MINUTES OF THE 72ND MEETING OF DRUGS TECHNICAL ADVISORY BOARD HELD ON 27TH JUNE, 2016 AT NIRMAN BHAWAN, NEW DELHI

PRESENT

1. Dr. Jagdish Prasad, — Chairman
   Director General of Health Services,
   Nirman Bhawan, New Delhi.

2. Shri C. Hariharan — Member
   Director in-charge,
   Central Drugs Laboratory,
   Kolkata-700016

3. Dr. Muzaffar Ahmad — Member
   Rep. Medical Council of India
   New Delhi

4. Dr. A. K. Tehlan, — Member
   Director, Central Research Institute,
   Kasauli (HP) -173205

5. Dr. Nilima Kshirasagar, — Member
   Chair in Clinical Pharmacology, ICMR
   1501-2, Datta Tower,
   Dr. Vijay Kumar Walimbe Marg,
   Mumbai – 400012

6. Shri O. S. Sadhawani, — Member
   Controlling authority & Joint Commissioner,
   Food & Drugs Administration, Mumbai
   Maharashtra - 400051

7. Dr. A. K. Tiwari — Member
   Indian Veterinary Research Institute,
   Izatnagar

8. Prof. M. D. Karvekar, — Member
   #1449, Sector, 7, 4th Main
   21st Cross, H.S.R. Lay Out
   Bangalore, 560102

9. Dr. G. N. Singh, Member Secretary
   Drugs Controller General (India)
   FDA Bhawan, New Delhi-110002

SPECIAL INVITEES

1. Dr. V. K. Bahl
   Prof. Department of Cardiology,
   AIIMS, New Delhi

2. Dr. Devi Shetty
   Founder & Chairman, Narayana Hrudayalaya
   Bengaluru

CDSCO REPRESENTATIVES

1. Dr. S. Eswara Reddy,
   Joint Drugs Controller,
   CDSCO, HQ, New Delhi

2. Dr. V. G. Somani,
   Joint Drugs Controller,
   CDSCO, HQ, New Delhi

3. Shri R. Chandrashekar,
   Deputy Drugs Controller (India)
   CDSCO, HQ, New Delhi

Dr. G. B. Gupta, Prof and Head, Department of Medicine, Pt. Jawahar Lal Nehru Memorial Medical College, Dr. B. Suresh, President, Pharmacy Council of India, Dr. H. G. Koshia, Commissioner, FDCA, Gujarat, Dr. Rao V. S. V. Vadlamudi, Hyderabad, Dr. Madhu Dixit, CDRI, Lucknow, Dr. A. Marthanda Pillai, Thiruvananthapuram, Shri Sheju Purushothaman, RDTL, Kerala and Shri Sudhir Mehta, Chairman, M/s. Torrent Pharmaceuticals Ltd., Ahmedabad could not attend the meeting because of their other commitments.

Dr. Jagdish Prasad, Chairman, DTAB welcomed all the members and special invitees and requested DCG(I) to initiate the proceedings. Thereafter, Dr. G. N. Singh, Member-Secretary, DTAB welcomed the chairman and members and informed them about the

various steps taken by the Government for strengthening the drug regulatory system in the country. He explained briefly about DTAB Agenda.

Thereafter, agenda items taken up for deliberation.

AGENDA NO. 1

CONSIDERATION OF PROPOSAL TO MAKE SEPARATE RULES NAMELY MEDICAL DEVICE RULES, 2016 UNDER THE DRUGS AND COSMETICS ACT, 1940 TO REGULATE MANUFACTURE, IMPORT, CLINICAL INVESTIGATION, SALE AND DISTRIBUTION OF MEDICAL DEVICES IN THE COUNTRY.

1.1 The members were briefed that presently, medical devices, notified as drugs are regulated under the provisions of Drugs and Cosmetics Act, 1940, and Drug and Cosmetic Rules, 1945. However, Drugs and medical devices are distinct from each other in various aspects such as, design, manufacturing, quality control, clinical investigation, etc.

1.2 It was pointed out that in view of the concerns raised by various Stakeholders from time to time regarding non-applicability of various regulatory provisions meant for drugs to medical devices, draft Medical Device Rules, 2016 for regulation of medical devices have been prepared after obtaining inputs from various stakeholders. These rules provide for regulation of import, manufacture for sale, sale, distribution, clinical investigation, etc. of Medical Devices.

1.3 The draft Medical Devices Rules, 2016 have 11 parts and 8 Schedules. The rules provide for scope, definitions, risk based classification (A, B, C and D) notified bodies, provisions for manufacture, import, sale and distribution, labeling, clinical investigations, performance evaluation in case of in-vitro diagnostics, duties and powers of medical device officers and medical device testing officers notified bodies, etc

1.4 The DTAB, after deliberations, on each part of the proposed rules, recommended that the draft Medical Devices Rules, 2016 may be notified at the earliest

possible. However, DTAB the the following changes may be considered by the Government :

(i) the rules should provide that the manufacturer should supply the medical device along with package insert;

(ii) the requirement to conduct local clinical trial should be exempted in case of New Medical devices approved by USFDA provided the applicant has submitted data regarding clinical trials conducted in that country;

(iii) the periodicity for payment of retention fee, as proposed in the draft Rules, could be kept at five years instead of one year; and

(iv) rules may provide that a manufacturer shall intimate the CLA or SLA, as the case may be, in case he closes down his manufacturing site.

AGENDA NO. 2

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES, 1945 TO MAKE PROVISIONS FOR PROVIDING EVIDENCE AND DATA ABOUT THE STABILITY OF THE DRUG PRODUCTS BY THE MANUFACTURERS

2.1 The members were briefed that the proposal to amend the Drugs and Cosmetics Rules, 1945 to make provisions for submission of stability data of drugs as a requirement for approval had been deliberated in the 65th meeting of DTAB held on 25.11.2013 and that it was considered necessary that provision be made in the rules for stability testing as it is a major factor for ensuring the quality of drugs.

2.2 The Board had deliberated, upon the matter and recommended that the condition for stability products as condition of license may be incorporated in rule 71, 71-B & 76 and whereverelse considered necessary. In respect of amendment of Schedule 'Y', it recommended that WHO may be further consulted and if required, more data be generated for further consideration of the matter.

2.3 The recommendations of the Board had been considered by the Central Government and a draft notification was published vide GSR 68(E) dated 03.02.2015 inviting comments from stakeholders.

2.4 The comments have been received from various stakeholders. Briefly, the major comments are that it would adversely affect the SMEs and increase the cost of majority of medicines, etc.

2.5 DTAB after deliberations, reiterated its earlier recommendation that submission of stability data should be made mandatory, prior to the grant of approval, for manufacturing of drugs and recommended that the rules may be finalized at the earliest

AGENDA NO. 3

CONSIDERATION OF THE PROPOSAL TO PREPARE GUIDELINES AND PROCEDURE FOR RECALL OF DRUGS UNDER THE DRUGS AND COSMETICS RULES, FOR EFFECTIVE RECALL OF NOT OF STANDARD QUALITY, ADULTERATED AND SPURIOUS DRUGS BY THE MANUFACTURERS AS WELL AS CHEMISTS

3.1 The members were briefed that the Rule 74(j), Rule 78(i), Para 27 and 28 of Schedule 'M' and also conditions of license under the Drugs and Cosmetics Act and Rules, provide requirement of product recalls, complaint and adverse reactions for recall of 'Not of Standard Quality', adulterated and spurious drugs. It was informed that there is, no uniform and time bound procedure followed by State Licensing Authorities for effective recall of drugs by the manufacturers as well as sale licensees. It does not provide specific time-frames for effective recall in case of substandard, adulterated or spurious drugs.

3.2 The Board was briefed that concerns have been expressed that in the absence of any guidelines or mechanism to freeze the sale and manufacture of such drugs within the short period of time, from further availability to the consumers, such drugs are not withdrawn from the market in time. The problem is more acute in case of drugs manufactured in one State and found sub-standard in another State.

3.3 It was stated that earlier, CDSCO had prepared guidelines on recall and rapid alert system for 'Not of Standard Quality', 'Adulterated' and 'Spurious Drugs'. In the 45th DCC meeting held on 4th and 5th February 2013. The guidelines were discussed and circulated to the members of the Committee. The members were also requested to follow these guidelines for the purpose of recall and rapid alert. The guidelines were also uploaded on the CDSCO website for information and necessary action of

stakeholders. However, concerns about lack of proper implementation of recall and alert system in the country still exist.

3.4 In view of the above, it is necessary to make these guidelines legally mandatory for manufacturers, importers, distributors and retailers and it is, therefore proposed that appropriate amendment be made in Drugs and Cosmetics Rules, 1945 to incorporate provisions for effective recall of such drugs.

3.5 The DTAB, after deliberations recommended, that the recall procedures need to be clearly spelt and made part of the Rules. It recommended that a Group could be constituted to examine the proposal in detail.

AGENDA NO. 4

CONSIDERATION OF MAKING PROVISION UNDER DRUGS & COSMETICS RULES MAKING IT MANDATORY TO SUBMIT data from BIOEQUIVALENCE (BE) STUDY PRIOR TO THE GRANT OF LICENCE FOR MANUFACTURING THE DRUG IN THE COUNTRY

4.1 The members were briefed that for obtaining permission to manufacture new drug formulations, an application has to be made as per requirements and guidelines specified under Schedule Y to the Drugs and Cosmetics Rules, 1945 which include chemical and Pharmaceutical information, animal pharmacological and toxicological data, clinical data of safety & efficacy, regulatory status in other countries, etc. including results of bioequivalence study/clinical trial in Indian population, as appropriate.

4.2 It was also briefed that presently, after the new drug is approved in the country, it continues to be considered a new drug for a period of four years from the date of its first approval. During the said period, all subsequent applicants seeking to market such drug, are required to conduct bioequivalence study of oral formulation before obtaining new drug permission from DCG(I).

4.3 For manufacture of drugs which are no more new drugs i.e. after completion of four years from the date of approval, licences to manufacture such drugs are issued by the concerned State Licensing Authorities. However, Drugs and Cosmetic Act and Rules do not require an applicant to submit bioequivalence study data for drug formulations, to the State Licensing Authorities for grant of manufacturing licence which are no longer considered as “new drug”.

4.4 Bioequivalence study is important in determining the therapeutic equivalence i.e. identical therapeutic response in patients between a test formulation and a previously approved standard formulation containing same drug in same amount and same dosage form manufactured by different companies. It was informed that Prof. Ranjit Roy Chaudhury Committee had recommended to make Bioequivalence study mandatory for drugs.

4.5 The Drugs Consultative Committee in its 47th meeting held on 30th and 31st July, 2014 deliberated upon this matter. The Committee had, after deliberations, not recommended including the requirement of conducting a BA / BE study as a rule due to lack of availability of uniform infrastructure for conduct of such studies in the country.

4.6 Concerns have been raised from time to time regarding lack of requirement of Bioequivalence study for grant of manufacturing license for drugs by State Licensing Authorities and impact of the absence of such studies on quality and efficacy of drugs. Keeping these concerns in view, it is considered that submission of data from BE study should be necessary for grant of licence for manufacture of drugs which are no more new drugs in addition to other requirements. However, internationally, Biopharmaceutics Classification System (BCS) is used to differentiate the drugs on the basis of their solubility and permeability. Drugs are classified in the four classes based on the aforesaid criteria.

4.7 The DTAB, after deliberations, recommended that submission of bioequivalence data should be made mandatory prior to grant of licence for manufacturing drugs in the country. However, it has suggested that Biopharmaceutics Classification System (BCS) should be adopted and to begin with, conduct of BE study should be made mandatory only for category II and IV of the BCS system. For the drugs already marketed in the country, three years time may be given of submission of BE study data. The Board has further recommended that a Group should be constituted to lay down the modalities for identification of the reference drug for the conduct of BE studies.

AGENDA NO. 5

CONSIDERATION OF THE PROPOSAL TO PROHIBIT MANUFACTURE FOR SALE, SALE AND DISTRIBUTION OF DICLOFENAC INJECTION IN DOSES HIGHER THAN 3 ML UNDER THE SECTION 26A OF THE DRUGS AND COSMETICS ACT, 1940 TO PREVENT DECLINE IN VULTURE POPULATION IN LIGHT OF THE ORDERS OF THE HON'BLE HIGH COURT AT MADRAS

5.1 The members were briefed that the Central Government amended rule 105 under the Drugs and Cosmetics Rules, 1945 vide G.S.R. 558(E), 17.07.2015 regulating the packing of Diclofenac formulation in single unit pack only. The amendment was challenged in the Hon'ble High Court of Madras. While hearing both sides, the Hon'ble Court held that DTAB in its 63rd meeting constituted a sub-committee to examine the issues related to the use of Diclofenac Sodium Injection and decline in vulture population with the following members.

Dr. S.D. Seth, Advisor CTRI, National Institute of Medical Statistics, ICMR, New Delhi.
Dr. Y.K. Gupta, Professor & Head, Department of Pharmacology, AIIMS, New Delhi.
Dr. N.K. Gupta, Director Professor, Department of medicine, Maulana Azad Medical College, New Delhi

5.2 However, the DTAB in its 64th meeting agreed that rule 105 may suitably be amended to restrict the pack size of Diclofenac injections for human use in single unit dose pack only without waiting for the report of the sub-committee. Therefore, the Hon'ble High Court has directed that the sub-committee should examine the proposal and submit its report within two months.

5.3 The Board was apprised that in view of the direction of the Hon'ble Court, the sub-committee stands constituted and the report of the sub-committee after finalization may be presented before the Hon'ble Court with the approval of the Chairman.

5.4 The DTAB, after deliberations, authorized the Chairman to submit the report to the Hon'ble Court after it is finalized by the sub-committee.

AGENDA NO. 6

CONSIDERATION OF THE PROPOSAL TO PROHIBIT THE MANUFACTURE FOR SALE OR FOR DISTRIBUTION OF THE DRUG BUCLIZINE AS APPETITE STIMULANT UNDER THE PROVISIONS OF SECTION 26A OF DRUGS AND COSMETICS ACT, 1940 IN PUBLIC INTEREST

6.1 The members were briefed that the PSC in its 59th report on the functioning of CDSCO has made several observations regards approval of various drugs for marketing in the country including the Buclizine as Appetite Stimulant.

6.2 As per action taken note on the 59th PSC report, it has been decided that various drugs on which the Hon'ble PSC has made observations, would be referred to the New Drug Advisory Committee (NDAC)/Subject Expert Committee (SEC) for examination and review to decide on the continued marketing of these drugs and updating of their product monographs in the light of recent knowledge and regulatory changes overseas.

6.3 Accordingly, the proposal was deliberated in NDAC (renamed as SEC) (Gastroenterology & Hepatology) meeting held on 15.03.2013, 22.08.2013 and 19.02.2016. The recommendation are as follows:

"Buclizine is one of the drugs which was reviewed by the Parliamentary Standing Committee (PSC) which raised concerns on the safety and efficacy of the drug as an appetite stimulant without clinical trial. The drug is used in children for which no scientific data are available. The firm presented the summarized PSUR data but no clinical trial study report on adult or children to justify the use of the drug as an appetite stimulant. Therefore, the Committee opined that the continued marketing of the drug as an appetite stimulant is not recommended".

6.4 In this regard, the attention of the DTAB is invited to the action taken note on 59th report of Parliamentary Standing Committee on functioning of CDSCO, and the fact that it has been decided that whenever a drug is banned due to adverse drug

reactions in countries with well-developed and efficient regulatory system viz. USA, UK, EU, Australia, Japan and Canada, the manufacture, import and marketing of such drugs would be immediately put under suspension till the safety of the drug is examined and established in the country.

6.5 In view of the above, DTAB may consider the proposal to prohibit the manufacture for sale or for distribution of the drug Buclizine as appetite stimulant under the provisions of Section 26A of Drugs and Cosmetics Act, 1940 in public interest while continuing the marketing for the indications “symptomatic treatment of various allergic conditions (rhinitis, conjunctivitis and urticaria) and for prevention and treatment of motion sickness”

6.6 The DTAB, after deliberations, endorsed the proposal for prohibiting the manufacture, sale and distribution of Buclizine for the indication “as appetite stimulant”. The DTAB further decided that a sub-committee comprising of Dr. B.Suresh, Dr. Shiv Kumar Sarin and Dr. S. K. Acharya should be constituted to examine continued marketing of the drug for other indications and submit its report.

AGENDA NO. 7

CONSIDERATION OF THE ISSUE OF BANNING OF PACKAGING OF PHARMACEUTICAL PRODUCT IN PET/PLASTIC BOTTLES BY DTAB

7.1 The members were briefed that the issue of prohibiting the use of plastic / PET containers in pharmaceutical products was earlier considered by the DTAB in its 65th meeting held on 25.11.2013 and 71st meeting held on 13.05.2016 in view of reports of leaching of harmful chemicals from plastic bottles to the contents on long storage.

7.2 It was recommended in the 65th meeting that in the first phase, the use of plastic / PET containers in liquid oral formulations for primary packaging of paediatric formulations as well as formulations meant for geriatrics, women in reproductive age group and pregnant women should be phased out and banned. However, the pharmaceutical industry may be given an adequate time of six months for smooth switch over.

7.3 In the light of the recommendations made by Dr. M. K. Bhan Committee and the 'Report of Plastic Hazard Committee' of the All India Institute of Hygiene & Public Health, Kolkata which was prepared in collaboration with the National Test House, Kolkata, the matter was deliberated again in the 71st meeting and the members agreed that leaching does take place in liquid oral preparations and it increases at higher temperatures. In India, there are wide variations of temperatures which may go as high as 45 to 46 °C centigrade and chances of leaching further increases. Even though small dosages may not show any immediate harm but continuous exposure especially to the vulnerable group is a matter of concern.

7.4 DTAB agreed with the findings of AIIHPS, Kolkata and also method of tests adopted by the National Test House, Kolkata. Based on these evidences, DTAB in its 71st meeting, recommended that the report may be forwarded to the Ministry of Health and Family Welfare for its consideration and finalization of the draft rules to prohibit the use of Polyethylene Terephthalate or plastic containers in the liquid oral formulations for primary packaging of drug formulations for pediatric use, geriatric use and for use of pregnant women and women of reproductive age group.

7.5 The recommendations of the 71st DTAB were submitted to the Ministry of Health and Family Welfare for further action. However, the Ministry of Health and Family Welfare had requested DTAB to clearly spell out the reasons for recommending the prohibition of Polyethylene Terephthalate or plastic containers in the liquid oral

formulations for primary packaging of drug formulations for pediatric use, geriatric use and for use of pregnant women and women of reproductive age group.

7.6 The DTAB after deliberations reiterated its earlier recommendations and concluded that the minutes of its 65th and 71st meetings are self explanatory.

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