, the importers should be asked to make arrangement for drawing of samples under sterile conditions.

6. If the manufacturer premise is located outside the city, Govt. approved private testing laboratories facilities to be utilized and the technical staff from the port offices may be deputed to supervisethe drawing of samples.

7. Usually $\sqrt{n}+1$ number of samples may be drawn, where n is number of containers /batches as per requirements.

Dispatch of Samples

1. It is responsibility of the Port Officer to ensure that all samples intended for test, are sent to laboratory as early as possible.

2. The first part of the sample (original) is for test, the second part (Duplicate)is to be retained in the Port Office.

3. Samples drawn from bulk containers to be sent to the laboratories with a code number in order to maintain secrecy. Only the name of the drug be mentioned.

4. Port officer should ensure that the seal of the samples should remain intact at required temperature / cold chain shall be maintained during the transportation.

5. In case of sample of vaccine send to CDL Kasauli, Port officer should send the details/documents such as (a) number of doses imported (b) Copy of release certificate from the country of origin (English translation copy to be attested by notary) **(Annexure P-8).**

a) Testing of samples

In following port offices of CDSCO mini Drug Testing laboratories are available and functional.

- Navi Mumbai (Seaport)
- Bangalore (Airport),
- Ahmedabad (Airport),
- Mumbai (Airport)
- New Delhi (Airport),

- Hyderabad (Airport)

Wherever mini Drug Testing Laboratories are available on the port office, same shall be used for testing as far as possible The facilities of the mini drug testing Laboratories shall also be used for sampling of the consignments of bulk drugs, in case no proper arrangement could be made by the Importer.

Apart from the above said Mini Drug Testing Laboratories at Port Offices, the samples may also sent to following drug testing laboratories depending on the nature of imported items /consignments drawn by the Port offices of CDSCO.

- Central Drugs Laboratory, Kolkata,
- Central Drugs Laboratory, Kasauli,
- Central Drug Testing Laboratory, Mumbai,
- Central Drug Testing Laboratory, Chennai,
- Regional Drug Testing Laboratory, Chandigarh,
- Regional Drug Testing Laboratory, Guwahati,
- Indian Pharmacopoeial Commission (IPC), Ghaziabad,
- Indian Veterinary Research Institute, Izzatnagar,
- National Institute of Biologicals, NOIDA,
- Homeopathic Pharmacopoeial Laboratory, Ghaziabad

Any other private drug testing laboratories approved by the Licencing authority under the Drugs and Cosmetics Act and Rules made there under, which are available across the Country in the vicinity of port offices

The following criteria to be followed for sending of samples to the laboratory for testing purpose.

1. Any bulk drug/ formulation imported for the first time to be sent toCDL/ CDTL/ RDTL.
2. Any bulk drug/formulation on routine to be sent to CDL/CDTL or anyGovernment Approved Private Testing Laboratory.
3. The following products to be forwarded to CDL Kasauli:

a) Sera
b) Solution of serum proteins intended for injection.
c) Vaccines.
d) Toxins.
e) Antigens.
f) Anti-toxins.

g) Sterilized surgical ligature and sterilised surgical suture.

h) Bacteriophages:

Note-The samples of Oral Polio Vaccine may also be send at (a) Pasture Institute of India, Conoor, (b) Enterovirus Research Center (ICMR),Haffkine Institute Compound parel Mumbai and (c) NIB Noida.

1. The following products to be forwarded to NIB Noida:

a. Blood grouping reagents.

b. Diagnostic kits for human immunodeficiency virus, Hepatitis B SurfaceAntigen and Hepatitis C Virus.

c. Blood products-

- Human Albumin;
- Human Normal Immunoglobulin (intramuscular and intravenous);
- Human Coagulation Factor VIII;
- Human Coagulation Factor IX;
- Plasma Protein Fractionation;
- Fibrin Sealant Kit;
- Anti Inhibitor Coagulation complex.

d. Recombinant products such as-

- Recombinant insulin and insulin analogue;
- r-erythropoietin (EPO);
- r-Granulocyte Colony stimulating Factor (G-CSF).

e. Biochemical kits

- Glucose Test Strips;
- Fully Automated analyzer based glucose reagents.]

f. Enzymes and Hormones such as

- Streptokinase (Natural and Recombinant)
- Human Chorionic Gonadotropins (HCG)
- Human Menopausal Gonadotropins(HMG)

g. Bacterial Vaccines Such as Bacillus Calmette Guerin (BCG)

h. Viral Vaccine

i. Live Attenuated Measles Vaccine

j. Live Attenuated Rubella Vaccine

k. Cell culture Rabies Vaccine

2. Veterinary Vaccines/Anti-sera/Toxoids/Diagnostic Antigens for Veterinary use 100% to IVRI, Izzatnagar

3. Haemorrhagic Septicaemia Vaccine and Ranikhet Disease Vaccine samples to be sent to Chaudhary Charan Singh National Institute of Animal Health, Baghpat, UP.

4. Testing of human blood and human blood products including components, to test for freedom from HIV antibodies should be sent to National Institute of Communicable Disease, Department of Microbiology, Delhi/National Institute of Virology, Pune/ Centre for Advanced Research in Virology, Christian Medical College, Vellore

5. Sample of VDRL antigen 100% to be sent for testing at the Laboratory of the Serologist and Chemical Examiner to the Government of India, Calcutta

6. Homoeopathic medicines to Homeopathic Pharmacopeial laboratories (HPL),Ghaziabad

7. Medical Devices are to be sent for test as directed by the DCG (I).

The following laboratory have been notified for carrying out test and evaluation of medical devices, as Central Medical Device Testing Laboratory:

- **The National Institute of Biologicals, Noida** - In-Vitro Diagnostics for human Immunodeficiency virus, Hepatitis B Surface Antigen and Hepatitis C Virus, Blood Grouping sera, Glucose Test Strip, Fully Automated Analyser Based Glucose Reagent.
- **The Central Drugs Testing laboratory, Chennai** – Condoms.
- **The Central Drugs Laboratory, Kolkata** - Surgical Dressings, Surgical Cotton, Surgical Bandages, Disinfectant.

- **The Regional Drugs Testing Laboratory (RDTL), Guwahati** - Disposable Hypodermic Syringes, Disposable Hypodermic Needle, Disposable Perfusion Sets, I.V. Cannulae.

- **The Central Drugs Testing Laboratory, Mumbai** - Intra Uterine Devices (IUD) and Falope Rings.

Note: Testing of the imported consignments are also to be undertaken on any other laboratory which is notified /approved for the purpose time to time.

Letter of Guarantee

1. Pending testing report, to avoid demurrage if the importer gives an undertaking in writing not to dispose of the drugs without the consent of Customs commissioner etc., the goods can be released on L/G for test (on Stamp Paper). A proforma is attached. **(Annexure: P-9).**

2. Drugs requiring cold storage such as sera, vaccines, may be released forthwith conditionally on L/G for test etc., for proper storage pending the completion of the formalities. A proforma is attached **(Annexure: P-10).**

3. If there are any labelling defects and importer desire to rectify the defects at their place, they may be allowed to be clear the consignment on L/G for rectification of labelling and/or test. A proforma is attached **(Annexure: P-11)**

   Note: Goods on L/G should not be permitted to be taken out of the city of import unless otherwise directed by the DDC(I) of the concerned Zone as a special case. Drugs should not be released on L/G for producing Registration Certificate or Import Licenses for Drugs, Cosmetics and Medical Devices unless otherwise directed by the DCG(I)

Procedure to be followed on receipt of Test Reports

1. If the consignment on test by the laboratory are found to be of standard quality and are labelled as prescribed, they may be released. If the consignment is released on L/G, same should be recommended for cancellation to Customs.

2. If the goods, on test, are declared to be not of standard quality, the Customs Commissioner is informed about this along with 2 copies of the test Report. The proforma of the Communication for action under Rule 41(1) used is given in **Annexure: P-12,** intimation about such imports are made to the Drugs Controller General (India) with copies to the other Port Offices, the proforma used for such communication is given in **Annexure: P-13.**

3. On the basis of the advice of the Port Officers the Customs will issue a show cause memo to the firm concerned. Proforma of show Cause memo generally used is given in **Annexure: P-14**. On the basis of the party‘s reply the case will be finally adjudicated after ascertaining views of the Port Officers.

4. In case the importers appeal to Customs for a retest by submitting sufficient evidence like manufacturer‘s protocols of test on the items in question, the case should be referred to the Deputy Drugs Controller (India) for orders along with comments of the Port Officer. If the Deputy Drugs Controller (India) so directs, a fresh sample shall be drawn, should be sent for retest to the any Government laboratory. Test report so received should be sent to the Deputy Drugs

Controller (India). The orders passed by the Deputy Drugs Controller (India) on the basis of such retest are final.

5. Where the defect is such, that the importers undertake to recondition the goods up to the required standard, they must submit along with their appeal –

a) The method that will be adopted for re-processing of Bulk Drugs.

b) A declaration to the effect that in the event after the reconditioning failing to comply with the prescribed standards of the quality, the material to be surrendered for destruction.

c) If the Deputy Drugs Controller (India) agrees to the party's request for re-processing, the importers must be asked to execute a Letter of Guarantee to the Commissioner of Customs to that effect (**Annexure: P-9)**.

6. In case of grossly substandard / spurious / adulterated drugs, Commissioner of customs is to be informed stating that the import of these goods constitutes an offence u/s.10 (bb) etc. of Drugs & Cosmetics Act, read with Section 11 ibid read with 11 (k) of the Customs Act 1962 and liable for absolute confiscation u/s. 111 (d) and shall punishable u/s. 135 and prosecution can be launched u/s. 137 of Customs Act 1962 by the Customs Authority under intimation to DDC(I). A proforma used for such communication is given in (**Annexure: P-15).**

7. In case of not of standard quality, other than those mentioned in point 6 above, the importers may be given the option by the Customs to reship the goods to the country of origin if they so desire or forfeit them to the Customs for destruction.

TIMELINES FOR ACTIVITIES REQUIRING CARGO CLEARANCES AT PORT OFFICES OF CDSCO

Port Offices of CDSCO shall follow the following timelines for issuance of NOC in respect of release of imported consignments: (**Annexure-16).**

S. No.	Activity	Timeline
1	NOC to be granted only based on documents checks.	2 – 3 hours
2	NOC to be granted after document checks and physical inspection without involving lab-testing.	24 – 48 hours
3	NOC to be granted after document checks, physical inspection, drawing of samples and testing by a laboratory.	48 – 72 hours*

***** In case of consignments where sampling is done, consignments may be releasedbased on Letter of Guarantee submitted by the importer.

<u>Drugs having dual use</u>

1. Import of Substances not intended for medicinal use excluding those intended to be used as drugs after further purification or rendering them sterile requires permission from DDC(I).

2. There are substances which are covered under the definition of the drug but are not used for medicinal purpose and are used in other industries like textile industries, chemical industries and food industries etc. or are used as a starting material / intermediate for synthesis of other drugs.

3. After release of the goods, the same to be informed to the concerned State Drug Controller and the Zonal officer for post import check.

4. The port office shall inform the applicants requiring NOC for drug items under dual use that they should apply to Zonal officers along with undertaking with other documents as NOC from DDC(I) is compulsory for release of such goods.

Gifts for free distribution

1. Import of drugs by Charitable Trusts / NGOs / UNICEF etc. when exempted from payment of duty by the Ministry of Finance for free distribution to the needy and poor people in India are to be released after inspection of the goods and after obtaining an undertaking from the importer regarding status and function of their activities after obtaining the NOC from the DCG(I)

2. Date expired medicines/banned drugs and items covered under NDPS Act should not be permitted.

Homeopathic Medicines

1. No new Homeopathic medicine shall be imported except under Rule 30 AA and in accordance with the permission in writing of the Licensing Authority / DCGI

2. No Homeopathic medicine shall be imported unless it is labelled in conformity with the Rules in Part IX A The samples drawn shall be sent to Homeopathic Pharmacopoeial Laboratory, Ghaziabad or any public testing Laboratory

Import of Traditional Drugs/Medicines

1. In case of import of Ayurvedic, Siddha and Unani Drugs/medicines , invoice, packing list, manufacturer‘s test report, mfg, license, specimen sample, label, certificate of Country of origin, certificate of free sale may be examined before giving NOC by port office. Samples may be drawn from import consignment consignment and may be tested for pharmacopeial standards or other relevant standards. Labelling of imported Ayurvedic, Siddha and Unani Drugs/Medicine should comply with Rule 161 of The Drugs Rules 1945 (Part XVII, Labelling, packing, and limit of alcohol in Ayurvedic including Siddha or Unani drugs) of D&C Rule.

HERBAL PRODUCTS

For any Herbal Products other than traditional medicines mentioned above, permission from DCG(I) is required

Re-Imports

In case of re-import of drugs and cosmetics of Indian origin by the manufacturer /exporter due to certain reasons, samples may be drawn for complete test including specific test in which the consignment was reported to have failed and release the goods thereafter if found to be standard.

Sample to be sent to the Government / approved laboratories. In case the re-imported material is found to be NSQ, then based on the under taking of the manufacturer, the consignment may be released for reprocessing. The decision of release for reprocessing or not to release shall be taken by the concerned DDC(I). Simultaneously, the matter to be informed to the concerned State Drug Controller / Zonal Officer for the re-import check.

When the quantity of re-imported sample is less and not intended for re-use/re-processing, the drawing of samples for testing may not be mandatory. The decision for release of such consignments shall be taken by concerned Deputy Drug Controller (I).

BIOLOGICAL SAMPLES

The biological samples for import or export if not exempted as per Notification No.19/2015-2020 dated 04.08.2016 shall be referred to ICMR for getting NOC. **(Annexure P-17)**

Export of Drugs, Cosmetics and Medical Devices

1. In case of export consignments also, before the Shipping Bills are finally passed, ADC's No Objection should be obtained for consignments of Drugs, Cosmetics and Medical devices . The exporter should follow all the instructions given by the O/o ADC(I) prior to the actual export of the goods.
2. DGFT Public Notice 173 (RE-2008)/2004-2009 dated 13th April 2009 mentions the ADC's Role. A copy of Public Notice is attached herewith in the (**Annexure: P-18).**
3. NOC from O/o ADC(I) for export consignments to any countries shall not be insisted, If the shipping bills are filed by the manufacturers himself, having valid licence under Drugs and Cosmetics Act and rules. A copy of Public Notice is attached herewith in the (**Annexure: P-19).**
4. Export permits issued by the Narcotic Commissioner for Narcotic and Psychotropic substances and precursor chemicals and quarterly and annual statements of exports to be forwarded to DCGI / Narcotic Commissioner for onward transmission to International Agencies.
5. The permission from DCG(India) is required for the schedule P drugs for which shelf life more than mentioned in Schedule P is claimed.
6. In case of neutral code, the consignment may be allowed as long as the identity of the manufacturer is ascertained with licence/code number available on the top.
7. Any circular/notification issued by DCGI from time to time with respect to quality of exported drugs, cosmetics and medical devices should be followed during examination of shipping bills.

DOCUMENTS TO BE SCRUTINIZED FOR SHIPPING BILLS

1. Particulars in the form of ADC Export Sheet (**Annexure: P-20** for format)
2. Shipping Bill, Purchase Bill, Wholesale Licence for Drugs under Rule 61 for Drugs Rules 1945 and Medical Devices in Form MD-42.
3. In case of Cough syrups, test reports received from the notified Laboratories shall be accompanied.

4. Compliance to Rule 94 of Drugs Rules 1945, Rule 34 of Cosmetics Rules and Rule 45 of Medical Device Rules 2017
5. Compliance to DGFT notification number 72/2023 dated 11.03.2024 (**Annexure: P-21).**

Export of Drugs for personal use:

NOC for the Small quantities of drugs to be exported for personal use for Indian citizen going abroad or Foreign citizen returning back to other country, may be granted from O/o ADC(I) on referred by Customs.

Provided the applicant along with a application shall submit the recent date prescription, purchase bill, ID proof of the sender and Passport copy of the recipient. The medicines shall be verified by the port officer.

Annexure – P-1

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
DEPARTMENT OF COMMERCE
DIRECTORATE GENERAL OF FOREIGN TRADE
UDYOG BHAVAN, NEW DELHI-110011

POLICY CIRCULAR NO. 9(RE-2003)/2002-2007 Dated :30 .6.2003

To
All Licensing Authorities
All Commissioners of Customs

Sub : Imports of approved & unapproved drugs under the Advance Licensing Scheme – Exemption from Registration procedure.

Attention is invited to Notification No.2(RE-2003)/2002-2007 dated 31.3.2003 vide which certain types of drugs & pharmaceuticals have been placed under free category and their imports have been subjected to the registration and other requirements administered by the Drugs Controller General of India under the provisions of Drugs & Cosmetics Act.

2. Subsequent to the above Notification, representations have been received from various Drug Manufacturers Associations requesting for exemption from registration requirements of the Drugs & Cosmetics Act for imports under the Advance Licensing Scheme. The requests have been considered and It has been decided that import of approved & unapproved drugs under the Advance Licensing Scheme will not be subjected to the Registration procedure and the imports will be permitted subject to the following conditions:

i. Import license will only be given against an existing valid export order and to the extent raw material is required as per that order.

ii. The Drug Controller would be a member of the Advance Licensing Committee.

iii. A copy of the license would be endorsed to the Drug Controller and the concerned State Drug Controller.

iv. Drug Controller along with the State Drug Controller would make random checks.

v. Any violation is punishable under the Foreign Trade Development and Regulation Act and the Customs Act. The Drug Controller could also make provisions for penalizing the Drug Manufacturing Units in terms of suspension or cancelling of his license.

vi. Pre import condition will have to fulfilled.

Export obligation will be fulfilled within a period of six months from the date of issuance of the license.

3. Similarly, 100% EOU/EPZs & SEZs would also be exempted from the condition of registration. However, if they make supplies to the domestic market, they will have to follow the formalities of registration as under the Drugs & Cosmetics Act.

4. Representations have also been received regarding issuance of Form-10 under the Drugs & Cosmetics Act for manufacturers. It is clarified that Form -9 issued by the registered manufacturers should also be accepted for the purpose of issuing Form-10 license under the Drugs & Cosmetics Act.

5. In addition as far as imports of drugs/raw materials for purposes of (i) clinical trials & (ii) for formulation development is concerned, it is clarified that exemption in such cases will be permitted on case to case basis.

This issue with the approval of the DGFT.

(DR. PRATIMA DIKSHIT)
JT.DIRECTOR GENERAL OF FOREIGN TRADE

Annexure – P-2

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
DEPARTMENT OF COMMERCE
DIRECTORATE GENERAL OF FOREIGN TRADE
UDYOG BHAVAN, NEW DELHI-110011

POLICY CIRCULAR NO. 15
(RE-2003)/2002-2007 Dated: 17.09.2003

To
All Licensing Authorities
All Commissioners of Customs

Sub: Exemption from registration procedure for import of all types of approved and unapproved drugs under the Advance Licensing Scheme

A number of representations have been received from members of the exporting community and Trade Bodies/Associations, after the issuance of Policy Circular No.9 dated 30.6.2003. The following clarifications are made in this regard:

2. The exemption from registration procedure of the Drugs & Cosmetics Act will not only cover those drugs listed in Notification No.2 dated 31.3.2003 but all drugs.

3. (a) Applicants wishing to avail of the benefit of exemption from registration procedure under the Drugs & Cosmetics Act will apply for an Advance Licence in accordance with the instructions contained in Policy Circular No.9 dated 30.6.2003. The Licensing Authority will make an endorsement on the licence that the exemption has been granted in terms of Policy Circular No.9 dated 30.6.2003.

(b) Other applicants who comply with the registration procedure under the Drugs & Cosmetics Act may apply for a Advance licence as per the existing EXIM Policy provisions & procedures.

4. For ratification of advance licences issued under Para 4.7 of the Handbook of Procedure (Vol. I), the representative of the Drugs Controller General of India (DCGI) will be a member of the ALC at DGFT Hqrs. For items where SION is fixed, the existing prescribed procedure will be followed and a copy of the Advance Licence will be endorsed to DCGI & State Drugs Controller Office. Copies of advance licences issued under Para 4.7 and amendments recommended by ALC will also be endorsed to the State Drugs Controller's office.

5. The exemption from Registration formalities does not cover Advance Licence under deemed exports, Advance Licence for annual requirements, DFRC & DEPB.

6. All importers making imports against advance licences, which have not been issued in terms of Policy Circular No.9, will either follow the registration procedure and utilise the licence OR get a fresh licence issued in terms of Policy Circular No.9 to clear their consignments.

7. The export obligation period for the advance licences issued as per Policy Circular No.9 dated 30.6.03 will be fulfilled within a period of six months from the date of import of the first consignment (and not from date of issuance of licence as laid down in Policy Circular No.9 dated 30.6.03). Para 4.22.1 of Handbook of Procedures (Vol. I) shall however be applicable for advance licences issued under Policy Circular 9 dated 30.09.2003 for the purpose of extension in export obligation period.

This issues with the approval of the DGFT.

(DR. PRATIMA DIKSHIT)
JT. DIRECTOR GENERAL OF FOREIGN TRADE

Annexure – P-3

ADC SHEET FORMAT FOR IMPORT

B/E No. & Date	:
Invoice No. & Date	:
Importer's Name & Address	:
Supplier Name & Address	:
Import License No. & Valid Date	
(Form-10/Form-11/Adv.Lic.No/	
100% EOU) Number	:
Any Permission / Endorsement letter	:
From The SCG(I)	
Exchange Rate(FC=INR)	:

S.No.	Product Name & Batch No.	D/M (A)	D/E (B)	Date of Landing (C)	Total Shelf life in days(D) =(B)-(A)	Residual Shelf Life in days(E) =(B)-(C)	Residual Shelf Life in age(F) =(E)/(D)x 100	Quantity Batch wise	Unit Price	Total amount (FC & INR)

Annexure –P-4

File No. Import/Misc./89/2015-DC
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Import & Registration Division)

FDA Bhawan, Kotla Road
New Delhi-110002
Dated: 17/9/2020

Notice

Subject: Documents required for the import -Reg.

The imported Drugs and Cosmetics are regulated as per the Chapter III of Drugs and Cosmetics Act, 1940 and Rules there under. Each importer is required to comply with the conditions of the import license or the NOCs issued under the said Act.

In light of ease of doing business and for utilizing fast track system of Risk Management System, with ICEGATE integration for online clearance of imported Drugs and Cosmetics, it is proposed that the human interface may be reduced by devising method, while ensuring that the integrity of drug/cosmetic, its packages and seal is intact before the release and out of charge. Therefore, it is responsibility of the importer to ensure the same and furnish the undertaking with each Integrated Declaration or Bill of entry that the packaging is not damaged/broken/destroyed and the content of drug/cosmetic has not deteriorated in the following prescribed format:

FORMAT FOR UNDERTAKING

I (Name & Address of Importer) ----------hereby undertake with respect to the consignment imported vide Bill of Entry No. -------Dated---------- that the drug/cosmetic packages seal is intact, the packaging is not damaged/ broken/destroyed and the content of drug has not deteriorated.

Importer

Name and signature with Stamp & Date
(Authorized person)

This is for information and necessary action for utilizing ICEGATE and integration with RMS.

(Dr. V.G. Somani)
Drugs Controller General (India)

To

All the stakeholders through website of CDSCO

Annexure P-5

No. 29/Misc/03/2020-DC(89)

Government of India

Directorate General of Health Services

Central Drugs Standard Control Organization

(Medical Devices Division)

FDA Bhawan, Kotla Road,
New Delhi, Dated 19/6/2020

To,

All Zonal/ Sub- Zonal/ Port Offices of CDSCO

Sub: - Clarification regarding import of diagnostic kits/ reagents for Research Use Only (ROU) for academic research purpose.

Sir,

This is with reference to the subject cited above.

In this regard, it is to clarify that the products meant for "Research Use Only" to be used in academic research institutions and not meant for any diagnostic or therapeutic purpose are not being regulated under provisions of Drugs & Cosmetic Act and Medical Devices Rule there under. This is already clarified through FAQ Q. No. 17 Document no. CDSCO/IVD/FAQ/02/17 published in CDSCO website and letter of this office vide no. 29/Misc/3/2012-DC(09) dated 13/07/2012 (Copy enclosed).

However, the applicant needs to submit an undertaking in this regard at the concern port office of CDSCO stating that the imported products shall be used by the research institution for academic research purpose only and shall not be used for any in-vitro diagnostic/ therapeutic purpose in diagnostic labs/ hospitals. Such products shall be labelled as "for research use only".

Yours faithfully,

(Dr. V. G. Somani)
Drugs Controller General (India)

Annexure P-6

F. No. 12-01/22-DC (Pt-142)
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(New Drugs Division)

FDA Bhawan, Kotla Road
New Delhi- 110002
Dated: 7/7/2022

To

All Zonal/Sub-Zonal/Port Offices of CDSCO

Subject: Clarification regarding import of non-drug / lab kits shipments related to clinical trial / clinical research purposes

Sir,

This office has received representation regarding challenges being faced by sponsors conducting clinical trial / clinical research in importing of ancillary items including non-drug items / lab kits / equipment / accessories etc. which are necessitated for conducting clinical research / clinical trial as per approved protocol.

In this regard, for encouraging research and clinical development and for streamlining the import of such items, the sponsor / importer may submit an undertaking along with the copy of clinical trial / clinical research approval obtained by sponsor / importer, at the concerned Port Office of CDSCO stating that such imported items are being imported and will be used for clinical trial / clinical research purpose only and will not be diverted for any other purposes, as per applicable rules, based on which such import consignments may be cleared at the port of import.

Yours Faithfully,

V.G.S.

(Dr. V.G. Somani)
Drugs Controller General (India)

Annexure P-7

F. No.X-11026/45/2017-BD
Directorate General of Health Services
Office of Drugs Controller General (India)
(Biological Division)

FDA Bhawan, Kotla Road,
New Delhi 110002
Dated: 05 JUN 2017

Office Memorandum

Subject: Testing of sample of Imported Vaccine –regarding

Central Drugs Laboratory, Kasauli, Himachal Pradesh-173204, vide its letter No. CDL/2017/1334 dated 11-Apr-2017 informed this Directorate regarding missing information/documents for the imported vaccine samples submitted for testing through various Port Offices. The copy of CDL letter is enclosed here with for necessary action and strict compliance.

(Dr. G. N. Singh)
Drugs Controller General (India)

To,

All Port Offices of CDSCO

Copy to:

1. CDSCO website for information to all stakeholders
2. Central Drugs Laboratory, Kasauli, Himachal Pradesh-173204

Annexure P-8

GOVERNMENT OF INDIA

केन्द्रीय औषधि प्रयोगशाला
CENTRAL DRUGS LABORATORY
केन्द्रीय अनुसंधान संस्थान
Central Research Institute
कसौली, हिमाचल प्रदेश – 173204
Kasauli, Himachal Pradesh, PIN 173204

टेलीग्राम / Telegram: अनुसंधान / PROBLEM
फैक्स / Fax: 0091-1792-272049 - 272016
दूरभाष / Tel: 0091-1792-272046 -272578
email id: cdlkasauli@cdsco.nic.in
संख्या / No: CDL/2017/1334
दिनांक / Dated: 11 APR 2017

To

Dr. G. N. Singh,
Drugs Controller General (India),
FDA Bhawan, Kotla Road,
Near Mata Sundri College, ITO,
New Delhi – 110 002.

Subject:- Testing of samples of Imported Vaccine – regarding.

Sir,

As you are aware, that CDL is receiving samples of various vaccines through various Port Offices of CDSCO across the country for marketing in India.

In this regard, this is to bring to your kind notice that the following information/documents are found to be missing at the time of submission to update the records at CDL.

1. **Number of doses imported.**
2. **Copy of release certificate from the country of origin (English translation copy to be attested by notary public).**
3. **CDL will not issue the lot release certificate as per standard format in case the batch has not been imported completely or the import quantity is not mentioned in the documents submitted.**

Hence it is requested to please advise the port offices under your kind control to ascertain the information as desired.

Yours faithfully

(Dr. Arun Bhardwaj)
Head

No.CDL/2017/1335-1338
C.R.I., Kasauli, dated the:
Copy for information to:
1. ADC(I), CDSCO, Air Cargo Unit, Indira Gandhi International Airport, New Delhi- 110 037
2. ADC(I)/Incharge, New Custom House Annexe, Ballard Estate, Fort, Mumbai – 400 038.
3. ADC(I), Custom House, Mezzamine Floor, 15/1, Strand Road, Kolkata – 700 001.
4. ADC (I), Custom House, 2nd floor, Road No. 66, Chennai – 600 001.

(Dr. Arun Bhardwaj)
Head

Annexure - P-9

The President of India Date :

Through the Collector of Customs,

LETTER OF GUARANTEE

(Vide Provision to Rule 40 of the Drugs and Cosmetic Rules, 1945)

1. Bill of Entry No. Date.

2. I.G.M. No. Lines No. Date.

3. Steamer Name /Flight Name S.S. / Flight Name No. Date

Description of goods.

Marks and Numbers.

Packing and Quantity.

Country of Origin.

8. C.I.F. ValueRs.

Name & Address of Supplier

Name & Address of Manufacturer

LETTER OF UNDERTAKING FOR TEST

In consideration of the Collector of Customs or any Officer on his behalf having permitting to clear the above goods not withstanding his decision to detain the same goods under the above mentioned Rule 40 of the Drugs and Cosmetics Rules 1945 on having reason to doubt whether the above mentioned goods comply with the provisions of Chapter III of the Drugs & Cosmetics Act 1940 and rules there under.

We hereby undertake :-

That we shall arrange for inspection of the goods as soon as they arrive in the go-down and follow the instructions of representative of the O/o. Assistant Drugs Controller (I), with regard to drawing of samples for test, rectification of labelling defects etc., if any.

That we shall not dispose of the said goods without the consent of the Collector of Customs or any Officer on his behalf in writing.

That we shall return the said goods in whole or in part as the Collector of Customs or any officer on his behalf may direct within ten days of receipt of a notice from the Collector of Customs or any officer on his behalf to return the goods.

That we shall reship or surrender the said goods within two months of the receipt of any order to that effect from the Collector of Customs or any officer in his behalf.

That we shall forthwith pay such find and / or penalty and be liable for such punishment as the collector of Customs or any Officer on his behalf or magistrate may impose under Section II of the drugs & Cosmetics Act, 1940 as read with the relevant provisions of the Customs Act, 1962 and Under Section 13 of the Drugs & Cosmetics Act, 1940.

Any amount due under this bond may be recovered in the manner laid down in the subsection of the Section 142 of the Customs Act, 1962 without prejudice to any other mode or recovery.

The undertakings referred to above is given in view of rule 40 of the drugs and Cosmetics Rules 1945. The goods will be stored in our

Go-down at: _____

Signature of the Importer
WITNESS:

(1)

(2)
ACCEPTED ON BEHALF OF THE
PRESIDENT OF INDIA.

Annexure – P-10

The President of India

Date :

Through the Collector of Customs,

LETTER OF GUARANTEE (Direct Delivery)
(Vide Provision to Rule 40 of the Drugs and Cosmetic Rules, 1945)

1. Bill of Entry No. Date.

2. I.G.M. No. Lines No. Date.

3. Steamer Name /Flight Name S.S. / Flight Name No. Date

4. Description of goods.

5. Marks and Numbers.

6. Packing and Quantity.

7. Country of Origin.

8. C.I.F. Value Rs.

9. Name & Address of Supplier

10. Name & Address of Manufacturer

LETTER OF UNDERTAKING FOR TEST

In consideration of the Collector of Customs or any officer on his behalf having permitting to clear

the above goods no with standing his decision to detain the same goods under the above mentioned Rule 40 of the Drugs and Cosmetics Rules 1945 on having reason to doubt whether the above mentioned goods comply with the provisions of Chapter III of the Drugs and Cosmetics Act 1940 and the Rules there under.

We hereby undertake:

1) That we shall arrange for inspection of the goods as soon as they arrive in our go-down by a representative of Asst. Drugs Controller (India) and obey his instructions as regards drawing samples under proper conditions and rectification of labelling defects if any etc

2) That we shall not dispose of the said goods without the consent of the Collector of Customs or any officer on his behalf in writing.

3) That we shall return the said goods in whole or in part us the Collector of Customs or any officer on his behalf nay direct within ten days of receipt of a notice from the Collector of Customs or any officer on his behalf to return the goods.

4) That we shall reship or surrender the said goods within two months of the receipt
of any order to that effect from the Collector of Customs or any Officer on his behalf.

5) That we shall forthwith pay such fine and /or penalty and be liable for such Punishment as the collector of Customs or any Officer on his behalf or Magistrate may impose under Section II of the Drugs and Cosmetics Act, 1940 as red with the relevant provisions of the customs Act, 1962 and under Section 13 of the Drugs and Cosmetics Act, 1940.

Any amount due under this bond may be recovered in the, manner laid down in subsection of the Section 142 of the Customs Act, 1962 without prejudice to any other mode of recovery.

The undertakings referred to above is given in view of Rule 40 of the Drugs and Cosmetics Rules, 1945. The goods will be stored in our

Go-down at ……

Signature of Importers.

WITNESS:

(1)

(2)

ACCEPTED ON BEHALF OF THE
PRESIDENT OF INDIA.

Annexure – P-11

The President of India Date
Through the Collector of Customs,
Custom House

LETTER OF GUARANTEE
(Vide Provision to Rule 40 & 96 of the Drugs and Cosmetic Rules, 1945)

1. Bill of Entry No. Date.

2. I.G.M. No. Lines No. Date.

3. Steamer Name /Flight
Name S.S. / Flight Name No. Date

4. Description of goods.

5. Marks and Numbers.

6. Packing and Quantity.

7. Country of Origin.

8. C.I.F. Value Rs.

9. Name & Address of Supplier

10. Name & Address of Manufacturer

LETTER OF GUARANTEE FOR LABELING

In consideration of the Collector of Customs or any officer on his behalf having permitting to clear the goods mentioned above, although the same have contravened the following provisions of the Drugs & Cosmetics Act, 1940 and the Rules there under, namely Rules 40 & 96

We hereby undertake:

1. That we shall label the goods mentioned above as required under the above rules within a month or such extended period as the Collector of Customs or any officer on his behalf may allow.

2. That we shall not dispose of the said goods without the consent of the Collector of Customs or any officer on his behalf in writing.

3. That we shall return the said goods in whole or in part us the Collector of Customs or any officer on his behalf nay direct within ten days of receipt of a notice from the Collector of Customs or any officer on his behalf to return the goods.

4. That we shall reship or surrender the said goods within two months of the receipt of any order to that effect from the Collector of Customs or any Officer on his behalf.

5. That we shall forthwith pay such fine and /or penalty and be liable for such Punishment as the collector of Customs or any Officer on his behalf or Magistrate may impose under Section II of the Drugs and Cosmetics Act, 1940 as red with the relevant provisions of the customs Act, 1962 and under Section 13 of the Drugs and Cosmetics Act, 1940.

Any amount due under this bond may be recovered in the, manner laid down in subsection of the Section 142 of the Customs Act, 1962 without prejudice to any other mode of recovery.

The undertakings referred to above is given in view of Rule 40 & 96 of the Drugs and Cosmetics Rules, 1945. The goods will be stored in our

Go-down at ……
Signature of Importers.

WITNESS:

(1)

(2)

ACCEPTED ON BEHALF OF THE
PRESIDENT OF INDIA.

Annexure –P12

File No. Office of the

Assistant Drugs Controller (India)

Mumbai / Kolkata / Chennai / Delhi

Ahmadabad / Hyderabad/Cochin

Date:

1. Name and address of the Importer.
2. Name and address of the Manufacturer.
3. Description of Goods.
4. Quantity Imported
5. C.I.F. Value
6. Bill of Entry No Date :
7. I.G.M. No. Line No. Date.
8. Steamer Name / S.S. / Flight Name No. Date

….

The Sample drawn from the above consignment and forwarded for test to the Director, Central Drugs Laboratory, Kolkata /Central Research Institute, Kasauli / NIB Noida / NARI –NIV Pune / IVRI –Izzat Nagar, CDTL, Mumbai, Chennai, Chandigarh has since reported to be "NOT OF STANDARD QUALITY" as defined in the Drugs and Cosmetics Act, 1940 and the Rules there under for the reasons given below:-

"The Sample does not conform to…….. in respect of ……(state the reasons)"

Reasons:

1)

2)

As such the import of the subject drug is prohibited under Section 10 (a) of the Drugs and Cosmetics Act and the goods are liable to absolute confiscation under Section 111(d) of the Customs Act, 1962. The importers, may however please be given the option to have the goods wither reshipped to the country of origin or have them destroyed in the presence of Assistant Drugs Controller (India) or a Custom Officer, provided under Rule 41 (1) of the Drugs and Cosmetics Rules.

In this connection two copies of the relevant test report received from the Director, Central Drugs Laboratory, Kolkata /Central Research Institute, Kasauli / NIB Noida / NARI –NIV Pune / IVRI –Izzat Nagar, CDTL, Mumbai, Chennai, Chandigarh are enclosed, one of which may please be retained for your record and the other forwarded to the importer along with the show cause memo to be issued to them.

The goods are lying in the docks /air-shed/ were cleared on a Letter of Undertaking for test pending the receipt of the test report.

Party's reply when received may please be forwarded to this office.

A.D.C.(India) / Dy. Commissioner of Customs

Annexure –P13

File No. Office of the

Assistant Drugs Controller (India)

Mumbai / Kolkata / Chennai / Delhi

Ahmadabad / Hyderabad/Cochin

Dt.
To
The Drugs Controller (India),
Dte. General of Health Services,
New Delhi .

Subject: - Testing of ……..Manufactured by M/s……

MEMORANDUM

Reference B/E No. ……..Date…….

A sample of the subject drug sent for test under Rule 40 of the Drugs and cosmetics Rule from a consignment imported by M/s……
(Name and full address of the importers), has since been reported by the Director, C.D.L.
Kolkata / CDL Kasauli / NIB Noida / NARI –NIV Pune / IVRI –Izzat Nagar, CDTL, Mumbai, Chennai, Chandigarh as "NOT OF STANDARD QUALITY" as defined in the Drugs and Cosmetics Act and the Rules there under for the reasons given below :
"The Sample does not conform to ……..
in respect of
……
……...

State the Reasons:

(1)

(2)

(Vide Test Report No. Dt. Refers)

The Quantity imported is ……and the C.I.F. Value ……
……
……

The Customs authorities have been advised to take necessary action under Rule 41(1) of the Drugs and Cosmetics Rules in respect of the above goods which are lying in the Docks / were cleared on Letter of undertaking for test.

The action taken may please be approved.

Asstt. Drugs Controller (India)

Copy forwarded for information to: The A.D.C.(India) , Mumbai / Kolkata / Chennai / Delhi /Ahmadabad / Hyderabad Technical Officer , Cochin .

Annexure – P-14

No.

Subject: Dated:

……

The goods specified above have on test been found to be not of standard quality. A copy of the test report is attached herewith for your information. The import of these goods are prohibited under Section 10(a) of the Drugs and Cosmetics act read with Section 11 of the same act and liable to absolute confiscation under Section 111 (d) of the Customs act, 1962.

You are hereby required to show cause why action should not be taken to confiscate the goods under Section……of the Customs Act.

You are required to indicate whether you would like to re-export the goods to the country of origin as per option given in rule 41 (1) of the Drugs and Cosmetics Rules, 1945.

You are further required to show cause why a personal penalty should not be imposed on you under the aforesaid section.

Your written explanation should be presented within ……day hereof to the undersigned along with all the documentary evidence. You should also indicate in the written explanation whether you wish to be heard in person before the case is adjudicated.

If you fail to submit the written explanation in time or do not appear before the adjudicating authority when the case is posted for hearing, the case will be adjudicated on the basis of the evidence on record without any further reference to you.

Appraising Department
Dated…….

DY. COMMISSIONER OF CUSTOMS,

To,

Annexure – P-15

File No. Office of the

Assistant Drugs Controller (India)

Mumbai / Kolkata / Chennai / Delhi

Ahmadabad / Hyderabad/Cochin

Dt.

Name and address of the Importer

Name and address of the Manufacturer

Description of Goods.

Quantity Imported

C.I.F. Value

6. Bill of Entry No Date :

7. I.G.M. No. Lines No. Date.

8. Steamer Name / S.S. / Flight Name No. Date

Annexure –P-16

File No. Import/Misc./39/2018-DC (Pt.-12)
Government of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(Import & Registration Division)

FDA Bhawan, Kotla Road
New Delhi-110002
Dated: 10 SEP 2021

NOTICE

Subject: Timelines for activities requiring minor and major procedures for cargo clearances at port offices of CDSCO -Reg.

The NCTF working group on PGA Regulations and procedures was constituted in accordance with the decision taken by the Steering Committee in its 5th meeting. The third meeting of the working group on PGA Regulations and Procedures was held on 27.07.2021, wherein one of the decision taken by the working group is as under:

"PGAs should publish timelines for activities requiring minor and major procedures for cargo clearances on their websites by 01.10.2021."

In this regard, Port Offices of CDSCO shall follow the following timelines for issuance of NOC in respect of release of imported consignments:

S. No.	Activity	Timeline
1	NOC to be granted only based on documents checks.	2 – 3 hours
2	NOC to be granted after document checks and physical inspection without involving lab-testing.	24 – 48 hours
3	NOC to be granted after document checks, physical inspection, drawing of samples and testing by a laboratory.	48 – 72 hours*

* In case of consignments where sampling is done, consignments may be released based on Latter of Guarantee submitted by the importer.

(Dr. V. G. Somani),
Drugs Controller General (I)

To,

1. All Port Office of CDSCO.
2. All Zonal/Sub-Zonal office of CDSCO.
3. CDSCO website.

Copy to:

1. The Under Secretary(R), Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi

Annexure –P-17

To be Published in the Gazette of India Extraordinary Part-II, Section - 3, Sub-Section (ii)

Government of India
Ministry of Commerce & Industry
Department of Commerce
Directorate General of Foreign Trade
Udyog Bhawan

Notification No. 19 /2015-2020
New Delhi, Dated: 4 August, 2016

Subject: Import/export policy for Human Biological Samples for commercial purposes: amendment Schedule – 1 (Import Policy) and Schedule – 2 (Export Policy) of ITC (HS), 2012.

S.O. (E): In exercise of powers conferred by Section 3 of FT (D&R) Act, 1992, read with paragraph 1.02 and 2.01 of the Foreign Trade Policy, 2015-2020, as amended from time to time, the Central Government hereby inserts Import Policy for Human Biological Samples for commercial purposes under General Notes 17 to Schedule – 1 (Import Policy) and Export Policy for Human Biological Samples for commercial purposes under General Notes 4 to Schedule – 2 (Export Policy) of ITC (HS), 2012 as under:

> "The import of human biological samples by the Indian diagnostic laboratories / Indian Clinical Research Centres for lab analysis / R & D testing or export of these materials to foreign laboratories should be permitted by Customs authorities at the port of entry / exit without prior approvals (import licence / export permit) from any other Government agency, provided the concerned Indian company / agency submits an undertaking that they are following and will follow all the applicable rules, regulations & procedures for safe transfer and disposal of the biological samples being imported / exported as per the related norms / regulations set by WHO* / DGFT** [SCOMET items in Export Policy of ITC (HS), 2012, Schedule – 2 (Export Policy)] / Ministry of Environment, Forests and Climate Change***, Government of India, to the Customs authorities at the port of entry / exit along with the details of such samples".

2. **Effect of this Notification**: Policy condition for import /export of human biological samples for commercial purposes is laid down.

* (i) http://apps.who.int/iris/bitstream/10665/149288/1/WHO_HSE_GCR_2015.2_eng.pdf?ua=1)
(ii) http://www.who.int/csr/resources/publications/biosafety/en/Biosafety7.pdf

** http://dgft.gov.in/exim/2000/scomet/scomet2011.pdf

*** (i) http://envfor.nic.in/legis/env/env1.html
(ii)http://envfor.nic.in/legis/hsm/hsm3.html

(Anup Wadhawan)
Director General of Foreign Trade
E-mail: dgft[at]nic[dot]in

[Issued from F.No.01/89/180/Misc.82/AM-05/PC-2 (A)]

Annexure – P-18

DGFT PUBLIC NOTICE

-COPY OF-

PUBLIC NOTICE NO.173 (RE-2008)/2004-2009

Dated 13th April, 2009

1. In exercise of the power conferred under Paragraph 2.4 of the Foreign Trade Policy, 2004-2009, as amended from time to time, it has been decided to notify, with immediate effect, procedure /guidelines to strengthen the enforcement mechanism available under the Drugs and Cosmetics Act, 1940, to ensure that counterfeit drugs do not get exported out of the country.

2. Export of Drugs & Pharmaceuticals covered under the provisions of Drugs & Cosmetics Act 1940 and the rules made there under , which is being regulated by Drugs Controller General of India (DCGI) in the Ministry of Health & Family Welfare , shall be as per the requirements given hereunder :

Every exporter of Drugs & Pharmaceuticals at the time of shipment shall submit, along with other required documents, the following:

(i) A copy of Certificate of Analysis issued by the manufacturer for the subject product; Or

(ii) A copy of Certificate of Analysis issued by approved laboratory of the importing country/FDA; Or

(iii) A copy of Certificate of Analysis issued by a laboratory approved by Drugs Controller under Drugs

& Cosmetics Act 1940 and the rules made there under.

Wherever required the officials of the Drugs Control Department posted at the port offices shall retain a sample of the subject consignment for the purpose of reference and tracking of the manufacturer / exporter of the subject product.

1. This issue in Public Interest.

sd/-

(R.S.Gujral)

Director General of Foreign Trade
& Ex-Officio Additional Secretary to the
Govt.of India

F.No. 01/91/180/648/AM09/Export Cell

Issued by:

Ministry of Commerce and Industry
Department of Commerce
Director General of Foreign Trade
New Delhi

Annexure P-19

No. DCGI/MISC/2015 (199)
Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health and Family Welfare

FDA Bhavan, Kotla Road,
New Delhi 110002

Dated: 21st March, 2018

NOTICE

In partial modification of Notice of even number dated 11.12.2015, removing the requirement of 'No Objection Certificate' (NOC) with respect to shipping Bills from the Port offices of Central Drugs Standard Control Organisation for the export consignments to USA, Canada, Japan, Australia and European Union, it has been decided that in addition to the above countries, the NOC for export consignments to any other countries shall not be insisted, if such shipping bills are filed by the manufacturer himself, having valid license under Drugs and Cosmetics Act and Rules.

This is being done to bring ease in the drug regulatory practices in India relating to export of drugs, medical devices and cosmetics. All the stakeholders are however required to comply with the regulatory requirements of the importing countries as per their specific needs.

(Dr. S Eswara Reddy)
Drugs Controller General (India)

To

1. Port/Seaport/Zonal and Sub-Zonal offices of CDSCO.
2. Custom offices at the port/seaport/airport offices.
3. State/UT Drug Controllers.
4. Joint Secretary (R), Ministry of Health &Family Welfare.
5. Joint Secretary, Department of Commerce.
6. Associations of the concerned sector.
7. Web site of CDSCO.

Copy to:

1. PPS to Director General Health Services, MoHFW.
2. Joint Secretary, Department of Revenue.
3. Shri S.P. Sahu, Chief Commissioner, Customs (Systems).
4. Joint Secretary, Department of Pharmaceuticals.

Annexure – P-20

ADC SHEET FORMAT FOR EXPORT

PORT OF LOADING			ADC SHEET FOR EXPORT				
Entry No	S/B No & Date	Invoice No & date	DETAILS OF ITEM & CATEGORY. WITH MFG. DATE, EXP. DATE & BATCH NO.	Name & Address of Exporter With DSL/DMI.No	Name & address of Consignee	FOB Value INR	Remarks/ CHA details
				Duly signed and stamped by the exporter			

Annexure P -21

[To be Published in the Gazette of India Extraordinary Part-II, Section - 3, Sub-Section (ii)]
Ministry of Commerce & Industry
Department of Commerce
Directorate General of Foreign Trade
Vanijya Bhawan, New Delhi

Notification No. 72/2023
New Delhi, Dated: 11th March, 2024

Subject: Amendment in export Policy of Human Biological Samples under Chapter-30 of ITC HS schedule-2 of export policy.

S.O. (E). — In exercise of powers conferred by Section 3 read with section 5 of the Foreign Trade (Development & Regulation) Act, 1992 (No. 22 of 1992), as amended, read with Para 1.02 and 2.01 of the Foreign Trade Policy, 2023, the Central Government hereby amends Export Policy under chapter 30 related to Human Biological Samples, as under:

HS Code	Item Description	Revised Export Policy	Revised Policy Condition
30021020	Antisera and other blood fractions and immunological products, whether or not modified or obtained by means of biotechnological processes	Free subject to NOC	1. Any human biological materials/samples/products which are related to activities covered under the provision of Drugs & Cosmetics Act 1940 & Rules thereunder are free for export subject to No objection from CDSCO. 2. Any human biological materials/samples/products **NOT** covered under (1) above are free for export subject to No objection from ICMR/DHR.
30021091	Antisera and other blood fractions and immunological products, whether or not modified or obtained by means of biotechnological processes		
30021210	For diphtheria		
30021220	For tetanus		
30021230	For rabies		
30021240	For snake venom		
30021290	Other		
30029010	Human Blood		

2. Effect of the Notification:

Export Policy of Human Biological Samples under Chapter 30 of ITC HS schedule-2 of export policy is amended to the extent that export of item that contains Human biological materials/samples/products under chapter 30 is free subject to the NOC from Central Drugs Standard Control Organization (CDSCO) or Indian Council of Medical Research (ICMR), Department of Health Research (DHR).

11.3.2024

(Santosh Kumar Sarangi)
Director General of Foreign Trade
Ex-Officio Additional Secretary, Government of India
E-mail: dgft@nic.in

(Issued from F. No. 01/91/191/48/AM23/EC/e-35188)

	TITLE	Division Name	QMS Monitoring Division
	SOP for publishing the list of names of imported Human vaccine declared as illegal on the CDSCO website	Document No.	QMS-GNL-023
		Revision No.	00
		Effective Date	
		Page No.	

Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

Control Status

1.0 Purpose

To lay down a procedure for publishing the list of names of imported Human vaccine declared as illegal on the CDSCO website.

2.0 Scope

This document is applicable to the imported Human vaccine declared as illegal as per the provisions of Drugs and Cosmetics Act, 1940 and Rules, 1945.

3.0 Responsibility

3.1 The concerned port officer of CDSCO shall be responsible for identifying the illegally imported Human vaccine, reporting to DCGI Secretariat, Customs Authority and CDSCO Biological division as well as initiating further action in the matter.

3.2 DCG (I) Secretariat shall be responsible for publishing the list of declared illegally imported Human vaccine including names of importers and vaccine manufacturers.

3.3 JDC(I)/ DDC(I) though concerned ADC(I) shall be responsible for monitoring the preparation of the list and publishing in the CDSCO website.

3.4 DCG (I) shall be responsible for overall compliance of the SOP.

3.5 CDSCO IT cell shall be responsible for maintenance of database for illegal imported Human vaccine on www.cdsco.gov.in website.

4.0 Accountability

QMS Monitoring Division and DCG (I).

5.0 Procedure

5.1 The concerned port officer of CDSCO shall intimate the details of Human Vaccine, which are found to be imported in contravention of Drugs and Cosmetics Act and Rules there under to CDSCO, HQ by e-mail on dci@nic.in and vaccine-bio@cdsco.nic.in along with the copy to Zonal / Sub Zonal and port offices of CDSCO.

5.2 The concerned port officer shall furnish the information as per the Performa given below.

Imported illegal Human Vaccine details:

Sr. No.	**Name of product**	**Batch no., Mfg. date, Exp. date**	**Quantity**	**Manufacturing License No./Import Lic. No. if any**	**Name of importer**	**Name of manufacturer with address**

5.3 The information as in 5.2 shall be forwarded through levels of DIs/ADCs/DDC (I)/ JDC (I) to DCG (I) whenever such decision shall be taken in Biological division.

5.4 After approval from DCG (I), the division head or Secretariat of DCG (I) office shall send the e-mail information along with soft copy of information to CDSCO IT cell for publication of information and maintain the same as record. The timeline for processing and approval of such case shall be within 7 days from the receipt of information.

5.5 The detail of such vaccine shall be uploaded on www.cdsco.nic.in website within 72 hrs and updated on monthly basis.

5.6 The concerned port officer shall forward monthly updated status of such cases for updating the information on website.

6.0 Annexure / Format

Nil

7.0 References

Doc. No.	Title
1	Drugs and Cosmetics Act, 1940 and Rules, 1945

8.0 Abbreviation

Acronym	Full Form
CDSCO	Central Drugs Standard Control Organization
DCG(I)	Drugs Controller General (India)
QMS	Quality Management System
DDC(I)	Deputy Drugs Controller (India)
ADC(I)	Assistant Drugs Controller(India)
DI	Drugs Inspector
IT	Information Technology
SOP	Standard Operating Procedures

9.0 Revision History

Revision No.	Reason(s) for Revision

00	New SOP

Chapter-13

GUIDANCE DOCUMENT FOR CRISIS MANAGEMENT

Central Drugs Standard Control Organization (CDSCO)
Directorate General of Health Services, Ministry of HEALTH AND Family Welfare,
Government of India
FDA Bhavan, ITO, Kotla Road, New Delhi-110002

1. Introduction

Public health emergencies including disease outbreaks, epidemics and pandemics continue to be a major concern worldwide including India. While majority of the reported outbreaks include those of acute diarrhoeal diseases, vector borne diseases, food poisoning and measles, in recent years many outbreaks/epidemics, Public Health Emergencies of International Concern and pandemics like Zika virus disease, Influenza H1N1 pandemic and the COVID-19 pandemic have challenged and strained the public health systems in various parts of world including India.

A crisis can be defined as an unexpected set of circumstances, which represents an immediate and significant threat to Public. A crisis is a major catastrophe that may occur either naturally or as a result of human error. It can include tangible devastation, such as the destruction of lives or assets

Health crisis is considered as an unforeseen occurrence or a combination of circumstances that poses a significant public health risk not limited to the spread of diseases but also the lack of access to the safe, efficacious and quality medical products. To address such public health issues relating to accessibility of medical products, co-ordinated response of regulatory authorities i.e CDSCO/State/UT, Regulatory authorities are of paramount importance. After assessing related risks, if routine response procedures are not considered sufficient, urgent, and coordinated action is required to manage and control the situation.

2. Scope

This document presents the framework and role of Indian Regulatory Authorities in the development, evaluation and approval of vaccines, therapeutics and diagnostics in the management of health crises in the fast track mode as well as accessibility of registered products.

The document is based on principles that put patient safety first while acknowledging the critical importance of compliance with regulations including global regulations. Regulatory activities are often fundamental to the management of the crisis.

This document is developed to meet the need to have better international, national and subsequent coordination in the regulatory/ policy field of medicines regulators in a consistent manner. It addresses the roles and responsibilities of RAs in this process and also aims to identify the opportunities for international collaboration. It also covers procedures for RAs dealing with health crises, through a structure of communication among CDSCO, States/UT regulatory authorities, laboratories for information exchange and with other government institutions (e.g ICMR, DBT, DST, DOP), AEFI Secretariat, PVPI through identified responsible focal points.

3. Procedures

Control over the import, manufacture, distribution and sale of drugs, cosmetics and medical devices in the country are regulated under the provisions of the Drugs and Cosmetics Act, 1940 & Rules made thereunder i.e. Drugs Rules, 1945, Medical Devices Rules, 2017, New Drugs & Clinical Trials Rules, 2019 and Cosmetics Rules, 2020.The objective of the drug regulatory system is to ensure availability of safe, effective and quality

drugs, cosmetics and medical devices based on scientific excellence and best possible regulatory practices under the said Act and Rules.

Since health crises are unpredictable, dynamic, and have the potential to escalate into a Public Health emergency, CDSCO & State Drug Control authorities (this may include co-ordination with international organization) should be prepared to act, preferably early at the beginning of a crisis, to escalation where possible.

In order to prepare for health crises quickly, efficiently, and in a coordinated manner following areas are required to be emphasized.

3.1 **Development, Evaluation And Approval of Vaccines, Therapeutics and Diagnostics in the management of health crises in the fast track mode :**

A. **Providing scientific support to the timely development of high quality, safe and effective Vaccines, Therapeutics and Diagnostics during public health emergencies.**

CDSCO will provide guidance on regulatory pathway for providing scientific support to the timely development of high quality, safe and effective Vaccines, Therapeutics and Diagnostics during public health emergencies.

The details are as under -

I. Any firm having a Drug/Vaccine under development for crisis/emergency situation can directly approach DCG(I) through Public Relations Office for seeking guidance for regulatory pathway.

II. Any firm or research institute having protocol for repurposing of existing drugs/vaccines for treatment of emergency/crisis will also be given priority for review and approval.

III. Application for clinical trial permission and application to import and or to manufacture Drug/Vaccine for sale and distribution would be processed on priority though expedited review/accelerated approval.

IV. Any firm having Drug/Vaccine already approved for crisis/emergency in any other country can directly approach DCG(I) through Public Relations Office regarding expedited review/accelerated approval for marketing in India.

V. Data requirement for animal toxicity study, clinical study, stability study etc. may be abbreviated deferred, or waived on case to case basis depending upon the type of vaccine, nature of drug, plant from which the drug is extracted & its experience in case of Phyto- pharmaceuticals.

VI. Applications to manufacture or impel Drug/Vaccine for test, analysis and further use BA/BE or Clinical Trial may be processed on priority.

VII. In case of emergency, Import license (Form 10) may be granted without Registration Certificate (Form 41) subject to approval of Central Government.

B. **Urgent need for new treatments or vaccines in the face of an emerging health threat.**

This applies to situations where there are true unmet needs for medical treatmentsor vaccines, the demand for regulatory actions, given a lack of available treatments/ vaccines. Nationally, regulatory authorities of all states should provide the necessary support for these mechanisms, when requested to. Additionally, in this context, it remains the responsibility of Regulatory authorities to identify new medical products under assessment to participate in various collaborative initiatives in the regulatory field with each other and to facilitate

development and availability of the novel technologies wherever required.

C. Quick Review Process and Fast Track Approval

This process is well defined in New Drugs and Clinical Trial Rules 2019 under second schedule as below:

(a) Accelerated Approval Process: Accelerated approval process may be allowed to a new drug for a disease or condition, taking into account its severity, rarity, or prevalence and the availability or lack of alternative treatments, provided that there is a prima facie case of the product being of meaningful therapeutic benefit over the existing treatment.

I. In such case, the approval of the new drug may be based on data generated in clinical trial where surrogate endpoint shall be considered rather than using standard outcome measures such as survival or disease progression, which are reasonably likely to predict clinical benefit, or a clinical endpoint. These should be measurable earlier than irreversible morbidity or mortality (IMM) and reasonably likely to predict clinical benefit.
II. After granting accelerated approval for such drug, the post marketing trials shall be required to validate the anticipated clinical benefit.
III. Accelerated approval may also be granted to a new drug if it is intended for the treatment of a serious or life-threatening condition or disease of special relevance to the country, and addresses unmet medical needs. This provision is intended to facilitate and expedite review of drugs so that an approved product can reach the therapeutic armamentarium expeditiously.
IV. If the remarkable efficacy is observed with a defined dose in the Phase II clinical trial of investigational new drug for the unmet medical needs of serious and life threatening diseases in the country, it may be considered for grant of marketing approval by the Central Licencing Authority based on Phase II clinical trial data. In such cases, additional post licensure studies may be required to be conducted after approval to generate the data on larger population to further verify and describe the clinical benefits, as per the protocol approved by the Central Licencing Authority.
V. The type of information needed to demonstrate the potential of a drug to address an unmet medical need will depend on the stage of drug development. Early in development, such potential should be sufficiently demonstrated based on nonclinical models, a mechanistic rationale and pharmacologic data. Later in development, prior to new drug approval such potential should be demonstrated through clinical data to address an unmet medical need.

(b) Situations where quick or expeditious review process can be sought for approval of a new drug after clinical development: -

(i) In situation where the evidence for clinical safety and efficacy have been established even if the drug has not completed the all or normal clinical trial phases, the sponsor or applicant may apply to the licencing authority for expedited review process wherein the licencing authority will examine and satisfy the following conditions. –

a) it is for a drug that is intended to treat a serious or life threatening or rare disease or condition;
b) if approved, the drug would provide a significant advantage in terms of safety or efficacy;

c) there is substantial reduction of a treatment-limiting adverse reaction and enhancement of patient compliance that is expected to lead to an improvement in serious outcomes;

(ii) the sponsor or applicant may also apply to the licencing authority for expedited review process for new drugs developed for disaster or defence use in extraordinary situation, such as war time, the radiation exposure by accident or intention, sudden deployment of forces at areas with higher health risk, where specific preventive and treatment strategy is required, where new intervention in the form of new drug, route of delivery or formulation has been developed and where real life clinical trial may not be possible. The permission for manufacture of such new drug may be granted if following conditions are satisfied: -

a) The preclinical data makes a case for claimed efficacy;
b) there is no possibility of obtaining informed consent from the patient or his legally acceptable representative, as the case may be, adopting inclusion and exclusion criteria and strict protocol adherence by each subject;
c) there is no established management or therapeutic strategy available as on date and proposed intervention has clear possible advantage;
d) such approval can be used only for one time. The subsequent approval shall only be granted once detailed efficacy report of such intervention is generated.

(iii) the new drug is an orphan drug as defined in clause (x) of rule 2 of these Rules.

3.2. Unavailability of products due to crisis, where already registered products are in short supply or unavailable

The access to medical products is primary responsibility of Department of Pharmaceuticals (DoP), Ministry of Chemical and Fertilizers. Unavailability of medical products used to prevent or treat a serious or life-threatening disease, for which there is no other available source with sufficient supply of that product available, is very challenging and can easily evolve into a crisis. Regulatory authorities play an important role in minimizing negative impact on patients, healthcare facilities and clinicians. Examples in this category may include a viral pandemic where antivirals,other medicines, or vaccines are in shortage or unavailable.

In this case, consultations and information exchange are of value. Different approaches could be applied,varying from consultations through email until it is possible to establish a mechanism for regular virtual or face-to-face meetings.

For collection of data/information methodologies like survey at supply chain, hospitals, uploading of data in an online database system etc. may be adopted.
CDSCO along with State Drugs Control department & other departments have an important role for monitoring and mitigating the shortage of medicine and device/diagnostics. This may include taking feedback from the industry on daily basis regarding the production of emergency drugs, devices, diagnostics and dispatch to distribution points, verification of the availability of API, excipients, KSM for the uninterrupted production of emergency medical products.

In order to meet the drug requirement in the country during Covid 19 pandemic situation, monitoring of production and availability of drugs was carried out by creating a COVID Drugs Management Cell (CDMC), which was a joint exercise between Central Drugs Standards Control Organization (CDSCO), Ministry of

Health and family Welfare (MoHFW) and the Department of Pharmaceuticals (DoP). Daily meetings of the CDMC were conducted to review and prioritize the actions required with respect to the issues surrounding drug production and availability.

4. Crisis Management Cell

To manage health crisis, a crisis management cell will be constituted which will comprise of Heads of zonal/sub-zonal/port offices/states/UT Drugs Control Department, Heads of laboratories. The cell would meet on regular basis during the crisis or it would meet as and when required to strategize priorities and respond with regulatory agility. To facilitate the process, the cell would co-opt as many members as necessary, depending upon the nature and context of crisis. The crisis cell will also function to support DCG (I), for giving inputs to the technical advisory committee of the crisis management group of disaster management cell, MOHFW, govt. of India.

5. Quality or safety issues of the products in the supply chain:

Quality or safety issues for products can be addressed with

a- Effective supply chain management
b- Proper storage
c- Regular sampling at various levels which may include manufacture, distributors and retailers.
d- Audit at manufacturing/ supply chain site
e- Import of quality API and excipients, pre and post import check.

6. Some principles of crisis management by CDSCO:

Collaboration – creating and sustaining broad and transparent relationships among stakeholders to support trust, collaboration, consensus, information exchange and rapid communication.

Communication – Timely and clear communication is critical in handling a current crisis and preparing for future crises.

Comprehension – considering all threats, phases, scenarios, stakeholders, and impact related to a global health crisis scenario.

Confidentiality – regarding restricted information and the use of secure communication channels. Depending on the type of information exchanged, ad-hoc confidentiality agreements may be established, or sponsor agreement to share information amongst RAs may be obtained.

Coordination – synchronizing the activities of all relevant stakeholders to achieve a common purpose.

Flexibility – using creative and innovative approaches in solving global health crises challenges. This includes collaborative regulatory initiatives to foster the development and availability of new medicines and technologies.

Integration – ensuring aligned efforts (including on aligning regulatory requirements and flexibilities) and transparency among all domestic levels of government and stake holders.

Patient-focus – ensuring that the safety of patients (including the welfare of 'healthy people') is the guiding principle for regulatory actions and decisions.

Professionalism – applying scientific-based approaches and engagement with education, training, experience, ethics, and feedback.

Foresight – anticipating future crises, using forward-planning, to take preventive and preparatory measures against damage in global public health.

Risk-based – using sound risk management principles (assessment, management, and communication) in assigning priorities and resources.

Transparency – conducting organizational operations and decisions with (the related principles of) accountability, trustworthiness, and transparency and the goal of building and maintaining trust among CDSCO members and partners. Use of the CDSCO website to promote information to all stakeholders.

Regulatory Reliance, agility, flexibility –this is an effective tool which is required to be used as and when the situation demands.

7. Appendix

Contact List of CDSCO, State Regulatory Authorities, laboratories.

8. References

- Drugs & Cosmetics Act & Rules, 1945
- ICMRA Guidelines
- Disaster Management Guidelines of MoHFW
- New Drug & Clinical Trials Rule, 2019

Appendix

S.no.	Office	Officer Name	Designation	Contact	Email
1	HQ	Dr. Rajeev Singh Raghuvanshi	DCG(I)	+91-11-23236965 (D)	dci@nic.in
2	NIHFW, Delhi	Dr. S.Eswara Reddy	JDC(I)	+91-11-23502999(D), 23216367, Ext – 124	Se.reddy@nic.in

3	HQ	Dr. V.G.Somani	JDC(I)	011-23502913(D), 23502917, Ext-314	v.g.somani30@cdsco.nic.in
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25	HQ	Mr. Sanjeev Kumar	DDC(I)	+91-11-2321-6367, Ext – 221/312 9868440470	sanjeevkumar15@cdsco.nic.in
26	HQ	Mrs. Kavita Sharma	DDC(I)	+91-11-2321-6367, Ext - 212 9810812720	Kavita.s@cdsco.nic.in
27	HQ	Mrs. Kavita Sharma	DDC(I)	+91-11-2321-6367, Ext - 102 9810812720	Kavita.s@cdsco.nic.in

28	HQ	Mrs. Kavita Sharma	DDC(I)	+91-11-2321-6367, Ext – 405 9810812720	Kavita.s@cdsco.nic.in
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33	Kolkata (East Zone)	Sh. Arup Kumar Chatterjee	DDC(I)	033 – 22870513 / 22801391	arupkc@cdsco.nic.in
34	Mumbai (West Zone)	Sh. Shiv Kumar (West Zone 1) Sh. Jayant Kumar (West Zone 2)	DDC(I)	91-22- 23002279, 23002215, 23092971	shivkumar27@cdsco.nic.in jayant@cdsco.nic.in
35	Chennai (South Zone)	Dr. K M Srinivasan	DDC(I)	044-28278186, 28268186	srinivasan.km@cdsco.nic.in
36	Ahmedabad (Zonal Office)	Dr. Ravi kant Sharma	DDC(I)	079-22850706, 22850707	rk.sharma66@nic.in
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40	Varanasi	Sh. Mukesh Kumar	ADC(I)		mukesh@cdsco.nic.in
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44	Guwahati	Mr. Dinesh Kumar	ADC(I)	0361-2332628 8510806616 (M)	dinesh.kumar@cdsco.nic.in dineshkumar012@cdsco.nic.in
45	Vishakhapatnam	Mrs. K. Bhuvaneswari	ADC(I)	0891-2729315, 2725315	k.bhuvana@cdsco.nic.in
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47	Ahmedabad Airport	Sh. Shashi Paul	ADC(I)	079-29700619,	shashi.paul@cdsco.nic.in
48	Bangalore Air Port	Mrs. M. Shakuntala,	ADC(I)	080-27688312,	maheshadci@cdsco.nic.in
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50	Chennai Sea Port	Sh. Nitin M Jadhav	ADC(I)	044-25212041, 25254385,25254364	jadhav.nitin@cdsco.nic.in.
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53	Goa Sea & Air Port	Dr. Krishan Kumar Bhardwaj	ADC(I)	0832-2201001	Krishan.bhardwaj@cdsco.nic.in
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56	Indore (ICD)	Sh. Mahesh N Anjinappa	ADC(I)	0261-2207500	mahesh.na@cdsco.nic.in
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	CDL				
67	CDL, Kolkata	Dr. Saroj Kumar Ghosh	Director I/c	033 -22299541	cdlkol@cdsco.nic.in
68	CDL, Kasauli	Sh. Sushil Kumar Sahu	Director I/c	01792-272046	cdlkasauli@cdsco.nic.in

S.No.	State	Officer Name	Designation	Contact No.	Email
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3	Assam	Mr. Biswajit Talukdar	Drug Controller & SLA	7086084833	drugscontrolassam@gmail.com
4	Bihar	Mr. Uday Shankar	Drug Controller & SLA	9430099336	sdcbihar-bih@gov.in
5	Chhattisgarh	Mr. Deepak Soni, IAS	Drug Controller	8827755265	controllerraipur@gmail.com
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17	Mizoram	Mr. Lal sawma	Director & SLA	9436152192	mizoramfda2@gmail.com
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		Mr. Ajay Patak	SLA	9414355650	
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Chapter-14

VACCINE INSPECTION

Part A

		TITLE		Division Name	QMS Monitoring Division
		Procedure for Qualifying Inspector for inspection of Vaccine/ Biological Manufacturing Facilities		Document No.	QMS-INS-001
				Revision No.	00
				Effective Date	
				Page No.	
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 Purpose

To lay down a procedure for qualifying inspector for the inspection of Vaccine/ Biological Manufacturing Facilities.

2.0 Scope

This document is applicable for qualifying inspectors for the inspection of Vaccine/ Biological Manufacturing Facilities.

3.0 Responsibility

3.1. Head of CDSCO Zonal/ Sub-zonal offices shall be responsible for recommending the names of the Inspectors to be qualified.

3.2. QMS Monitoring Division shall be responsible to assess the performance of the inspectors whose names are recommended by Head of CDSCO Zonal/ Sub-zonal offices to be qualified as Qualified Inspector.

3.3. DCG(I) shall be responsible for designating the Qualified Inspector.

4.0 Accountability

Head of CDSCO Zonal/ Sub-zonal offices, Head of QMS Monitoring Division and DCG(I)

5.0 Procedure

5.1. **Pre requisite for Qualified/ Lead Inspector**

5.1.1. Drugs Inspector(s) who have not less than 18 months experience in the manufacture or testing of at least one of the substance specified in Schedule-C of Drugs & Cosmetics Act and Rules or who have gained experience of not less than three years in the inspection of firm manufacturing any of the substances specified in Schedule-C of Drugs & Cosmetics Act and Rules during the tenure of their services as Drugs Inspectors.

5.1.2. Drugs Inspectors who have undergone at least two GMP training (General GMP training and GMP training in the area of vaccines/ sterile products) shall be considered.

5.1.3. Drugs inspector who has accompanied a Qualified Inspector as a member of inspection team for a minimum of three inspections of Vaccine / Biological Manufacturing Facilities.

5.1.4. Drugs Inspectors shall be deputed for inspection along with Senior Inspector who may be Zonal Head and experienced in inspection of Vaccine / Biological Manufacturing Facilities.

5.1.5. Drugs Inspector who shall inspected Vaccine / Biological Manufacturing Facilities as a Lead Inspector for at least two inspections under the supervision and monitoring of the Zonal head after the three accompanied inspections.

5.2. Drugs inspector who have satisfactorily performed in the inspections of Vaccine/ Biological Manufacturing Facilities for at least five inspections (according to point No 5.1.3 and 5.1.5) and meet basic experience and training requirements as per current version of SOP No. QMS-INS-001 may be recommended by the Head of Zonal/ Sub-zonal offices to QMS Monitoring Division as per the current version of Annexure-I of this SOP to be designated as a Qualified Inspector.

5.3. Drugs inspector of CDSCO (HQ) who meets entire "Pre-requisite for Qualified Inspector" shall be recommended by Head of Biological Division/ QMS Monitoring Division to be designated as Qualified Inspector in case of inspection for pre-authorization and post approval.

5.4. QMS Monitoring Division in consultation with Head of Biological Division shall assess the qualifying criteria and performance of the Drugs Inspectors whose name was recommended by the Head of Zonal/ Sub-zonal offices on the basis of review of inspection report, documentation, review procedures, etc.

5.5. DCG(I) shall designate the Drugs Inspector(s) as Qualified Inspector as per the recommendations of the Head of QMS Monitoring Division and Head of Biological Division.

5.6. QMS Monitoring Division shall publish list of Qualified/ Lead Inspector on CDSCO website as per current version of Annexure-II of SOP No. QMS-INS-001.

5.7. **Requalification of Inspector:**

5.7.1. If the qualified inspector at the supervisory level has not conducted any GMP inspection in 03 years or has not attended any refresher training then he/she shall be disqualified and the list of the qualified inspector shall be updated accordingly. Such inspectors, if they intent to remain as qualified inspector shall be re-qualified after passing the written examination conducted by the QMS Monitoring Division or by participating in 02

inspections as a team. The list of Qualified Inspector or Lead Inspector shall be updated accordingly.

5.7.2. In case of other Qualified Inspector or Lead Inspector, minimum 5 GMP inspections in 03 years shall be the criteria for requalification of the inspector as Qualified Inspector or Lead Inspector.

6.0 Annexure / Format

Annexure / Format No.	Title
Annexure-I (QMS-INS-001)	Format for "List of Drugs Inspectors recommended by zonal/ sub-zonal Head to be qualified as Qualified/ Lead Inspector"
Annexure-II (QMS-INS-001)	Format for "List of Qualified Inspectors or Lead Inspectors for Vaccine/ Biological Manufacturing Facilities"

7.0 References

Doc. No.	Title
1	The Drugs and Cosmetics Act and Rules

8.0 Abbreviation

Acronym	Full Form
SOP	Standard Operating Procedure
DCG(I)	Drugs Controller General (India)
DDC (I)	Deputy Drugs Controller (India)
QMS	Quality Management System

9.0 Revision History

Revision No.	Reason(s) for Revision

00	Created New

Annexure-I of QMS-INS-001

Format for "List of Drugs Inspectors recommended by zonal/ sub-zonal Head to be qualified as Qualified/ Lead Inspector"

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

S.No.	Name of Drugs Inspector(s)	Details of Basic and Advanced GMP training attended	Name and address of Vaccine/ Biological Manufacturing Facilities	Name of Qualified/ Lead Inspector who accompanied in inspection	Remarks, if any

Signature of Head of Zonal/ Sub-zonal Head

Annexure-II of QMS-INS-001

Format for "List of Qualified Inspectors or Lead Inspectors for Vaccine/ Biological Manufacturing Facilities"

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

S. No.	Name	18 months experience in manufacturing/ testing or 3 year experience in inspection of manufacturing sites of products specified in Schedule-C & C1 (Yes/No)	Training completed on GMP-Basic and Advanced (Yes/No)	Whether minimum inspections of vaccine manufacturing site completed as per SOP No. QMS-INS-001 (Yes/No)	Whether name of Drugs Inspector(s) recommended by the Zonal/ Sub-zonal Head	Qualified Lead Inspector for manufacturing of Vaccine/ Biological Manufacturing Facilities

QMS Monitoring Division **Biological Division**

		TITLE		Division Name	QMS Monitoring Division
		Procedure for Preparation of Annual Central Inspection Plan for Vaccine Manufacturing Facilities		Document No.	QMS-INS-002
				Revision No.	01
				Effective Date	
				Page No.	
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

Control Status

1.0 Purpose

To lay down a procedure for preparation of Annual Central Inspection Plan for Vaccine Manufacturing Facilities and its implementation.

2.0 Scope

This document is applicable for preparation of Annual Central Inspection Plan by CDSCO (HQ) for all types of inspections to be carried out as per Rule 79 of Drugs and

Cosmetics Rules, Section 22 (a), (b) & (c) of Drugs and Cosmetics Act which includes all routine special, concise, for-cause inspections using risk based approach viz. pre authorization inspection grant, renewal, issuance of test license, additional products, post approval changes, market surveillance test results, AEFI, complaints, recalls and any other inspection initiated by CDSCO due to non-compliance.

3.0 Responsibility

6.1 QMS Monitoring Division shall be responsible for review & finalization of draft Annual Central Inspection Plan for Vaccine Manufacturing Facilities using risk based approach and uploading finalized Annual Central Inspection Plan on CDSCO website.

6.2 The Head of CDSCO Zonal/Sub-Zonal and Head of Biological Division shall be responsible for the execution of the plan.

4.0 Accountability

Head of CDSCO Zonal/Sub-Zonal, Head of Biological division and QMS Monitoring division.

5.0 Procedure

8.1 DI/ADC(I) of concerned CDSCO Zonal/Sub-Zonal offices shall be responsible for preparation of draft Annual Central Inspection Plan for Vaccine Manufacturing Facilities using risk based approach as per Annexure-I.

8.2 The preparation of inspection plan shall be based on the applications received and considering the risks associated with a particular facility/product.

8.3 The site of inspection may be prioritized based on the two different kinds of risks - an intrinsic risk and a compliance-related risk.

8.3.1 The intrinsic risk estimated for a site reflects the complexity of the site, its processes and products as well as the criticality of the products. These items (complexity and criticality) usually remain fairly constant regardless of the compliance status of the site. Therefore,

one usually cannot estimate this risk on the basis of inspection deficiencies or compliance history.

8.3.2 The compliance-related risk that is estimated for the site reflects the GMP compliance status of the site immediately following the most recent inspections at the site. When this risk is being estimated, number of deficiencies identified during the last inspection and the criticality of the deficiencies shall be taken into account.

8.4 For determining the criticality of deficiencies, Technical Guide for Classification of Deficiency and Guidance document for zonal and sub zonal offices shall be referred.

8.5 **Factors which may be useful to consider are:**

8.5.1 Areas that were not inspected (or that were not inspected in detail) during the most recent inspection at the site.

8.5.2 AEFI cases, complaints, test results or recalls

8.5.3 Major changes in the building, equipment, process and Post Approval Changes.

8.5.4 Robustness of the Quality Management System, including its approach to Quality Risk Management.

8.5.5 General GMP compliance history, recurring non-compliance issues.

8.5.6 Significant failures to address previous GMP deficiencies.

8.6 During the preparation of Annual Central Inspection Plan, it is also to be ensured that all the vaccine sites are included at least once a year as per Rule 52 of Drugs and Cosmetics Rules.

8.7 The inspection required for following applications like pre-authorisation inspection, grant or renewal, issuance of test license, endorsement of additional products, post approval changes (supplement), market surveillance test results, AEFI, complaints, recalls shall be considered as basis for preparation of the inspection plan and shall be further updated by the CDSCO(HQ).

8.8 The Annual Central Inspection Plan shall be prepared in the format as per current version of Annexure-II of SOP no. QMS-INS-002. In case, concerned zonal/ sub-zonal offices make any deviation from the plan the same shall be communicated to QMS Monitoring Division within seven working days along with the revised dates of inspection.

8.9 The inspection shall be carried out and copy of inspection report along with the recommendation of the zonal/ sub-zonal offices shall be submitted to CDSCO (HQ) with copy endorsed to Biological Division and QMS Monitoring Division for further necessary action.

Note: The current version of SOPs QMS-INS-003 (Procedure for planning and preparation of GMP Inspection) and QMS-INS-004 (Procedure for conducting GMP Inspection, report writing and Review of inspection Report) shall be used for compliance of this procedure.

8.10 Zonal/ sub-zonal offices shall prepare and submit a report on monthly status of the inspections carried out along with the recommendations of head of CDSCO Zonal/Sub-zonal office to QMS Monitoring Division as per the current version of Annexure-III of SOP No. QMS-GNL-024.

8.11 The Head of Biological Division shall provide a list of Vaccine Manufacturing Sites which are not producing commercial batches of Human Vaccine during preparation of Annual Central Inspection Plan every year to QMS Monitoring Division as per Annexure-III of this SOP. These sites shall not be covered under Central Inspection Plan for routine inspection. List as per Annexure-III shall be prepared and uploaded in CDSCO website. This list may be updated from time to time.

8.12 QMS Monitoring Division shall upload finalized Annual Central Inspection Plan on CDSCO website till last week of December every year.

6 .0 **Annexure / Format**

Annexure/Format No.	Title
Annexure-I (QMS-INS-002/F01-00)	Format for Worksheet for Quality Risk Management Tool.
Annexure-II (QMS-INS-002/F02-00)	Format for Annual Central Inspection Plan For Vaccine Manufacturing Facilities.
Annexure-III (QMS-INS-002/F03-00)	List of Vaccine Manufacturing Sites which are not producing commercial batches during preparation of Annual Central Inspection Plan.

7.0 **References**

Doc. No.	Title
1	Drugs and Cosmetics Act 1940 and Rules, 1945.
2	PIC/S: A recommended model for Risk-based inspection Planning in the GMP environment. PI 037-1, 2 Appendices 1 January 2012
3	Guidance Document for Functions and Responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO, 2011.
4	Technical Guide for Classification of Deficiency

8.0 **Abbreviation**

Acronym	Full Form
QMS	Quality Management System
DI	Drugs Inspector
CDSCO	Central Drugs Standard Control Organization
DCG(I)	Drugs Controller General, India

DDC (I)	Deputy Drugs Controller, India
ADC (I)	Assistant Drugs Controller, India
SOP	Standard Operating Procedure
INS	Inspection
AEFI	Adverse Event Following Immunisation
GMP	Good Manufacturing Practices

9.0 **Revision History**

Revision No.	**Reason(s) for Revision**
00	New SOP
02	Editorial Corrections

Annexure-I of QMS-INS-002

"Format for Worksheet for Quality Risk Management Tool"

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

<table>
<tr><th colspan="3">PART A – Preliminary Information about the Site</th></tr>
<tr><td>Site Name</td><td colspan="2"></td></tr>
<tr><td>Site Address</td><td colspan="2"></td></tr>
<tr><td>Licence Number (if any)</td><td colspan="2"></td></tr>
<tr><td>FP or API Manufacturer?</td><td colspan="2"></td></tr>
<tr><td>Last Inspection Date</td><td colspan="2"></td></tr>
<tr><td>Name of previous lead Inspector</td><td colspan="2"></td></tr>
<tr><th colspan="3">PART B – The Intrinsic Risk Associated with the Site</th></tr>
<tr><th>Risk Factor</th><th>Risk Score</th><th>Matrix for Estimating the Intrinsic Risk</th></tr>
<tr><td>The Complexity of the site, its processes and products, is regarded as:</td><td>1 2 3

Circle one</td><td rowspan="2"><table>
<tr><th rowspan="2">Complexity</th><th colspan="3">Criticality</th></tr>
<tr><th>1</th><th>2</th><th>3</th></tr>
<tr><td>1</td><td>1 (Low)</td><td>2 (Low)</td><td>3 (Med)</td></tr>
<tr><td>2</td><td>2 (Low)</td><td>4 (Med)</td><td>6 (High)</td></tr>
<tr><td>3</td><td>3 (Med)</td><td>6 (High)</td><td>9 (High)</td></tr>
</table>
Use the above matrix and record the Intrinsic Risk associated with the site below:

Low □ Medium □ High □</td></tr>
<tr><td>The Criticality of the products manufactured by the site, or the criticality of the analytical testing or other service offered provided by the site, is regarded as:</td><td>1 2 3

Circle one</td></tr>
<tr><th colspan="3">PART C – The Compliance-related Risk based on the last Inspection</th></tr>
</table>

The compliance risk indicated by the most recent deficiency profile of the site is:	Low □ Medium □ High □	• No Major or Critical Deficiencies • 1 to 5 Major Deficiencies: Number of Majors = __ • 1 or more Critical Deficiencies or more than 5 Majors (Note: Customize as appropriate)

PART D – The Risk-Rating assigned to the Site

Complete the matrix below by combining the Intrinsic risk score and the Compliance-related risk score to determine the Risk Rating for the site.

Compliance Risk	**Intrinsic Risk**		
	Low	**Medium**	**High**
Low	Risk Rating = A	Risk Rating = A	Risk Rating = B
Medium	Risk Rating = A	Risk Rating = B	Risk Rating = C
High	Risk Rating = B	Risk Rating = C	Risk Rating = C

The Risk Rating associated with this site is: A B C

PART E – The Recommended Frequency for Routine Inspections at the Site

A	Reduced Freq, 2 to 3 yrs
B	Moderate Freq, 1 to 2 yrs
C	increased Freq, < 1 yrs

Using the Risk Rating, the recommended frequency for routine inspections at the site is an inspection every:

_____ Years or _____ Months

Annexure-II of QMS-INS-002

"Format for Annual Central Inspection Plan for Vaccine Manufacturing Facilities"

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

S. No.	Name and address of the manufacturing site	Vaccines manufactured (category wise list)	Date of last inspection with no of days & team	Purpose of last inspection (grant /renewal /post-approval changes, AEFI, follow-up, routine)	Major deficiencies detected	Compliance met till date, if any	AEFI reported/ changes / Product complaints, failure, if any	Proposed time of Inspection

Annexure-III of QMS-INS-002

"List of Vaccine Manufacturing Sites which are not producing commercial batches during preparation of Annual Central Inspection Plan"

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

List of Vaccine Manufacturing Sites which are not producing commercial batches during preparation of Annual Central Inspection Plan

S.No	Name and Address of Manufacturing site
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	

		TITLE		Division Name	QMS Monitoring Division
		Procedure for planning and preparation of GMP Inspection		Document No.	QMS-INS-003
				Revision No.	00
				Effective Date	
				Page No.	
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 Purpose

To lay down a procedure for planning and preparation of GMP Inspection.

2.0 Scope

2.1. This document is applicable for Planning and preparation of all kind of inspections by the inspectors of CDSCO viz. Routine, special, concise and for-cause inspections.

3.0 Responsibility

3.1. The DI/ADC(I) of CDSCO Zonal/ Sub-zonal offices shall be responsible for planning and preparation of inspection.

3.2. The Head of CDSCO Zonal/ Sub-zonal offices shall be responsible for overall compliance of the SOP.

4.0 Accountability

Head of CDSCO Zonal/ Sub-zonal offices, QMS Monitoring Division and DCG(I)

5.0 Procedure

5.1. Composition of the inspection team

5.1.1. Two to three inspectors from CDSCO of which one trained & qualified Inspector shall be designated as the team leader, one expert from CDL, Kasauli and one inspector from SLA.

Drugs Inspectors/ADC(I)/DDC(I) from CDSCO(HQ) shall be a part of the inspection team for onsite evaluation, Marketing authorization and Post Approval Changes or as & when decided by DCG(I).

5.1.2. The mode of inspection may be hybrid where CDSCO (HQ)/Expert may join virtually/physically.

5.2. Responsibility of the Inspection Team

The responsibility of the Inspection Team shall be as follows:

- To conduct a GMP inspection
- To agree on the inspection's scope
- To discuss and resolve, where possible, any major problems which may occur during the inspection process
- To ensure that all Drugs Inspectors play an active role in the inspection process
- To make decisions on inspection findings by way of consensus, however, where this is not possible, the Team Leader makes the final decision
- To prepare an inspection report

5.3. Responsibility of the Team Leader

The Team Leader shall be responsible to organize, coordinate and lead during all stages of the inspection and act as spokesperson.

5.4. Preparing for Inspection

5.4.1. After receiving file of the firm by the deputed inspection team member (s), a review should be made relating to the firm to be visited from the documents available in the office file. This may include:-

5.4.2. Application for grant/renewal with supporting documents.

5.4.3. If already granted/renewed.

5.4.3.1 Drug Manufacturing License.

5.4.3.2 The Marketing Authorization for the applied products.

5.4.3.3 Site Master File.

5.4.3.4 Evaluation of
Product records (process flow, process validation and stability studies),
Process of Handling adverse drugs reaction (AEFI)
Market complaint handling,
Product recall record,
NSQ reports, if available,
Discrepancies pointed out in previous inspection reports etc.

5.5. The inspection team prepare day wise inspection plan (1-3) days or (1-5) days depending on the scope of inspection (size of facility, products, etc. and planning should be made using risk based approach

5.6. Communications with local Authority on site and purpose of inspection and regarding the schedule of inspection

6.0 Annexure / Format

Nil

7.0 References

Doc. No.	Title
1	The Drugs and Cosmetics Rules, 1945.

2	Guidance Document for Functions and Responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO.
3	WHO Technical Report Series

8.0 Abbreviation

Acronym	Full Form
QMS	Quality Management System
DI	Drugs Inspector
SLA	State Licensing Authority
CDL	Central Drug Laboratory
CDSCO	Central Drugs Standard Control Organization
DCG(I)	Drugs Controller General, India
ADC(I)	Assistant Drugs Controller, India
SOP	Standard Operating Procedure
INS	Inspection
GMP	Good Manufacturing Practices
WHO	World Health Organization
NSQ	Not of Standard Quality
NIB	National Institute of Biologicals

9.0 Revision History

Revision No.	Reason(s) for Revision

00	New SOP

		TITLE		Division Name	QMS Monitoring Division
		Procedure for conducting GMP inspection, report writing & review of inspection report		Document No.	QMS-INS-004
				Revision No.	01
				Effective Date	
				Page No.	832 of 1103
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 Purpose

To lay down a procedure for conducting GMP inspection and report writing.

2.0 Scope

This document is applicable for inspection for grant/ renewal of Licence/ Post Approval Changes/ Issuance of CoPP/ Sudden Inspection (Unannounced) and for-cause inspection (compliant investigation, change assessment, etc.) by the inspectors of CDSCO.

3.0 Responsibility

3.1 The DI/ADC(I) of CDSCO Zonal/ Sub-zonal offices and SLA are responsible for conduct of GMP inspection and report writing.

3.2 The Head of CDSCO Zonal/ Sub-zonal offices, Head of Vaccine Division and QMS Monitoring Division shall be responsible for overall compliance of the SOP.

4.0 Accountability

Head of CDSCO Zonal/ Sub-zonal offices, Head of QMS Monitoring Division and DCG(I)

5.0 Procedure

5. "Procedure for planning and preparation of GMP inspection" (QMS-INS-003), which describes the steps immediately before the conduct of an inspection and particularly the planning and preparation of GMP inspection.

5.2. **Inspection for Grant/ Renewal of CoPP/ Manufacturing License/ Marketing Authorization/ Routine inspection**

- On the basis of adequacy of application joint inspection needs to be planned by the Head of CDSCO Zonal/Sub-zonal offices in co-ordination with SLA with inspection team comprising of Drugs Inspectors from concerned CDSCO Zonal/Sub-zonal offices and SLA.

- The inspection needs to be carried out as per requirements prescribed under Drugs & Cosmetics Act and Rules and current WHO GMP guidelines related to products, procedures, etc. made thereunder utilizing inspection checklist as per WHO-GMP guidelines as per Annexure-I of this SOP.

- The inspectors shall examine all portions of premises, plan and appliances and also inspects the process of manufacture intended to be employed or being employed, standardizing and testing of the drugs to be manufactured or being manufactured and enquire into the professional qualification of technical staff to be employed. They shall also examine and verify the statements made in the application in regard to their correctness and the capability of the applicant to comply with the requirements of the competent technical staff,

manufacturing plant, equipment (Manufacturing & testing) and requirement of GMP (Schedule-M read with requirement of maintenance of records as laid down in Schedule-U).

- The inspectors shall conduct an opening meeting with the key personnel of the manufacturing site wherein the scope and purpose of the inspection should be discussed.
- Systemic inspection should be carried out by taking rounds, interviewing the personnel, observing the activities and looking into relevant documents. The deficiencies should be discussed with the personnel during the course of inspection for better understanding.
- Inspector should carry put inspection on the basis of CDSCO guidance document, Schedule-M of Drugs & Cosmetics Rules and applicable current WHO guidelines (latest and relevant version of applicable WHO TRS) for inspection of Vaccine products including vaccines.
- During the course of inspection inspectors should critically look into (but not limited to) following details using risk based approach:

5.2.7.1. Adequacy of Quality Management System.

5.2.7.2. Design and layout of manufacturing areas, flow of personnel and materials, adequacy of segregation.

5.2.7.3. Nature of construction and finishes.

5.2.7.4. Ventilation system, water system, drainage system, steam and gases.

5.2.7.5. Decontamination and waste disposal system.

5.2.7.6. Classification of manufacturing areas.

5.2.7.7. Qualification of premises and systems as appropriate.

5.2.7.8. Health, hygiene and gowning requirements for personnel.

5.2.7.9. Adequacy of general GMP training and need based training of the personnel, aseptic practices for aseptic / sterile products.

5.2.7.10. Design and location and suitability of equipment

5.2.7.11. Preventive maintenance program.

5.2.7.12. Qualification, calibration of equipment BMR & BPR of bulk and finished products, sourcing of materials, vendor approvals.

5.2.7.13. Control over maintenance, characterization and handling of seed strains.

5.2.7.14. Control, storage and handling of materials.

5.2.7.15. Line clearance, labeling and segregation practices.

5.2.7.16. Logging of activities (Specifically for critical manufacturing steps, IPQC steps, cleaning, weighing and environmental monitoring).

5.2.7.17. Transport handling and use of starting materials and packing materials.

5.2.7.18. Monitoring of process operation.

5.2.7.19. Adequacy of change control, deviation control procedures.

5.2.7.20. Sanitation and cleaning.

5.2.7.21. Adequacy of documentation and document control system (Specifications, procedures, records, protocols and reports).

5.2.7.22. Quality Control Practices on RM/PM/FG testing, sampling, quarantine control.

5.2.7.23. Stability studies- SOP, Protocol and reports.

5.2.7.24. Validation practices- Adequacy of VMP, validation and qualification protocols and reports for premises, system, equipment, processes, cleaning, analytical methods and computer (as applicable).

5.2.7.25. Adequacy of studies and control procedure followed for product change over.

5.2.7.26. Traceability of activities.

5.2.7.27. SOP on reprocessing, if any.

5.2.7.28. Complaint handling and related SOPs, records and investigation results.

5.2.7.29. Depth and comprehensiveness of Self Inspection System and compliance.

5.2.7.30. Adequacy of Corrective and Preventive Action system.

5.2.7.31. Trend analysis, risk assessment, annual product review, utilization of alert and action limits in processing and relevant monitoring.

5.2.7.32. Adequacy of recall system.

5.2.7.33. Handling of rejected material.

5.2.7.34. Adequacy of cold chain management.

5.2.7.35. Animal testing facilities (building with proper HVAC, waste disposal and management etc.)

5.2.7.36. Control system on printed packaging material.

5.2.7.37. Review of compliance of last inspection findings.

5.3. **Inspection For-Cause/ Sudden Inspection**

- Complaint investigation may be carried out jointly or independently.
- During the course of complaint investigation in addition to verification of general things as mentioned above specific records with respect to the products in question needs to be verified (BMR, BPR, testing, specification, deviation, changes made, etc.) to see whether the subject batch of product is manufactured and tested as per the GMP requirements or not.
- Control sample of subject product also needs to be verified physically.
- Whether the firm has carried out complaint investigation or route cause analysis needs to be verified. If any direct or in-direct assignable route cause is detected the impact of that cause on other batches also needs to be verified.
- If required samples may be drawn judiciously from the available stocks or control samples and sent for testing or evaluation to Central Drug Testing Laboratories.

- The report of complaint investigation shall be written by the inspection team immediately (not more than 7 days) and forwarded to CLAA/ SLA with specific comment that whether there is any possibility of availability of complaint product at the manufacturer's level.

5.4. **Inspection for Post Approval Changes**

- Inspection to verify the suitability of changes if required for route adoption.
- The inspection for change verification is to be carried out jointly or independently.
- In case of changes like:

5.4.3.1. Major up gradation of production facilities

5.4.3.2. Major change in equipment

5.4.3.3. Change in critical source of material

- The report for change verification is compiled and forwarded to SLA and CLAA with clear comments on due diligence taken by the manufacturer for justification of change.
- Any other inspection may be carried out as directed by SLA / CLAA on the lines of GMP assessment inspection carried out for grant or renewal of licenses with specific emphasis on any issue in question and reported accordingly.

5.5. **Joint inspection with other external agencies:**

Joint inspection may be carried out by Indian NRA along with NRA representative of other countries or any other regulatory body.

5.6. **Procedure for Inspection Report Writing**

- Drugs Inspector(s) shall be responsible for inspection of manufacturing site and writing of inspection report.
- The inspection report should include the items shown in the proposed model inspection report as per current version of Annexure-II of SOP No. QMS-INS-004.

- The report should be prepared in a timely manner (not more than 15 working days) after an inspection, with the participation of all members of the inspection team under the coordination of the lead inspector.

- The report should be reviewed in accordance with the quality system of the inspectorate by Head of CDSCO Zonal/ Sub-zonal offices.

- The inspection report should, as appropriate, be written in the third person, passive voice and the past tense.
  Example: "Cleaning logs for rooms and equipment were maintained in all areas of the factory."

- All the observations that are considered as deficiencies/ non-compliances should be listed under Part-3 of the inspection report.

- Each observation included in an inspection report should be referenced to the relevant GMP text, WHO guidelines or conditions or commitments under the Drugs and Cosmetics Act and Rules made there under.

- An observation that cannot be reasonably referenced should not be listed as a deficiency.

- The non-compliance statement should include the requirement (R), evidence (E) and deficiency (D).

  Example: (R) The relevant cleaning records and source data should be kept in cleaning validation reports; (E) the source of three samples taken for recovery testing during the process equipment validation was not traceable; (D) cleaning validation reports did not include sufficient data.

- Deficiencies/noncompliance statements should distinguish whether the defect lies in the system itself or in a failure to comply with the system.
  For instance, when cleaning is found to be suboptimal, it is important to know whether the standard operating procedures (SOPs) are inadequate or lacking, or whether adequate written procedures exist but are not being followed by personnel.

- **Where more than one deficiency relates to the same basic quality system failure, the deficiencies should be grouped and listed as a single observation, under a heading that reflects the basic system failure.**

- Deficiencies should be reported with a focus on risk to patient health and/ or need for corrective and preventive action (CAPA).

- The report should not include comments that could be construed as proposed specific solutions to issues raised. Recommendations should relate to recommended regulatory action as appropriate.

- Each deficiency should be classified as critical, major or other, according to the following definitions, which may be adapted according to the national or regional legal context.

5.6.14.1. A *critical* deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

5.6.14.2. A *major* deficiency may be defined as a non-critical observation that:

a) has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
b) indicates a major deviation from the GMP guide;
c) indicates a failure to carry out satisfactory procedures for release of batches;
d) indicates a failure of the person responsible for quality assurance/ quality control to fulfil his or her duties;
e) consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

5.6.14.3. A deficiency may be classified as *other* if it cannot be classified as either *critical* or *major*, but indicates a departure from GMP. A deficiency may be other either because it is judged as minor or because there is insufficient information to classify it as *major* or *critical*.

5.6.14.4. Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of an *other* deficiency may be categorized as *major*.

5.6.14.5. A deficiency that was reported at a previous inspection and was not corrected may be reported with a higher classification.

5.6.14.6. One-off minor lapses or less significant issues are usually not formally reported, but are brought to the attention of the manufacturer during the inspection.

5.6.14.7. The status of compliance with WHO GMP guidelines and schedule M should be determined by the nature and number of deficiencies:

a) When there are other deficiencies only:

i. The site is considered to be operating at an acceptable level of GMP compliance,

ii. The manufacturer is expected to provide CAPAs,

iii. CAPAs are evaluated and followed up during the next routine inspection.

b) When there are other and a few major deficiencies (e.g. < 6 as per 5.6.11):

i. The site is compliant with GMP after assessing the CAPAs,

ii. CAPAs for all deficiencies to include actions implemented and/or planned, timelines and documented evidence of completion, as appropriate,

iii. CAPAs are evaluated on paper and may or may not include an on-site, follow-up inspection.

c) When there are critical or several major deficiencies (e.g. ≥ 6 as per 5.6.11):

i. The site is considered to be operating at an unacceptable level of compliance with GMP guidelines,

ii. Another inspection will normally be required,

iii. Administrative and/or legal enforcement actions are applied as necessary.

! In case of critical deficiencies identified during inspection as defined above, the report shall be prepared immediately (not more than 7 days) and reviewed in accordance with the SOPs.

5.7 Review

5.7.1 Review record of joint inspection report needs to be prepared as notes.

5.7.1.1 Review of the inspection report shall be done by Zonal Head / Division Head and forwarded to all concerned with comments as a part of QMS review within 30 days from the date of inspection.

5.7.1.2 In case of for cause/ sudden inspection as per 5.3, review of the inspection report shall be done by Zonal Head / Division Head and forwarded to CLAA/SLA with comments as a part of QMS review immediately (not more than 10 days) from the date of inspection.

5.7.1.3 Review of inspection process (when required) shall be done by the QMS division or the person nominated by QMS division as a part of QMS function (internal audit, QMS review etc.)

5.8 Action plan

5.8.1 The firm shall be asked to submit CAPA plan within 30 days for major and other deficiencies and in case of deviation of submission, same may be furnished by the firm with justification to the concerned zonal office.

5.8.2 CAPA plan received shall be reviewed within 30 days by concerned zonal, sub zonal office and if there is any further clarification required from the firm, it shall be communicated to the firm for reply within 30 days. If the CAPA plan is found satisfactory by the concerned office, same may be forwarded to CDSCO (HQ). If found satisfactory it shall be accepted.

5.8.3 In case of critical deficiencies action plan should be followed as per Rule 85 (1) of the Drugs and Cosmetic Act 1940.

6.0	**Annexure/Format No.**	**Title**
	Annexure–I (QMS-INS-004/F01)	Checklist for GMP Inspection
	Annexure–II (QMS-INS-004/F02)	Format for ‘Inspection Report’

7.0	**References**	
	Doc. No.	**Title**
	1	The Drugs and Cosmetics Rules, 1945.
	2	Annexure-IV of WHO Technical Report Series no. 996
	3	Guidance Document for Functions and Responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO, 2011.
8.0	**Abbreviation**	
	Acronym	**Full Form**
	GMP	Good Manufacturing Practices
	CoPP	Certificate for Pharmaceutical Product
	DI	Drugs Inspector
	CDSCO	Central Drugs Standard Control Organization
	CAPA	Corrective and Preventive Action
	DCG(I)	Drugs Controller General, India
	DDC(I)	Deputy Drugs Controller, India
	ADC(I)	Assistant Drugs Controller, India
	SOP	Standard Operating Procedure
	WHO	World Health Organization
9.0	**Revision History**	
	Revision No.	**Reason(s) for Revision**
	00	New SOP
	01	Editorial correction & change in title

Annexure-I of QMS-INS-004
"Checklist for GMP Inspection''

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

Name & address of Company		**Products manufactured**	**Location of Production**
M/s.			
Contact No.:			
Email:			
Fax No.:			
Inspection type: (Mark all that apply)		**Name of inspectors**	**Affiliation of inspectors**
External			
Routine			
Concise			
Special			
Internal			
Annual			
Semi-annual			
Announced			

Unannounced			
Follow-up			
Re-inspection			
Pre-licensing			
Department(s) being inspected Production Quality Control Quality Assurance Maintenance & Utilities		**Date(s) of Inspection**	**Date of most recent previous routine inspection (internal or external):**
Whether floor plans of facility available (Yes/ No)			
Whether airflow patterns, differential pressures and classification of production areas indicated (Yes/ No)			
Flow patterns for personnel, supplies, raw materials, product, and waste for production areas indicated (Yes/ No)			
<u>Summary of Senior Personnel-A:</u> (Use next page if these departmental divisions are not appropriate, or for other department designations)			

ADMINISTRATION **Position Title**	**Name**	
PRODUCTION DEPARTMENT **Position Title**	**Name**	**Qualifications**
ANIMAL FACILITIES **Position Title**	**Name**	**Qualifications**
ENGINEERING/MAINTENANCE **Position Title**	**Name**	**Qualifications**
QUALITY CONTROL DEPT **Position Title**	**Name**	**Qualifications**

S.No.	Audit Item	Yes	No	NA	Observations (Indicate N.O. if not observed)
1.0 A	**General**				
1.	Is there an organizational chart? What departments are identified? Production department(s) ➢ Filling ➢ Labelling/Packaging ➢ Quality Control ➢ Engineering/Maintenance ➢ Quality Assurance ➢ Receiving/Warehousing ➢ Shipping/Distribution ➢ Purchasing ➢ Animal Procurement/Care				
2.	Are there job descriptions for key personnel?				

	Are they appropriate to the activities of the department?				
3.	➢ Number of engineering staff……. • Number sufficient? • Qualifications adequate? • Experience sufficient? ➢ Number of production staff…… • Number sufficient? • Qualifications adequate? • Experience sufficient? ➢ Number of quality control staff… • Number sufficient? • Qualifications adequate? • Experience sufficient? ➢ Number of quality assurance staff….. • Number sufficient? • Qualifications adequate? • Experience sufficient? ➢ Number of animal care staff….. • Number sufficient? • Qualifications adequate? • Experience sufficient?				
4.	Is there a clear separation of responsibility for production from QC?				
5.	Is there a clear separation of personnel from different areas handling animals, microorganisms, and product? By written procedure?				
6.	Are the names and qualifications of those responsible for approving the lot processing records registered with the NCA?				
1.0 B	**Key Personnel**				
1.	Are there sufficient key personnel to supervise assigned functions?				

	Production Filling Labeling/Packaging Quality Control Engineering Maintenance Quality Assurance Other Departments: (Plz Specify)				
2.	Are they skilled/ trained in fields such as biology, microbiology, chemistry veterinary medicine, chemical or industrial engineering, etc.? Engineering Production Department(s) Filling Quality Control Quality Assurance Animal Care				
1.0 C	**Training**				
1.	Are there on the job training procedures for new employees?				
2.	Are training and education records available? Are they current? Are they filed with the supervisor? Engineering/Maintenance Production Department(s)				

	Filling Quality Control Quality Assurance Animal Care				
3.	Does a GMP training programme exist? For new employees? Annual update for all staff? Are records maintained?				
4.	Is there training in containment procedures? By written procedures? Are records maintained?				
1.0 D	**Personal Hygiene**				
1.	Are appropriate protective apparel required? Is there a gowning SOP for production staff? For other staff entering production areas? (Engineering/Maintenance; Cleaners; QC samplers; QA auditors) For staff in the Quality Control Lab?				
2.	Are staff instructed to report health or medical problems that may have an adverse effect on the product?				
3.	Is there a medical monitoring programme to ensure protection of staff and product? Vaccination where applicable? For all employees?				

	For contractors?				
4.	Do controlled entry requirements exist for: Production areas? Testing areas? Animal areas? Do procedures exist for preventing unauthorized entry into: Production areas? Storage areas? Quality control areas? Animal areas? Are the procedures in writing?				
2.0 A	**General**				
1.	Is the building used for manufacturing of product suitably located and constructed, and of adequate size to facilitate cleaning, maintenance and proper operation?				
2.	Are areas clearly defined and appropriately controlled:				
a.	For quarantine and storage of starting materials?				
b.	For storage of in-process material?				
c.	For manufacturing and processing operations?				
d.	For control and laboratory operations?				
e.	For quarantine and storage of finished products?				

f.	For holding of rejected material?				
g.	For ancillary usage, e.g. rest rooms, maintenance workshops?				
h.	For animal housing?				
3.	Does the building design prevent the entry of insects, vermin and other animals?				
4.	Plumbing				
a.	Do adequate drains exist? Are they designed with an atmospheric break to prevent back-siphonage from sewer?				
b.	Are traps being maintained to ensure adequate performance?				
5.	Does the design of the facility achieve a unidirectional flow of materials, personnel, product and waste so as to avoid cross-over of clean and dirty (infectious) material?				
6.	Is the lighting provided adequate for the conditions necessary for the work being conducted in the area?				
7.	Are facility layout drawings including mechanical, electrical and architectural kept up-to-date following changes? Is revalidation of facilities performed following refurbishment?				
8.	**Campaign production**				
a.	Is the facility designed and constructed to permit production in campaigns?				
b.	Has campaign changeover been validated (effectiveness of changeover)?				

c.	Is there a documented procedure for changeover that described decontamination, removal of equipment, etc.? Is the procedure followed?				
d.	It there a campaigning schedule available?				
9.	**Do washing facilities include:**				
a.	Hot and cold water?				
b.	Soap or detergent?				
c.	Clean toilet facilities that are easily accessible to working area?				
d.	Clean hand drying facilities?				
10.	**Are the premises satisfactory with respect to:**				
a.	Neatness and cleanliness?				
b.	State of repair, e.g. paint work, cracks in floors, ceilings or walls, door seals etc.?				
c.	Exposed piping or electrical wiring?				
d.	Blocking of air ducts?				
e.	Equipment blocking corridors or exits?				
2.0 B	**Support Systems**				
1	**Support systems, including those identified below**				
a	Support systems, including those identified below:				
b	Is there a planned maintenance program on each system?				

	Is it followed?				
c	Are there specs and written procedures for the operation of the systems, sampling plan, sites monitored and alert and action levels defined?				
d	Are definitive action steps taken to resolve conditions that are out of specification?				
2	**HVAC System**				
a	Are pre-filters present in heating, ventilation and air-conditioning (HVAC) systems and replaced on a routine basis?				
b	Are high-efficiency particulate air (HEPA) filters tested for integrity, at least annually?				
c	Are HEPA Filters terminally located?				
d	Are duct work materials impervious to disinfectants that may cause corrosion?				
e	Are duct work and filters located outside the clean rooms?				
f	If fumigation procedures are used, is the facility designed to permit effective fumigation?				
g	Is the number of air changes per hour adequate for defined areas?				
h	Is the airflow adequate? {Minimal pressure differential (1.21 mm H_2O) maintained?}				
i	Is room temperature and humidity effectively controlled?				
3	**Compressed air**				

a	Is the air supply free from oil?				
b	Is the air supply filtered through a sterilizing grade air filter?				
c	Is humidity controlled?				
4	**Clean steam**				
a	Is clean steam used for sterilization product contact surfaces?				
b	Is the distribution system constructed of stainless steel treated to prevent corrosion and sloped for drainage?				
5	**Water for injection (WFI) system**				
a	Is the design of the WFI system				
b	Is there a holding tank for the WFI system, is it fitted with a sterilizing grade vent filter that is integrity tested?				
c	If WFI is stored on a continuous circulation, is it held at $\geq$ 80^{o}C? If not circulated, is it discarded every 24 hours or diverted for suitable use?				
d	Is WFI used as a lubricant on the re-circulating pumps?				
e	Are all the dead-legs within acceptable length?				
2.0 C	**Sterile Processing**				
1	Are the aseptic manufacturing areas and operations consistent with the WHO guidelines for sterile pharmaceutical products provided in TRS 823, Section 17, page 59ff?				
2	**Does the aseptic manufacturing area include**				

a	Smooth, hard non-particulate generating cleanable floors, walls and ceiling? Able to withstand cleaning, disinfecting reagents?				
b	No horizontal pipes or conduits located over exposed components, in-process material, production or product contact surfaces?				
c	Environmental controls, e.g. temperature, humidity and viable and non-viable particles? Are there specifications for these controls?Has the system been validated?				
d	Air supplied through HEPA filters?(terminal filters should be employed for final formulation and filling activities)				
e	Environmental monitoring system, e.g. temperature, humidity and particulates?				
f	Fixtures (electrical outlets and lighting, etc.) flush mounted and sealed to prevent air leakage, water access?				
g	Identification of all pipes or conduits for air, clean steam or liquids?				
h	Properly equipped gowning area/air-lock?				
i	The ability to achieve appropriate air standards (Grade A, B, C, D) during operation?				
j	Appropriate air flow design including segregated air systems for different				

	aspects of the processing, e.g. fermentation and filling?				
k	Appropriate air flow design so that the area is flushed by HEPA filtered air exhausted through return ducts (not blocked by equipment)?				
l	The ability to maintain the appropriate pressure differentials between work areas with different Grades of air?				
3	**Does the aseptic manufacturing area exclude:**				
a	Access doors for servicing equipment and fixtures? (Should only be from outside area)				
b	Drains?				
c	Sinks?				
4	Is the vaccine processing area isolated and independent of any space used for any other purpose?				
5	Are the facilities appropriately designed and validated to comply with relevant containment levels assigned to organisms involved in the manufacturing process?				
6	Is the aseptic manufacturing area cleaned according to a validated procedure? Is it followed? Is the cleaning data recorded?				
3.0 A	**Adequacy**				
1	Is the equipment appropriately designed, constructed and maintained?				

2	Are steps taken to prevent any substances required for operation, such as lubricants or coolants, from coming in contact with in-process or finished products?				
3	Are equipment surfaces that contact components or products of a non-interactive nature?				
4	Are process pipe lines or service lines whose contents come in contact with products or product contact surfaces sloped to allow proper drainage?				
3.0 B	**<u>Cleaning and Maintenance</u>**				
1	Is the equipment suitably located to facilitate its use, cleaning and maintenance?				
2	Are equipment and utensils cleaned, maintained and sanitized as appropriate to prevent malfunction or cross-contamination?				
3	Are piping systems, valves and vent filters properly designed to facilitate cleaning and sterilization? NOTE: Maintaining closed systems through the use of “clean in place” and “sterilize in place” is preferable.				
4	Are the valves on primary containment vessels (e.g. fermenters) steam sterilized?				
5	Are non-fiber releasing filters used for filtration?				
6	Are filters used for sterile filtration integrity tested before and after use?				

7	Are calibrations and validation being performed adequately?				
8	Are autoclaves and sterilizing ovens fitted with effective, proper air filters and are these integrity tested? Are HEPA filters used for the ovens?				
9	Are supplies and equipment which are exposed to pathogens during processing kept separate from unused items to prevent cross-contamination?				
3.0 C	**SOPs and Records**				
1	Are there written procedures (SOPs) for cleaning and maintenance of equipment and utensils and are they followed?				
2	**Do these SOPs include:**				
a	Assignment of responsibility for cleaning?				
b	Defined schedules for cleaning and materials used?				
c	Descriptions of methods, equipment and materials used?				
d	Instruction for protection of clean equipment from contamination?				
e	Inspection of equipment for cleanliness immediately before use?				
f	Assignment of identification number?				
g	Documentation in record books?				
3	Are cleaning and sanitizing agents validated and approved for use by QC?				
4	Is clean equipment identified as such?				

5	Are calibrations and qualifications properly recorded?				
6	Are all certifications within date?				
7	Are there preventive maintenance programs and consistent records of work performed?				
4.0 A	**Adequacy of starting materials**				
1	Are there approved specifications for all starting material or raw material used in the manufacturing process and are they released by Quality Control?				
2	**To ensure the quality of raw materials:**				
a	Is there a quarantine and release system?				
b	Are the conditions of storage evaluated?				
c	Do the contracts with vendors ensure quality and stability, including reporting of changes in manufacture?				
3	**For raw material of animal origin:**				
a	Are the details of source, origin, and method of manufacture documented?				
b	Are they stored in controlled environments?				
c	Are expiry dates given and is there a retest policy?				
d	Are rejected materials properly segregated form acceptable material?				
e	Have viral removal and inactivation procedures been validated?				

4	Are biological materials that may contain infectious organisms screened or tested prior to entry into laboratories or manufacturing sites?				
5	**Do Master/Working Cell Banks and Seed Stocks have detailed records of:**				
a	History of cells including the number of generation doublings or passages of virus? Is there a maximum limit?				
b	Characterization according to the WHO TRS relevant to the product?				
c	Demonstration of purity?				
d	Manufacturing procedures?				
e	Appropriate storage and security with continuous monitoring of temperature, alarms and backup power supply?				
f	Inventory log?				
g	Adequately segregated storage to avoid mix-up or cross-contamination with other material?				
h	Storage split into 2 separate locations?				
i	Routine monitoring of stability (viability/purity)?				
j	Demonstration of identity?				
4.0 B	**Processes**				
1	**Master Formula (MF):**				
A	Does the MF adequately describe the complete production process?				
B	Is the MF up-to-date and approved by QC/QA?				

C	Is the Batch Production Record form and adequate representation of the MF?				
2	**Process validation:**				
A	Has each phase of the production process been validation protocol?				
B	Is re-validation done when required, and performed appropriately?				
3	Aseptic fill:				
A	Are suitable precautions taken to maintain aseptic conditions during the filling process?				
B	Is each filling process validated by a simulated media fill?				
C	Does the simulation use suitable medium, fill sufficient numbers of vials, and cover the full complexity of operations?				
4	Are time and temperature limits established for the completion of production phases?				
5	Are viral removal and inactivation processes validated, if applicable?				
6	Are in-process intermediate materials tested for identity, quality, strength and purity? Alternatively, are there valid certificates of quality issued from the suppliers?				
7	Is there bio-burden monitoring of starting, raw, and in-process materials before sterilization?				
8	Are alert and action limits established for environmental monitoring, and are				

	effective measures taken when limits are exceeded?				
9	Are criteria for microbial limits, physico-chemical characteristics and endotoxins established for water systems and are effective measures taken when limits are exceeded?				
4.0 C	**<u>Sterilization/Depyrogenation</u>**				
1	Are all sterilization/depyrogenation processes and cycles validated and current?				
2	Is there a sufficient supply of pure steam to assure the simultaneous and proper operation of the validated number of autoclaves?				
3	Are systems for filter sterilization validated and are conditions still the same as when validation was performed?				
4	Is an expiry date given to sterilized items and is there a maximum time period established between washing and sterilization? Are storage conditions for sterilized items specified and appropriate?				
5	Are the filters tested immediately before and after use for integrity by an appropriate method such as the bubble point test?				
6	Are in-line sterilizing filters used for routine addition of gases, media, solutions, etc. to fermenters?				
4.0 D	**Identification**				

1	If a component/material is transferred to a new container, is the new container identified with:				
A	Component/material name or item comes?				
B	Receiving or control number?				
C	Amount in container?				
2	Are dispensing/addition operations adequately supervised in that each component/material dispensed is examined by a second person to ensure:				
A	The component/material was released by QC?				
B	The amount agrees with the batch record?				
C	The container is properly identified?				
D	The components/material are added in the batch by one person and verified by a second person?				
3	Are actual yield and percentages of theoretical yield determined at the conclusion of each phase of operation with documentation of any losses?				
4	Are the yield calculations verified by a second person?				
5	Are all containers, lines and major equipment identified at all times during production for content and phase of operations/				
6	Is major equipment identified with an identification number, which is recorded in the batch processing records (BPR) during production?				

7	Are all deviations from SOPs documented and subject to review by QA/QC for approval or corrective action?				
8	Are there written procedures established to specify action taken with regard to the identification and disposition of material in the environmentally controlled room and in the autoclave if the automatic system fails or malfunctions?				
9	Are records made of the mode, date, duration, temperature and other conditions relating to each sterilization cycle of equipment ad supplies used in production. Are they maintained in a manner that permits identification of the product with the particular manufacturing and sterilization process?				
10	Are sterilized items identified by a sterilization reference number?				
11	Are inspections of areas undertaken immediately prior to use to ensure that all materials from previous operation have been removed and are these procedures adequate?				
12	Are all autoclave and dry heat sterilized items marked with heat sensitive indicators/				
5.0 A	**Adequacy**				
1	Are specifications, standards, sampling plans, test procedures or other laboratory control mechanisms including any revision, reviewed and approved by Quality Assurance?				

2	Are any deviations from these specs, standards, etc. recorded and justified?				
3	Do laboratory controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, test procedures and reference substances, designed to assure that tested materials conform to appropriate standards of identity, strength, quality and purity?				
4	**Do these laboratory controls include:**				
a	Determination of compliance with written specifications for acceptance of each lot within each shipment of materials of holding of products?				
b	Description of sampling and testing procedure for in-process materials?				
c	Retest policy, identifying the rationale and criteria for retests, number of samples, and the documentation required?				
d	A comprehensive calibration/certification intervals, acceptance criteria and provisions for remedial action?				
5	Are reagents, culture media, etc. properly labeled, preparation recorded in lab books and expiry dates given?				
6	Is appropriate testing done on each batch of product required to be free of objectionable microorganisms?				
7	Are there written sampling and testing plans for raw materials, intermediates, and final product that include method of sampling and the number of units per				

	batch to be testes and are they followed?				
5.0	**Reference Reagents**				
1	Are all reference reagents kept secure, properly stored, identified and their integrity maintained?				
2	Are the tests results of all references and standards analyzed at appropriate intervals for statistical variation from the expected value?				
5.0 C	**Validation, Calibration and Stability Programme**				
1	Are the accuracy, sensitivity, specificity and reproducibility of test methods established, documented, validated and subject to regular review and updating?				
2	Is there a written testing programme designed to assess the stability characteristics of each product to determine the appropriate storage conditions and expiration dates?				
3	Is there a retention sampling system?				
4	Does the retention sample quantity consist of at least twice the quantity needed to perform all required tests (except for sterility and pyrogens)?				
5	Are retention samples of each lot of final product stored under conditions consistent with product labeling?				
6	Are these samples at least visually examined annually for evidence of deterioration? Is this recorded?				

6.0 A	**General**				
1	Are there records for :				
a	All materials used?				
b	All standard operating procedures?				
c	Each lot and/or batch processing and distribution?				
d	All complaints and their investigation?				
e	All equipment, including cleaning, maintenance and validation?				
f	Cleaning, maintenance and environmental control of the premises?				
2	Are all records"				
a	Dated?				
b	Signed by the person performing the task (and, for all critical steps, by the person checking it)?				
c	Kept at the work station during the entire operation?				
d	Retained and available for inspection at least 2 years after the expiry date of the lot/batch?				
6.0 B	**Lot/Batch Processing Records (BPR)**				
1	**Does the BPR indicate**				
a	The name, strength and dosage of the product?				
b	The date of manufacture?				
c	The lot and batch identification no.?				
d	Assurance that the copy of the master processing record is accurate?				

e	Changes in the master processing record approved by QA prior to starting the operation?				
f	The complete formulation of the lot/batch?				
g	The batch number of each component or other in-process material and, when applicable, the sterilization number				
h	The SOPs used?				
i	The yield obtained at different stages of manufacture, both actual measured values and as a percentage of the expectation?				
j	A record of each step followed?				
k	A record of all major equipment used?				
1	A record of all in-process control samples taken and of the results obtained?				
m	A sample of the label on the final container?				
n	Identification of packaging materials, containers, closures used?				
o	Inspection of the processing area before and after use?				
p	Precautions taken and special or unusual observations made throughout the manufacture of the lot?				
q	Investigation of all unusual observations for the batch and, where relevant, from samples of other batches of the product?				

r	For rejected lots/batches, a record of disposal or reprocessing?				
2	Are all batch processing records reviewed and signed appropriately as indicated by:				
a	A BPR review document or checklist describing the review process?				
b	A dated signature of the person responsible for approving the manufacturing operations?				
c	An analytical report, dated and signed by the responsible person, showing whether the lot/batch complies with the specifications?				
d	Decision on release or rejection of the lot/batch by the quality control department?				
3	Are the BPRs maintained on file for 2 years past the expiry date?				
6.0 C	**Documentation of Equipment Used**				
1	Are records on the use, cleaning, sterilization and maintenance of equipment kept in individual logs for each piece of equipment?				
2	Are these records dated and signed in chronological order?				
3	Do the records include information of lot/batch including identification numbers and dates?				
7.0 A	**Procurement**				
1	Are there SOPs for animal procurement?				

2	Is a specific individual in department, authorized to order animals?				
3	Do contracts with suppliers assure the quality and consistency of the animals provided?				
4	If the animals come from the manufacturer's own breeding colony, are there SOPs for the maintenance and testing of the colony?				
7.0 B	**Receipt and Evaluation**				
1	Are there SOPs covering the receipt of animals, including identification of the responsible person and required documentation?				
2	Are the newly received animals placed in quarantine**?**				
3	Are there SOPs for evaluating the health status of animals prior to use?				
7.0 C	**Care**				
1	Are there SOPs covering housing, feeding, handling and care of the animals?				
2	Are there SOPs for identification and isolation of any sick animal?				
3	Are any sicknesses of animals, treatment and preventive measures recorded?				
7.0 D	**Allocation of Animals to Use**				
1	Are the specifications for animals used in production or quality control tests written in the respective SOPs?				

2	Is there a clear system of identification of animals allocated for each test or use?				
7.0 E	**Facilities**				
1	Are there enough animal rooms of appropriate design to allow separate housing of:				
a	The breeding colony?				
b	Different animal species?				
c	Animals in quarantine?				
d	Sick animals?				
e	Animals on-test including tests with hazardous infectious and non-infectious materials?				
2	Are there facilities and SOPs for collection and disposal of animal waste and of dead animals, to minimize disease hazards and environmental contamination?				
3	Are there facilities and SOPs for cleaning, sanitizing, sterilizing and maintaining supplies and equipment including animal cages and racks?				
4	Are there specially designated areas for animal inoculation and sample taking, aseptic surgery, autopsy, radiography, histology and other laboratory tests?				
5	Are there separate storage areas for equipment, animal feed and bedding which are protected from infection/contamination, and with refrigeration where needed?				

6	Is equipment suitably located for operation, inspection, cleaning and maintenance?				
7	Is there separate space for locker, shower, toilet and washing facilities for staff working in the animal facilities?				
8	Is there an appropriate functioning environmental control system?				
9	Is there an implemented pest control system that is documented, validated and approved by QA showing absence of interference with the tests and maintaining animal welfare?				
10	Is the HVAC system appropriate with temperature and humidity control, and adequate air changes/hour?				
11	Is there a time-controlled lighting system?				
12	Is there an appropriate noise control system?				
13	Is emergency power available in the event of power failure?				
8.0 A	**General**				
1	Are there records on suppliers, contractors and consultants?				
2	Are there records of their qualification?				
3	Are there records on up-dating documents?				
8.0 B	**SOPs**				
1	Are there SOPs written and approved for all manufacturing and testing activities?				

2	Are the SOPs reviewed on a regular and defined schedule? At least annually?				
3	Are revisions of SOPs approved by an authorized person?				
4	Is there a system for distribution of SOPs and for revocation of outdates SOPs?				
5	Is it clear that SOPs are used and followed in both production and QC?				
8.0 C	**Equipment**				
1	Is there a system for validation and regular re-validation of all equipment, including revalidation after repairs?				
2	Is there a system for calibration of all instruments?				
3	Is there a system to report, investigate and record all deviations from specifications or malfunctioning of equipment?				
8.0 D	**Environmental Monitoring**				
1	Is there monitoring of air for microbes?				
2	Is there monitoring of air for particulates?				
3	Is there monitoring of surfaces for microbes?				
4	Is there monitoring of compressed gas for microbes?				
5	Is there monitoring of compressed gas for particulates?				
6	Is there monitoring of water for microbes and endo- toxins?				

7	Is there a defined schedule for environmental monitoring? Is it appropriate to each stage of the production process? Do the records indicate the schedule is followed?				
8.0 E	**Intermediates and Final Products**				
1	Is the stability of the final products and, if applicable, of the intermediates monitored?				
2	Is there a quarantine and release system for intermediates and final products, including clear identification of the status (quarantine, released, rejected, etc.)?				
3	Is there a system for reprocessing of unsatisfactory and returned products, subject to prior approval by quality control?				
4	Is there a system for rapid evaluation and investigation of complaints received from the field?				
5	Is there a system for rapid and effective recall of products? Is there provision for the notification of the national control authority (NDCA)?				
8.0 F	**Quality Control**				
1	Is the QC department independent from production?				
2	Are all QC tests validated?				
3	Does the QC Laboratory have SOPs describing sampling, testing,				

	documentation and precise criteria for release?				
4	Is the QC monitoring consistency of production using trend analysis?				
5	Is the QC Laboratory involved in all decisions that may concern the quality of the product?				
8.0 G	**Inspections**				
1	Is there a system for regular self-inspection of each manufacturing and test area?				
2	Are the inspections followed up to ensure that appropriate action was taken to correct deficiencies?				
3	Following the national control authority's (NCA) inspection of the manufacturer, is there a system to follow up any recommendations received from NCA?				
4	Is there a system for inspection of contractors in respect of any manufacturing or testing activities contracted out?				
9.0 A	**Packaging Materials**				
1	Do primary and printed packaging materials have specification describing qualitative and quantitative requirements?				
2	Are standard operating procedures for the receipt, sampling and testing of packaging materials available?				
3	Are incoming materials stored in controlled areas until released from quarantine?				

4	Are released material secured in controlled areas and is inventory maintained?				
5	Are control or reference numbers assigned to each lot for traceability and control purposes?				
6	Are all label texts approved by the national control authority prior to use and is there a master file of approved labeling held by the responsible person?				
9.0 B	**Labelling and Packaging Operations**				
1	Are SOPs available for the labeling and packaging operations for equipment and material delivery to the floor and are these easily accessible to the operators?				
2	Are labeling and packaging operations properly physically segregated to prevent mix-up of product or packaging materials?				
3	Is reconciliation performed to ascertain the number of labels issued, used and, if applicable, returned to stock? Is the data recorded on the packaging batch records?				
4	Is there a specification for permissible reconciliation limits and action to be taken in the event of exceeding these?				
5	Is all labeled product accounted for including those destroyed during and at the completion of the operation?				
6	Is there an inspection of the line made before and after each labeling and				

	packaging operation? Is it documented and signed by the responsible person?				
9.0 B	**Labelling and Packaging Operations, continued**				
7	Is the name, strength and batch number prominently displayed at each operation?				
8	Is there adequate on-line control of the labeled or packaged product including the quality of printed text?				
9	Are the pieces of equipment used during labeling operations calibrated and certified as operating correctly before and during labeling operations?				
10	Are there documented time and temperature limitations for the labeling and packaging operations?				
11	Are incidents and deviations recorded and appropriate QA actions taken?				
12	Is there a quality control mechanism for assigning lot numbers and expiry dating prior to labeling operations?				
13	Are samples of printed labels and packaging material used for the batch kept with the records				
14	Is there a segregated and secure quarantine storage area for finished goods awaiting QC release?				
9.0 C	**Storage and Distribution**				
1	Do records allow rapid identification of all customers who have received any amount of an identified lot/batch?				

2	Are records kept on the time, temperature and other conditions of storage before distribution?				
3	Do records show the date, quantity, mode of package and dispatch of each lot/batch to the customer?				
4	Are there standard operating procedures for the storage of released finished product to the dispatch area?				
5	Are standard procedures available for warehousing?				
6	Are standard procedures available that describe the shipping, final transit conditions and instruction for storage through the distribution chain, especially the cold chain?				
7	Are the shipping methods, especially the cold chain, validated and routinely monitored?				
8	Are records detailed and retrievable so that a rapid recall of any particular lot is achievable? Is the recall process delegated to the responsible person?				
9	Are records maintained for 2 years after the expiry date?				
10.0 A	**Facility Design**				
1	Is the air handling system capable of maintaining the designed containment level (e.g. are supply and exhaust systems adequate for the level of containment required)?				
2	Where applicable, are HEPA filters installed in the exhaust system?				
3	Can the HEPA filters be tested in situ?				

4	Is the air pressure in the manufacturing area appropriate to the surrounding areas?				
5	Are the rooms designed to permit satisfactory cleaning and decontamination?				
6	If the procedure requires the availability of a wash sink, is it close to the exit of room?				
7	Are all conduits, piping and duct work properly sealed in the area to maintain containment?				
8	Are all liquid and gas services protected by backflow prevention devices to prevent contamination?				
9	Are all traps protecting drains maintained properly?				
10.0 B	**Equipment**				
1	Is the primary containment equipment designed to limit or prevent contact between operators and microorganisms?				
2	Is the equipment designed, constructed and installed to permit ease of decontamination and cleaning?				
3	Are the appropriate classes of Biosafety Cabinets used for the relevant microorganisms, and are they certified annually?				
4	Is the process equipment designed to minimize aerosol generation (including sampling devices)?				
5	Is the process equipment designed to contain organisms within a closed				

	system (e.g. fermenters or other culture vessels)? Are seals and mechanical devices associated with the equipment designed to prevent leakage and do exhaust gases pass through HEPA filtration and/o incineration?				
6	Is the process equipment capable of being decontaminated using a validated inactivation procedure?				
10.0 C	**Operational Practices and Procedures**				
1	Are there standard operating procedures for decontamination of process equipment and facilities? Have these procedures been validated and is the performance monitored?				
2	Is the equipment tested regularly for integrity of containment capability?				
3	Are standard operating procedures available and displayed outlining emergency procedures in the event of a spill or accidental release of contaminant?				
4	Is there a list displayed of responsible individuals to be contacted in the event of an emergency?				
5	Do personnel have specific training in the procedures for handling the pathogenic agents used and the method of using containment equipment?				
6	Are there SOPs for dress codes specified for containment levels applicable and is access controlled and secured? Is there a health and medical surveillance program?				

7	Are showers available where applicable?				
8	Is there a health and medical surveillance program?				
9	Are biohazard signs used and posted where applicable?				
10	Are SOPs available for the transport of microorganisms in closed systems or container to and from the area?				
11.0 A	**General**				
1	Pest control programme :				
a	Is there a pest control programme? Is it in writing and is it followed?				
b	Are pesticides used?				
c	Is their use controlled so as to avoid product contamination?				
d	Are there records of pesticide usage?				
e	Is pesticide storage controlled/				
f	Has QA approved the pesticides and the programme?				
2	Are sewage, refuse, trash controlled and/or disposed of in a safe, timely and sanitary manner?				
3	Are adequately constructed waste containers located in appropriate areas?				
4	Are bagged/boxed items stored off the floor and spaced to allow for cleaning and proper identification?				
5	Do written procedures for cleaning and sanitation include :				

a	Assignment of responsibility for sanitation?				
b	Details of cleaning schedules, methods equipment and material?				
c	Routine evaluation of the effectiveness of disinfectants and cleaning agents, and chronological record of the agents used?				
d	Information to be recorded?				
e	Validation for effectiveness of cleaning/sanitation, and validation of removal of residual cleaning/sanitizing agents?				
f	Are the procedures followed and are records maintained?				
6	Are equipment and chemicals used in cleaning appropriately maintained and stored?				

Remarks: Detail inspection report with signature of inspection team members attached with this checklist.

Annexure-II of QMS-INS-004

Format for 'Inspection Report'

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

Part-1	**General Information**
Manufacturer details:	
Company information:	*Name of manufacturer*
Corporate address of manufacturer	*Corporate Address of the firm* *Phone No.: +91-* *Fax No.: +91-* *Contact telephone no.: +91-* *E mail:*
Contact person, telephone number and email address:	*9) Name:* *Designation:* *Contact No.: +91-* *Email I.D:* *10) Name:* *Designation:* *Contact No.: +91-* *Email I.D:*
Constitution of firm:	*Public/Private Limited/ Partnership/others (Specify)*
Name of Directors:	*Name of directors*
Inspected site:	*Address of the manufacturing site*

	Fax No.: +91- *Contact telephone no.: +91-* *E mail:*
Manufacturing licence number and other regulatory accreditations:	5.
Summary of activities performed at the site:	*For example, manufacture of active pharmaceutical ingredient(s) (APIs), manufacture of finished pharmaceutical products (FPPs), intermediates or bulk packaging, laboratory testing, batch release, distribution and importer activities.*
Product details	*Type of products manufactured at premise*
Inspection details	
Date(s) of inspection(s)	
Type and purpose of inspection:	*For example, initial, routine, follow-up, special*
Inspection Team:	*Name(s) and agency affiliations of lead inspector, inspector(s), accompanying experts and observers*
Competent Regulatory Authority:	*For foreign inspections, state whether the national regulatory authority (NRA) of the country where the inspection took place was informed and whether it took part in the inspection*
GMP guidelines used for assessing compliance:	*List the relevant guidelines stating the title of the guidelines, the title of the publication and web address where the guidelines can be accessed, for example:* 1. Drugs & Cosmetics Act & Rules made there under. 2. WHO Good Manufacturing Practices for Pharmaceutical Products: Main Principles, Annex 2 WHO Technical Report Series, No. 986.
Introduction:	
Brief summary of the manufacturing activities:	*Description of main activities (including, e.g. FPP(s) or API(s) manufactured and their reference/registration/active pharmaceutical ingredient master file (APIMF)/drug master file (DMF)/certificate of suitability to the monographs of the European Pharmacopoeia (CEP)*

<table>
<tr><td></td><td colspan="5">numbers, as appropriate); other manufacturing activities carried out on the site (e.g. manufacture of cosmetics, research and development); use of outside scientific, analytical or other technical assistance in manufacture and quality control Brief description of the quality management system of the firm responsible for manufacture. Reference can be made to a site master file if one is available</td></tr>
<tr><td rowspan="11">History:</td><td>S. No.</td><td>Date of inspection</td><td>Inspecting authority</td><td>Purpose</td><td>Compliance status</td></tr>
<tr><td>1.</td><td></td><td></td><td></td><td></td></tr>
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<tr><td>10.</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Major change since previous inspection</td><td colspan="5"></td></tr>
<tr><td>Planned future changes, if any</td><td colspan="5"></td></tr>
<tr><td>GMP-related recalls from the market of any product in the past two years</td><td colspan="5"></td></tr>
<tr><td>Scope and limitations:</td><td colspan="5">For example, blocks inspected, areas of interest, focus of inspection Out-of-scope: areas, activities or product lines not inspected Restrictions: constraints noted in inspecting specific areas</td></tr>
</table>

Areas inspected:	*For example, dosage form(s) included in the inspection*			
Key persons met:	**S.No.**	**Name**	**Designation**	**Department**
	1.			
	2.			
	3.			
	4.			
	5.			
	6.			
	7.			
	8.			
	9.			
	10.			

Part-2	**Brief summary of the findings and recommendations (where applicable)**
1.	**Location and surroundings:**
	Describe about Location and surroundings of the firm.
2.	**Pharmaceutical quality system:**
	Describe the pharmaceutical quality system (PQS) in place and how well the elements are institutionalized and implemented including the quality risk management (QRM) and product quality review (PQR).
3.	**Quality Risk Management:**
	Briefly describe how the Quality Risk Management is implemented.
4.	**Product Quality Review:**
	Briefly describe how the Product quality review is performed and evaluated.
5.	**Good Manufacturing Practices for Pharmaceutical Products:**
	Briefly describe how the elements of GMP are implemented
6.	**Sanitation and Hygiene:**
	Describe procedures and records relating to sanitation and hygiene for personnel, premises, equipment, production materials, cleaning materials and others that could become a source of contamination

7.	**Qualification and Validation:**
	Describe policies, procedures, records and any other evidence for qualification and validation and how the validation status is monitored and maintained
8.	**Complaints:**
	Describe procedures, responsibilities and records for handling complaints, including extension of investigation to other batches, possibility of counterfeits, trending and consideration for recall and notification of competent authorities
9.	**Product recalls:**
	Describe the existence of a recall procedure and evidence of its effectiveness; provisions for notification of customers and competent authorities and segregation of recalled products
10.	**Contract production, analysis and other activities:**
	Describe how contractors are evaluated, how compliance with marketing authorization is ensured, existence of comprehensive contracts and clarity of responsibilities and limits
11.	**Self-inspection, quality audits and suppliers' audits and approval:**
	a) Self-inspection: describe the procedures and items for self-inspection and quality audits; constitution of self-inspection team(s); frequency of self-inspection; existence of self-inspection schedules and report; system for monitoring follow-up actions. *b) Suppliers' audits and approval: describe procedures for evaluation and approval of suppliers including applications of risk management principles, especially determining the need and frequency for on-site audits.*
12.	**Personnel:**
	Describe availability of adequate numbers of sufficiently qualified and experienced personnel, clarity of their responsibilities, limits and reporting hierarchy. Qualifications, experience and responsibilities of key personnel (head of production, head(s) of the quality unit(s), authorized person) and procedures for delegation of their responsibilities
13.	**Training:**
	Describe comprehensiveness of procedures and records for induction, specialized and continuing training and evaluation of its effectiveness; coverage of GMP and concepts

	of quality assurance during training; training of visitors and evaluation consultants and contract staff
14.	**Personal hygiene:**
	Describe system in place for initial and regular health examination of staff appropriate to their responsibilities. Measures and facilities to impart, maintain and monitor knowledge of a high level of personal hygiene. Measures to ensure personnel do not become a source of contamination to the product, including hand-washing and gowning. Appropriate restriction of smoking, eating, drinking, chewing and related materials from production, laboratory and storage areas
15.	**Premises:**
	Description of the appropriateness of the location, design, construction and maintenance of premises to minimize errors, avoid cross-contamination, permit effective cleaning and maintenance; measures for dust control; specific measures for ancillary areas, storage areas, weighing areas, production areas and quality control areas; measures for appropriate segregation and restricted access; provisions for appropriate lighting, effective ventilation and air-control to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity
16.	**Water System:**
	Describe about various generation of water and its monitoring.
17.	**Air Handling Unit:**
	Describe about various HVAC and monitoring.
18.	**Equipment:**
	Describe the adequacy of the numbers, type, location, design and construction, and maintenance of equipment to minimize errors, avoid cross-contamination, permit effective cleaning and maintenance; use, cleaning and maintenance procedures, records and logs; calibration of balances and other measuring instruments; status labelling
19.	**Materials:**
	Describe measures in place to select, store, approve and use materials (including water) of appropriate quality and how these measures cover starting materials, packaging materials, intermediate and bulk products, finished products, reagents, culture media and reference standards. Describe also the measures for the handling

	and control of rejected, recovered, reprocessed and reworked materials; recalled products; returned goods; and waste materials
20.	**Documentation:**
	Describe the comprehensiveness and adequacy of the documentation system in place (labels; specifications and testing procedures, starting, packaging materials, intermediate, bulk products and finished products; master formulas; packaging instructions; batch processing and packaging records; standard operating procedures (SOPs) and records) and how principles of good documentation and data management (attributable, legible, contemporaneous, original, accurate (ALCOA)) are institutionalized, implemented and maintained
21.	**Good practices in production:**
	Describe procedures, facilities and controls in place for production (processing and packaging); prevention of risk of mix-up, cross-contamination and bacterial contamination during production
22.	**Good practices in quality control:**
	Describe the extent of the organizational and functional independence of the quality control function and the adequacy of its resourcing. Describe the procedures, facilities, organization and documentation in place which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be compliant with the requirements. Describe the procedures for the control of starting materials and intermediate, bulk and finished products; test requirements; procedures and responsibilities for batch record review; procedures, records and facilities for initial and ongoing stability studies; policy, procedures, facilities and records for retention samples.
23.	**Stability Studies:**
	Describe about the arrangement made for stability testing of applied product.
24.	**Media Simulation Studies: (For Sterile API/ Drug Product manufacturing facilities)**
	Describe about the media simulation study performed by the firm along with frequency, outcomes, deviation, if any for sterile product manufacturing facilities.
25.	**Seed Lots and Cell Banks: (For Biological Product Manufacturing facility)**

	Describe about the seed lot and Cell Bank system, subculturing process, Master and Working Seed/ Cell Bank systems, storage, etc.
26.	**Use of animals: (For Biological Product Manufacturing facility)**
	Describe about the location & premise and facility provided for animals, range of animals used for production and testing, ventilation system, monitoring, measure to prevent mixup, decontamination procedures, etc.
27.	*Other heading can be included by inspection team as per the facility/ product inspected.*

Samples taken (if any):	
Assessment of the site master file (if applicable):	
Annexes attached:	1. 2. 3.

Part-3	**List of deficiencies**		
	S.No.	**Deficiencies**	**References**
Critical:	1.1.		
	1.2.		
Major:	2.1.		
	2.2.		
Other:	3.1.		
	3.2.		
	3.3.		

Part-4	**Outcome**
Initial Conclusion:	*Statement regarding the GMP status, including information on any restrictions in scope.* *The following guidance may be used to determine the outcome of the inspection based on the nature and number of deficiencies observed:* • *other deficiencies only: operating at an acceptable level of compliance with GMP guidelines;* • *other and a few (e.g. < 6) major deficiencies: decision on level of compliance to be made after receipt and evaluation of CAPAs;*

	• *any critical or several (e.g. ≥ 6) major deficiencies: operating at an unacceptable level of compliance with GMP guidelines.*
Part-5	**List of GMP guidelines referenced in the inspection**
References:	1. Schedule-M of Drugs & Cosmetics Act & Rules made there under 2. WHO Technical Reports Series (give specific WHO TRS No.)

Part-6	**Assessment of company response, final conclusion, risk rating and next due date**
Brief narrative on the adequacy of the company's response to issues to be addressed:	
Final conclusion:	*Final statement of GMP compliance, including information on any restrictions in scope*
Risk rating following the inspection	For example, low (L), medium (M), high (H), critical (C)
Date next inspection due (for planning purposes):	*The inspectorate may decide to include this information for internal use only*
Name(s) & Signature(s) of inspection team with Date:	

		TITLE		Division Name	QMS Monitoring Division
		Procedure for oversight of Central Inspection Plan, procedures and practices		Document No.	QMS-INS-005
				Revision No.	01
				Effective Date	
				Page No.	892 of 1103
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

Control Status

1.0 Purpose

To lay down a procedure for oversight of inspection Plan, procedures and practices and to evaluate the plan against actual performance.

2.0 Scope

This document is applicable to assess the effectiveness of Central Inspection Plan, procedures and practices against actual performance and its implementation by the concerned zonal office and also to evaluate the plan against actual performance.

3.0 Responsibility

3.1 QMS Monitoring Division shall ensure the effective implementation of the recommendation through Head of Vaccine Division.

3.2 Head of CDSCO Zone/ Sub-zone/ Head of Vaccine Division shall be responsible for the effective implementation of the recommendations.

3.3 Head of Vaccine Division shall be responsible for overall compliance of this SOP.

4.0 Accountability

4.1 Head of CDSCO Zonal/ Sub-zonal offices, Head of Vaccine Division and QMS Monitoring Division.

4.2 DCG(I) shall supervise and fix the accountability of an individual for overall compliance of this SOP.

5.0 Procedure

5.1 Head of CDSCO Zonal/ Sub-zonal shall plan inspection of vaccine manufacturing units as per Central Inspection Plan published in CDSCO website or circulated by the QMS Monitoring Division.

5.2 The inspection team shall prepare inspection report as per the current version of SOP No. QMS-INS-004 and inspection report shall be initially reviewed by Head of CDSCO Zonal/ Sub-zonal office.

5.3 Head of CDSCO Zonal/ Sub-zonal office shall forwarded inspection report along with his clear recommendation to Vaccine Division, CDSCO (HQ) for further review.

5.4 Head of Vaccine Division shall review the inspection report with respect to purpose of inspection, recommendations of inspection team, recommendations of Head of CDSCO

Zonal/ Sub-zonal office, etc. and shall forward the copy of inspection report to QMS Monitoring Division along with his clear recommendations for final quality review.

5.5 QMS Monitoring Division shall perform the quality review the inspection report with respect to following:

5.5.1 Whether inspection was carried out as per the Central Inspection Plan published on CDSCO Website, if not, any deviation is intimated to QMS Monitoring Division by concerned Zonal/ Sub-zonal Head as per current version of SOP No. QMS-INS-002.

5.5.2 Whether preparation and planning of GMP inspection is carried out as per current version of SOP No. QMS-INS-003 like composition of team, duration of inspection, preparation of inspection plan using risk based approach, etc.

5.5.3 Whether inspection was carried out in presence of qualified Lead Inspector.

5.5.4 Whether conduct of inspection and writing of inspection report is carried out as per current version of SOP No. QMS-INS-004 like inspection report format, categorization of observations, reference for observations, etc.

5.5.5 Whether clear recommendations of Head of Zonal/ Sub-zonal office on inspection report, communication of observations to the firm by Zonal/ Sub-zonal offices or State Licensing Authority is enclosed with inspection report.

5.5.6 Whether clear recommendations of Head of Vaccine Division on inspection report is enclosed with inspection report when submitted to QMS Monitoring Division by Vaccine Division.

5.6 Each Zonal/ Sub-zonal office shall submit monthly inspection status of Human Vaccine Manufacturing Units as per the current version of Annexure-III of SOP No. QMS-GNL-024 to QMS Monitoring Division on monthly basis in first week of every month.

5.5 QMS Monitoring Division may provide his recommendations with respect to assessment of inspection report, performance of Drugs inspector, etc. to concerned Zonal/ Sub-zonal office after approval by the DCG(I), if applicable.

5.6 QMS Monitoring Division may also participate in the inspection of vaccine manufacturing facilities to review the inspection procedures on case to case basis.

5.7 Details of manufacturing units inspected in a calendar year shall be prepared as per Annexure-I of this SOP and maintained in QMS Monitoring Division and may be uploaded in the CDSCO website after completion of the particular year, if required.

6.0 Annexure / Format

Annexure/Format No.	Title
Annexure-I (QMS-INS-005/F01-00)	List of Manufacturing Units Inspected

7.0 References

Doc. No.	Title
1	The Drugs and Cosmetics Act and Rules, 1945.
2	Guidance Document for Functions and Responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO.

8.0 Abbreviation

Acronym	Full Form
CDSCO	Central Drugs Standard Control Organization
DCG(I)	Drugs Controller General, India
SOP	Standard Operating Procedure

9.0 Revision History

Revision No.	Reason(s) for Revision
00	New SOP
01	Editorial correction

Annexure-I of QMS-INS-005

'List of Manufacturing Units Inspected'

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

S. No.	Name of Manufacturing unit	Month											
		JAN	**FEB**	**MAR**	**APR**	**MAY**	**JUN**	**JUL**	**AUG**	**SEP**	**OCT**	**NOV**	**DEC**
1.	**(Zone Name)**												
	Name of Manufacturing Unit and address			√				√					
	(Zone Name)												
2.	Name of Manufacturing Unit and address			√						√			

	Indicates no inspection carried out during the month
√	Indicates inspection carried out during the month

Prepared By:		**Approved By:**

		TITLE		Division Name	QMS Monitoring Division
		Procedure on Regulatory Action following Inspection		Document No.	QMS-INS-006
				Revision No.	01
				Effective Date	
				Page No.	897 of 1103
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 Purpose

To lay down a procedure for initiation of Regulatory action following finding, comments and recommendations made by the inspection team in the inspection report of the manufacturing units of Vaccines and biologicals.

2.0 Scope

This document is applicable to all applications made on Form-27D to the Licensing and Central Licensing Approving Authority for grant or renewal of license on Form 28D as prescribed in the latest Drugs and Cosmetics Act and Rules made there under.

3.0 Responsibility:

3.1 The personnel at a level of DI shall follow the controls for issuance and withdrawal of Licenses as per the SOP.

3.2 The ADC (I) shall be responsible for implementation of the licensing of Biological products as laid down in the SOP.

3.3 Head Biological Division and QMS Monitoring Division shall be responsible for the regular monitoring of compliance of this SOP.

4.0 Accountability

Head of Biological, Head of QMS Monitoring Division and DCG (I)

5.0 Procedure

5.1 All regulatory actions needs to be taken as per the provisions of the latest Drugs and Cosmetics Act and Rules made there under (Rule 81 to 85).

5.2 On the basis of recommendations of joint inspection report submitted to CLAA & SLA carried out for Grant/ Renewal of License/ issuance of Certificate of Pharmaceuticals Product (COPP)/ Post Approval Changes and For-cause inspections (complaints investigation, change assessments, etc.) regulatory actions need to be initiated as follows:

5.2.1 If grant or renewal of license is recommended, then State Licensing Authority after examination forward inspection report and duly signed license in triplicate on Form 28D along with products list to CLAA for approval. CLAA after scrutiny of report approves the license and sends two copies of the license to SLA for issue to the applicant.

5.2.2 If deficiencies are pointed out for compliance, it is to be communicated to the firm for submission of compliance through SLA/CLAA (HQ or Zonal office). The Zonal officer shall be responsible for verification of compliance, once the compliance report is submitted by the firm. (refer SOP QMS-INS-004)

5.2.3 If deficiencies are pointed out and application is rejected, it needs to be informed to the applicant with reasons by SLA/CLAA.

5.2.4 If critical / major deficiencies, as defined in current version of, SOP titled – "Procedure for conducting GMP inspection, report writing & review of inspection report" SOP No. QMS-INS-004, are pointed out and whether regulatory action is recommended or not recommended, need to be examined by SLA & CLAA in the inspection reports.

5.2.5 On the basis of review of criticalities of deficiencies regulatory action needs to be taken by CLAA/SLA like :

5.2.5.1 Stop manufacture, sale or distribution order or show cause notice need to be issued to the manufacturer stating that why such an order should not be passed and ask the manufacturer to reply within specified time of receipt of copy of the order (e.g. not more than 7 days).

5.2.5.2 Then based on the reply and personal hearing, as the case may be, suspension / cancellation of license or withdrawal of show cause notice / stop manufacture, sale or distribution order may be issued by SLA/CLAA.

5.2.6 Manufacturer, if complies with the deficiencies and inform to the regulatory authorities, the compliance report and document need to be scrutinized and on the strengths of compliance report further joint inspection may be carried out. (refer SOP QMS-INS-004).

5.2.7 If the satisfactory compliance is reported then revocation of stop manufacture, sale or distribution order / suspension of license may be done.

6.0 Annexure / Format

Nil

7.0 References

Doc. No.	Title
1	The Drugs and Cosmetics Act 1940 &Rules 1945
2	Applicable latest WHO guidelines.
3	Guidance Document for Functions and Responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO, 2011.

8.0 Abbreviation

Acronym	Full Form
DCGI	Drugs Controller General, India
QMS	Quality Management System
ADC (I)	Assistant Drugs Controller, India
DI	Drugs Inspector
DDC (I)	Deputy Drugs Controller, India
SOP	Standard Operating Procedure
SLA	State Licensing Authority
CLAA	Central Licensing Approval Authority

9.0 Revision History

Revision No.	Reason(s) for Revision
00	New SOP
01	Editorial correction- added SOPs reference

Chapter-15

CLINICAL TRIAL & BA/BE INSPECTION PROCEDURES

OBJECTIVES:

The aims of the programme are:

i. To verify GCP compliance to protect the rights, safety and well being of the subjects involved in clinical trial
ii. To verify the credibility and integrity of clinical trial data generated
iii. To verify the compliance with various regulatory provisions as per Drugs & Cosmetics Rules.

The purpose of this programme is to provide direction to inspectors/CDSCO officers for conducting inspection of site of clinical trial, sponsor / CRO's facilities involved in clinical trial and information to investigators, sponsor/ CRO'S about procedures for inspection and follow up of action.

SCOPE AND EXTENT OF THE PROGRAMME:

Clinical trial inspection programme covers all clinical trial sites and sponsor / CRO's facilities involved in clinical trial of drugs including biological and medical device covered under Drugs & Cosmetics Act.

Selection of studies:

Inspection can be carried out as a routine surveillance or for any specific cause(s).Study may be selected for inspection based on, but not restricted to the following criteria:

- Nature of study
- For regulatory decision based on clinical trial data
- Data irregularities
- Complaints
- Vulnerability of subjects
- Number of CT including number of subject enrolled at a particular site

INSPECTION ASSIGNMENTS:

CDSCO HQ will issue instruction to the CDSCO Officers /Inspectors to conduct the inspection identifying the Clinical trial, name, address, contact number of clinical trial site, sponsor / CRO's facilities to be inspected. It may also identify the type and purpose of the inspection and provide background materials like study protocol, CRF etc.

PREPARING FOR INSPECTION:

The inspector shall go through the information/SOPs (QMS/INS/007) provided by CDSCO HQ and develop a plan for conducting the inspection.

SCHEDULING THE INSPECTION:

Inspection of clinical trial site would generally be pre-announced to ensure availability of the Investigator / Sub- Investigator and other personnel along with study records at the time of the inspection. The date of inspection and other arrangements would be finalised by the CDSCO Officers / Inspector(s) in coordination with the investigator /sponsor/ CRO. Under some specific circumstances unannounced inspection of clinical trial sites can be carried out as per the direction of CDSCO HQ. Inspection of CRO/Sponsor can be conducted without prior notice.

CONDUCTING THE INSPECTION CLINICAL TRIAL SITES (QMS/INS/008):

The inspection includes verification of essential documents to determine whether the trial related activities were in accordance with the protocol, GCP guidelines published by CDSCO and New Drugs and Clinical Trial Rules 2019 as well as other applicable regulatory requirements. When inspection is carried out after completion of the clinical trial, it will include comparison of data generated by the sponsor with source documents at the clinical trial sites and Case Record Form (CRF) in the investigator‘s files. If it is a routine surveillance or ―for cause inspection of an ongoing clinical trial, the comparison will generally include source documents and CRF.

OPENING INTERVIEW:

Inspector should meet investigator / key person of Sponsor and present his / her identity card. The inspector should provide verbal summary of methods and procedures to be followed during the inspection. During opening interview following main activities should be found out:

¬ Investigator prior education and GCP experience, GCP training provided by the sponsor.

¬ Who did what, when, where and how with respect to following:

- Obtaining Informed consent of subjects,
- Screening and admission of subjects to the study,
- Receipt, handling, administration, return of investigational product,
- Collection and analysing of data,
- Recording, transcribing and reporting of data to sponsor,
- Archiving the data

¬ How did the investigator identify the subjects for the study,

¬ Date of enrolment first and last subject

¬ About Ethics Committee the site is using

¬ Whether the investigator has copies of protocol, permission from CDSCO, undertaking by the investigator etc.

¬ Information about unexpected and serious adverse events (if any) occurred at the site,

¬ Information about monitoring/auditing of the site by sponsor/CRO.

ORGANIZATION & DELEGATION OF RESPONSIBILITIES:

Inspector shall verify / obtain following: ¬ Brief about study site. ¬ Status of the study. ¬ Whether investigator has agreement with sponsor for the study. ¬ Whether financial & Confidentiality agreement with Investigator and concerned laboratory (ies) in place. ¬ In Investigator undertaking

protocol title, Investigator‘s name, address, telephone no of site, qualification, Name & address of laboratories, Name of Sub-Investigator etc are in-compliance with Schedule Y of Drugs & Cosmetics Rules 1945. ¬ Obtain list of all clinical trials performed by investigator.

The list should have information such as

- Protocol Number
- Protocol Title
- Name of Sponsor/CRO
- Study date

¬ Determine whether authority for conducting various Clinical trial related activities were delegated properly by the Investigator to the competent personnel so that investigator was able to supervise the study adequately.

Obtain a list of personnel with delegated activity.

¬ Documents following;

- Date of EC / IEC approval including initial review of protocol, amendment, ICD etc.
- Date of screening of first subject,
- Date of signing ICF by the first subject
- Date of first administration of IP,
- Date of last follow up of any subject,

¬ List the name and address of facilities involved in laboratory test required by protocol. Verify accreditation status and adequacy of these facilities to perform the specified test,

¬ Obtain a copy of site enrolment log,

¬ Determine whether SOP‘s for various activity are established and documented,

STUDY PROTOCOL:

¬ Determine if, there are any difference between protocol provided to CDSCO and the protocol in the Investigator‘s file with respect to following:

- Version number and effective date
- Eligibility of Subject (Inclusion/ Exclusion Criteria)
- No of Subject
- Dosage
- Route of administration
- Frequency of dosage
- Randomization & Blinding process
- Verify whether Investigator follow the protocol as approved
- Version number and EC approval of amendments

SUBJECT RECORD & INFORMED CONSENT

¬ Review the Informed Consent Form (ICF) signed by the subjects. If the number of subjects at site is relatively

small (e.g.20or less) 100% of the ICF can be reviewed. Determine the following:

¬ whether ICF have all the elements enlisted in New Drugs and Clinical Trial Rules 2019,
¬ whether IC has been obtained from each subjects prior to participation of the subject in the study,
¬ whether signature/thumb impression of the subjects have been affixed with date,
¬ whether in case of illiterate subjects or illiterate representative of a subject, there are signature and details of an impartial witness,
¬ Have witness/ signature been personally dated,
¬ Have patient signature been personally dated?
¬ Has the dated signature of the designated person for administering informed consent (IC) been affixed?
¬ Is the designated person for administering IC medically qualified?
¬ If IC has been administered by a designated person who is not medically qualified, is there evidence that subject's queries of a medical nature were answered by a medically qualified person or the investigator?
¬ Is the completed ICF signed and dated by the investigator?

SOURCE DOCUMENTS AND CASE RECORD FORM:

¬ Verify condition, completeness, legibility, accessibility of the investigators source data file.
¬ Determine whether subjects who were enrolled and /or completed the study meet inclusion and exclusion criteria;
¬ Determine whether subject received the test drug with respect to dose and frequency specified according to the protocol;
¬ Determine whether safety/ efficacy end point data was collected and reported in accordance with the protocol;
¬ Does medical record mentions subject ID/ name /hospital registration number / and indication that subjects are participating in a clinical trial
¬ Whether all adverse events were reported in CRF;
¬ Compare the source document with CRF and determine whether source data have been correctly transcribed in CRF;
¬ Verify whether all SAE‘s have been reported to the sponsor (within 24 hours) and EC (within 7 working days);
¬ Verify whether adequate medical care have been given to the subject especially in the event of inter current illness, adverse events including abnormal lab parameters.
¬ Verify the causality assessment report of serious adverse events (SAEs) including deaths. ¬ Report details of SAE including deaths which are related to clinical trials.
¬ Verify and report details of compensation provided in case of study related injuries or deaths. In case of no compensation has been paid, reason for the same should be obtained and documented from both the Sponsors and Ethics Committee.

ETHICS COMMITTEE (EC) / INDEPENDENT ETHICS COMMITTEE (IEC):

¬ Identify the name , address of the EC/ IEC in the approval letter and compare it with that stated in investigators undertaking;

¬ Verify if IEC approval letter mention study code , Protocol title and version number of the protocol, list of other documents reviewed, list of members present at the meeting, quorum of five members as specified in Schedule Y satisfied, date, time , venue of the meeting, signature and date of member secretary / Chairman; ¬ In case the site does not have an IEC, verify whether following are in place:

- Statement of the investigator / institution that approval granted by another IEC would be abided by & statement from the approving IEC that they would take responsibility for ongoing supervision of the site;
- Has the investigator submitted reports of all SAEs to the IEC and appraised the EC/IEC about the trial progress?

SPONSOR VERIFY/ DETERMINE:

¬ Whether a clinical trial Investigators agreement has been signed for this study with the sponsor;

¬ Whether investigator maintains copies of all reports submitted to the sponsor;

¬ Whether all SAE are reported to sponsor within 24 hours;

¬ Whether all CRFs were submitted to sponsor after completion of study;

¬ Whether all dropouts and reasons thereof were reported to sponsor;

¬ The method and frequency of monitoring the progress of the study by the sponsor;

¬ Whether a log of onsite monitoring visit is maintained at the site;

TEST DRUG ACCOUNTABILITY

¬ Review individual subject record to verify the correct dose administration with respect to dose, frequency, route of administration;

¬ Determine whether unqualified /unauthorised persons administered/dispensed the test drug

¬ Determine whether adequate record of qty. of test drug received , dispensed/ destroyed/returned is maintained;

¬ Determine whether storage condition/monitoring method are as per protocol/recommendation;

¬ Whether trial medication are maintained under controlled access;

¬ Have un-used trial medications been returned to the sponsor or disposed of according to protocol? In case of destruction at site, is there a certificate of destruction on file?

¬ Are the drugs dispensing records being maintained properly?

¬ Are the records for reconciliation of all IPs received from the sponsor maintained?

RECORD RETENTION

¬ Is adequate space available at the site for retention of documents

¬ Determine whether documents are maintained properly and for the period as specified and necessary measures have been taken for accidental and premature destruction;

¬ Determine who maintained custody of the documents and means for assuring prompt action;

CONCLUDING THE INSPECTION:

The inspector should conclude the inspection with final discussion with the Investigator. During discussion the inspector should explain inspection finding .

The inspector may also issue a list of observation at the conclusion of inspection. The inspector should conclude the inspection with final discussion with the Investigator. During discussion the inspector should explain inspection finding .The inspector may also issue a list of observation at the conclusion of inspection.

INSPECTION OF CRO/SPONSOR:

The inspection includes verification of essential documents to compare practice and procedure followed by the CRO/Sponsor to that committed in the clinical trial application and GCP guidelines published by CDSCO and New Drugs and Clinical Trial Rules 2019 as well as other applicable regulatory requirements. Inspection of CRO/Sponsor can be conducted without prior notice. During inspection following aspects may be verified.

DOCUMENTS SUBMITTED TO CDSCO AND REGULATORY APPROVALS OBTAINE.

¬ Clinical Trial application and DCGI approval letter

¬ Import license application (Form 12/ Form CT 16) and import licence obtained (Form 11/ Form CT 17) Copy of license in Form 29 from State Licensing Authority (in case of manufacture of test drugs)

¬ Export NOC for biological samples

¬ List of investigators

¬ Investigator Undertaking as per New Drugs and Clinical trial Rules 2019

¬ Investigator's brochure

¬ Protocol and Protocol amendments

¬ Patient Information Sheet and Informed Consent Form

¬ Case Record Form

¬ Ethics Committee approval and notifications to CDSCO

¬ Unexpected and Serious Adverse Event Reports

¬ Study report

ORGANISATION AND PERSONNEL:

¬ Company profile and overall structure,

¬ Organization chart for management of the clinical trial, Structure and responsibilities for all activities involving investigational products. Departments, functions, and key personnel responsible for Protocol development, Investigator's brochure, Case Record Form, Informed consent form (ICF), translations and amendments, Selection of investigators, Regulatory approval, Ethics Committee (EC) approval, Monitoring, Quality assurance Adverse Event (AE) Reporting, Data Management, Statistical Analysis, Electronic Records/Clinical Database, Clinical Supplies-Investigational Products (IP) Archival. ¬ Identify and determine the personnel responsible for following:

- Authority to review and approve study documents

- For final evaluations and decisions in the review of study
- For obtaining & reviewing adverse events and reporting to CDSCO
- Monitors/CRO(s) with job descriptions and qualifications
- Job description of key stake holders
- Verify clinical personnel training record
- To obtain a list of external service providers and contractors and documentation of the service they provide. • Verify that SOPs followed for various responsibilities and clinical trial related activities.

SELECTION AND MONITORING OF INVESTIGATORS:

¬ Obtain list of all investigators along with Investigator Undertaking, Signed Investigator Agreements

¬ Criteria for selection of sites

¬ Information provided to sites viz. Informed consent form, Protocol, Reports/publications of previous trials, Investigator's Brochure, Product labelling, Training, All versions and updates etc.

¬ Investigator‘s non-compliance (If any)

- Deviations from CDSCO regulations
- Deviations form protocol
- How sponsor handles serious deviations from approved protocol or NDCT 2019 /Indian GCP Guidelines.

STEPS FOR CORRECTION:

- Verify whether any investigators terminated? Review monitoring reports reported to CDSCO,
- Any Non-compliant investigator /terminated? Reasons?

SELECTION OF MONITOR:

- List all monitors for study duration
- Selection criteria for monitors
- Job descriptions/responsibilities
- Qualifications
- Training Records and CVs
- Reporting structure
- Monitoring SOP Frequency, scope and process, Obtain a copy of SOP and check compliance, If no SOPs, interview monitors to check how monitoring was done , Monitoring Plan, Monitoring Reports

¬ Review the Pre trial and periodic trial visit report in respect of following content: • Process of verifying compliance to protocol

- Process of verifying investigator responsibilities
- Ethics Committee Approvals Amendments/Re-approval Communication-progress reports/SAEs etc Validity / Completeness.
- Informed Consents, Confirmation of consent and process of consent.
- Use of IEC approved forms.
- Adequacy of consent documentation, completeness

- Which CRFs were compared to source docs? When and who verified CRFs against source data (hospital records, office charts, laboratory reports, etc.) at the study site. Form for data verification
- Check copy of any SOPs and guidelines for data verification
- Data correction handling, Compliance to Monitoring Plan, Frequency, Follow up etc.

QUALITY ASSURANCE (QA)

¬ Verify SOP for QA audits and operation of quality assurance unit

¬ Describe how the audit and monitoring are separated

¬ Obtain list of audited trial

ADVERSE EVENTS REPORTING

¬ Verify sponsor‘s method for following up of adverse events and for dissemination of AE information to others Investigators:

¬ Obtain list of SAE reported, Including death

¬ Verify the timeline for reporting the SAE to CDSCO and other Investigators /EC;

¬ Verify the causality assessment report of serious adverse events (SAEs) including deaths.

¬ Report details of SAE including deaths which are related to clinical trials.

¬ Verify and report details of compensation provided in case of study related injuries or deaths. In case of no compensation has been paid, reason for the same should be obtained and documented from both the Sponsors and Ethics Committee.

DATA COLLECTION AND HANDLING

¬ Study tabulations: List of all studies for marketing Authorization

¬ Data Tabulations: Number of subjects. Verify if number in CT application same as marketing Authorization application(compare to CRFs submitted)

¬ If any subjects not included in the marketing Authorization application? Why not included?

¬ Review of SOPS to verify compliance to assure the integrity of safety and efficacy data collected from clinical investigators

¬ Verify that the SOPs were followed and document any deviations ¬ Deviations/Data queries resolutions

¬ Statistical processes

¬ Primary endpoints Compare the tabulations with CRFs and source documents

¬ Record retention

ELECTRONIC RECORD AND CLINICAL DATABASE:

¬ Person responsible for designing and developing data base

¬ Can it be modified, or has it been modified? If so, by whom?

¬ If the clinical investigator can modify it, how would the sponsor be aware of any changes?

¬ Validation :Person responsible, Process, Documentation of process

¬ Error logs maintained for errors in software and systems?

¬ Do error logs identify corrections made?

DATA COLLECTION

Following aspects may be verified:

¬ Responsibilities : Authorization to access the system, to enter data and to change data

¬ Use of electronic data capture or data transcription from paper CRFs into an electronic record

¬ Audit trail: to record Changes to electronic records, Person Responsible for the change and Time of the change

¬ Process of data transmission from the clinical investigator to sponsor or CRO

COMPUTERIZED SYSTEM SECURITY

Following aspects may be verified:

¬ Management of system access e.g. access privileges, authorization/de-authorization procedures, physical access controls

¬ Records of authorized personnel , Names, Titles. Description of their access privileges

¬ Access methods e.g., identification code/password combinations, tokens, biometric signature, electronic signatures, digital signatures

¬ Data security in case of disasters, e.g., power failure

¬ Contingency plans and backup files

¬ Controls in place to prevent data from being altered, browsed, queried, or reported via external software applications that do not enter through the protective system software

INVESTIGATIONAL PRODUCT(IP):

Following aspects may be verified:

¬ Transferred data from central lab to sponsor

¬ Integrity Procedures to ensure integrity of IP from manufacturing to receipt by the clinical investigator.

¬ If IP met required release specifications by review of the Certificate of Analysis?

¬ Storage of IP and the conditions of storage

¬ Process of verification of IP integrity during shipment to investigator.

¬ IP label

¬ If the test article was recalled, withdrawn, or returned?

ACCOUNTABILITY

Following aspects may be verified:

- Names and addresses of clinical investigators receiving IP Shipment, date (s), quantity, batch number.
- Final disposition of the test article.
- Detailed audit if serious violations are suspected.
- Sufficient records to reconcile IP usage (compare the amount shipped to the investigators to the amount used and returned or disposed of).

- Check whether all unused or reusable supplies of IP returned to the sponsor when either the investigator(S)

discontinued or completed participation in the clinical investigation, or the investigation was terminated. If the test article was not returned to the sponsor, describe the method of disposition and determine if adequate records were maintained.

REPORTING OF INSPECTION:

The Inspection should be documented in writing in both during and after inspection. After the inspection a narrative report containing details of inspection finding should be prepared and submitted to CDSCO (HQ).

	TITLE		Division Name	QMS Monitoring Division
	Procedure for Preparing GCP Inspection		Document No.	QMS-INS-007
			Revision No.	00
			Effective Date	
			Page No.	911 of 1103

Prepared By		Approved By		Authorized By	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 Purpose

To lay down a procedure for preparing GCP inspection and to provide directions to inspectors for conducting inspection at clinical trial site.

2.0 Scope

This document is applicable to the concerned division of CDSCO to set a uniform procedure for preparing GCP inspection.

3.0 Responsibility

3.1 The Inspector/ ADC(I)/ DDC(I) shall be responsible for implementation of the SOP.

3.2 The DDC(I) and ADC(I) of concerned division shall be responsible for overall compliance of the SOP.

4.0 Accountability

DCG (I) or his designee

5.0 Procedure

5.1 Central Inspection Plan

5.1.1 CDSCO-HQ shall prepare tentative central inspection plan (Annexure-I) on risk based approach taking in to account the clinical trial permission issued, number of clinical trial at particular site, number of enrolment of subjects, date of initiation of trial at a particular site, nature of investigational SAEs, AEs reported product, nature of study, vulnerability of subjects, previous data, compliance history of the investigator/ sponsor/ ethics committee, etc. if any.

5.1.2 Based on the tentative central inspection plan, the inspections shall be conducted by the Zonal/ Sub-Zonal Office during the conduct of clinical trial or after completion of clinical trial as the case may be for verification of GCP compliance. Inspections during conduct of clinical trials give more appropriate information. Accordingly, based on evaluation of risk/ criticalities involved in product under study or trial itself, such inspection may be carried out.

5.1.3 The Zonal/Sub Zonal office may also plan inspection depending on the complaints/ media reports or any other situations which warrants unannounced inspections.

5.2 Inspection Initiation

5.2.1 Inspection shall be planned for surveillance/ to verify compliance to GCP to take regulatory decisions or any specific cause(s).

5.2.2 The site and date of inspection may be planned by CDSCO (HQ) or Zonal/Sub-Zonal Head on the basis of tentative central inspection plan.

5.2.3 Before initiation of inspection, Zonal/ Sub-Zonal Head may take information about status of the trial (Ongoing, completed etc.) from the Sponsor/ Investigator or CDSCO-HQ.

5.2.4 The Inspector shall be deputed from the CDSCO Head Quarter or Zonal/Sub-Zonal offices of CDSCO, who may be accompanied by an officer from State Drugs Control Authority & subject expert.

5.2.5 The mode of inspection may be hybrid where CDSCO (HQ)/ expert may join virtually or physically.

5.2.6 Divisional/ Zonal /Sub-Zonal Head may ask for documents/ information from the sponsor/ CRO/ Investigator or Ethics Committee, if required by Inspector.

5.2.7 Routine inspection may need less detail than for cause inspections, or inspections for specific products or systems.

5.2.8 Inspector shall review protocol and other relevant documents before Inspection.

5.2.9 Inspector shall prepare a comprehensive inspection plan and communicate to the inspection site or concern.

5.3 **Review of documents and information**

5.3.1 Essential information and documentation is identified, obtained and reviewed. This obtained/ collected information is reviewed and evaluated by the inspection team. Results of this review are incorporated into the inspection plan.

5.3.2 Necessary information needed which is used to evaluate the essential aspect to be included in the conduct of the inspection, may be derived from a number of sources: Dossier, reference documents, guidelines, legislation, inspection SOPs etc. A guide to the documentation that may be reviewed whichever is available/ gathered prior to the start of an inspection is listed in the Annexure-II of the SOP and in CDSCO guidance document for GCP inspection.

5.4 **Inspection plan**

5.4.1 Inspector shall prepare the inspection plan based on the scope of inspection and reviewed documents.

5.4.2 The inspection plan shall be general in outline and define the relevant aspects of the clinical trial sites and scope that are to be covered during the inspection with various aspects of GCP.

5.4.3 The inspection plan shall include timelines for the inspection.

5.4.4 Inspection shall be planned as per CDSCO Guidance on Clinical Trial Inspection & GCP inspection checklist published on website & Guidance document for functions and responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO (along with additional points as per current rules and requirements of clinical trial). Accordingly, the inspection checklist shall include all points as per current regulations, Indian GCP guidelines and other applicable guidelines.

NOTE: Rules and checklist update may not be concurrent in some cases; rules shall take the precedence over the checklist

5.5 **Inspection announcement**

5.5.1 The Zonal/ Sub-Zonal or CDSCO-HQ announces the inspection to the Sponsor/ Investigator/ Ethics Committee contact address.

5.5.2 The responsible personnel at the selected sites are informed of the forthcoming inspection except in case of unannounced inspection.

5.5.3 Inspection dates for the selected sites are communicated to the sites, in accordance with the timelines in the site inspection plans.

5.5.4 The Inspector(s) shall ensure that the relevant parts of the inspection plans are communicated to the responsible personnel at the site.

5.6 **Practical preparation**

5.6.1 The need for preparation may differ between inspections, depending on the type of inspection, type of trial, therapeutic area and product, location of the inspection, number of selected sites, etc.

5.7 Other responsibilities of Inspector(s) shall be:

- The verification of the location of the sites and for the co-ordination of the inspection team.
- Keeping the inspection documentation up to date and secure.
- Checking that the confidentiality requirements are adhered.

- To conduct the inspection at the site in accordance with the legal requirements and SOPs.
- Adhering to the timelines

6.0 Annexure / Format

Annexure/Format No.	Title
Annexure-I (QMS-INS-007/F01)	Tentative Central Inspection Plan for Clinical Trial Inspections (Vaccines) for year XXXX
Annexure-II (QMS-INS-007/F02)	Documents/ information used for review prior to the start of the GCP inspection

7.0 References

Doc. No.	Title
1	The Drugs and Cosmetics Act, 1940.
2	New Drugs and Clinical Trial (NDCT) Rules, 2019
3	CDSCO Guidance on Clinical Trial Inspection
4	Guidance document for functions and responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO
5	Good Clinical Practices (GCP) Guidelines
6	Guideline for Good Clinical Practice ICH E6(R2)

8.0 Abbreviation

Acronym	Full Form
CDSCO	Central Drugs Standard Control Organization

DCGI	Drugs Controller General (India)
QMS	Quality Management System
DDC (I)	Deputy Drugs Controller, India
ADC (I)	Assistant Drugs Controller, India
DI	Drugs Inspector
GCP	Good Clinical practices
SOP	Standard Operating Procedure
INS	Inspection

9.0 Revision History

Revision No.	Reason(s) for Revision
00	New SOP

Annexure-I of QMS-INS-007

'Tentative Central Inspection Plan for Clinical Trial Inspections (Vaccines) for year XXXX'

Central Drugs Standard Control Organization
Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India
FDA Bhavan, ITO, Kotla Road, New Delhi -110002
FDA Bhavan, ITO, Kotla Road, New Delhi -110002

Tentative Central Inspection Plan for Clinical Trial Inspections (Vaccines) for year XXXX

S. No.	Name of Sponsor /CT permission holder	Name of Investigational product	Protocol no. and study title	Name of Investigator / Address of clinical trial site	CT approval with date	Remarks

Note: 1) This is a dynamic inspection plan based on the clinical trials approval and may be updated as and when required.
2) Inspections may be planned by Zonal/Sub-Zonal offices as per the specific situation which may be arise from time to time.

Annexure-II of QMS-INS-007

'Documents/ information used for review prior to the start of the GCP inspection'

'**Central Drugs Standard Control Organization**

Directorate General of Health Services, Ministry of Health and Family Welfare,

Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

DOCUMENTS / INFORMATION FOR REVIEW PRIOR TO THE START OF THE GCP INSPECTION WHICHEVER AVAILABLE

1. **Overview of the conduct of the study:**

S.No	Contents
1	Total number of sites/ locations
2	Inclusion rate, screening, randomization, etc.
3	SAEs, ADRs
4	Drop out frequency
5	Time frame of trial
6	Annual reports, final report
7	Presence of a similar/extension protocol

2. **Sites**

S.No	Contents
1	Investigator(s)/ co-investigator(s) CVs and qualifications
2	Information on sites involved/selected (including e.g. pharmacy clinical departments X-ray, MRI, Echo, ECG, CT, CROs)

3. **Lab**

S.No	Contents
1	Local/ Central
2	Type of labs involved
3	Type of examinations/ tests
4	Special equipment/ procedures

4. Sponsor

S.No	Contents
1	Responsibilities defined in contracts
2	CRO(s) involved
3	Protocol, amendments, investigator's brochure
4	CRFs
5	Printout (of parts) of the clinical database
6	Quality management (QC, QMS)
7	Sponsor SOPs related with the scope of the inspection

5. Trial Medication

S.No	Contents
1	GMP
2	Manufacturing
3	Labelling
4	Blinding procedures
5	Randomization list

6	Quality documentation

6. Ethics

S.No	Contents
1	Patient information/informed consent
2	Patient recruitment
3	Insurance
4	Updates of safety information
5	IEC opinion

7. Local inspectorate

S.No	Contents
1	Availability of qualified inspectors
2	Availability of qualified GMP inspectors (if the scope of the inspection covers IMP)
3	Recruitment of external experts
4	Time schedule

8. Local legal regulations

S.No	Contents
1	Applicable GCP and legal requirements
2	Notification/ approval of protocol
3	Importation of investigational products
4	Announcement of inspection to the competent authority
5	Trial medication: import license, labeling, storage, destruction

6	SAE reporting

****

	TITLE		Division Name	QMS Monitoring Division
	Procedure for Conducting GCP Inspection		Document No.	QMS-INS-008
			Revision No.	00
			Effective Date	
			Page No.	922 of 1103

Prepared By		Approved By		Authorized By	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 Purpose

To lay down a procedure for conducting GCP inspection applicable for any clinical trial site to be inspected.

2.0 Scope

This document is applicable to the concerned division/ Zonal/ Sub-Zonal Offices of CDSCO to set a uniform procedure for carrying out GCP inspections.

3.0 Responsibility

3.1 Inspector/ADC(I)/ DDC(I) shall be responsible for implementation of the SOP.

3.2 The ADC (I) and DDC(I) of concerned Division/ Zone/ Sub-zone shall be responsible for overall compliance of the SOP.

4.0 Accountability

Zonal/Sub-Zonal Head, Division Head & DCG (I) or his designee.

5.0 Procedure

5.1 This procedure takes into account:

5.1.1 *"**Procedure for preparing for GCP inspections'*** (QMS-INS-007), which describes procedure for preparing GCP inspection.

5.1.2 *"**Procedure for reporting on GCP inspections"*** (QMS-INS-009), which describes the contents of GCP inspection reports and the procedure for their approval.

During the preparation of the inspection an inspection plan is prepared. This plan shall depend on the scope of the inspection of clinical trial site. The Inspector shall conduct the inspection at the selected site.

5.2 Opening meeting

Before the start of the inspection there shall be opening meeting between the inspector(s) and the inspectee(s). Guidance document for functions and responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO.

The purpose of an opening meeting is to:

- Introduce the inspector(s) to the inspectee(s).
- Apprise the scope and the objectives of the inspection in brief.
- Identify the distribution of duties and functions for the conduct of the trial among the inspectee(s).
- Provide a short summary of the methods and procedures to be used to conduct the inspection.
- Confirm that the resources, documents and facilities needed by the inspector(s) are available.

- Confirm the time and date for the closing meeting and any interim meetings.
- Clarify the inspection plan, if necessary.

5.3 Conduct of the inspection/ collecting information

5.3.1 The inspection activities should be detailed on the inspection plan. Nevertheless during the inspection, the inspector(s) may adjust the plan to ensure that the inspection objectives are achieved.

5.3.2 Sufficient information to fulfill the inspection objective(s) should be collected through the examination of relevant documents with direct access, interviews and observation of activities, equipment and conditions in the inspected areas.

5.3.3 If access to records or copying of documents is refused for any reason or there is any withholding of documents or denial of access to areas to which the inspector has legal access, these refusals should be documented and included in the inspection observations.

5.3.4 Inspection shall be conducted as per CDSCO Guidance on Clinical Trial Inspection & GCP inspection checklist (Annexure-I) published on website & Guidance Document for Functions and Responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO. (Along with additional points as per current rules and requirements of clinical trial). Accordingly, the inspection checklist shall include all points as per current regulations, Indian GCP guidelines and other applicable guidelines.

NOTE: Rule and checklist update may not be concurrent in some cases, rules shall take the precedence over the checklist.

5.4 Inspection observations

5.4.1 All observations of the inspection should be documented. If appropriate, copies should be made of records containing discrepancies or illustrating non-compliance.

5.4.2 At the end of the inspection, the inspector(s) should review all observations to determine which are to be reported as non-compliance and/or quality system deficiencies. The inspector(s) should then ensure that these are documented in a clear, concise manner and are supported by objective evidence.

5.4.3 All reported observations (findings) should be identified with reference to specific requirements of the standard(s) or other related documents against which the inspection has been conducted. The names and titles of persons interviewed or present during the inspection meetings and the details of the inspected organization should be documented.

5.5 Closing meeting with the inspectee(s)

5.5.1 At the end of the inspection, the inspector(s) should hold a closing meeting with the inspectee(s). The main purpose of this meeting, is to present inspection findings to the inspectee(s) to ensure that the results of the inspection are clearly understood and that there is no misinterpretation by either the inspector(s) or the inspectee(s).

5.5.2 Issues to be followed up by the inspectee(s) shall be addressed, including any additional documents that may need to be sent to the inspection team.

5.5.3 During this meeting the inspector(s) shall give details on the inspection reports according to the *"Procedure for reporting observations of GCP inspection"* (QMS-INS-009).

6.0 Annexure / Format

Annexure/Format No.	Title
Annexure-I (QMS-INS-008/F01)	GCP Inspection Checklist

7.0 References

Doc. No.	Title
1	The Drugs and Cosmetics Act, 1940.
2	New Drugs and Clinical Trial (NDCT) Rules, 2019

3	CDSCO Guidance on Clinical Trial Inspection
4	Guidance document for functions and responsibilities of Zonal, Sub-Zonal and Port Offices of CDSCO.
5	Good Clinical Practices (GCP) Guidelines
6	Guideline for Good Clinical Practice ICH E6(R2)

8.0 Abbreviation

Acronym	**Full Form**
CDSCO	Central Drugs Standard Control Organization
DCGI	Drugs Controller General, India
QMS	Quality Assurance
DDC(I)	Deputy Drugs Controller, India
ADC(I)	Assistant Drugs Controller, India
DI	Drugs Inspector
GCP	Good Clinical Practices
SOP	Standard Operating Procedure
INS	Inspection

9.0 Revision History

Revision No.	**Reason(s) for Revision**
00	New SOP

Annexure-I of QMS-INS-008

'GCP Inspection Checklist'

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

GCP INSPECTION CHECKLIST

(This list is not all inclusive; item may be added &/or deleted as per the Study/Site/Sponsor/Lab)

I. General		
1.	Name and address of the clinical trial site	
2.	Date of Inspection	
3.	Inspection Team Members:	
4.	Personnel present during Inspection (with name and role/designation.)	
5.	Address & Contact details of Investigator:	
6.	Name & address of the Sponsor	
7.	Name & address of clinical trial NOC holder	

8.	Name & address of EC	
9.	Protocol Title	
10.	Protocol Number Version/date Protocol amendments, if any.	
11.	Investigational Product	
12.	Stage of study: (Mark the relevant)	(A) Before Trial Commencement ☐ (B) During Conduct of the trial ☐ (C) After Completion of Trial ☐
13.	Type of Inspection	Surveillance ☐ For Cause ☐

II. LEGAL & ADMINISTRATIVE ASPECTS

S. no.	Item	Yes	No	NA	Remarks
1.	Clinical trial NOC from O/o DCGI (Note: mention along with Protocol no., Ver., date)				
2.	NOC for subsequent protocol amendments, if any from O/o DCGI				
3.	Ethics Committee approval date (Note: mention along with Protocol no., Ver., date)				
4.	Table 4 of Third Schedule of New Drugs and Clinical Trial Rules, 2019				

5.	Whether valid financial agreement between the Sponsor, Investigator & Institution available.				
6.	Whether liability of involved parties (Investigator, Sponsor and Institution) clearly agreed.				
7.	Is the valid clinical trial Insurance available?				
8.	Site Initiation date				
9.	Date of screening of first subject,				
10.	Date of signing ICF by the first subject				
11.	Date of Last Patient-Last Follow-Up (if applicable)				
12.	Whether SOP for various activities are established and documented.				
13.	Verify, whether the hospital/institute/site has adequate emergency care facilities to handle emergency situation.				
III. Organization & Personnel					
1.	Assure that signed & dated, Curriculum Vitae is available for the Investigator, Sub Investigator /Co-Investigator				
2.	Confirm the educational qualification of the Investigator with registration by Medical Council of State/India.				
3.	Confirm the GCP, New Drugs and Clinical Trial Rules, 2019 and protocol specific training of Investigator, Sub-Investigator/Co-Investigator and its team.				
4.	Determine whether authority for conducting various clinical trial activities were delegated properly by				

	Investigator to competent personnel (obtain the list of personnel and duty delegation log).				
5.	Check whether the person whom the authority is delegated is adequately qualified and trained for the activity/activities assigned.				
6.	Obtain the list of all clinical trials performed by Investigator (Preferably for last three years)				
7.	Ensure that the Investigator is involved in conduct of not more than three clinical trials at a time.				
IV. Conduct of Trial					
A.	**Screening of subjects**				
1.	Check and review the informed consent for the screening of the subjects.				
2.	Check site screening log & enrolment log and obtain authenticated copy.				
3.	**Check whether the subjects are meeting the inclusion/exclusion criteria as per the approved protocol w.r.t review of source documents &/or CRF.**				
3.1	Clinical Examination by Investigator (Check patient file/Source documents)				
3.2	Verify ,Clinical Laboratory Evaluation (Check Blood Cell Counts, Biochemical test, Urine analysis etc.as required by protocol)				
3.3	Verify X-Ray, MRI, ECG, USG or any other technique required to ascertain the inclusion/exclusion criteria.				
3.4	Verify, Whether all conditions of Clinical trial NOC are followed or not?				
B. Subject record and Informed consent:					
1.	Whether ICF have all the elements enlisted in Table 3 of Third Schedule of New Drugs and Clinical Trial Rules, 2019.				

	Whether ICF is approved by Ethics Committee prior to consent process.				
2.	Whether IC has been obtained from each subject prior to participation of the subject in the study.				
3.	Whether signature/thumb impression of the subjects/legal representative have been affixed with date.				
4.	Whether in case of illiterate subjects or illiterate representative of a subject, there are signature and details of an impartial witness.				
5.	Have witness/ signature being personally dated. (If applicable).				
6.	Have patient/witness signature been personally dated?				
7.	Has the dated signature of the designated person for administering informed consent (IC) been affixed?				
8.	Is the designated person for administering IC medically qualified?				
9.	If IC has been administered by a designated person who is not medically qualified, is there evidence that subject's queries of a medical nature were answered by a medically qualified person or the investigator?				
10.	Is the completed ICF signed and dated by the investigator?				
11.	Check weather re-consenting is done for changes in ICF, if any.				
B.1	**Audio-Visual recording of Informed Consent Process (For vulnerable subject population in clinical trial of New Chemical Entity or New Molecular Entity (NCEs) clinical trial and Anti-**				

	HIV & Anti-Leprosy drugs Audio recording as per requirements of New Drugs and Clinical Trial Rules, 2019.				
1.	Whether audio-visual recording is performed for all subjects, independently.				
2.	Is audio-visual recording conducted in a room conducive to recording of disturbance free audio and video of the consent process?				
3.	Check whether the video recording is free from disturbance to ensure that the image is recognizable and the audio is clearly audible.				
4.	Check whether the recording of informed consent process is preserved safely.				
	C. Source Documents and Case Record Form				
1.	Verify condition, completeness, legibility, accessibility of the investigators source data file. (source data includes study subject's files, recording from automated instruments, tracings, X-ray and other films, laboratory notes, photograph negatives, magnetic media, hospital records, clinical and office charts, subject's diaries, evaluation checklists and pharmacy dispensing records)				
2.	Whether subject received the test drug with respect to dose and frequency according to the protocol;				
3.	Determine whether safety/efficacy end point data (Clinical, laboratory examination results) were collected and reported in accordance with the protocol				
4.	Does medical record mentions subject ID/ name /hospital registration number / and indication that subjects are participating in a clinical trial				

5.	Compare the source document with CRF and determine whether source data have been correctly transcribed in CRF;				
6.	Verify the drop-outs and reason for drop-out of subject is appropriately recorded.				
7.	Whether the withdrawal of subject from the study is recorded and appropriately justified in accordance with approved protocol.				
8.	Verify whether Standard Operating Procedure of handling of Serious Adverse Event occurred in clinical trial is available.				
9.	Verify whether all SAE's have been reported by the Investigator, Sponsor & EC to the Central Licencing Authority as per the timelines in New Drugs and Clinical Trial Rules, 2019.				
10.	Verify Whether SOP for medical care during serious adverse event is available or not.				
11.	Verify whether adequate medical care have been given to the subject especially in the event of inter current illness, adverse events including abnormal lab parameters;				
12.	Verify whether all study related activities are performed at site approved by O/o DCGI.				
V. Sponsor					
1.	Whether investigator maintain copies of all report submitted to the sponsor;				
2.	Whether all CRF were submitted to sponsor after completion of study;				
3.	Determine whether all dropout and reason thereof were reported to sponsor;				

4.	Determine the method and frequency of monitoring the progress of the study by the sponsor and corrective action by site.				
5.	Whether sponsor appointed a monitor with appropriate qualification and experience to monitor trial at the site.				
6.	Whether a log of onsite monitoring visit is maintained at the site.				
7.	Is monitor submits visit report with deviations if any to the sponsor.				
8.	Whether sponsor performed an audit as a part of QMS in order to independent and separate from routine monitoring of quality control function.				
9.	In case the investigator and sponsor agrees to prematurely terminate or suspend the study for any reason, whether it was promptly informed to study subjects, Ethics Committee and Central Licensing Authority.				
VI. Investigational Product					
1.	Review individual subject record to verify the correct dose administration with respect to dose, frequency, route of administration				
2.	Determine whether unqualified /unauthorized persons administered/dispensed the test drug				
3.	Determine whether adequate record of quantity of test drug received, dispensed is maintained. (Check the test drug reconciliation and verify the leftover drug or balance on the day of inspection).				
4.	Determine whether storage condition/monitoring method are as per protocol/recommendation;				

5.	Whether trial medication are maintained in secured manner with controlled access;				
6.	Have un-used trial medications been returned to the sponsor or disposed of according to protocol?				
7.	Are the drugs dispensing records being maintained properly?				
8.	Whether the records for reconciliation of all IP's are maintained?				
9.	Are electronic or hand-written temperature logs available for the storage area of the investigational products?				
10.	Verify that investigation product is appropriately labelled. (For clinical trial use only).				
VII. Ethics Committee					
1.	Identify the name, address of the EC/ IEC in the approval letter and compare it with one stated in Investigator Undertaking.				
2.	Verify the Status of EC-whether Institutional or Independent, Check Registration certificate				
3.	Verify if EC approval letter mention study code , title and version number of the protocol, list of other documents reviewed, list of members present at the meeting, quorum of five members as per Chapter III of NDCT Rules, 2019 satisfied, date, time, venue of the meeting, signature and date of member secretary / Chairman.				
4.	Verify whether the EC recorded minutes of meeting.				

5.	Verify whether EC is performed on site monitoring of the clinical trial approved (Frequency and SOP)				
6.	Verify whether EC members have conflict of interest in the approved trial, if yes then the member should abstain from such approval meeting.				
7.	Verify whether the communications between Investigator and EC are available for changes, Serious Adverse Event and deviations occurred in clinical trial.				
VIII. Pathology Laboratory (for Screening/ Assessment)					
1.	Name and address of the clinical laboratory used in the study. (Local and Outside).				
2.	Whether financial & Confidentiality agreement with Investigator and concerned laboratory (ies) in place.				
3.	Is investigator/Sponsor verified the accreditation status and adequacy of the facilities to perform the specified tests as per protocol.				
4	Verify whether the SOP for sample preparation, handling and transportation is available. Verify the appropriateness of the SOP.				
IX. Quality Assurance					
1.	Verify whether SOP for all procedures conducted at site are available i.e. have a copy of Site Specific and Trial specific SOPs				
2.	Verify the essential components of SOP like who prepared, checked, authorized and when, frequency of SOP revision				

3.	Whether SOPs for all operation like screening and Informed consent Process, AV recording of ICP of vulnerable population in NCE-CTs, SAEs & its Management, Communication with EC/Sponsor/CDSCO, GCP/NDCT Rules, 2019, training to trial team, training assessment				
4.	Whether SOPs for all operation like IP handling and distribution to study subjects, blood samples collection, processing preservation and transportation to local laboratory.				
5.	Whether SOPs for all operation of storage cabinets, refrigerators/deep freezers used to store samples and IP are available.				
6.	Verify, whether records for job description/responsibilities, qualification and training for all personnel involved in the clinical trial is maintained and stored.				
7.	Verify whether the activities performed are in compliance with duty delegated by Investigator.				
8.	Verify whether concern staff is adequately trained and records maintained there of				
9.	In case of vaccines, are a spillage SOP available and the study team trained to handle such an incidence?				
X. Record keeping and data handling					
1.	Is adequate space available for document retention?				
2.	Determine whether documents are maintained properly and for the period as specified.				

3.	Whether necessary measures have been taken to prevent accidental or premature destruction.				
4.	Whether the archival access controlled or restricted to authorized personnel.				
5.	Weather SOP available to document all steps in data management in order to allow step by step retrospective assessment of data quality and study performance.				
6.	Whether corrections in documents carry the date and initials of Investigators and authorized person.				
XI. Electronic data processing					
1.	Is electronic data processing is done by authorized person?				
2.	Verify whether list of authorized persons to make changes is maintained				
3.	Verify if provision for recording of trail of changes and deletions made is available.				
4.	Whether the hardware and software use for data recording and processing is validated				

Collect authenticated copies as exhibit wherever any Critical &/or Major non-compliance has been observed.

****

Part C

GUIDANCE ON CLINICAL TRIAL INSPECTION

CENTRAL DRUGS STANDARD CONTROL ORGANIZATIONDIRECTORATE GENERAL OF HEALTH SERVICES MINISTRY OF HEALTH & FAMILY WELFARE

GOVT. OF INDIA

January-2023

1 ABBREVIATIONS

AE	Adverse events
CRO	Clinical Research Organisation
CRF	Case Record Form
CT	Clinical Trial
CV	Curriculum Vitae
EC	Ethics Committee
ICF	Informed Consent Form
IEC	Institutional Ethics Committee
IP	Investigational Product
SOP	Standard Operating Procedure
SLA	State Licencing Authority

CLINICAL TRIAL INSPECTION PROGRAMME

2 Objectives :

The aims of the programme are:

a. To verify GCP compliance to protect the rights, safety and well being ofthe subjects involved in clinical trial

b. To verify the credibility and integrity of clinical trial data generated

c. To verify the compliance with various regulatory provisions as perNew Drugs and Clinical Trial Rules, 2019

The purpose of this programme is to provide direction to inspectors/ CDSCO officers for conducting inspection of site of clinical trial, sponsor/ CRO's facilities involved in clinical trial and information to investigators, sponsor/ CRO'S about procedures for inspection and follow up of action.

3 Scope and extent of the programme:

Clinical trial inspection programme covers all clinical trial sites and sponsor / CRO's facilities involved in clinical trial of drugs including biological and medical device covered under Drugs & Cosmetics Act.

4 Planning for Inspection:

Inspection can be conducted before, during or after a clinical trial iscompleted.

4.1 Selection of studies:

Inspection can be carried out as a routine surveillance or for any specific cause(s).Study may be selected for inspection based on,but not restricted to the following criteria:

- **4.1.1** Nature of study
- **4.1.2** For regulatory decision based on clinical trial data
- **4.1.3** Data irregularities
- **4.1.4** Complaints
- **4.1.5** Vulnerability of subjects
- **4.1.6** Number of CT including number of subject enrolled at a particular site

4.2 Inspection assignments:

CDSCO HQ will issue instruction to the CDSCO Officers

/Inspectors to conduct the inspection identifying the Clinical trial, name, address, contact number of clinical trial site, sponsor / CRO's facilities to be inspected. It may also identify the type and purpose of the inspection and provide background materials like study protocol, CRF etc.

4.3 Preparing for inspection:

The inspector shall go through the information provided by CDSCOHQ and develop a plan for conducting the inspection.

4.4 **Scheduling the inspection**:

Inspection of clinical trial site would generally be pre-announced to ensure availability of the Investigator / Sub- Investigator and other personnel along with study records at the time of the inspection.

The date of inspection and other arrangements would be finalised by the CDSCO Officers / Inspector(s) in coordination with the investigator /sponsor/ CRO.

Under some specific circumstances unannounced inspection of clinical trial sites can be carried out as per the direction ofCDSCO HQ.

Inspection of CRO/Sponsor can be conducted without prior notice

5 Conducting the inspection:

5.1 Clinical Trial Sites:

The inspection includes verification of essential documents to determine whether the trial related activities were in accordance with the protocol, GCP guidelines published by DGHS, Govt. of India and New Drugs and Clinical Trial Rules, 2019 as well as other applicable regulatory requirements. When inspection is carried out after completion of the clinical trial, it will include comparison of data generated by the sponsor with source documents at the clinical trial sites and Case Record Form (CRF) in the investigator's files. If it is a routine surveillance or "for cause" inspection of an ongoing clinical trial,the comparison will generally include source documents and CRF.

5.1.1 Opening interview:

Inspector should meet investigator / key person of Sponsor and present his / her identity card. The inspector should provide verbalsummary of methods and procedures to be followed during the inspection.

During opening interview following main activities should be foundout:

5.1.1.1 Investigator prior education and GCP experience, GCP training provided by the sponsor.

5.1.1.2 Who did what, when, where and how with respect tofollowing:

- Obtaining Informed consent of subjects,
- Screening and admission of subjects to the study,
- Receipt, handling, administration, return of investigational

product,

- Collection and analysing of data,
- Recording, transcribing and reporting of data to sponsor,
- Archiving the data

5.1.1.3 How did the investigator identify the subjects for the study,
5.1.1.4 Date of enrolment first and last subject
5.1.1.5 About Ethics Committee the site is using
5.1.1.6 Whether the investigator has copies of protocol, permission from CDSCO, undertaking by the investigator etc.
5.1.1.7 Information about unexpected and serious adverse events(if any) occurred at the site,
5.1.1.8 Information about monitoring/auditing of the site by sponsor/CRO.

During the interview other relevant facts may also befound out.

5.1.2 ORGANIZATION & DELEGATION OF RESPONSIBILITIES:

Inspector shall verify / obtain following:

5.1.2.1 Brief about study site.
5.1.2.2 Status of the study.
5.1.2.3 Whether investigator has agreement with sponsor for thestudy.
5.1.2.4 Whether financial & Confidentiality agreement with Investigator and concerned laboratory (ies) in place.
5.1.2.5 In Investigator undertaking protocol title, Investigator's name, address, telephone no. of site, qualification, Name & address of laboratories, Name of Sub-Investigator etc. are in-compliance with New Drugs and Clinical Trial Rules, 2019.

5.1.2.6 Obtain list of all clinical trials performed by investigator. The list should have information such as

- Protocol Number
- Protocol Title
- Name of Sponsor/CRO
- Study date

5.1.2.7 Determine whether authority for conducting various Clinical trial related activities were delegated properly by the Investigator to the competent personnel so that investigator was able to supervise the study adequately. Obtain a list of personnel with delegated activity.

5.1.2.8 Documents following;

- Date of EC / IEC approval including initial review of protocol, amendment, ICD etc.
- Date of screening of first subject,
- Date of signing ICF by the first subject
- Date of first administration of IP,
- Date of last follow up of any subject,

5.1.2.9 List the name and address of facilities involved in laboratory test required by protocol. Verify accreditation status and adequacy of these facilities to perform the specified test,

5.1.2.10 Obtain a copy of site enrolment log,

5.1.2.11 Determine whether SOP's for various activity are established and documented,

5.1.3 <u>Study Protocol</u>

5.1.3.1 Determine if, there are any difference between protocol provided to CDSCO and the protocol in the Investigator'sfile with respect to following

- Version number and effective date
- Eligibility of Subject (Inclusion/ Exclusion Criteria)
- No of Subject
- Dosage
- Route of administration
- Frequency of dosage
- Randomisation & Blinding process

- Verify whether Investigator follow the protocol as approved
- Version number and EC approval of amendments

5.1.4 Subject record & Informed consent:

5.1.4.1 Review the Informed Consent Form (ICF) signed by the subjects. If the number of subjects at site is relatively small (e.g.20 or less) 100% of the ICF can be reviewed. Determine the following:

5.1.4.2 whether ICF have all the elements enlisted in Table 3 of Third Schedule of New Drugs and Clinical Trial Rules, 2019,

5.1.4.3 whether IC has been obtained from each subjects prior to participation of the subject in the study,

5.1.4.4 whether signature/thumb impression of the subjects have been affixed with date,

5.1.4.5 whether in case of illiterate subjects or illiterate representative of a subject, there are signature and detailsof an impartial witness,

5.1.4.6 Have witness/ signature been personally dated,

5.1.4.7 Have patient signature been personally dated?

5.1.4.8 Has the dated signature of the designated person foradministering informed consent (IC) been affixed?

5.1.4.9 Is the designated person for administering IC medically qualified?

5.1.4.10 If IC has been administered by a designated person who is not medically qualified, is there evidence that subject's queries of a medical nature were answered by a medicallyqualified person or the investigator?

5.1.4.11 Is the completed ICF signed and dated by the investigator?

5.1.5 Source Documents and Case Record Form

5.1.5.1 Verify condition, completeness, legibility, accessibility of the investigators source data file.

5.1.5.2 Determine whether subjects who were enrolled and /or completed the study meet inclusion and exclusion criteria;

5.1.5.3 Determine whether subject received the test drug withrespect to dose and frequency specified according to the protocol;

5.1.5.4 Determine whether safety/ efficacy end point data was collected and reported in accordance with the protocol;

5.1.5.5 Does medical record mentions subject ID/ name /hospital registration number / and indication that subjects areparticipating in a clinical trial

5.1.5.6 Whether all adverse events were reported in CRF;

5.1.5.7 Compare the source document with CRF and determine whether source data have been correctly transcribed in CRF;

5.1.5.8 Verify whether all SAE's have been reported to the sponsor and EC (within 24 hours);

5.1.5.9 Verify whether adequate medical care have been given tothe subject especially in the event of inter current illness, adverse events including abnormal lab parameters;

5.1.6 Ethics Committee (EC) / Independent EthicsCommittee (IEC):

5.1.6.1 Identify the name, address of the EC/ IEC in the approvalletter and compare it with that stated in investigators undertaking;

5.1.6.2 Verify if IEC approval letter mention study code, Protocoltitle and version number of the protocol, list of other documents reviewed, list of members present at the meeting, quorum of five members as specified in New Drugs and Clinical Trial Rules, 2019 satisfied, date, time , venue of the meeting, signature and date of member secretary / Chairman;

5.1.6.3 In case the site does not have an IEC, verify whether following are in place:

- Statement of the investigator / institution that approval granted by another IEC would be abided by & statement from the approving IEC that they would take responsibility for ongoing supervision of the site;
- Has the investigator submitted reports of all SAEsto the IEC and apprised the EC/IEC about the trial progress?

5.1.7 Sponsor:

Verify/ determine:

5.1.7.1 Whether a clinical trial Investigators agreement has beensigned for this study with the sponsor;

5.1.7.2 Whether investigator maintains copies of all reports submitted to the sponsor;

5.1.7.3 Whether all SAE are reported to sponsor within 24 hours;

5.1.7.4 Whether all CRFs were submitted to sponsor after completion of study;

5.1.7.5 Whether all dropouts and reasons thereof were reportedto sponsor;

5.1.7.6 The method and frequency of monitoring the progress ofthe study by the sponsor;

5.1.7.7 Whether a log of onsite monitoring visit is maintained atthe site;

5.1.8 Test Drug Accountability:

5.1.8.1 Review individual subject record to verify the correct dose administration with respect to dose, frequency, route of administration;

5.1.8.2 Determine whether unqualified/ unauthorised persons administered/dispensed the test drug

5.1.8.3 Determine whether adequate record of qty. of test drug received, dispensed/ destroyed/returned is maintained;

5.1.8.4 Determine whether storage condition/monitoring method are as per protocol/recommendation;

5.1.8.5 Whether trial medication are maintained under controlled access;

5.1.8.6 Have un-used trial medications been returned to the sponsor or disposed of according to protocol? In case of destruction at site, is there a certificate of destruction on file?

5.1.8.7 Are the drugs dispensing records being maintained properly?

5.1.8.8 Are the records for reconciliation of all IPs received from the sponsor maintained?

5.1.9 Record retention:

5.1.9.1 Is adequate space available at the site for retention of documents

5.1.9.2 Determine whether documents are maintained properly and for the period as specified and necessary measures have been taken for accidental and premature destruction;

5.1.9.3 Determine who maintained custody of the documents and means for assuring prompt action;

5.1.10 Concluding the Inspection:

The inspector should conclude the inspection with final discussion with the Investigator. During discussion the inspector should explain inspection finding. The inspector may also issuea list of observation at the conclusion of inspection.

5.2 Inspection of CRO/Sponsor

The inspection includes verification of essential documents to compare practice and procedure followed by the CRO/Sponsor to that committed in the clinical trial application and GCP guidelines published by DGHS, Govt. of India and New Drugs and Clinical Trial Rules, 2019 as well as other applicable regulatory requirements. Inspectionof CRO/Sponsor can be conducted without prior notice.

During inspection following aspects may be verified.

5.2.1 Documents submitted to CDSCO and regulatoryapprovals obtained.

5.2.1.1 Clinical Trial application and DCGI approval letter

5.2.1.2 Import license application (Form CT-16) and import licence obtained (Form CT-17) and application for grant of permission to manufacture formulation of unapproved active pharmaceutical ingredient (Form CT-12) & its permission (in Form CT-14). Application for grant of permission to manufacture unapproved active pharmaceutical ingredient in Form CT-13 and its permission in Form CT-15.

5.2.1.3 Export NOC for biological samples

5.2.1.4 List of investigators

5.2.1.5 Investigator Undertaking (as per Table 4 of Third Schedule of

New Drugs and Clinical Trial Rules, 2019)

5.2.1.6 Investigator's brochure

5.2.1.7 Protocol and Protocol amendments

5.2.1.8 Patient Information Sheet and Informed Consent Form

5.2.1.9 Case Record Form

5.2.1.10 Ethics Committee approval and notifications to CDSCO

5.2.1.11 Unexpected and Serious Adverse Event Reports

5.2.1.12 Study report

5.2.2 Organisation and personnel:

5.2.2.1 Company profile and overall structure,

5.2.2.2 Organization chart for management of the clinical trial, Structure and responsibilities for all activities involving investigational products. Departments, functions, and key personnel responsible for Protocol development, Investigator's brochure, Case Record Form, Informed consent form (ICF), translations and amendments, Selection of investigators, Regulatory approval, EthicsCommittee (EC) approval, Monitoring, Quality assurance Adverse Event (AE) Reporting, Data Management, Statistical Analysis, Electronic Records/Clinical Database,Clinical Supplies-Investigational Products (IP) Archival.

5.2.2.3 Identify and determine the personnel responsible for following

- Authority to review and approve study documents
- For final evaluations and decisions in the review of study
- For obtaining & reviewing adverse events and reporting to CDSCO
- Monitors/CRO(s) with job descriptions and qualifications
- Job description of key stake holders
- Verify clinical personnel training record
- To obtain a list of external service providers and contractors and documentation of the service they provide.
- Verify that SOPs followed for various responsibilities and clinical trial related activities.

5.2.3 Selection and monitoring of investigators

5.2.3.1 Obtain list of all investigators along with Investigator Undertaking, Signed Investigator Agreements

5.2.3.2 Criteria for selection of sites

5.2.3.3 Information provided to sites viz.

Informed consent form, Protocol, Reports/publications of previous trials, Investigator's Brochure, Product labelling, Training, All versions and updates etc.

5.2.3.4 Investigator’s non-compliance (If any)

- Deviations from CDSCO regulations
- Deviations form protocol
- How sponsor handles serious deviations from approved protocol or NDCT Rules, 2019 /Indian GCPGuidelines.

5.2.3.5 Steps for correction:

- Verify whether any investigators terminated? Review monitoring reports reported to CDSCO,
- Any Non-compliant investigator /terminated? Reasons?

5.2.3.6 Selection of monitor:

- List all monitors for study duration
- Selection criteria for monitors
- Job descriptions/responsibilities
- Qualifications
- Training Records and CVs
- Reporting structure
- Monitoring SOP Frequency, scope and process, Obtain a copy of SOP and check compliance, If noSOPs, interview monitors to check how monitoringwas done, Monitoring Plan, Monitoring Reports

5.2.3.7 Review the Pre trial and periodic trial visit report in respectof following content:

- Process of verifying compliance to protocol
- Process of verifying investigator responsibilities
- Ethics Committee Approvals Amendments/Re-approval Communication-progress reports/SAEs etc. Validity/Completeness
- Informed Consents, Confirmation of consent and process of consent.
- Use of IEC approved forms.
- Adequacy of consent documentation, completeness
- Which CRFs were compared to source docs? When and who verified CRFs against source data(hospital records, office charts, laboratory reports,etc.) at the study site. Form for data verification
- Check copy of any SOPs and guidelines for data verification
- Data correction handling, Compliance to MonitoringPlan, Frequency, Follow up etc.

5.2.4 Quality Assurance (QA):

5.2.4.1 Verify SOP for QA audits and operation of qualityassurance unit

5.2.4.2 Describe how the audit and monitoring are separated

5.2.4.3 Obtain list of audited trial

5.2.5 Adverse events reporting:

5.2.5.1 Verify sponsor's method for following up of adverse events and for dissemination of AE information to others Investigators:

5.2.5.2 Obtain list of SAE reported, Including death

5.2.5.3 Verify the timeline for reporting the SAE to CDSCO and other

Investigators /EC;

5.2.6 Data collection and handling

5.2.6.1 Study tabulations: List of all studies for marketing Authorization
5.2.6.2 Data Tabulations: Number of subjects. Verify if number inCT application same as marketing Authorization application (compare to CRFs submitted)
5.2.6.3 If any subjects not included in the marketing Authorization application? Why not included?
5.2.6.4 Review of SOPS to verify compliance to assure the integrity of safety and efficacy data collected from clinical investigators
5.2.6.5 Verify that the SOPs were followed and document any deviations
5.2.6.6 Deviations/Data queries resolutions
5.2.6.7 Statistical processes
5.2.6.8 Primary endpoints Compare the tabulations with CRFs and source documents
5.2.6.9 Record retention

5.2.7 Electronic Record and Clinical database:

5.2.7.1 Person responsible for designing and developing database
5.2.7.2 Can it be modified, or has it been modified? If so, by whom?
5.2.7.3 If the clinical investigator can modify it, how would the sponsor be aware of any changes?
5.2.7.4 Validation :Person responsible, Process, Documentationof process
5.2.7.5 Error logs maintained for errors in software and systems?
5.2.7.6 Do error logs identify corrections made?

5.2.8 Data collection:

Following aspects may be verified:

5.2.8.1 Responsibilities : Authorization to access the system, to enter data and to change data
5.2.8.2 Use of electronic data capture or data transcription from paper CRFs into an electronic record
5.2.8.3 Audit trail : to record Changes to electronic records, Person Responsible for the change and Time of the change
5.2.8.4 Process of data transmission from the clinical investigator to sponsor or CRO

5.2.9 Computerized System Security:

Following aspects may be verified:

5.2.9.1 Management of system access e.g. access privileges,

authorization/de-authorization procedures, physical access controls

5.2.9.2 Records of authorized personnel , Names, Titles. Description of their access privileges

5.2.9.3 Access methods e.g., identification code/passwordcombinations, tokens, biometric signature, electronic signatures, digital signatures

5.2.9.4 Data security in case of disasters, e.g., power failure

5.2.9.5 Contingency plans and backup files

5.2.9.6 Controls in place to prevent data from being altered, browsed, queried, or reported via external software applications that do not enter through the protective system software

5.2.10 Investigational Product(IP):

Following aspects may be verified:

5.2.10.1 Transferred data from central lab to sponsor

5.2.10.2 Integrity Procedures to ensure integrity of IP from manufacturing to receipt by the clinical investigator.

5.2.10.3 If IP met required release specifications by review of the Certificate of Analysis?

5.2.10.4 Storage of IP and the conditions of storage

5.2.10.5 Process of verification of IP integrity during shipment to investigator.

5.2.10.6 IP label

5.2.10.7 If the test article was recalled, withdrawn, or returned?

5.2.10.8 Accountability:

Following aspects may be verified:

- Names and addresses of clinical investigators receiving IP Shipment, date (s), quantity, batch number.
- Final disposition of the test article.
- Detailed audit if serious violations are suspected.
- Sufficient records to reconcile IP usage (compare the amount shipped to the investigators to the amount used and returned or disposed of).
- Check whether all unused or reusable supplies ofIP returned to the sponsor when either the investigator(S) discontinued or completed participation in the clinical investigation, or the investigation was terminated. If the test article was not returned to the sponsor, describe the method ofdisposition and determine if adequate records weremaintained.

6 Reporting of inspection

The Inspection should be documented in writing in both during and after inspection. After the inspection a narrative report containing details of inspection finding should be prepared and submitted to CDSCO (HQ).

	TITLE		Division Name	QMS Monitoring Division
	Procedure for Reporting Observations of GCP Inspection		Document No.	QMS-INS-009
			Revision No.	00
			Effective Date	
			Page No.	

Prepared By		Approved By		Authorized By	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 Purpose

To lay down a procedure for reporting observations of GCP inspection applicable for any Clinical trial site to be inspected.

2.0 Scope

This document is applicable to the concerned division of CDSCO to set a uniform procedure for reporting the observations of GCP inspections.

3.0 Responsibility

Inspector/ ADC (I)/ DDC(I) shall be responsible for implementation of the SOP.

The DDC(I) and ADC(I) of concerned division / Zone/ Sub-Zone shall be responsible for overall compliance of the SOP.

4.0 Accountability

Head of Zonal /Sub-Zonal, Division Head, DCG (I) or his designee

5.0 Procedure

5.1 This procedure takes into account the following procedures:

5.1.1 ***"Procedure for preparing for GCP inspections"*** (QMS-INS-007) which describes procedure for preparing GCP inspection.

5.1.2 ***"Procedure for conducting GCP inspections"*** (QMS-INS-008), which describes the steps involved on conducting GCP inspection.

5.2 Inspection Report

5.2.1 The Inspection report should reflect the inspection procedures as described in "Procedure for conducting GCP inspections (QMS-INS-008)" and as per the CDSCO guidance on clinical trial inspection.

5.2.2 The validity and reliability of the data submitted are evaluated in accordance with the scope of the inspection and issues identified in the request for the inspection. Also any other major or critical findings may be addressed.

5.2.3 The Inspection Report may be prepared as per the format enclosed as "Annexure-I". The contents of the report may be amended in accordance with the scope of the individual inspection.

5.2.4 Items inspected shall be extensively described in the Inspection Report and the findings may be classified as minor, major and critical (refer "Annexure II" for Grading of observations).

5.2.5 Inspecting team shall provide an overall conclusion/ remarks/ recommendations on the conduct of trial and whether trial is conducted in compliance with GCP and New Drugs and Clinical Trial Rules, 2019.

5.3 Follow-up on Inspection Report

5.3.1 Inspector shall submit the inspection report to concerned division Head of HQ/ Zone/ Sub-Zone. After review of the inspection report, concerned Zonal, Sub Zonal Head shall forward it to CDSCO-HQ with his/ her recommendations/ remarks for further necessary action.

5.3.2 CDSCO (HQ) shall scrutinize the inspection report and shall forward the observations/ deficiencies to Investigator/ Sponsor/ Ethics committee for compliance or explanation (show cause/clarification) with specified time lines, as the case may be.

5.3.3 Once compliance report received from Investigator/ Sponsor/ Ethics committee, the compliance shall be reviewed by concerned inspector of the division of HQ / Zone/ Sub-Zone and subsequently by concerned Zonal, Sub-Zonal Head and same shall be forwarded to CDSCO (HQ) along with recommendations.

5.3.4 Once the response to show cause/ clarification is submitted by Investigator/ Sponsor/ Ethics committee the same shall be examined by Central Licensing Authority for compliance and closure of the report. Based on review action deemed fit shall be taken by Central Licensing Authority (CDSCO-HQ) as per provisions of New Drugs and Clinical Trial Rules, 2019 till the closure of the inspection.

6.0 Annexure / Format

Annexure/Format No.	Title
Annexure I (QMS-INS-009/F01)	Inspection report format
Annexure II (QMS-INS-009/F02)	Grading of observations

7.0 References

Doc. No.	Title
1	The Drugs and Cosmetics Act, 1940.
2	New Drugs and Clinical Trial Rules, 2019
3	CDSCO Guidance on Clinical Trial Inspection
5	Good Clinical Practices (GCP) Guidelines
6	Guideline for Good Clinical Practice ICH E6(R2)

8.0 Abbreviation

Acronym	Full Form
CDSCO	Central Drugs Standard Control Organization
DCGI	Drugs Controller General, India
QMS	Quality Management System
DDC (I)	Deputy Drugs Controller, India
ADC (I)	Assistant Drugs Controller, India
DI	Drugs Inspector
GCP	Good Clinical practices
SOP	Standard Operating Procedure
INS	Inspection

9.0 Revision History

Revision No.	Reason(s) for Revision
00	New SOP

Annexure-I of QMS-INS-009

'Inspection report format'

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

INSPECTION REPORT FORMAT

A. Administrative Information.

S.No	Contents	Details	Remarks
1	**Investigational Medicinal Products**		
2	**Test product:**	Name, active ingredient	
3	**Reference product:**	Name, active ingredient,	
4	**Trial protocol:**	Protocol title along with protocol version number	
5	**Sponsor:**	Name and full address	
6	**Inspection Reference:**	The CDSCO inspection reference number(s)	
7	**Inspected site:**	Name and full address	
8	**Principal Investigator:**	Name, position	
9	**Inspection date(s):**	Date(s), month and year	
10	**Inspector(s):**	Name of the Drug Inspector(s) and other inspector(s) and name of the competent authority/ies	

B. Background and general information

1. **Reasons/cause for the inspection.**

2. **Reference texts**

List of the main legal references applicable within the context of this inspection

3. **List of persons involved in the trial and contacted during the inspection:**
   - Investigators, nurses and other key persons involved in the trial:
   - At the pharmacy
   - At the laboratory (ies), technical departments etc.
   - From the sponsor, i.e. monitor, auditor, QA responsible person.

C. Administrative aspects of the trial.

1. Application/notification to competent authority.

- Protocol, amendments and patient information and consent.
- Contacts during the trial, i.e. adverse event reporting, change of expiry date(s), reports.

2. Contacts with the independent ethics committee

- Approval of protocol, amendment(s) and patient information and consent.
- List of IEC members and members present at the meeting.
- Contacts during the trial,

3. Contacts with other committees, any other validation or authorization.

- Authorization by local ethics committee of the hospital
- Authorization by local authorities for particular studies or subjects included.

D. Trial documents

S.No	Contents	Observations	Remarks
1	Protocol, version, date of signatures.		
2	Amendments, dates, signatures		
3	Patient information and consent		

4	Secrecy statement/agreement		
5	Randomization list, code envelopes		
6	Investigator's Brochure		
7	Laboratories, technical departments, reference values Investigators file		
8	Quality management at the site		
9	Archiving of trial documents, including archiving of hospital files		
10	Other essential documents of the trial.		

E. Conduct of trial.

- Interview with principal investigator and key members of the trial team
- Trial co-ordination
- Trial subjects: examination, inclusion and follow up
- Assessment and follow up of safety parameters

F. Documentation and reporting of data

- Procedures, data and files examined
- Informed consent
- Inclusion, exclusion criteria and efficacy parameters
- Recording and reporting of adverse events/reactions
- Treatment discontinuation
- Compliance, protocol and treatment.

G. Accountability of medicinal products

1. At the pharmacy / investigators site

- Documentation
- Receipt and storage
- (Randomisation, decoding)
- Dispensing
- Returns from clinic / trial subjects
- Destruction/recovery by the sponsor

2. Administration to trial subjects

- Documentation
- Compliance
- Returns

H. Laboratories, technical departments.

1. Certification or accreditation
2. Established quality control (external/internal) or other validation
3. Methods used

4. Reference data
5. Labelling and storage of samples
6. Transportation and samples examined
7. Documentation and archiving

I. Monitoring and auditing

a. Monitoring

i. Monitoring visits and procedures used
ii. Actions taken by the monitor
iii. Monitor visit log

b. Auditing

i. Audit and audit certificate
ii. Actions taken subsequent to the audit(s)

J. Summary, discussion and conclusions.

1. Closing meeting
2. List of observations made during the inspection with a reference to the GCP requirement not met and grading.

3. Summary and evaluation of observations
4. GCP compliance

K. Dates and signature(s) of Drug inspector and other inspector(s)

L. Response from the sponsor and investigator

An evaluation by the inspectors of the response

Done By:_____ **Checked By:**_____

Date:_____ **Date:**_____

Stamp:

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhavan, ITO, Kotla Road, New Delhi -110002

GRADING OF OBSERVATIONS

Grading of inspection findings.

1. **Critical**: Conditions, practices or processes that **adversely affect** the rights, safety or well being of the subjects and/or the quality and integrity of data.

   Critical observations are considered totally unacceptable.

   Possible consequences: rejection of data and/or legal action required

   Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/ or absence of source documents. Fraud belongs to this group.

2. **Major**: Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

   Major observations are serious deficiencies and are direct violations of GCP principles.

   Possible consequences: data may be rejected and/or legal action required

   Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

3. **Minor**: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Possible consequences: Observations classified as minor, indicate the need for improvement of conditions, practices and processes.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

4. **Comments**: The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

	TITLE	Division Name	QMS Monitoring Division
	Procedure for Conducting Overseas Inspection	Document No.	QMS-INS-010
		Revision No.	0
		Effective Date	
		Page No.	964 of 1103

Prepared By		Approved By		Authorized By	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 Purpose

To lay down a procedure for Conducting Ov**e**rseas Inspection

2.0 Scope

This document is applicable for inspection of overseas sites for which applications are submitted for registration of products in India.

3.0 Responsibility:

3.1 DCGI shall be responsible for nominating the team members.

3.2 Head – inspection team shall be responsible for planning, preparing and conducting the inspection.

3.3 The DCGI shall be responsible for the overall compliance of the SOP.

4.0 Accountability

DCG (I) and his designee.

5.0 Procedure

5.1 The DCG (I) shall appoint the members of inspection team.

5.1.1 One inspector shall be appointed to head the team.

5.1.2 Subject experts from laboratories/scientific institution, specialized in subjects as per the requirements of inspection may join the team as necessary.

5.2 Head of the inspection team will arrange the inspection date with the manufacturer and carry out the required preparatory steps for a GMP inspection as per SOP No.QMS-INS-003.

5.3 Inspectors shall act as per the code of conduct for public servants of Government of India for the handling of confidential information. Inspectors shall neither carry with them written or printed materials relating to other plants, nor disclose any information relating to another company.

5.4 The inspector's task is not only to find-out deficiencies. They must answer any professional queries put to them, while as far as a possible abstain from offering advice.

5.5 Inspections shall start with an opening meeting session, at which the manufacturer shall present about the site & its products and the inspectors shall present and discuss the inspection program along with job assigned to each inspection team members.

5.5.1 The inspectors shall inform the manufacturer about the documents to be examined by them after the facility tour.

5.6 There will be a preliminary tour of the site to allow the inspectors to get a general orientation of the site. It can start from material flow, personnel flow or any other form that suits the inspectors for a quick overview.

5.7 Over the course of the inspection the inspectors shall review all procedures, production and laboratory records, validations and any other record or documentation relating to production and control of the production process.

5.8 The inspection shall also include detailed tours of all production facilities, laboratories, stores, technical systems and the plant's record and documentation process centre.

5.8.1 The following specific issues shall be investigated,

5.8.1.1 The suitability of the facility for its purpose, including the orderliness of its layout and cleanliness

5.8.1.2 The production equipment its calibration and cleanliness, preventive maintenance and daily maintenance records.

5.8.1.3 Whether production records are fully maintained and in real time.

5.8.1.4 Critical systems: HVAC, water, clean compressed air, sewage and drainage, any other relevant systems.

5.9 Inspectors shall talk to the technical staff/operators who actually carry out the work.

5.10 Samples may be taken during the inspection as per discretion of the inspectors.

5.11 Non-compliances observed during the inspection shall be discussed with the manufacturer before the final meeting for clarification of any issues raised during the inspection to avoid misunderstanding.

5.12 On overseas inspections, where plant procedures and records are written in a language the inspectors do not know, it is the responsibility of the manufacturer to provide the inspectors a translator and a copy of English translation.

5.13 The inspectors shall ask plant representatives to furnish them copies of documents that are required to be submitted for further examination or as evidence of a deficiency noted during inspection.

5.13.1 The plant shall mark and sign the photocopied documents according to its usual internal practice.

5.13.2 The documents shall be collected into a file, which the inspectors shall take with them at the end of the inspection.

5.13.3 The documents carried by the inspector during overseas inspection shall be maintained as record.

5.14 The inspection shall conclude with a final session between inspectors and plant representatives. There can be a daily wrap-up meeting till the completion of the inspection.

5.14.1 The final session shall cover (at least) —

5.14.1.1 A detailed listing of the observations and deficiencies found by the inspectors during the course of their inspection;

5.14.1.2 Should a major deficiency come to light during the course of the inspection, representing a grave risk to public health, the inspectors shall take immediate steps to eliminate the risk.

5.15 Post-inspection activities

5.15.1 The inspectors shall summarize their observations as an Inspection Report. The report shall be sent to the manufacturer within 45 working days.

5.15.2 The inspectors shall maintain regular oversight over improvements introduced by the manufacturer.

5.16 Approximately 25% of sites from the received application (overseas) shall be inspected, 10% of these shall be those manufacturers having limited market presence. Apart from these, manufacturers with 5 or more major deficiencies during the previous audits shall be inspected in addition to the above criteria.

6.0 Annexure / Format

Nil

7.0 References

Doc. No.	Title
1	WHO GMP guidelines

8.0 Abbreviation

Acronym	Full Form
DCGI	Drugs Controller General, India
QMS	Quality Management System
SOP	Standard Operating Procedure

HVAC	Heating, Ventilation and Air-conditioning

9.0 Revision History

Revision No.	Reason(s) for Revision
00	Created New SOP

	TITLE		Division Name	QMS Monitoring Division
	Procedure for Qualifying Inspector for inspection of Clinical Trial Sites for GCP compliance		Document No.	QMS-INS-011
			Revision No.	00
			Effective Date	
			Page No.	

Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1. **Purpose**

To lay down a procedure for qualifying inspectors for the inspection of Clinical Trial Sites for Good Clinical Practices compliance.

2. Scope

This document is applicable for qualifying inspection for the inspection of Clinical Trial Sites for Good Clinical Practices

3. Responsibility:

3.1 Zonal /Sub-Zone head/Head-Biological division shall be responsible for recommending the name of the qualified inspector.

3.2 DCG(I) or his designee shall be responsible to assess the performance of the inspectors recommended to qualify as qualified inspector.

4. Accountability

Zonal /Sub-Zone head/Head-Biological division and QMS division.

5. Procedure

5.1 Pre requisite for Qualified GCP Inspector.

5.1.1 Drugs Inspector who have not less than 18 months experience in the manufacture or testing of at least one of the substance specified in Schedule C of the Drugs & Cosmetics Rules, 1945 or who have gained experience of not less than three years in the inspection of firm manufacturing any of the substances specified in Schedule C of the Drugs & Cosmetics Rules, 1945 during the tenure of their services as drugs inspector.

5.1.2 Drugs Inspector who has undergone at least one training for GCP shall be considered for conducting GCP inspection initially up to six months under the supervision of an inspector who is having training and experience of GCP inspection for minimum five years. Subsequently, the inspector who has conducted at least one GCP inspection shall be considered.

5.2 Based on the criteria mentioned in point no 5.1, list of the qualified GCP inspectors shall be prepared and published on website.

5.3 The inspection report of all GCP inspectors shall be reviewed by the supervisory officer at the level of JDC(I)/DDC(I)/ADC(I) who is trained in GCP and conducted GCP inspection.

5.4 If the supervisory level officer has not conducted any GCP inspection in last 3 years or has not attended any refresher training then he/she shall not be qualified as supervisory officer for GCP inspection.

5.5 In case of other qualified inspectors, minimum two GCP inspections in three years shall be criteria for requalification as qualified GCP inspector.

6. Annexure / Format

Nil

7. References

Doc. No.	Title
1	The Drugs and Cosmetics Rules,1945.

2	NDCT Rules, 2019

8. Abbreviation

Acronym	Full Form
GCP	Good Clinical Practices
DCG (I)	Drugs Controller General India
JDC (I)	Joint Drugs Controller (India)
DDC (I)	Deputy Drugs Controller (India)
ADC (I)	Assistant Drugs Controller (India)
DI	Drugs Inspector
SOP	Standard Operating Procedure
QMS	QMS Monitoring Division

9. Revision History

Revision No.	Reason(s) for Revision
00	Created New SOP

INSPECTION OF BIO EQUIVALENCE STUDIES

Inspection of the facilities carrying out BA/BE study should be carried out as per the inspection format given below: -

BIOANALYTICAL AND STATISTICAL PART
Name and address of the Site
Date: Inspectors:

VISIT OF THE ALB AND GENERAL ORGANIZATION

General organization of the site

Activity

Ask for the presentation of the laboratory and its general activities. Try to determine in particular. Does the test facility management ensure that principles of GLP are complied with in its facility?

Personnel:

Ask for an organization chart of the laboratory and note the following points: Number and categories of people employed

- Description of the qualifications, training and experience (CVs) and job responsibilities of the personnel.
- The review of these points should be more through for the personnel who worked on the trial, especially the experience of the people in charge of the method validation and analysis of the samples for the trail.

Quality Assurance:

Ask for a description of the quality assurance system set up at the laboratory. Check the existence, availability, accessibility and validity of the SOP's (ask for the list of the operating procedures used for the study)

Quality Assurance System	YES	NO	NC/NA
Does a Quality Assurance system exist in the test facility to ensure that studies performed are in compliance with the Principles of Good Laboratory Practice?			
Are records of qualifications, training, experience and job description for each professional and technical individual maintained.			
2. Visit of Facilities			
General			

Is the test facility of suitable size, construction and locations to meet the requirements of the study and to minimize disturbance that would interfere with the validity of the study?			
Does the design of the test facility provide an adequate degree of separation of the different activities to assure the proper conduct of the study?			
Facilities for Handling Test and Reference Items			
To prevent contamination or mix-ups, are there separate rooms or areas for receipt and storage of the test and reference items.			
Archive Facilities			
Are archive facilities provided for the secure storage and retrieval of study plans, raw data, final reports and samples of test items?			
Does the archives design and conditions protect the contents from untimely deterioration?			
Waste Disposal			
Is the handling and disposal of wastes carried out in such a way that the integrity of studies is not jeopardized? (This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures).			
3. Apparatus, Materials and Reagents			
Is the apparatus (including validated computerized systems) used for the generation, storage, and retrieval of data, and for controlling environmental factors relevant to the study, suitably located and of appropriate design and adequate capacity?			
Is the apparatus used in a study periodically inspected, cleaned, maintained and calibrated according to SOP‘s?			
Are records of these activities maintained?			
Is calibration, where appropriate, traceable to national or international standards of measurement?			
Does the apparatus and materials used in a study interfere adversely with the test systems?			
Are chemicals, reagents and solutions labelled to indicate identity (with concentration if appropriate), expiry date and specific storage instructions?			
Is information concerning source, preparation date and stability available? (The expiry date may be extended on the basis of documented evaluation or analysis)?			
4. Test and Reference Items			
Are records maintained for test item and reference item characterization, date of receipt, expiry date, and quantities received and used in studies?			
Are handling, sampling and storage procedures identified in order that the homogencity and stability are assured to the degree possible and contamination or mix-up are precluded?			
Does storage container(s) carry identification information, expiry date, and specific storage instructions?			

5. Standard Operating Procedures			
Does the test facility have approved written SOP's intended to ensure the quality and integrity of the data generated by that test facility?			
Are revisions to SOPs approved by the test facility management?			
Does each separate test facility unit or area have current SOP's relevant to the activities being performed therein available immediately? (Published text books, analytical methods, articles and manuals may be used as supplements to these SOPs).			

STUDY SPECIFIC INSPECTION

	YES	NO	NC/NA
1. Organization and Quality assurance			
Was the quality assurance in place at the time of the study?			
Were all the raw data of the study, logbooks, chromatograms, etc available?			
Were the qualification, background and experience of the study director appropriate?			
Were the personnel involved in the study trained on GLP?			
Was a pre study meeting organized where adequate information was given to all staff involved in the trial? Were monitor and audit reports available?			
Was the washout period compatible with the half life of the analyte?			
Note: The wash out period should ideally be equal to or more than five half life's of the moieties to be measured.			
2. Apparatus, Materials and Reagent			
Identify individual items of apparatus or special equipment used in the study, and examine the calibration, maintenance and service records for these items.			
Review the records relating to the stability of the test substances, analyses of test substance and formulations.			
Was the certificate analysis (COA) of teh reference standard available?			
Was the purity of the reference standard mentioned on the COA used in the calculations?			
Was the duration of the storage of the solution supported by the stability study data?			
Were the number of Quality Control and number of calibration samples prepared, consistent with the number of results reported?			
3. Method Validation			

Was the bioanalytical method used to determine drug/metabolite well characterized, standardized, fully validated and documented to yield reliable results that can be satisfactorily interpreted?			
Note: The validation of the analytical method can be envisaged to consist of two distinct phases. The prestudy involves the validation of the method on biological matrix human plasma samples and spiked plasma samples. The study phase in which the validated bioanalytical method is applied to actual analysis of samples to confirm the stability, accuracy and precision.			
Pre Study: Does following characteristics of the bioanalytical method evaluated and documented to ensure the acceptability of the performance and reliability of analytical results.			
1) Stability: a) Does the stability of the drug and/or active metabolites in the biological matrix under the conditions of the experiment (including any period ofr which samples are stored before analyses) established. b) Was the freezing and thawing cycles repeated at least three times? c) Does the absence of absorption by sampling containers and stoppers established?			
2) **Specificity / Selectivity:** It is the ability of an analytical method to differentiate and quantify the analyte in the presence of other components in the sample.			
Was the data generated to demonstrate that assay does not suffer from interference by endogenous compounds, degradation products, other drug likely to be present in study samples, and metabolites of the drug (s) under study?			
3) Sensitivity: is the capacity of the test procedure to record small variations in concentration. a) Was the chosen analytical method capable of assaying the drug/metabolites over the expected concentration range? b) Was sensitivity ensured at the lower limit of quantification?			
4) Precision and Accuracy: Precision is the degree of reproducibility of individual assays and Accuracy is the degree to which the —true value of the concentration of drug is estimated by the assay. a) Were replicate analyses of samples containing known amounts of the analyte done for the determination of accuracy and precision? b) Were a minimum of three concentrations in the range of expected concentrations found used as recommended (low, medium, high) for the determination of accuracy and precision?			

Note: Where low is the vicinity of the lowest concentration to measured, high is a value in the vicinity of Cmax and medium is a suitable intermediate value.			
c) Was the intra assay precision determined at each concentration level around the mean not above 15% coefficient of variation (CV) except for the LLOQ, where it should not exceed 20% CV?			
d) Was the inter assay precision determined at each concentration level around the mean not above 20% CV?			
e) For accuracy, was the mean value within 15% of the theoretical value.			
5) Recovery: Is there a documentation of extraction recovery at high, medium and low concentrations.			
6) Range of Linearity: Does the quantitative relationship between concentration and response adequately characterized over the entire range of expected sample concentrations.			
Note: For linear relationships, a standard curve should be defined by at least five concentrations. If the concentration response function is non -linear, additional points would be necessary to define the non -linear portions of the curve. Extrapolation beyond the standard curve is not acceptable.			
7) Analytical system stability: Does the reproducibility of the standard curve monitored to assure that analytical system remains stable over the time course of the assay.			
Note: A minimal design would be to run analytical standards at the beginning and at end of the analytical run.			
Study Phase: In general, with acceptable variability as defined by validation data, the analysis of biological sample can be done by single determination without a need for a duplicate or replicate analysis. The need for duplicate analysis should be assessed on a case-by-case basis. A procedure should be developed that documents the reason for reanalysis.			
Was the standard curve generated for each analytical run for each analyte?			
Quality control samples:			
Was the quality control sample prepared and stored as recommended.			
Repeat analysis: a) Was the reason for repeat analysis stated.			

b) Was the criteria for repeat analysis determined prior to running the study and recorded in the protocol/Lab SOP.			
Were the source documents (chromatograms, validation data of analytical methods used and calibration status of the instruments) identified, dated and signed?			
STATISTICS			
Does appropriate statistical methods used for data analysis			
Does sample size adequate for the study			
Does statistical procedures specified in the protocol (The protocol should specify methods for handling drop outs and for identifying biologically implausible outliers)			
Does this procedure lead to a decision scheme which is symmetrical with respect to the two formulations			
Does calculated 90% confidence interval for AUC and Cmax fall with in the range of 80- 125%			
Does non parametric 90% confidence interval for Tmax lie within a clinically acceptable range			
FINAL REPORT			
General:			
Is the final report of the study prepared			
Is the final report signed and dated by study director and scientist involved in the study to indicate the acceptance of responsibility for the validity of the data			
Does the corrections and additions to final report in the form of amendments			
Does the amendment specify the reason for corrections or additions			
Does these amendments signed and dated by the study director			
Content of the Final Report:			
Does final report include (as a minimum) the following sections,:			
A descriptive title Table of contents Name and address of the sponsor Name and address of any test facilities and test sites involved			

Name, credential and address of the responsible investigators and their signatures Experimental starting and completion dates. Description of study design Identification of test and reference item Report of protocol deviations Demography data of subjects Details of dropout and withdrawal Results An evaluation o and discussion of the results and where appropriate conclusions Archival of data			

INSPECTION OF BIOEQUIVALENCE STUDIES

CLINICAL PART
Name and address of the site
Date: Inspectors:

INSPECTION PROCEDURE CLINICAL PART

1. General organization of the site

Ask for an organization chart of the company and note the following points: - Number of staff including Doctors (Physician fulltime/On call), (Pharmacist and Nurse, Nursing assistant and Lab. Tech - Description of the qualifications, training and experience of the personnel (CVs) - Training program and records. Check the existence, availability, accessibility and validity of the standard operating procedures. Ask for a list of the standard operating procedures used for the trial.

2. Quality Assurance

Ask for a organization chart of the organization and note the following points: - Number and categories of people employed.

- Description of the qualifications, training and experience of the personnel (CVs)
- Training program and records.

Quality Assurance System	YES	NO	NO/NA
Is a quality assurance system established?			
Are records of training and assessment of knowledge of GCP maintained?			
Is there a list of sample signatures of authorized personnel?			
Facility			
Is DCGI operating license available?			
Was adequate space and facility available to house at least 16 volunteers			
Was adequate are available for dining Was adequate are available for recreation			
Was adequate are available for sleeping Any hospital attached in case of emergency?			
Additional space and facility should be provided for the following			
Office and administrative function			
Sample collection and storage			
Instrumental Laboratory			
Documentation archival room			
Facility for cleaning, washing and toilets			
Adequate resources:- Potential for recruiting the required number of suitable subjects within the agreed recruitment period?			
Adequate number of qualified staff for the foreseen duration of the trial to conduct the trial properly and safely			
Were qualification, readiness to use and maintenance of blood pressure measure device, X-ray devices and ECG recorder satisfactory?			
Was the space and number of beds suitable for the studies conducted?			
Was the blood sampling area designed and equipped to avoid mix ups and confusion between subjects and samples.			
Were the different watches synchronized?			
Intensive Care Unit			
Were the storage conditions appropriate and the drugs within their expiry dates?			
Was the readiness to use and maintenance of oxygen supply device appropriate?			
Was the readiness to use and maintenance of defibrillators and electronic monitoring system adequate?			
Clinical Laboratory			
Was qualification, readiness to use and maintenance of the equipment used adequate?			
Were expiry dates of reagents monitored			
Was the use and frequency of quality control adequate?			
Were the final results signed by qualified persons (not a technician)			
Blood processing area			

Was the system set up to avoid any confusion between samples (preparation and labelling of sampling tubes, distribution and handling the tubes)			
Was the qualification, readiness to use and maintenance of the centrifuges appropriate?			
Was the qualification, readiness to use and maintenance of deep freezers appropriate?			
Was there an alarm in case of failure and SOP on intervention in case of alarm?			
Were records of temperatures available?			
Pharmacy			
Were premises, storage conditions (segregation of products, temperature and humidity) adequate?			
Were records of shipments, delivery, receipt storage, retain, destruction and possibly returns kept and available?			
Archiving			
Was access to archive storage areas controlled, restricted and recorded?			
Were the records kept under conditions that will prevent deterioration including protection from fire?			
Are the records are maintained for at least 2 year after the expiration date of the batch			
Documentation of file movements			
Did quality systems exist?			
Are the standard operating procedures available?			
3. Study specific inspection			
Responsibilities			
Did the contract describe any transfer of responsibility?			
Up-to-date curriculum vitae of investigators /staff			
A list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties?			
Were the responsibilities in all areas described or allocated prior to initiation of study			
Was there any insurance cover for the study?			
Protocol			
Was the version number of protocol used in the study versus the version number of the approved protocol identical?			
Protection of trial subjects			
Was the independence of Ethic Committee satisfactory?			
Was the time taken for the review of the study protocol and related documentation sufficient?			
Consent form			
Were informed consent forms signed by all subjects ?			
Was the language and level of complexity adequate for the volunteers?			
Was the information on compensation and insurance in case injury provided and understandable ?			

Was the information on quality of blood taken and sampling method (multi-puncture or canula) given?			
Responsibilities of the investigator			
Was a CV of principal investigator available and up to date?			
Was given to all staff involved in the trial?			
Were the signatures of the staff involved in the study recorded?			
Responsibilities of sponsor and monitor			
Was the study monitored?			
Was the monitor present at least 3 times during the study (site assessment prior to study, staff education, during study and end of study)?			
Was the monitor independent from the Quality Assurance department?			
Were the monitoring reports and audit reports available and documented before release of the final study report?			
Record keeping and Handling of Data			
Were case report forms used?			
Was each page of the case report identified for the subject and study?			
Were the lab results, ECG, vital signs before and after administration (temperature, Blood pressure, X-rays, consistent and coherent?			
Was the data reported on the CRF derived from source documents are consistent with the source documents?			
Were all corrections to CRFs and to raw data made in a way which does not obscure the original entry (with reason if not obvious and initials of investigator)?			
Was the selection of the subjects based on the inclusion and exclusion criteria documented?			
When deviations occurred, were they explained in accordance with the protocol?			
Was the dosing procedure described in an SOP?			
Were records of dosing (Administration) including mouth check and the date and time of dosing for each subject available as per SOP?			
Did the documentation of dosing confirm that each subject received the product dispensed for that subject and that for each product received the identity was checked?			
Was, after check of the records, the dosing done according to the randomization code?			
Were standardized meals, snacks and drinks planned and provided to study subjects in accordance with the clinical trial protocol?			
Was the clinical report prepared?			
Was the data reported in the clinical report derived from source documents?			
Biological Samples Handling and Accountability			
Were there documented procedures for the collection, preparation, transport and storage of samples?			
Was the labelling of collected samples clear to ensure correct identification and traceability of each sample?			

Was the equipment used for taking the samples sterile, within its shelf-life and for single use?			
Were the people in charge of blood sampling appropriately qualified and experienced?			
Were the actual time of sampling documented?			
Was the following details are explained in the protocol, Anticoagulant Centrifugation: speed, duration, temperature			
Was there a record of the storage and retrieval of the samples			
Was the storage and retrieval procedure defined in an SOP?			
Were the packages, boxes or containers adequately identified?			
Were the storage conditions (temperature, etc.) monitored and recorded?			
Were the refrigerators and freezers equipped with a temperature recording system?			
Pharmaceutical Products Handling and Accountability			
Were all study medication kept in a securely locked area accessible only to authorized persons?			
Were records of the products used available as dosage form, strength, batch number, expiry date, certificate of analysis, other coding that identifies the specific characteristic of the product tested?			
Was the shipping letter of the test and reference products from the sponsor to the investigator available?			
Were the records of delivery and receipt of the test and comparator products available?			
Was the investigational product stored properly?			
Were the investigational products labelled for clinical research purpose only?			
Was the dispensing done according to the randomization code			
Archive facilities			
Was access to archive storage areas controlled, restricted and recorded?			
Were the records kept under conditions that will prevent deterioration including protection from fire?			
Documentation of file movements			
Inspection preliminary conclusion based on the number of findings			
Critical finding (s)			
Major finding (s)			
Other finding (s)			
Conclusion			
Are additional information requested as a follow up of the inspection to reach a conclusion?			
Area additional information requested as a follow up of the assessment to reach a conclusion?			
The study was found done at an acceptable level of compliance with GCP?			

Chapter-16

SOPs on Matter related to administrative Work

CENTRAL DRUGS STANDARD CONTROL ORGANISATION
(Directorate General of Health Services)
Ministry of Health & Family Welfare

		TITLE		Division Name	Adminsitration
		Maintenance of Service records/leave records of Gazetted and Non-Gazetted		Document No.	SOP/003
				Revision No.	00
				Effective Date	
				Page No.	
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 OBJECTIVE:

To lay down the procedure for maintenance of service records in service book of Gazetted and Non-Gazetted Staff as per FRs, SRs & GFRs rules.

2.0 **SCOPE:**

This SOP is applicable to all staff (permanent or temporary) at CDSCO.

3.0 RESPONSIBILITIES:

3.1. Head Clerk who supervises all the activities of administrative work.

4.0 DEFINITION(S):

Service Book: Service book is a record of every event occurring in the official life of a government servant. It has to be maintained for every government servant holding a permanent or a temporary post except for those who are not likely to be in service for more than one year or those holding non pensionable service (SRs 196 and 197). Service book in form MSO (T)-27 (Revised) must be opened for all government servants from the date of entry into service and is to be maintained till his service is ceased.

5.0 PROCEDURE:

5.1 After receiving any order regarding promotion, confirmation, suspension, reduction in rank, withholding of increments, recovery loss, leave without pay, service break, award of President Police Medal/Indian Police Medal etc. for any Gazetted/ Non-Gazetted Staff, the said information to be updated in the service book of the individual and a copy of the order is attached with the service book.

5.2 All the leave details with respect to Earned & Medical should be recorded immediately and verified through HOO half yearly

5.3 Any increment in the salary is to be updated in the service book of the individual and a copy of the order is attached with the service book.

5.4 Any LTC (Leave Travel Concession) taken from home to visiting place is to be updated in the service book of the individual.

5.5 Any encashment of earn leave is to be updated in the service book of the individual

5.6 Any conformation, promotion or suspension in the service period of an individual is to be updated in the service book of the individual.

5.7 Periodic inspection of service book

6.0 ABBREVIATION(S)

CDSCO – Central Drug Standard Control Organisation

HOO – Head of the Office

HC – Head Clerk

CENTRAL DRUGS STANDARD CONTROL ORGANISATION
(Directorate General of Health Services)
Ministry of Health & Family Welfare

		TITLE		Division Name	Administration
		Matters related to promotion of Grade C & D posts		Document No.	SOP/004
				Revision No.	00
				Effective Date	
				Page No.	
Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

1.0 OBJECTIVE:

To lay down the procedure for matters related to promotion of posts.

2.0 SCOPE:

This SOP is applicable to all staff (permanent or temporary) at CDSCO

3.0 RESPONSIBILITIES:

3.1 Head Clerk who supervises all the activities of administrative work.

3.2 Departmental Promotion Committee

3.3 Head of the Office

4.0 DEFINITION(S):

Promotion: Change of designation to higher position from lower position.

5.0 PROCEDURE:

5.1 FOR PROMOTION OF POSTS

5.1.1 Promotion is based on the principles of "Selection cum Seniority" as specified in the respective RR. The DPC should assess the suitability of the employees for promotion on the basis of their Service Records

and with particular reference to the CRs for last five preceding years irrespective of the qualifying service prescribed in the Service/Recruitment Rules.

5.1.2 A noting is prepared by HC for the approval for promotion of posts from HOO.

5.1.3 After authorization by HOO, DPC meeting is conducted where its members as specified in the respective RR fix the promotion criteria and decide that the recommended person is fit or unfit for the promotion.

5.1.4 A clearance from the Vigilance by HOO/Department should also be obtained before making actual promotion of officer approved by DPC to ensure that no disciplinary proceedings are pending against the officer concerned.

5.1.5 The panel for promotion drawn up by DPC for 'selection' posts would normally be valid for one year. It should cease to be in force on the expiry of a period of one year or when a fresh panel is prepared, whichever is earlier.

5.1.6 After above procedure, order for promotion and fixation of pay may be issued by HOO.

6.0 ABBREVIATION(S)

CDSCO – Central Drug Standard Control Organization

HOO – Head of the Office

HC – Head Clerk

DPC - Departmental Promotion Committee

RR – Recruitment Rules

7.0 REFERENCES:

1. Department of Personnel and Training, OM No. 22011/4/91-Estt.(A) dated 14. 9.1992

2. Administrative Services (Recruitment & Promotion) rules, 1991

Chapter 17

PSUR/PVPI/AEFI Related Work

File No. : PSUR-11011(15)/2/2024-eoffice

भारत सरकार / Government of India

स्वास्थ्य एवं परिवार कल्याण मंत्रालय /Ministry of Health and Family Welfare

स्वास्थ्य सेवा महानिदेशालय / Directorate General of Health Services

केंद्रीय औषधि मानक नियंत्रण संगठन / Central Drugs Standard Control Organization

FDA Bhawan, New Delhi
Date:

ORDER

07 AUG 2024

Subject: The Guidance for Industry on Pharmacovigilance Requirements for Human Vaccine (Version 2.0).

The "Guidance for industry on Pharmacovigilance requirements for Biological Products" earlier prepared and published in 2012, and was revised in 2017. The said document is now further revised in consultation with the AEFI Secretariat and IPC-PVPI as per New Drugs and Clinical Trial Rules, 2019 and introduction of Signal Review Panel for Human Vaccines by AEFI Secretariat, (MoHFW) and online submission of Periodic Safety Update Reports through SUGAM Portal as "**Guidance for Industry on Pharmacovigilance requirements for Human Vaccines, Version 2.0**". A draft was published to solicit suggestions/comments/objections from the stakeholders through CDSCO website on 29.05.2024. Now, the said guidance document is updated after consultation with the AEFI Secretariat and IPC-PVPI and it is published after considering the stakeholder's suggestions/comments/objections.

Dr. Rajeev Singh Raghuvanshi
Drugs Controller General (India)

PREFACE

This is in consonance with the objective of the Drugs & Cosmetics Act 1940 and Rules made thereunder and New Drugs and Clinical Trials Rules 2019 and other functions of CDSCO wherever applicable. These guidelines are intended for the guidance of the Marketing Authorization Holders (MAHs) i.e. manufacturers and importers of Human Vaccines. The procedure set out to facilitate the industry to submit the documentsas per the requirements of Drugs and Cosmetics Act 1940 and Rules 1945. Guidance documents may be amended from time to time as per requirements after obtaining necessary approval from the Competent Authority.

FOREWORD

The Central Drugs Standard Control Organization (CDSCO), being the apex regulatory authority for approval of drugs in India, is committed to safeguard and enhance the Public Health by assuring the safety, efficacy and quality of drugs including vaccines, cosmetics and medical devices.

India has extensive Pharmacovigilance activities for vaccines as part of post licensure submissions in form of PSURs, PMS studies, AEFI case reports and Individual Case Safety Reports (ICSRs). The present document is developed to provide the guidance to all the stakeholders including the MAH on the coordinated activities of the various departments within the Ministry of Health & Family Welfare to work together and enhance the pharmacovigilance of vaccines.

The present document is developed to provide the guidance to all the stakeholders including the MAHs about Vaccine Safety Monitoring, Audits and Inspection; Risk Management Plan (RMP) wherever applicable and Periodic submission of Risk Benefit Evaluation Report i.e., PSUR to the Licensing Authority.

The guidance document has been prepared in line with the Drugs & Cosmetics Act 1940 and Rules made thereunder and NDCT Rules, 2019 to provide guidance for the MAH to perform specific safety study throughout the product life cycle and to define the roles and responsibilities of all the stakeholders namely CDSCO, PvPI at IPC, Immunization Division, MAH, private and public practitioners and outlines the Risk Minimization Action Plan. This could provide guidance to the manufacturers and importers of vaccines in the country to strengthen their AE/AEFI Pharmacovigilance system to ensure patient safety.

List of Abbreviations

Abbreviations	Full Forms
AE	Adverse Event
ADR	Adverse Drug Reaction
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
CAPA	Corrective And Preventive Actions
CDL	Central Drugs Laboratory
CDSCO	Central Drugs Standard Control Organization
CIOMS	Council for International Organizations of Medical Sciences
CoWIN	Covid Vaccine Intelligence Network
CRF	Case Report Form
CLA	Central Licensing Authority
DCG (I)	Drugs Controller General (India)
DIO	District Immunization Officer
DLP	Data Lock Point
DOV	Date of Vaccination
FCIF	Final Case Investigation Form
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professionals
ICSR	Individual Case Safety Reports
IPC	Indian Pharmacopoeia Commission
ITSU	Immunization Technical Support Unit
MA	Marketing Authorization
MAH	Marketing Authorization Holder

MoHFW	Ministry of Health & Family Welfare
NCC	National Coordination Centre
NRA	National Regulatory Authority
NTAGI	National Technical Action Group on Immunization
PIL	Patient Information Leaflet
PBRER	Periodic Benefit Risk Evaluation Report
PCIF	Preliminary Case Investigation Form
PI	Prescribing Information
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PVMF	Pharmacovigilance System Master File
PVOIC	Pharmacovigilance Officer-In charge
PvPI	Pharmacovigilance Programme of India
QA	Quality Assurance
SAE	Serious Adverse Events
SEPIO	State EPI Officer
SIO	State Immunization Officer
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPEAC/CEPI	Safety Platform for Emergency Vaccines/ Epidemic Preparedness Innovations
UIP	Universal Immunization Programme

1. INTRODUCTION

Over the last three decades, India has become a vibrant hub of vaccine manufacturing units with state-of-the-art facilities at par with the International manufacturing standards. India can now boast of producing safe, effective and affordable vaccine products which safeguard millions of children at domestic and International level. This responsibility warrants additional efforts of constant vigilance of vaccine products moving in the market.

The pre-market mandatory clinical trial has little scope to assess the inherent risks associated with the nature of antigens /excipients in formulations or that cropping up due to specific manufacturing process and raw materials used.

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, post marketing surveillance which may be passive or stimulating have major role to assess the actual safety aspects of the vaccine product. Safety datacollection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

This guidance document focuses on pharmacovigilance activities on a vaccine product circulating in the market throughout its life cycle post licensure period. This guidance uses the term pharmacovigilance to mean all scientific and data gathering activities relating to the detection, assessment, understanding and prevention of adverse events. As per WHO, Vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization. The primary goal of vaccine pharmacovigilance is early detection, assessment, timely response to adverse events, signal management and continuous benefit risk assessment. In this guidance document, safety signal refers to a concern about a new risk or a new aspect of an already known risk or excess of adverse events compared to what would be expected to be associated with a product's use.

Signals can be identified from post marketing data and other sources, such as preclinical data and events associated with other products in the same pharmacological class.

Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

1.1 OBJECTIVE

This document intends to be an aid for the MAHs and for other allied stakeholders who play active role in launching, introduction, distribution and bringing the vaccine products to end users, to implement an effective PV System for ensuring patient safety. The main focus of this guideline is to identify the risks, formulate the risk profile of a vaccine and its administration programme, design of appropriate pharmacovigilance plan to mitigate such risks and to explore the missing critical information which did not emerge during pre- market phase-I/II/III trials and therefore safety profile had not been established.

1.2 BACKGROUND

The decision to approve a vaccine is based on its having a satisfactory balanceof benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the vaccine can change over time through expanded use in terms of subject characteristics and the number of patients exposed. In particular, during the early post marketing period, the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe.

Once a vaccine is marketed, new information might emerge, which may have an impact on the risks/benefits ratio of the product. Evaluation of this information should be a continuous process in consultation with regulatory authorities. Detailed evaluation of the information generated through pharmacovigilance activities is important for all vaccine products to ensure their safe use. The risk- benefit balance can be improved by reducing risks to patients through effective pharmacovigilance system that can enable information feedback to the users of medicines in a timely manner.

1.3 RATIONALE

This document rationally places guidance that all MAHs of Human vaccines (importers and manufacturers) should establish and implement an appropriate effective pharmacovigilance system with adequate number of qualified, trained, experienced manpower to collect, collate and analyze all AEFI (minor, severe and serious) as per Fifth Schedule of New Drugsand Clinical Trials Rules, 2019. This Pharmacovigilance system within the company should conduct decisive causality assessment (AEFI Surveillance and Response — Operational Guidelines 2024) of the collated AEFI cases, after due investigation and prepare case closure report. In a comprehensive PSUR, all such information shall have to be placed as per the norms stipulated in Fifth Schedule of New Drugs and Clinical Trials Rules, 2019 and submitted to the Licensing Authority i.e. DCG (I) in CDSCO (HQ) within the stipulated time period. After review of the submitted PSUR, CDSCO shall convene the meeting of PSURcommittee within a reasonable time period and give opportunities to the concerned MAHs to present their case and PSUR in general. Based on the recommendation of the PSUR committee the vaccine Licensing Authority i.e. DCG (I) will take appropriate regulatory action in accordance with Drugs & Cosmetics Act 1940 and Rules 1945 made thereunder, so as to monitor the safety and effectiveness of human vaccine in the market so as to safeguard the public health. MAHs must have a Pharmacovigilance system in place that enhances the overall quality of the receipt, processing and reporting of AE/ AEFI while ensuring that accurate and complete information with respect to patient safety is provided to CDSCO.

1.4 SCOPE

This document has been framed in compliance with the provisions made under Fifth Schedule of New Drugs and Clinical Trials Rules 2019, Schedule M of Drugs & Cosmetics Act 1940 and Good Clinical Practices (GCP) Guidelines of India, AEFI Surveillance and response operational Guidelines to provide guidance to MAHs (Importers and Manufacturers of Human Vaccine) of India to establish their Pharmacovigilance System for collection,detection, assessment, monitoring, and prevention all AE/ AEFI cases pertaining to vaccine products across the domestic and export market, after due investigation & causality assessment at their end and collate all such cases in PSUR for periodic reporting to the Licensing Authority i.e. DCG(I) in CDSCO. This document does not include all other New Drugs and animal vaccine moving in the market.

This document is designed to facilitate compliance by the industry and to enhance consistency in the implementation of the regulatory requirements regarding Good Pharmacovigilance Practices.

This document provides adequate information in a systematic manner for reporting serious adverse event or adverse event following immunization when the product is in the market and would enable the systematic sharing of information between CDSCO, Pharmacovigilance Programme of India (PvPI) and the Universal Immunization Program (UIP), Ministry of Health and Family Welfare.

The roles and responsibilities of the CDSCO are as per the Drugs and Cosmetics Act, 1940 and Rules made thereunder.

In case, the Pharmacovigilance Programme of India receives AEFI information the same shall be shared with the AEFI Secretariat under the Immunization Division (MoHFW). The AEFI Secretariat will process the AEFI cases for causality assessment and signal detection and management and present the data to the National AEFI Committee (for approval of results of causality assessment) and the Signal Review Panel (for signalassessment) and further recommendations to CDSCO for regulatory actions. The Licensing Authority may also advise the MAH to conduct Phase IV trial in case of demonstration of product safety,

efficacy and dose definitions. These trials may not be considered necessary at the time of New Drug approval but may berequired by the Licensing Authority for optimizing the product use. They may be of any type but should have valid scientific objectives, for example, epidemiological studies, etc.
The Immunization Division under Ministry of Health and Family Welfare collects information on adverse event related to Universal Immunization Program (UIP) vaccines on a regular basis through the AEFI surveillance system.Information on serious adverse events is collected in the Case Reporting Form (CRF) and details of the investigation of the reported event are collected in the Case Investigation Form (CIF) by the DIO with all supporting documents such hospital records, post mortem reports, etc. These are then shared with the SIO who presents it to the state AEFI committee which assigns the causality. In addition to the state AEFI committee, causality assessments are also done at the national level by AEFI Secretariat. The causality assessment results inthe form of a linelist are shared with the CDSCO for further analysis and necessary regulatory actions.
The AEFI Secretariat will share line-listing in excel (.xls) format with CDSCO for deaths and clusters on a weekly basis and all serious and severe cases on a monthly basis. Limited line list will be in excel format and will have state, age, sex, Date of Vaccination (DOV), antigens administered, manufacturing details (name, batch number and expiry date) and reason for reporting. CDSCO will share linelist details for vaccines relevant to the particular manufacturer with instructions that these are being shared with the MAH for internal review and not for investigations in the field.
In tandem is the process of signal management for vaccines being done at the AEFI Secretariat. A Signal Review Panel for vaccines assesses and reviews the detailed signal assessments at regular interval and the recommendations are then forwarded through the proper channel to CDSCO for further dissemination to MAHs. A detailed process is outlined in further sections.

2. ROLES AND RESPONSIBILITIES OF AUTHORITIES

2.1 Central Drugs Standard Control Organization

The Central Drugs Standard Control Organization (CDSCO) under DGHS in Ministry of Health and Family Welfare (Govt. of India) acts as the nodal agency (NRA) for regulation of "Drugs" as defined in section 3(b) (i-iv) in Drugs & Cosmetics Act 1940 to ensure the Quality, safety, efficacy of all human vaccines (defined as Drugs). CDSCO is empowered under Drugs & Cosmetics Act 1940to grant permission, licenses for marketing within the country. CDSCO is also mandated by Ministry of Health and Family Welfare, Govt. of India, to conduct a nation-wide pharmacovigilance programme in coordination with the Indian Pharmacopoeia Commission (IPC) located at Ghaziabad which is the National Coordination Centre (NCC) of many ADR monitoring centers established in various medical colleges across the country.
The Roles and Responsibilities of CDSCO are as per the Drugs and Cosmetics Act 1940 and Rules made thereunder. CDSCO is responsible to take appropriate regulatory decision and actions on the basis of recommendations of NCC-PvPI at IPC, Ghaziabad and AEFI programme of Immunization Division of Ministry of Health and Family Welfare, New Delhi.
CDSCO is also responsible to take regulatory decisions on the basis of recommendations shared by Signal Review Panel of Vaccines where-in a detailed analysis of the PMS, PSUR, AEFI data is done by expert committee. CDSCO (HQ) then reviews the recommendations and shares them with MAHs for necessary actions.
The regulatory recommendations are disseminated to MAHs through proper channel by CDSCO. As a part of the condition of the Marketing Authorization, the MAH is also required to submit PMS/PSUR after licensure of the product.The PSURs is to be submitted every six months for first two years of the approval/ Marketing and annually for subsequent years, till the product is categorized as 'New Drug'. The Licensing Authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. PSUR furnished by the Importers/Manufacturers of vaccines holding

marketing authorization is deliberated in PSUR Expert Committee Meetings conducted by CDSCO. The PSUR data is also considered while reviewing the UIP vaccine safety database for signals by the AEFI Secretariat.
The Licensing Authority may also advise the MAH to conduct Phase IV trials which go beyond the prior demonstration of product safety, efficacy and dose definitions. These trials may not be considered necessary at the time of new vaccine approval but may be required by the Licensing Authority for optimizing the vaccine's use. They may be of any type but should have valid scientific objectives.

2.2 Pharmacovigilance Programme of India (PvPI), Indian Pharmacopoeia Commission (IPC)

The Central Drugs Standard Control Organization (CDSCO), Directorate Generalof Health Services under the aegis of Ministry of Health & Family Welfare, Government of India has initiated a nation-wide Pharmacovigilance programme for protecting the health of the patients by assuring drug safety. Later the MoHFW recasted these programmes on 15th April 2011 vide an order number X.11035/7/2011-DFQC shifting the National Coordination Centre from AIIMS, New Delhi to IPC, Ghaziabad. The programme is coordinated by the IndianPharmacopoeia Commission, Ghaziabad as the National Coordination Centre (NCC). The center operates under the supervision of a Steering Committee. Indian Pharmacopeia Commission, Ghaziabad is an autonomous organization under the MoHFW, having mandate for preparation of standards for all drugs including bulk antigens and vaccine products, publication of Indian Pharmacopoeia (IP) with monographs for all drugs including vaccines, publication of National Formulary of India (NFI), preservation of reference standards for Drugs, however, the vaccine reference standards on behalf of IPC are maintained by CDL (Kasauli). IPC is also the National Coordination Centrefor all ADR Monitoring Centers across the country to collect, collate AE/ADRs for all drugs, including vaccines. Major roles and responsibilities of PvPI at IPC includes development and implementation of pharmacovigilance system in India, enrolment of all hospitals/medical colleges in the program covering north, south, east and west ofIndia, encouraging HCPs in reporting of adverse reaction to drugs, vaccines, medical devices and biological products along with collection of case reports and data in the suspected adverse drug reaction reporting form.
The long-term goal of PvPI at IPC includes developing and implementing electronic reporting system (e-reporting), to develop reporting culture amongst HCPs. The adverse events following vaccinations, which are reported from the AMCs, are shared with the AEFI Secretariat, for examination and after validation for signal assessments. The AEFI Secretariat has established a Signal ReviewPanel for vaccines which share the recommendations and updates to the National AEFI Committee and CDSCO for regulatory actions.

2.2.1 Role of PvPI at IPC

- To monitor Adverse Drug Reactions (ADRs) in Indian population.
- To create awareness amongst health care professionals about theimportance of ADR reporting in India.
- To monitor benefit-risk profile of medicines
- Generate independent, evidence based recommendations on thesafety of medicines.
- Support the CDSCO for formulating safety related regulatorydecisions for medicine.
- Communicate findings with all key stakeholders.

- ❖ To share the Adverse Reactions reported for UIP vaccines to AEFI Secretariat through CDSCO for data analysis and discussion in the Signal Review Panel of vaccines (MoHFW) for appropriate action.

2.3 AEFI Secretariat, Immunization Division of Ministry Of Health and Family Welfare

Immunization is one of the most cost effective public health interventions resultingin reduction of morbidity and mortality of children. Under the Universal Immunization Programme (UIP), Govt. of India is providing vaccination to prevent eleven vaccine preventable diseases (VPDs) namely, Diphtheria, Pertussis,Tetanus, Polio, Measles, Hepatitis B and Tuberculosis.

IMMUNIZATION SCHEDULE IN UNIVERSAL IMMUNIZATION PROGRAM

Vaccine	VPD	Due Age	Max age
BCG	Tuberculosis	At birth	till one year of age
Hepatitis B - Birth dose	Hepatitis B	At birth	within 24 hours
OPV-0	Polio	At birth	within the first 15 days
OPV 1, 2 & 3		At 6 weeks, 10 weeks & 14 weeks	till 5 years of age
Pentavalent 1, 2 & 3** (Diphtheria+ Pertussis + Tetanus + Hepatitis B +Hib)	Diphtheria, Pertussis , Tetanus , Hepatitis B , Haemophilus Influenzae B	At 6 weeks, 10 weeks & 14 weeks**	1 year of age
Fractional IPV (Inactivated Polio Vaccine)	Polio	At 6 ,14 weeks and 9 month	1 year of age
Rotavirus	Rotavirus	At 6 weeks,10 weeks & 14 weeks	1 year of age
Pneumococcal Conjugate Vaccine (PCV)	Pneumococcal Disease	At 6 weeks & 14 weeks At 9 completed months - booster	1 year of age
Measles/ Rubella 1st dose ##	Measles , Rubella	At 9 completed months-12 months.	5 years of age
Japanese Encephalitis – 1 (Where applicable)	Japanese Encephalitis	At 9 months-12 months	15 years of age
Vitamin A (1st dose)		At 9 months	5 years of age (1 lakh IU)
DPT Booster-1	Diphtheria, Pertussis , Tetanus	16-24 months	7 years of age
Measles/ Rubella 2nd dose ##	Measles , Rubella	16-24 months	5 years of age
OPV Booster	Polio	16-24 months	5 Years

Japanese Encephalitis – 2 (Where applicable)	Japanese Encephalitis	16-24 months	till 15 years of age
Vitamin A (2nd to 9th dose)		At 16 months. Then, one dose every 6 months.	up to the age of 5 years
DPT Booster-2	Diphtheria, Pertussis Tetanus	5-6 years	7 Years of age
Td	Tetanus	10 years & 16 years	16 Years
Td-1	Tetanus	Early in pregnancy	Give as early as possible in pregnancy
Td-2*	Tetanus	4 weeks after TT-1*	
Td- Booster	Tetanus	If received 2 TT doses in a pregnancy within the last 3 years*	

2.3.1 Immunization Division brief from MoHFW

In 2012, AEFI Secretariat was established with due approval of MoHFW with mandate of collection, collation, line listing, reporting, sharing with partner organizations (e.g. CDSCO), investigation, causality analysis and signal assessment of AEFIs.

Adverse events following use of vaccine, whether in the Universal Immunization Programme (UIP) or private sector, pediatric vaccines or vaccines used in adults or for international travel, etc. should be reported to the AEFI surveillance system and CDSCO. All cases involving serious unexpected adverse reactions must be reported to the licensing authority within fifteen days of initial receipt of the information by the applicant (MAH).

AEFI Secretariat manages AEFI data (adverse events reported as hospitalizations, deaths, etc. following vaccination), follows up with states for investigations, and facilitates causality assessments of cases at national level. The Secretariat provides strategic vision to improve AEFI surveillance and vaccine safety under overall guidance of the National AEFI Committee and National AEFI Technical Collaborating Centre at Lady Hardinge Medical College (LHMC), New Delhi. Signal management is another core function of the secretariat and regular bimonthly meetings of the signal review panel are conducted to review the signals. It supports MoHFW in taking policy decisionsrelated to AEFI surveillance and vaccine safety. The national AEFI surveillance guidelines are developed and updated by the AEFI Secretariat with support of WHO-India Country Office.

Adverse Events Following Vaccinations can be serious or non-serious. Serious AEFIs such as death, life-threatening, hospitalization, disability, congenital anomaly/ birth defect and cluster or community concern need to be reported immediately through CRF and investigated timely in the CIF. Serious AEFIs are reported on SAFE-VAC directly or through UWIN. Non-Serious AEFIs are reported in UWIN. Numbers of minor and serious AEFI are also reported every month through Health Management Information System (HMIS). For COVID-19 vaccines also AEFIs have been collected routinely from Co-WIN Chapter. A self-reporting Chapter also is functional for reporting AEFIs by the vaccine recipients.

Serious AEFIs are investigated by Drug inspectors deputed by the concerned State Drug Control Department and the concerned CDSCO (zonal) office as members of the district AEFI committee which investigates AEFIs with the DIO. The drug inspectors are responsible for collecting samples of implicated vaccine vials and other concomitant drugs, diluents, etc. after a decision has been made to do so by the district AEFI committee in consultation with the State Immunization Officer. The collected vaccine

samples are sent to CDL, Kasauli for testing and analysis.
The state AEFI committee conducts a causality assessment to the report and sends to the National level within pre-defined timelines. These are then collated and are put up to the National AEFI Committee for review and assessment. The role of the AEFI Committees at different administrativelevels is to strengthen AEFI reporting, conduct thorough investigation, reduce program error and timely detection of signals. The reporting can occur from any level of government or private sector including the private practitioner in the CRF form. Refer to the National AEFI Surveillance and Response Operational Guidelines of Ministry of Health & Family Welfare, Govt. of India for details.

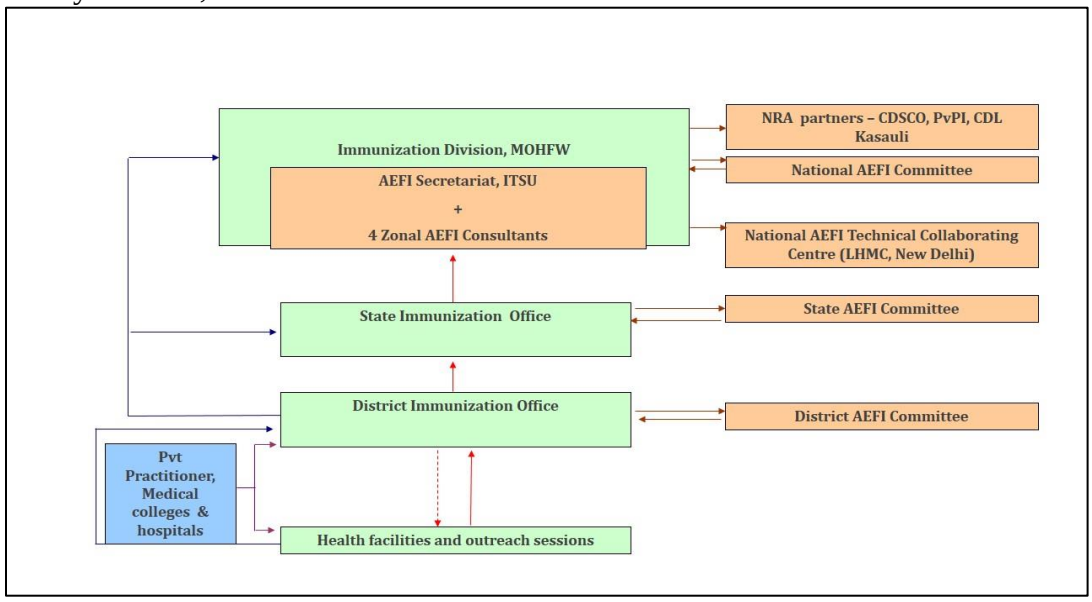


Figure 1: AEFI Secretariat Organogram

Each serious event (s) should be followed up to determine the cause for its occurrence (causality assessment). The causality assessment is done by the state AEFI committee/ National AEFI committee depending on the urgency of the situation. The AEFI Secretariat shares a linelist in excel format with CDSCO for deaths and clusters on a regular basis and all serious and severe cases on a regular interval. linelist will be in excel format and will have state, age, sex, DOV, antigens administered, manufacturing details (name, batch number and expiry date) and reason for reporting. Based on the causality assessment report detailed inspection related to GMP, product etc. and further regulatory action are initiated by CDSCO as and whenever required.
Also as mentioned in the AEFI operational guidelines, in case of an urgent situation, the state AEFI committee along with the state drug control authorities should immediately inform AEFI Secretariat, Immunization Division to take the following steps together with the CDSCO.

- Report the findings of the investigation of the state government & Govt. of India.
- The details of the implicated vaccine or product should be submitted to Govt. of India immediately so that regulatory decision could be considered by CDSCO in accordance with D&C Act 1940 and rules made thereunder.
- CDSCO along with CDL, Kasauli & Immunization Division will co-ordinatea re-evaluation of the quality of the vaccine & communicate to the manufacturer (by CDSCO), if necessary.

2.3.2 Signal Detection and Management for Vaccines

A structured approach for spontaneous reporting (Active and Passive Surveillance) of AEFI is an important

element of vaccine safety monitoring. The evaluation of safety signals is part of vaccine safety vigilance and is essential to ensure that regulatory authorities and immunization programme have the most up-to-date information on benefits and risks. The benefit-risk balance of many vaccines is dynamic and may change over time, or may appear to change over time, and this may impact pharmacovigilance activities. Council for International Organizations of Medical Sciences 2010 defines Signal as "Information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a vaccine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verification action." The rapid detection of vaccine safety signals of global importance is complemented by a scientifically sound assessment of the signals through signal management process performed to determine whether there are new risks associated with vaccine or whether known risks have changed, and includes any related recommendations, decisions, communications and tracking. A database is created of all the Adverse Events(AEs) reported and this database is assessed for trend analysis and safety signals regularly. A trend analysis report on evaluation of AEFIs (minor, serious and severe, causality assessed cases and global updates is prepared to monitor the trends for different vaccines over a period of time in differentage groups on fortnightly basis.

The signal management process includes the following steps: signal detection, validation, confirmation, analysis, prioritization, evaluation, and recommended actions, tracking of follow-up activities, communication, andrisk minimization. AEFI database considers Proportional Reporting Ratio (PRR), chi-square ($\chi 2$) statistics, Information Component (IC) and IC025; followed by detailed qualitative assessment of the vaccine-event combinations. A Signal Review Panel which is an independent body at the national level consisting of experienced professionals in the field of clinical pharmacology, medicine, infectious diseases, pediatrics, dermatology, neurology, cardiology, regulatory authority members (CDSCO), (including a Chairperson and a Member Secretary) assesses information on potential signals of possible importance for public health, drug regulation, and science from the data base for both regular UIP and COVID-19 vaccines on a bi-monthly basis. The Panel reports its findings and recommendation to the National AEFI Committee, and the Ministry of Health and Family Welfare (MoHFW). The regulatory recommendations are then forwarded through the proper channel to CDSCO for further dissemination to MAHs.

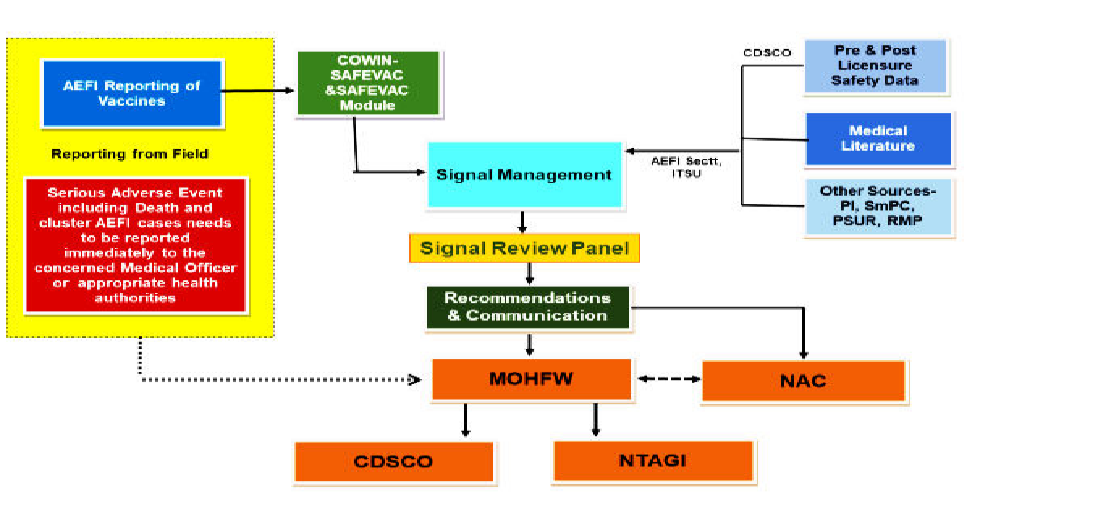


Figure 2: Signal Management Process for Vaccines: At National Level (MOHFW: Ministry of Health and Family Welfare (Immunization Division); AEFI Sect, ITSU: Adverse Events Following Immunization Secretariat, Immunization Technical Support Unit, Immunization Division, MOHFW; NAC: National AEFI Committee; CDSCO: Central Drugs Standard Control Organization (DCGI office); NTAGI: National Technical Advisory Group on Immunization; PI: Prescribing Information; SmPC: Summary of Product Characteristics; RMP: Risk Management Plan; PSUR: Periodic Safety Update Report)

Signal Management Process for Vaccines: At National Level

The Signal review Panel and National AEFI Committee may recommend any or combination of the following:

1) No need for further evaluation or action at this point of time, other than routine pharmacovigilance.
2) Seek additional information such as:
    a) Manufacturer will submit additional data regarding the signal available with it;
    b) Manufacturer will report specifically regarding this signal at the time of submission of regular PSUR or submit an ad-hoc PSUR to CDSCO;
    c) Manufacturer will conduct a post-authorization safety study andsubmit its final results to CDSCO
3) Ask manufacturer to
    a) Update product information, PSURs and/or Risk Management Plan(RMP) with specific recommended changes.
    b) Implement additional risk minimization measures such as thepreparation of educational materials, etc.

The regulatory recommendations from the signal review panel are shared with CDSCO to be shared with MAHs for further action which includes inclusion of recommended adverse events in the Summary of Product Characteristics for the said vaccine. Considerations of risk-benefit with regards to the impact on patients' or public health are kept in mind throughout the decision-making process.

2.3.4 Strengthening Safety Surveillance for New Vaccine Introduction or Pandemic Preparedness

New vaccines may be introduced by following the due regulatory and programmatic processes (in the case of routine vaccines) or through emergency use authorization (as for COVID-19 vaccinations). Preparations are required for both situations to enable improved monitoring of vaccine safety. One of the major challenges faced when a new vaccine is introducedis the non-availability of a complete safety profile of the vaccine. Safety data available at the time of introduction is usually limited to clinical trial data.

The regulators determine that the potential benefits outweigh the potential risks of the vaccine and a final analysis will include all safety data accumulated from phase I, II and III studies. After approval of a vaccine, stringent follow-up is essential to monitor vaccine safety in routine use through phase IV (Post Marketing Trial), Post Marketing Surveillance or observational or non- interventional study for active surveillance, Post Marketing Surveillance including assessment of Adverse Events Following Immunization (AEFI) and Adverse Events of Special Interest (AESI).

COVID-19 vaccines were new vaccines, were granted Emergency Use Authorization /approval for restricted use in emergency situations due to the threat of the pandemic. These vaccines underwent modified but rigorous processes of safety assessment prior to their approval. In order to further ensure monitoring of safety and efficacy, the drug regulator directed manufacturers to put in place systems for post-marketing assessment of vaccines in accordance with the general guidelines specified in the Fifth Schedule of the New Drugs and Clinical Trials Rules, 2019. Well-functioning regular passive AEFI surveillance systems can identify rare, serious adverse events following the introduction of new vaccines.

Passive Adverse Events Following Immunization (AEFI) surveillance system captures minor, severe, and serious adverse events and can provide trends and potential signals requiring further studies and assessments. Many new vaccines/COVID-19vaccines are built using novel platforms or platforms rarely used on a mass scale. Based on the experiences from existing/past vaccines or vaccine platforms on which vaccines are developed, a list of potential AESIs areidentified to prioritize enhanced vaccine safety surveillance. For COVID-19 vaccines in India, the Immunization Technical Support Unit (ITSU) under the guidance of a Technical Advisory Group (TAG) has undertaken a multi-centric AESI sentinel surveillance study involving 16 medical colleges across India to understand the risk of occurrence of select AESIs following COVID-19 vaccines. From the list of 23 AESIs shortlisted by SPEAC/CEPI, 10 AESIs were studied. From a public health perspective, timely and effectivecommunication of signal information to relevant stakeholders is the linchpin upon which effective pharmacovigilance practice rests. Understanding the balance between the benefits and risks of vaccination is essential to ensure informed and adequate public health decision-making.

2.4 PSUR/PV/AEFI Division at CDSCO

PSUR/PV/AEFI Division at CDSCO Headquarter monitors all post licensure activities of vaccine related to AEFI surveillance, PSUR review, PV Inspection, Audit and any other data on vaccine safety as and whenever required as per Drugs and Cosmetics Act 1940 and Rules made thereunder.
The PSUR/PV/AEFI Division shall also be responsible for

- **i)** The coordination with NCC-PvPI (IPC, Ghaziabad) and AEFI Secretariat, Immunization Division, Ministry of Health and Family Welfare for the various AEFI reported in the field.
- **ii)** To attend various meeting with the stakeholders for coordination purpose or whenever situation arises.
- **iii)** Collecting all the AE/ SAE reported by the MAHs, various stakeholders, Immunization Division and IPC, which shall be reviewed by the PSUR Expert Committee constituted for this purpose for taking further regulatory action.

PMS/ PSUR being conditions for Market Authorization and Licensing and therefore to ensure the regulatory conformance and proper design of post- marketing studies, this division shall work with coordination of the licensing division. This division is responsible for collecting, compiling and collating the data received from the MAH as per the requirements of Fifth Schedule of New Drugs and Clinical Trials Rules 2019. The compiled PMS/ PSUR data will then be reviewed by the advisory committee constituted by the DCG (I). Based on the analysis of the PSUR Expert Committee, regulatory decision will be taken by CDSCO.
Further, all cases involving serious unexpected adverse reactions must be reported to the Licensing Authority within 15 days of initial receipt of the information by the industry. The regulatory decision shall be taken in accordance with Drug & Cosmetics Act 1940 and Rules made thereunder. If marketing of the new drug is delayed by the applicant after obtaining approvalto market, such data will have to be provided on a deferred basis beginning from the time the new drug is marketed.

2.4.1 Sharing of AEFI with Marketing Authorization Holder:

The AEFI Secretariat will share limited linelist in excel format with CDSCO for deaths and clusters on a weekly basis and all serious and severe cases on a monthly basis. Limited linelist will be in excel format

and will have state, age, sex, DOV, antigens administered, manufacturing details (name, batch number and expiry date) and reason for reporting. CDSCO will share linelist details for vaccines relevant to the particular manufacturer with instructions that these are being shared with the MAH for internal review and such data after assessment has to be part of PSUR. The source of reports received may be mentioned accordingly to avoid duplication.

3. PHARMACOVIGILANCE PLAN

The MAH will develop a comprehensive pharmacovigilance plan as outlined below.

3.1 Pharmacovigilance Methods

The best method to address a specific situation can vary depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identifiedrisk, potential risk or missing information is the issue and whether signal detection, evaluation or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, the MAH should employ the most appropriate design. Following are the key methods used in pharmacovigilance.

3.1.1 Individual Case Safety Report

After obtaining either a manufacturing license and/or Import registration and /or import license from the office of DCG (I) at CDSCO (HQ), all MAHs shall place the vaccine products in the market and simultaneously initiate collection, collation and monitoring of all serious & severe and minor AEFI cases across the country by choosing an appropriate method of vigilance activities as follows:

A) Passive Surveillance - Spontaneous Reports

A spontaneous report is an unsolicited communication by HCPs or consumers to a MAH, regulatory authority that describes one or more adverse events in a patient who was given one or more biological products and that does not derive from a study or any organized data collection scheme.
Spontaneous reports play a major role in the identification of safety signals once a drug/ vaccine is marketed. In many instances, a MAH can be alerted to rare adverse events that were not detected in earlier clinical trials or other pre- marketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse events. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs/vaccines. The data accompanying spontaneous reports are often incomplete, and the rate atwhich cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug/vaccine.

B) Stimulated Reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods. Such methods include online reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information.
During the early post-marketing phase, MAH might actively provide health professionals with safety information and at the same time encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by MAH representatives, bydirect mailings or faxes, etc.). Stimulated adverse event reporting in the early post-marketing phase can lead MAH to notify HCPs of new therapies and provide safety information early in use by the general population. This should be regarded as a form

of spontaneous event reporting, and thus data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

C) Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug/vaccine through a risk management program. Patients who fill a prescription for this drug/vaccine may be asked to complete a brief survey form and give permission for later contact In general; it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

All the SAE shall be reported within 15 days to the Licensing Authority.

3.2 Periodic Safety Update Report

PSUR are important pharmacovigilance documents. They provide an opportunity for MAHs to review the safety profile of their products and ensure that the SmPC and Package Leaflet within reasonable time frame. Periodic Safety Update Reports (PSUR) present the world-wide safety experience of a medicinal product/vaccines at defined times post-authorization, in order to report all the relevant new safety information from appropriate sources; relate these data to patient exposure; summarize the market authorization status in different countries and any significant variations related to safety; create periodically the opportunity for an overall safety re-evaluation; indicate whether changes should be made to product information in order to optimize the use of the product. The MAH shall submit the PSUR report as per fifth schedule of New Drugs and Clinical Trial Rules 2019. A detailed description of PSURs is presented in chapter 4.3.

3.3 Post Marketing Trial (Phase-IV)

Phase IV (Post marketing) trial include additional drug-drug interactions, dose-response or safety studies and trials designed to support use under the approved indications, e.g. mortality or morbidity studies etc. Such trial will be conducted under an approved protocol with defined scientific objectives, inclusion and exclusion criteria, safety efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population. In such trial the ethical aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provisions including that for compensation in case of clinical trial related injury or death and good clinical practices guidelines. In such study, the study drug/vaccine may be provided to the trial subject free of cost unless otherwise there is specific concern or justification for not providing the drug/ vaccine free of cost, to the satisfaction of the Central Licencing Authority and the Ethics Committee.

4. PHARMACOVIGILANCE CHAPTERS

4.1 Pharmacovigilance System Master File

4.1.1 Introduction

The Pharmacovigilance System Master File (PVMF) provides a description of the pharmacovigilance system used by the MAH with respect to vaccine products marketed by them. The PVMF is not a part of the marketing authorization dossier and is maintained independently by the MAH.

4.1.2 Scope

The scope of this chapter is to provide guidance to MAH to create and maintain the PVMF at their site. This describes the different documents to be created, updated, controlled, archived and traceable, whenever required.

4.1.3 Contents of the PVMF

The PVMF should contain all information related to MAH's PV system and cover the following sections:

4.1.3.1 Pharmacovigilance personnel and their responsibilities

A qualified and trained personnel should be authorized by the company management as Pharmacovigilance Officer In-charge (PVOIC) with responsibilities for dealing PV activities at MAH's organization. The PVOIC should be a medical or pharmacy professional trained in the collection and analysis of AE reports. The PVOIC shall be responsible for the following:

- Development of training programes and organizing training for staff of PV department;
- Identification of PV activities and framing of SOPs, revision of SOPs;
- Establishment and maintenance of QMS of PV department;
- The PVOIC should reside in India and respond to queries of regulatory authorities. The information related to the PVOIC provided in the PVMF should include:
  - Contact details (Name, Address, Phone, E-mail);
  - Summary, curriculum vitae with the key information on the role of the PVOIC;
  - A description of the responsibilities stating that the PVOIC has sufficient authority over the PV system in order to promote, maintain and improve compliance;
  - Person-in-charge to work in the absence of PVOIC.

4.1.3.2 Pharmacovigilance Organization Structure

4.1.3.2.1 Marketing Authorization Holder

The Pharmacovigilance system organogram at MAH site should be included in the PVMF. The authorized signatory should be clearly indicated. The description of PV system at MAH site should be provided in PVMF.

4.1.3.2.2 Contract Research Organization (CRO)

If, MAH assigns the responsibilities of PV activities of their vaccine products to any CRO, then the information of the company(ies) including their allied PV departments involved and the relationship(s)

between Contract Research Organizations & operational units relevant to the fulfilment of PV obligations should be provided. It should include:

- The PV organizational structure of the CRO's showing the organogramof the PV department;
- Name & address of the organization, where the PV functions are undertaken such as collection of AEs, ICSRs processing, preparation & submission of PSURs, signal detection, Risk Management Plan (RMP), post-marketing surveillance and management of safety variations;
- Delegated activities (contracts and agreements as per Indian law);
- Service providing system (e.g., medical information, auditors, patient support programme providers, study data management etc.);
- Commercial arrangements (distributors, licensing partners, co-marketingetc.);
- Technical providers (hosting of computer systems and validation etc.)

4.1.3.3 Sources of safety data

The PVOIC will be responsible to collect data, reports, publications related to safety of all vaccine products marketed by the MAH. The main sources for safety data will be as follows:

- Medical information inquiries;
- "Contact us" emails, website inquiry forms and helpline etc.;
- Vaccine Product market complaints-Receipt, handling and disposal;
- MAH employees involved in PV activities;
- Spontaneous information from patient or their care givers and follow up of information;
- Published literature;
- Spontaneous reporting by HCPs including pharmaceutical sales representatives;
- Reports from internet, digital media or social media;
- Patient-support programmes;
- Reports from National Regulatory Authorities;
- Contract partners involved in PV activities;

4.1.3.4 Pharmacovigilance Processes

4.1.3.4.1 Description

A description and flow-diagram of the entire PV process, data handling, records control and archives of PV performance and covering the following aspects should be included in the PVMF:

- The procedures for ICSR collection, collation, processing, assessment, reporting and

follow-up; should clarify the activities;

- ❖ Compilation of all ICSRs and preparation & submission of PSURs ofnew drugs in accordance with the New Drugs and Clinical Trials Rules, 2019 as amended from time to time;
- ❖ Review of ICSR, detection of signal (if any), Drug/ vaccine Safety Alerts, CAPA;
- ❖ Communication of Drug/ vaccine safety concerns to Consumers, HCPs and the National Regulatory Authorities;
- ❖ SmPCs and PILs with history of updates and revisions.

4.1.3.4.2 SOPs should include the following

- ❖ Description of the process, data handling and records of PV performance;
- ❖ ICSR collection, collation, follow-up, assessment and reporting;
- ❖ Risk Minimization Plan for safety concerns identified;
- ❖ Causality Assessment of reported AE/AEFI;
- ❖ PSUR scheduling, preparation and submission;
- ❖ Quality issue, recall or withdrawal of vaccine products;
- ❖ Training procedures, evaluations and documentations;
- ❖ Signal detection and evaluation process;
- ❖ Communication of safety concerns to consumers, HCPs and regulatoryauthorities;
- ❖ Implementation of safety variations in PILs/SmPCs;
- ❖ Safety data exchange agreements, if any;
- ❖ Safety data archival and retrieval;
- ❖ PV audit & inspections;
- ❖ Routine PV Internal Audit;
- ❖ Quality Control for PV activities;

4.1.3.4.3 Computerized systems and database

The location, functionality and operational responsibility for computerized systems and databases for receiving, collating and reporting safety information should be described in PVMF. Validation status of computer system functionality with change control, if any; nature of testing; back-up procedures should also be described. The MAH can have data collection in Excel spreadsheets to record and track the data.

4.1.3.4.4 QMS in Pharmacovigilance

The QMS should be established in PV activities, which should include:

- ❖ **Document and record control:** The MAHs should retain the soft copy back-up of all PV documents for indefinite time and hard copies for at least 10 years. The MAHs

shall maintain an e-logbook for recording primary information received for every Adverse Events reported.

- **Trainings:** A summary of trainings records and files should be available at the PV site of MAH. Staff should be appropriately trainedfor performing PV related activities, including any individual, who may receive safety reports.
- **Auditing:** The QA of the company should supervise/facilitate the internal & external audits of PV system. The audit report must be documented within the quality system; with a brief description of the CAPA associated with the significant findings, the date it was identified and the anticipated resolution date(s) with cross reference to the audit report and the documented CAPA plan(s).

4.1.3.5 Pharmacovigilance System Performance

The key indicators for the performance of PV system e.g., number and quality of ICSRs, CAPA needs to be identified and measured for annual trend analysis.
They should contain evidence of the ongoing monitoring of the PV systemperformance including compliance of the main PV output. The PVMF should include a description of the monitoring methods applied and contain as a minimum the following:

- An explanation of how the correct reporting of ICSRs is assessed. In the annexure, figures/graphs should be provided to show the timelines of submission;
- A description of any metrics used to monitor the quality of submissions and performance of PV. This should include information provided by the regulatory authority regarding the quality of ICSR reporting, PSURs or other submissions;
- An overview of the timelines of PSUR reporting;
- An overview of the methods used to ensure the timelinesof safety variation submissions compared to internal and competent authority deadlines including the tracking of required safety variations that have been identified but not yet submitted;
- Wherever applicable, an overview of adherence to RMP commitments, or other obligations or conditions of marketing authorization(s) relevant to PV.

4.1.4 Annexures to the PVMF

- A list of biological products including the name of the vaccine product, active substance(s) and excipients with approvals;

- ❖ A list of contract agreements covering delegated activities including the vaccine products;
- ❖ A list of tasks delegated by the PVOIC for PV;
- ❖ A list of all completed audits (regulatory as well as internal)and a list of audit schedules.

4.2 Collection, Processing, Reporting of Individual Case Safety Reports by MAH

4.2.1 Introduction

This section highlights the general principles for Collection,Processing & Reporting of Individual Case Safety Reports associated with vaccine products for human use.

4.2.2 Structure & Processes

4.2.3 Collection and Collation of ICSR

The MAHs will collect the Adverse Events of their marketed vaccine from different sources. The AE data collection tool for ICSR reporting to CDSCO by MAH is annexed in appendix D (Annexure 1). The following sources/methods required to be established by MAHs to strengthen spontaneous reporting.

4.2.2.1 Medical inquiries

The MAHs should have a process in place to record all the medical inquiries related to their vaccine and documents including follow-up information or clarifications with a patient/consumer or HCPs. For inquiries that relate to safety of the vaccine, MAHs should ensure that there is a mechanism in place to transfer details of such cases to the PV point of contact.

4.2.2.2 "Contact us", e-mails and website inquiry forms

The MAH should consider the mechanism(s) by which incoming information via "Contact us" on their MAH portal, through e mail addresses and website inquiry forms is monitored to allow theidentification and transfer of PV data to the designated PV person in an appropriate time frame to meet the regulatory requirement.

4.2.2.3 MAH's employees

The employees of the MAH designated for the PV work, should be trained timely on the type of the information received and data collected from the various sources. These employees should be well versed in dealing with the information i.e., how to report particular Adverse Events? The data captured manually by the medical representative during a discussion with HCP regarding an AE or other safety related issue should be retained and he/she should be aware of reporting the same to the PV personnel of the respected MAHs.

4.2.2.3.1 Contractual partners

There could be different types of contractual arrangements existing in the pharmaceutical industry like loan licensing, contract manufacturing, distribution etc. The responsibilities regarding PV activities among partners should be clearly defined in a drug/vaccine safety data exchange agreement. Contractual partners are a potential source of ICSR and mechanisms should be in place for the exchange of these ICSR in an appropriate manner & timeframe to meet

regulatory requirements.

4.2.2.3.2 Information on Adverse Events from the internet or digital media

The MAHs should regularly screen relevant websites or digital media (including newspapers) or social media under their management or responsibility for potential reports of Adverse Events. The frequency of the screening should allow for potential valid ICSR to be reported to the competent authorities within the appropriate reporting timeframe based on the date of the information was posted on the website/digital media. MAHs may also consider utilizing their websites/portals to facilitate the collection of Adverse Events.

4.2.2.3.3 Solicited Reports

Solicited reports of suspected AE/AEFI are those derived from organizeddata collection systems, which include clinical trials, non- interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or HCPs, compassionate use or name patientuse, or information gathering on efficacy or patient compliance. Reports of suspected AE/AEFI obtained from any of these data collection systemsshould not be considered spontaneous.

4.2.2.3.4 Miscellaneous sources for reporting

The MAH should have other methods like e-mail, fax, online submission, mobile app, helpline, postal letters etc. to report Adverse Events. Patient identity should be kept confidential.

4.2.3 Literature Monitoring

The scientific and medical literature is a significant source of information for monitoring the safety and benefit-risk profile of vaccine products, particularly in relation to the detection of new safety signals or emerging safety issues. MAHs should perform monthly literature review of their vaccine products by using electronic literature data base (such as PubMed, Science Direct, Scopus etc.). Any AE identified by this process need to be processed as per spontaneous ICSR. The MAHs are advised to submit vaccine ICSR to CDSCO along with the complete literature reference including Digital Object Identifier (DOI) or copy of full-length article, wherever feasible.

4.2.4 Follow-up of ICSR

When initial ICSR is received, the information on Adverse Event may be incomplete. Thus, the ICSR should be followed up as necessary to obtain the required information for clinical evaluation of the ICSR.
For serious ICSRs, at least two follow-up attempts must be made and documented. For non-serious ICSRs, at least one follow-up attempt must be made and documented. While reporting to CDSCO, the MAH should clearly indicate that the reported ICSR is either initial or follow up.

4.2.5 Processing of ICSR

4.2.5.1 ICSR receipt

4.2.5.1.1 Date of receipt

The MAH should record the date of receipt for each Adverse Events; thisapplies to both initial notification and any follow-up communication.

4.2.6 Validation of reports

All reports of Adverse Events should be validated by authorized signatories of MAHs before reporting them to National Regulatory Authority i.e. CDSCO.

4.2.7 Reporting of ICSR

Only valid ICSR would qualify for reporting to National Regulatory Authority. Each valid ICSR should have the following minimum criteriafor reporting: -

I. An identifiable patient (one or more identifier such as, patient initial, age, gender, weight);

II. An Adverse Event

III. A suspected Vaccine (along with manufacturer details and batch number, including brand name if any);

IV. An identifiable reporter (source);

The fields to describe the above four criteria are as follows: -

4.2.6.1 Identifiable patient should have the following information

- Patient Initials: Write first letters of name & surname e.g., Mukesh Kumar should be written as MK.
- Age or date of birth: Write either the date of birth (DD/MM/YYYY)or age of the patient at the time of an Adverse Event occurred.
- Gender: Male/Female/Transgender
- Weight: In case of adult (in Kg) and in case of infant use value upto two decimals.

Note: If any of this information is available, the ICSR will still be considered. Any one of the above can define the identifiable patient for case processing.

4.2.6.2 An Adverse Event

- Date of onset of adverse event (DD/MM/YYYY)
- Date of stop of adverse event
- Describe adverse event: Provide the description of the event interms of nature, localization, etc.

4.2.6.3 A suspected pharmaceutical product/ Human Vaccine

The details of suspected vaccine(s) such as vaccine name (brand or generic), Batch No/Lot No., expiry date, marketing authorization holder/ manufacturer

details, dose, route, frequency, dates of therapy started & stopped, and indication should be provided. Other details are as follows:

1. **De-challenge & Re-challenge:** Consideration of de-challenge and re-challenge differs for vaccines compared with other medicinal products. Vaccines are frequently administered only once or with long intervals, and serious AEFIs often prevent further vaccine administration; hence re-challenge information is only rarely available. De-challenge may not be applicable to vaccines, given their long-term immunological effects**.**
2. **Concomitant drugs/ vaccine:** The details like dose, route, and frequency of all concomitant drugs should be provided in the same manner as that of suspected drugs including self-medication, Over the Counter medication, herbal medications, etc. with therapy dates.
3. **Relevant tests/ laboratory data/ investigation:** Mention relevant laboratory tests /investigation data before & after Adverse Events.
4. **Other relevant history:** The relevant medical history of patient including pre-existing medical conditions (e.g., allergies, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction) and concurrent condition, if any.
5. **Seriousness of the event:** If, any adverse event is seriousin nature, tick the appropriate reason for seriousness as-

- **Death:** If, the patient died, mention the cause and date of death.
- **Life-threatening:** If, the patient was at substantial risk of dying at the time of Adverse Events.
- **Hospitalization /prolongation of existing hospitalization:** If, Adverse Events caused hospitalization or increased the hospital stay of the patient.
- **Disability:** If, Adverse Events resulted in a substantial disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly:** If, exposure of the drug/vaccine prior to conception or during pregnancy may have resulted in a birth defect.
- **Other medically important condition:** When the event does not fitto above conditions, but the event may have put the patient at riskand required medical or surgical intervention to prevent any one of the above conditions.

6. **Outcomes:** Tick the outcome of the adverse event at the time of reporting as-

- **Recovered/resolved:** If, the patient recovered/resolved from theadverse event.
- **Not recovered/ not resolved:** If, the patient did not recover/resolve from the adverse event.
- **Recovering/ resolving:** If, the patient is recovering/resolving from the adverse event.
- **Fatal:** If, the patient died.
- **Recovered/resolved with sequelae:** If, the patient has completely recovered from the adverse event (mention the date of recovery) or recovered with sequelae (e.g., scar).
- **Unknown:** If, the outcome is not known.

4.2.6.4 An identifiable reporter (source)

- **Name & address:** A reporter must mention his/her name, addressand contact details. The identity of the reporter will be maintained confidential.
- **Date of report:** Mention the date on which he/she reported the Adverse Events.
- **Reporter qualification:** Qualification of the reporter needs to be mentioned.

4.2.8 Coding of Adverse Event

For the purpose of ICSR reporting (expedited and periodic) to National Regulatory Authority, MAHs are required to code Adverse Events, Indication preferably using latest version of MedDRA.

4.2.9 Reporting time lines

All cases involving serious unexpected adverse reactions/ AEFIs must be reported to the licensing authority (CDSCO) within fifteen days of initial receipt of the information by the applicant (MAH) through email pharma.covig@cdsco.nic.in**.**

All individual case information with respect to AE/AEFI received from India and rest of the world are also to be reported by MAHs along with PSUR report in compliance to section 1. (5).(C)(v) (g) of Fifth Schedule of New Drug and Clinical Trials Rules, 2019 to National Regulatory Authority (CDSCO). PSURs shall be submitted through Online Sugam Portal as per CDSCO Circular vide File no.: PSUR-13011(14)/2/2024-eoffice dated 26.02.2024 and File no.: PSUR-11011(15)/1/2024-eoffice dated 25.06.2024 within prescribed time frame as per New Drug and Clinical Trials Rules, 2019.

Note: The adverse events due to lack of efficacy, medication error, off-label use etc. must also be reported by MAH to National Regulatory Authority.

4.3 Causality Assessment

The MAHs should preferably follow WHO Vaccine AEFI causality assessment scale/ AEFI Surveillance and Response Operational Guidelines 2024 for establishing a causal relationship between the suspected vaccine and Adverse Events by trained Pharmacovigilance Professionals as prescribed in G.S.R. 287 (E) dated 08.03.2016. For said scale, refer ANNEXURE-5.

4.3.5 Special Population

4.3.5.1 Use of a biological product during pregnancy orbreast-feeding

Where during pregnancy, a woman has been exposed to any potentialteratogenic medication/ vaccine, the follow up should be done till the delivery or child birth to assess the adverse outcome of maternal exposure. When an active substance (or one of its metabolites) has a long half-life, this should be taken into account when assessing the possibility of exposure of the embryo, if the vaccine product was taken before conception.

Reports of exposure to biological products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationship between any reported Adverse Events and the exposure to the suspected Human Vaccine.

Individual cases with an adverse outcome associated with a Human Vaccine following exposure during pregnancy are classified as serious reportsand should be reported:

- Reports of congenital anomalies or developmental delay in fetusor child;
- Reports of fetal death and spontaneous abortion;
- Reports of serious suspected adverse reactions/events in the neonate.

However, in certain circumstances, reports of pregnancy exposure with no suspected events may necessitate reporting. This may be a condition of the marketing authorization or stipulated in the risk management plan; for example, pregnancy exposure to Human Vaccine contraindicated in pregnancy or vaccine products with aspecial need for surveillance because of a high teratogenic potential. A signal of a possible teratogenic effect (e.g., through a cluster of similar abnormal outcomes) should be notified immediately to the National Regulatory Authority.

Note: AEs which occur in infants following exposure to a biological product from breast milk should also be reported.

4.3.5.2 Use of a biological product in pediatric or elderly population

The collection of safety information in pediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a case is reported by a HCPs, or consumer in order to be able to identify potential safety signals specific to a particular population.

4.3 Preparation and Submission of Periodic Safety Update Report

4.3.1. Introduction

The Periodic Safety Update Report is a document for evaluation of the benefit- risk profile of a vaccine products submitted by the MAH at defined time points as per Drugs and Cosmetics Act, 1940 and New Drugs & Clinical Trials Rules, 2019 there under during the post-marketing phase.

4.3.2. Objective

This chapter defines the recommended format, content and timelines of PSUR submission in conformity with New Drugs and Clinical Trials Rules-2019 of the Drugs and Cosmetics Act, 1940. PSURs are intended to be submitted to national regulatory authority i.e. CDSCO in order to monitor the safety and efficacy of vaccine products marketed in India.
The main objective of a PSUR is to present a comprehensive, concise and critical analysis of new or emerging information on the risks and benefits of the vaccine products in approved indications. The PSUR, is therefore, a tool for post-marketing evaluation at defined time points in the life cycle of a vaccine product.

4.3.3. Post marketing assessment of New Drugs

(1) When a new drug is approved for marketing, assessment of safety and efficacy of the drug/vaccine are generally based on data from a limited number of patients, many studied under the controlled conditions of randomized trials. Often, high risk patients and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events.

(2) In actual clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, concomitant drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed. Therefore, subsequent to approval of a new drug, the new drug shall be closely monitored and post marketing assessment of its benefit-risk profile shall be carried out.

(3) A person intending to import or manufacture any new drug for sale or distribution shall have a pharmacovigilance system in place for collecting, processing and forwarding the adverse event report to the Central Licensing Authority emerging from the use of the new drug imported or manufactured or marketed by the applicant in the country.

(4) The pharmacovigilance system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be

a medical officer or a pharmacist trainedin collection and analysis of adverse event reports.

(5) Post marketing assessment of new drug may be carried out in different ways as under: -

(A) Phase IV (Post marketing) trial- Phase IV (Post marketing) trial include additional drug-drug interactions, dose-response or safety studies and trials designed to support use under the approved indications, e.g. mortality or morbidity studies etc. Such trial will be conducted under an approved protocol with defined scientific objectives, inclusion and exclusion criteria, safety and efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population. In such trial the ethical aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provisions including that for compensation in case of clinical trial related injury or death and good clinical practices guidelines. In such study, the study drug/ vaccine may be provided to the trial subject free of cost unless otherwise there is specific concern or justification for not providing the new drug free of cost, to the satisfaction of the Central Licensing Authority and the ethics committee.

(B) Post marketing surveillance study or observational or non- interventional study for active surveillance- Such studies are conducted with a new drug under approved conditions of its use under a protocol approved by Central Licensing Authority with scientific objective. Inclusion or exclusion of subject are decided as per the recommended use as per prescribing information or approved package insert. In such studies, the study drugs/ vaccine is the part of treatment of patient in the wisdom of the prescriber included in the protocol. The regulatory provisions and guidelines applicable for clinical trial of a new drug are not applicable in such cases as drugs/ vaccines are already approved for marketing.

(C) Post marketing surveillance through periodic safety update reports- As part of post marketing surveillance of new drug the applicant shall furnish PSURs in accordance with the procedures as follows;

i. The applicant shall furnish PSURs in order to-

a) report all relevant new information from appropriate sources;

b) relate the data to patient exposure;

c) summarize the market authorization status in different countries and any significant variations related to safety; and

d) Indicate whether changes shall be made to product informationin order to optimize the use of product.

ii. Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one periodic safety update reports. Within the single periodic safety update reports separate presentations of data for different dosage forms,indications or separate population need to be given.

iii. All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The periodic safety update reports shall be submitted every six months for the first two years after approval of the new drug is granted to the applicant. For subsequent two years — the periodic safety update reports need to be submitted annually. Central Licensing Authority may extend the total duration of submission of periodic safety update reports if it is considered necessary in the interest of public health. Periodic safety update reports due for a period must be submitted within thirty calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the LicensingAuthority within fifteen days of initial receipt of the informationby the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed. **Vaccines and Biologicals are always considered as New Drug, unless specified, otherwise, by the Licensing Authority.**

iv. New studies specifically planned or conducted to examine a safety issue should be described in the periodic safety update reports.

v. A PSUR should be structured as follows:

(1) Title Page: The title page of periodic safety update reports should capture the name of the vaccine; reporting interval; permitted indication of such vaccine; date of permission of the vaccine; date of marketing of vaccine; licensee

name and address.

(2) Introduction: This section of periodic safety update reports should capture the reporting interval; vaccine intended use, mode of action, therapeutic class, dose, route of administration, formulation and a brief description of the approved indication and population.

(3) Current worldwide marketing authorization status: This section of periodic safety update reports should capture the brief narrative over view including details of countries where the vaccine is currently approved along with date of first approval, date of marketing and if product was withdrawn in any of the countries with reasons thereof.

(4) Actions taken in reporting interval for safety reasons: This section of periodic safety update reports should include a description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the licence holder, sponsor of a clinical trial, regulatory authorities, data monitoring committees, or ethics committees.

(5) Changes to Reference Safety Information (RSI): This section should include any significant changes in reference safety information within the reporting interval. Such changes include information relating to contraindications, warnings, precautions, adverse events, and important findings from ongoing and completed clinical trials and significant non-clinical findings, if any.

Note: Even if there is no significant change in RSI (Prescribing Information Leaflet & Company Core Data Sheet/Summary of Product Characteristics), MAHs should submit recent dated approved RSI.

(6) Estimated patient exposure: This section of periodic safety update reports should provide the estimates of the size and nature of the population exposed to the vaccine. Brief descriptions of the methods used to estimate the subject or patient exposure should be provided,

6.1. <u>Cumulative subject exposure in clinical trial</u>

This section of the PSUR should include the following information in tabular format as referred below:

- ❖ Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational vaccine product, placebo, and/or active comparator(s) since the date of first approval for conducting an interventional clinical trial in any country (Refer Appendix-B, Table 01).
- ❖ More detailed cumulative subject exposure in clinical trials should be presented, if available (e.g. sub- grouped by age, sex, and racial/ethnic group) important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered (Refer Appendix-B, Table No. 02 & 03);
- ❖ Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered.
- ❖ If, clinical trials have been or are being performed in special population (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided as appropriate.
- ❖ When, there are substantial differences in the time of exposure between subjects randomized to the investigational vaccine product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or - years).
- ❖ New drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of AE/AEFI, particularly, when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate.
- ❖ If, the SAEs from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available.
- ❖ For individual trials of particular importance, demographic characteristics should be provided separately, if available.

6.2 Cumulative and interval patient exposure from marketing experience from India

Interval patient exposure refers as the patient exposure occurring between two data lock points of PSUR. Separate estimations should be provided for interval exposure and, when possible, cumulative exposure (since the date of marketing authorization) from India. (Refer Appendix- B, Table No. 04 and 05). The estimated number of patients exposed should be provided, when possible, along with the method(s) used to determine the same. If an estimate of the number of patients is not available, alternative estimated measures of exposure should be presented along with the method(s) used to derive them, if available. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. If applicable, data of special population and vulnerable population should be identified and submitted. The data should be presented according to the following categories:

6.2.1 Post-approval exposure

An overall estimation of patient exposure should be provided. In addition, the data should be presented by indication, sex, age, dose, formulation, and region, wherever applicable. Depending upon the product, other relevant variables, such as vaccinations, etc. should be described. Whenever, there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible. Some industries may be running some programmes for ensuring patient safety such as patient support programme, if in this programme, any safety concern or serious AE/AEFI is observed, it should also be communicated to CDSCO.

6.2.2 Post-approval use in special population

Where the approved vaccine has been used in special population, the cumulative estimated patient exposure should be provided with methodof calculation.
Sources of such data may include non-interventional studies designedto obtainthis information, such as registries.
The following are the examples of special population:

- Pediatric population;
- Elderly population;
- Pregnant or lactating women;
- Patients with hepatic and/or renal impairment;
- Patients with other relevant co-morbidity;
- Patients with disease severity different from that studied in clinical trials;
- Sub-population carrying relevant genetic polymorphism(s);
- Patients of different racial and/or ethnic origin;
- Any other vulnerable population.

6.2.3 Other post-approval use

If the MAH becomes aware of any specific pattern of use of a vaccine product, which may be relevant for assessment of product safety, a brief description should be provided. Examples of

such patterns of use are new drug abuse, misuse (such as use of antibiotics in viral infection) and use beyond that recommended in the reference product information.

6.3 Cumulative and interval estimated patient exposure from marketing experience from rest of the world

The estimations should be provided separately for interval exposure(since the data lock points of the previous PSUR) and, when possible, cumulative exposure from the date of approval in the rest of the world. (Refer Appendix-B, Table 06 and 07). The data should be presented as mentioned in the section 6.2.

7. Presentation of individual case histories

This section of Periodic Safety Update Reports should include the individual case information available to a license holder and provide brief case narrative, medical history, indication treated with suspect drug, causality assessment.

Provide following information:

7.1 Reference prescribing information

In this section, updated reference prescribing information of a new drug should be provided by the MAH.

7.2 Individual cases received from India

The CIOMS & Line-listing of ICSRs should contain the information such as: age, gender, seriousness criteria, AE/AEFI start/stop date, therapy start/stopdate of suspected/concomitant drug/vaccine, dose, route of administration, and indication of suspected/concomitant drug/vaccine, relevant past medical history, outcome & causality assessment in tabulated form as annexed in Appendix D (Annexure 1& 2).

7.3 Individual cases received from rest of the world

In this section Individual cases received from rest of the world should be provided by the MAH same as above 7.2.

7.4 Cumulative and interval summary tabulations of SeriousAdverse Events from clinical investigations

This section of the PSUR should provide a brief narration of the serious adverse events as mentioned in the Appendix B that provides a cumulative summary tabulation of SAE reported in the MAHs, clinical trials, from the first authorization to conduct a clinical trial in any country worldwide to the data lock point of the current PSUR. The MAHs should explain any omission of data (e.g., clinical trial data might not be available for vaccine products marketed for many years). The tabulation(s) should be organized by SOC, for the new drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme.

Data can be integrated across theprogramme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by trial, indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on theSAEs.

- ❖ Appendix B, Table 8 provides cumulative tabulations of SAEs from clinical trials.
- ❖ While tabulating SAEs from clinical trials only those criteria should be used which are defined in NDCT Rules, 2019. This should not include non- serious adverse events.
- ❖ The causality assessment, where has been done should also be mentioned as related and not-related.
- ❖ While coding SAE (Table 8) and AE/AEFI (TAB), Preferred Term (PT) and System Organ Class (SOC) should be used.

7.5 Cumulative and interval summary tabulations from post marketing data sources

This section of the PSUR should provide background for the Appendix that provides cumulative and interval summary tabulations of AE/AEFI from the date of marketing authorization to the data lock point of the current PSUR. The tabulation should include:

- ❖ Serious and non-serious AE/AEFI from spontaneous ICSR, including reports from HCPs, consumers, scientific literature, and regulatory authorities
- ❖ Serious adverse events from non-interventional studies
- ❖ Solicited reports of serious AE/AEFIs

For special issues or concerns, additional tabulations of adverse events can be presented by indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the datapresented (Refer Appendix-B, Table 09).

8. Studies

This section of periodic safety update reports should capture the brief summary of clinically important emerging efficacy or effectiveness and safety findings obtained from the licence holder, sponsored clinical trialsand published safety studies that became available during the reporting interval of the report which has potential impact on product safety information.

- **(i)** Summaries of significant safety findings from clinical trials during the reporting period;
- **(ii)** Findings from non-interventional Studies;
- **(iii)** Findings from non-Clinical Studies;
- **(iv)** Findings from literature

8.1 Completed clinical study

A brief summary of clinically important safety and efficacy findings obtained from completed trial during the reporting interval should be provided. This information can be presented in a narrative format or as a synopsis (Refer ICH- E3). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

8.1.1 Ongoing clinical study

If the manufacturer and/or importer is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unbinding of subjects with Adverse Events), this sub- section should briefly summarize the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

8.1.2 Long-term follow-up

Wherever applicable, this sub-section should provide information from long- term follow-up of subjects from clinical trials of new drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products, tissue engineering and biotech products). These are referred as Advanced Therapy Medicinal Products (ATMPs).

8.1.3 Other therapeutic uses of biological product

This should include clinically important safety information from other programmes, if and when conducted by the manufacturer and/or importer that follow a specific protocol (e.g., expanded access programmes, compassionate use programmes, particular patient uses and other organized data collection).

8.2 Findings from non-interventional Studies

This section should summarize relevant safety information or information with potential impact on the benefit or risk evaluations, from MAH - sponsored non-interventional studies that became available during the reporting interval (e.g., observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from new drug utilization studies, when applicable to multiple regions.

8.3 Information from other clinical trial sources

8.3.1 Other clinical trials

This sub-section should summarize information accessible with reasonable effort from any other clinical trial/study sources to the MAH during the reporting interval (e.g. including results from pooled analyses or meta-analyses of randomized clinical trials, and safety information provided by co-development partners or from investigator-initiated trials).

8.3.2 Medication errors

This sub-section should summarize relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. This information may be received by the manufacturer and/or importer via spontaneous reporting systems, medical information queries, customer complaints, screening of digital media, patient support programmes, or other available information sources.

8.4 Findings from non-Clinical Studies

This section should summarize major safety findings from non-clinical *in vivo* and *in vitro* studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting interval.

8.5 Findings from literature

This section should summarize new and significant safety findings, either published in the scientific literature, Alerts published by USFDA/EMEA or other regulatory agencies, relevant to the approved vaccine product that the manufacturer and/or importer became aware of during the reporting interval.
Literature searches for PSUR should be as wide as possible and should also include studies reporting safety outcomes in groups of subjects and other products containing the same active substance.
This should include:
Pregnancy outcomes (including termination) with or without adverseoutcomes

- Use in pediatric populations
- Compassionate supply, named patient use
- Lack of efficacy
- Asymptomatic overdose, abuse or misuse
- Medication error where no adverse events occurred Important non-clinical safety findings

9. Other Information

This section of PSURs should include the details about signal and Risk Management Plan in place by licence holder (if any).

(a) Signal and risk evaluation: In this section, licence holder will provide the details of signal and risk identified during the reporting period and evaluation of signals identified during the reporting period.

(b) Risk management plan: In this section, licence holder willprovide the brief details of safety concern and necessary action taken by him to mitigate

these safety concerns.

9.1 Lack of efficacy in controlled clinical trials

Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy (ies), for vaccine products intended to treat or prevent serious or life-threatening illnesses could reflect a significant risk to the treated population and should be summarized in this section.

9.2 Late-breaking information

This section should summarize information on potentially important safety and efficacy/effectiveness findings that arise within 15 days after the data lock point of the PSUR in preparation. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the manufacturer and/or importer, a data monitoring committee, or a regulatory authority has taken for the safety reasons.
Any significant change proposed to the reference product information which has occurred after the data lock point of the report, but before submission should also be included in this section, where feasible. Such changes could include a new contraindication, warning/precaution, or new AE/AEFI.

9.3 Overview of signals: new, ongoing, or closed

- A new signal is a signal that the MAH became aware of during the reporting interval. A new clinically important information on a previously closed signal that became available during the reporting period of the PSUR (i.e., a new aspect of a previously refuted signal or recognized risk likely to warrant further action to verify) would also constitute a new signal. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the data lock point of the PSUR. Examples would include new information on a previously:
- Closed and refuted signal, which would result in the signal being re- opened; Identified risk which is indicative of a clinically significant difference in the severity of the risk, e.g., transient increase in liver enzymes are identified risks and new information is received indicative of a more severe outcome such as hepatic failure; neutropenia is an identified risk and a well-documented and unconfined case report of agranulocytosis is received;
- Identified risk for which a higher frequency of the risk is newly found, e.g., in a sub population; and
- Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population

or other risk minimization activities.

Refer Appendix-C, include a tabular listing of all signals ongoing orclosed at the data lock points of the PSUR.

When a regulatory authority has requested that a specific safety concern (not considered a signal) be monitored and reported in a PSUR, the MAH should summarize the result of the analysis of such safety concern in this section even if it is negative.

10. Overall Safety Evaluation

10.1 Benefit Evaluation

This section of PSURs should capturethe overall safety evaluation of the drug/ Vaccine based upon its risk benefit evaluation for approved indication.

The purpose of this section is to provide:

- Important identified risks;
- Important potential risks;
- Important missing information.
- In case a signal was indicated in previous interval report and now has been refuted because of new evidences which resulted in closure, should be specifically mentioned here.
- An evaluation of new information with respect to previously recognized identified and potential risks
- An updated characterization of important potential and identified risks, where applicable and
- A summary of the effectiveness of risk minimization activities (if any)in any country or region, which may have utility in other countries or regions.

These evaluations of subsections should not summarize or repeat information presented in previous sections of the PSUR, but shouldinstead provide an interpretation of the information, with a view towards characterizing the profile of those risks assessed as important.

10.2.1 Important baseline efficacy/effectiveness information

This section summarizes information on the efficacy/effectiveness of the vaccine product as of the beginning of the reporting interval, and provides the basis for the benefit evaluation. This information should relate to the approved indication(s) of the vaccine product listed in the referenceproduct information

For vaccine products with multiple indications, population, and/or routes of administration, the benefit should be characterized separately by these factors, wherever relevant. The level of detail provided in this section should be sufficient to support the characterization of benefit in PSUR and the benefit-riskassessment.

10.2.2 <u>Newly identified information on efficacy/ effectiveness</u>

Wherever necessary, for some product's new information on efficacy/effectiveness in approved indications that may have become available during the reporting interval should be presented in this section.

New information about efficacy/effectiveness in uses other than the approved indication(s) (off-label

use) should not be included, unless relevant for the benefit-risk evaluation in the approved indication. Information on additional indications approved during the reporting interval should also be included in this section. New information on efficacy /effectiveness might also include changes in the therapeutic environment that could impact efficacy/effectiveness over time, e.g., vaccines, emergence of resistance to anti- infective agents.

10.2.3 Characterization of benefits

This sub-section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorized indications. When there are no new relevant benefit data, this sub-section should provide a characterization of the information in sub-section "Important baseline efficacy and effectiveness information". When there is a clear information about the benefit and no significant change in the risk profile in this reporting interval, the integration ofbaseline and new information in this sub-section should be provided. This sub-section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, as follows:

- A brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across clinical trials/studies
- New information that challenge the validity of a surrogate endpoint, if used
- Clinical relevance of the effect size
- Generalizability of treatment response across the indicated patient population, e.g., information that demonstrates lack of treatment effect in a sub-population
- Adequacy of characterization of dose-response
- Duration of effect
- Comparative efficacy

A determination of the extent to which efficacy findings from clinical trialsare generalizable to patient populations treated in medical practice.

10.2.4 Benefit risk analysis evaluation

This section should provide an integration and critical analysis of the key information. This section also provides the benefit-risk analysis, andshould not simply duplicate the benefit and risk characterization presentedin subsections mentioned above.

10.2.5 Benefit-Risk context- medical need and important alternatives

This sub-section should provide a brief description of the medical need for the vaccine product in the approved indications, andsummarize alternatives (medical, surgical, or other; including no treatment).

10.2.6 Benefit-Risk analysis evaluation

A benefit-risk balance is specific to an indication and population. For products approved for more than one indication, benefit-risk profiles should be evaluated and presented for each indication individually. If there are important differences in the benefit-risk profiles among populations within an indication, benefit-risk evaluation should be presented by population, if possible. The benefit-risk evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks, and should consider the following points:

- Whereas previous sections included all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections shouldbe carried forward for integrationin the benefit-risk evaluation.
- Consider the context of use of the vaccine product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated.
- With respect to key benefit(s), consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all.
- With respect to risk, consider its clinical importance, e.g., nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients, and whether it arose from off-label use, a new use, or misuse.
- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be described.
- Provide a clear explanation of the methodology and reasoning used for benefit-risk evaluation:
- The assumptions, considerations, and judgement or weighing that support the conclusions of the benefit-risk evaluation, should be clear.
- If a formal quantitative or semi-quantitative assessment of benefit- risk is provided, a summary of the methods should be included.
- Economic considerations (e.g., cost-effectiveness) should not beincluded in the benefit-risk evaluation.

Note: When there is important new information or an ad hoc PSUR has been requested, a detailed benefit-risk analysis is warranted.

Conversely, where little new information has become available duringthe reporting interval, the primary focus of the benefit-risk evaluation might consistof an evaluation of updated interval safety data.

11. Conclusion

This section of PSURs should provide the details on the safety profile of drug(s)/ Vaccine(s)and necessary action taken by the license holder in this regard.
Based on the evaluation of the cumulative safety data, and the benefit-risk analysis, the manufacturer and/or importer should assess the need for further changes to the reference product information and propose changes as appropriate. In addition, and as applicable, the conclusion should include preliminary proposal(s) to optimize or further evaluate the benefit-risk balance, for further discussion with the national regulatory authority. This may include proposals for additional risk minimization activities. These proposals should also be considered for incorporation into the Risk Management Plan.

12. Appendix

The appendix includes the copy of marketing authorization in India, copyof prescribing information, RMP, adverse events Line listings in standard format (India & Global), CIOMS forms with narrative of Individual Case Safety Report.

4.4. Quality Management System at MAH Site

4.4.1. Introduction

This Chapter contains guidance for the MAHs for the establishment, maintenance, performance, performance and quality assurance ofPV system.

4.4.2. Scope

This guidance document is applicable to all MAHs who hold marketing authorization for manufacture or import of vaccine products in Indian market.

4.4.3. Structures and Processes

4.4.3.1 Pharmacovigilance system

All MAH should have the PV system which should comply with the quality management system including requirements of NDCT Rules 2019, revised Schedule M of the Drugs & Cosmetics Act, 1940, and Rules made thereunder.
The PV system at MAH should have an organogram describing PV personnel's roles and responsibilities, procedures, processes and resources, including management of resources,

compliance and records.

4.4.3.2 Quality Management System (QMS) of PV

The QMS in PV is a framework of policies, procedures and systemnecessary to ensure quality related to detection, assessment, understanding, evaluation and prevention of adverse events on vaccine products.
The quality management system is based on the following activities:

- **Quality planning:** Establishing structures of PV system, planning, effective integration and consistent processes for safety;
- **Quality adherence:** Carrying out tasks and responsibilities in accordance with quality requirements such as collection of ICSRs, completeness of report, case narrative, data management, causality assessment, signal management, etc.;
- **Quality control and assurance:** By monitoring the parameters describedunder quality adherence;
- **Quality improvements:** Taking Corrective and Preventive measures, as and when required, to ensure patient safety.

4.4.3.3 Requirements and Responsibilities of QMS at MAH site

MAH should have a sufficient number of competent and appropriately qualified, and trained personnel for the performance of PV activities.
In case, where MAH has completely outsourced the PV activities, througha valid contract, the outsourced agency/institution should comply with the above statement. It should be notified to CDSCO with authorized legaldocuments. The responsibility of adhering to PV QMS will ultimately lie with MAH.
The managerial staff in the organization should be responsible for compliance of PV Guidance Document for MAH's Vaccine Products.

4.4.3.4 Training of MAH personnel for PV

The personnel involved in PV activities should receive induction (within one month of joining and continued trainings with proper evaluation of performance, thereafter. The organization should maintain the training plans and records of trainings. The organization should keep identifying the continued training needs.

4.4.3.5 Facilities and equipment for PV

Achieving the required quality for the conduct of PV processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes. Facilities and equipment should include office space, Information Technology (IT) systems and storage space (electronic). They should be located, identified, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for PV System. Facilities and equipment which are critical for the conduct of PV should be subject to appropriate checks, qualification and/or validation activities to provetheir suitability for the intended purpose.

4.4.4. Specific quality system procedures and processes

4.4.4.1. Compliance management by MAH

For the purpose of compliance, MAHs should have specific quality system procedures and processes in place in order to ensure the following:

- Continuous monitoring of PV data, the examination of options for risk minimization and prevention and that appropriate measures are taken by the MAH.
- Scientific evaluation of all information on the risks of vaccine products in regards to patients or public health, in particular to their adverse events in human beings arising from use of the product within or outside the terms of its marketing authorization or associated with occupational exposure
- Submission of accurate and verifiable data on all AEFIs to the regulatory authority within the legally required time-limits
- Quality, integrity and completeness of the information submitted onthe risks of vaccine products, including processes to avoid duplicate submissions and to validate signals
- Effective communication with regulatory authority, including communication on new or changed risks, the PVMF, risk management systems, PSURs and CAPAs.

4.4.4.2. Record management

The MAH shall record all PV information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information. As part of a record management system, specific measures should,therefore be taken at each stage in the storage and processing of PV data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorized personnel respecting the medical and administrative confidentiality of thedata. The electronic copies of the PV records should be stored indefinitely. It is expected that the MAHs should retain the soft copy back-up of all PV documents for indefinite time and hard copies for at least 10 years. The MAHs shall maintain an e-logbook for recording primary information received for every Adverse Events reported.

4.4.4.3. Documentation of the quality system

All elements, requirements and provisions adopted for the quality system should be documented in a systematic and orderly manner in the form of written policies and procedures. For the requirements of documenting the quality system.

4.4.4.4. Critical PV processes

The following PV processes should be considered as critical:

- ❖ Benefit-risk evaluation;
- ❖ Establishing, assessing & implementing risk management systems and evaluating the effectiveness of risk minimization;
- ❖ Collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of ICSRs from any source;
- ❖ Signal management;
- ❖ Scheduling, preparation (including data evaluation and quality control), submission and assessment of PSURs;
- ❖ Interaction between the PV and product quality defect systems;
- ❖ Communication about safety concerns between MAHs and licensing authority in particular notifying changes to the benefit-risk balance of vaccine products;
- ❖ Communicating information to patients and HCPs about changes to the benefit-risk balance of vaccine productsfor the aim of safe and effective use of vaccine products;
- ❖ Keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the regulatory authority;
- ❖ Implementation of variations to marketing authorizations for safety reasons according to the urgency required;
- ❖ Provisions for events that could severely impact on the organization's staff and infrastructure in general or on the structures and processes for PV in particular; and
- ❖ Back-up systems for urgent exchange of information within an organization, amongst organizations sharing PV tasks as well as between MAHs and competent authorities.

4.4.4.5. Monitoring the effectiveness of QMS in PV

The QMS in PV should be continuously monitored for its effectiveness by theMAH through the following processes:

- ❖ System reviews by those responsible for management
- ❖ Audits
- ❖ Compliance monitoring

- ❖ Inspections
- ❖ Evaluating the effectiveness of actions taken with biological products for the purpose of minimizing risks and supporting their safe and effective use in patients.

The organization may use performance indicators to continuously monitor the good performance of PV activities in relation to the quality requirements. The requirements for the quality system itself are laid out in this Chapter and its effectiveness should be monitored by managerial staff, who should review the documentation of the quality system at regular intervals with the frequency and the extent of the reviews to be determinedin a risk-based manner.
Reviews of the quality system should include the review of SOPs and work instructions, deviations from the established quality system, audits and inspections reports as well as the use of the indicators referred to above.

4.4.4.6. Responsibilities of the MAH in relation to the PVOIC for PV

The pharmacovigilance system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of AEFI/AE reports.
A qualified and trained personnel should be authorized by the company management as Pharmacovigilance Officer In-charge (PVOIC) with responsibilities for dealing PV activities at MAH's organization. The PVOIC should be a medical or pharmacy professional trained in the collection and analysis of AE reports. The PVOIC shall be responsible for the following:

- ❖ Development of training modules and organizing training for staff ofPV department;
- ❖ Identification of PV activities and framing of SOPs, revision of SOPs;
- ❖ Establishment and maintenance of QMS of PV department;

The PVOIC should reside in India and respond to queries of regulatory authorities including PvPI, IPC whenever required. The information related to the PVOIC provided in the PVMF should include:

- ❖ Contact details (Name, address, phone, e-mail);
- ❖ Summary, curriculum vitae with the key information on the role of thePVOIC;
- ❖ A description of the responsibilities guaranteeing that the PVOIC hassufficient authority over the PV system in order to promote, maintain and improve compliance;
- ❖ Details of Person-in-charge to work in the absence of PVOIC;

4.5. Audit & Inspection of Pharmacovigilance System at MAH Site

4.5.1. Introduction

This chapter provides insights into planning, conducting, reporting and follow-up of PV inspections by regulatory authorities/officials responsiblefor inspection.

4.5.2. Objectives

The objectives of PV audits and inspections are as below:

- ❖ To verify by examination and evidence, the appropriateness of the implementation and operation of the PV system including its quality systems.
- ❖ To assess and establish that the MAH has qualified personnel, robust system and facilities to conduct PV activities
- ❖ To identify, record and address non-compliance, which may pose a riskto public health
- ❖ To take regulatory action, wherever considered necessary based on the result of the inspections/audits.

The results of an inspection will be provided to the inspected MAH, who will be given the opportunity to comment on any non-compliance identified. Any non-compliance should also be rectified by the MAH within stipulated time period through the implementation of CAPA plan.

4.5.3. Inspection Types

The Inspections of PV can be routine or targeted to MAHs suspected of being non-compliant.

4.5.3.1. Routine inspection

These are planned and informed inspection of the PV system of MAH. The focus of these inspections is to determine that the MAH has personnel, systems and facilities in place to meet the regulatory PV obligations for the marketed vaccine products in India.

4.5.3.2. Targeted inspections

These inspections are conducted as and when there is trigger and the regulatory authority determines that inspection is the only way. Triggeringfactors for such type of inspections are as below (**but not limited to**):

- ❖ Continuous delays or omission and poor-quality reporting of ICSRs/PSURs/RMPs.
- ❖ Failure to provide the asked information or data within the deadline specified by regulatory authority.
- ❖ Delays or failure to carry out specific obligations related to the monitoring of vaccine product safety, identified at the time of the marketing authorization.
- ❖ Delays in the implementation or inappropriate implementation ofCAPAs.
- ❖ Sudden vaccine product withdrawal and recall.
- ❖ Any major changes in PV system.
- ❖ Any emerging safety issue relating to any drug/ vaccine product held by the MAH.

4.5.4. Inspection Procedure

4.5.4.1. Inspection Planning

PV inspection should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. Arisk-based approach to inspection planning will enable the frequency and scope of inspections to becarried out.
The PV inspection team will comprise CDSCO Officials and representative from PvPI & other experts if required.
The inspection will be planned based on the following:

- ❖ Compliance history identified during previous PV inspections, ifany.
- ❖ Re-inspection date recommended by the inspectors as a result of compliance of previous inspection submitted by MAH,
- ❖ MAH with sub-contracted/ outsourced/ Third Party PV activities (qualified person responsible for PV functions in India, reportingof safety data, etc.) and multiple firms employed to perform PV activities;
- ❖ Changes to the PV safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- ❖ Changes in contractual arrangements with PV service providers or the organizations at which PV is conducted;
- ❖ Delegation or transfer of PVMF management.

4.5.4.2. Organization to be inspected

Any party carrying out PV activities in whole or in part, on behalf of, or in conjunction with the MAH may be inspected, in order to confirm their capability to support the MAH's compliance with PV obligations.

4.5.6. Regulatory Actions:

In the event of non-compliance, the regulatory authority shall take the necessary measures to ensure that a MAH is in compliance with NDCTR-19 of D&C Act 1940 and Rules made thereunder.

4.6. Submission of Risk Management Plan

4.6.1. Introduction

At the time of marketing authorization, information on the safety of a biological product is relatively limited as the clinical studies are carried out in relatively small number of subjects, restricted population in terms of age, gender, ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and follow up.
A biological product is authorized on the basis that at the time of authorization, the benefit-risk balance is positive. The product may have multiple risks of varying degree associated with it and individual risks will vary from product to product. All actual or potential risks might not have been identified at the time of initial authorization. Many risks will only be discovered and

characterized during post- marketing phase.
The aim of Risk Management Plan (RMP) is to document the risk management system considered necessary to identify, characterize and minimize a vaccine product's important risks. The Risk Minimization strategy involves continuous monitoring of efficacy and safety profile-Risk Identification, Risk Assessment, Risk Characterization, Risk Communication and Risk Mitigation.

4.6.2 Objective

- ❖ Identification and characterization of risk to update the safety profile of the vaccine product(s);
- ❖ Indicate how to characterize further the safety profile of the vaccine product(s);
- ❖ Document measures to prevent or minimize the risks associated with a vaccine product, including an assessment of the effectiveness of interventions;
- ❖ Document post-marketing obligations that have been imposed as a condition of the marketing authorization;
- ❖ Document any change in the risk profile of a vaccine product(s) after marketing authorization.

The RMP document is a dynamic, stand-alone document which should be updated throughout the life-cycle of vaccine products.

The License holder will provide the details of safety concern and necessary actions taken by him to mitigate any safety concern in the applications of PSUR.

4.6.3. Description of RMP

4.6.3.1. Vaccine product overview

The MAH should provide an overview of a vaccine product including:

- ❖ Active Pharmaceutical Ingredient(s) information, name of MAH, date and country of first launch/authorization worldwide (if applicable), chemical class, indication (s), mechanism of action, route of administration, pharmaceutical form and strength.
- ❖ Information on the excipients used in the formulation of a vaccine product should be provided.
- ❖ Administrative information on the RMP such as data lock point, date submitted and version number of all parts of RMP.

4.6.3.2. Safety specifications

The MAH should provide a synopsis of the safety profile of a vaccine product(s) and should include, what is known and unknown about the vaccine product(s) safety. The safety specification consists of following subsections:

4.6.3.2 Epidemiology, indication (s) and target population(s)

This section should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin.

4.6.3.2.2. Non-clinical part of the safety specifications

This section should present a summary of important non-clinicalsafety findings like toxicity related information, interactions etc.

4.6.3.2.3. Clinical trial exposure

This section includes the data on the patients studied in clinical trials. This should be stratified for relevant categories (age, gender, indication, ethnicity, exposure to special population-pediatric, geriatric etc.) and also by the type of clinical trial.

4.6.3.2.4. Populations not studied in clinical trials

This section describes, which sub-populations within the expected target population have not been studied or have only been studied to a limited degree in the clinical trial population. Limitations of the clinical trials should also be presented in terms of the relevance of exclusion criteria such as pediatric population, geriatrics population, pregnant/lactating women, hepatic /renal impairment patients etc.

4.6.3.2.5. Post-marketing experience

This section should provide information on the number of patients exposed during post-marketing phase; how the vaccine product has been used in clinical practice, labelled and off-label use including use in the special populations mentioned above? This should also include any action taken by any regulatory authority/MAH for safety reason.

4.6.3.2.6. Identified and potential risks

This section provides information on the important identified and potential risks associated with the use of a vaccine product and potential AE/AEFI associated with other vaccine and pharmaceutical products, foods, other substances, and the important pharmacological class effects.
The risk data should include frequency, public health impact, risk factors, preventability, potential mechanism, evidence source/strength.

4.6.3.2.7. Summary of the safety concerns

At the end of the RMP document, summary of the "Safety concerns/measures" of vaccine products should be provided.

4.6.3.3. PV activities

MAH should list the various PV activities involved to identify a new safety concern or further characterize known safety concerns or investigation of potential safety concerns, whether it is real or notand how missing information will be sought? PV activities can be divided into routine PV activities and additional PV activities. For each safety concern, the MAH should list their planned PV activities for that concern. PV plans should be proportionate to the risks of the product. If routine PV is considered sufficient for post-marketing safety monitoring, without the need for additional actions (e.g. safety studies) "routine PV" should be carried out against the safety concern.

4.6.4 Nature and rate of known Risks versus Benefits

Comparing the characteristics of the product's adverse effects and benefits may help clarify whether a Risk Management Action Plan (MAP) could improve the product's benefit-risk balance. The characteristics to be weighedmight include the

- types, magnitude, and frequency of risks and benefits;
- populations at greatest risk and/or those likely to derive the most benefit;
- existence of treatment alternatives and their risks and benefits;
- Reversibility of adverse events observed.

4.6.5 Preventability of adverse effects

Serious adverse effects that can be minimized or avoided by preventive measures around drug/ vaccine prescribing are the preferred candidates for Risk MAPs.
Probability of benefit: If factors are identified that can predict effectiveness, a Risk MAP could help encourage appropriate use to increase benefits relative to known risks. A risk minimization tool is a process or system intended to minimize known risks. Tools can communicate particular information regarding optimal product use and can also provide guidance on prescribing, dispensing, and/or using a product in the most appr opriatesituationsor patient populations. A number of tools are available and may be used asrequired. A variety of tools are currently used in risk minimization plans. These fall within three categories:

- Targeted education and outreach: targeted education and outreach to communicate risks and appropriate safety behaviors to healthcare practitioners or patients.
- Reminder systems: processes or forms to foster reduced-risk prescribing and use, and
- Performance-linked access systems: that guide prescribing, dispensing, and use of the product to target the population and conditions of use most likely to confer benefits and to minimize particular risks.

4.6.6 Targeted education and outreach

It is recommended that MA holders consider tools in the targeted education and outreach category.

(a) When routine risk minimization is known or likely to be insufficient to minimize product risks or

(b) As a component of Risk MAPs using reminder or performance- linked access systems.

Sponsors are encouraged to continue using tools, such as education and outreach, as an extension of their routine risk minimization effortseven without a Risk MAP.
Tools which may be used as routine risk minimization efforts even without a Risk MAP may be:

- Training programs for healthcare practitioners or patients;
- Continuing education for healthcare practitioners such as product-focused programs developed by sponsors and/or sponsor-supported accredited CE programs;
- Prominent professional or public notifications;
- Patient labeling such as Medication Guides and patient package inserts Promotional techniques such as direct-to-consumer advertising highlighting appropriate patient use or product risks;
- Patient-sponsor interaction and education systems such as disease management and Patient access programs;
- Healthcare practitioner letters.

In addition to informing healthcare practitioners and patients about conditions of use contributing to product risk, educational tools can inform them of conditions of use that are important to achieve the product's benefits.
On the other hand, deviations from the labeled dose, frequency of dosing, storage conditions, or other labeled conditions of use might compromise the benefit achieved, yet still expose the patient to product related risks. Risks and benefits can have different dose- response relationships. Risks can persist and even exceed benefits when products are used in ways that minimize effectiveness. Therefore, educational tools can be used to explain how to use products in ways that both maximize benefits and minimize risks.
It is recommended that tools in the reminder systems category be used in addition to tools in the targeted education and outreach category when targeted education and outreach tools are known or likely to be insufficient to minimize identified risks. Tools in the reminder system include systems that prompt, remind, double- check or otherwise guide healthcare practitioners and/or patients in prescribing, dispensing, receiving, or using a product in ways that minimize risk. Examples of tools in this category are as follows:

i. Patient education that includes acknowledgment of having read the material and an agreement to follow instructions. These agreements are sometimes called consent forms.

ii. HCPs training programs that include testing or some other documentation of physicians' knowledge and understanding.

iii. Enrolment of physicians, pharmacies, and/or patients in special data collection systems that also reinforce appropriate product use.

iv. Limited number of doses in any single prescription or limitationson refills of the product.

v. Specialized product packaging to enhance safe use of the product.

vi. Specialized systems or records that are used to attest that safety measures have been satisfied (e.g. Prescription stickers, physician attestation of capabilities).

4.6.7 Performance-Linked Access Systems

Performance-linked access systems include systems that linkproduct access to laboratory testingresults or otherdocumentation. Tools in this category, because they are veryburdensome and can disrupt usual patient care, should beconsidered only when Products have significant or otherwise unique benefits in a particular patient group or condition, but unusual risks also exist, such as irreversible disability or death, and Routine risk minimization measures, targeted education andoutreach tools, and reminder systems are known or likely to be insufficient to minimize those risks.

4.6.8 Selecting and Developing the Best Tools:

Maintain the widest possible access to the product with the least burden to the healthcare system that is compatible with adequate risk minimization (e.g., a reminder system tool should not be used if targeted education and outreach would likely be sufficient).

Identify the key stakeholders who have the capacity to minimize the product's risks (such as physicians, pharmacists, pharmacies, nurses, patients, and third party payers) and define the anticipated role of each group. Seek input from the key stakeholders on the feasibility of implementing and accepting the tool in usual healthcare practices, disease conditions, or lifestyles, if possible. Examples of considerations could include (but would not be limited to) patient and healthcare practitioner autonomy, time effectiveness, economic issues, and technological feasibility.

Acknowledge the importance of using tools with the least burden some effect on Healthcare practitioner- patient, pharmacist-patient, and/or other healthcare relationships. It is recommended that MA holders periodically evaluate each Risk MAP tool to ensure it is materially contributing to the achievement of Risk MAP objectives or goals.

4.6.9 Risk minimization activities

The MAH should have the approved & updated Package inserts, Product labelling, Product Information Leaflet (PIL), pack size, risk minimization activities. The MAH should also consider when appropriate to have additional Risk minimization activities like educational material, communication letter to HCPs etc.

For each safety concern, the following information should be provided:

- Objectives of the risk minimization activities;

- ❖ Routine risk minimization activities;
- ❖ Additional risk minimization activities (if any), individual objectives and justification,
- ❖ How the effectiveness of each (or all) risk minimization activities will be evaluated in terms of attainment of their stated objectives?
- ❖ What the target is for risk minimization? i.e. what are the criteria for judging success?
- ❖ Milestones for evaluation and reporting.

5. PROCEDURES FOR IMPLEMENTING AN EFFECTIVE PHARMACOVIGILANCE SYSTEM

(a) Obligations for MAH:

In accordance with the Govt. Gazette Notification No. GSR 227 (E) dated March, 19th March 2019, for the purpose of Post Market Surveillance, the MAH shall have a pharmacovigilance system in place for collecting, processing and forwarding the reports to the Licensing Authorities for information on Adverse Event Following Immunization (AEFI) emerging from the use of the vaccine manufactured and marketed by the MAH in the country. The system shall be managed by qualified and trained personneland officer-in-charge of collection and processing of data shall be a Medical Officer or a pharmacist trained in collection and analysis of AE/AEFI.

Hence, the MAHs should establish an appropriate pharmacovigilance system by assuming the responsibilities and liabilities for its vaccine product(s) circulating in the market and should ensure that appropriate action may be taken whenever safety concerns arise after due investigation and scientific evaluation. The MAHs should appoint as per the norms laid down in Fifth Scheduleof New Drugs and Clinical Trials Rules 2019 under Drugs & Cosmetics Act 1940 a qualified and trained personnel with duly given responsibilities for continuously monitoring of the vaccine products at his disposal

(b) AEFI Case Reporting:

Documented standard procedure should compile but not be limited to the following:

I. Provisions for timely and thorough review to determine whether the complaint represents an AE/AEFI;

II. Personnel responsible to receive the incoming correspondence(phone calls, letter, email, etc.) relating to potential AE/AEFI through product complaints;

III. How an unique identifier is assigned to each case; and

IV. Clear and defined processes on AE/AEFI complaint, evaluation and follow-up.

c) Manufacturers and importers should have in place systems and procedures for the receipt, handling, evaluation and reporting of AE/AEFIs that are adequate to effectively sustain AEs/AEFI reporting. All casesinvolving serious unexpected adverse reactions must be reported to the licencing authority within fifteen days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant afterobtaining

approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

In case of manufacturer, distributing countries specific PSUR should be compiled and submitted in a separate section within the PSUR data. All theSAE reported in the distributing countries shall be reported within 15 days.

d) MAHs should have in place adequate procedures for AE/AEFI receipt, handling, evaluation and reporting and should include but not be limited tothe following.

i. Requirement to report to CDSCO within 15 days of receipt by the MAH, reports of serious AE/AEFI occurring within India, and serious unexpected AE/AEFI occurring outside of India and any unusual failure in efficacy for new drugs occurring within India, if applicable;

ii. Address all the specific Indian regulatory requirements such, as when notification is required, serious and non-serious adverse events, unusual failure in efficacy of new drugs, if applicable, retention of all records associated with AE/AEFIs, etc.;

iii. Requirement to have a qualified health care professional to evaluateand assess AE/AEFI reports, including the process to review AEs.

iv. Identifying the 4 minimum criteria (an identifiable reporter (source), an identifiable patient, a suspect product and an adverse events) forsubmitting a case;

v. Identifying key personnel who are responsible for forwarding the AE reports to the Licensing Authority;

vi. Procedure on how complaints and AEs are tracked/logged in;

vii. Procedure on how the MAH is to be notified of foreign serious unexpected AEs/AEFIs;

viii. The responsibilities for the final approval of AE/AEFI evaluation and appropriate follow-up;

ix. Requirement to conduct a critical analysis of AE reports received and preparation of a summary report on an annual basis, or at the requestof the Licensing Authority (CDSCO). As per Para 6.11 of part I Good Manufacturing Practices For Pharmaceutical Products: Main Principles of Schedule M revised vide G.S.R. No. 922(E) dated 28th December 2023 of Drugs and Cosmetics Act and Rules, the licensee shall have a Pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information

on the AEFI/AEs emerging from the use of drugs/ vaccines manufacturedor marketed or imported by the licensee. The licensee shall have a pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the AEFI/AEs emerging from the use of drugs/ vaccines manufacturedor marketed by the licensee.

e) Importers should have in place adequate procedures for AE/AEFI receipt, handling, evaluation (for determination of complaints or AE/AEFI) and forwarding AE/AEFI to the MAH and should include but not be limited to the following:

i. Procedure on how complaints and AE/AEFI are tracked/logged in;

ii. Procedure on how complaints are assessed in order to determine if it is an AE/AEFI;

iii. Identifying key personnel who are responsible for forwarding the AE/AEFI reports to the MAH; Requirement to report AE/AEFI to the MAH within an appropriate timeframe to allow for expedited reporting (if required); and all SAEs to be reported within15 days of receipt of information to CDSCO. This should be read in conformity with para 4, under heading Post Marketing Surveillance sub para iii of Fifth Schedule of New Drugs and Clinical Trials Rules 2019 of Drugs and Cosmetics Rules.

iv. Requirement to follow up with the MAH to ensure that AE/AEFI have been assessed and sent to Drugs Controller General (India), if required;

v. Requirement to maintain records of all AE/AEFI received andAE/AEFI sent to the MAHs and subsequent correspondence; and ensure that as per Drugs and cosmetics Rules, As per Para 6.11 of part I Good Manufacturing Practices For Pharmaceutical Products: Main Principles of Schedule M revised vide G.S.R. No. 922(E) dated 28th December 2023of Drugs and Cosmetics Act and Rules, the licensee shall have a Pharmacovigilance system in place for collecting, processing and forwarding the reports to the licensing authorities for information on the AEFI/AEs emerging from the use of drugs/ vaccines manufactured or marketed orimported by the licensee reports of serious- AEFI/AEs resulting from the use of a drugs/ vaccines along with comments and documents are forthwith reported to concerned Licensing Authority (CDSCO).

f) Procedures should be written, reviewed and approved by qualified personnel.

g) Procedures should be made available to all relevant personnel involved in pharmacovigilance activities before the procedures are effective.

h) Procedures should be reviewed on a periodic basis to ensure that they accurately reflect current practice.

i) Changes to procedures should be tracked and documented.

j) Deviations from procedures relating to pharmacovigilance activities should be documented

k) When part or all pharmacovigilance activities are performed by a third party, MAH and importers should review procedures to ensure that procedures are adequate and compliant with applicable requirements stated in New Drugs and Clinical Trials Rules 2019. Copies of the procedures should be readily available to the inspector/ regulator.

l) MAHs

i. The AE/AEFI evaluation, including but not limited to, seriousness and expectedness assessment should be completed in a manner which would ensure expedited reporting timelines are met. For both domesticand foreign reports, the expectedness should be determined from the relevant labeling such as the product monograph, labeling standards, information approved for market authorization, or the product label.

ii. Mechanisms should be in place to determine whether an AE/AEFI qualifies for 15 day expedited reporting. When a case is found not reportable, justification is provided and documented.

iii. For AE/AEFI reports that qualify for expedited reporting, the 4 minimum criteria (an identifiable reporter (source), an identifiable patient, a suspect product and an adverse event) for submitting a case are met.

iv. Process should be in place for determining if a solicited report is to be submitted to Licensing Authority in an expedited fashion (within 15 days).

v. A qualified health care professional evaluates and assesses AE/AEFI to determine whether the AE/AEFI qualifies for expedited 15-day reporting.

m) <u>Reports of AEFI cases from 2 or more sources</u>

i. A mechanism should be in place to identify AEFI data that werereported to the MAH more than once.

ii. When similar reports are found, verifications should take place todetermine if they are duplicate reports.

iii. Multiple copies of the same AE/AEFI reports should be nullified withinthe

iv. Pharmacovigilance system and the record of nullification should be maintained, allowing for auditing of the nullified record in the future.

v. Documented procedure and process should be in place describingwhen

AE/AEFI reports may be nullified.

vi. Documentation related to nullified cases should be retained.

vii. Additional information received for previously submitted AE/AEFI reports

viii. Upon receipt of follow-up information, AE/AEFI reports should be re-evaluated.

ix. Follow-up information received for previously submitted AE/AEFI reports must be sent to Licensing Authority within the prescribed timelines. Reference should be made to the initial report by including the MAH number specific to the report either in the follow-up report or on the fax cover sheet.

x. All reportable AE/AEFI that have been upgraded to serious upon receipt of follow- up information are to be sent to Licensing Authority within the prescribed timelines

xi. Rationale for changing the seriousness of an AE/AEFI report should be documented.

xii. Process for seeking follow-up information and submitting it to Licensing Authority should be in place. All attempts to obtain follow-up information should be documented.

n) Reporting of AE/AEFI data

All AEs shall be reported to Licensing Authority (CDSCO) inaccordance with New Drugs Clinical Trials Rules 2019.

o) Importers

All suspected AE/AEFI received should be sent to the MAH within an appropriate time frame to allow for expedited reporting (if required), and should therefore be reported to Licensing Authority by the MAH in accordance with the requirements of the New Drugs Clinical Trials Rules2019, if required.

Importers should follow-up with the MAH to ensure that AE/AEFI have been assessed and submitted, if required.

p) Literature SearchMAHs

i. The process, including but not limited to how the search is done, the database(s) used, and the periodicity of those searches describing the search in the literature should be written in a procedure.

ii. AE/AEFI found during literature searches should be classifiedaccording to their seriousness and expectedness. These assessments should be retained and be well documented.

iii. AE/AEFI reports from the scientific and medical literature must be reported to

Licensing Authority in accordance with the New Drugs Clinical Trials Rules 2019.

iv. Results of the literature searches should be documented.

v. When literature search is performed by a third party, contractual agreements describing each party's responsibilities should exist.

q) Periodic Internal Audit

MAHs and Importers

An Internal Audit program that covers all departments that may receive AE/AEFI reports or that are involved in pharmacovigilance activities may help to ensure compliance with the appropriate sections of the News and Drugs and Clinical Trials Rules 2019 applicable to AEFI/AEs reporting. Internal Audit programs should be in place and should include but not be limited to the following;

I. A comprehensive written procedure that describes the functions of the Internal Audit program.

II. Periodic Internal Audit that are carried out at defined frequencies, which are documented. If no AEs have been received, the periodic self- inspections should include a simulation exercise.

III. Reports on the findings of the Internal Audit and on corrective actions. These reports should be reviewed by appropriate senior MAH management. Corrective actions should be implemented in a timely manner.

r) Periodic Internal Audit should be conducted by personnel independent from the pharmacovigilance department and that are suitably qualified to perform and evaluate the inspections.

s) Personnel and Training

MAHs and Importers

The individual in charge of the pharmacovigilance department should bequalified by pertinent training and experience relevant to their assigned responsibilities. the qualified pharmacovigilance professional;

i. Should have knowledge of all applicable sections of the D&C Act 1940 and Rules made there under, New Drug and Clinical Trials Rules 2019 and GCP Guidelines related to the AEs reporting requirements, and of key pharmacovigilance activities performed as part of the MAH's pharmacovigilance system.

ii. Should be responsible for establishing and managing/maintaining a system

which ensures that information concerning all suspected AEs that are reported to the personnel of the MAH and to medical representatives is collected and evaluated.

iii. All personnel involved in pharmacovigilance activities, which may include customer service, sales representatives and receptionists, should have their specific duties recorded in a written description and have adequate authority to carry out their responsibilities.

iv. All personnel involved in pharmacovigilance activities should be awareof the principles of pharmacovigilance that affect them, and all personnel should receive relevant training.

v. When responsible personnel are absent, qualified personnel should beappointed to carry out their duties and functions.

vi. A qualified health care professional with adequate experience and training, should be available to evaluate information in respect of a potential AE/AEFI, assesses the seriousness, expectedness, and report ability of AE/AEFI, and determine if the AE/AEFI report qualifies for expedited reporting (within 15 days) and if the report is to beincluded in the annual summary

vii. Training should be provided prior to implementation of new or revised procedures. Records of training should be maintained.

viii. Consultants and contractors should have the necessary qualifications, training, and experience to fulfill their New Drugs Clinical Trials Rules 2019.

t) <u>Contractual Agreements</u>

MAHs and Importer

i) Contractual agreement should exist with every party that conducts pharmacovigilance activities, including third- party private label or other MAH whose name is included in the product information or appears on the labeland should include;

a. who is responsible for determining if a complaint is a potential AE/AEFI,

b. Who is responsible to report AE/AEFI,

c. Who is responsible for preparing the ASR, including the critical analysis of the annual summary reports, and what process is utilized to conduct the critical analysis,

d. Who is responsible for conducting literature searches?

e. Processes by which an exchange of safety information, including timelines and regulatory reporting responsibilities, are taking place between the MAH

and its partners (including, but not limited to, consultants and contractors).

f. To notify other party if changes to procedures are made.

ii) In the case of foreign MAHs, the contractual agreement should specify to send known AE/AEFI to the local MAH in a timely manner so as to promote compliance with regulatory reporting obligations.

iii) In the case where the importer is responsible for the pharmacovigilance activities, the contractual agreement should specify that the foreign MAH is to send the AE/AEFI data to the importer in a timely manner.

iv) All records (including, but not limited to, contractual agreements and safety data/ AE/AEFI data) should be available on the premises of the MAH and the importer for auditing purposes

v) When there is a transfer of market authorization/mergers, contractual agreement should exist between the previous MAH and the new one outlining each party responsibility.

vi) Contractual agreement should be shared and signed off by each party.

vii) Contractual agreement should be reviewed periodically in order to reflect current regulations and practices.

u) Validation of Computerized Systems

MAHs, Importer, and all parties involved in pharmacovigilance activities who use an electronic system. Data of the validation of system(s) used for recording, evaluating, and tracking complaints and AE/AEFI should be available.

Computerized systems should be validated and systems are periodically and suitably backed up at predefined intervals. It should be identified what electronic data and records will be collected, modified, imported and exported, archived and how they will be retrieved and transmitted. Electronic sourcedata, including the audit trail should be directly accessible by investigators, monitors, auditors, and inspectors without compromising the confidentiality of participants' identities.

6. DEFINITIONS

A. Adverse Event (AE)

Any untoward medical occurrence (including a symptom / disease or an abnormal laboratory finding) during treatment with a Human vaccine /pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given. Also see Serious Adverse Event.

B. Adverse Event Following Immunization (AEFI)

This is defined as any untoward medical occurrence which followsimmunization and which does not necessarily have a causal relationship withthe use of the vaccine. The adverse event may be any unfavorable or unintended sign, an abnormal laboratory finding, a symptom or a disease.

C. Adverse Drug Reaction (ADR)

I. In case of approved pharmaceutical products: A noxious and unintended response at doses normally used or tested in humans

II. In case of new unregistered pharmaceutical products (or those products which are not yet approved for the medical condition where they are being tested): A noxious and unintended response at any dose(s).

The phrase ADR differs from AE, in case of an ADR there appears to be a reasonable possibility that the adverse event is related with the medicinal product being studied. Adverse drug reactions are type A (pharmacological) or type B (idiosyncratic). Type A reactions represent an augmentation of the pharmacological actions of a drug. They are dose-dependent and are, therefore, readily reversible on reducing the dose or withdrawing the drug. In contrast, type B adverse reactions are bizarre and cannot be predicted from the known pharmacology of the drug.

D. Market Authorization Holder (MAH)

For the purpose of this guidance document means the manufacturer or the importer of the drug/ vaccine, who has valid manufacturing or import license.

E. Cluster

Two or more cases of the same event or similar events related in time, geography, and/or the vaccine administered.

F. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

An AE or ADR that is associated with death, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening. This is to be read along with the definition as mentioned in Drugs & Cosmetics Act 1940 and Rules 1945 there under as- A Serious adverse event is an untoward medical occurrence during clinical trial that is associated with death, in patient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.

G. Suspected Serious Adverse Reaction (SSAR)

An adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product/ vaccine in question set out.

- ❖ In the case of a licensed product, in the summary of productcharacteristics (SmPC) for that product.
- ❖ In the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question.

H. Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out.

- ❖ In the case of a licensed product, in the summary of productcharacteristics (SmPC) for that product.
- ❖ In the case of any other investigational medicinal product, in the IBrelating to the trial in question.

I. Third Party

For the purpose of this guidance documents means that the entity who is northe manufacturer neither the importer.

7. REFERENCES

1 ICH Guideline. E2E: Pharmacovigilance Planning;
2 Drugs and Cosmetics Act 1940 & Rules 1945– Fifth Schedule of New Drugs and Clinical Trials Rules 2019;
3 Guidance for Industry – Development and Use of Risk Minimization Action Plans – US FDA;
4 National AEFI Surveillance & Response Operational Guideline 2024;
5 WHO AEFI Guidelines;
6 Pharmacovigilance Guidance Document for Marketing Authorization Holders of Pharmaceutical Products;
7 Good Pharmacovigilance Practices (GVP) Guidelines.

Appendix

Annexure:1

CASE REPORTING FORM (CRF)

To be filled by doctor and sent to District Immunization Officer within 24 hours *Mandatory Field

AEFI Case ID: IND (AEFI) / ST / DST / YR / NUM (from SAFE-VAC, for all vaccines except COVID-19 vaccines)

AEFI Case ID: IND (CO-AEFI) / ST / DST / YR / NUM (from Co-WIN - SAFE-VAC, for COVID-19 vaccines)

Section A: Reporter and notifier details

Name of doctor reporting / filling this form*: Contact phone number*: E mail*: Place of present posting*: Designation*: Address of present posting:	Reporting Date: __ __ / __ __ / __ __ __ __ (date when this form is prepared) Date case visited and examined / interviewed: __ __ / __ __ / __ __ __ __ (date when the case visited or interviewed)
Notified by (Name)*: Date notified: __ __ / __ __ / __ __ __ __ (date when the case informed to reporting doctor)	Designation of notifier (please circle): ASHA / AWW / Health worker / Government doctor / Private practitioner or hospital / Parent / Community / Media / Others Specify: _____
Address of session site*: Village or Urban area: Block Name: District: State:	Place of Vaccination*: Govt Health Facility / Outreach / Private Health Facility / Others (specify): _____ Source of vaccine: Government supply / Privately purchased / Others (specify): _____
Date of Vaccination*: __ __ / __ __ / __ __ __ __ Time of Vaccination: __ __ : __ __ AM/PM	Vaccination in*: Routine Immunization / Campaign (MI, Pulse Polio, MR, JE, COVID 19) / Others (specify):_____ Type of Session Site: Fixed / outreach / mobile / school / others (specify):_____

Section B : Patient details

Patient Name*																			

Date of Birth * DD/MM/YYYY	Age: _____ years ___ Months ___ days	Sex*	Male / Female

Mother's Name																			
Spouse / Father / Guardian's name*																			

Complete Address* with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)*

P	I	N	-							P	H	O	N	E*	-										

For women in reproductive age group:

1. Status of pregnancy at the time of vaccination: Yes / No / Don't know
2. If Yes, duration of pregnancy at the time of vaccination: 1-3 months / 4-6 months / 7-9 months
3. Lactating at the time of vaccination: Yes / No / Don't know

Section C : Details of vaccine(s) and diluent(s) administered to the AEFI case during this session (to be filled by MO incharge or DIO of area where vaccination took place)

Name of vaccines administered to this case (write vaccine & diluent details in separate rows)*	Dose no. (birth / zero / 1st / 2nd / 3rd / booster 1 / booster 2 / campaign)*	Name of Manufacturer / Brand Name*	Batch / Lot No.*	Mfg. date	Expiry date	Date & Time of vaccine reconstitution / opening vaccine vial	No. of **OTHER** beneficiaries who received vaccine from **SAME** vial in this session

Section D : Details of adverse event(s)

1. Type of Adverse Event: Serious / Severe
2. If serious AEFI specify: Death / Hospitalization / Cluster / Persistent or significant disability / Congenital anomaly or birth defect / Media, community or parental concern

If this is a part of a cluster*: Yes / No / Unknown

If yes number of other cases in the cluster _____ Cluster ID (as generated by SAFE-VAC):

Adverse event(s) - clinical* (TICK AS MANY AS APPLICABLE):

☐ Severe local reaction	☐ Fever	☐ Seizures	☐ Injection site abscess
☐ Sepsis	☐ Encephalopathy	☐ Toxic shock syndrome	☐ Thrombocytopenia
☐ Allergic reaction	☐ Anaphylaxis	☐ Intussusception	☐ Lymphadenitis
☐ Acute Flaccid Paralysis	☐ Hypotonic Hypo-responsive Episode (HHE)	☐ Unexplained Death	☐ Anxiety reaction

Additional for COVID vaccine

☐ Joint pain / swelling of recent onset	☐ Painful single limb swelling	☐ Chest pain / fainting / palpitation
☐ Recent ECG / Echo / angiography changes	☐ Breathlessness / difficulty in breathing / worsening of existing respiratory problem	
☐ Altered sensorium / Loss of consciousness	☐ Acute disseminated encephalomyelitis	☐ Guillain-Barre syndrome
☐ Meningoencephalitis	☐ Mono-neuropathy / Poly-neuropathy	☐ Rashes
☐ Loss of taste / smell	☐ Acute liver injury / Acute Liver Failure	☐ Chilblain-like lesions /vasculitis
☐ Acute kidney injury / Acute Renal Failure / Hematuria / Oliguria / Edema of legs / Hypertension		☐ Lymphadenopathy
☐ Coagulation / bleeding disorder (Thromboembolism, Hemorrhage)		
☐ Worsening of existing disease (Cardiac / Respiratory / Liver / Kidney / Diabetes etc.)		☐ Others (specify).....

Pregnancy related events

☐ Maternal death ☐ Fetal loss (abortion) ☐ Premature delivery ☐ Still birth ☐ Neonatal mortality ☐ Congenital anomaly in newborn

Date & Time of first symptom*: DD / MM / YYYY at ___:___AM/ PM	Hospitalization (In-patient admission)*: Yes / No
Name and address of hospital:	
Date & Time of hospitalization*: DD / MM / YYYY at ___:___AM / PM	Hospital Reg. No. (OPD/Admission/Bed Head Ticket):
If hospitalized, outcome*: Discharged / Still Hospitalized / Left Against Medical Advice (LAMA) / Absconded / Referred / Death / Brought dead	
Current status of patient*: Recovered completely / recovered with sequalae / still under treatment / death / unknown	
Date & Time of Death*: DD / MM / YYYY (if died) at ___:___AM / PM Place of death: Home / Hospital / On the way to hospital / Others	Post mortem done: Yes / No / Unknown Date of Post mortem: DD / MM / YYYY
Describe AEFI (sequence of events, signs and symptoms after vaccination) *:	

Signature and name of Reporting Medical Officer:

Section E: Decision making details

District Immunization Officer to complete and submit in **SAFE-VAC / Co-WIN SAFE-VAC (for COVID-19 vaccines)** within 24 hours of receiving the above information. SAFE-VAC: https://safevac.nhp.gov.in; Co-WIN - SAFE-VAC:

Date report received at District level: __ __ / __ __ / __ __ __ __

Date investigation planned: __ __ / __ __ / __ __ __ __

DIO/ District Nodal Person *(Officer forwarding this report)*

Name ..... Designation..... Mobile No*: .....

Email id*: ..... Signature..... Date/ Seal: .....

Complete Office address (with Pin code) .....

.....

For any support or help, write to: aefiindia@gmail.com; safevac.chi@gmail.com

Annexure-2:

CASE INVESTIGATION FORM (CIF)

(To be submitted in SAFE-VAC / Co-WIN – SAFE-VAC within 21 days of notification) *Mandatory Field

AEFI Case ID : IND (AEFI) / ST / DST / YR / NUM (from SAFE-VAC, for all vaccines except COVID-19 vaccines)

AEFI Case ID : IND (CO-AEFI) / ST / DST / YR / NUM (from Co-WIN - SAFE-VAC, for COVID-19 vaccines)

Section A: Basic details (Please refer to CRF of this case for personal details of patient)

Name of the Lead Investigator*:	Designation*:
Contact phone number* : E mail*:	Date of case visit and investigation: __ __ / __ __ / __ __ __ __ (date when the case was contacted/investigated)
Address of session site*: Village or Urban area: Block Name: District: State:	Place of Vaccination*: Govt Health Facility / Outreach / Private Health Facility / Others (specify): _____ Source of vaccine: Government supply / Privately purchased / Others (specify): _____
Date of Vaccination*: __ __ / __ __ / __ __ __ __ Time of Vaccination: __ __ : __ __ AM/PM	Vaccination in*: Routine Immunization / Campaign (MI, Pulse Polio, MR, JE, COVID 19 / Others (specify):_____ Type of Session Site: Fixed / outreach / mobile / others (specify):_____

Section B : Patient details

Patient Name*:				
Date of Birth of patient * DD/MM/YYYY	Age: _____ years ___ Months ___ days	Sex*:	Male	Female
Mother's Name:				
Spouse/Father's Name:				
Complete Address* with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)*:				
PIN:	Phone:			

For women in reproductive age group:

1. Status of pregnancy at the time of vaccination: Yes / No / Don't know
2. If Yes, duration of pregnancy at the time of vaccination: 1-3 months / 4-6 months / 7-9 months
3. Lactating at the time of vaccination: Yes / No / Don't know

Section C : Details of vaccine(s) and diluent(s) administered to the AEFI case during this session (to be filled by MO incharge or DIO of area where vaccination took place)

Name of vaccines received (write vaccine & diluent details in separate rows)*	Dose no. (birth / zero / 1st / 2nd / 3rd / booster 1 / booster 2 / campaign)*	Name of Manufacturer/Brand name*	Batch / Lot No.	Expiry date*	Mfg. date	Date & Time of opening vaccine vial / vaccine reconstitution	No. of OTHER beneficiaries who received vaccine from SAME vial in this session

Date & Time of first symptom*: DD / MM / YYYY at ___:___AM/ PM	Hospitalization*: Yes / No
Name and address of hospital:	
Date & Time of hospitalization*: DD / MM / YYYY at ___:___AM / PM	Hospital Reg. No. (OPD/Admission/Bed Head Ticket):

Date & time of death*: DD / MM / YYYY (if died) at ___:___AM/ PM Place of death: Home / Hospital / On the way to hospital / Others	Post mortem done: YES / NO / Unknown If done, date of post mortem: DD / MM / YYYY
If hospitalized, outcome *: Discharged / Still Hospitalized / Left Against Medical Advice (LAMA) / Absconded / Referred / Death / Brought dead	
Current status of patient*: Recovered completely / recovered with sequalae / still under treatment / death / unknown	
Describe AEFI (sequence of events, signs and symptoms after vaccination)*:	

Section D **Relevant patient information prior to immunization:**

Criteria	Finding	Provide details here if "yes" marked to any question@
Any past history of similar reaction event (without vaccination)?	Yes / No / Unknown	
Any adverse event after previous vaccination(s)	Yes / No / Unknown	
Any history of allergies for drugs, vaccine, food or other products?	Yes / No / Unknown	
Any concomitant medication at the time of vaccination, if any (If yes, name the drug, indication, doses, treatment dates/duration)?	Yes / No / Unknown	
Any pre-existing illness / comorbidity / congenital disorder?	Yes / No / Unknown	
Any pre-existing acute illness 30 days prior to vaccination?	Yes / No / Unknown	
Any history of hospitalization 30 days prior to vaccination (mention reason)?	Yes / No / Unknown	
Family history of any disease (relevant to AEFI) or allergy	Yes / No / Unknown	
Has the patient tested COVID-19 positive prior to this vaccination? If yes- Type of test (RTPCR/Rapid test/CBNAAT/TRUNAAT): Date of the test:	Yes / No / Unknown	
Has the patient been in contact with a COVID-19 positive individual within 30 days prior to vaccination?	Yes / No / Unknown	
Has the patient developed symptoms compatible with COVID-19 in the past?	Yes / No / Unknown	

If patient is an infant or baby born to pregnant woman vaccinated during pregnancy, give birth details:	Remarks
1. Birth Weight:	
2. Duration of pregnancy ☐ Full term ☐ Pre-mature ☐ Postdated ☐ Unknown	
3. Place of birth ☐ Home delivery ☐ Institutional ☐ Unknown	
4. Delivery procedure ☐ Normal ☐ Caesarian ☐ Assisted with forceps/vacuum ☐ Unknown	
5. Any antenatal / postnatal complications: Yes / No / Unknown; if yes please specify	

Section E **Detailed clinical assessment, investigation, diagnosis and treatment of reported AEFI case@**

@Instructions:

- *In case of Unexplained Death in infant* - please fill Verbal Autopsy form as per the guidelines
- *If patient has taken medical care* - attach copies of all available documents (including OPD prescriptions, prescription for concomitant medication, case sheet, discharge summary, laboratory/investigation reports and post mortem reports, if available) and then complete additional information NOT AVAILABLE in the attached documents
- *If patient has not taken any medical care* - obtain history, examine the patient and write down your findings below (add additional sheets as required)

Source of information (✓ *all that* apply): ☐ AEFI Case Reporting Form ☐ Examination by the investigator ☐ Medical case records ☐ AEFI Verbal autopsy form ☐ Interview with patient / caregiver ☐ Telephonic enquiry with patient / caregiver ☐ Interview with treating physician ☐ Other_____

Date of examination: Signs and Symptoms:

Consciousness: Alert / Drowsy / Unconscious / Other (specify and describe) .....

Vitals: Pulse ..... Temperature ..... Respiratory rate ..... BP ..... Weight .....

Skin: Rash/Cyanosis/Petechiae/Pallor/Jaundice/Others (specify and describe) .....

COVID-19 test status after vaccination (if conducted, with date and type of test)

Test conducted: Y / N If Y, date of test: Test result: Positive / Negative / Not known Type of test:

Has anyone in the family of the patient tested COVID 19 positive after vaccination? Y/N. If Y, then date of test:

Has the patient developed symptoms compatible with COVID 19 infection after vaccination? Y/N. If Y, then date of test:

Systemic examination findings (mention the important positive and negative findings):

Treatment provided:

Provisional / Final diagnosis (as per the treating doctor and/or the Investigation team [encircle one] , if no medical care received):

Section F Investigation at vaccination site

Details of vaccines provided on vaccination day at the site linked to AEFI

Number immunized for each vaccine at session site. Attach record if available.													
	Vaccine name												
	No of doses administered												
	Number of vaccine vials used												

1. Sequence of patient -
   a. At session site on day of vaccination:
      ☐ Within the first half beneficiaries at the session site ☐ Within the last half beneficiaries the session site ☐ Unknown
   b. For a multi dose vaccine vial (since the vial has been opened):
      ☐ Within the first half beneficiaries of the vaccine vial ☐ Within the last half beneficiaries of the vaccine vial ☐ Unknown

   If required, sequence of vaccination of all subjects (affected and not affected) should be established and mentioned on a separate sheet

2. Multidose vials administered to the case		No. of beneficiaries vaccinated from each vial on session day	No. of beneficiaries vaccinated from same vial since opening or reconstitution	No. of times each vial was issued to sessions before being issued to this session
a.				
b.				
c.				
d.				
e.				

3. Is this case a part of a cluster?	Yes / No / Unknown
A If yes, how many other cases have been detected in the cluster?	
B Did all the cases in the cluster receive vaccine from the same vial?	Yes / No / Unknown
C If no, Number of vials used in the cluster	

4. If similar events have been reported from other session sites, comments:

Immunization practices at the place (s) where concerned vaccine was used (based on observations and assessment)			
5. **Syringes and Needles Used:**			
• Were/Are AD syringes used for immunization? • If no specify the type of syringes:	Yes / No / Unknown		
Specific key findings/additional observations and comments:			
6. **Reconstitution: (complete only if applicable, ✓ NA if not applicable)**			
• Reconstitution procedure (✓)	Status		
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
• Were/Are the diluents used same as recommended by the manufacturer?	Yes	No	NA
7. **Vaccine handling and vaccination** (examine the available used vaccine vials and observe an immunization session, if needed)			
• Noncompliance to recommendations for use of this vaccine (e.g. any contraindication ignored?)	Yes / No / Unknown		
• Wrong selection of the beneficiary(ies) (e.g. NOT age appropriate for the vaccine)	Yes / No / Unknown		
• Unsterile condition of the vaccine (ingredients) or diluent administered (sterile/unsterile)	Yes / No / Unknown		
• Abnormal vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances, etc.)	Yes / No / Unknown		
• Error in vaccine reconstitution/preparation by the vaccinator (e.g., wrong product, wrong diluent, improper mixing, improper syringe filling etc.)	Yes / No / Unknown		
• Date and time of opening the vial clearly NOT mentioned on the vials being used in the session under observation	Yes / No / Unknown		
• Error in vaccine handling (break in cold chain during transport, storage and/or immunization session etc.)	Yes / No / Unknown		
• Error in vaccine administration (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes / No / Unknown		
Specific key findings/additional observations and comments:			

Section G Cold Chain and Transport (Answer the following based on observations and assessment)	
Last vaccine storage point:	
• The temperature of the ILR/vaccine storage refrigerator monitored (thermometer and documentation)	Yes / No
○ If, 'yes', any deviation outside of 2- 8°C after the concerned vaccine vial was received at cold chain point	Yes / No
○ If, 'yes' attach relevant monitoring documents separately	
• Correct procedure of storing vaccines, diluents and syringes followed	Yes / No / Unknown
• Any other item (other than vaccines and diluents) available in the refrigerator or freezer	Yes / No / Unknown
• Partially used reconstituted vaccines available in the refrigerator	Yes / No / Unknown
• Unusable vaccines (expired, no label, VVM stage 3 & 4, frozen) available in the refrigerator	Yes / No / Unknown
• Unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) available in the store/refrigerator	Yes / No / Unknown
Specific key findings / additional observations and comments:	
Vaccine Transportation:	
• Type of vaccine carrier used	4-icepacks / 2-icepacks / other
• Conditioned ice-pack used in the vaccine carrier	Yes / No / Unknown
• Vaccine carrier sent to the session site on the same day of vaccination	Yes / No / Unknown
• Vaccination carrier returned from the session site on the same day of vaccination	Yes / No / Unknown
• All empty/partially used/unused vaccine vials (and diluents) return to cold chain point on the same day of vaccination	Yes / No / Unknown
• Comment on vaccine handling (any error, e.g. Break in cold chain during transport, storage and/or immunization session etc.)?	
Specific key findings/additional observations and comments:	

Section H Community Investigation (Please visit locality and interview parents/ others)

Any similar events reported recently in the locality? Yes / No/ Unknown
If Yes, Describe:

If Yes, How many events / episodes and the category of people affected (children, adults, any specific locality/area)?

Of those affected, how many are
- Vaccinated:_____
- Not Vaccinated:_____
- Unknown:_____

Other findings beyond vaccine or vaccination:

Section I District AEFI Committee Review

a)	*What was the provisional diagnosis of the case concluded by the District AEFI committee?*		
b)	*Please describe the events, clinical and epidemiological findings in support of provisional diagnosis.*		
c)	*Any biological product sent (CSF, Blood, urine, tissue extracts) for testing? Note: for AEFI resulting within 28 days following JE vaccine, send sample of CSF, Serum to nearest NIV lab in Pune or Gorakhpur or Mumbai*		
d)	Did the district AEFI committee recommend sending vaccine samples for quality testing?	Yes	No
e)	Was local drug inspector involved in collecting additional samples?		
f)	Specify any other relevant investigation done and attach reports.		

Details of Vaccine/ Diluent samples sent to CDL Kasauli

Vaccine/Diluent Name	Site of collection	Used Vial/Amp. Quantity	Batch no, Lot no, date of expiry	Date Sent	Unused Vial / Amp. Quantity	Batch no, Lot no, date of expiry	Date Sent

Details of Syringe/ Needle samples sent to CDL Kolkata

Type of Syringes	Quantity	Site of collection	Batch no, Lot no, date of expiry	Date Sent	Type of Needles	Quantity	Batch no, Lot no, date of expiry	Date Sent

Based on the investigation, answer the following: *(Please provide explanation in the remark column for any 'yes')*

A	Could the vaccine given to this patient have quality defect or is substandard or falsified?	Yes / No / Unable to assess	Remark
B	In this case, was there an error in prescribing or non-adherence to recommendations for use of this vaccine? (e.g. use beyond the expiry date, wrong recipient etc.)	Yes / No / Unable to assess	Remark
C	In this case, was the vaccine (ingredients) or diluent administered in an unsterile manner?	Yes / No / Unable to assess	Remark
D	In this case, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	Yes / No / Unable to assess	Remark
E	When this case was vaccinated, was there an error in vaccine reconstitution / preparation by the vaccinator (e.g., wrong product,	Yes / No / Unable to assess	Remark

	wrong diluent, improper mixing, improper syringe filling etc.?		
F	In this case, was there an error in vaccine handling? (e.g. Break in cold chain during transport, storage and/or immunization session etc.)?	Yes / No / Unable to assess	Remark
G	In this case, was the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes / No / Unable to assess	Remark
H	In this case, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety etc.)?	Yes / No / Unable to assess	Remark

Section J: Attached copies of reports / documents etc. with this Case Investigation Form:

S. No.	List of document copies received (check appropriate box)	Available and submitted with CIF	Will be available, pending for submission	Not applicable	Applicable, but not available	Remarks (if any)
1.	Case Reporting Form (CRF)					
2.	Hospital patient treatment records / hospital discharge summary *(in case of hospitalized cases)* / doctor's OPD prescription / day care treatment record / OPD treatment record)					
3.	Doctor's prescription / treatment record for past / preexisting illness					
4.	Any clinical laboratory test report (Pathology / Microbiology / Hematology / Blood / CSF / Urine / AFP / any radiology imaging report / EEG report, etc.)					
5.	Post Mortem Report – preliminary *(in case of death)*					
6.	Post Mortem Report – final *(in case of death)*					
7.	Verbal Autopsy Form (in case of unexplained death/ not hospitalized)					
8.	Laboratory result of vaccine (if sent for testing)					
9.	Laboratory result of syringes/other drugs (if sent for testing)					
10.	Any other document relevant to case					

District AEFI Committee members

Name	Designation	Phone Number	Signature
1.			
2.			
3.			
4.			
5.			
6.			
7.			

Section K: DIO/ RCHO/ District Nodal Person *(Officer forwarding this report)*

DIO/ DRCHO/ District Nodal Person *(Officer forwarding this report)*

Name ..... Designation..... Mobile No*: .....

Email id*: ..... Signature..... Date/ Seal: .....

Complete Office address (with Pin code) .....

.....

District Immunization Officer to complete and submit in SAFE-VAC / Co-WIN SAFE-VAC (for COVID-19 vaccines) within 21 days of receiving the above information. SAFE-VAC: https://safevac.nhp.gov.in; Co-WIN - SAFE-VAC: https://www.cowin.gov.in/

For any support or help, write to: aefiindia@gmail.com; safevac.chi@gmail.com

Annexure-3:

Serious AEFI Case Notification Form – ADR Monitoring Center*	
ICSR No. _____	Reporting Format No.
Name & address of ADR Monitoring center (AMC):	
Patient Name	
Age: _____	Sex: Male/Female
Father/Husband's Name	
Complete Address of the Case with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)*	
PIN - PHONE -	
Date of Vaccination: __ __ / __ __ / __ __ __ __ Address of health facility where vaccinated (include name of village/urban area, block, DISTRICT and STATE)#:	
Name of vaccines with dose received (if known)	
Date of first symptom (D D M M Y Y Y Y)	Time of first symptom (H H M M) (AM/PM)
Hospitalization:(No/ Yes) Date- (D D M M Y Y Y Y)	Time of hospitalization (H H M M) (AM/PM)
Name and address of hospital (if hospitalized):	CR No./MRD No _____
Current status (encircle)	Death / Still Hospitalized / Recovered & Discharged with sequelae /Recovered completely and discharged / Left Against Medical Advice (LAMA) / Not hospitalized
If died, Date of Death (D D M M Y Y Y Y)	Time of Death (H H M M) (AM/PM)
Describe AEFI (signs and symptoms):	
Name & signature of AMC Coordinator/ Medical officer: Email: Contact No.	
*Date form sent to District Immunization Officer# (where patient was vaccinated)- __ __ / __ __ / __ __ __ __	
*Date form sent to State Immunization Officer# (where patient was vaccinated)- __ __ / __ __ / __ __ __ __	
*Date form sent to PVPI, Ghaziabad- __ __ / __ __ / __ __ __ __	
*Date form sent to Immunization Division / AEFI Secretariat (aefiindia@gmail.com)- __ __ / __ __ / __ __ __ __	
Name & signature of Pharmacovigilance Associate: E mail: Contact number:	

#The case is to be notified to the DIO of the district where the vaccine was administered.
***This form should be scanned and emailed simultaneously to DIO, SEPIO, PVPI and AEFI Secretariat.**

Annexure-4

AEFI – LABORATORY REQUEST FORM (LRF)

(To be completed by Drug Inspector/DIO. Vaccine/logistics sample should be sent with LRF)

AEFI category (Encircle): **Death / Hospitalized / Cluster / Disability/Others(specify)**_____

State		Case ID IND (AEFI) / Year / Serial No.	State Code / District Code /
District			
Block			

Name of Drug Inspector/DIO:	Date of filling LRF :
Designation:	Mobile No.:
Land Line (with STD Code) :	Fax No.:

Case Name				
Date of Birth	Age (in Months): (in days, if < 1 month) .....Days	---- months	Sex (please tick)	☐ Male ☐ Female

Complete Address of the Case with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)*

PIN- PHONE-

Date of vaccination	D D M M Y Y Y Y	Date of Onset	D D M M Y Y Y Y
Date of collection of specimen	D D M M Y Y Y Y	Time of collection of specimen	H H M M (AM PM)

1. Precise description of samples:

a) For vaccine/diluents specimens: (to be transported in reverse cold chain)

Mention vaccine/diluent	Quantity Sent	Name of Manufacturer (in BLOCK Letters)	Batch No.	Manufacturing Date	Expiry Date

b) For logistics specimens: (AD, Reconstitution, Disposable syringes)

Mention	Quantity	Name of Manufacturer	Batch No.	Manufacturi	Expiry

c) For Biological sample/specimen: (CSF, Blood, Urine, tissue samples etc including post-mortem tissue samples if any)

S no.	Type of sample	Date	Laboratory name

2. Test requested:
3. Preliminary clinical diagnosis of District AEFI committee:

4. Name & complete address of officials to whom laboratory results should be sent:

Send to	Complete address	Phone/Fax	Mobile	Email-ID
State Drug Controller				

State EPI Officer				
State Cold Chain Officer				
District Immunization Officer (DIO)				
Immunization Division (MoHFW)				
Others (specify)				

To be completed by lab officials after receiving the specimen

Date of receipt of specimen at laboratory	D	D	M	M	Y	Y	Y	Y

Name of person receiving specimen(s) at laboratory	

Condition of specimen upon receipt at lab (*encircle*)	Good*	Poor	Unknown

Comments by pathologist, virologist or bacteriologist:

Date specimen results sent from this lab	D	D	M	M	Y	Y	Y	Y

Name of laboratory professional	

Signature

Landline No. :	Fax No.:	Email Id:

Annexure-5

AEFI Causality Assessment Form-2023 (National)

NATIONAL ID	STATE		DISTRICT
PATIENT'S NAME	**VACCINE (S) GIVEN**		**REASON FOR REPORTING**
VACCINATION BY (ROUTINE / CAMPAIGN)	**DATE OF BIRTH**	**AGE**	**DATE OF DEATH**
DATE OF VACCINATION	**DATE OF FIRST SYMPTOMS**	**DATE OF HOSPITALIZATION**	**OUTCOME**

Status of Case documents availability

(1) CRF (Yes / No) (2) CIF (Yes / No) (3) Hospital records (Yes / No/ NA) (4) Post Mortem (Yes / No /NA)

(5) Verbal Autopsy (Yes / No /NA) (6) State CA (Yes / No) (7) Other documents (Yes / No / NA)

Documents availability checked & printed by - Name: ..... Date: ..... Signature: .....

Case documents Screening status

Case screened by : Name: ..... Date: ..... Signature: .....

Is this case a part of Cluster: Yes / No / NA, If Yes, Reported cluster / Indentified cluster No. of cases:

Final status of Case : F0 / F1 (If F0, mention reason) : .....

Case Summary:

Details of causality assessment by CA Sub & National committee (To be filled after CA Meeting)

	Valid Diagnosis	Classification
1. Valid Diagnosis & CA classification given by state AEFI committee		
2. Valid Diagnosis & CA Classification given by CA Sub committee experts		

3. Whether conclusion of CA Sub committee expert is consistent with conclusion of State AEFI Committee ? a) YES b) NO c) NA

If no, reason there of .....

4. Remarks (Quality review feedback by sub committee to State).....

Final Status of Causality Assessment

Details	Date		Status	Remarks (If F3 / F4)
Case discussed in CA Sub committee meeting			F2 / F3	
Case discussed in CA Sub committee meeting			F2	
Case discussed in NACM			F4 / F6	
Case discussed in NACM			F6	

STATE	DISTRICT	NATIONAL ID
«STATE»	«DISTRICT»	«NATIONAL_ID»

Step 1 (Eligibility)

Name Of the Patient	Name of one or more vaccines administered before this event	What is the valid Diagnosis?	Does the diagnosis meet a case definition?
«CHILD»			
Create your question on causality here Has the_____vaccine/vaccination caused_____(the event for review in step 2-valid diagnosis)			

Is this case eligible for causility assessment? Yes / No; If, "Yes", proceed to step 2

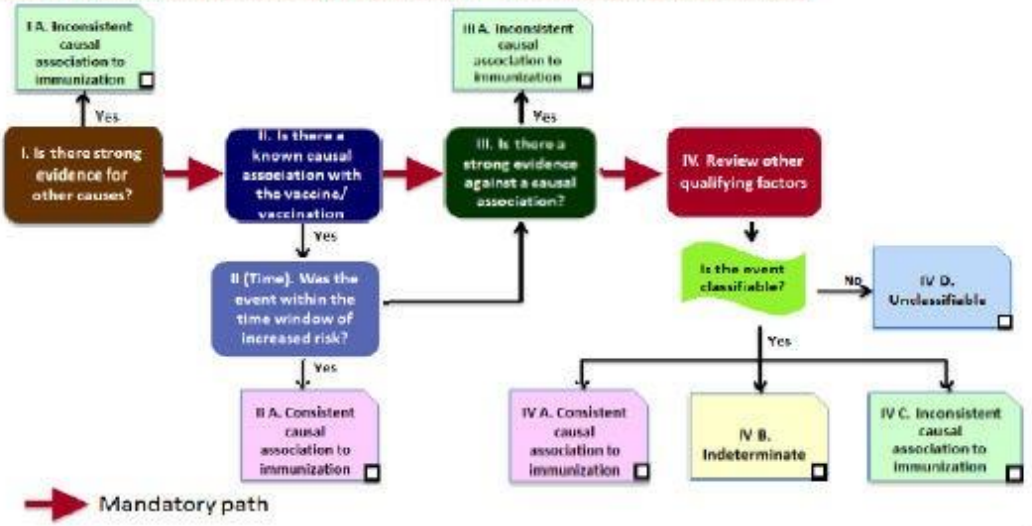
Step 2 (Event Checklist) ✓ (check) all boxes that apply

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	☐☐☐☐	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product		
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	☐☐☐☐	
2. Is there a biological plausibility that this vaccine could cause such an event?	☐☐☐☐	
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	☐☐☐☐	
Vaccine quality		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	☐☐☐☐	
Immunization error		
5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐☐☐☐	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	☐☐☐☐	
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐☐☐☐	
8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐☐☐☐	
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐☐☐☐	
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐☐☐☐	
Immunization anxiety (Immunization Triggered Stress Response - ITSR)		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	☐☐☐☐	
III. Is there strong evidence against a causal association?		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) **against** a causal association between the vaccine and the event?	☐☐☐☐	
IV. Other qualifying factors for classification		
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	☐☐☐☐	
2. In this patient did such an event occur in the past independent of vaccination?	☐☐☐☐	
3. Could the current event have occurred in this patient without vaccination (background rate)?	☐☐☐☐	
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	☐☐☐☐	
5. Was this patient taking any medication prior to the vaccination?	☐☐☐☐	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	☐☐☐☐	

Y: Yes N: No UK: Unknown NA: Not applicable or Not available

STATE	DISTRICT	NATIONAL ID
«STATE»	«DISTRICT»	«NATIONAL_ID»

Step 3 (Algorithm) review all steps and ✓ all the appropriate boxes



Notes for Step 3:

Step 4 (Classification) ✓ all boxes that apply

Adequate information available

A. Consistent with causal association to immunization

- ☐ A1. Vaccine product-related reaction (As per published literature)
- ☐ A2. Vaccine quality defect-related reaction
- ☐ A3. Immunization error-related reaction
- ☐ A4. Immunization anxiety-related reaction (ITSR**)

B. Indeterminate

- ☐ B1. *Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)
- ☐ B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent with causal association to immunization

C. Coincidental

- ☐ Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine

Adequate information not available

☐ **Unclassifiable**

Specify the additional information required for classification :

Tick Reason for Unclassifiable:

1. Supporting documents (Hospital Records/ Post Mortem- Histopathology, Chemical analysis/ Verbal autopsy) not available
2. Documents are available but inadequate information in records.
3. Standard Reporting format (CRF/PCIF/FCIF) not available (incomplete documents)

*B1. This is a potential signal and maybe considered for investigation
** Immunization Triggered Stress Response

Summarize the classification logic in the order of priority:

With available evidence, we could conclude that the classification is _____ because:

With available evidence, we could NOT classify the case because:_____

STATE	DISTRICT	NATIONAL ID
«STATE»	«DISTRICT»	«NATIONAL_ID»

Level of certainty as per Brighton's Classification (with reason for the same)

Feedback on the case for District / State / Others (specify):

S.N.	Name of Experts	Signature	Date
1			
2			
3			
4			

Appendix B

Example of summary tabulations

Note: *These examples can be modified by manufacturer and/or importer to suit specific situations, as appropriate.*

Table 01: Estimated cumulative subject exposurefrom clinical trials

Treatment	Number of Subjects
Biological product	
Comparator	
Placebo	

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomization schemes for ongoing trials.

Table 02: Cumulative subject exposure to "New Drug"from completed clinical trials by age and sex*

	Number of Subjects		
Age Range	**Male**	**Female**	**Total**

Table 03: Cumulative subject exposure to "New Drug" from completed clinical trials by racial/ethnic group*

Racial/Ethnic Group	Number of Subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

*Data from completed trial as of [date]

Table 04: Cumulative exposure from marketing experience from India

Indication	Sex		Age				Dose / Strength			Formulation		
	Male	Female										
Overall												
Indication 1												
Indication 2*												

Includes cumulative data obtained from month/day /year through month/ day/ year, where available.

Table 05: Interval exposure from marketing experience from India

Indication	Sex		Age				Dose/ Strength			Formulation		
	Male	Female										
Indication 1												
Indication 2*												

Includes interval data obtained from month/day /year through month/day/year, wherever available

Table 06: Cumulative exposure from marketing experience from rest of the world

Indication	Sex		Age				Dose/ Strength			Formulation			ROW (which ever applicable)				
	Male	Female											EU	Japan	Mexico	US/Canada	Other
Overall																	
Indication 1																	
Indication 2*																	

Includes cumulative data obtained from month/day/year through month/day/year,where available

Table 07: Interval exposure from marketing experience from rest of the world

Indication	Sex		Age				Dose/ Strength			Formulation			ROW (which ever applicable)				
	Male	Female											EU	Japan	Mexico	US/Canada	Other
Indication 1																	
Indication 2*																	

Includes interval data obtained from month/day/year through month/day/year, wherever available

Table 08: Cumulative tabulations of Serious Adverse Events fromclinical trials

System OrganClass	Investigational Product		Active Comparator		Placebo*	Causality Assessment (Related (R) and Notrelated (NR)
Preferred Term	Listed	Not Listed	Listed	Not Listed		
Blood and lymphatic system disorders						
Anemia						
Bone Marrow Necrosis						
Cardiac						
disorders						
Tachycardia						
Ischemic cardiomyopathy						

Table 09: Number of AE/AEFIs using the term (System Organ Class(SOC) and preferred term (PT) from Post-Marketing Sources

	Report Sources (Literature, Spontaneous, solicited or any other)					Non-interventional post-marketing sources	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative		Interval	Cumulative
SOC 1							
PT							
SOC 2							
PT							

Appendix C

Tabular Summary of Safety Signals that were ongoing or closed during the reporting Interval (Reporting Interval: DD-MM-YYYY to DD-MM-YYYY)

Signal term*	Datedetected @	Status (ongoing or closed)#	Date closed (for closed signals)	Source of Signal**	Reason for evaluation & summary of key data @@	Method of signal evaluation	Action(s) taken or planned##
Stroke	MM/YYY	Ongoing	MM/YY Y	Meta analysis (published trials)	Statistically significant increase in frequency	Review meta-analysis and available data	Pending
Thrombosis with Thrombocytopenia Syndrome	MM/YYY	Closed	MM/YYY	Spontaneous case reports & one case report in Phase IV trial	Rash already an identified risk SJS not reported in pre authorization CTs. 4 apparently unconfounded reports within 6 months of approval; plausible time to onset	Targeted follow up of reports with site visit to one hospital. Full review of cases by manufacturer and/or importer dermatologist and literature searches	RSI updated with a Warning and Precaution DHPC sent to oncologists Effectiveness survey planned 6 months post DHPC. RMP updated.

***Signal term:** A brief descriptive name of a medical concept for the signal. The description may evolve and be refined as the signal is evaluated. The concept and scope may, or may not, be limited to specific term(s), depending on the source of signal.*

***@ Date detected (month/year):** Month and year the manufacturer and/or importer became aware of the signal.*

***#Status:** Ongoing: Signal under evaluation at the data lock point of the PSUR. Provide anticipated completion date, if known; closed: Signal for which evaluation was completed before the data lock point of the PSUR*

***Note:** A new signal of which the manufacturer and/or importer became aware during the reporting interval may be classified as closed or ongoing, depending on the status of signal evaluation at the data lock point of the PSUR.*

*$ **Date closed (month/year):** Month and year when the signal evaluation was completed.*

***Source of signal:** Data or information source from which a signal arose. Examples include, but may not be limited to, spontaneous Adverse Event Reports, clinical trial data, scientific literature, non-clinical study results, or information requests or inquiries from a regulatory authority.*

*@@ **Reason for evaluation:** A brief summary of key data and rationale for further evaluation.*

*## **Actions taken or planned:** State whether or not a specific action has been taken or is planned for all closed signals that have been classified as potential or identified risks. If any further actions are planned for newly or previously identified signals under evaluation at the data lock point, these should be listed. Otherwise leave blank for ongoing signals.*

Appendix D

Annexure- 1

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	
	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

Annexure- 2

Standard Line-listing (excel) Format as per CIOMS Form

Excel Column	Standard Line listing Content	
A	Sr. no.	
B	Case UID	
C	Year	
D	Country	
E	Reaction Information	Pt. Initials (if available)
F		Age (Years)
G		Weight (Kg)
H		Male/ Female
I		Reaction/ Event Onset Date
J		Describe Reaction/ Event (DD/MM/YYYY)
K		Adverse Event Preferred Term (PT)
L		System Organ Class (SOC Name)
M		Relevant tests/ laboratory data with dates, if any
N		Event Listed/ Non-Listed
O		Event Serious/ Non-Serious
P		SAE Category (PATIENT DIED, HOSPITALIZATION, LIFE THREATENING, DISABILITY, CONGENITAL ANOMALY, OTHER MEDICALLY SIGNIFICANT)
Q	Suspected Drug(s)/ Vaccine Information	Suspected Drug(s)/ Vaccine
R		Antigen/ API Name
S		Daily Dose (ml/mg/gm)
T		Route of Administration
U		Indication for use
V		Therapy Dates (from/to) (DD/MM/YYYY)
W		Therapy Duration
X		Did Reaction/Event Abate after Stopping Drug/Vaccine
Y		Did Reaction/Event reappear after re-introduction?
Z		Batch/ Lot Number
AA	Concomitant Drug(s)/ History	Concomitant Drugs/ Vaccines
AB		Dates of Concomitant Drugs/ Vaccines (DD/MM/YYYY)

AC		**Other Relevant History**
AD	**Manufacturer/ or MAH Information**	**MAH Name & Address**
AE		**MFR Control No.**
AF		**Report Source (HCP, STUDY, LITERATURE, REGULATORY AUTHORITY, OTHER)**
AG		**Report Type (Initial/ Follow-up)**
AH		**Date of this Report (DD/MM/YYYY)**
AI	**Outcome**	**Recovered, Recovering, Not recovered, Fatal, Recovered with sequelae, Unknown**
AJ	**Event Summary**	**Reporter Verbatim**
AK		**Case Narrative**
AL		**PvOI/PSUR Comments**
AM	**Causality**	**Reporter Causality**
AN		**Company Causality**
AO		**Causality as per AEFI Surveillance & Response Operational Guidelines or WHO AEFI Classification i.e., A(A1,A2,A3,A4), B (B1,B2), C or unclassifiable**
AP	**Date of initial receipt of the information received by the applicant/ MAH (DD/MM/YYYY)**	
AQ	**Date of submission of CIOMS Form to CDSCO (via email/Hard File) by Applicant/ MAH (DD/MM/YYYY)**	
AR	**Remarks (if any)**	

Note: Do not merge the excel cells, do not let cells blank, if information is not available, NA shall be filled. Global & India specific data may be entered in same excel sheet as country option is provided in "D" column.

	TITLE	Division Name	PSUR/PvPI/AEFI Division
	Procedure for handling of Complaints or reports on Adverse Events Following Immunization (AEFI)	Document No.	BIV-P-29
		Revision No.	01
		Effective Date	
		Page No.	

Prepared By		**Approved By**		**Authorized By**	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

Control Status

1.0 Purpose

To lay down a procedure for handling the complaints and reports received on Adverse EventsFollowing Immunization (AEFI) from all accessible sources.

2.0 Scope

This document is applicable to all Complaints and reports on Adverse Events Following Immunization.

3.0 Responsibility

Overall responsibility lies with Head of Division, PSUR/PV/AEFI & Vaccines and others responsibility are given in the description below.

4.0 Accountability

Head of concerned division PSUR/PV/AEFI Division, Biological Division and head of CDSCO.

5.0 Procedure

5.1 Process Inputs

S. No.	Input	Source	Freq./When	Ref.Doc.	Review Criteria
5.1.1	Initial report Received via email/e-office along with supporting documents	Submission of AEFI report by MAHs or FIR, PIR or DIR by UIP along with necessary documents.	After receipt of AEFI report from firm or UIP.	Drugs and Cosmetics Act, 1940 and Rules there under 1945, NDCT Rules, 2019, Guidance for Industry-Pharmacovigilance	Verification of the report based on guidance document and Fifth Schedule of New Drugs and Clinical Trial Rules 2019.

				Requirements for Human Vaccines.	
5.1.2	Unique Identification No. (E. Comp. No./ E-office F.No.) for application received by this office	Central Registering Unit	After receipt of the application	Nil	Verifying every application if proper Identification No. has been allotted e-receipt/E.Comp.No.
5.1.3	Responses to Queries raised during review of report	Submission of AEFI by MAHs or UIP.	Only when query is raised	Query letter and other relevant documents	Verification of the query response to the information sought vide the query letter

5.2 Process Interface

S. No.	Activity	Responsibility	Ref. Doc.
5.2.1	Screening of Report and allotment to PSUR/PV/AEFI Division	Officer from CRU Division/PVPI/PSUR	Guidance for Industry-Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024
5.2.2	Reports that are received in the division via e-office are marked by the NO to officers for review.	Head of the AEFI Division	Guidance for Industry-Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024
5.2.3	Review of report include scientific assessments	RO/NO/DDA	Guidance for Industry-Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024
5.2.4	If submitted reports are not sufficient, query to be raised to concerned applicant organization for providing more details or reports	Head of the AEFI Division	Guidance for Industry-Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024
5.2.5	If during review it is considered that the new or serious adverse event or cluster has occurred, a letter is forwarded to concern zonal office to start the investigation on the matter.	Head of CDSCO/ Head of the AEFI Division	Guidance for Industry-Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024
5.2.6	Zonal office shall initiate the investigation by verifying the current status of cold chain, storage of product etc. and investigation of	Zonal/ Sub zonal office/ Head of the PSUR/PV/AEFI Division	Guidance for Industry-Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024

	manufacturing site, if necessary. The investigating officer shall also collect samples of product and send it to CDL, Kasauli for testing, if required.		
5.2.7	CDL Kasauli shall send the test report back to zonal officer with all necessary details. If the product is declared as "Not of Standard Quality" by testing	Zonal/ Sub zonal office/ Head of the PSUR/PV/AEFI Division	Guidance for Industry- Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024
5.2.8	Also AEFI division, Ministry of Health and Family Welfare shall forward the First Information Report (FIR), Preliminary Investigation Report (PIR) & Detailed Investigation Report (DIR) along with causality assessment report to CDSCO (HQ).	Head of the AEFI Division	Guidance for Industry- Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024
5.2.9	Based on the details submitted by zonal offices and AEFI division, the regulatory decision on the compliant shall be made by Head of AEFI division in concurrence with the Head of Vaccine division and with the approval of DCGI.	Head of the AEFI Division	Guidance for Industry- Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024
5.2.10	The regulatory decision made on complaint shall be communicated by Biological Division to SLA/Zonal office and/or manufacturer as the case may be within the stipulated time period for necessary action.	Head of the AEFI Division	Guidance for Industry- Pharmacovigilance Requirements for Human Vaccines, AEFI Operational Guidelines, 2024

5.3 Process Output

S. No.	Output	To	Ref. Doc.
5.3.1	Query Letter	MAH of Human Vaccines	

5.3.2	Regulatory Action	MAH of Human Vaccines/SLA/Complaint	

5.4 Process Monitoring

S. No.	Monitoring Brief	Acceptance Criteria	Freq./When	Resp.	Ref. Doc.
5.4.1	Process Time	-	After receipt of the application	Head of the AEFI Division	

8.0 References (incl. ext. origin docs)

6.1 Drugs & Cosmetics Act 1940 & Rule 1945

6.2 Guidance for Industry- Pharmacovigilance Requirements for Biological Products.

6.3 AEFI, Surveillance and Response Operational Guidelines, Ministry of Health andFamily Welfare.

9.0 Abbreviations

AEFI	Adverse Event Following Immunization
FIR	First Information Report
DIR	Detailed Investigation Report
PIR	Preliminary Investigation Report
UIP	Universal Immunization Programme
GMP	Good Manufacturing Practices
CDSCO	Central Drugs Standard Control Organization
SLA	State Licensing Authority
DCG (I)	Drugs Controller General (India)
NO	Nodal Officer
RO	Reviewing Officer
DDA	Deputy Decision Authority
CDL	Central Drugs laboratory\

10.0 Revision history

Revision No.	Reason(s) for Revision
00	New SOP
01	Due to revision in AEFI operational Guidelines, 2024

	TITLE		Division Name	PSUR/PVPI/AEFI Division
	SOP to prepare & evaluate Key Performance Indicators for activities related to Pharmacovigilance		Document No.	BIV-P-28
			Revision No.	00
			Effective Date	
			Page No.	

Prepared By		Approved By		Authorized By	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

Control Status

1.0 Purpose

To lay down a procedure to prepare & evaluate Key Performance Indicators (KPI) for Zonal/Sub-zonal offices and Biological Division of CDSCO (HQ) with respect to activities related to Pharmacovigilance.

2.0 Scope

This document is applicable to prepare & evaluate Key Performance Indicators for PSUR/PVPI/AEFI Division of CDSCO (HQ) with respect to activities related to Pharmacovigilance.

3.0 Responsibility

3.1 Head of PSUR/PVPI/AEFI Division of CDSCO (HQ), New Delhi shall be responsible for submission of KPI with regard to Pharmacovigilance related activities.

3.2 QMS Monitoring Division shall be responsible for evaluation of KPI data.

4.0 Accountability

Head of PSUR/PVPI/AEFI Division, Biological Division and Head of CDSCO.

5.0 Procedure

5.1 Head of PSUR/PVPI/AEFI Division, CDSCO-HQ, New Delhi shall submit Key Performance Indicators of activities related to Pharmacovigilance as per the current version of Annexure I once in three months.

5.2 PSUR/PVPI/AEFI Division shall compile and evaluate the KPI data based on the number of complaints received including from Biological Division, DCG (I) secretariat and prepare KPI considering the activities as the main criteria to define performance indicator.

5.3 **Evaluation criteria for KPI**

5.3.1 The minimum threshold value for meeting the acceptance criteria is based on the no. of inspection carried and no. of PSUR meetings convened based on the PSUR received in the division.

5.3.2 Zonal/Sub-zonal offices and PSUR/PVPI/AEFI Division shall maintain 100% score for maintaining timelines & compliance to SOP.

6.0 Annexure/Format

Annexure/Format No.	Title
Annexure-I	KPI for Zonal/Sub-zonal offices for activities related to Pharmacovigilance
Annexure-II	KPI for Zonal/Sub-zonal offices for activities related to PSUR

7.0 References

Doc. No.	Title
1	Guidance document for Zonal/Sub-zonal offices
2	New Drugs and Clinical Trial Rules, 2019

8.0 Abbreviations

Acronym	Full Form
CDSCO	Central Drugs Standards Control Organization
DCG(I)	Drugs Controller General (India)
QMS	Quality Management System
SOP	Standard Operating Procedures
KPI	Key Performance Indicators

CDL	Central Drugs Laboratory
NSQ	Not of Standard Quality

9.0 Revision History

Revision No.	Reason(s) for Revision
00	New SOP

Annexure-I of BIV-P-28

'Key Performance Indicators for activities related to Pharmacovigilance'

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

FDA Bhawan, ITO, Kotla Road, New Delhi- 110002

Zone/Sub-Zone:

Month:

S. No.	Name and address of manufacturing site	Vaccine administered	Date of inspection	Inspection Team	Purpose of inspection (AEFI)	Recommendation of Zonal/Sub-zonal Head on inspection report	Remarks

Annexure-II of BIV-P-28

'KPI of different activities performed by **PSUR/PV/AEFI Division**'

Central Drugs Standard Control Organization

Directorate General of Health Services, Ministry of Health and Family Welfare,
Government of India
FDA Bhawan, ITO, Kotla Road, New Delhi -110002

PSUR/PV/AEFI Division: **Period:**

S. No.	Number of PSUR Expert Committee Meetings held	No. of Vaccines proposal deliberated	Minutes of Meeting	Action taken

Period	No of PV Inspections carried on	Action taken

	TITLE		Division Name	PV Division
	Procedure for planning, preparation and conducting pharmacovigilance inspection and report writing.		Document No.	PV-INS-001
			Revision No.	01
			Effective Date	
			Page No.	1088 of 1103

Prepared By		Approved By		Authorized By	
Name		Name		Name	
Designation		Designation		Designation	
Sign		Sign		Sign	
Date		Date		Date	

Control Status

1.0 Purpose:

To lay down procedures for planning, preparation and conducting pharmacovigilance (PV) inspection and report writing in accordance with the Fifth Schedule, NDCT Rules-2019.

2.0 Scope:

This document is applicable for planning, preparation and conducting pharmacovigilance inspection and report writing for verification of compliance with Fifth schedule of NDCT Rules, 2019 at the site of manufacturer and importer where the Pharmacovigilance System is established.

3.0 Responsibility:

3.1 DDC (I) of zonal/sub zonal office/ DDC(I) PvPI/PSUR shall be responsible for planning, preparation, conducting inspection and report writing in coordination with PvPI/PSUR division, CDSCO, HQ.

3.2 The head of concerned zone/sub zone shall be responsible for overall compliance of the SOPs.

4.0 Accountability:

Head of QMS shall be responsible for overall compliance of the SOPs.

5.0 Procedure:

Pharmacovigilance inspection at the MAH's pharmacovigilance site shall be carried out in order to verify compliance with Fifth Schedule of NDCT Rules, 2019.

5.1 Planning of PV Inspection

5.1.1 Routine Inspection:

5.1.1.1 CDSCO (HQ) shall issue a letter to all vaccine manufacturers/importers to furnish the following documents to PSUR Division at CDSCO, HQ (not limited to);

- Summary of established PV system
- Name, email ID of PvOI
- Name, address, contact details of the current premises where PV system is established or operational.
- Self-Inspection report (if any).

5.1.1.2 The routine inspection is usually PV system inspection and the objectives of inspection shall be to verify that MAH has personnel, system, facilities and procedures in place to meet regulatory requirements as per Fifth Schedule of NDCT Rules, 2019.

5.1.1.3 Inspection shall be prioritized based on the potential risk to public health, nature of products, extent of use, numbers of products that the MAH has in Indian market.

5.1.2 For targeted inspection/unannounced inspection:

The targeted inspection shall be conducted as and when there is a trigger. The following triggering factors on risk based approach (but not limited to) shall be considered:

- Continuous delays or omission or poor quality in the reporting of ICSRs/PSUR/RMPs.
- Failure to provide the requisite information or data within deadline specified by DCG(I).
- Delay or failure to carry out specific PV obligations.
- Previous inspection experience, if any/ history of compliance.
- Delay in implementation of appropriate corrective and preventive action(s) (CAPA)
- Product withdrawal without prior notice to DCG(I).
- Other sources of information or complaints.
- Number of product permission held by MAHs.
- Number of PV staff/personnel.
- Any emerging safety issue relating to any vaccine product held by the MAH.

- Number of product recall or associated complaints
- Any change with respect to PvOI (Pharmacovigilance officer in-Charge) or major changes in PV system.

5.1.3 Inspection team:

5.1.3.1 Composition of team:

The team shall comprise of

- One or two Drugs Inspector(s) from concerned zonal/sub zonal office& trained Drugs Inspector shall be designated as team leader.
- Drugs Inspector from CDSCO, HQ shall participate onsite inspection or virtually as per convenience.
- One PvPI expert from National Coordination Centre.
- Participation of Pharmacovigilance expert may be opted if needed (e.g. Complaint Investigation)
- The inspection shall be carried out preferably on site. However, in emergency situation inspection may be carried out by virtual mode or in hybrid mode.

5.1.3.2 Responsibility of inspection team:

Responsibility of inspection team shall be as follows:

- To conduct PV inspection
- To agree on inspection scope
- To discuss and resolve, wherever possible, any major problem which may occur during the inspection process.
- To ensure that all team members play an active role in the inspection process.
- To make decision on inspection findings by way of consensus, however, where this is not possible, the team leader shall make the final decision.
- To prepare an inspection report.

5.1.3.3 Responsibility of the team leader:

The team leader shall be responsible to organise, coordinate, lead during all stages of inspection and act as spokesperson.

5.1.3.4 Preparing for inspection:

The designated inspection team shall review the related documents available in the office file in coordination with PSUR division. This shall include review of the following documents (but not limited to):

- Summary of established PV system
- Name and email ID of PvOI
- Name, address, contact detail of the premises where PV system is established.
- Self-Inspection report (if any).
- PSUR data of product for verification at site, if needed.
- Any recent changes made at the PV site etc.
- Any data or information not submitted by MAH shall be noted for communication to the firm.
- Preparation and sharing of tentative inspection agenda with the MAH at least 7 days before the inspection in case of routine inspection.
- List of all SOPs.
- The checklist (annexure 1) for inspection shall be given to MAH for filling the self-appraisal by the manufacturer at least 7 days before inspection.

5.2 Procedure for conducting Inspection of Pharmacovigilance system:

5.2.1 Routine inspection:

5.2.1.1. Inspection shall be carried out as per the requirements of NDCT Rules 2019. (The inspection checklist is enclosed as **Annexure 1** for aide memoire purpose during inspection).

5.2.1.2 The inspection team shall conduct an opening meeting with the key personnel of the Pharmacovigilance site wherein the scope and purpose of the inspection shall be discussed. Systematic inspection shall be carried out by taking rounds, interviewing the key personnel, observing the activities and looking into relevant documents/electronic system. The deficiencies should be discussed with the firm's personnel during the course of inspection for better understanding, if appropriate.

5.2.1.3 The inspection team shall examine all portion of PV system, the process of adverse event collection and processing, software used (if any), and shall verify the professional qualification of technical staff to be employed. The team shall also examine and verify the statement made in the PSUR application, if any in regard to their correctness and the capability of the applicant to comply with the requirements of competent technical staff.

5.2.1.4 During the course of inspection, inspection team shall critically look into following details using a risk-based approach (not limited to): -

- Adequacy of Quality Management System& availability of PVMF (Pharmacovigilance Mater File).
- Adequacy of qualification, training and competency of the personnel responsible for the PV system.
- Reviewing the procedures, activities, personnel and facilities in place at the firm.
- Operation of PV system.
- Depth and comprehensiveness of Self Audit review.
- Review of compliance of last inspection findings.

- At the end of the inspection, a closing meeting shall be conducted and the observations are to be discussed with the in charge of PV system of MAH.

5.2.2 Targeted Inspection/un announced inspection:

The following activities (not limited to) shall be verified:

- Reviewing the standard procedures, activities, personnel's and facilities to verify the cause or trigger factor.
- During the targeted inspection in addition to verification of general things as mentioned above specific records with respect to the product in question and safety concern if any needs to be verified.
- Verification of significant changes made to PV system, e.g. changes in safety database, contracted site etc.
- Examination of relevant computerized system and facilities to verify documents archives and computer server room, as applicable.
- Review of ICSR in safety database, if needed.
- Verification of compliance to last inspection findings.
- Verification of appropriateness of CAPA.

5.3 Inspection findings:

Each inspection shall result in an inspection report and the finding shall be classified into critical, major and minor.

5.3.1: Critical: Fundamental weakness in the PV systems or practices that adversely deviate from the PV regulations and or affected the rights and safety of patients, or poses a potential risk to public health

5.3.2 Major: It's a significant weakness in one of more PV processes or practices, or a fundamental weakness in part of one or more Pv processes or practices that is detrimental to the whole processes and/ or could potentially adversely affect the rights, safety or well being of patients and or could potentially pose a risk to public health and or represents a violation of applicable regulatory requirements which is however not considered serious.

5.3.3 Minor: It's a weakness in the part of one or more PV processes or practices that is not expected to adversely affect the hold Pv systems all process and or the rights, safety or wellbeing of patients.

5.4 Writing of an Inspection Report:

5.4.1 Inspection report shall be prepared by the team mentioning the details of the manufacturer/importer (MAH), names of team members, date of inspection, purpose of inspection and observation(s), if any, made during the inspection along with the recommendation.

5.4.2 Checklist shall be filled properly and the Inspection report shall include all the elements of PV system as per Fifth Schedule of NDCT Rules, 2019.

5.4.3 The observation (s) shall include the general information about the PV unit located in

MAH site, personnel, documentation and records (e.g. specification, compliance history of contractor where relevant, known safety concern about the product marketed by the MAH, recent organization changes such as merger or acquisition if any, SOP's, self-inspection, number of MA held by MAH in the country and any other additional risk minimization activities taken up by MAH etc).

5.4.4 Inspection report shall contain the deficiency(ies) pointed out at the time of inspection which shall be listed serially and shall be classified as mentioned under section 5.3.

5.4.5 Recommendation shall be given on the basis of observations mentioned in the inspection report and level of compliance and needs to be signed by team members.

5.4.6 Duly signed inspection report along with inspection checklist shall be submitted to the concerned head of zonal/sub zonal office of CDSCO for review.

5.5 Inspection follow up:

When non – compliance with PV obligations is identified during an inspection, follow up shall be taken until a CAPA is completed. The following follow-up actions shall be considered, as appropriate:

5.5.1 Review of the MAH's CAPA plan;

5.5.2 Review of the periodic progress reports, when deemed necessary;

5.5.3 Re- inspection to assess appropriate implementation of CAPA plan;

5.5.4 Requests for submission of previously un submitted data, submission of variations e.g., to amend product information; submission of impact analyses, e.g., following review of data that were not previously considered during routine signal detection activities;

5.5.5 Request for issuing safety communications, including amendments of marketing and or advertising information;

5.5.6 Other product related actions depending on the impact of the deficiencies and the outcome of follow up action (this may include recalls or actions relating to the marketing authorizations or clinical trial authorizations).

5.6 Review and Recommendation:

The concerned head of zonal/sub zonal office shall review the inspection report with respect to completeness of all inspection points as mentioned under section 5.2.1/5.2.2 (not limited to) and forward the inspection report with specific recommendation along with evidences (if any) to DCG(I) for further review and taking appropriate regulatory action, if any, for conclusive outcomes.

6.0 Annexure/Format:

Inspection Checklist/Annexure 1

7.0 References:

Document no.	Title
1.	Guidance for industry on Pharmacovigilance requirements for biological products
2.	Pharmacovigilance Guidelines for Marketing Authorization holders of Pharmaceutical products in India
3.	SOP for SOPs
4.	NDCT Rules,2019

8.0 Abbreviation:

Acronyms	Full form
DI	Drugs Inspector
ADC(I)	Assistant Drugs Controller (India)
DDC(I)	Deputy Drugs Controller(India)
DCG(I)	Drug Controller General (India)
SOP	Standard Operating Procedure
PV	Pharmacovigilance
MAH	Marketing Authorisation Holder (Manufacturer and importer of Human use vaccine)
NDCT	New Drugs and Clinical Trials Rules,2019
AEFI	Adverse Events Following Immunization
ICSR	Individual Case Safety Report
PVOI	Pharmacovigilance Officer In-charge
RMP	Risk Management plan

PSUR	Periodic Safety Updated Report
CAPA	Corrective Action and Preventive Action
PvPI	Pharmacovigilance program of India
IPC	Indian Pharmacopoeia Commission
PVMF	Pharmacovigilance Master File
MAA	Marketing Authorization Applicant

9.0 Revision History:

Revision No.	Reason(s) for revision
00	Created new
01	1) 4.0 Accountability: It is included that Head of QMS shall be responsible for overall compliance of the SOPs instead DCG(I). 2) 5.1.3 Inspection team: It is included that • One PvPI expert from National Coordination Centre • Participation of Pharmacovigilance expert may be opted if needed (e.g., Complaint Investigation)

Annexure-I

Inspection Checklist for Pharmacovigilance system

Introduction		Mention the following 1. Date and time of inspection 2. Inspectorate staff and their designation 3. Objective of inspection 4. Detailed address & contact details of site of Inspection
Company Profile		
Company name		M/s xxxxxxxxxxxxxxx Xxxxxxxxxxxxx XXXX, state, INDIA
Company's registered office	Y / N	If Yes, Mention postal address with PIN code, telephone No. and contact person's e-mail and website of the company
Company's main Activities		Strike Off 1. Import Stock, Sale ……. ( ) 2. Manufacture, Stock, Sale……..( )
Medicinal Products Dealt by the company		Bio-therapeutics 1. …… 2. ……. Human Vaccine 1. …… 2. ……. 3. ……. Others 1……

List of all operational licences for the above mentioned activities		1. Mfg. Lic.…… 2. Import Lic.…… 3. Sale/ stock Lic…… 4. Any Other Lic…….
PV - SYSTEM		
Company's PV- Head work station (Global)	Y / N	If Yes, Mention postal address with PIN code, telephone No. and contact person's e-mail and website of the company
Company's PV- Head work station (INDIA)		If Yes, Mention postal address with PIN code, telephone No. and contact person's e-mail and website of the company
Company's PV branch offices (INDIA)	Y / N	If Yes, Mention postal address with PIN code, telephone No. and contact person's e-mail and website of the company
PV Officer In charge ,India	Y / N	If Yes, Mention the following; 1. Name, contact No, E-mail 2. Educational Qualification 3. Training: 4. Experience:
Total number of PV staff working full time in the company (India)		Also verify the organogram provided by the company
No. of Temporary staff working partly within the company		If Yes, Mention their job particulars in brief
PV system staff arrangement hierarchy	Y / N	If yes, please attach the organogram
PV-QA exists or not	Y / N	If Yes, pl. clarifies,

		1. No. of staff 2. Their designation 3. Work flow 4. SOPs 5. Duties & responsibilities
Whether PV-operation is independent of the PV-QA	Y / N	If No, where the conflicting points are remain.
Periodic safety update reports (PSURs)	Y / N	If yes, pl. clarifies, 1. Personnel involved, their qualification, training, experience 2. Whether separate staff for bio therapeutics, vaccine, pharmaceuticals 3. Medical writing by whom, training, experience, Qualification. 4. PSUR scheduling, 5. Format and content, Timeline of submission
Risk-management system	Y / N	If yes, pl. Clarify, 1. Who does what ? 2. When Does ? 3. How done ? 4. Risk-management plan format and content, 5. Compliance with risk-minimisation measures which are beyond routine pharmacovigilance
Sourcing of ADRs	Y / N	1. Who are involved in sourcing ? 2. The list of Sources for each drug 3. How they collect ADRs 4. Whether they log each ADR 5. Check the integriety of the log –book. 6. What are the after-process of each logged ADR.
Management and reporting of adverse reactions	Y / N	If yes, Receipt of human adverse drug reactions(ADRs) from all sources which is emerging from use of a new drug, collection and processing and forwarding the ADRs reports to Central Licensing Authorities CLA and follow up processes etc.
Quality management system (QMS)	Y / N	If yes, Facilities and equipment for pharmacovigilance, Audit (internal- and external) and CAPA process, Initial and on-going training, evaluation of training, maintenance of training records and retraining , if needed etc.
PV-System Related Documents		

PV system staff Job Description (JD)	Y / N	If yes, Total number 1. For permanent Staff 2. Temporary staff 3. Hired agency staff
List of SOPs prepared?	Y / N	Check that the activities are serially presented according to the flow of activities and numbered accordingly
All SOPs are logically formatted in uniform pattern?	Y / N	Check duplication of job responsibilities, if any, whether overloaded, overlapped duties? Validity?
PV Master document prepared	Y / N	If yes, mention 1. Identification No. Version No. 2. Implementation date 3. Archival Area 4. Access Control 5. Reference Document. for preparation of PV-Master File
Whether PV-master Document complies to CDSCO PV guideline for MAH	Y / N	If no. where are the deviations 1. …… 2. …… 3. …….. 4. ……
Job responsibilities, defined for each staff	Y / N	If yes, mention and verify, with 1. Organogram 2. Whether signed by the competent authority in the company
TRAINING		
Training module prepared?	Y / N	Verify the module and mention salient features

Training conducted for the staff	Y / N	If yes, mention 1. No. of staff trained / schedule 2. Outcome 3. Records / data
PV activities Out sourced?	Y / N	If yes, mention 1. No. of parties 2. Names of each party 3. Duties assigned to each party 4. Agreement no. & date of contract with each party.
Product quality	Y / N	If yes, review of quality complaints and trend analysis
ARCHIVAL		
Archiving	Y / N	If yes, incharge officer, access control, Record management, Archiving facilities
Paper based Documents		
Computer based documents		
Linkages with Global data base		
Data mining by Doctors	Y / N	Allowed or not? If allowed how it is protected ?
Data Sharing ?		
Data publication ?		
Current Status of Clinical Trial, If any including Phase-IV trials, Development Safety Update Reports (DSUR) and Investigator Brochure(IB) details.		

MOST IMMEIDATE
BY FAX/SPEED POST

F. No. A.22011/01/2012-D
Government of India
Ministry of Health & Family Welfare
Directorate General of Health Services
Central Drugs Standard Control Organization
FDA Bhawan, Kotla Road,

New Delhi. Dated the 10th December, 2012

To

DDC(I)'s/DDC(I) I/c,
CDSCO's Zonal Offices at Ghaziabad, Mumbai, Chennai,
Kolkata, Hyderabad and Ahmedabad.

Subject:- Constitution of Adverse Event Following Immunization (AEFI) Cells at all Zonal offices of CDSCO.

Sir

I am directed to say that it has been decided that an Adverse Event Following Immunization (AEFI) Cell will be constituted at all Zonal HQs of CDSCO with immediate effect. The said cell will consist of at least one Drugs Inspector and one TDA who will work exclusively for the Adverse Event Following Immunization (AEFI) activities.

2. This has the approval of DCG(I).

Yours faithfully,

(Pitam Singh)
Deputy Director Admn.(Drugs)

Copy to:-

i)Personal staff of DCG(I).
ii)PA to DDA(D).
iii)Guard file.

GBT/RS/SS/NRS/2023-24
Government of India
Central Drugs Standard Control Organization
Directorate General of Health Services

ITO, Kotla Road,
FDA Bhawan, New Delhi
Date: 26 DEC 2023

Office Order

It was felt necessary that the activities of all subordinate offices under the control of Drugs Controller General (India) should be uniform and all activities are implemented rationally with transparency, accountability and predictability. Accordingly, the Guidance documents for Zonal, Sub-Zonal & Port offices was prepared in 2011 and implemented since then. It sets out nature of work that Zonal, Sub-Zonal and port offices generally carried out and the guidelines about the policy that should be followed in disposing of work & duties.

In recent times there are many changes in the procedures of Zonal, Sub-Zonal and port offices activities due to introduction of new Rules and regulation, online system through SUGAM portal and delegation of some activity to state drugs authority etc. Hence it is needed to amend/revise the Guidance documents inline with the recent procedures followed by Zonal, Sub-Zonal & post offices.

In view of the above, to undertake the revision of Guidance documents for Zonal, Sub-Zonal & Port offices a team has been constituted comprising following officials to revise the related work: -

Sr. No.	Name of Officer with Designation	Work Allotted	Related annexures of Guidance documents
1	Sh. Assem Sahu, Dy. Drugs Controller (I)	Guidance, pre-screening checklist and inspection checklist for: - 1. Grant of Manufacturing license of Medical Devices and IVDs	Annexure E, Annexure K, Annexure T
2	Sh. Sanjeev Kumar, Dy. Drugs Controller (I)	Time lines for all activity, All SOPs related to Zonal, Sub-Zonal and Port offices. Guidance, pre-screening checklist and inspection checklist for: - 1. Grant of manufacturing License 2. Issuance of CoPP/ WHO GMP	Annexure A, Annexure B, Annexure D, Annexure G, Annexure H, Annexure J, Annexure M, Annexure N, Annexure O, Annexure P, Annexure Q, Annexure S,
3	Sh. K. Narendran, Dy. Drugs Controller (I)		
4	Sh. Jayant Kumar, Dy. Drugs Controller (I)	Guidance, pre-screening checklist and inspection checklist for: - 1. Issuance of test license under form 11, CT 11, CT14, CT 15, CT 17 etc. 2. Grant of license of Public Testing laboratory.	Annexure F, Annexure L, Annexure U, Annexure V, Annexure W
5	Dr. Ajay Sachan, Dy. Drugs Controller (I)	SOPs, Guidance for enforcement activity including sampling, procedure for NSQ handling and disposal, prosecution, raids,	-

		investigation and any intelligence activity etc.	
6	Dr. Santosh Indraksh, Dy. Drugs Controller (I)	SOPs, Checklist, inspection format and guidance for Written Confirmation	
7	Sh. Navneet Pratap Singh, Dy. Drugs Controller (I)	Activities of port offices	-
8	Sh. Sushant Sharma, Dy. Drugs Controller (I)	Guidance, pre-screening checklist and inspection checklist for: - 1. Grant and renewal of license of blood centres. 2. Issuance of dual use NOC 3. Clinical Trial and BA/BE inspection procedure.	Annexure C, Annexure I, Annexure R, Annexure Y, Annexure Z

The team shall submit the zero draft with respect to their responsibilities within 60 days at whogb-cdsco@cdsco.nic.in for preparation of first draft by team comprising of following officials from CDSCO: -

Sr. No.	Name & Designation	Title
1	Sh. A.K.Pradhan, Joint Drugs Controller (I)	Chairperson
2	Dr. Rubina Bose, Dy. Drugs Controller (I)	Member
3	Dy. Drugs Controller (I) from Zone /port office	Member
4	Sh. Sushant Sharma, Dy. Drugs Controller (I)	Convener
5	Any other officials nominated by Drugs Controller General (India)	Member

The team may opt any officials/ supportive staff for finalization of draft version.

The guidance once drafted & reviewed will be shared with all officials (DDC (I) level) of CDSCO HQ/Zones/ Sub-Zone/ port offices for further deliberation before finalization.

(Dr. Rajeev Singh Raghuvanshi)
Drugs Controller General (India)

To,
All concerned.