MINUTES OF THE 65TH MEETING OF DRUGS TECHNICAL ADVISORY BOARD HELD ON 25TH NOVEMBER, 2013 IN THE CHAMBER OF DGHS, NIRMAN BHAWAN, NEW DELHI – 110002

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. J.A.S. Giri — Member
   815A, Road No. 41
   Jublee Hills, Hyderabad-500033

4. Dr. C. Nath, — Member
   Central Drug Research Institute
   Lucknow

5. Dr. Anshu Sethi Bajaj, — Member
   Medical Council of India,
   New Delhi

6. Dr. B.P.S. Reddy, — Member
   CMD, Hetero Drugs Ltd.
   Hyderabad

7. Dr. A. K. Tiwari — Member
   Indian Veterinary Research Institute
   Izatnagar-243122 (U.P.)

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

CDSCO REPRESENTATIVES

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

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

3. Shri Lalit Kishore
   Consultant, DCG(I)
   CDSCO, New Delhi

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

Dr. Sunil Gupta, Director, CRI, Kasauli, Dr. S.D. Seth, Advisor, CTRI, ICMR, New Delhi, Dr. Dharam Prakash, Delhi; Dr. K. Chinnaswamy, Coimbatore, Dr. J.K. Rajvaidya, Bhopal, Dr. Dhrubajyoti Bora, Guwahati, Shri Satish Gupta, Controller Drugs and Food, J&K, Jammu, and Prof. B. Suresh, President, Pharmacy Council of India could not attend the meeting because of their pre-occupation.

Dr. G. N. Singh, Drugs Controller General (India) and Member Secretary DTAB welcomed the Chairman and members of the Board and requested the Chairman to initiate the proceedings as the quorum was complete. Dr. Singh further stated that the present DTAB was constituted by the Ministry of Health and Family Welfare vide

Gazette notification S. O. 722(E) dated 08.04.2011. Under the Drugs and Cosmetics Act, 1940, the nominated and elected members shall hold office for three years. Accordingly, the process of reconstitution of the Board is required to be initiated.

The Chairman gave his concurrence for the reconstitution of the Board.

Dr. B.P.S. Reddy requested that the Chairman of the Board as well as Member Secretary should visit Hyderabad and have direct interaction with the manufacturers of the drugs in that area. The Chairman agreed to the request and asked the Member Secretary to arrange the visit sometime in the last week of January or so.

AGENDA NO. 1

ACTION TAKEN REPORT ON THE MATTERS ARISING OUT OF THE 63rd & 64th MEETINGS OF DRUGS TECHNICAL ADVISORY BOARD HELD ON 16th MAY, 2013 & 19TH JULY, 2013 AT NEW DELHI.

63rd meeting (Agenda No. 3)

The Board approved the Action Taken Report on the minutes of the 63rd meeting held on 16th May, 2013 as well as 64th meeting held on 19th July, 2013. In the case of agenda no. 3 of 63rd meeting members desired that the Department of AYUSH may be requested to provide the details of the deliberations of the Sub-Committee and the recommendations, if any, for further consideration.

AGENDA NO. 2

CONSIDERATION OF THE REPRESENTATION OF HIM JAGRITI, UTTARANCHAL WELFARE SOCIETY AGAINSTS PACKAGING OF PHARMACEUTICAL PRODUCTS IN PET / PLASTIC BOTTLES LEADING TO PUBLIC HEALTH AND ENVIRONMENTAL HAZARD

The Chairman opened the discussion on the issue of primary packaging materials in pharmaceutical liquid orals suspension and dry syrups stating that concerns have been raised about the safety of the plastic/pet containers used in the packing of pharmaceuticals, food and water. The HIM JAGRITI, Uttaranchal Welfare Society, Dehradun had forwarded a representation to the Secretary, Ministry of Health & Family Welfare, Directorate General Health Service and Drug Controller (I) , wherein it was requested to impose a ban on polyethylene terephthalate (PET) bottles (both colour and non-colour) as primary packaging material in pharmaceutical liquid orals, suspensions and dry syrups with immediate effect as it has severe adverse effects on human health due to the presence of endocrine disruptors. It is stated that leaching takes place under varying storage-temperature conditions and the age of the packaging (leaching becomes faster in hot/warm conditions, and also as the packaging becomes old). The leached elements can cause several diseases including cancer and physical infirmities. Many chemical additives that give plastic products desirable performance properties have grave negative environmental and human health effects. These effects include:-

- Direct toxicity, as in the case of lead, cadmium and mercury;
- Carcinogens, as in the case of diethylthexyl phthalate (DHP); and
- Endocrine disruption, which can lead to cancers, birth defects, immune system suppression and developmental problems in children.

Further, the HIM Jagriti in his representation has raised following three major concerns:

(1) That PET may yield endocrine disruptors;

(2) That Phthalates leach from PET/plastic bottles; and

(3) That antimony leaches from PET bottles.

The representation of HIM Jagriti, Uttaranchal Welfare Society against packaging of pharmaceutical products in PET / plastic bottles due to public health and environmental hazard was deliberated in the 63rd meeting of Drugs Technical Advisory Board held on 16th may, 2013 in the committee room, FDA Bhavan, Kotla Road, New Delhi after the deliberation the board constituted an Expert Committee under the Chairmanship of Dr. Y. K. Gupta, Prof. & HOD, Department of Pharmacology, AIIMS, New Delhi to examine the issue.

The meeting of the Expert Committee was held on 12.07.2013 and the committee after deliberations gave the following recommendations.

> "The committee finally concluded that the information provided in the representation of HIM JAGRITI and according to the available literature, is not sufficient enough to establish a definite correlation of causality of plastic container for pharmaceutical products and adverse health effects. However, this is an important public health concern and needs detailed investigation. Also, the 'absence of evidence' may not be considered as 'evidence of absence' of the potential harmful effects of packaging of pharmaceutical products in plastic containers. This issue also needs to be viewed from environmental hazard being posed by the use of plastic containers.
>
> A scientific evidence needs to be generated in a time bound manner through systematic studies as elaborated above, to arrive at answers to the following questions a) The extent of leachbility from plastic container used for packing different drugs formulation, b) The type of toxicants leached, c) Health hazard due to exposure of the leached toxicant.
>
> On the basis of the evidence so generated and keeping in view the risk assessment and also environmental hazards, a phasing out plan may then be considered."

In order to generate scientific evidence on leachbility in common drugs available in plastic bottles samples were sent to Central institute of Plastic Engineering and Technology (CIPT), Guindy, Chennai and Laboratory for Advanced Research in Polymeric Materials (LARPM), Bhubaneswar. However, these labs have shown their inability to carry out the assessment of leachbility of PET Bottles. CISR has now been requested to provide information about the laboratories in the country having facility to test the extent of leachbility from plastic containers used for packing different drug formulations.

The PET Container Manufacturers Associations also represented to the Director General Health Services stating that PET packaging with its inherent strength such as product safety, eco-friendliness and recyclability will continue to be used in food, beverage and pharmaceuticals packaging. The PET is universally safe and environment friendly packaging material. The literature attached to the representation, however, did not address the issues raised by HIM Jagriti

The pharma industry was earlier using glass bottles only as primary packaging material for pharmaceuticals. The switch over to packing in plastic / PET bottles by the industry is not based on any scientific studies to show that packing of drug formulations in plastic/PET bottles does not have any harmful effect on the drug formulations and there are no releases of endocrine disruptors due to leaching. India has large variation in temperatures. In summer days temperature rises to 40-45 degree centigrade and exposure of plastic bottles to such a high temperature may result in adverse effect on the drug formulations packed plastic bottles and the high temperature may result in increased leachbility. The harmful effects because of the packaging and leachbility may be further magnified in the case of drug formulations.

The members opined that the reports of environmental / health hazards because of increasing exposure to endocrine disrupter chemicals known as phthalates etc. are increasing. Therefore, it would be in the public interest specially considering the precautionary principle that the children, geriatrics, women in reproductive age group and pregnant women are not exposed to the hazards involved in the packaging of drugs in plastic / PET containers.

The DTAB after deliberations 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.

AGENDA No. 3

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES, 1945, TO PROHIBIT USE OF ANIMALS IN TESTING OF COSMETICS

The Member Secretary, briefed the members that Smt. Maneka Gandhi, MP, Lok Sabha had written to the office of DCG(I) that the harmonization of India's regulations with that of Europe's cosmetics regulations will ensure an immediate up-gradation of India's safety standards in cosmetics testing using non-animal methods and that the world market for Indian Cosmetics would remain unaffected. The European Union in a directive issued made testing on animals completely illegal in the EU for cosmetics in 2013, irrespective to the fact whether there is an alternative method available or not.

The Bureau of Indian Standards, which prepare standards for cosmetics, in the meeting of the Cosmetics Sectional Committee, PCD 19, under the Chairmanship of Drugs Controller General (India), held on 25.02.2013 decided that the Indian Standard (IS 4011:1997-Method of Test for Safety Evaluation of Cosmetics) shall be amended to provide that 'The manufacturer of cosmetics products containing novel ingredients may submit the safety data based on alternative non-animal test methods for to the concerned State Licensing Authority for their consideration and approval.'. The BIS has since amended the standard IS 4011:1997.

The Secretary, Health and Family Welfare desired that the use of animals in testing of cosmetics should also be prohibited under the Drugs and Cosmetics Rules, 1945. Accordingly, it was proposed to amend the Drugs and Cosmetics Rules, 1945 by inserting the following rule.

> "148-C. *prohibition of testing of cosmetics on animals.-* Animals shall not be used for testing of cosmetics."

The DTAB after deliberations agreed to the proposed amendment.

AGENDA NO. 4

CONSIDERATION OF THE ISSUE OF MISUSE OF OXYTOCIN INJECTION BY THE DAIRY OWNERS TO EXTRACT MILK FROM MILCH ANIMALS AND ITS HARMFUL EFFECTS

The Members were briefed 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 as well as on the consumers was raised by Smt. Maneka Gandhi, Member of Parliament, Lok Sabha. The drug oxytocin has medical use for induction and augmentation of labour, to control post partum bleeding and uterine hypo tonicity. The alleged abundant availability and use of the drug in a clandestine way, however, is a matter of great concern for public health.

Under the Drugs & Cosmetics Rules, 1945, the sale of the oxytocin injection is regulated under Schedule H of the said Rules which require the drug to be dispensed on the prescription of a Registered Medical Practitioner only. Further, to avoid its bulk sale, oxytocin injection, a provision was made that the Oxytocin Injection shall be packed in single unit blister pack only.

In spite of the above provisions, the reports of manufacture and sale of the drug in clandestine way in large quantities and its misuse by the farmers or dairy owners have been received from time to time and matter was raised on various forums. The manufacture and sale of the drug with or without a licence for such clandestine activity is an offence under the Drugs and Cosmetics Act, 1940.

The matter was considered in the 46th meeting of the Drugs Consultative Committee held on 12th & 13th November, 2013 and the committee after deliberations recommended that the manufacture and sale of the oxytocin injections should be banned for veterinary use under section 26A of the Drugs and Cosmetics Act, 1940 along with the condition that the manufacturers of bulk drug should supply the active pharmaceutical drug only to the manufacturers licensed for manufacture of formulations for human use.

The Department of Animal Husbandry, Dairying and Fisheries, Ministry of Agriculture, whose opinion was sought in respect of banning of Oxytocin for Animal use has opined that the ban on production and use of Oxytocin for veterinary use is not recommended. The drug has therapeutic application in case of expulsion of fetus, retention of placenta. However, that drug should be used strictly with the prescription of the veterinarian.

Dr. A. K. Tiwari, from IVRI also agreed that the drug has definite use in veterinary practice and as such should not be prohibited.

The DTAB after deliberations agreed that as the drug has a definite use for therapeutic purposes, it need not to be prohibited. It however, agreed to the suggestion that the manufacturers of bulk drug should supply active pharmaceutical drug only to the manufacturers licensed for manufacture of formulations and the formulations meant for veterinary use are sold to the veterinary hospitals only.

It was further recommended that the State Drugs Controllers may be asked to curb the misuse of the drug through increased surveillance and raids conducted on the

possible hideouts of clandestine manufacture and sale of this drug and take strict action against the offenders.

AGENDA NO. 5

CONSIDERATION OF THE PROPOSAL TO REVIEW THE BANNING OF THE DEXTROPROPOXYPHENE, ANALGIN, FDCS OF FLUPENTHIXOL AND MELITRACEN PROHIBITED UNDER SECTION 26A OF THE DRUGS AND COSMETICS ACT, 1940

The Member Secretary stated that the manufacture for sale, sale and distribution of the following drugs was suspended through Gazette notifications issued under Section 26A of the Drugs and Cosmetics Act, 1940 as the use of these drugs was reported to be restricted / prohibited in certain countries because of the safety issues involved and likely risks to human beings with their use.

Sr. No.	Drug	G.S.R. No.
1.	Dextropropoxyphene and formulations containing Dextropropoxyphene for human use.	**G.S.R. 332(E) dated 23.05.2013**
2.	Analgin and all formulations containing Analgin for human use.	**G.S.R. 378(E) dated 18.06.2013**
3.	Fixed Dose Combination of Flupenthixol + Melitracen for human use.	**G.S.R. 377(E) dated 18.06.2013**

An Expert Committee, under the Chairmanship of Director General of Health Services, examined the safety issues of these drug preparations in a meeting held on 26.08.2013.

The Expert Committee gave the following recommendations in respect of use of these drugs:

1. **DEXTROPROPOXYPHENE**

The committee noted that the reason for ban of the drug was that US Food and Drug Administration had on 19.11.2010 recommended against continued prescribing and use of the drug because new data showed that the drug can cause serious toxicity to the heart, even when used at therapeutic doses. On request of USFDA, companies voluntarily withdrew the drug from the United States market. The Committee for Medicinal Products for Human Use (CHMP) of European Medicine Agency (EMA) also concluded that the benefits of dextropropoxyphene do not outweigh its risks, and recommended that all marketing authorisations for dextropropoxyphene containing medicines should be withdrawn throughout the European Union (EU).

Experts were however of the view that QT prolongation is with 600 mg per day of dextropropoxyphene whereas the dose of the drug in Indian patients is only up to 300 mg per day. The drug may be put under focused Pharmacovigilance programme or shall have a well-designed controlled clinical trial for the evaluation of safety in Indian subjects. Some experts were of the view that dextropropoxyphene is the only opioid drug available for treatment of cancer pain.

The committee after detailed deliberation decided that the use of the drug can be continued in cancer pain only subject to following conditions.

1. Dose of the drug should not be more then 300mg per day.
2. The package insert, promotional literature, labeling of the drug, etc. should clearly mention the “Use of drug for cancer pain only”.
3. The firm should sensitize doctors for use of drug in cancer pain only.
4. The firm should also submit the safety data from Indian population within period of six months.

2. **ANALGIN**

The members pointed out that the duration of treatment of Analgin is only for few days, therefore the committee recommended that the use of Analgin may be

continued as per approved indication at present i.e. “Severe pain or pain due to tumor and also for bringing down the temperature in refractory cases when other antipyretics fail to do so.

3. **FDC OF FULPENTHIXOL & MELITRACEN**

FDC of Flupenthixol with melitracen was approved on 28.10.1998 for the treatment of psychogenic depression, depressive neuroses, marked depression and psychosomatic affection accompanied by anxiety and apathy. The FDC was prohibited in view of the fact that the drug was not permitted to be marketed in the country origin i.e Denmark as well as countries like USA, Britain, Canada European Union and Japan.

The issue of continued marketing of FDC of Flupenthixol + Melitracen was also examined by New Drug Advisory Committee (Neurology & Psychiatry) and the Committee after deliberation felt that rationality and essentiality of continued marketing of this FDC is questionable as

- Melitracen is reported to be not efficacious as a single agent in depression.
- Flupenthixol use is associated with potentially serious neurologic side effects.Subsequent to the ban of the FDC

Member pointed out that Fulpenthixol is Anti-Psychotic drug and Melitracen is an anti-depressant drug and the combination of these two drugs may leads to increase in extra pyramidal side effects.

After detailed deliberation the committee recommended that the use of FDC of Flupenthixol with melitracen should be discontinued from the country.

In the meanwhile the manufacturers of the product i.e. M/s Lundbeck as well as M/s Mankind Pharma approached the Hon’ble High Court of Karnataka for stay of the notification.

The Hon’ble High Court of Karnataka vide order dated 14th August 2013 quashed the notification and remanded the matter back to reconsider afresh and

take a decision one way or other in accordance with the Law. The Hon'ble High Court has also mentioned in its order that pending reconsideration, the respondents shall have the liberty to regulate the manufacture and sale in the manner as observed supra by imposing such conditions if need be.

In view of the order of the Hon'ble High court, the Ministry of Health and Family Welfare was requested for issuing a fresh notification under section 26A of the Drugs and Cosmetics Act stating that the FDC of Flupenthixol + Melitracen shall be sold by retail on the prescription of Psychiatrist only and label as well as package insert/ promotional literature shall mention following warning in red bold letter:

Warning: To be sold on the prescription of registered Psychiatrist only.

The members were informed that the issue of suspension of manufacture for sale, sale and distribution of analgin and its formulations was considered in the 64th meeting of the DTAB held on 19th July, 2013 and the Board had opined that the drug is used as analgesic for short period as and when necessary. It is not indicated for long term use. There are no adequate reports of agranulocytisis at present associated with the use of the drug which may warrant suspension / prohibition the drug in the country. The drug should be allowed to be marketed for severe pain or pain due to tumor only and also brining down temperature in refractory cases when other anti-pyretics fail to do so. These recommendations were forwarded to the Ministry of Health and Family Welfare for their consideration and taking further action in the matter.

In respect of Dextropropoxyphene, the members agreed to the recommendations of the Expert Committee that the drug may be permitted to be marketed for a limited use for cancer patients and should be labeled in bold letters "for use in cancer patients for pain only".

In the case of FDC of Flupenthixol with melitracen, the DTAB agreed with the recommendations of the New Drug Advisory Committee that the use of the drug should be discontinued from the country. The Hon'ble High Court of Karnataka may be informed accordingly.

AGENDA NO. 6

CONSIDERATION OF THE PROPOSAL TO AMEND RULE 122 (E) TO INCLUDE NEW DRUG DELIVERY SYSTEMS INCLUDING MODIFIED RELEASE DOSAGE FORMS OF DRUG FORMULATION AS NEW DRUG

The Member Secretary briefed the members that the Task Force set up by The Ministry of Health and Family Welfare, for the purpose of formulating a long term policy for strengthening the Drug Sector, under the chairmanship of Dr. V. M. Katoch, Secretary, HR, and DG, ICMR recommended that each New Drug Delivery System including modified release dosage form whether a copy of a studied and approved drug or another one should be treated as a new drug and accordingly subjected to the requirement of complete studies as a new drug.

The Controlled Release Formulations of a drug are reported to be vastly different from each other with respect to their efficacy and toxicity. Composition as well as the process of manufacture of the carrier of the controlled release formulations has an impact on the clinical performance of Active Pharmaceutical Ingredient in the controlled release formulation.

It was therefore been proposed that the explanation under rule 122 (E) of Drugs and Cosmetics Rules needs to be amended so that it covers all New Drug Delivery System including modified release dosage form of the drugs as new drugs along with all vaccines, recombinant DNA (r-DNA) derived drugs as under.

> "(i) All vaccines, recombinant DNA (r-DNA) derived drugs and all New Drug Delivery Systems including modified release dosage forms of a drug formulation shall be new drugs unless certified otherwise by the Licensing Authority under Rule 21;"

The matter was also considered in the 44th meeting of the Drugs Consultative Committee held on 20th July, 2012 and the committee agreed to the proposed amendment. It however, further desired that the term 'modified release' may be defined under the rules for the purpose of clarity.

The DTAB after deliberations agreed to the proposed amendment. It was, however, clarified that these applications will not treated as Investigation New Drugs (IND) applications. CDSCO shall prepare guidelines in respect of New Drug Delivery Systems for the information of the industry as well as regulatory authorities.

AGENDA NO. 7

CONSIDERATION OF THE PROPOSAL TO AMEND RULE 96 FOR LABELING OF VACCINES WITH SPECIFIC REFERENCE TO THE ORIGIN OF THE VACCINE

Dr. G. N. Singh, Drugs Controller General (I) explained that WHO during the National Regulatory Authority assessment at Central Drugs Standard Control Organization in respect of vaccines manufactured in the country expressed a concern that the vaccine which are manufactured by using different source of antigen have been labeled with the same manufacturing license number without having any unique identification number which otherwise does not provide the correct information in respect of the origin of the vaccine.

As per Rule 122 E all vaccines are considered as new Drugs and any change in the source of antigen, the New Drug approval is required to be obtained from the Licensing Authority. However, there is no specific provision under Rule 96 for labeling of the vaccine with specific reference to its origin.

It was therefore, been proposed that Rule 96 may be amended to include New Drug Approval number on the label of the vaccine granted by the Licensing Authority as defined under rule 21(b) of the Drugs and Cosmetics Rules.

The matter was also considered in the 44th meeting of the Drugs Consultative Committee held on 20th July, 2012 and the committee agreed to the proposed amendment.

DTAB after deliberations agreed to the proposed amendment.

AGENDA NO. 8

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

The Member Secretary explained to the members that in order to ensure that the drug formulations marketed in the country are stable till the end of the shelf life, it was necessary that the requirement of stability studies should be brought under the condition of license (s) for manufacture drugs especially in rule 71, 71-B in rule 76 etc. It was therefore proposed that the following condition should be incorporated under the rule 71, 71-B, 76 or wherever consider necessary.

> "The applicant shall, while applying for license to manufacture drugs, furnish to the Licensing Authority evidence and data justifying that the drugs are stable for proposed shelf life under the condition of storage recommended. The data shall be generated as per Appendix IX of Schedule Y".

He further stated that WHO in his publication TRS 937, Guidelines on long term stability conditions for India, has put India in Zone IV b and the long term stability studies are required at 30ºC at 70% RH or 30ºC at 75 ± 5% RH instead of 30ºC ± 2ºC / 65% RH ± 5% RH for 12 months. In view of this Appendix IX of Schedule 'Y' relating to Stability Testing of New Drugs where long term study conditions for drug substances and formulations intended to be stored under general conditions is mentioned as 30ºC ± 2ºC / 65% RH ± 5% RH for 12 months is required to be amended to read as 30ºC ± 2 / 70% RH OR 30ºC ± 2/ 75 ± 5% RH for 12 months.

The proposals were also considered in the 46th DCC meeting held on 12th & 13th November, 2013 and it recommended the proposed amendments.

The DTAB after deliberations agreed that the condition for stability of the products as condition of license may be incorporated in rule 71, 71-B & 76 and wherever consider necessary. In respect of amendment of Schedule 'Y' it recommended that WHO may be further consulted and if required more data to be generated for further consideration of the matter.

AGENDA NO. 9

CONSIDERATION OF THE PROPOSAL TO AMEND ENTRY NO 35 OF SCHEDULE K RELATING TO HOMEOPATHIC HAIR OILS HAVING ACTIVE INGREDIENTS UPTO 3X POTENCY ONLY SO AS TO EXEMPT ITS SALE FROM WHOLE SALE AS WELL AS RETAIL SALE LICENSES

Member Secretary, briefed the members that a representation was received from the Aswini Homeo Pharmacy, Hyderabad for the exemption of Homeopathic Hair Oils from all sale licence activities. He has stated that on the basis of his request earlier an exemption was provided under Schedule K in respect of Homeopathic Hair Oils having active ingredients upto 3X potency in respect of licence in Form 20C (retail sale) only. It has been stated that while there are no restriction on the sale of Homeopathic hair oils by retail, but no such exemption has been given to wholesalers who distribute the preparation throughout the country.

The Drugs & Cosmetics Rules were amended under the Gazette Notification no. G.S.R. 917 (E) dated 22-12-2009 under which the following exemption was provided under Schedule 'K' for the sale of Homeopathic Hair Oils having active ingredients upto 3X potency as under:

> "The provision of Chapter IV of the Act and the rules made thereunder which require them to be covered with a sale licence in Form 20C, subject

to the condition that such a product has been manufactured under a valid drug manufacturing license and are sold in the original sealed packing of the licensed manufacturers".

The draft amendment published vide G.S.R. 789(E) dated 15.11.2008 on the recommendation of the DTAB had proposed complete exemption from sale licence from both wholesale and retail licence as under:

> "The provision of Chapter IV of the Act and the rules made thereunder which require them to be covered by a sale licence, subject to the condition that such a product has been manufactured under a valid drug manufacturing license and are sold in the original sealed packing of the licensed manufacturers".

During the finalization of the draft rules, on the basis of the comments received from the Drugs Control Department, Government of NCT of Delhi, the exemption was limited to specific sale licence in Form 20C only (retail sale).

The members noted that the Department of AYUSH had earlier stated that popularity of Homeopathic Hair Oil / Arnica Hair Oil is not up to the mark. If this oil is permitted to be sold for sale by grocery shops / other shops as being done for Ayurvedic / Unani oils, there will be healthy competition and the sale will be enhanced.

The DTAB after deliberations recommended that the exemption clause may be amended so as to exempt the Homeopathic Hair Oils having active ingredients upto 3X potency from both whole sale and retail licence.

AGENDA NO. 10

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES, 1945, TO PROHIBIT IMPORT OF COSMETICS TESTED ON ANIMALS

The Member Secretary, stated that representations have been received from the Humane Society International, India, Rama Chandra Khuntia, MP, Rajya Sabha, Rud raraju Padmaraju, member AICC, Hyderabad and others for a ban on the import and sale of cosmetic product in India where either the final formulation or any raw ingredient has been subject to new animal testing by or on behalf of the manufacturers. It has been stated that banning of the import and sale of newly animal tested cosmetics will help consumers to make a compassionate choice. It would position our country ahead of other “BRICS” nations in the area of ethical consumerism. The European Union, in March, 2013 has prohibited the sale of animal tested cosmetics in the EU countries.

The European Union had in 2009 initiated measures for banning marketing of cosmetics tested on animals. In March, 2013 EU has imposed prohibition of the marketing of the cosmetics and their ingredients which have been tested on animals irrespective of the fact that whether alternate method in place of toxicity study to prove the safety of the cosmetic products is in place or not. However, other countries of the world including USA, Australia, Japan etc has not yet made such provision which prohibits the marketing of cosmetics tested on animals.

The Board noted that the Ministry of Health & Family Welfare is already in the process of prohibiting the use of animals in testing of cosmetics manufactured in the country. India should therefore take a lead in prohibiting the import of cosmetics tested in animals also.

The DTAB recommended that a suitable provision may be added under the Drugs & Cosmetics Rules to prohibit the import of cosmetics tested on animals.

AGENDA NO.11

CONSIDERATION OF THE ACTION TO BE TAKEN IN RESPECT OF FIXED DOSE COMBINATION OF DRUGS LICENCED BY STATE LICENSING AUTHORITIES BUT HAVE BEEN RECOMMENDED BY THE NEW DRUG ADVISORY COMMITTEES TO HAVE NO THERAPEUTIC JUSTIFICATION FOR MARKETING

The Member Secretary briefed the members that the fixed dose combinations of two or more drugs combined for the first are considered as a 'new drugs' and their safety and efficacy is required to be examined by the office of DCG(I) as a new drug before these are permitted to be marketed in the country. The State Licensing Authorities before granting the licence to manufacture such combination are required to ensure that the applicant has the approval in writing from DCG(I) as new drug before granting the licence to manufacture such drug formulation.

It was however, been observed that in many cases the State Licensing Authorities have granted licences for manufacture of fixed dose combinations falling under the definition of the new drug without prior approval from the DCG(I). The Ministry of Health and Family Welfare had issued directions under Section 33P of the Drugs and Cosmetics Act to the State / UT Governments to advise the State Drug Control Authorities to refrain from grant of any such manufacturing licences without the prior approval of the DCG(I).

The Parliamentary Standing Committee on Health and Family Welfare in its 59th Report, while examining the functioning of CDSCO also examined the question of marketing of fixed dose combinations in the country. The Committee observed that the end result is that many FDCs in the market have not been tested for efficacy and safety. This can put patients at risk and to remove such unauthorized FDCs from the market, the Central Government can either issue directions under Section 33P to States to withdraw the licences of FDCs granted without prior DCG(I) approval or the Central Government can itself ban such FDCs under Section 26A.

In view of the above the office of DCG(I) had written to all State / UTs Drugs Controllers on 15.01.2013 for directing the manufacturers in their States / UTs to prove the safety and efficacy of such FDCs before CDSCO within a period of 18 months, failing which such FDCs will be considered for being prohibited for manufacture and marketing in the country.

The applications received for grant of permission to market the FDCs considered as new drugs are examined by CDSCO in consultation with the New Drug Advisory Committees (NDACs) constituted by the Ministry of Health and Family Welfare. The office of DCG(I) in the meantime has received over five thousand application of the FDCs which have not been approved by the DCG(I) in respect of their safety and efficacy. Some of the FDCs were examined by the NDACs also. The NDACs while examining the FDCs have found certain FDCs do not have therapeutic justification or rationality for their marketing in the country. In view of this permission to market these FDCs were not granted. These FDCs are however, considered to be available in the market as these appear in the monthly indexes of medical specialties. In view of the large number of the applications guidelines and procedures are required to be prepared for the examination of the FDCs.

DTAB after deliberations recommended that a sub-committee under the chairmanship of Dr. B. Suresh, President, Pharmacy Council of India may be constituted with the approval of the Chairman, to give its recommendations and suggest guidelines for examinations of such FDCs and the action to be taken in such cases.

AGENDA NO. 12

CONSIDERATION OF THE PROPOSAL TO AMEND SCHEDULE D OF THE DRUGS AND COSMETICS RULES, 1945 TO EXCLUDE DRUGS IMPORTED FOR FURTHER PURIFICATION WITHOUT FOLLOWING THE PROCESS OF REGISTRATION AND IMPORT LICENCE

The Member Secretary stated that reports have been received that many importers are importing Bulk Drug or Active Pharmaceutical Ingredients as Crude Drug or Feed Grade etc. for further purification. Such crude and feed grade drugs are nothing but impure or not of standard quality drugs imported from unregistered, non-GMP sources. These drugs are then marketed after purification or sterilization as drugs for medicinal purposes.

These types of drugs are normally produced at unregistered, non-GMP sources and are imported by bypassing registration procedure under misleading names and after minor purification are sold for use in drug formulations. These drugs cannot be considered safe for use and can put patient at risk.

The Guidance Document for Zonal & Port Offices (already on the website of CDSCO) mentions that *"The import of drug under dual use for purification or rendering it sterile will not be considered under dual use".*

As per all International guidelines (i.e. ICH, WHO, MHRA guidelines) drug molecules after N-1 step shall be prepared in GMP, therefore, it is very important for patient safety, that completely formed Drug molecules imported for further purification purposes shall not be exempted from provisions of Chapter III (specially registration requirement).

Importers of such drugs take the plea that the import of such crude drugs do not come under the ambit of the Drugs and Cosmetics Rules, in view of the exemption provided under Schedule-D item no. 1 which exempts “substances not intended for medicinal use”.

The DTAB after deliberations felt that drugs should be permitted to be imported provided they conform to the prescribed standards and substance having therapeutic

value and having the end use for use in the human is considered as a drug. In view of this the DTAB recommended that the class of drugs under item 1 of schedule D should be amended to read as under:

> "Substances not intended for medicinal use excluding those intended to be used as drugs after further purification or rendering them sterile".

AGENDA NO. 13

CONSIDEARTION OF THE PROPOSAL TO GRANT PERMISSION FOR CONDUCTING THE CLINICAL TRIAL OF AN INJECTABLE CONTRACEPTIVE CYCLOFEM AND NET-EN BY ICMR

The Member Secretary, briefed the members that the office of DCG(I) had received an application from Dr. Malabika Roy, Scientist-F, Division of RHN, ICMR, New Delhi for conducting study entitled "Pre-programme introduction of Injectable Contraceptive Cyclofem and NET-EN through district hospitals and NGO clinics- An ICMR Task Force study."The NET-EN is Norethisterone Enanthate 200 mg as a two monthly injectable hormonal contraceptive.

The "Fixed Dose Combination of Oestrogen and Progestin (other than oral contraceptive) containing per tablet estrogen content of more than 50 mcg (equivalent to Norethisterone Acetate) and fixed dose combination injectable preparations containing synthetic Oestrogen and Progesterone" was prohibited by the Ministry of the Health and Family Welfare under section 26A of the Drugs and Cosmetics Rules, 1945 under entry number 27 of the list of banned drugs vide Gazette Notification G.S.R. 743(E) dated 10.08.1989.

Earlier a proposal of ICMR to conduct clinical trial in the country with the injectable preparations containing Medroxyprogesterone acetate and estradiol cypionate (Cyclofem) as monthly contraceptive was recommended by the DTAB in its 48th meeting held on 08th July, 1999 for the reason that the clinical trial could continue

without disturbing the present prohibitory status and the drugs would be imported for limited purpose of clinical trial only.

The proposal was deliberated in 61st meeting of DTAB held on 24th July, 2012 also. The Board after deliberation recommended that an expert committee consisting of Gynecologists, Pharmacologists may be constituted by the DCG(I) to examine the safety and efficacy of Cyclofem especially in the light of the fact that such contraceptive injections are prone to cause reduction in bone mineral density (BMD). The proposal of was deliberated in New Drug Advisory Committee (NDAC) (Reproductive and Urology) of the CDSCO on 17.09.2013. The Committee recommended for the grant of permission of conducting clinical trial with Cyclofem and NET-EN subject to the following condition:-

1. The study should be titled as extended phase III clinical trial.
2. The study should be conducted at multispecialty hospitals having emergency facilities and Institutional Ethics Committee registered with CDSCO.
3. Details of such sites along with Undertaking by Investigators as per Appendix VII of Schedule Y should be submitted.
4. Informed Consent Documents as per appendix V of schedule Y should be submitted.
5. Undertaking as per Rule 122DAB for compensation and providing medical management as per the rule in case of injury/death in clinical trial.
6. Denotification of the banning of Cyclofem i.e. Fixed Dose Combination Injectable preparations containing synthetic Oestrofen and Progesterone.
7. The recommendation may be placed before DTAB for further consideration.

During deliberation the members were of the view that the proposal also includes the requirement of the amendment of the entry number 27 of the list of banned drugs also.

The DTAB recommended that an Expert Committee consisting of at least three Gynecologists, three endocrinologists, Dr. Anoop Mishra and Dr. Y. K. Gupta, HOD, Department of Pharmacology, AIIMS, New Delhi under the

Chairmanship of DGHS may be constituted to examine the essentiality of the clinical trial as well as the requirement, if any, of the amendment of entry number 27 in respect of the FDC of injectable preprations containing synthetic oestrogen and progesterone, in the context of present day knowledge.

Meeting ended with the vote of thanks to the Chair.

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