File No. 4-01/2013-DC (Misc. 13-PSC) (Pt. II) (Sub Part-1)
Govt. of India
Directorate General of Health Services
Central Drugs Standard Control Organization
(FDC Division)

Dated: 11 JAN 2024

NOTICE

Subject: Evaluation of certain pre 1988 permitted Fixed Dose Combinations (FDCs) de novo for manufacture for sale in the country without due approval from Central Licensing Authority -regarding.

This is with reference to this office letter dated 15.01.2013 whereby all the State/UT Drugs Controllers were requested to ask the concerned manufacturers in their State to prove the safety and efficacy of FDCs within 18 months which were permitted by State Licensing Authorities without due approval from the office of DCG(I).

In continuation to Hon'ble Supreme Court order dated 15.12.2017 and 14.02.2019, Accordingly, Ministry of Health & Family Welfare vide order No. X11035/53/2014-DFQC (Part-IV) dated 02.02.2021 constituted an Expert Committee under the Chairmanship of Dr. M. S. Bhatia, Professor & Head, D/o Psychiatry, University College of Medical Sciences, New Delhi for examining certain pre-1988 FDCs denovo licensed for manufacturing for sale in the country without due approval from Central Licensing Authority.

The Expert Committee submitted its report accordingly on these 19 FDCs claimed to be pre-1988 after holding a series of meetings as well as by providing hearing to the stakeholders wherein, the Committee after detailed deliberation recommended for generation of data w.r.t. following 03 FDCs:-

Sr. No.	Name of FDC as per the public notice	Recommendations
1.	Paracetamol IP 500mg + Phenylephrine Hydrochloride IP 10mg + Caffeine Anhydrous IP 32mg tablets	The committee recommended for continued manufacturing and marketing of the FDC with the condition to generate safety and efficacy data by way of conducting Phase IV Clinical Trial. Accordingly, Phase IV Clinical Trial is required to be conducted to generate the data within time frame of one year.

2.	Caffeine Anhydrous IP + Paracetamol IP + Phenylephrine Hydrochloride IP + Chlorpheniramine Maleate IP (15mg + 500mg + 5mg + 2mg, 30mg + 500mg + 5mg + 2mg, 30mg + 500mg + 10mg + 2mg, 30mg + 500mg + 10mg + 4mg & 30mg + 650mg + 10mg + 2mg) tablets	The committee recommended for continued manufacturing and marketing of FDC with following conditions: a. FDC shall be sold by retail on the prescription of a R.M.P. only b. Package insert should also mention caution for patients suffering from cardiovascular diseases. c. Dose of Paracetamol in the FDC should be minimum 500mg The Committee also recommended to conduct a Randomized comparative, Phase IV Clinical Trial comparing the FDC with the individual ingredients present in the FDC. Accordingly, Phase IV Clinical Trial is required to be conducted to generate the data within time frame of one year.
3.	Paracetamol IP 250mg + Propyphenazone 150mg + Caffeine 30mg tablets	The committee recommended for continued manufacturing and marketing of the FDC for mild to moderate Headache with the conditions that: a. FDC shall not be taken more than 5 to 7 days b. FDC to be sold by retail on the prescription of a R.M.P. only". c. Further, the firm(s) shall conduct Active PMS study to generate safety and efficacy data on the FDC. Accordingly, Active Post Marketing Surveillance is required to be conducted to generate the data within time frame of one year.

With the approval of Ministry, it has been now decided to follow the pathway for clearance of such subsequent applications as under:-

1. Documents required in case of manufacturers already holding licenses from State Licensing Authority (SLA) before 01.10.2012 for the proposed FDCs shall at least contains:-
    a) Form CT-21 (duly filled, signed and stamped)
    b) Fees as specified in sixth schedule of New Drugs and Clinical Trials Rules 2019 through Bharatkosh.
    c) Name and composition of the FDC
    d) Product Permission issued by SLA
    e) Copy of Manufacturing license in Form 25/28

f) Phase IV trial protocol / commitment for conducting Active Post Marketing Surveillance study protocol, as the case may be.

2. Documents required in case of new manufacturers for the proposed FDCs shall at least contain:-
    a) Form CT-21 (duly filled, signed and stamped)
    b) Fees as specified in sixth schedule of New Drugs and Clinical Trials Rules 2019 through Bharatkosh.
    c) Name and composition of the FDC
    d) Product Permission issued by SLA in Form 29
    e) Copy of Manufacturing license in Form 25/28
    f) Stability studies data (06 months accelerated)
    g) Test Specifications of the FDC alongwith Method of Analysis
    h) Phase IV trial protocol / commitment for conducting Active Post Marketing Surveillance study protocol, as the case may be.

3. All the manufacturers who are already holding licenses from State Licensing Authorities for such FDCs before 01.10.2012 and did not apply to DCG (I) are required to submit their applications to this Directorate at the earliest but not later than 6 months, failing which their applications will not be considered and their licenses will be considered as without legal validity.
4. Manufacturers shall comply with the recommendation of the expert committee w.r.t. revision of the prescribing information/label.

In view of above, all concerned stakeholders are required to follow above procedure for clearance of such cases.

Yours faithfully,

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

To:-
All State/UT Drugs Controllers/All Zonal/Sub Zonal offices of CDSCO.

Copy to:-
1. PPS to Secretary/AS(F&D)/JS(R), Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi.
2. Indian Drug & Pharmaceuticals Associations/Website of CDSCO.

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In continuation to Hon'ble Supreme Court order dated 15.12.2017 and 14.02.2019, Ministry of Health & Family Welfare accordingly, vide order No. X11035/53/2014-DFQC (Part-IV) dated 02.02.2021 constituted an Expert Committee under the Chairmanship of Dr. M. S. Bhatia, Professor & Head, D/o Psychiatry, University College of Medical Sciences, New Delhi for examining 19 pre-1988 FDCs denovo licensed for manufacturing for sale in the country without due approval from Central Licensing Authority.

The Expert Committee submitted its report on these 19 FDCs claimed to be pre-1988 after holding a series of meetings as well as by providing hearing to the stakeholders wherein, the Committee after detailed deliberation considered following 02 FDCs as rational with certain conditions: -

Sr. No.	Name of FDC as per the public notice	Recommendations
1.	Imipramine Hydrochloride IP + Diazepam IP (25mg + 2mg & 25mg + 5mg) tablets	The committee recommended for continued manufacturing and marketing of the FDC. FDC shall be indicated for co-morbid anxiety conditions and duration of the treatment should not exceed 6 to 8 weeks.
2.	Chlorpheniramine Maleate IP + Ammonium Chloride IP + Sodium Citrate IP (2mg + 100mg + 50mg/5ml & 2.5mg + 125mg + 55mg/5ml Syrup	The committee noted that the firms are manufacturing the FDC in different strengths. The committee also noted that as per literature available, Sodium Citrate is administratered 0.3gm to 1gm in divided doses in a day and Chlorpheniramine Maleate is administratered 4mg to 16mg in divided doses in a day. After detailed deliberation, the Committee recommended for

		continued manufacturing and marketing of the FDC with the condition that the firm should modify the prescribing information/label by clearly mentioning the dose schedule for adults and children keeping in view of the above stated dose range without exceeding the maximum permissible dose.

Accordingly, with the approval of the Ministry of Health and Family Welfare, it has been now decided to follow the following pathway for grant of product license by SLAs for these FDCs:

1. Applicants shall submit the requisite fees preferably through Bharatkosh for each FDC to CDSCO as specified under Drugs and Cosmetics Act, 1940 and existing Rules thereunder.
2. The applicant shall submit application to the concerned SLA as per the provisions of Drugs and Cosmetics Rules 1945 for grant of product manufacturing license giving the details of FDCs, stability studies data (06 months accelerated), Test Specification of the FDC alongwith Method of Analysis as well as label and other documents as required for grant of product license under Drugs and Cosmetics Rules.
3. State Licensing Authority shall grant the product license of such FDCs without NOC from DCG (I), if conditions of license under the Drugs and Cosmetics Rules, which need to be verified by SLA, are found to have been fulfilled. The SLAs shall verified the quality of such FDCs of each applicant/manufacturer, before grant of license.
4. Every manufacturer permitted to manufacture these FDCs shall submit the periodic safety update reports (PSURs) as per New Drugs and Clinical Trial Rules, 2019 to the Central Licensing Authority as defined in Rule '3' i.e. DCG(I). Failure to submit the PSURs shall be considered as contravention of these Rules.
5. Manufacturers shall comply with the recommendation of the expert committee w.r.t. revision of the prescribing information/label.

In view of above, you are requested to ask the concerned stakeholders to follow the above procedure for obtaining the manufacturing license w.r.t. FDCs declared as rational by Dr. M. S. Bhatia Committee.

Yours faithfully,

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

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