MINUTES OF THE 60th MEETING OF DRUGS TECHNICAL ADVISORY BOARD HELD ON 10TH OCTOBER, 2011 IN THE COMMITTEE ROOM, FDA BHAVAN, KOTLA ROAD, NEW DELHI – 110002

PRESENT

1. Dr. R.K. Srivastava, Director General of Health Serivces, Nirman Bhawan, New Delhi.	Chairman
2. Sh. P.K.Guha, Director, Central Drugs Laboratory, 3, Kyd Street, Kolkata-700016	Member
3. Dr. B. Suresh, President, Pharmacy Council of India, New Delhi-110002	Member
4. Dr. B.R. Jagashetty, Drugs Controller, Karnataka, Palace Road, Banalore-560001	Member
5. Sh. Satish Gupta, Controller Drugs & Food (J&K), Drugs Control Organization, Patoli Mangotrian, Jammu-180002	Member
6. Dr. B.P.S. Reddy, CMD, Hetero Drugs Pvt. Ltd., Hyderabad	Member
7. Dr. S. D. Seth, Advisor CTRI, National Institute of Medical Statistics, ICMR, Ansaari Nagar, New Delhi-110002	Member
8. Dr. J.K. Rajvaidya, Government Analyst, Drugs Testing Laboratory, Food and Drugs Administration M.P., Idgah Hills, Bhopal-462001	Member

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

10. Dr. Umesh Drimir — Representing Director IVRI
    Representative of Director,
    Indian Veterinary Research Institute,
    Izatnagar-243122 (U.P)

INVITEE

1. Dr. G.N. Singh,
   Secretary cum Scientific Director,
   Indian Pharmacopeia Commission,
   Ghaziabad.

2. Dr. Sushma Dureja
   Deputy Commissioner,
   Ministry of Health and Family Welfare
   New Delhi

CDSCO REPRESENTATIVES

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

2. Shri A.K. Kukreti
   Assistant Drugs Controller (India)
   CDSCO, New Delhi

3. Dr. S.Eswara Reddy
   Assistant Drugs Controller (India)
   CDSCO, New Delhi

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

5. Shri Rishikant Singh
   Legal Consultant, DCG(I)
   CDSCO, New Delhi

Dr. T.K. Chakraborty, Director, CDRI, Lucknow, Prof. K.K. Talwar, Chairman, Board of Governors, MCI, New Delhi, Dr. Dharam Prakash, Delhi, Dr. B. Hemant, Director CRI, Kasuli, Dr. D. Bora, Guwahati, Dr. C. Gopalakrishnamurty, Hyderabad and Shri Yatendra Raj Mehta, Drug Testing Laboratory, Jaipur could not attend the meeting because of their pre-occupation.

Dr. Surinder 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 forum was complete as per bye-laws.

Dr. R.K. Srivastava, DGHS and Chairman of the Board in his address stressed the importance of the DTAB, a constitution body to render advice to the Government on various matters. The decisions taken by this august body has impact on the healthcare system of the country. The members of the DTAB are from different backgrounds and their contributions are important in arriving at decisions which has a bearing on the health policies and well being of the patients. The decisions taken by this committee may have direct impact on the pharmaceuticals industry but the main focus should remain public health.

AGENDA NO. 1

ACTION TAKEN REPORT ON THE MATTERS ARISING OUT OF THE 59th MEETING OF DRUGS TECHNICAL ADVISORY BOARD HELD ON 24th June, 2011 AT NEW DELHI

The members Secretary briefed members on the actions taken by his office on the various recommendations of DTAB in 59th meeting held on 24th June, 2011.

The members after deliberations approved the action taken report on the agenda items of the 59th meeting.

AGENDA NO. 2

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES, FOR MAKING PROVISIONS FOR CLINICAL TRIAL INSPECTIONS

Dr. Surinder Singh, DCG(I) briefed the members that while the Drugs and Cosmetics Rules, 1945, provides that clinical trials in the country on new drugs are required to be conducted in accordance with the permissions granted by the licensing authority and in compliance to Schedule Y to the said rules and Good Clinical Practice Guidelines. There are no specific conditions of permissions and provision for inspections of the sponsor/CRO and trial sites.

It was therefore proposed that certain mandatory conditions for the conduct of clinical trials should be incorporated under the Rules including inspection of the clinical trial sites and premises of sponsors/CROs by the officers of the CDSCO to verify that the trials are being conducted in accordance to the protocols approved, Schedule Y and conditions of permission to conduct the clinical trial. For this purpose a new rule '122 DAB – permission to conduct clinical trial' is required to be inserted under the Drugs and Cosmetics Rules incorporating conditions that are required to be complied by the applicant during the conduct of the clinical trial including inspection of the premises related to clinical trials. A provisions for taking action in case the sponsor / CRO fails to comply with the conditions required to be complied with during the conduct of the trial along with a provision for appeal to the Centre Government against action of the licensing authority is also required to be included. A comprehensive draft of the proposed amendments was placed for consideration of the members.

The Chairman stated that these amendments would create additional responsibilities of CDSCO in terms of carrying out inspections and ensuring that clinical trials are conducted in accordance to the provisions provided under the Drugs and Cosmetics Rules. The members may like to consider and recommend to the Central Government for providing additional infrastructure and manpower to cope up with this additional task.

The members agreed that it is high time that provisions for inspection of clinical trials and for taking actions against violation of the conditions of clinical trials are incorporated under the Drugs and Cosmetics Rules.

The Board then deliberated the proposed amendments in detail and approved the draft rules with certain minor changes. It also recommended that the Central Government may provide necessary additional manpower and infrastructure to handle the responsibility. The final draft as recommended by the DTAB is placed at **Annexure I.**

AGENDA NO. 3

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES, FOR REGISTRATION OF ETHICS COMMITTEES AND INCORPORATION OF SCHEDULE Y-II PROVIDING REQUIREMENTS AND GUIDELINES FOR REGISTRATION OF ETHICS COMMITTEES

DCG(I) briefed the members that under Schedule Y to the Drugs and Cosmetics Rules, the Ethics Committees are responsible for protecting the rights, safety and well being of trials subjects. Ethics Committees are required to monitor the documents to be used in recruitment of subjects and obtaining their informed consent. These committees also have a continuing responsibility of regular monitoring of the compliance to the Ethical aspects of the trial including payment of compensations etc to the trial subjects.

Concerns have, however, been expressed that many Ethics Committees do not discharge their obligations properly in respect of review of Ethical aspects of clinical trials to safeguard the interests of research subjects. Allegations have been made that many Ethics Committees instead of acting as watchdogs for the well being of research subjects, act as mere rubber stamp for reviewing, approving and monitoring of clinical trials. In the cases of Independent Ethics Committees functioning outside the institute where the trial is being conducted, it is difficult to get information as to how these were constituted, who their members were and how these were selected. Many of the

committees do not have written Standard Operative Procedures under which they operate.

It was therefore, proposed that the Ethics Committees which review and accord approval of clinical trials should be registered with the Central Drugs Standard Control Organization (CDSCO) and details of its members, method of working etc available with the Licensing Authority. This will ensure that these Ethics Committees constituted in the proper manner monitor the trials in accordance with the requirements of Schedule Y and GCP guidelines.

The Drugs and Cosmetics Rules were therefore proposed to be amended by incorporating rule 122DAC relating to registration of Ethics Committees and insertion of new Schedule Y-II laying down the requirements and guidelines for registration of Ethics Committees. A comprehensive draft of the proposed amendments was placed for consideration of the members.

The Chairman stated that the Ethics Committee is an empowered committee to take many decisions in respect of Ethical aspects as well as compensation to be paid to the trial subjects in case of injury or death, it should therefore have powers to invite Experts for their opinion to arrive at judicious decisions. Such experts may however not have any voting rights.

The members unanimously agreed that the Ethics Committees should be registered with the CDSCO to ensure that these are properly constituted and functional in accordance to the responsibilities assigned under Schedule Y and are regulated under the Drugs and Cosmetics Rules.

The members then examined the proposed amendment and recommended certain changes in the proposed draft. The DTAB recommended that the Drugs and Cosmetics Rules may be amended after incorporating the proposed changes. The revised draft as recommended by DTAB is placed at **Annexure II.**

AGENDA NO. 4

CONSIDERATION OF THE PROPOSAL FOR AMENDMENTS IN SCHEDULE Y TO THE DRUGS AND COSMETICS RULES IN RESPECT OF APPROVAL OF CLINICAL TRIAL BY ETHICS COMMITTEES AND ANIMAL TOXICITY REQUIREMENTS FOR CLINICAL TRIALS

DCG(I) stated that Schedule Y was last amended in 2005 and certain amendments were required to be made especially in respect of the provisions relating to the approval of clinical trials by the Ethics Committees, to harmonize animal toxicity studies with the international requirements as requested by ICMR and to make a provision that manufacturers permitted to market new drugs and collecting PSUR data should have pharmacovigilance system in place.

A. In regard to the approval of clinical trials under Para 2 'Clinical trials' of Schedule Y, it has been stated that the trial sites may accepts the approval granted by the Ethics Committee of another trial site or the approval granted by an Independent Ethics Committee. This provision permits the sponsor / CRO to obtain Ethics Committee approval from an Ethics Committee situated at another trial site or Independent Ethics Committee set up outside the institute resulting in many cases bypassing of the Ethics Committee of the institute where the trial is being conducted and there may not be proper supervision of the trial as required under Schedule Y and GCP guidelines. In view of this, it was proposed to amend the clause (i) of the sub Para (1) Approval of clinical trial, under **Para 2. Clinical Trials** as under:

(i) The clinical trials of new drugs are required to be conducted at the trial sites, which have their own Ethics Committees. The trial shall be initiated only after the permission has been granted by the Licensing Authority under Rule 21(b), and the approval granted by the Ethics Committee of the institute where trial is proposed to be conducted. The Bioequivalence or bioavailability studies of drugs approved elsewhere and required for

new drug approval in the country and/or of drugs approved in the country for marketing may be conducted at centres which may not have their own Ethics Committee. In such cases Ethics Committee approval may be obtained from an independent Ethics Committee set up outside the institute, but in the same area and registered with the said licensing authority. In the case of a multi-centric clinical trial, where protocol version is the same at all trial sites, the Ethics Committee(s) of respective sites should accord their approval and accept responsibility for the study at the trial site prior to the initiation of the trial. The Licensing Authority shall be duly informed of the approval of the respective Ethics Committee(s) as prescribed in Appendix VIII."

DTAB after deliberations agreed to the proposed amendments.

B. The Appendix III of Schedule Y specify animal toxicity requirements. Para 1.8 relates to animal toxicity requirements for clinical trial and marketing of a new drug. It is provided that long term toxicity requirements for the drugs having duration of more than 1 month of human administration is six months (24 weeks) animal toxicity studies. The Director General, ICMR in his letter to the Drugs Controller General (India), has pointed out that while examining a request for phase II clinical trial by M/s. Ranbaxy Laboratories, during the IND committee meeting, it was observed that Schedule Y requires 24 weeks repeated dose toxicity study for clinical trial of more than one month of human exposure, while as per US FDA and EMEA guidelines for clinical trial between 2 weeks and 6 months, the duration of toxicity study should be same as that of human exposure. It was also stated that these International guidelines are of 2009 (EMEA) and 2010 (US FDA) and looking into prevention of cruelty of animals, there is a need to have a relook at schedule Y which was finalized in 2005.

In view of the above international guidelines for clinical trials and recommendations of ICMR, it was proposed that the animal toxicity requirements under Para 1.8 of Appendix III should be amended as under.

Route of administaration	Duration of proposed human administration	Human phases for which study is proposed to be conducted	**Long term toxicity requirements**
Oral, or parentral or transdermal	>1 wk but upto 2 wk	I,II,III	**2sp; 2wk**
	Upto 2 wks	Marketing permission	**2 sp; 4 wk**
	>2 wk but upto 4 wk	I, II,III	**2 sp; equal to duration of human exposure**
		Marketing permission	**2 sp; 12 wk**
	> 4 wk but upto 12 wk	I,II,III	**2 sp; equal to duration of human exposure**
		Marketing permission	**2 sp; 24 wk**
	> 12 wk but upto 24 wks	I,II,III	**2 sp; equal to duration of human exposure**
		Marketing permission	**2 sp; Rodent 24 wks, non-rodent 36 wks**
	> 24 wks	I,II,III	**2 sp; Rodent 24 wks, non-rodent 36 wks**
		Marketing permission	**2 sp; Rodent 24 wks, non-rodent 36 wks**

Further under Male fertility study the clause '*Phase I, II, III in male volunteers/patients'* may also be amended to read as **'Phase III in male volunteers/patients'.**

The DTAB after deliberation agreed to the proposed amendment.

C. One of the requirements of Schedule Y is that the applicant permitted to market a new drug is required to furnish Periodic Safety Update Reports (PSUR) to the CDSCO. For capturing such reports, the manufacturer should have a pharmacovigilance system in place to monitor clinical safety of new drugs. It is therefore considered necessary to make it mandatory for the applicant applying for permission to market a new drug to have its own pharmacovigilance system to collect and process the adverse drug reaction reports.

It was therefore proposed to introduce the following clause under conduct Para (3) sub Para (4) pertaining to Post Marketing Surveillance

> "The applicant should have a Pharmacovigilance system in place for collecting, processing and forwarding the report to the licensing authority for information on adverse drug reaction emerging from the use of the drug manufactured / marketed by the applicant in the country. The system should be managed by qualified and trained personnel. The officer in-charge of collection and processing of data should preferably be a medical officer trained in analysis of adverse drug reaction reports."

DTAB after deliberations agreed to the proposed amendment.

AGENDA NO. 5

CONSIDERATION OF THE PROPOSAL TO AMEND RULE 122E OF THE DRUGS AND COSMETICS RULES, 1945 FOR DELETION OF THE CLAUSE 'OR ITS INCLUSION IN THE INDIAN PHARMACOPOEIA, WHICHEVER IS EARLIER' AND AMENDMENT OF FORM 44 FOR DELETION OF CLAUSE 'PATENT STATUS OF THE DRUG'

A. DCG(I) briefed the members that the Indian Pharmacopoeia, provides standards of identity, purity and strength of the drugs included in it. The Indian Pharmacopoeia now being published by the Indian Pharmacopoeia Commission, include standards of certain drugs which are otherwise considered as new drugs under the Drugs and Cosmetics Rules, as introduction of a drug in the Pharmacopoeia is not considered to be related to its status as a new drug.

The definition of New Drug under Rule 122E however, provides that a new drug shall continue to be considered as new drug for a period of four years from the date of its first approval **or its inclusion in the Indian Pharmacopoeia, whichever is earlier.** Under the said rule many of the State

Licensing Authorities interpret that a drug is no longer a new drug once it is included in the Indian Pharmacopoeia and permission to manufacture such a drug could be granted without mandatory permission from CDSCO. Once the permission is granted by the State Licensing Authority, the manufacturer of the drug would not be required to submit the Periodic Safety Update Reports (PSUR) for evaluation of the safety of the new drug during the period of four years of its introduction in the market.

Secretary cum-scientific Director, Indian Pharmacopoeia Commission, Ghaziabad has therefore proposed that in the circumstances the clause **'or its inclusion in the Indian Pharmacopoeia, whichever is earlier'** may be deleted from the definition of the term new drug under Rule 122E.

DTAB after deliberations agreed to the proposed amendment with prospective effect.

B. The DCG (I) stated that the Form – 44 pertaining to the application for permission to market a new drug has an entry at serial number 8 seeking **'patent status of the drug'**. However, the Drugs and Cosmetics Rules, as well as Schedule Y to the said Rules do not take into account the patent status of the drug for the purpose of consideration of the application for grant of permission to import and/or manufacture a new drug or to undertake clinical trial. It was therefore proposed to delete the entry in the Form-44.

The DTAB after deliberations recommended that as the amendment relates to the patent issue, the ICMR may be requested to constitute a committee including stakeholders in the matter and give its opinion for further consideration.

AGENDA NO. 6

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES, 1945 FOR THE PURPOSE OF INTRODUCTION OF PHYTOPHARMACUETICALS AND INCORPORATION OF SCHEDULE YIII TO PROVIDE GUIDELINES FOR PERMISSION FOR MANUFACTURE OF NEW PHYTOPHARMACUETICALS OR FOR THEIR CLINICAL TRIALS IN THE COUNTRY

DCG(I) briefed the Members that an expert committee under the Chairmanship of Dr Nitya Anand, who is also the Chairman of the scientific body of the Indian Pharmacopoeia Commission, was constituted for drawing up regulatory guidelines for Phytopharmacueticals for their quality control and to ensure that these are safe for use.

The committee after thorough evaluations and deliberations has recommended the need to amend the Drugs and Cosmetics Rules, 1945 for the purpose of providing definition of Phytopharmacueticals and incorporation of Schedule YIII to provide guidelines for permission for manufacture of new Phytopharmacueticals or for their clinical trials in the country.

The DTAB accepted the recommendations of the committee in principle and recommended that suitable draft rules may be prepared for incorporation of provisions relating to Phytopharmaceuticals including Schedule Y-III based on the recommendations of the committee.

AGENDA NO. 7

CONSIDERATION OF THE PROPOSAL TO EXAMINE THE RATIONALITY OF CERTAIN FIXED DOSE COMBINATIONS (FDCS) PERMITTED BY THE OFFICE OF DCG(I) BUT CONSIDERED IRRATIONAL BY A COMMITTEE CONSTITUTED BY THE HON'BLE HIGH COURT OF BOMBAY, NAGPUR BENCH

DCG (I) briefed the Members that Hon'ble High Court Court of Judicature at Bombay, Nagpur Bench during the hearing in a petition number 18/2010 relating to Court on its own motion Vs. Union of India on 08.09.10 directed that the DCG(I), which is the authority under the Drugs and Cosmetics Act, to consider whether the following FDCs approved by them and referred to in the list are entitled to be approved with reference to the parameters set out by the Committee constituted by the Hon'ble Court.

1. Pantoprazole + Domeperidone
2. Cefadroxil +Clavulanic Acid
3. Telmisartan +Amlodipine
4. Ceftazidime +Tazobactum
5. Cefipime + Tazobactum
6. Cefixime + Cloxacillin
7. Amlodipine +Metoprolol
8. Esomeprazole + Itopride
9. Cefixime +Cloxacillin + Lactobacillus
10. Trandalopril + Verapamil
11. Rabeprazole + Itopride

The court was apprised by the Office of DCG (I) that the FDCs referred to in the order will be placed before the DTAB for its consideration.

DTAB after deliberations recommended that the FDCs referred to by the Hon'ble Court may be referred to the Expert Committee examining the rationality of 294 FDCs, to examine their safety and efficacy; and the Hon'ble Court apprised accordingly.

AGENDA NO. 8

CONSIDERATION OF THE PROPOSAL TO NOTIFY THE LIST OF MEDICAL DEVICES AND DIAGNOSTIC DEVICES UNDER SECTION 3(b) (iv) OF THE DRUGS AND COSMETICS ACT, 1940

DCG(I) briefed the members that at present 14 medical devices are being regulated as drugs under the Drugs and Cosmetics Rules for regulating their quality in the country. The DTAB had earlier desired that more number of medical devices should be regulated for their quality control. The office of DCG(I) has therefore prepared a further list of 22 medical devices to be notified as drugs under the Drugs and Cosmetics Act.

1. Occluders
2. Pacemakers
3. Implantable Defibrillators
4. Cardiac Patches
5. Peripheral Stents
6. Surgical Meshes
7. Dental Devices
8. Tissue Adhesives
9. Brain Implants
10. Internal Prosthetic Devices
11. Tracheostomy Tubes
12. Endotracheal Tubes
13. Aspiration Tubes
14. Perfusion Tubes
15. Medical Thermometers
16. Blood Pressure Apparatus
17. Implantable Clips
18. Annuloplasty rings

19. Guidewires
20. Heart Lung Pack
21. Incontinence Devices
22. In-vitro Diagnostic Devices for Malaria, Dengue, Tuberculosis, Human Leukocyte Antigen, Cancer Markers and Blood Glucose Test Strips

The members approved in principle that above medical devices are required to be regulated for their quality control in the country. They however observed that an effective control over the quality of medical devices can only be achieved, if the specific regulations to regulate the quality of medical devices as medical devices are in place. Standards for these medical devices and system of checking the quality should also be specified. They however, approved that these medical devices are approved

The DTAB after deliberations recommended that the above medical devices, though approved in principle, may be notified only after the regulations to regulate the quality of medical devices as stated above are incorporated under the Drugs and Cosmetics Act and Rules.

AGENDA NO. 9

CONSIDERATION OF THE PROPOSAL TO REGULATE CERTAIN MEDICAL DEVICES UNDER THE DRUGS AND COSMETICS RULES, CONSIDERED AS SUB FAMILIES TO THE MEDICAL DEVICES NOTIFIED UNDER THE DRUGS AND COSMETICS ACT, IN 2005.

DCG(I) briefed the members that the quality of 14 notified medical devices is at present being regulated under the Drugs and Cosmetics Rules. These medical devices were notified under the notification GSR 365(E) dated March 17, 1989 and S.O. 1468(E) dated October, 6, 2005 issued by the Ministry of Health and Family Welfare in

pursuance of the sub clause (iv) of clause (b) of section 3 of the Drugs and Cosmetics Act.

It was however observed that certain medical devices which were considered to be covered under the categories of notified devices are being imported and marketed in the country without the mandatory registration and import licence as required under the Drugs and Cosmetics Rules. A list of 19 such medical devices was prepared by the office of DCG(I) which were considered to be covered under the notified devices.

The Expert Committee on Medical Devices considered the matter on 30.09.2009. The Expert Committee after deliberations opined that the following devices may be regulated as sub-family of the earlier 14 notified Medical Devices.

S. No.	**Name of Device**	**Class of notified device**
1.	Spinal Needles	Disposable Hypodermic Needles
2.	Insulin Syringes	Disposable Hypodermic Syringes
3.	Three Way Stop Cock as an accessory of I.V. Cannula/Catheter/Perfusion Set	Disposable Perfusion Sets
4.	Introducer Sheath	I.V. Cannula
5.	Cochlear Implant	Internal Prosthetic Replacement
6.	Closer Wound Drainage Set	Catheter
7.	AV Fistula Needles	Disposable Hypodermic Needles
8.	Extension Line as a accessory of infusion Set	Disposable of Perfusion Set
9.	Ango Kit/PTCA/Cath Lab Kit	I.V. Cannula/Disposable Perfusion Set
10.	Measure Volume Set	Disposable Perfusion Set
11.	Flow Regulator as a accessory of Infusion Set	Disposable Perfusion Set

The DTAB after deliberations agreed to the recommendations of the Expert Committee for regulation of the quality of these devices under the already notified devices.

AGENDA NO. 10

CONSIDERATION OF THE RECOMMENDATIONS OF THE EXPERT COMMITTEE (SUB COMMITTEE OF DTAB) FOR GIVING A BOX WARNING ON THE LABEL OF THE FORMULATIONS CONTAINING NIMESULIDE

DCG(I) stated that Nimesulide, a cyclo-oxygenase (COX)-2 inhibitor, is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, post-operative pain, dental pain, and fever since 1995 in India.

European Medicines Agency (EMEA) in 2007 recommended certain restrictions on the use of Nimesulide containing medicinal products. The DTAB in its 58th meeting held on 9.11.2009 constituted an Expert Committee for examination of the safety aspects of the drug Nimesulide along with certain other drug formulations which were restricted /prohibited in certain other countries.

The Expert Committee examined the safety and continued marketing of Nimesulide in the country in its meetings held on 5.5.2010, 9.11.2009 and 8.01.2010.

The Committee examined the toxicity aspect of the drug in its meeting held on 5.5.2010 and the members were of the opinion that in general NSAIDs have been associated with idiosyncratic hepatotoxicity in susceptible patients. Nimesulide, which has been in use in several countries, may be associated with rare but serious cases of liver dysfunction and hepatic injury. However Nimesulide, a selective cyclo-oxygenase (COX)-2 inhibitor features a low profile of gastrointestinal side effects and generally shows good tolerability. Risk of liver injury for Nimesulide is comparable to the most other currently used NSAIDs. The Expert Committee after deliberations made the following recommendation in respect of the use of the drug in the country.

"The following "Box Warning" should be mentioned on label as well as package insert and other promotional literature of formulation containing Nimesulide.

"Use of Nimesulide should ordinarily be restricted to 10 days. If longer clinical use is warranted, liver function test should be accessed periodically".

The Committee in its meetings on 9.11.2009 and 8.01.2010 examined the use of Nimesulide in children and recommended that the use of single molecule formulations or any fixed dose combination of Nimesulide in any dose in children below 12 years of age should be discontinued. Accordingly, the manufacture, sale and distribution of Nimesulide formulations for human use in children below 12 years of age was prohibited under section 26A of the Drugs and Cosmetics Act, 1940, vide Gazette notification GSR 82(E) dated 10.02.2011.

Another press release of European Medicines Agency (EMA), dated 23.06.2011 has stated that its use has been restricted to the treatment of acute pain and primary dysmenorrhoea. It issued a recommendation that it should no longer be used for the treatment of painful osteoarthritis.

The members after deliberations agreed that the box warning should be mentioned on the label as recommended by the Expert Committee and the manufacturers may be asked to conduct phase IV studies (post marketing trial) about the use of the drug for osteoarthritis in the country and the drug should be placed for focussed ADR monitoring under the Pharmacovigilance Programme of India.

AGENDA NO. 11

CONSIDERATION OF THE PROPOSAL TO EXAMINE THE CONTINUED MARKETING OF THE FIXED DOSE COMBINATION OF DEXTROPROPOXYPHENE WITH PARACETAMOL AND DICYCLIMINE

DCG(I) stated that the DTAB in its 57th meeting held on 23.2.2009 examined the entry number 55 of the list of banned drugs which prohibited manufacture /marketing of Fixed dose combination of dextropropoxyphene with any other drug other than anti-spasmodics and /or non-steroidal anti-inflammatory drugs (NSAIDs) and recommended that the entry may be amended to read as under:

> *"55. Fixed Dose Combination of dextropropoxyphene with any other drug other than one antispasmodic or one non-narcotic analgesic or one anti-inflammatory drug"*

M/s Wockhardt Ltd., Mumbai, made a representation to the then Secretary, Ministry of Health and Family Welfare that their product Spasmo Proxyvon (FDC of dextropropoxyphene with paracetamol and diclomine) is in use for the last 35 years and there is no safety concern reported so far. A double blind clinical study was conducted by the firm to establish efficacy and safety of the product. The Secretary Health and Family Welfare desired that DTAB or its sub-committee may give M/s. Wockhardt Ltd., a personal hearing to examine the matter. The DTAB in its 58th meeting held on 09.11.2009 recommended that the Expert Committee may give personal hearing to M/s. Wockhardt Ltd. Accordingly, the Expert Committee in its meeting held on 22nd July, 2010 examined the issue of marketing of FDC of dextropropoxyphlene with paracetamol and dycylomine. M/s. Wockhardt Ltd., gave detailed presentation before the Committee on rationality, safety, efficacy of the said FDC.

The committee after deliberations recommended that a well designed, multicentric statistically powered clinical trial should be conducted with the three drug combination before the matter is considered further.

The members were further informed that *dextropropoxyphene* and its combination products were recommended by USFDA in November, 2010 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. European Medical Agency (EMA), Health Canada, United Kingdom and New Zealand also withdrew *dextropropoxyphene* containing medicines. The matter is under consideration of the Expert Committee and its recommendations are still awaited.

The DTAB deliberated the matter and accepted the recommendations of the sub-committee that well designed, multicentric, statistically powered clinical trial should be conducted with the three drug combination to establish efficacy and safety of the product.

AGENDA NO. 12

CONSIDERATION OF THE PROPOSAL TO INCLUDE DMPA (DEPO-PROVERA) AS INJECTABLE HARMONAL CONTRACEPTIVE IN THE FAMILY PLANNING PROGRAMME BY THE GOVERNMENT OF INDIA

The Department of Family Welfare in the Ministry of Health and Family Welfare desired that Depot medroxyprogesterone acetate (DMPA) may be included in the family planning programme by the Government of India to provide alternative choice available to the women for family planning.

DMPA (medroxyprogesterone acetate) is an hormonal injectable contraceptive having Depot medroxyprogesterone. The sustained level of medroxyprogesterone acetate present in the injection suppresses ovulation in the women. It can protect against pregnancy for a period of 11-14 weeks. DMPA, when administered at the recommended dose to women every 3 months, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. These actions produce its contraceptive effect.

While it has long been known that Depo-Provera causes bone loss, it has recently been discovered that the osteoporotic effects of the injection grow worse, the

longer Depo-Provera is administered and may remain long after the injections are stopped, and may be irreversible. For these reasons, on November 17, 2004 the United States Food and Drug Administration and Pfizer agreed to put a black box warning on Depo-Provera's label, to highlight special problems particularly those that are serious, and to give healthcare professional a clear understanding of a potential medical complication associated with the drug.

The question of use of DMPA as contraceptive for family planning was earlier considered by the DTAB under the directions of the Hon'ble Supreme Court of India in the case of Drug Action Forum vs. Union of India (698/1993) in respect of use of hazardous drugs in the country and the list included DMPA also. The matter was considered by DTAB in a special meeting held on 16th Feb. 1995 to examine the recommendation of the technical sub-committee on the issues raised by Drug Action Forum. The DTAB in the case of Depo Provera (DMPA) gave the following recommendation.

> "The members had agreed for continued private marketing of Depo Povera Injection. The drug, however, is not recommended for inclusion in the Family Planning Programme."

The Department of Family Welfare stated that during this span of 15 years since the DTAB's recommendations, there have been many positive changes in the health care delivery system in India especially at the peripheral health facilities. Target Free Approach introduced in the Reproductive & Child Health Programme in 1996 wherein centrally determined targets are no longer the driving force behind the programme.

The members were however, informed that an Expert Committee in the Department of Family Welfare was examining the issue of use of DMPA in the family planning programme.

The DTAB, deferred the agenda and requested that Department of Family Welfare may place the proposal for consideration in the next meeting along with the detailed recommendations of the Expert Committee in the matter for further consideration.

AGENDA NO. 13

CONSIDERATION OF THE RECOMMENDATIONS OF THE EXPERT COMMITTEE SET UP IN THE 58TH MEETING TO EXAMINE ISSUES RELATED TO THE ADVERTISEMENT OF EMERGENCY CONTRACEPTIVE (EC) PILLS.

DCG(I) briefed the members that on the recommendations of the Department of Family Welfare exemption for advertisement of emergency contraceptive pills was granted by the office of DCG(I) in 2007 to M/s Cipla Ltd., Mumbai, M/s Incense Care, Bangalore and M/s PSI, New Delhi to advertise EC pills under the condition that the advertisement should be free from obscenity and should follow Code of Ethics and provide basic information about the use of the pill. The DTAB in its 55th meeting held on 06.07.2007 had recommended for issue of notification under Section 15 off the Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954 to permit advertisement of EC pills.

Concerns were however, raised over the sale of EC pills as non prescription drug at the chemists shop and its advertisement in the electronic media. It was apprehended that the drug may be misused leading to dangerous side effects. The proposed notification for advertisement was therefore, kept on hold by the Ministry of Health and it desired that the issue may be re-examined by DTAB.

The DTAB in its 58th meeting held on 09.11.2009 constituted an Expert Committee to examine issues related to the Advertisement of Emergency Contraceptive (EC) Pills containing Levonorgestrel. The Expert Committee considered the matter in its meeting held on 15.12.2009 and gave following recommendations.

1. The drug is safe for use in young as well as elder women. It has no serious side effects even after multiple uses. However, it should be promoted as emergency contraceptive only and not as regular means of contraception.
2. The notification under the DMR (OA) Act permitting the advertisement as recommended by DTAB may be issued.

3. The public sector of Government of India should also advertise in print and electronic media including radio to promote EC pills so that the rural population is also made aware of its availability.
4. Guidelines should be developed for regulating the advertisements of EC pills.
5. The advertisements should carry emphasis on using regular contraceptive methods and EC pills should be promoted for use in emergency only. It should not stigmatize abortions as an option. The side effect of disruption of menstrual cycles should be included in the advertisement. The advertisement should not look obscene and follow Code of Ethics.
6. If required, the committee may also initiate screening of the advertisement and it may co-opt a representative of an NGO, Principal of a reputed women college and a representative of Standard Advertising council as its members. The script of the advertisement may be reviewed by the committee before these are permitted to be advertised in print of electronic media to ensure that it follows Code of Ethics.

The DTAB after deliberations agreed that the advertisement of EC Pills may be permitted as per recommendations of the Expert Committee.

AGENDA NO. 14

CONSIDERATION OF THE PROPOSAL TO EXAMINE PROVISION OF LOAN LICENSING SYSTEM UNDER THE DRUGS AND COSMETICS RULES

DCG(I) briefed the members that a system of loan licensing is permitted under the Drugs and Cosmetics Rules for capacity utilization in manufacturing units. Loan licences are granted under rule 69A and 75A to the applicants who do not have their own arrangements for manufacture but intend to avail manufacturing facilities owned by the licencee. The loan licence has been defined under Rule 69A as under:

> "Explanation.-For the purpose of this rule a loan licence means a licence which a licensing authority may issue to an applicant who does not have his own arrangements for manufacture but who intends to avail himself of the manufacturing facilities owned by a licensee in Form 25."

The definition provided above in its true sense does not permit grant of loan licence to the applicant who had its own arrangement for manufacture.

The Ministry of Health has therefore desired that the DTAB may examine the definition of the loan licence under the Drugs and Cosmetics Rules, as to whether it requires any amendment in the light of the policies pursued by the State Licensing Authorities.

The proposal was also considered in the 41st meeting of the Drugs Consultative Committee held on 28th October, 2010. The DCC after deliberations recommended that the definition of the term Loan Licence may be amended to read as under:

> **"Explanation.-For the purpose of this rule a loan licence means a licence which a licensing authority may issue to an applicant who intends to avail the manufacturing facilities owned by a licensee in Form 25."**

Similarly the definition provided under Rule 75A may also be amended to read as under:

"Explanation.-For the purpose of this rule a loan licence means a licence which a licensing authority may issue to an applicant who intends to avail the manufacturing facilities owned by a licensee in Form 28."

The DTAB after deliberations agreed to the proposed amendment in the Drugs and Cosmetics Rules.

AGENDA NO. 15

CONSIDERATION OF THE PROPOSAL TO AMEND SCHEDULE D OF THE DRUGS AND COSMETICS RULES IN RESPECT OF THE EXTENT OF CONDITIONS OF EXEMPTIONS IN THE CASE OF IMPORT OF SUBSTANCES NOT INTENDED FOR MEDICINAL USE

DCG(I) stated that Schedule D of the Drugs and Cosmetics Rules, 1945 under Entry 1 provides exemption to the substances not intended for medicinal use, from the provisions of chapter III of the Act and Rules thereunder. Dual purpose items are being imported by manufacturers of food items, cosmetics, textile industry, chemical industry etc. However there are possibilities of import of drugs products under the garb, 'not for medicinal use' to avoid registration and import licence under the Drugs and Cosmetics Rules. In view of this, CDSCO had taken a view that a blanket exemption from registration and from provisions contained in chapter III of the Act, as given in Schedule D to the Drugs and Cosmetics Rules should not be given for import of such categories of drugs which are not intended for medicinal use or for drugs which may themselves not be used as drugs but are used for manufacture of other drugs.

The office of DCG(I) had earlier issued a circular number 6-2 /2004-DC dated 13.12.2005 stating that the importer will have to make an application to CDSCO Hqrs, where case to case examination will be done and after due scrutiny,

permission to import dual purpose drugs for non-medicinal uses without registration and import licence will be granted.

In order to make the above decision applicable universally, the condition under Schedule D is proposed to be amended by incorporating the following clause under the extent and conditions of exemption.

> 'Further, permission from licensing authority as defined in Rule 21(b) has been obtained for import of the substance for non-medicinal use without registration and import licence.'

The DTAB after deliberations agreed to the proposed amendments in the Schedule D to the Drugs and Cosmetics Rules.

AGENDA NO. 16

CONSIDERATION OF THE PROPOSAL TO SHIFT KETAMINE HYDROCHLORIDE FROM SCHEDULE H TO SCHEDULE X OF THE DRUGS AND COSMETICS RULES

DCG(I) briefed the members that Ketamine hydrochloride is a commonly used anaesthetic available in injectable form. The drug is official in Indian Pharmacopeia and is a Schedule H drug under the Drugs and Cosmetics Rules. Drug is stated to have abuse potential. It is evaporated to form a powder which is snorted or swallowed by the drug addicts. Ketamine is also smuggled from India to East Asian countries for abuse. It was therefore proposed necessary that domestic control over the sale of drug should be further restricted.

The proposal to shift Ketamine hydrochloride from Schedule H to Schedule X of the Drugs and Cosmetics Rules was considered in the 41st meeting of the Drugs Consultative Committee held on 28th October, 2010 and DCC agreed to the proposal.

The inclusion of the drug in Schedule X would result in more restrictions in storage, transportation and use of the drug in the country.

The DTAB after deliberations agreed to the proposed amendment in the Drugs and Cosmetics Rules.

AGENDA NO. 17

CONSIDERATION OF THE PROPOSAL TO INCLUDE SINDOOR (IS:14649:1999) UNDER SCHEDULE S OF THE DRUGS AND COSMETIECS RULES

DCG(I) stated that a complaint was received that toxic and environmentally unfriendly sindoor/kumkum products are being sold at religious shrines as well as retail outlets in the country. The commercially available sindoor contains chemical dies, synthetic materials and lead salts and can cause skin disorders. It contains toxic low grade commercial red lead oxide along with other synthetic or natural bulking materials.

It has however, been claimed by certain manufacturers that if such products are not marketed as cosmetics and sold for religious purposes only, it is not mandatory to obtain a licences under the Drugs and Cosmetics Act. Matter was considered by the Hon'ble Madras High Court (K. Bhimraj vs. State of Tamil Nadu: Crl, M.P. 10957 of 1986) and it was opined that sale and distribution of kumkum /sindoor made from dyes, colors and pigments can be permitted only if it is manufactured after obtaining a licence under the Drugs and Cosmetics Act.

The matter was considered in the 41st meeting of the Drugs Consultative Committee held on 28th October, 2010 and it recommended that Schedule S to the Drugs and Cosmetics Rules may be amended to include Sindoor under it along with the BIS standard (IS:14649:1999) to ensure that the product is manufactured under a licence and conforms to the standards.

The DTAB after deliberations agreed to the proposed amendment in the Drugs and Cosmetics Rules.

AGENDA NO. 18

CONSIDERATION OF THE PROPOSAL TO INCLUDE OSELTAMIVIR PHOSPHATE AND ZANAMIVIR FORMULATIONS UNDER THE SCHEDULE H OF THE DRUGS AND COSMETICS RULES

DCG(I) briefed the members that at the time of spread of Swine Flu in 2009, the Ministry of Health and Family Welfare issued a Gazette Notification GSR 677(E) dated 15th September, 2009 under Section 26B of the Drugs and Cosmetics Act to regulate and restrict the manufacture, sale and distribution of the drugs 'Oseltamivir phosphate' and Zanamivir and preparations based thereon. It was felt that Oseltamivir is the only drug available for treatment of H1N1 virus influenza in humans and an inappropriate use would lead to the H1N1 virus developing resistance to the drug, thereby rendering it ineffective.

Since then an indigenous H1N1 vaccine has been developed in the country in the year 2010. Three vaccine manufacturers have already been granted permission to manufacture and market H1N1 vaccine i.e. Serum Institute of India-Pune, Cadila Healthcare (Zydus) – Ahmadabad and Bharat Biotech, Hyderabad. The availability of vaccine has resulted in lowering the incidence of H1N1 viral infections. Moreover the drug is at present being used as the first line treatment in the American subcontinent, Europe, Japan etc. for cure from seasonal influenza.

In view of the above it was proposed to withdraw the said notification and include the drug under Schedule H of the Drugs and Cosmetics Rules. This would help in stocking the drug by the chemists and increased availability of the drugs on the prescriptions of a Registered Medical Practitioner.

The DTAB after deliberations agreed that the notification issued under Section 26B of the Drugs and Cosmetics Act, may be withdrawn and the drug included under Schedule H of the Drugs and Cosmetics Rules.

AGENDA NO. S-1

CONSIDERATION OF THE PROPOSAL TO AMEND SCHEDULE Y TO THE DRUGS AND COSMETICS RULES FOR SPECIFYING NUMBER OF TRIALS SUBJECTS to BE INCLUDED IN THE PHASE I, PHASE II AND PHASE III CLINICAL TRIALS ON NEW DRUGS

DCG(I) briefed the members that the present Schedule Y to the Drugs and Cosmetics Rules, do not specify the numbers of trial subjects to be included in the phase I, phase II and phase III clinical trials. Similar provision was earlier available under Schedule Y prior to its amendment in 2005. The Good Clinical Practice guidelines for clinical trials in India also specify the numbers of trial subjects to be included in the phase I, phase II and phase III clinical trials.

It was therefore proposed that the following clauses may be inserted in Schedule Y to ensure uniformity in selection of subjects in different phases of clinical trials.

Phase I

These studies are usually carried out in healthy adult volunteers using clinical, physiological and biochemical observations. At least two subjects should be used on each dose. These may be carried out at one or two centers.

Phase II

In phase II trials normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centers and carried out by

clinicians specialized in the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.

Phase III

If the drug is already approved / marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3 to 4 centers primarily to confirm the efficacy and safety of the drug, in Indian patients when used as recommended in the product monograph for the claims made.

If the drug is a new drug substance discovered in India and not marketed in any other country, phase III data should be obtained on at least 500 patients distributed over 10-15 centers. In addition, PSUR data on adverse drug reactions observed during use of the drug should be collected in 1000-2000 patients after approval for marketing of the drug. Such data may be collected through clinicians who give written consent to use the drug as recommended and to provide a report on its efficacy and adverse drug reactions in the treated patients.

The DTAB after deliberations agreed to the proposed amendment in Schedule Y to the Drugs and Cosmetics Rules.

AGENDA NO. S-2

CONSIDERATION OF THE PROPOSAL TO DROP THE DRAFT RULES PUBLISHED UNDER GAZETTE NOTIFICATION GSR 635(E) DATED 13.10.2006 REGARDING AMENDMENT IN SCHEDULE D, SCHEDULE F(II) AND SCHEDULE M OF THE DRUGS AND COSMETICS RULES RELATING TO EXEMPTION IN RESPECT OF IMPORT OF DRUGS AND STANDARDS FOR SURGICAL DRESSINGS

DCG(I) briefed the members that a Gazette notification GSR 635(E) dated 13.10.2006 was published on the basis of the recommendations of the DTAB in its 54th meeting held on 02.08.2005. The proposed amendments related to amendment in Schedule D of the Drugs and Cosmetics Rules for exemption to the drug formulations imported as gift / donations by registered charitable institutions for distribution to the patients, amendment in Schedule F(II) regarding standards for surgical dressing and bandage cloth and requirements under Schedule M for manufacture of non-sterilized and non-medicated surgical dressing. The finalization of the draft rules could not be under taken due to various administrative difficulties and the Committee on Subordinate Legislation was requested time and again to grant extension of time to enable the Government to process the matter further.

In the intervening period, the Government of India had constituted Indian Pharmacopeia Commission to draft and publish standards of drugs marketed in the country under the Indian Pharmacopeia and other proposals also required a relook about their essentiality and requirement after the lapse of a period of six years.

The Ministry of Health therefore desired that DTAB may give its opinion as to whether these proposed amendments could be dropped and proposals reconsidered if required in the context of present knowledge and requirements in the country.

The DTAB after deliberations agreed to the dropping of the draft rules published under the said notification.

Annexure I

Proposed amendments to Drugs and Cosmetics Rules, 1945 for Clinical Trial Inspections

A. In the Drugs and Cosmetics Rules, 1945, in Part X-A, after Rule 122 DAA, the following rule shall be inserted:

Rule 122 DAB: (1). Permission to conduct Clinical Trial : The Licensing Authority as defined in clause (b) of rule 21, after being satisfied that the data submitted along with the application in support of proposed Clinical trial is adequate, shall issue permission to conduct clinical trial subject to the following conditions, along with any other specific trial related condition(s) as considered necessary in the conduct of the trial;

1. Clinical trial shall be conducted in compliance to the approved protocols, requirements of Schedule Y, 'Good Clinical Practice (GCP)' Guidelines for Clinical Trials in India and other applicable regulations.
2. Approval of the Ethics Committee shall be obtained before initiation of the study.
3. Ethical aspects of the clinical trial as described in the "Ethical Guidelines for Biomedical Research on Human Participants" published by Indian Council of Medical Research (ICMR), New Delhi shall be complied with.
4. Clinical trial shall be registered at Clinical Trials Registry – India (CTRI) before enrolling first patient in the study.
5. Annual status report on clinical trial viz. ongoing, completed or terminated shall be submitted to the licensing authority. In case the trial is terminated, the detailed reasons for the same shall be communicated to the said licensing Authority.
6. Any Suspected Unexpected Serious Adverse Reaction (SUSAR) occurring during clinical trial shall be communicated within fourteen calendar days to Licensing Authority and to the other investigator(s) participating in the study, as per Appendix XI of Schedule Y.
7. In case of study related injury or death, the applicant will provide complete medical care as well as compensation for the injury or death and statement to this effect shall be incorporated in the Informed Consent Document.

Further, the details of compensation provided shall be intimated to the licensing authority.

8. The premises of sponsor /CROs and clinical trial site shall be open to inspection by the officer of Central Drugs Standard Control Organization, who may be accompanied by an officer of the concerned State Drug Control Authority, to verify compliance to the requirements of Schedule Y, Good Clinical Practices guidelines and other applicable regulation.

9. The sponsor/CROs, Investigators shall allow officer of CDSCO, who may be accompanied by an officer of the concerned State Drug Control Authority, to enter with or without prior notice, any premises of sponsor/ CROs, clinical trial site to inspect, search and seize any record, data, document, books, Investigational drugs etc. related to clinical trials and provide adequate replies to any queries raised by the inspecting authority in relation to the conduct of clinical trial.

(2). If any sponsor/ CROs, investigators conducting clinical trial fail to comply with any of the above condition the Licensing Authority may after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reason thereof take following action:

a. Issue warning letter giving details of deficiency found during the inspection, which might affect the right or well being of subject or the validity of the study conducted at that site.

b. Recommendation that study may be rejected.

c. Suspension/cancellation of clinical trial permission.

d. Restriction of an Investigator, sponsor/CRO, to conduct future clinical trial.

(3). The sponsor /CROs, investigators against whom action as mentioned above has been taken by the licensing authority, may within ninety days of the receipt of the copy of the order by him prefer an appeal to the Central Government and the Central Government may after giving an opportunity of being heard, confirm, reverse or modify such order.

Annexure II

Proposed amendments to Drugs and Cosmetics Rules, 1945 for Registration of Ethics Committee

A. In the Drugs and Cosmetics Rules, 1945, in Part X-A, after Rule122 DAA, the following rule shall be inserted:

Rule 122 DAC- Registration of Ethics Committee (EC)

(1) No Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration of the committee with the licensing authority as defined in clause (b) of Rule 21.

(2) An application for registration of Ethics Committee shall be made to the licensing authority in accordance with the requirements prescribed in Schedule Y-II.

(3) The licensing authority after being satisfied that the requirements of the rules have been complied with and the conditions of the registration will be observed, may grant registration subject to the condition stated therein.

(4) The ethics committee will review and accord its approval to a clinical trial as per the Good Clinical Practice Guidelines for Clinical Trials in India, Schedule Y and other applicable regulatory requirements for safeguarding rights, safety and well being of the trial subjects.

(5) In case of clinical trial related injury or death, the Ethics Committee shall review the serious adverse events report and recommend for providing compensation. The quantum of the compensation to be paid by the sponsor shall be decided by the Ethics Committee in accordance with the guidelines issued by the CDSCO with the concurrence of Ministry of Health and Family Welfare for the purpose.

(6) The Ethics Committee shall allow inspector / official of CDSCO to enter the premises of the committee to inspect any record, data, document etc. related to clinical trial and provide adequate replies to any queries raised by the inspecting authority in relation to the conduct of clinical trial.

(7) The registration, unless it is sooner suspended or cancelled, shall be valid for a period of five years from the date of issue.

(8) If the licensing authority is not satisfied, he shall reject the application and shall inform the applicant of the reasons for such rejection and the conditions which must be satisfied before the registration can be granted.

(9) If the Ethics Committee fails to comply with any of the conditions of registration, the licensing authority may after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefore, suspend or cancel the registration for such period as considered necessary.

(10) The Ethics Committee (EC), whose registration has been suspended or cancelled by the licensing authority, may within ninety days of the receipt of the copy of the order by him prefer an appeal to the Central Government and the Central Government may after giving an opportunity of being heard, confirm, reverse or modify such order.

Explanation:
For the purpose of this part an Ethics Committee is a committee comprising of medical / scientific and non-medical /non-scientific members, whose responsibility is to verify the protection of the rights, safety and well-being of human subjects involved in a clinical trial. Ethics Committees may be named as: (1) Institutional Review Board (IRB), (2) Ethics Review Board or (3) Independent Ethics Committees (IECs) set up for the purpose outside the institute. The Ethics Committee shall be responsible for reviewing and approving the "Protocol", the suitability of the investigator(s), facilities, methods and adequacy of information to be used for obtaining and documenting "Informed Consent" of the study subjects and adequacy of confidentiality safeguards.

SCHEDULE Y-II
(See Rules 122 DA, 122 DAA, 122 DAC)

Requirements and Guidelines for registration of Ethics Committee (EC)

1- Scope:

Ethics Committees shall review every research proposal on human subjects and should evaluate the possible risks to the subjects, expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice issues. In case of clinical trial related injury or death the Ethics Committee should review and make recommendation for compensation to be paid by the sponsor in stipulated manner and time period.

These guidelines are not stand alone guidelines and are not in derogation of any other rules or guidelines applicable to the clinical trials.

2- Composition of Ethics Committees:

a) Ethics Committee should have at least seven members and should appoint from among its member a Chairperson (who is from outside the Institute,) and a Member Secretary, other members should be mix of Medical/ Scientific and nonmedical/ Non Scientific members including lay public as specified in Appendix VIII of Schedule Y.
b) The committee must include at least one member whose primary area of interest / specialization is non-Scientific and at least one member who is independent to institution.
c) The Ethics Committee should have as its members, individuals from other Institutions or Communities if required.

d) Members should be conversant with the provisions of clinical trials under the Schedule Y, Good Clinical Trial Practice Guidelines for clinical trials in India and other regulatory requirements to safeguard the rights, safety and well being of the trial subjects.
e) The members representing as basic medical scientists and clinicians should have Post graduate qualification and adequate experience in their respective fields and aware of their role and responsibilities as committee members.
f) Based on the requirement of research area e.g. HIV, Genetic disorder etc, specific patient group may also be included in the Ethics Committee as far as possible.
g) There should be no conflict of interest. The members shall voluntarily withdraw from the Ethics Committee while making a decision on an application which evokes a conflict of interest which should be indicated in writing to the Chairperson prior to the review and should be recorded so in the minutes.
h) Subject experts or other experts may be invited to the meetings for their advise but would not be having any voting rights.

3- Information required to be submitted by the applicant for registration of Ethics Committee:

a. Name of the Ethics Committee
b. Authority under which the Ethics Committee has been constituted, membership requirements, the term of reference, conditions of appointment and the quorum required.
c. The procedure for resignation, replacement or removal of members.
d. Address of the office of the Ethics Committee.
e. Name, address, qualification, organizational title, telephone number, fax number, e-mail, mailing address and brief profile of the Chairperson.
f. Names, qualification(s), organizational title, telephone number, fax number, e-mail and mailing address of the members of Ethics Committee. The information should also include members specialty (Primary Scientific or Non-scientific), member's affiliation with institution(s) and patient group representation, if any.
g. Details of the supporting staff.
h. Type of research reviewed by the committee (e.g. pharmaceuticals, devices, epidemiological, retrospective, herbals etc.).
i. Documents reviewed for every clinical trial protocol.
j. Information in respect of number of meetings of the committee and documentation of the minutes of these committees concerning clinical trials:
k. The information regarding review of serious adverse events reported during the conduct of the trial.
l. The Standard Operative Procedures (SOPs) to be followed by the committee in general.
m. Standard Operative Procedures followed by the committee for vulnerable population.
n. Policy regarding training for new and existing committee members along with SOPs.
o. Policy to monitor /prevent the conflict of interest along with SOPs.
p. Has the committee been audited/inspected before? If yes, by whom.
q. If the committee has been audited/inspected before, give details.

4- Maintenance of Record:

All documentation and communication of an EC are to be dated, filed and preserved according to the Standard Operative Procedures (SOPs). Strict confidentiality is to be maintained during access and retrieval procedures. Records should be maintained for the following:

1. The constitution and composition of the Ethics Committee;
2. The curriculum vitae of all the committee members;
3. Standard Operating Procedures (SOPs) of the committee;
4. National and international guidelines;
5. Copies of the Protocol, data collection formats, CRFs, investigational brochures etc. submitted for review;
6. All correspondence with committee members and investigators regarding application, decision and follow up;
7. Agenda of all EC meetings;
8. Minutes of all EC meetings with signature of the Chairperson;
9. Copies of decisions communicated to the applicants;
10. Record of all notification issued for premature termination of a study with a summary of the reasons;
11. Final report of the study including microfilms, CDs and Video-recordings.

All records must be safely maintained after the completion / termination of the study for not less than 5 years from the date of completion or termination of the trial.

5. The Ethics Committee shall be open for inspections by the officers of Central Drugs Standard Control Organization to verify compliance to the requirements of Schedule Y, Good Clinical Practices guidelines and other applicable regulation.

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(Extract of the Minutesof 60th meeting of DTAB held on 10th October, 2011)

AGENDA NO. 3

CONSIDERATION OF THE PROPOSAL TO AMEND THE DRUGS AND COSMETICS RULES, FOR REGISTRATION OF ETHICS COMMITTEES AND INCORPORATION OF SCHEDULE Y-II PROVIDING REQUIREMENTS AND GUIDELINES FOR REGISTRATION OF ETHICS COMMITTEES

DCG(I) briefed the members that under Schedule Y to the Drugs and Cosmetics Rules, the Ethics Committees are responsible for protecting the rights, safety and well being of trials subjects. Ethics Committees are required to monitor the documents to be used in recruitment of subjects and obtaining their informed consent. These committees also have a continuing responsibility of regular monitoring of the compliance to the Ethical aspects of the trial including payment of compensations etc to the trial subjects.

Concerns have, however, been expressed that many Ethics Committees do not discharge their obligations properly in respect of review of Ethical aspects of clinical trials to safeguard the interests of research subjects. Allegations have been made that many Ethics Committees instead of acting as watchdogs for the well being of research subjects, act as mere rubber stamp for reviewing, approving and monitoring of clinical trials. In the cases of Independent Ethics Committees functioning outside the institute where the trial is being conducted, it is difficult to get information as to how these were constituted, who their members were and how these were selected. Many of the committees do not have written Standard Operative Procedures under which they operate.

It was therefore, proposed that the Ethics Committees which review and accord approval of clinical trials should be registered with the Central Drugs Standard Control Organization (CDSCO) and details of its members, method of working etc available with the Licensing Authority. This will ensure that these Ethics Committees constituted in the proper manner monitor the trials in accordance with the requirements of Schedule Y and GCP guidelines.

The Drugs and Cosmetics Rules were therefore proposed to be amended by incorporating rule 122DAC relating to registration of Ethics Committees and insertion of new Schedule Y-II laying down the requirements and guidelines for registration of Ethics Committees. A comprehensive draft of the proposed amendments was placed for consideration of the members.

The Chairman stated that the Ethics Committee is an empowered committee to take many decisions in respect of Ethical aspects as well as compensation to be paid to the trial subjects in case of injury or death, it should therefore have powers to invite Experts for their opinion to arrive at judicious decisions. Such experts may however not have any voting rights.

The members unanimously agreed that the Ethics Committees should be registered with the CDSCO to ensure that these are properly constituted and functional in accordance to the responsibilities assigned under Schedule Y and are regulated under the Drugs and Cosmetics Rules.

The members then examined the proposed amendment and recommended certain changes in the proposed draft. The DTAB recommended that the Drugs and Cosmetics Rules may be amended after incorporating the proposed changes. The revised draft as recommended by DTAB is placed at **Annexure II.**

Annexure II

Proposed amendments to Drugs and Cosmetics Rules, 1945 for Registration of Ethics Committee

B. In the Drugs and Cosmetics Rules, 1945, in Part X-A, after Rule122 DAA, the following rule shall be inserted:

Rule 122 DAC- Registration of Ethics Committee (EC)

(1) No Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration of the committee with the licensing authority as defined in clause (b) of Rule 21.

(2) An application for registration of Ethics Committee shall be made to the licensing authority in accordance with the requirements prescribed in Schedule Y-II.

(3) The licensing authority after being satisfied that the requirements of the rules have been complied with and the conditions of the registration will be observed, may grant registration subject to the condition stated therein.

(4) The ethics committee will review and accord its approval to a clinical trial as per the Good Clinical Practice Guidelines for Clinical Trials in India, Schedule Y and other applicable regulatory requirements for safeguarding rights, safety and well being of the trial subjects.

(5) In case of clinical trial related injury or death, the Ethics Committee shall review the serious adverse events report and recommend for providing compensation. The quantum of the compensation to be paid by the sponsor shall be decided by the Ethics Committee in accordance with the guidelines issued by the CDSCO with the concurrence of Ministry of Health and Family Welfare for the purpose.

(6) The Ethics Committee shall allow inspector / official of CDSCO to enter the premises of the committee to inspect any record, data, document etc. related to clinical trial and provide adequate replies to any queries raised by the inspecting authority in relation to the conduct of clinical trial.

(7) The registration, unless it is sooner suspended or cancelled, shall be valid for a period of five years from the date of issue.

(9) If the licensing authority is not satisfied, he shall reject the application and shall inform the applicant of the reasons for such rejection and the conditions which must be satisfied before the registration can be granted.

(9) If the Ethics Committee fails to comply with any of the conditions of registration, the licensing authority may after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefore, suspend or cancel the registration for such period as considered necessary.

(10) The Ethics Committee (EC), whose registration has been suspended or cancelled by the licensing authority, may within ninety days of the receipt of the copy of the order by him prefer an appeal to the Central Government and the Central Government may after giving an opportunity of being heard, confirm, reverse or modify such order.

Explanation:
For the purpose of this part an Ethics Committee is a committee comprising of medical / scientific and non-medical /non-scientific members, whose responsibility is to verify the protection of the rights, safety and well-being of human subjects involved in a clinical trial. Ethics Committees may be named as: (1) Institutional Review Board (IRB), (2) Ethics Review Board or (3) Independent Ethics Committees (IECs) set up for the purpose outside the institute. The Ethics Committee shall be responsible for reviewing and approving the "Protocol", the suitability of the investigator(s), facilities, methods and adequacy of information to be used for obtaining and documenting "Informed Consent" of the study subjects and adequacy of confidentiality safeguards.

SCHEDULE Y-II
(See Rules 122 DA, 122 DAA, 122 DAC)

Requirements and Guidelines for registration of Ethics Committee (EC)

5- Scope:

Ethics Committees shall review every research proposal on human subjects and should evaluate the possible risks to the subjects, expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice issues. In case of clinical trial related injury or death the Ethics Committee should review and make recommendation for compensation to be paid by the sponsor in stipulated manner and time period.

These guidelines are not stand alone guidelines and are not in derogation of any other rules or guidelines applicable to the clinical trials.

6- Composition of Ethics Committees:

i) Ethics Committee should have at least seven members and should appoint from among its member a Chairperson (who is from outside the Institute,) and a Member Secretary, other members should be mix of Medical/ Scientific and nonmedical/ Non Scientific members including lay public as specified in Appendix VIII of Schedule Y.
j) The committee must include at least one member whose primary area of interest / specialization is non-Scientific and at least one member who is independent to institution.
k) The Ethics Committee should have as its members, individuals from other Institutions or Communities if required.
l) Members should be conversant with the provisions of clinical trials under the Schedule Y, Good Clinical Trial Practice Guidelines for clinical trials in India and

other regulatory requirements to safeguard the rights, safety and well being of the trial subjects.

m) The members representing as basic medical scientists and clinicians should have Post graduate qualification and adequate experience in their respective fields and aware of their role and responsibilities as committee members.
n) Based on the requirement of research area e.g. HIV, Genetic disorder etc, specific patient group may also be included in the Ethics Committee as far as possible.
o) There should be no conflict of interest. The members shall voluntarily withdraw from the Ethics Committee while making a decision on an application which evokes a conflict of interest which should be indicated in writing to the Chairperson prior to the review and should be recorded so in the minutes.
p) Subject experts or other experts may be invited to the meetings for their advise but would not be having any voting rights.

7- Information required to be submitted by the applicant for registration of Ethics Committee:

e. Name of the Ethics Committee
f. Authority under which the Ethics Committee has been constituted, membership requirements, the term of reference, conditions of appointment and the quorum required.
g. The procedure for resignation, replacement or removal of members.
h. Address of the office of the Ethics Committee.
e. Name, address, qualification, organizational title, telephone number, fax number, e-mail, mailing address and brief profile of the Chairperson.
f. Names, qualification(s), organizational title, telephone number, fax number, e-mail and mailing address of the members of Ethics Committee. The information should also include members specialty (Primary Scientific or Non-scientific), member's affiliation with institution(s) and patient group representation, if any.
g. Details of the supporting staff.
h. Type of research reviewed by the committee (e.g. pharmaceuticals, devices, epidemiological, retrospective, herbals etc.).
i. Documents reviewed for every clinical trial protocol.
j. Information in respect of number of meetings of the committee and documentation of the minutes of these committees concerning clinical trials:
k. The information regarding review of serious adverse events reported during the conduct of the trial.
l. The Standard Operative Procedures (SOPs) to be followed by the committee in general.
m. Standard Operative Procedures followed by the committee for vulnerable population.
n. Policy regarding training for new and existing committee members along with SOPs.
o. Policy to monitor /prevent the conflict of interest along with SOPs.
p. Has the committee been audited/inspected before? If yes, by whom.
q. If the committee has been audited/inspected before, give details.

8- Maintenance of Record:

All documentation and communication of an EC are to be dated, filed and preserved according to the Standard Operative Procedures (SOPs). Strict confidentiality is to be maintained during access and retrieval procedures. Records should be maintained for the following:

12. The constitution and composition of the Ethics Committee;
13. The curriculum vitae of all the committee members;
14. Standard Operating Procedures (SOPs) of the committee;
15. National and international guidelines;
16. Copies of the Protocol, data collection formats, CRFs, investigational brochures etc. submitted for review;
17. All correspondence with committee members and investigators regarding application, decision and follow up;
18. Agenda of all EC meetings;
19. Minutes of all EC meetings with signature of the Chairperson;
20. Copies of decisions communicated to the applicants;
21. Record of all notification issued for premature termination of a study with a summary of the reasons;
22. Final report of the study including microfilms, CDs and Video-recordings.

All records must be safely maintained after the completion / termination of the study for not less than 5 years from the date of completion or termination of the trial.

5. The Ethics Committee shall be open for inspections by the officers of Central Drugs Standard Control Organization to verify compliance to the requirements of Schedule Y, Good Clinical Practices guidelines and other applicable regulation.

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