MINUTES OF THE 73rd MEETING OF DRUGS TECHNICAL ADVISORY BOARD HELD ON 01st AUGUST, 2016 AT DGHS, NIRMAN BHAWAN, NEW DELHI

PRESENT

1.	Dr. Jagdish Prasad, Director General of Health Services, Nirman Bhawan, New Delhi.	Chairman
2.	Shri C. Hariharan Director in-charge, Central Drugs Laboratory, Kolkata-700016	Member
3.	Dr. A. K. Tehlan, Director, Central Research Institute, Kasauli (HP) -173205	Member
4.	Dr. Madhu Dixit, Central Drugs Research Institute, Chattar Manzil , P.B.NO.173, Lucknow-226001	Member
5.	Dr. Nilima Kshirasagar, Chair in Clinical Pharmacology, ICMR 1501-2, Datta Tower, Dr. Vijay Kumar Walimbe Marg, Mumbai – 400012	Member
6.	Dr. H. G. Koshia, Commissioner, FDCA Gujarat Block No.8, Dr. J. M. Bhawan Gandhi Nagar, Gujarat -382010	Member
7.	Dr. Rao V. S. V. Vadlamudi Flat F-6, Vora Towers, 8-3 – 224, Yousufguda road Madhuranagar, Hyderabad – 500038	Member
8.	Dr. P.Dhar Principal Scientist, Indian Veterinary Research Institute, Izatnagar	Member

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

10. Dr. B. Suresh , Member
President,
Pharmacy Council of India, New Delhi

11. Dr. G. B. Gupta, Member
Professor and Head, Department of Medicine
Pt. Jawaharlal Nehru Memorial Medical College
Raipur – 492001, Chattisgarh

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

CDSCO REPRESENTATIVES

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

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

3. Shri A. K. Pradhan,
   Deputy Drugs Controller (India)
   CDSCO (HQ), New Delhi

4. Shri R. Chandrasekhar,
   Deputy Drugs Controller (India)
   CDSCO (HQ), New Delhi

5. Mrs. Rubina Bose,
   Deputy Drugs Controller (India)
   CDSCO (HQ), New Delhi
6. Mr. A.C.S. Rao, DDC (I) CDSCO HQ

Secretary, Medical Council of India, Shri, O.S. Sadhawani, Controlling Authority and Joint Commissioner, FDA Mumbai, Dr. A. Marthanda Pillai, Ananthapuri Hospital and Research, Kerala, Smt. Sushma M. Saptarshi, Assistant Director & Government Analyst, Drugs Control Laboratory, Mumbai, Shri Sheju Purushothaman, Government Analyst, Regional Drugs Testing Laboratory, Kerala and Shri Sudhir Mehta, Chairman, M/s. Torrent Pharmaceuticals Ltd., Ahmedabad could not attend the meeting because of their other commitments.

Dr. G. N. Singh, Member-Secretary, DTAB welcomed the Chairman and members and explained briefly about DTAB Agenda. He then requested the Chairman to initiate the proceedings as the quorum was complete.

Thereafter, Dr. Jagdish Prasad, Chairman, DTAB welcomed all the members and desired that more frequent meetings of DTAB should be held to consider the important matter relating to Drug Control Administrator.

Thereafter, the Chairman started discussion on the agenda items one by one.

AGENDA No. 01

AMENDMENT OF SCHEDULE Y TO DRUGS AND COSMETICS RULES, 1945 INSERTING NON-ANIMAL TEST METHODS AS ALTERNATE OPTION FOR DRAIZE TEST FOR OCULAR TOXICITY STUDY AND DERMAL TOXICITY STUDY.

The members were briefed that DCGI has received representations to amend Schedule-Y to Drugs and Cosmetics Rules, 1945 to replace the use of Draize test by alternative non-animal methods.

To examine the feasibility to replace Draize test which is applied on rabbit eyes and skin by alternative methods for testing of eyes and skin irritation and corrosion DCG

(I) constituted a committee under the Chairmanship of Dr. Y.K. Gupta, Prof. and Head, Dept. of Pharmacology, AIIMS, New Delhi. The Committee along with the invited experts and representative from PETA, have examined the issue in its two meetings held on 23rd May, 2016 and 01st July, 2016. The Committee had sought comments / feedback from different stakeholders in specific format through a notice uploaded in CDSCO website to examine the issue in detail. In response, comments were received from five organizations including one pharmaceutical company. The details of the organizations are as under:-

1. PeTA, India
2. Human Society International, India
3. Mahatma Gandhi – Doerenkamp Center for Alternatives, Bharthidasan University, Tiruchirapalli
4. Blue Cross of India, Chennai
5. M/s Sun Pharmaceuticals

Except M/s Sun Pharmaceuticals, all other organizations have given their opinion in favour of replacing the Draize test by non-animal test methods. However, M/s Sun Pharma, who is major Indian pharmaceutical house involved in new drug development including ophthalmic preparations, have requested not to mandate the alternative tests but allow in-vivo tests also for such pre-clinical toxicological tests considering the limitation of in-vitro test based on the molecule characteristics.The firm has mainly opined that:

- They do not have the capability/ capacity for in-vitro alternate methods. Development of this capacity building will take atleast 3 years
- No single alternative test can replace the in-vivo test completely as each test has some limitations. These limitations are mentioned in OECD guidelines.

The Committee after taking into consideration the views of stakeholders as well as current global scenario in this regard has recommended that:

a. The Indian regulatory system should adopt progressive nature in adopting the alternate methods to animals in toxicity testing as and where possible.

b. The alternate methods should be validated as sufficient alternative for equal predictability of potential toxicity of pharmaceutical products.

c. It is also important to consider whether single in-vitro test, as stand alone, is acceptable or a battery of test is required for reliable assessment and under what circumstances, such single or multiple in-vitro tests, will not be acceptable as alternate to Draize test.

d. The applicant of new drug should be encouraged to make application to the regulator for conduct of in-vitro alternate methods in place of Draize test and if the regulator has no specific reservation / requirement, may accept it.

e. The intent should be to gradually phase out the Draize test by replacing it with in-vitro tests.

f. For this purpose, the Draize test should be accepted for two years. During this interim period, all the testing laboratories should develop the capacity for in vitro testing facility and validate them. After one year, a stock taking of progress in capacity building should be reviewed.

The Committee also recommended that in rare situation where alternate test is not acceptable for acute dermal / ocular toxicity test and with specific reasons, the Draize test is asked for, the following principles should be applied:-

a. A known molecule with known irritant properties / adverse effects should not be used.

b. In case of potential mild irritant, the test should be undertaken minimizing the inflict of pain, may be with the use of appropriate local anesthetic.

c. The test should be done starting with the least possible concentration.

d. In case of a drug / pharmaceutical product intended for ophthalmic use, is found to be an unacceptable irritant, the toxicity testing should be done sequentially, first by skin irritation study followed by eye irritation study.

Based on the recommendations of the Committee it is proposed to amend the Schedule Y to Drugs and Cosmetics Rules, 1945 appropriately by inserting provisions so that acute Dermal toxicity study and Ocular toxicity study, wherever required may be replaced by validated non-animal alternative tests to Draize test, wherever possible.

Accordingly, a draft of draft rules amending the Appendix III of Schedule Y to the Drugs and Cosmetics Rules, 1945 has been prepared which is as under:

Draft rules

1. (1) These rules may be called Drugs and Cosmetics (_____Amendment) Rules, 2016.

   (2) They shall come into force on the date of their final publication in the Official Gazette.

2. In the Drugs and Cosmetics Rules, 1945, in Schedule Y, in Appendix III relating to Animal Toxicology (non-clinical toxicity studies), in Para number 1, in sub-Para number 1.4 relating to Local Toxicity,-

   (A) in the note (i) relating to Dermal toxicity study, for the words “The study should be done in rabbit and rat. Daily topical (dermal) application of test substance in its clinical dosage form should be done. ” the following words shall be substituted, namely:-

   “The study may be done in rabbit and rat. The initial toxicity study may be carried out by validated non-animal alternative tests, where such alternatives are available. In rabbit and rat studies, daily topical (dermal) application of test substance in its clinical dosage form should be done.”;

   (B) in note (vi) relating to Ocular toxicity study (for products meant for ocular instillation), after the words “need to include a recovery group.” and before the words “Duration of the” following shall be inserted, namely:-

"Such initial studies may be carried out by validated non-animal alternative tests, where such alternatives are available."

DTAB after detailed deliberations agreed to the proposed amendment and stated that the draft rules are appropriately worded, which emphasizes to use "validated methods" for selection of alternative non-animal test procedures which are available in International guidelines.

AGENDA No.S-1

CONSIDERATION OF THE PROPOSAL FOR AMENDMENT IN APPENDIX XII OF SCHEDULE Y UNDER THE DRUGS AND COSMETICS RULES, 1945 TO HAVE FOCUSSED APPROACH IN RESPECT OF PASSING ORDERS BY THE LICENSING AUTHORITY FOR PAYMENT OF COMPENSATION IN CASE OF SERIOUS ADVERSE EVENTS OF INJURY OR DEATH RELATED TO THE CLINICAL TRIAL.

Members were briefed that the Schedule Y to the Drugs and Cosmetics Rules, 1945 under Appendix XII mandates the Licensing Authority to determine the cause of of serious adverse events (SAEs) of injury or death and pass orders as deemed the necessary in every SAE of injury and death in clinical trial. The relevant provisions are as under:

1. <u>In case of death</u>

<u>Para (6) (b) (i) (F) of Appendix XII of Schedule Y</u>

"The Licensing Authority shall consider the recommendations of the Expert Committee and shall determine the cause of death and pass orders as deemed necessary".

2. <u>In case of injury</u>

<u>Para (6) (b) (ii) (C) of Appendix XII of Schedule Y</u>

“The Licensing Authority shall determine the cause of injury and pass order as deemed necessary. The Licensing Authority shall have the option to constitute an independent Expert Committee, wherever considered necessary, to examine such serious adverse events of injury, which will recommend to the Licensing Authority for arriving at the cause of the injury and also the quantum of compensation in case clinical trial related injury, to be paid by the Sponsor or his representative whosoever had obtained permission from the Licensing Authority as defined under rule 21(b) for conducting the clinical trial”.

In order to bring clarity and have focused approach in the procedures for payment of compensation in case of serious adverse events (SAEs) of injuries and deaths in clinical trial, above rules are proposed to be amended to provide that the Licensing Authority shall pass order only in cases where the SAEs of injuries and deaths are found to be related to the clinical trial.

Accordingly, the existing provisions under Paras (6) (b) (i) (F) and (6) (b) (ii) (C) of Appendix XII of Schedule Y which require the Licensing Authority to pass order in each case of SAE of injury and death, irrespective of whether the SAE is related or unrelated to clinical trial, may be deleted as under:

1. In case of death

Para (6) (b) (i) (F) of Appendix XII of Schedule Y

“The Licensing Authority shall consider the recommendations of the Expert Committee and shall determine the cause of death ~~and pass orders as deemed necessary”.~~

2. In case of injury

Para (6) (b) (ii) (C) of Appendix XII of Schedule Y

“The Licensing Authority shall determine the cause of injury ~~and pass orders as deemed necessary.~~ The Licensing Authority shall have the option to constitute an independent Expert Committee, wherever considered necessary, to examine such serious adverse events of injury, which will recommend to the Licensing Authority for arriving at the cause of the injury and also the quantum of compensation in case clinical trial related injury, to be paid by the Sponsor or his representative whosoever

had obtained permission from the Licensing Authority as defined under rule 21(b) for conducting the clinical trial".

While agreeing to the proposed amendment, the DTAB, however, after detailed deliberations recommended that the reports of serious adverse events (SAEs) of injury and death occurring in clinical trial should be analyzed by the respective Ethics Committee (EC) taking into consideration the opinion of the respective Investigator and the Sponsor to determine the cause of the injury or death and recommend for payment of compensation in case of injury or death related to the clinical trial. While analyzing the reports, the EC may take help of the causality assessment experts. It may not be necessary for Licensing Authority to examine all the reports of SAEs to determine the cause of injury or death and issue order for payment of compensation. However, in cases where the trial participants or his/her nominee(s) as the case may be, do not agree with the decision of the EC, the report of SAE should be referred to the Licensing Authority i.e. DCG(I) for final examination and decision. Accordingly, the Board recommended for amendment of the relevant Rule and the Schedule Y to the Drugs and Cosmetics Rules, 1945.

However, till such time, the above amendment providing analysis of reports of SAEs at the level of the EC, is made in the Rule and the Schedule, the Board agreed to the proposed amendment as per the agenda to provide that the Licensing Authority i.e. DCG (I) shall pass order only in cases where the SAEs of injuries and deaths are found to be related to the clinical trial. So far as providing medical management in case of SAE of injury is concerned, the same should be provided by the Sponsor as long as required or till such time it is established by the EC that the SAE is not related to the clinical trial, whichever is earlier.

AGENDA No. S-2

CONSIDERATION OF THE PROPOSAL FOR AMENDMENT OF RULE 122DA OF DRUGS AND COSMETICS RULES, 1945 IN RESPECT OF CLINICAL TRIAL FOR ACADEMIC PURPOSES TO PROVIDE THAT SUCH CLINICAL TRIAL IS REQUIRED TO BE CONDUCTED IN COMPLIANCE WITH THE "ETHICAL

GUIDELINES FOR BIOMEDICAL RESEARCH ON HUMAN PARTICIPANTS" PUBLISHED BY ICMR GUIDELINES FOR CONDUCT OF CLINICAL TRIALS IN INDIA.

The Rule 122 DA the Drugs and Cosmetics Rules, 1945 was amended on 16.03.2016 providing that no permission for conduct of clinical trial intended for academic purposes in respect of approved drug formulation shall be required for any new indication or new route of administration or new dose or new dosage form where,-

(a) the trial is approved by the Ethics Committee; and

(b) the data generated is not intended for submission to Licensing Authority

The Ethics Committee shall, however, inform the Licensing Authority about the cases approved by it and also about cases where there could be an overlap between the clinical trial for academic and regulatory purposes and where the said authority does not convey its comments to the Ethics Committee within a period of thirty days from the date of receipt of communication from the Ethics Committee, it shall be presumed that no permission from the Licensing Authority is required.

The Board was briefed that concerns have, however, been raised by the stakeholders regarding the specific guidelines/ principles to be followed especially in respect of general ethical issues including the safety management, reporting, assessment of the serious adverse events (SAEs), etc. in such clinical trials.

Since, these clinical trials are basically academic biomedical research on human participants, not meant for regulatory submission for approval of any new drugs, it was mentioned that the statement of ethical principles as contained in the "Ethical Guidelines for Biomedical Research on Human Participants" published by ICMR should be applicable in conduct of such clinical trials. However, the existing regulatory provision in respect of such academic clinical trials, does not mention the applicability of these principles.

In view of above, it is proposed to amend the Rule 122 DA of the Drugs and Cosmetics Rules, 1945 appropriately to provide that the basic ethical principles as contained in the "Ethical Guidelines for Biomedical Research on Human Participants"

published by ICMR are applicable in conduct of above mentioned clinical trials intended for academic purposes.

DTAB after deliberations agreed to the proposed amendment.

After deliberations of the three agenda, the members raised the issue of delay in taking actions on the recommendations of the DTAB. The Board desired that necessary action on all the recommendations of the DTAB should be taken within a time frame of 6 weeks. In case, action could not be taken on any particular recommendation within the time frame, the same should be brought back to the notice of the Board in its immediate subsequent meeting.

Thereafter, while discussing the issue of promotion of generic medicines, the members mentioned about the availability of both branded-generic and generic-generic medicines in the country unlike in other country like USA, where, till the validity of patent of a medicine, only one brand of the medicine is available and after the expiry of the patent, the medicine is allowed to be marketed by other firms only in generic name alongwith the name of the manufacturer. The DTAB desired the issue may be kept as an agenda for discussion in its next meeting.

The meeting ended with vote of thanks to the Chair.

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