MINUTES OF THE 70TH MEETING OF DRUGS TECHNICAL ADVISORY BOARD HELD ON 18TH AUGUST, 2015 AT CDSCO, HQ, FDA BHAWAN, KOTLA ROAD, 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. A. K. Tehlan, — Member
   Director, Central Research Institute,
   Kasauli (HP) -173205

4. Dr G. B. Gupta, — Member
   Vice Chancellor
   Chhattisgarh Ayush and Health Science University,
   Raipur,

5. Shri Sudhir Mehta, — Member
   Chairman, M/s. Torrent Pharmaceuticals Ltd.,
   Ahmedabad

6. Dr. B. Suresh — Member
   President, Pharmacy Council of India,
   Temple Lane, Kotla Road,
   P.B. No.7020, New Delhi-110002

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

8. Shri O. S. Sadhawani, — Member

Controlling authority & Joint Commissioner,
Food & Drugs Administration, Mumbai
Bandra Kurla Complex, Bandra (E)
Mumbai, Maharashtra - 400051

9. Dr. H. G. Koshia, — Member
Commissioner, FDCA, Gujarat
Block No. 8, Dr. J. M. Bhawan,
Gandhi Nagar, Gujarat – 382010

10. Dr. Madhu Dixit, — Member
Central Drugs Research Institute,
Chattar Manzil , P.B.NO.173,
Lucknow-226001

11. Dr. Rao V. S. V. Vadlamudi — Member
Flat F-6, Vora Towers,
8-3 – 224, Yousufguda road
Madhuranagar, Hyderabad – 500038

12. Dr. P. Dhar — Member
Principal Scientist,
Indian Veterinary Research Institute,
Izatnagar

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

14. Dr. Muzaffar Ahmad — Member
Rep., Medical Council of India,
Pocket 14, Sector-8, Dwarka- Phase I
New Delhi - 110077

15. Dr. A. Marthanda Pillai, — Member
Ananthapuri, Hospital and Res. Institute,
Thiruvananthapuram,

16. Dr. G. N. Singh, — Member Secretary

Drugs Controller General (India)
FDA Bhawan, New Delhi-110002

INVITEES

1. Dr. B. S. Prakash,
   Assistant Director General (ANP)
   Room No. – 406, ICAR, Ministry of Agriculture,
   Krishi Bhawan, New Delhi

2. Dr. Ajay Kumar Dang,
   Principal Scientist, Dairy Cattle Physiology Division,
   NDRI, Karnal – 132001, Haryana

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 Lalit Kishore
   Consultant, DCG(I)
   CDSCO, New Delhi

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

5. Shri A. K. Pradhan,
   Deputy Drugs Controller (India)
   North Zone, Ghaziabad

Shri Sheju Purushothaman, Government Analyst, RDTL, Kerala could not attend the meeting because of their other commitments.

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, Dr. Jagdish Prasad, Chairman, DTAB welcomed all the members and stated that there should be SOP for calling the agenda items for DTAB from all the stakeholders on the website of CDSCO and all the agendas which are important and relevant shall be put up to DTAB for discussion.

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

AGENDA NO. 1

CONSIDERATION OF THE PROPOSAL TO RESTRICT OR PROHIBIT THE OXYTOCIN INJECTION BECAUSE OF ITS MISUSE BY DAIRY OWNERS TO EXTRACT MILK FROM MILCH ANIMALS

The Chairman briefed the members that the issue of continued misuse of oxytocin injections by the dairy owners for extracting milk from milch animals and its harmful effects on the health of cows and buffaloes was deliberated by the DTAB from time to time. In the 69th meeting held on 22.04.2015 DTAB reiterated its earlier recommendations that the drug need not be prohibiting as it has definite use for therapeutic purposes. The problem of misuse of oxytocin is more related to stricter control over the manufacture and sale of the drug especially through clandestine channels. The dairy owners get the drug manufactured at dubious premises from unscrupulous suppliers. Constant surveillance by the State Drug Regulatory Authorities and other such regulatory agencies can only curb the misuse of the drug. It was however, further decided that the issue may be further examine with experts from outside especially related to the Animal Husbandry for recommendations.

Accordingly, Dr. B. S. Prakash, Assistant Director General (ANP), Ministry of Agriculture, Krishi Bhawan, New Delhi, Dr. Ajay Kumar Dang, Principal Scientist, Dairy Cattle Physiology Division, NDRI, Karnal, Haryana and 3. Dr. Mihiar Sarkar, Principal Scientist, Division of Physiology & Climatology, IVRI, Izatnagar were invited to the meeting. Dr. Mihiar Sarkar however, could not attend the meeting because of his pre-occupation.

Shri O. S. Sadhwani, Joint Commissioner, FDA, Maharashtra stated that the drug manufactured in accordance to the Drugs and Cosmetics Rules, 1945 has high costs and is not used by milkmen for extracting milk from the cows. The raw material or the bulk drug is clandestinely smuggled into the country from the border States which is than crudely manufactured clandestinely and sold to dairy owners at very cheap rate. It only needs sustained efforts through constant surveillance to curb the menace.

Dr. B. S. Prakash informed that extensive work has been done on the use of oxytocin in milch animals and A Status Report of ICMR - ICAR Technical Working Group was compiled by him on the extent of use of oxytocin in milch animals. As per European agency for evaluation of medicinal products, there are no data on mutagenicity, carcinogenicity and teratogenicity. Oxytocin is inactivated by the reduction of disulfide - chain in the kidney, liver and lactating mammary gland. The drug oxytocin is used by medical practitioner's world over for medical purposes and has a place in veterinary medicine.

Some members pointed out that the cheap crude drug used for clandestine manufacture might belong to some surreptitiously smuggled material from the neighboring countries.

After deliberations the members agreed that the drug legitimately manufactured in the country is required for medical purposes and as such cannot be prohibited. The misuse of the drug in a crude form, can only be curbed through constant surveillance by the Regulatory authorities.

AGENDA NO. 2

CONSIDERATION OF THE PROPOSAL TO AMEND DRUGS AND COSMETICS RULES, 1945 TO PRESCRIBE TIME LIMITS FOR THE GOVERNMENT LABORATORIES TO FURNISH TEST REPORTS ON THE STATUTORY SAMPLES SENT FOR TEST

The members were briefed that the Public Accounts Committee (2012-2013) of the Ministry of Health and Family Welfare in its 84th report considered the recommendations of the DCC in its 43rd meeting held on 14.11.2011, in respect of prescribing time limits for the Government Drug Testing Laboratories to furnish test reports on the statutory samples sent for test and made the following observations.

> "The Committee are deeply concerned to note the observation of the Drug Consultative Committee (DCC) that under the Drugs and Cosmetics Rules, it may be difficult to prescribe a definite time frame for the Government Laboratories to furnish the test report. They are equally concerned to find that the time lines followed by CDL, Kolkata i.e. 60 days for HPCL testing, 45 days for Normal Chemical Testing and 90 days for Biological Products are being prescribed as model time lines, in a very casual manner, for other Government Laboratories to follow. In view of the fact that several cases of submission of test reports after a lapse of one year and administering of drugs to the patients before obtaining the test results have been detected by the Audit, the Committee impress upon the Ministry to have a serious relook at the matter and again take up the issue with the DCC, if required by incorporating suitable Amendments in the Drugs and Cosmetic Rules, so that a definite, uniform but speedy timeline for submitting the test reports is laid down and scrupulously adhered to by all the Government Laboratories, eliminating thereby the remotest possibility of administering substandard/contentious/spurious drugs to the beneficiaries."

The proposal was considered by the DCC in its 48th meeting held on 24.07.2015 and members were of the view that drugs are required to be tested for all the test prescribed under the Pharmacopoeia to declare them as of standard quality or not. Biological products require certain sophisticated testing for animal testing. For Patent Proprietary medicines, method of analysis has to be procured from the licensing authority or the manufacturer for testing such products. Testing laboratories have also

to obtain the reference standards for comparison during the testing. Apart from this laboratories receive large number of statutory samples for test and the laboratories do not have sufficient manpower, equipment, reagents and other infrastructure for completing the test and analysis in specified time limits.

After deliberations the DCC however, recommended that an upper limit of sixty days for the Government Drug Testing Laboratories for furnishing the test reports on statutory samples of drugs may be prescribed, while simultaneous efforts should be to strengthened the laboratories in terms of man power, equipments, reagents and other infrastructure to adhere to the said time lines.

The matter was deliberated in detailed and the members were of the view that the pharma industry has made tremendous progress in the last three decades by drug testing facilities in the Government labs have not been strengthened to match the growth. There is acute shortage of manpower, equipments and infrastructure in many of the State Laboratories. The sample load also has a bearing in delayed testing of the drugs. The State Drug Control Authorities must prioritize and move for the strengthening of the State Drug Laboratories under the Central schemes launched by the Central Government to strengthen Drug Regulatory Infrastructure.

DTAB recommended that for prescribing time limits for Government laboratories, a directive may be issued by the Government to the State Governments / Drug Control Authorities to adhere to a time limits of sixty days for furnishing the test reports on statutory samples by the Government Drug Testing Laboratories except in the cases of seras and vaccines and other such special products which may require animal testing. Following guidelines may be followed to avoid unnecessary delays.

i. In the case of the patent and proprietary medicines, the Drug Inspector, sending the sample should simultaneously obtain the method of analysis from the manufacturer or the licensing authority and forward to the Government analysis.

ii. The laboratory should arrange for reference standard, if required, in advanced so that the testing is not delayed.

iii. In the rare case where the Government analyst is of the opinion that he will not be able to adhere the time limit he may see extension of time limit for completing the test explaining the reasons for the delay.

The matter may also be discussed in the Government Analyst conference for ensuring timely compliance of the directions.

Simultaneously the Drugs and Cosmetics Rules, 1945 may also be amended for providing sixty days limit for the Government analyst to give the test report except in the cases where animal testing is required. It may also be provided that in specific cases where it is not possible for the Government analyst to test the samples within the time limit he may seek extension of time giving specific reasons for delay in testing.

AGENDA NO. 3

CONSIDERATION OF THE PROPOSAL TO AMEND RULE 64 OF THE DRUGS AND COSMETICS RULES, 1945 IN RESPECT OF QUALIFICATION OF THE COMPETENT PERSON

The members were briefed that the Rule 64 of the Drugs and Cosmetics Rules, 1945 prescribes conditions to be satisfied before a licence for wholesale is granted or renewed. In the second proviso to sub-rule (2) requirements of the area and the qualification of the competent person in the case of licence in 20-B and 21-B (wholesale licence) has been prescribed as under.

"Provided further that in respect of an application for the grant of a licence in Form 20-B or Form 21-B or both, the licensing authority shall satisfy himself that the premises in respect of which a wholesale licence is to be granted are:-

(i) of an area of not less than ten square meters; and

(ii) in the charge of a competent person, who—

(a) is a Registered Pharmacist, or

(b) has passed the matriculation examination or its equivalent examination from a recognised Board with four years' experience in dealing with sale of drugs, or

(c) holds a degree of a recognised University with one year's experience in dealing with drugs:"

The proposal to amend the above rule in regard to qualification of the competent person was considered by the Drugs Consultative committee in its 48th meeting held on 24.07.2015. The DCC recommended that the provisions under clause (b) relating to the qualification of matriculation examination may be deleted.

The members were of the view that time has come when the drugs should be handled only by the trained pharmacist who are qualified to handle drugs and are aware of good storage and distribution practices.

The DTAB recommended that the clause (b) and clause (c) in the above sub-rule may be deleted. A protection clause may also be provided that the academic qualification shall not apply to the persons already registered prior to the date of final notification.

AGENDA NO. 4

AMENDMENT OF SCHEDULE M III RELATING TO REQUIREMENTS OF FACTORY PREMISES FOR MANUFACTURE OF MEDICAL DEVICES AND IN-VITRO DIAGNOSTIC REAGENTS OR KITS UNDER THE DRUGS AND COSMETICS RULES, 1945

The members were briefed that the Schedule M III provides requirements of factory premises for manufacture of medical devices under the Drugs and Cosmetics Rules, 1945. The present rule introduced in 1994 relates only to three medical devices namely sterile perfusion and blood collection sets, sterile hypodermic syringes and needles, while large number of devices has since been notified and is being regulated under the provision of the Drugs and Cosmetics Rules, 1945.

The proposal to introduce a revised Schedule M III relating to the quality of medical devices and in-vitro diagnostics reagents or kits was considered in the 68th meeting of the DTAB held on 16.02.2015 and a sub-committee was constituted consisting of the following members for having a comprehensive review of Schedule M III.

i. Dr. B. Suresh, President, Pharmacy Council of India

ii. Dr. G. B. Gupta, Vice-Chancellor, Ayush and Health Sciences University of Chhattisgarh, G. E. Road, Raipur – 492001, Chhattisgarh

iii. Shri O. S. Sadhawani, Controlling authority & Joint Commissioner, FDA, Maharashtra

iv. Dr. H. G. Koshia, Commissioner, FDCA, Gujarat

v. Representative, Association of Indian Medical Device Industry (AIMED)

vi. Representative, CII, Medical Technology Division, New Delhi

vii. Representative, Association of Diagnostic Manufacturers of India

viii. Dr. V. K. Bahl, Prof. & Head of Deptt of Cardiology, AIIMS, New Delhi

ix. Dr. R. K. Jain, Prof., Lady Hartinge Medical College, New Delhi

x. Dr. Manoj Kumar, Dir. Professor, Orthopaedics, Maulana Azad Medical College, New Delhi

The matter was considered by the sub-committee in its meeting held on 12.06.2015 and committee considered the various suggestions received from the stakeholders and finalized the Schedule M III on the quality management system for notified medical devices and in vitro diagnostics.

The DTAB accepted the recommendations of the sub-committee and recommended that the Schedule M III may be incorporated under the Drugs and Cosmetics Rules, 1945 and relevant rules amended for the application of the Schedule exclusively for medical devices. The Schedule M should be applicable in the case of drugs only. Copy of the Schedule M III is **annexed**.

AGENDA NO. 5

CONSIDERATION OF PROPOSAL FOR NOTIFICATION OF HEART LUNG PACK, CUSTOM TUBING PACK AND PERFUSION PACKS USED IN CARDIAC SURGERIES AS MEDICAL DEVICES UNDER SECTION 3(B) OF THE DRUGS AND COSMETICS ACT, 1940

The members were briefed that Heart Lung Packs including Custom Tubing Pack and Perfusion Packs are used exclusively in combination with Heart Lung Machine and other devices of the system , such as Oxygenator , Blood Cardioplegia Delivery Systems. The set is used exclusively for transportation of blood and other liquids between the patient & extracorporeal system. This set is not a standard product .It is assembled according to the customer's specifications. Pack components include, but are not limited to table line, arterial and venous lines, pump lines, arterial filter by pass loops.

Heart Lung Pack was earlier categorised under notified category of "Disposable Perfusion Sets" vide notification G.S.R. 365(E) dated 17.03.1989 and is being regulated under the provisions of Drugs & Cosmetics Act & Rules thereunder. In view of the absence of specific notification and proper guidelines, the Medical Devices Associations were facing problems in import and manufacture of these medical devices.

The DTAB after deliberations agreed that a clarification may be issued indicating that Heart Lung Packs, Custom Tubing Pack and Perfusion Packs for Cardiac surgeries are medical devices covered under the category of disposable perfusion sets.

AGENDA NO. 6

CONSIDERATION OF PROPOSAL TO REGULATE ENDOMETRIAL ABLATION DEVICES AS MEDICAL DEVICES UNDER SECTION 3(b) OF THE DRUGS & COSMETICS ACT, 1940

The members were briefed that **Endometrial Ablation Devices** are intended for treating heavy menstrual Bleeding (HMB) in woman in an outpatients setting. The Endometrial ablation device comprises of disposable single use device which is connected to counter-top size generator. The device is temporarily and non-invasively inserted into the uterus through the vagina without any surgical incision. No anesthesia is required. Once inside the uterus, it delivers controlled electromagnetic heat for 60-90 seconds or less to the lining of the uterus. The dielectric heat raises the temperature to over 50°C and creates thermal necrosis of the endometrium. After the heating is complete, the device is removed from the uterus and is discarded. This heating of the lining alters its nature thereby reducing or eliminating menstrual bleeding. The entire procedure is performed in the gynaecologist's office without anesthesia. The device is not an implant (such as the copper – T). The device does not deliver any pharmaceutical or chemical agents to the uterus.

The device is manufactured in Germany and it has CE certification. The product is at present being imported into the country as unregulated devices.

The Subject Expert Committee (Reproductive & Urology) considered the matter on 16.01.2015 & 29-04-2015 and recommended that the device is of critical nature, it need to be regulated to ensure its quality.

The DTAB after deliberations recommended that **ablation devices** may be notified under Section 3(b) (iv) of the Drugs and Cosmetics Act, 1940.

AGENDA NO. 7

CONSIDERATION OF PROPOSAL TO AMEND RULE 115 OF DRUGS & COSMETICS RULES WITH RESPECT TO APPLICABILITY OF THE TEST FOR STERILITY FOR MEDICAL DEVICES BY INTRODUCING SEPARATE PROVISION FOR MEDICAL DEVICES UNDER THE PROVISIONS OF DRUGS & COSMETICS RULES

The members were briefed that the Medical Devices Associations have represented for the amendment in the existing Rule 115 of Drugs & Cosmetics Rules with respect to Batch Release criteria for medical devices by adding 115A, and permit batch release criteria of EO Sterile Medical Devices on the basis of biological indicator & process validation, release criteria of Gamma Sterile Devices on basis of indicator & process validation instead of 14 Days Sterility Test as for drugs product. Medical devices may be released on the basis of Parametric Release and by using Biological Indicators.

The Drugs and Cosmetics Rules, 1945, rule 115 provides application of tests for sterility as under:

"Application of tests for sterility—the tests shall be applied

(a) to samples taken from each batch of the substance before the operation of filling and sealing the containers in which it is to be issues has commenced except preparations, which after being sealed in the containers are to be sterilized by heat, in a manner satisfactory to the Licensing Authority; and
(b) to the contents of sample containers when ready for issue."

Under this rule each batch of the sterile product shall undergo sterility testing as per Indian Pharmacopoeia before it is released into the market. The sterility test involves incubation of media for 14 days.

The members felt that as the matter relates to patient safety and as such medical devices cannot be permitted to be released only on the basis of Parametric Release and by using Biological Indicators.

AGENDA NO. 8

CONSIDERATION OF THE PROPOSAL TO INCLUDE ULTRASOUND EQUIPMENT UNDER THE PURVIEW OF SECTION 3 OF THE DRUGS AND COSMETICS ACT, 1940 AS MEDICAL DEVICES

The members were briefed that the Central Supervisory Board (CSB), constituted under the Pre-conception and Pre-natal Diagnostics Techniques Act (PC & PNDT Act), 1994 in its 22nd meeting held on 13th October, 2014 recommended that Ultrasound machines and its accessories may be brought under Section 3 of the Drugs and Cosmetic Act, 1940 so that these are regulated under the Drugs and Cosmetics Act, 1940 for their manufactured and import.

The members felt that in the absence of comprehensive provisions relating to quality control of such devices it would be difficult to regulate these devices under the Drugs and Cosmetics Act, 1940 at present. The Drugs and Cosmetics (Amendment) Bill, 2015 proposed to be introduced in the Parliament has comprehensive provision for regulating of medical devices in general in accordance with the requirements and conditions applicable to such devices. Once these provisions come into force all such dev ices will be covered under the Drugs and Cosmetics Act, 1940.

AGENDA NO. 9

CONSIDERATION OF THE PROPOSAL TO SIMPLIFY THE PROVISIONS RELATING TO REGISTRATION OF COSMETICS IMPORTED INTO THE COUNTRY UNDER THE DRUGS AND COSMETICS RULES, 1945

The members were briefed that in the 68th meeting of the DTAB held on 16.02.2015, a sub-committee consisting of the following members to examine the issue and suggest suitable changes in the present rules so that the difficulties of the importers of cosmetics are addressed without compromising the quality and safety of the cosmetics imported into the country.

i. Shri O. S. Sadhawani, Joint Commissioner, FDA, Maharashtra

ii. Representative of the DCG(I)

The sub-committee was constituted in view of the difficulties expressed by certain importers in respect of compliance to the various provisions introduced under the Drugs and Cosmetics Rules, 1945 in respect of registration of cosmetics imported into the country.

The sub-committee considered the matter in its meetings held on 12.06.2015. A copy of the recommendations of the sub-committee is at **annexure B.**

The sub-committee recommended certain amendments in rule 129, 129H, 135A and 145D and the proposed amendments are given in bold letter as under.

1. "Rule-129: Registration of cosmetic products imported into the country.- No cosmetic shall be imported into India unless the product is registered under the Rules by the licensing authority appointed by the Central Government under rule 21 or by any person to whom such powers may be delegated under rule 22 ***or unless otherwise the products are complying with the standards specified in Drugs and Cosmetics Rules, 1945***"

2. "Rule 129H: Labelling and Packing of Cosmetics:- No cosmetic shall be imported unless it is packed and labelled in conformity with the rules in Part XV. Further the label of imported cosmetics shall bear registration certificate number of the product and the name and address of the registration certificate holder for marketing the said product in India ***or in case the products are not registered, the importer shall give undertaking at the port entry that products are manufactured by the manufacturer stated on the label ".***

3. "Rule 135A: Import of cosmetics containing mercury compounds prohibited.-No cosmetic shall be imported which contains mercury compounds**.** ***Provided the presence of traces of unintentional mercury should not exceed 1 parts per million (ppm) in finished cosmetics. Provided further that for those cosmetics intended for use only in the area of the eye, level of mercury should not exceed more than 65 parts per million (0.0065 percent) of mercury, calculated as the metal, as a preservative"***

4. "Rule 145D: Prohibition of manufacture of cosmetics containing mercury compounds.-No cosmetic containing mercury compounds shall be manufactured. ***Provided the presence of traces of unintentional mercury should not exceed 1 parts per million (ppm) in finished cosmetics. Provided further that for those cosmetics intended for use only in the area of the eye, level of mercury should not exceed more than 65 parts per million (0.0065 percent) of mercury, calculated as the metal, as a preservative***"

The committee also recommended for simplification of the import registration procedures as under:

i. **Undertaking regarding products not tested on animals:**

The Manufacturer either legal or actual /brand owner of the products/ Indian subsidiaries can submit a one-time self-declaration that the applied products have not been tested on animals on and after 12.11.2014 along with import registration dossiers to CDSCO. The acknowledgement copy for submission of this undertaking as received by the applicants from CDSCO can be produced at port offices in future for clearing their future consignments.

ii. **Frees sale certificate from the responsible person instead of the actual manufacturer:**

Free sale certificate issued by National Regulatory Authority or other competent associations/organizations from the country of the legal manufacturer in addition to the actual manufacturer from country of origin can be considered.

iii. **Letter of Authorization (LOA) in case of third party manufacturing outside India:**

In the cases where the brand owner is located in India and gets its products manufactured from sites located outside India a LOA can be considered in place of Power of Attorney (POA).The overseas manufacturer has to give acceptance of LOA and conditions on appostilled copy.

iv. **Import of Bulk cosmetics- Requirement of a certificate of Free Sale (CFS):**

Applicants can obtain Free Sale Certificate (FSC) either from the country of origin or any other major market where the same product is freely sold. Alternatively bulk importers could get the bulk cosmetics tested in India at a Government laboratory to obtain custom clearance.

The sub-committee further recommended that requirements of rule 129 for compulsory registration may be kept in abeyance till the above rule is notified.

The DTAB after deliberations agreed to the proposed amendments and the guidelines for simplification of import registration procedures. It recommended for a provision that the cosmetics imported without prior registration shall be subject to test at the time of import. A system of online registration of such import may also be initiated. CDSCO should maintain details of the cosmetics imported in the case of import of cosmetics without registration.

AGENDA NO. 10

CONSIDERATION OF THE DIRECTIONS OF THE HON'BLE HIGH COURT OF JUDICATURE OF PATNA FOR ANALYZING THE COMPONENTS OF INGREDIENTS AND THEIR EFFECT ON HUMAN BODY IF CONSUMED AS FOOD IN RESPECT OF THE NEUTRACETUCAL PRODUCTS UNDER CONSIDERATION IN THE CASE OF CWJC OF 2425 OF 2006

The members were briefed that in the 68th meeting of the DTAB held on 16.02.2015, a sub-committee consisting of the following members was constituted for analyzing the component of ingredients of each products and its effect on the human body if consumed as a food and come to the conclusion whether the products would fall under the classification of the Drugs and Cosmetics Act, 1940 or under the Prevention of Food Adulteration Act as Food as per directions of the Hon'ble High Court of Patna in the matter of CWJC OF 2425 OF 2006.

1. Dr. G. B. Gupta, Vice-Chancellor, Ayush and Health Sciences University of Chhattisgarh, G. E. Road, Raipur – 492001, Chhattisgarh
2. Prof. M. D. Karvekar, #1449, Sector, 7, 4th Main, 21st Cross, H.S.R. Lay Out, Bangalore, 560102.
3. Shri O. S. Sadhawani, Controlling authority & Joint Commissioner, FDA, Maharashtra, Bandra Kurla Complex, Bandra (E). Mumbai – 400051
4. Dr. S. K. Sharma, Prof. & Head, Department of Medicines, AIIMS, New Delhi-110029
5. Dr. A. K. Gadpayle, Medical Supd., Dr. RML Hospital, New Delhi
6. Dr. Hansraj, Cons. & Prof. Department of Medicines, RML Hospital, New Delhi
7. Dr. M. K. Daga, Director & Prof., Department of Medicines, Maulana Azad medical College, New Delhi
8. Dr. V. G. Somani, Joint Drugs Controller (India), CDSCO, HQ, FDA Bhawan, New Delhi.

The sub-committee examined the issue and recommended the following guidelines for the classification of these products.

1. Ingredients which are covered under the range as prescribed under schedule “V” of the Drugs and Cosmetics Rules for Tablets, capsules, granules are classified as drug, while those powders like Farex, Oats and Cereal fortified vitamins are exempted from the provisions of chapter IV under schedule K of Drugs and Cosmetics Rules.

2. Ingredients which fall below the range as prescribed under schedule “V” shall be classified as food. However if there is a claim for treatment, mitigation or prevention of any diseases or disorder then it will be classified as drug.

3. Fortified powders which are supposedly exempted under schedule K and for Special Medicinal Products (SMP) to be used as substitute for food shall not be considered as food if the label of the product indicates name of disease.

4. Ingredients which are within Recommended Daily Allowance (RDA) levels but fall under the range as prescribed under schedule V Drugs and Cosmetics Rules shall be classified under drug as it is already mentioned in the rules.

5. Products containing ingredients which are neither covered under Schedule V nor fall within RDA, these can be classified as unapprovable products under Drugs and Cosmetics Rules unless otherwise specifically permitted by the Licensing Authorities of drugs based on major purpose of item (like food/drug).

6. The Committee also opined that both the authorities shall implement the enforcement on the product standards as per the principles given above (for withdrawing or approving the products). It was also generally accepted by the Committee that the Fixed Dose Combinations of Vitamins and Minerals etc. which are given in schedule “V”, shall be considered as generally safe as was opined in various expert Committees on the subject. Whenever there is additional ingredients, than those given in schedule V, including some of herbal ingredients, a separate and conscious view has to be taken about safety and efficacy of drug.
7. Committee also observed that there are no pure chemical vitamins in Ayush product; therefore, any product containing herbal ingredients shall be dealt by food or drug authority based on above principles.

The sub-committee also discussed each product as per directions of the Hon'ble High Court of Patna and gave its recommendations.

The DTAB after detailed deliberations accepted the report, however, recommended that the report of the Sub-Committee may be put on the website of CDSCO for comments from the public within one month of its uploading. The comments shall then be further examined by the Sub committee and then put up to DTAB.

AGENDA NO. 11

CONSIDERATION OF THE PROPOSAL TO MAKE A PROVISION UNDER THE DRUGS AND COSMETICS RULES, 1945 FOR PROVIDING EXEMPTION IN RESPECT OF PROVISIONS OF SCHEDULE M RELATING TO GOOD MANUFACTURING PRACTICES IN THE CASE OF MANUFACTURE OF DRUGS FOR EXPORT ONLY

The members were briefed that India is exporting about 56% of its annual production. Ministry of Commerce and Industry has time and again stated that the manufacture of drugs in the country are required to comply with the conditions of Good Manufacturing Practices prescribed under Schedule M of the Drugs and Cosmetics Rules, 1945 even in cases when the importing country does not require compliance to these requirements, while following international requirements as specified by the importing countries. Compliance to the additional requirements only add cost and time to the exporters. It has also been stated that even US FDA have specific provisions under their domestic laws for exempting exports from application of domestic laws subject to certain conditions.

In order to create ease of business it was recommended by the Ministry of Commerce to provide a general exemption for manufacture for exports in respect of Schedule M in the cases where the manufacturer is following international requirements as specifying by the importing county.

The DTAB after deliberations agreed to provide the following exemption under Schedule K of the Drugs and Cosmetics Rules, 1945 for the manufacture of drugs for export only.

Class of drugs	*Extent and conditions of exemption*
Bulk drug or finished formulation manufactured for export only.	*The provisions of Chapter IV of the Act and rules thereunder which require the licensee to conform to the provisions of Good Manufacturing Practices as prescribed under Schedule M subject to the condition that the manufacturing facilities have been inspected and registered by the regulatory authorities of the importing country in respect of compliance to the good manufacturing practices for the purpose of import into that country.*

AGENDA NO. 12

CONSIDERATION OF THE PROPOSAL TO AMEND RULE 3-A OF THE DRUGS AND COSMETICS RULES, 1945 IN RESPECT OF TESTING OF VACCINES BY THE NIB, NOIDA

Rules 3-A of the Drugs and Cosmetics Rules prescribes the functions which a laboratory may discharge as Central Drugs Laboratory in respect of the drugs specified therein.

The members were briefed that the National Institute of Biologicals (NIB), Noida is a notified lab under sub-rule (8) of rule 3-A for testing following categories of drugs as appellate laboratory.

(1) Blood grouping reagents.

(2) Diagnostic kits for human immunodeficiency virus, Hepatitis B Surface Antigen and Hepatitis C Virus.

(3) Blood products-

(4) Recombinant products such as-

(5) Biochemical kits-

The National Institute of Biologicals was proposed to be declared as Central Drug Laboratory for testing of the following vaccines also which are at present being tested at CDL, CRI, Kasauli.

(a) BCG vaccine;

(b) Live Attenuated Measles vaccine;

(c) Live Attenuated Rubella vaccine;

(d) Cell culture rabies vaccines.

DTAB after deliberations did not agree to the proposed amendment.

AGENDA NO. 13

CONSIDERATION OF THE PROPOSAL TO AMEND RULE 124-A OF THE DRUGS AND COSMETICS RULES, 1945 IN RESPECT OF STANDARDS FOR VETERINARY DRUGS

The members were briefed that the Indian Pharmacopoeia (IP) 2014 now includes under it a separate volume for veterinary drugs. The standards for identity, purity and strength for veterinary drugs included in the Indian Pharmacopoeia are required to be those as may be specified in the Indian Pharmacopoeia.

The rule 124-A at present separately prescribe standards for veterinary drugs as under:

> **"124-A. Standards for veterinary drugs.-** For drugs intended for veterinary use, the standards shall be those given in the current edition for the time being in force of the British Pharmacopoeia Veterinary."

The Drugs Consultative committee in its 48th meeting held on 24.07.2015 had also recommended that rule 124-A may be omitted under the Drugs and Cosmetics Rules, 1945.

It was proposed to omit rule 124-A of the Drugs and Cosmetics Rules, 1945 as the rule 124 includes all drugs included in the IP and separate provisions for veterinary drugs is no longer required.

The DTAB recommended that rule 124-A has become redundant and therefore should be omitted.

AGENDA NO. 14

CONSIDERATION OF THE PROPOSAL FOR RECONSTITUTION OF A SUB-COMMITTEE OF DTAB ON HOMEOPATHIC MEDICINES TO DELIBERATE TECHNICAL MATTER RELATING TO HOMEOPATHY AND GIVE ITS RECOMMENDATIONS TO DTAB FOR FURTHER CONSIDERATION

The members were briefed that the Ministry of AYUSH has forwarded the proposal of reconstitution of the sub-committee of DTAB on Homeopathic medicines with following members, to deliberate on technical matters relating Homoeopathy which would then be placed before DTAB for its consideration before giving final recommendations to the Government.

1. Chairman : Advisor (Homeopathy) Ministry of AYUSH.
2. Co-Chairman: Director General, Central Council for Research in Homoeopathy.
3. Official members:
   - (i) Director, Homoeopathic Pharmacopoeia Laboratory, Ghaziabad
   - (ii) Director (Homoeopathy), Govt. of Uttar Pradesh
   - (iii) Representative of Drugs Controller General (India)

4. Non-official Members:
   - (i) Dr. Dilip Panakada (HOD-Pharmacy), NIH, Kolkata;
   - (ii) Dr. Chaturbhuja Nayak, Ex-Director General, Central Council for Research in Homoeopathy;
5. Representative of Homoeopathic Drug Manufacturing Industry
   - (i) Managing Director, Kerala State Co-Operative, Homoeopathic pharmacy, Kerala
   - (ii) Representative of Federation of Homoeopathic Manufacturers' Association of India (FOHMI);

(iii) Representative of All India Homoeopathic Associations;

6. Member Secretary: Dr. Srinivas Rao Chinta,
Assistant Adviser (Homoeopathy), Ministry of AYUSH.

The DTAB after consideration agreed to the constitution of the sub-committee with the above members.

AGENDA NO. 15

CONSIDERATION OF THE PROPOSAL TO INCLUDE CERTAIN DRUGS UNDER SCHEDULE H OR H1 AS PER RECOMMENDATIONS OF THE DRUGS CONSULTATIVE COMMITTEE MEETING HELD ON 24.07.2015

The members were briefed that the in the 48th meeting of the Drugs Consultative Committee meeting held on 24.07.2015. It was recommended that the following drugs should be included in Schedule H or H1 of the Drugs and Cosmetics Rules, 1945 and matter placed before DTAB.

1. **ETIZOLAM**
2. **LORAZEPAM**
3. **CLONAZEPAM**

It was observed that the drugs Lorazepam and Clonazepam are already covered under Schedule H. The DTAB recommended that the drug Etizolam should also be included in Schedule H. It was further recommended that the new drugs approved by the DCG(I) for marketing as Schedule H or Schedule H1 drugs should also be included in the respective Schedules.

AGENDA NO. 16

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES, 1945 IN RESPECT OF THE PROVISIONS RELATING TO THE BLOOD BANKS AND BLOOD DONATION CAMPS AS PER RECOMMENDATIONS OF NATIONAL CORE BLOOD BANK ASSESSMENT COMMITTEE CHAIRED BY DR. JAGDISH PRASAD, DIRECTOR GENERAL OF HEALTH SERVICES

The members were briefed that the a meeting of National Core Blood Bank Assessment Committee under the Chairmanship of Dr. Jagdish Prasad, DGHS was held on **26th May, 2015 at** New Delhi. During the meeting the following issues related to blood banking were discussed.

1. Bulk transfer of whole blood and components between blood banks
2. Blood storage centres
3. NOC from State Blood Transfusion Council for application for licensure to any blood bank
4. Criteria for Regional Blood Transfusion Council

The specific recommendations which required amendments to the Drugs and Cosmetics Rules were considered by the DTAB as under:

1. **Bulk transfer of whole blood and components may be allowed between blood banks where there is facility to store and monitor the same.**

   The following clause under rule 122 P relating to conditions of licence for blood banks to be inserted.

   "(xiv) the whole human blood and blood components in bulk may be transferred, under prescribed storage conditions, to another blood bank which have facilities to store and monitor blood distribution. The recipient blood banks shall not further transfer units obtained from another blood bank except to another blood storage centre or a patient.

2. **Blood Donation camps may be conducted by all government, IRCS and blood banks possessing No Objection Certificate from the SBTC, including hospital based corporate blood banks.**

   In Part XII B of the Schedule F, under the heading "**II BLOOD DONATION CAMPS"** the following entries may be inserted.

   "(e). a private hospital blood bank."

3. **Any hospital can apply to become a blood storage centre, as already permitted under the Drugs and Cosmetics Act.**

   The following entry under clause 2 at serial number 5(B) of Schedule K shall be omitted.

   > "(2) The captive consumption of Whole Human Blood I.P. or its components in the First Referral Unit, Community Health Centre, Primary Health Centre and / or any Hospital shall not be more than 2000 units annually."

The members appreciated that the National Core Blood Bank Assessment Committee has done a great job in easing out the availability of the blood in the country and might help in making blood available to the needy patients.

The DTAB agreed to the proposed amendments to the Drugs and Cosmetics Rules, 1945.

AGENDA NO. 17

CONSIDERATION OF THE ISSUES RAISED BY SMT. MANEKA SANJAY GANDHI, HON'BLE MINISTER OF WOMEN AND CHILD DEVELOPMENT REGARDING PRE-CLINICAL / TOXICITY STUDIES ON ANIMALS UNDER SCHEDULE Y OF THE DRUGS AND COSMETICS RULES, 1945

The members were briefed that the Smt. Maneka Sanjay Gandhi, Hon'ble Minister of Women and Child Development had written to the Union Minister of Health and Family Welfare, regarding pre-clinical / toxicity studies on animals under Schedule Y of the Drugs and Cosmetics Rules, 1945. It has been stated that India being signatory of OECD Council Act related to mutual acceptance of data is under obligation to respect the data generated by other country regarding pre-clinical / toxicity studies and therefore there is no need for CDSCO to undertake further studies. The molecules of interest

have been those that are approved by multiple regulatory agencies and have been through many animal studies which have been made available on sites and published in scientific journals. Under the current regulations of item 4, Appendix-I of Schedule Y of Drugs and Cosmetics Act, 1940, additional tests on animals are then ordered.

As the issue was related to pre-clinical or toxicity studies on animals under APPENDIX I AND APPENDIX III of Schedule Y, the matter was placed before the IND committee in its meeting 06.08.2015 and the Committee gave the following recommendations.

> "The Committee deliberated and agreed with the statement mentioning that, for drugs approved in other countries where complete toxicological data generated in GLP certified laboratory and in alignment with the requirements prescribed under Drugs and Cosmetics Act, 1940 and Rules, 1945 (Schedule Y), further toxicity study may not be required if complete data as per prescribed requirements is submitted during application for new drug approval.
> It may also be explored, in line with international practices, to encourage the use of other alternative methods than animal studies, wherever such robust validated methods are available for small or large animals."

The DTAB after deliberations agreed to the recommendations of the IND committee and further recommended that under item 4, Appendix I of Schedule Y, it may be mentioned that if authentic data on animal toxicology as per requirements of **annexure III** has been submitted with the technical data, then repeat animal testing for permission for a new drug or clinical trial is not necessary.

AGENDA NO. 18

CONSIDERATION OF THE PROPOSAL TO EXTENT THE VALIDITY OF THE LICENCE TO IMPORT DRUGS FOR TEST AND ANALYSIS UNDER FORM 11 AND LICENCE TO MANUFACTURE DRUGS FOR TEST AND ANALYSIS UNDER FORM 29 FROM ONE YEAR TO THREE YEARS

The members were briefed that the Under the rule 33 of the Drugs and Cosmetics Rules, 1945 small quantities of drugs, the import of which is otherwise prohibited under the Act, are permitted to be imported for the purpose of examination, test and analysis in Form 11. The Form under serial number 3 provides the validity period of one year from the date of issue stated in the Form. Similarly licence to manufactured drugs for the purpose of examination, test or analysis is granted in Form 29 under rule 89 of the said rules. Here also the validity of the licence is for one year from the date of issue as specified in the Form.

Representations were received from the Drug Manufacturer Associations that for the purpose of clinical trials and drug development, the licencees have to approach the licensing authorities for grant of fresh licence every year. Department of Commerce have also recommended in the various meetings to increase the validity of these licences from one year to three years for creation ease of business in the vital sector of clinical trials and drug development.

The DTAB agreed to the proposed recommendations that the validity of the licences in Form 11 and in Form 29 to be increased from one year to three years.

AGENDA NO. 19

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES FOR MAKING A PROVISION FOR IMPORT OF DRUGS BY CHARITABLE HOSPITALS AS DONATION FOR THE TREATMENT OF PATIENTS IN THEIR HOSPITALS

The members were briefed that the many of the charitable hospitals run by dedicated missionaries receive drugs as free donation from many countries for the treatment of the patients in their respective hospitals. The Drugs and Cosmetics Rules, 1945 do not have any specific provision for such imports. The consignments are cleared on the basis of the no objection certificate provided by the Licensing Authority.

It was therefore proposed to introduce a provision under the Drugs and Cosmetics Rules, 1945 for import of small quantities of drugs received as free donation by such hospitals provided that the drugs are not prohibited for import into the country and the following rule may be inserted under the Drugs and Cosmetics Rules, 1945.

“Import of drugs by the charitable hospitals free of cost.-

small quantities of drugs received as free donation by a charitable hospital for the purpose of treatment of the patients in the hospital may be imported provided the drugs are given to the patients free of cost. The drugs should not be not prohibited for import and permitted to be marketed in the country with residual shelf life of one year or more. The drugs shall be given free of cost to the patients.”

The DTAB after deliberations agreed to the proposed amendment.

AGENDA NO. 20

CONSIDERATION OF THE PROPOSAL FOR INTRODUCTION OF CERTAIN GUIDELINES TO FACILITATE THE EASE OF BUSINESS IN RESPECT OF THE PROCEDURES FOR REGISTRATION AND IMPORT LICENCE UNDER THE DRUGS AND COSMETICS RULES, 1945

The members were briefed that the import of drugs is regulated under the system of registration and import licence under the Drugs and Cosmetics Rules, 1945. The manufacturers who intend to export drugs to India are required to have registration certificate to ensure that drugs from only authentic sources are permitted in the country. The drugs are imported under the import licences granted to the importers.

The concerns were raised on the bottlenecks faced by Indian agents, manufacturers and exporters because of lack of guidelines in respect of various issues like fees to be charged, change of letters requirements of documents etc.

The Ministry of Commerce also requested that necessary guidelines may be issued to address the difficulties of the importers of drugs and creating ease of business in pharma sector.

The following guidelines were proposed to be followed to facilitate ease of business in respect of the procedures for registration and import licence under the Drugs and Cosmetics Rules, 1945.

1. The fee for fresh registration certificate should not be insisted upon the case there is only a change of address of the registered office of the manufacturer abroad or his Indian agent as these changes do not impact the quality or the manufacturing site.

2. The import licence may be granted at the address of the importers as mentioned in the wholesale licence or manufacturing licence. The licence may however, be dispatch to the registered office of the importer if required. The address of the wholesale licence shall also be mentioned on the licence where physical transaction of the material will take place.

3. The products which are considered as drugs in India but are licenced as food products or excipients in other countries are not regulated as drugs and as such do not have Good Manufacturing Practices certificates or free sale certificate in the country of origin. Such products may be approved on the basis of equivalent / alternative certificate provided such certificates have

been issued on the basis of the inspection. The products at the time of import may be subjected to test to ensure its quality.

The DTAB approved to the above guidelines. It however, further recommended that fees for import registration in the country should be increased from one lakhs rupees to five lakhs rupees.

AGENDA NO. 21

CONSIDERATION OF THE RECOMMENDATIONS OF THE DEPARTMENT OF FAMILY WELFARE TO CONSIDER THE ISSUE OF INTRODUCTION OF INJECTABLE CONTRACEPTIVE DMPA IN THE PUBLIC HEALTH FACILITIES UNDER THE NATIONAL FAMILY PLANNING PROGRAMME

The members were briefed that the request has been received by the DGHS, Chairman of DTAB from Dr. Rakesh Kumar, Joint Secretary, Ministry of Health and Family Welfare for the consideration of the clearance of introduction of the 'injectables' contraceptive DMPA in the public health system under National Family Planning Programme by DTAB.

The National Consultative Meeting on Expanding the Basket of Choice in Family Planning was held on 24.7.2015. The Co-Chairs Dr. Sunita Mittal and Dr. Sudha Prasad moderated and facilitated the session and a consensus on the following points was arrived at:

- Injectables are a suitable and feasible method for introduction in the program. The studies of ICMR with Net-EN and Mesigyna injectables has been conducted successfully in India and the product has been in the private sector with the concurrence of DCG(I) for the last twenty years with no untoward events reported, a pilot is therefore not required before including it in the basket of choice under FP.

- Injectable is an important contraceptive method and much in demand by the community, therefore it should be introduced pan India, at all levels up to the Sub centres. Restricting its availability only up to higher level like the Medical colleges / District Hospitals, will defeat the purpose of its introduction as a beneficiary.

The DTAB after deliberations agreed to the introduction of the 'injectables' contraceptive DMPA in the public health system under National Family Planning Programme.

AGENDA NO. 22

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES, 1945 FOR PROVIDING EXEMPTION IN THE CASE OF THE TRIALS UNDERTAKEN IN THE MEDICAL INSTITUTIONS OR HOSPITALS FOR ACADEMIC RESEARCH

clinical trials on new drugs are regulated under the provisions of the Drugs and Cosmetics Rules, 1945. Rule 122DA provides that 'No clinical trial for a new drug, whether for clinical investigation or any clinical experiment by any institution, shall be conducted except under, and in accordance with, the permission, in writing, of the Licensing Authority'. Further, Rule 122E includes not only the new molecules but also the new claims namely new indication, route of administration, dosage, etc. of already approved drugs.

Under these provisions conduct of clinical trial of already approved drugs for new claim by any Institution / Medical Researcher for academic purposes require prior permission of DCG(I).

Concerns were raised regarding difficulties in submission of application to DCG (I) for such clinical trials by the Investigators/medical students from different parts of the country and subsequently making presentation before the SECs for their approval. It was felt that the cumbersome procedures for obtaining permissions in each and every case of academic research is not permitting free growth of academic clinical research in the medical institutions.

The members were briefed that the Prof. Ranjit Roy Choudhury Committee had recommended that academic research may be approved by the Institutional Ethics Committees. The approval of DCG(I) should only be required if a new drug is being evaluated or a new use for an existing drug is being tried out. It was therefore decided by the Ministry of Health and Family Welfare that academic clinical research may be approved by the Institutional Ethics Committee, however, in the case of new drug is being evaluated or a new use of an existing drug is being evaluated, then approval of DCG (I) is required as per rules.

In the countries like USA which has well regulated clinical research provide exemptions for submission of IND application to USFDA under certain conditions depending on the intent of trial and the risk involved.

In view of the above it was proposed that a provision may be provided under the Drugs and Cosmetics Rules, 1945 that permission for clinical trial purely for academic research may be approved by the Institutional Ethics Committees. The approval of DCG(I) should be mandatory only when the new drug is being evaluated or a new use for an existing drug is being tried out under certain conditions.

A proviso to the rule 122 DA relating to application for permission to conduct clinical trial for new drug / investigational new drugs was proposed to be introduced as under to provide specific exemptions in the case of clinical trials for academic research as under:

Provided that permission for conduct of clinical trial is not required from the licensing authority if the study is related to already licenced or approved drug and drug formulations permitted to be marketed, for new indication, new route of administration, new dose, etc. for academic research purposes and complies with the following conditions.

i. The trial has been duly approved by the Ethics Committee.
ii. The data generated is not intended for submission to any regulatory authority.

The DTAB after deliberations agreed to the proposed amendment.

AGENDA NO. S-1

CONSIDERATION OF THE ISSUE OF BANNING OF PACKAGING OF PHARMACEUTICAL PRODUCTS IN PET / PLASTIC BOTTLES

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 it was recommended 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.

Accordingly a Gazette notification G.S.R. 701(E) dated 29.09.2014 was issued by the Government of India for amendment under the Drugs and Cosmetics Rules, 1945 for the purpose. A large number of comments were since received especially from the PET manufacturers associations etc. and the objections and suggestions so received are under consideration of the Government of India for the purpose of finalization.

The Chairman raised the issue for the consideration of the DTAB, in the light of the report of Plastic Hazards Committee of the All India Institute of Hygiene and Public Health, Kolkata in respect of testing the level of toxic chemicals in medicines and other formulations sold in PET bottles with respect to the safety limits.

A study was conducted at the All India Institute of Hygiene and Public Health in which samples of five different pharmaceutical preparations packaged in PET bottles were subjected to testing at National Test House, Kolkata. It was found that Antimony, Chromium, Lead and DEHP were present even at room temperature in all five samples. The concentration increased on exposure to higher temperature in the laboratory. The

committee recommended that the issue of cumulative exposure need to be address through large scale toxicological / toxicokinetic studies.

The DTAB after deliberations recommended that the finding of the committee may be forwarded to the Government of India for consideration and taking further action in the matter.

Annexure

SCHEDULE M-III
[See Rule 76]

QUALITY MANAGEMENT SYSTEM –FOR NOTIFIED MEDICAL DEVICES AND IN-VITRO DIAGNOSTICS

1. General

This schedule specifies requirements for a quality management system that shall be used by the manufacturer for the design and development, manufacture, packaging, labeling, testing, installation and servicing of medical devices and in-vitro diagnostics. If the manufacturer does not carry out design and development activity, the same shall be recorded in the quality management system and shall exclude the provisions of relevant clauses of this schedule. The manufacturer shall ensure the claims of conformity with this schedule to reflect the exclusions.

If any requirement(s) in Clause 7(product realization) of this schedule is(are) not applicable due to the nature of the medical device(s) and in-vitro diagnostics(s) for which the quality management system is applied, the manufacturer does not need to include such a requirement(s) in its quality management system.

The processes required by this schedule, which are applicable to the medical device(s)and in-vitro diagnostic devices, but which are not performed by the manufacturer are the responsibility of the manufacturer and are accounted for in the manufacturer's quality management system.

If a manufacturer engages in only some operations subject to the requirements in this part, and not in others, that manufacturer need only comply with those requirements applicable to the operations in which it is engaged.

It is emphasized that the quality management system requirements specified in this schedule are complementary to technical requirements for products.

Manufacturers of components or parts of finished devices and in-vitro diagnostics are encouraged to use appropriate provisions of this regulation as guidance.

2. Applicability

The provisions of this Schedule shall be applicable to manufacturers of finished devices, In-Vitro Diagnostics, mechanical contraceptives (Condoms, intrauterine Devices, Tubal Rings), surgical dressings, surgical bandages, surgical staplers, surgical sutures and ligatures, Blood and Blood Components Collection bags, intended for human or animal use that is manufactured in India.

3. Terms and definitions

3.1 Active implantable medical device

Active medical device which is intended to be totally or partially introduced, surgically or medically, into the human or animal body or by medical intervention into a natural orifice, and which is intended to remain after the procedure

3.2 Active medical device

Medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human or animal body or gravity

3.3 Advisory notice

Notice issued by the manufacturer, subsequent to delivery of the medical deviceand in-vitro diagnostic devices, to provide supplementary information and/or to advise what action should be taken in

- the use of a medical deviceand in-vitro diagnostic devices,
- the modification of a medical deviceand in-vitro diagnostic devices,
- the return of the medical deviceand in-vitro diagnostic devices to the organization that supplied it, or
- the destruction of a medical deviceand in-vitro diagnostic devices

3.4 Customer complaint

Written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical deviceand in-vitro diagnostic devicesthat has been placed on the market

3.5 Implantable medical device

Medical device intended

- to be totally or partially introduced into the Human or animal body or a natural orifice, or
- to replace an epithelial surface or the surface of the eye,

by surgical intervention, and which is intended to remain after the procedure for at least 30 days, and which can only be removed by medical or surgical intervention

3.6 Component means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

3.7 Design input means the physical and performance requirements of a device that are used as a basis for device design.

3.8 Design output means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record.

3.9 Design review means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.

3.10 Finished device means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized.

3.11 In-vitro Diagnostic devices: In-vitro Diagnostics referred in this schedule means diagnostics that fall under section 3(b)(i) of Drugs and Cosmetics Act

3.12 Management with executive responsibility means those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer's quality policy and quality system.

3.13 Medical device: Medical devices referred in this schedule means devices that are notified under section 3(b)(iv) of Drugs and Cosmetics Act.

3.14 Quality audit means a systematic, independent examination of a manufacturer's quality system that is performed at defined intervals and at sufficient frequency to determine whether both quality system activities and the results of such activities comply with quality system procedures, that these procedures are implemented effectively, and that these procedures are suitable to achieve quality system objectives.

3.15 Quality policy means the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility.

3.16 Quality system means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

3.17 Rework means action taken on a nonconforming product so that it will fulfill the specified DMR requirements before it is released for distribution.

3.18 Specification means any requirement with which a product, process, service, or other activity must conform.

3.19 Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

(1)Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.
(2)Design validation means establishing by objective evidence that device specifications conform with user needs and intended use(s).

3.20 Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

4 Quality Management System

4.1 General requirements

The manufacturer shall establish, document, implement and maintain a quality management system and maintain its effectiveness in accordance with the requirements of this schedule.

The manufacturer shall
a) identify the processes needed for the quality management system and their application throughout the organization,
b) determine the sequence and interaction of these processes,
c) determine criteria and methods needed to ensure that both the operation and control of these processes are effective,
d) ensure the availability of resources and information necessary to support the operation and monitoring of these processes,
e) monitor, measure and analyse these processes, and
f) implement actions necessary to achieve planned results and maintain the effectiveness of these processes.

These processes shall be managed by the manufacturer in accordance with the requirements of this schedule.

Where a Manufacturer chooses to outsource any process that affects product conformity with requirements, the Manufacturer shall ensure control over such processes. Control of such outsourced processes shall be identified within the quality management system.
NOTE Processes needed for the quality management system referred to above should include processes for management activities, provision of resources, product realization and measurement.

4.2 Documentation requirements

4.2.1 General

The quality management system documentation shall include
a) documented statements of a quality policy and quality objectives,
b) a quality manual,
c) documented procedures required by this schedule,
d) documents needed by the manufacturer to ensure the effective planning, operation and control of its processes,
e) records required by this schedule, and

Where this schedule specifies that a requirement, procedure, activity or special arrangement be
"documented", it shall, in addition, be implemented and maintained.

For each type or model of medical device/ In-vitro Diagnostics, the manufacturer shall establish and maintain a file either containing or identifying documents defining product specifications and quality management system requirements. These documents shall define the complete manufacturing process and, if applicable, installation.

Data may be recorded by electronic data processing systems or other reliable means, but documents and record relating to the system in use shall also be available in a hard copy to facilitate checking of the accuracy of the records. Wherever documentation is handled by electronic data processing methods, authorized persons shall enter or modify data in the computer. There shall be record of changes and deletions. Access shall be restricted by 'passwords' or other means and the result of entry of critical data shall be independently

checked. Batch records electronically stored shall be protected by a suitable back-up. During the period of retention, all relevant data shall be readily available.

4.2.2 Quality manual

The manufacturer shall establish and maintain a quality manual that includes

a) the scope of the quality management system, including details of and justification for any exclusion and/or non-application,

b) the documented procedures established for the quality management system, or reference to them, and

c) a description of the interaction between the processes of the quality management system.

The quality manual shall outline the structure of the documentation used in the quality management system.

The manufacturer shall prepare documentation in a form of a Site Master File containing specific information about the facilities, personnel and other details as prescribed in **Annexure A**.

4.2.3 Control of documents

Documents required by the quality management system shall be controlled. Records are a special type of document and shall be controlled according to the requirements given in the control of records. Documents shall be approved, signed and dated by the appropriate and the authorized person

A documented procedure shall be established to define the controls needed

a) to review and approve documents for adequacy prior to issue,

b) to review and update as necessary and re-approve documents,

c) to ensure that changes and the current revision status of documents are identified,

d) to ensure that relevant versions of applicable documents are available at points of use,

e) to ensure that documents remain legible and readily identifiable,

f) to ensure that documents of external origin are identified and their distribution controlled, and

g) to prevent the unintended use of obsolete documents, and to apply suitable identification to them if they are retained for any purpose.

Changes to document shall be reviewed, approved and maintained. Change records shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective.

The manufacturer shall ensure that changes to documents are reviewed and approved either by the original approving function or another designated function which has access to pertinent background information upon which to base its decisions.

The manufacturer shall define the period for which at least one copy of obsolete controlled documents shall be retained. This period shall ensure that documents to which medical devices/In-vitro Diagnostics have been manufactured and tested are retained for at least

one year after the date of expiry of the medical device/In-vitro Diagnostic as defined by the manufacturer.

4.2.4 Control of records

Records shall be established and maintained to provide evidence of conformity to requirements and of the effective operation of the quality management system. Records shall remain legible, readily identifiable and retrievable. A documented procedure shall be established to define the controls needed for the identification, storage, protection, retrieval, retention time and disposition of records.

The manufacturer shall retain the records for a period of time at least one year after the date of expiry of the medical device/In-vitro Diagnostics as defined by the manufacturer, but not less than two years from the date of product release by the manufacturer.

5 Management responsibility

5.1 Management commitment

Top management of the manufacturer shall provide evidence of its commitment to the development and implementation of the quality management system and maintaining its effectiveness by

a) communicating to the employees the importance of meeting customer as well as statutory and regulatory requirements,
b) establishing the quality policy,
c) ensuring that quality objectives are established,
d) conducting management reviews, and
e) ensuring the availability of resources.

5.2 Customer focus

Top management of the manufacturer shall ensure that customer requirements are determined and are met.

5.3 Quality policy

Top management of the manufacturer shall ensure that the quality policy

a) is appropriate to the purpose of the manufacturing facility,
b) includes a commitment to comply with requirements and to maintain the effectiveness of the quality management system,
c) provides a framework for establishing and reviewing quality objectives,
d) is communicated and understood within the manufacturers organization, and
e) is reviewed for continuing suitability.

5.4 Planning

5.4.1 Quality objectives

Top management of the manufacturer shall ensure that quality objectives, including those needed to meet requirements for product, are established at relevant functions and levels within the manufacturing organization. The quality objectives shall be measurable and consistent with the quality policy.

5.4.2 Quality management system planning

Top management of the manufacturer shall ensure that
a) the planning of the quality management system is carried out in order to meet the specified requirements, as well as the quality objectives, and
b) the integrity of the quality management system is maintained when changes to the quality management system are planned and implemented.

5.5 Responsibility, authority and communication

5.5.1 Responsibility and authority

Top management of the manufacturer shall ensure that responsibilities and authorities are defined, documented and communicated within the manufacturing organization.
Top management of the manufacturer shall establish the interrelation of all personnel who manage, perform and verify work affecting quality, and shall ensure the independence and authority necessary to perform these tasks.

5.5.2 Management representative

Top management shall appoint a member of management who, irrespective of other responsibilities, shall have responsibility and authority that includes
a) ensuring that processes needed for the quality management system are established, implemented and maintained,
b) reporting to top management on the performance of the quality management system and any need for improvement, and
c) ensuring the promotion of awareness of regulatory and customer requirements throughout the manufacturing organization.

5.5.3 Internal communication

Top management shall ensure that appropriate communication processes are established within the Manufacturing organization and that communication takes place regarding the effectiveness of the quality management system.

5.6 Management review

5.6.1 General

Top management shall review the organization's quality management system, at planned intervals, to ensure its continuing suitability, adequacy and effectiveness. This review shall include assessing opportunities for improvement and the need for changes to the quality management system, including the quality policy and quality objectives. Records from management reviews shall be maintained.

5.6.2 Review input

The input to management review shall include information on
a) results of audits,
b) customer feedback,
c) process performance and product conformity,
d) status of preventive and corrective actions,
e) follow-up actions from previous management reviews,
f) changes that could affect the quality management system,
g) recommendations for improvement, and
h) new or revised regulatory requirements as and when issued.

5.6.3 Review output

The output from the management review shall include any decisions and actions related to
a) improvements needed to maintain the effectiveness of the quality management system and its processes,
b) improvement of product related to customer requirements, and
c) resource needs.

6 Resource Management

6.1 Provision of resources

The manufacturing organization shall determine and provide the resources needed
a) to implement the quality management system and to maintain its effectiveness, and
b) to meet regulatory and customer requirements.

6.2 Human resources

6.2.1 General

Personnel performing work affecting product quality shall be competent on the basis of appropriate education, training, skills and experience. Number of personnel employed shall be adequate and in direct proportion to the workload. Prior to employment, all personnel, shall undergo medical examination including eye examination, and shall be free from communicable or contagious diseases. Thereafter, they should be medically examined periodically, at least once a year. Records shall be maintained thereof. All personnel shall bear clean body covering appropriate to their duties. Smoking, Eating, Drinking, Chewing or keeping food and drink shall not be permitted in production, laboratory and storage areas.

6.2.2 Competence, awareness and training

The manufacturer shall
a) determine the necessary competence for personnel performing work affecting product quality,
b) provide training or take other actions to satisfy these needs,
c) evaluate the effectiveness of the actions taken,
d) ensure that its personnel are aware of the relevance and importance of their activities and how they contribute to the achievement of the quality objectives, and
e) maintain appropriate records of education, training, skills and experience.
f) establish documented procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities.

6.3 Infrastructure

The organization shall determine, provide and maintain the infrastructure needed to achieve conformity to product requirements. Infrastructure includes, as applicable
a) buildings, workspace and associated utilities.
b) process equipment (both hardware and software), and
c) supporting services (such as transport or communication).

The manufacturer shall establish documented requirements for maintenance activities, including their frequency, when such activities or lack thereof can affect product quality. Records of such maintenance shall be maintained.

6.4 Work environment

The organization shall determine and manage the work environment needed to achieve conformity to product requirements. The following requirements shall apply.

a) The manufacturer shall establish documented requirements for health, cleanliness and clothing of personnel if contact between such personnel and the product or work environment could adversely affect the quality of the product.
b) If work environment conditions can have an adverse effect on product quality, the manufacturer shall establish documented requirements **as per annexure-C** of this schedule for the work environment conditions and documented procedures or work instructions to monitor and control these work environment conditions.
c) The manufacturer shall ensure that all personnel who are required to work temporarily under special environmental conditions within the work environment are appropriately trained and supervised by a trained person.
d) If appropriate, special arrangements shall be established and documented for the control of contaminated or potentially contaminated product in order to prevent contamination of other product, the work environment or personnel.

7 Product realization

7.1 Planning of product realization

The manufacturer shall plan and develop the processes needed for product realization. Planning of product realization shall be consistent with the requirements of the other processes of the quality management system. In planning product realization, the manufacturer shall determine the following, as appropriate:
a) quality objectives and requirements for the product;
b) the need to establish processes, documents, and provide resources specific to the product;
c) required verification, validation, monitoring, inspection and test activities specific to the product and the criteria for product acceptance;
d) records needed to provide evidence that the realization processes and resulting product meet requirements.

The output of this planning shall be in a form suitable for the manufacturer’s method of operations.

The manufacturer organization shall establish documented requirements for risk management (as per the IS/ISO 14971) throughout product realization. Records arising from risk management shall be maintained.

7.2 Customer-related processes

7.2.1 Determination of requirements related to the product

The manufacturer shall determine
a) requirements specified by the customer, including the requirements for delivery and post-delivery activities,
b) requirements not stated by the customer but necessary for specified or intended use, where known,
c) statutoryrequirements related to the product, and
d) any additional requirements determined by the manufacturer.

7.2.2 Review of requirements related to the product

The manufacturer shall review the requirements related to the product. This review shall be conducted prior to the manufacturer's commitment to supply a product to the customer and shall ensure that

a) product requirements are defined and documented,
b) contract or order requirements differing from those previously expressed are resolved, and
c) the manufacturer has the ability to meet the defined requirements.

Records of the results of the review and actions arising from the review shall be maintained.

Where the customer provides no documented statement of requirement, the customer requirements shall be confirmed by the manufacturer before acceptance.

Where product requirements are changed, the manufacturer shall ensure that relevant documents are amended and that relevant personnel are made aware of the changed requirements.

The manufacturer shall prepare documentation on Device(s) in a form of a Device Master File containing specific information as prescribed in **Annexure B**.

7.2.3 Customer communication

The manufacturer shall determine and implement effective arrangements for communicating with customers in relation to
a) product information,
b) enquiries, contracts or order handling, including amendments,
c) customer feedback, including customer complaints, and
d) advisory notices.

7.3 Design and development

7.3.1 Design and development planning

The manufacturer shall establish documented procedures for design and development. The manufacturer shall plan and control the design and development of product. During the design and development planning, the manufacturer shall determine
a) the design and development stages,
b) the review, verification, validation and design transfer activities (see Note) that are appropriate at each design and development stage, and
c) the responsibilities and authorities for design and development.

The manufacturer shall manage the interfaces between different groups involved in design and development to ensure effective communication and clear assignment of responsibility.
Planning output shall be documented, and updated as appropriate, as the design and development progresses.

NOTE Design transfer activities during the design and development process ensure that design and development outputs are verified as suitable for manufacturing before becoming final production specifications.

7.3.2 Design and development inputs

Inputs relating to product requirements shall be determined and records maintained. The design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patients.
These inputs shall include
a) functional, performance and safety requirements, according to the intended use,
b) applicable statutory and regulatory requirements,

c) where applicable, information derived from previous similar designs,
d) other requirements essential for design and development, and
e) output(s) of risk management.

These inputs shall be reviewed for adequacy and approved by designated individual(s)

Requirements shall be complete, unambiguous and not in conflict with each other.

7.3.3 Design and development outputs

The outputs of design and development shall be provided in a form that enables verification against the design and development input and shall be documented, reviewed, and approved prior to release.
Design and development outputs shall
a) meet the input requirements for design and development,
b) provide appropriate information for purchasing, production and for service provision,
c) contain or reference product acceptance criteria, and
d) specify the characteristics of the product that are essential for its safe and proper use.

Records of the design and development outputs shall be maintained.

Records of design and development outputs can include specifications, manufacturing procedures, engineering drawings, and engineering or research logbooks.

7.3.4 Design and development review

At suitable stages, systematic reviews of design and development shall be performed in accordance with planned arrangements
a) to evaluate the ability of the results of design and development to meet requirements, and
b) to identify any problems and propose necessary actions.

Participants in such reviews shall include representatives of functions concerned with the design and development stage(s) being reviewed, as well as other specialist personnel

Records of the results of the reviews and any necessary actions shall be maintained (see 4.2.4).

7.3.5 Design and development verification

Verification shall be performed in accordance with planned arrangements to ensure that the design and development outputs have met the design and development input requirements.
Records of the results of the verification and any necessary actions shall be maintained.

7.3.6 Design and development validation

Design and development validation shall be performed in accordance with planned arrangements to ensure that the resulting product is capable of meeting the requirements for the specified application or intended use. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches or their equivalence.
Design validation shall include software validation and risk analysis, where appropriate
Validation shall be completed prior to the delivery or implementation of the product.

Records of the results of validation and any necessary actions shall be maintained.
As part of design and development validation, the manufacturer shall perform clinical evaluations and/or evaluation of performance of the medical device/In-vitro Diagnostics.

NOTE 1 If a medical device /In-vitro Diagnostics can only be validated following assembly and installation at point of use, delivery is not considered to be complete until the product has been formally transferred to the customer.

NOTE 2 Provision of the medical device for purposes of clinical evaluations and/or evaluation of performance is not considered to be delivery.

7.3.7 Control of design and development changes

Design and development changes shall be identified and records maintained. The changes shall be reviewed, verified and validated, as appropriate, and approved before implementation. The review of design and development changes shall include evaluation of the effect of the changes on constituent parts and product already delivered. Records of the results of the review of changes and any necessary actions shall be maintained.

Note: -Each manufacturer shall establish and maintain a Design History Filefor each type of device. The Design History Fileshall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of design and development.

7.4 Purchasing

7.4.1 Purchasing process

The manufacturer organization shall establish documented procedures to ensure that purchased product conforms to specified purchase requirements. The type and extent of control applied to the supplier and the purchased product shall be dependent upon the effect of the purchased product on subsequent product realization or the final product.

The manufacturer shall evaluate and select suppliers based on their ability to supply product in accordance with the manufacturer's requirements. Criteria for selection, evaluation and re-evaluation shall be established.

Records of the results of evaluations and any necessary actions arising from the evaluation shall be maintained.

7.4.2 Purchasing information

Purchasing information shall describe the product to be purchased, including where appropriate

a) requirements for approval of product, procedures, processes and equipment,
b) requirements for qualification of personnel, and
c) quality management system requirements.

The manufacturer shall ensure the adequacy of specified purchase requirements prior to their communication to the supplier.

To the extent required for traceability, the manufacturer shall maintain relevant purchasing information, i.e. documents and records.

7.4.3 Verification of purchased product

The manufacturer shall establish and implement the inspection or other activities necessary for ensuring that purchased product meets specified purchase requirements. Where the manufacturer intends to perform verification at the supplier's premises, the manufacturer shall state the intended verification arrangements and method of product release in the purchasing information. Records of the verification shall be maintained.

7.5 Production and service provision

7.5.1 Control of production and service provision

7.5.1.1 General requirements

The manufacturer shall plan and carry out production and service provision under controlled conditions. Controlled conditions shall include, as applicable

a) the availability of information that describes the characteristics of the product,

b) the availability of documented procedures, documented requirements, work instructions, and reference materials and reference measurement procedures as necessary,

c) the use of suitable equipment,

d) the availability and use of monitoring and measuring devices,

e) the implementation of monitoring and measurement,

f) the implementation of release, delivery and post-delivery activities, and

g) the implementation of defined operations for labeling and packaging.

The manufacturer shall establish and maintain a record for each batch of medical devices/In-vitro Diagnostic devices that provides traceability and identifies the amount manufactured and amount approved for distribution. The batch record shall be verified and approved.

7.5.1.2 Control of production and service provision — Specific requirements

7.5.1.2.1 Cleanliness of product and contamination control

The manufacturer shall establish documented requirements for cleanliness of product if

a) product is cleaned by the manufacturer prior to sterilization and/or its use, or

b) product is supplied non-sterile to be subjected to a cleaning process prior to sterilization and/or its use, or

c) product is supplied to be used non-sterile and its cleanliness is of significance in use, or

d) process agents are to be removed from product during manufacture.

If the product is cleaned in accordance with a) or b) above, the requirements content in 6.4 (a) & (b) do not apply prior to the cleaning process

7.5.1.2.2 Installation activities

If appropriate, the manufacturer shall establish documented requirements which contain acceptance criteria for installing and verifying the installation of the medical device/In-vitro Diagnostic devices.

If the agreed customer requirements allow installation to be performed other than by manufacturer or its authorized agent, the manufacturer shall provide documented requirements for installation and verification. Records of installation and verification performed by the manufacturer or its authorized agent shall be maintained.

7.5.1.3 Particular requirements for sterile medical devices

The manufacturer shall maintain records of the process parameters for the sterilization process which was used for each sterilization batch. Sterilization records shall be traceable to each production batch of medical devices.

7.5.2 Validation of processes for production and service provision

7.5.2.1 General requirements

The manufacturer shall validate any processes for production and service provision where the resulting output cannot be verified by subsequent monitoring or measurement. This includes any processes where deficiencies become apparent only after the product is in use. Validation shall demonstrate the ability of these processes to achieve planned results.

The manufacturer shall establish arrangements for these processes including, as applicable
a) defined criteria for review and approval of the processes,
b) approval of equipment and qualification of personnel,
c) use of specific methods and procedures,
d) requirements for records, and
e) revalidation.

The manufacturer shall establish documented procedures for the validation of the application of computer software (and changes to such software and/or its application) for production and service provision that affect the ability of the product to confirm to specified requirements. Such software applications shall be validated prior to initial use. Records of validation shall be maintained.

7.5.2.2 Particular requirements for sterile medical devices

The manufacturer shall establish documented procedures for the validation of sterilization processes. Sterilization processes shall be validated prior to initial use. The records of validation of each sterilization process shall be maintained.

7.5.3 Identification and traceability

7.5.3.1 Identification

The manufacturer shall identify the product by suitable means throughout product realization, and shall establish documented procedures for such product identification. The manufacturer shall establish documented procedures to ensure that medical devices and In-vitro Diagnostics returned to the Manufacturer are identified and distinguished from conforming product.

7.5.3.2 Traceability

7.5.3.2.1 General

The manufacturer shall establish documented procedures for traceability. Such procedures shall define the extent of product traceability and the records required.
Where traceability is a requirement, the manufacturer shall control and record the unique identification of the product.

NOTE Configuration management is a means by which identification and traceability can be maintained.

7.5.3.2.2 Particular requirements for active implantable medical devices and implantable medical devices

In defining the records required for traceability, the manufacturer shall include records of all components, materials and work environment conditions, if these could cause the medical device not to satisfy its specified requirements.

The manufacturer shall require that its agents or distributors maintain records of the distribution of medical devices/In-vitro Diagnostics to allow traceability and that such

records are available for inspection. Records of the name and address of the shipping package consignee shall be maintained.

7.5.3.3 Status identification

The manufacturer shall identify the product status with respect to monitoring and measurement requirements. The identification of product status shall be maintained throughout production, storage, implant, usage and installation of the product to ensure that only product that has passed the required inspections and tests (or released under an authorized concession) is dispatched, used or installed.

7.5.4 Customer property

The manufacturer shall exercise care with customer property while it is under the manufacturer's control or being used by the manufacturer. The manufacturer shall identify, verify, protect and safeguard customer property provided for use or incorporation into the product. If any customer property is lost, damaged or otherwise found to be unsuitable for use, this shall be reported to the customer and records maintained.

NOTE Customer property can include intellectual property or confidential health information.

7.5.5 Preservation of product

The manufacturer shall establish documented procedures or documented work instructions for preserving the conformity of product during internal processing and delivery to the intended destination. This preservation shall include identification, handling, packaging, storage and protection. Preservation shall also apply to the constituent parts of a product.

The manufacturer shall establish documented procedures or documented work instructions for the control of product with a limited shelf-life or requiring special storage conditions. Such special storage conditions shall be controlled and recorded.

7.6 Control of monitoring and measuring devices

The manufacturer shall determine the monitoring and measurement to be undertaken and the monitoring and measuring devices needed to provide evidence of conformity of product to determined requirements.

The manufacturer shall establish documented procedures to ensure that monitoring and measurement can be carried out and are carried out in a manner that is consistent with the monitoring and measurement requirements.

Where necessary to ensure valid results, measuring equipment shall

a) be calibrated or verified at specified intervals, or prior to use, against measurement standards traceable to Bureau of Indian Standards wherever available ; where no such standards exist, the basis used for calibration or verification shall be recorded;

b) be adjusted or re-adjusted as necessary;

c) be identified to enable the calibration status to be determined;

d) be safeguarded from adjustments that would invalidate the measurement result;

e) be protected from damage and deterioration during handling, maintenance and storage.

In addition, the manufacturer shall assess and record the validity of the previous measuring results when the equipment is found not to conform to requirements. The manufacturer shall take appropriate action on the equipment and any product affected. Records of the results of calibration and verification shall be maintained.

When used in the monitoring and measurement of specified requirements, the ability of computer software to satisfy the intended application shall be confirmed. This shall be undertaken prior to initial use and reconfirmed as necessary.

8 Measurement, analysis and improvement

8.1 General

The manufacturer shall plan and implement the monitoring, measurement, analysis and improvement processes needed
a) to demonstrate conformity of the product,
b) to ensure conformity of the quality management system, and
c) to maintain the effectiveness of the quality management system.
This shall include determination of applicable methods, including statistical techniques, and the extent of their use.

Note: If relevant Indian standards are not available, International standards are applicable. In case no Indian/International standards are available, validated testing process of the manufacturer is applicable

8.2 Monitoring and measurement

8.2.1 Feedback

As one of the measurements of the performance of the quality management system, the manufacturer shall monitor information relating to whether the manufacturer has met customer / Regulatory requirements. The methods for obtaining and using this information shall be determined.
The manufacturer shall establish a documented procedure for a feedback system to provide early warning of quality problems and for input into the corrective and preventive action processes.

8.2.2 Internal audit

The manufacturer shall conduct internal audits at planned intervals to determine whether the quality management system
a) conforms to the planned arrangements, to the requirements of this schedule and to the quality management system requirements established by the manufacturer, and
b) is effectively implemented and maintained.

An audit programme shall be planned, taking into consideration the status and importance of the processes and areas to be audited, as well as the results of previous audits. The audit criteria, scope, frequency and methods shall be defined. Selection of auditors and conduct of audits shall ensure objectivity and impartiality of the audit process. Auditors shall not audit their own work.

The responsibilities and requirements for planning and conducting audits, and for reporting results and maintaining records shall be defined in a documented procedure.
The management responsible for the area being audited shall ensure that actions are taken without undue delay to eliminate detected nonconformities and their causes. Follow-up activities shall include the verification of the actions taken and the reporting of verification results.

8.2.3 Monitoring and measurement of processes

The manufacturer shall apply suitable methods for monitoring and, where applicable, measurement of the quality management system processes. These methods shall demonstrate the ability of the processes to achieve planned results. When planned results are not achieved, correction and corrective action shall be taken, as appropriate, to ensure conformity of the product.

8.2.4 Monitoring and measurement of product

8.2.4.1 General requirements

The manufacturer shall monitor and measure the characteristics of the product to verify that product requirements have been met. This shall be carried out at appropriate stages of the product realization process in accordance with the planned arrangements and documented procedures.

Evidence of conformity with the acceptance criteria shall be maintained. Records shall indicate the person(s) authorizing release of product. Product release shall not proceed until the planned arrangements have been satisfactorily completed.

8.2.4.2 Particular requirement for active implantable medical devices and implantable medical Devices wherever applicable

The manufacturer shall record the identity of personnel performing any inspection or testing.

8.3 Control of nonconforming product

The manufacturer shall ensure that product which does not conform to product requirements is identified and controlled to prevent its unintended use or delivery. The controls and related responsibilities and authorities for dealing with nonconforming product shall be defined in a documented procedure.

The manufacturer shall deal with nonconforming product by one or more of the following ways:

a) by taking action to eliminate the detected nonconformity;
b) by authorizing its use, release or acceptance under concession;
c) by taking action to preclude its original intended use or application.

The manufacturer shall ensure that nonconforming product is accepted by concession only if regulatory requirements are met. Records of the identity of the person(s) authorizing the concession shall be maintained. Records of the nature of nonconformities and any subsequent actions taken, including concessions obtained, shall be maintained.

When nonconforming product is corrected it shall be subject to re-verification to demonstrate conformity to the requirements. When nonconforming product is detected after delivery or use has started, the manufacturer shall take action appropriate to the effects, or potential effects, of the nonconformity.

If product needs to be reworked (one or more times), the manufacturer shall document the rework process in a work instruction that has undergone the same authorization and approval procedure as the original work instruction. Prior to authorization and approval of the work instruction, a determination of any adverse effect of the rework upon product shall be made and documented.

8.4 Analysis of data

The manufacturer shall establish documented procedures to determine collect and analyze appropriate data to demonstrate the suitability and effectiveness of the quality management system and to evaluate if improvement of the effectiveness of the quality management system can be made.

This shall include data generated as a result of monitoring and measurement and from other relevant sources. The analysis of data shall provide information relating to
a) feedback,
b) conformity to product requirements,
c) characteristics and trends of processes and products including opportunities for preventive action, and
d) suppliers.
Records of the results of the analysis of data shall be maintained.

8.5 Improvement

8.5.1 General

The manufacturer shall identify and implement any changes necessary to ensure and maintain the continued suitability and effectiveness of the quality management system through the use of the quality policy, quality objectives, audit results, analysis of data, corrective and preventive actions and management review.

The manufacturer shall establish documented procedures for the issue and implementation of advisory notices. These procedures shall be capable of being implemented at any time. Records of all customer complaint investigations shall be maintained. If investigation determines that the activities outside the manufacturer's organization contributed to the customer complaint, relevant information shall be exchanged between the organizations involved.

If any customer complaint is not followed by corrective and/or preventive action, the reason shall be authorized and recorded. Manufacturer require to notify adverse events and the manufacturer shall establish documented procedures to such notification to regulatory authorities.

8.5.2 Corrective action
The manufacturer shall take action to eliminate the cause of nonconformities in order to prevent recurrence. Corrective actions shall be appropriate to the effects of the nonconformities encountered. A documented procedure shall be established to define requirements for
a) reviewing nonconformities (including customer complaints),
b) determining the causes of nonconformities,
c) evaluating the need for action to ensure that nonconformities do not recur,
d) determining and implementing action needed, including, if appropriate, updating documentation,
e) recording of the results of any investigation and of action taken, and
f) reviewing the corrective action taken and its effectiveness.

8.5.3 Preventive action
The manufacturer shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence. Preventive actions shall be appropriate

to the effects of the potential problems. A documented procedure shall be established to define requirements for

a) determining potential nonconformities and their causes,
b) evaluating the need for action to prevent occurrence of nonconformities,
c) determining and implementing action needed,
d) recording of the results of any investigations and of action taken, and
e) reviewing preventive action taken and its effectiveness.

Annexure A

The manufacturer shall prepare a succinct document in the form of Site Master File containing specific information about the production and/or control of device manufacturing carried out at the premises. It shall contain the following information:

A GENERAL INFORMATION

I Brief information on the site (including name and address), relation to other sites

II Manufacturing activities

III Any other operations carried out on the site

IV Name and exact address of the site, including telephone, fax numbers, web site URL and e-mail address

V Type of medical devices handled on the site and information about specifically toxic or hazardous substances handled, mentioning the way they are handled and precautions taken

VI Short description of the site (size, location and immediate environment and other activities on the site)

VII Number of employees engaged in Production, Quality Control, warehousing, and distribution

VIII Use of outside scientific, analytical or other technical assistance in relation to the design, manufacture and testing

IX Short description of the quality management system of the company

X Devices details registered with foreign countries

B PERSONNEL

I Organisation chart showing the arrangements for key personnel

II Qualifications, experience and responsibilities of key personnel

III Outline of arrangements for basic and in-service training and how records are maintained

IV Health requirements for personnel engaged in production

V Personnel hygiene requirements, including clothing

C PREMISES AND FACILITIES

I Layout of premises with indication of scale

II Nature of construction, finishes/fixtures and fittings

III Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (including schematic drawings of the systems). Classification of the rooms used for the manufacture of sterile products should be mentioned

IV Special areas for the handling of highly toxic, hazardous and sensitizing materials

V Brief description of water systems (schematic drawings of the systems are desirable) including sanitation

VI Maintenance (description of planned preventive maintenance programmes for premises and recording system)

D EQUIPMENT

I Brief description of major production and quality control laboratories equipment (a list of the equipment is required)

II Maintenance (description of planned preventive maintenance programmes and recording system).

III Qualification and calibration, including the recording system. Arrangements for computerized systems validation.

E SANITATION

I Availability of written specifications and procedures for cleaning the manufacturing areas and equipments

F PRODUCTION

I Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters

II Arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage.

III Arrangements for reprocessing or rework

IV Arrangements for the handling of rejected materials and products

V Brief description of general policy for process validation

G QUALITY CONTROLS

I Description of the Quality Control system and of the activities of the Quality Control Department. Procedures for the release of finished products

H STORAGE

I Policy on the storage of medical device

E DOCUMENTATION

I Arrangements for the preparation, revision and distribution of necessary documentation, including storage of master documents

F MEDICAL DEVICE COMPLAINTS AND FIELD SAFETY CORRECTIVE ACTION

I Arrangements for the handling of complaints

II Arrangements for the handling of field safety corrective action

G SELF INSPECTION

I Short Description of the internal audit system

H CONTRACT ACTIVITIES

I Description of the way in which the compliance of the contract acceptor is assessed

Annexure B

The manufacturer shall prepare a succinct document in the form of Device Master File containing specific information about the device(s) manufacturing in the premises.

1.0 EXECUTIVE SUMMARY:

An executive summary shall be provided by the manufacturer and shall contain:
Introductory descriptive information on the medical device or Invitro Diagnostics, the intended use and indication for use, Class of Device, novel features of the device (if any), Shelf Life of the Device and a synopsis on the content of the dossier Information regarding Sterilization of the Device (whether it is sterile or Non-sterile; if sterile, mode of sterilization)

2.0 DEVICE DESCRIPTION AND PRODUCT SPECIFICATION, INCLUDING VARIANTS AND ACCESSORIES

2.1 Device Description
2.2 Product Specification
2.3 Reference to predicate and/or previous generations of the device

3.0 LABELLING

4.0 DESIGN AND MANUFACTURING INFORMATION

4.1 Device Design
4.2 Manufacturing Processes

5.0 ESSENTIAL PRINCIPLES (EP) CHECKLIST

6.0 RISK ANALYSIS AND CONTROL SUMMARY

7.0 PRODUCT VERIFICATION AND VALIDATION

7.2 Biocompatibility
7.3 Medicinal Substances
7.4 Biological Safety
7.5 Sterilisation
7.6 Software Verification and Validation
7.7 Animal Studies
7.8 Shelf Life/Stability Data
7.9 Clinical Evidence
7.10 Post Marketing Surveillance Data (Vigilance Reporting)

8. Additional Information in case of the Diagnostic kits

Product dossier showing the:

1. The details of source antigen or antibody as the case may be and characterization of the same. Process control of coating of antigen or antibody on the base material like Nitrocellulose paper, strips or cards or ELISA wells etc.
   Detailed composition of the kit and manufacturing flow chart process of the kit showing the specific flow diagram of individual components or source of the individual components.

2. Test protocol of the kit showing the specifications and method of testing. In house evaluation report of sensitivity, specificity and stability studies.
4. The detailed test report of all the components used/packed in the finished kit.
5. Pack size and labelling.
6. Product inserts.

Specific evaluation report, if done by any laboratory in India, showing the sensitivity and specificity of the kit.

Specific processing like safe handling, material control, area control, process control, and stability studies, storage at quarantine stage and finished stage, packaging should be highlighted in the product dossier.

Annexure C

"Environmental requirement for "Notified Devices"

Name of Device	Type of Operation	ISO Class
Cardiac stent/Drug Eluting Stent	Primary Packing and Crimping	5
	Washing, Ultrasonic cleaning &Drug coating	7
	Assembly, Wrapping & Packaging	8
	Laser cutting, Descaling, Annealing & Electro polishing	9
Heart Valve	Valve Packing	5
	Ultrasonic Cleaning & Visual Inspection	7
	Frame & Disc Assembly	7
Intra Ocular Lenses	Packing & Sealing	5
	Final Inspection	7
	Power Checking& Final Cleaning	8
	Tumble Polishing & Lathe Cutting	9
Bone Cements	Final Product Filling	5
	Sieving & Calcinations	7
	Powder Preparation, Granulation &Drying	8
Internal Prosthetic Replacement	Packing	5
	Product Preparation	7
	Component Preparation	8
Orthopedic Implants	Polishing &Cleaning & packaging (to be sterilized in factory premises)	7
	Polishing , cleaning & packaging (Non Sterile- to be sterilized in Hospital)	8
	Cutting, lathing	9
Catheters / I V Cannulae / Scalp Vein Set	Assembly, Coating, Wrapping & Packing	7
	Component Preparation & Cleaning	8
	Moulding	9

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