MINUTES OF THE 3RD MEETING OF TECHNICAL COMMITTEE HELD ON 29-04-2013 UNDER CHAIRMANSHIP OF DGHS FOR SUPERVISING CLINICAL TRIALS ON NEW CHEMICAL ENTITIES IN THE LIGHT OF DIRECTIONS OF THE HON'BLE SUPREME COURT OF INDIA ON 03.01.2013

Present:

1.	Dr. Jagdish Prasad, Director General of Health Services.	Chairman
2.	Dr. Ranjit Roy Chaudhury, National Professor of Pharmacology, Former Member, BOG – MCI, Y-85, Hauz Khas, New Delhi-110016	Member
3.	Dr. KamlakarTripathi, Prof., Dept. of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005.	Member
4.	Dr. Raju Titus Chacko, Prof. & Head, Dept. of Medical oncology, CMC, Vellore.	Member
5.	Dr. Nandini Kumar, Former Deputy Director General Sr. Grade, Co-Investigator, NIH Bioethics Project, National Institute of Epidemiology, ICMR, Chennai	Member
6.	Dr. Vinod Raina, Prof. & Head, Department of Medical Oncology, AIIMS, Ansari Nagar, New Delhi	Member
7.	Dr. S.N. Gaur, Professor & Head, Dept. of Respiratory, Medicine, VP Chest Institute, New Delhi.	Member

From CDSCO:

1. Dr. G.N. Singh,
   Drugs Controller General (India)

2. Sh. A.K. Pradhan,
   Deputy Drugs Controller (India)

DCG(I) welcomed the members and briefed them about the outcome of the second meeting of the Technical Committee which was held on 25.03.13. The minutes of the second meeting approved by the Chairman were already circulated to the members.

DCG(I) mentioned that the committee in its second meeting decided that only Institutional Ethics Committee would review and accord approval to any clinical trial protocol for the respective Institute. As regards Bioequivalence/ bioavailability (BA/BE) studies conducted in Bioequivalence study centres in various parts of the country, protocols may also be reviewed and approved by the Institutional Ethics Committees of the institutions located in the same area where the bioequivalence study centres are located depending on its scientific feasibility.

Further, the Apex Committee also in its meeting held on 28.03.13 agreed to the recommendations of the Technical Committee for registration of Institutional Ethics Committees as mentioned above and also recommended that the present practice of review and approval of BA / BE study protocols by Independent Ethics Committees should be discontinued within 60 days.

In view of above, presently CDSCO is registering only institutional ethics committees as per newly introduced Rule 122DD.

However, as per existing provisions under the Schedule Y to Drugs and Cosmetics Rules, trial site(s) may accept the approval granted to the protocol by the ethics committee of another trial site or the approval granted by an independent ethics committee (constituted as per Appendix VIII of the schedule), provided that the approving ethics committee(s) is/are willing to accept their responsibilities for the study at such trial site(s) and the trial site(s) is/are willing to accept such an arrangement and that the protocol version is same at all trial sites.

In view of above facts and circumstances, it may not be feasible legally to reject the registration of the Independent Ethics Committees, who fulfill the requirements as per the provision of Drugs and Cosmetics Rules.

The committee after detailed deliberation opined that BA/BE studies of approved drugs are not same as clinical trials of new drugs and agreed that applications for registration of Independent Ethics Committees can also be considered as per the requirements of Rule 122DD and Appendix VIII of Schedule Y to Drugs and Cosmetics Rules. However, these Independent Ethics Committees should be allowed to review and approve only protocols for Bioavailability/ Bioequivalence (BA/BE) studies of approved drug molecules subject to various conditions as specified in the Rules.

Further, these registrations will subject to intense monitoring of these committees by the zonal offices of CDSCO through inspection within 6 to 9 months of the grant of registration to check for the compliance of these committees as per the

requirements. In case of any non-compliance by these committees actions like suspension or cancellation of registration will be undertaken.

DCG(I) apprised the apprised that the details of recommendations of NDACs for approval of 33 global clinical trials for which permissions are yet to be granted by CDSCO were forwarded to the members of committee and sought guidance in the matter. The committee after detailed deliberation recommended for approval of these global clinical trials and opined that DCG(I) shall give approval of these cases after consideration and recommendations from the Apex Committee. However, DCG(I) shall ensure that the clinical trials are conducted only in medical colleges / institutions and not at any private clinics. The committee further recommended that the investigator must obtain approval of such clinical trial protocols from the ethics committee of the same institutes and the ethics committee is registered with DCG(I).

Some member desired that the procedures and requirements followed for approval of new indications / new dosage form / new route of administration etc. shall be made more simplified as compared to the detailed procedures and requirements for approval of clinical trial of new chemical entities / new drug molecules. The committee recommended that a detailed note in this regard may be forwarded by the member to DCG(I) for further consideration.

Committee was also apprised that as decided in the second meetings of Technical Committee as well as Apex Committee, the zonal offices of CDSCO have already been directed to maintain the records of the details of names, qualification etc. of Investigators, and clinical trial sites falling under their jurisdiction and also to constitute Expert Committees for visiting the clinical trial sites at least once in a year to verify the compliance of the Investigators, clinical trial sites as per Schedule-Y of Drugs & Cosmetics Rules, GCP Guidelines and other applicable regulatory requirements. The committee recommended that the zonal offices should submit their reports every 3 months to DCG(I). The zonal office should also be provided with a checklist to be followed by them during such inspections.

Further, the committee was also informed that as decided in earlier meetings, a condition that as and when the Chemical / Biological Entity is approved and launched in other country, the sponsor / applicant should file application for marketing the drug in India also is being stipulated in the clinical trial permissions being given by CDSCO for global clinical trials of NCEs. The applicants are also being asked to give undertaking in this regard at the time of submitting applications.

The committee was apprised about the updated status of evaluation of various applications of new drugs and clinical trials by the twelve New Drugs Advisory Committees (NDACs) as under:-

Out of total 1021 applications received for approval of clinical trials and various categories of new drugs including biological and fixed dose combinations, the NDACs have, so far, evaluated 749 applications in 64 meetings. Out of these 749

applications, 274 were related to approval of Global Clinical Trials (GCTs) including clinical trials of new chemical entities. Of these 274 GCT applications, NDACs after deliberation have recommended for approval of 236 applications and have not recommended for approval in case of the remaining 38 applications.

Since 03.01.2013, CDSCO has received a total of 91 applications for approval of clinical trials and new drugs including biological and fixed dose combinations. Since then the New Drug Advisory Committees have met a total of 17 times and have evaluated 259 proposals of clinical trials and New Drugs. Out of which 43 applications pertain to global clinical trials. Out of these 43 applications of global clinical trials, NDAC has recommended for approval in 38 cases.

The committee noted the above status of evaluation of applications by the NDAC and recommended that the NDACs, constituted on 31.03.2011, should be reconstituted. The members of the committee were requested to forward the names of such experts of various therapeutic areas for induction into the New Drug Advisory Committees.

The committee was informed that as advised by the Apex Committee in its first meeting held on 27.02.2013, the details of clinical trials including study title, sites, investigational product of 145 global clinical trials which were permitted by CDSCO in 2012 have been uploaded on CDSCO website.

Further, the committee was apprised that clearance of a total of 199 proposals for protocol amendments, grant of test license, NOC for export of biological samples and addition of study sites related to global clinical trials approved before 03.01.2013, have been considered and NOCs/Test Licenses granted by CDSCO recently. The committee noted the above cases of NOCs for amendments of protocol, test licenses etc. Committee further opined that processing of such cases be streamlined and NOCs / licenses etc. shall given by CDSCO without referring it to the committee.

The committee was informed that till date, a total of 755 applications for registration of Ethics Committees have been received which includes applications from both Institutional as well as Independent ethics committee. Out of this about 550 applications are from Institutional Ethics Committees and about 200 applications are from Independent Ethics Committees.

So far, CDSCO has processed 295 applications from Institutional Ethics Committees, out of which registration has been granted to 260 Committees and remaining 35 committees have been asked to submit further information.

As regards to examination of Serious Adverse Events (SAEs) of deaths occurring during clinical trials in light of the recent amendments in Drugs & Cosmetics Rules, the three Independent Expert Committees, constituted for the purpose, met on 23.04.2013 to discuss about the modalities to be followed for analysis of SAEs of

deaths including timelines and criteria for determination of quantum of compensation etc. As regards to the timelines required to be followed by the expert committee and DCG(I), the Independent Expert Committee after deliberation recommended that timelines for examination of SAEs of death by the Expert Committee should be extended from the existing one month to three months and the timelines for taking final decision on such cases by CDSCO should be extended from the existing three months to five months due to the detailed procedures like to be followed as under for proper examination of SAE of death to arrive at the cause of death as well as to determine the quantum of compensation in case of trial related deaths.

Timeline for deciding the quantum of compensation

The committee noted and deliberated in detail the process of arriving at compensation related deaths due to Clinical Trials. It was noted that the process essentially involves the following steps.

a. The Causality assessment to be completed by the Investigator and then communicated to the Ethics Committee, Sponsor and the Chairman of the Independent Expert Committee.

b. The detail of Causality Assessment is to be done which is based on the analysis of background of safety profile of drug, temporal relationship of Adverse Drug reactions, and effect of de-challenging if any.

c. Subsequently the causality assessment is to be done independently by the sponsor.

d. The Ethics Committee also to receive the case and give its recommendation about causality assessment and Quantum of compensation in case of clinical trial related deaths.

e. The three stake holders viz; Investigator, Ethics Committee & Sponsor will submit the report to Chairman of Independent Expert Committee. Office of the chairman of the Expert Committee will prepare the individual dossier after giving Unique ID No. The staff of the chairmen if the expert committee will scrutinize available information for completeness and will ask to Investigator, Ethics Committee and Sponsor for additional/ deficient information.

f. Subsequent to this, the case processing will start by the Independent Expert Committee Each case will be circulated to the members of Expert Committee.

g. Depending upon case and the available information, the Chairman may decide to call Principal Investigator for personal appearance in front of Expert Committee if required.

h. It is expected that the case may be finalized in one meeting, if additional information/ Evidence required related to SAE (Death) case by the independent Expert Committee. In such type of circumstances the case may go for Second Meeting for Discussion.

i. Considering all above steps involved in arriving at the conclusion of death related to Clinical Trial and the Quantum of Compensation, the required time to complete the task by Independent Expert Committee should be extended from 30 Days to 90 Days.

j. Accordingly time line for Final decision for Licensing Authority should also be extended from 3 months to 5 months to decide the compensation in SAE (Death) occurred during Clinical trials.

The committee after detailed deliberation recommended that the overall reporting and examination of Serious Adverse Events including deaths occurring during clinical trial and the timelines prescribed in the recently introduced Rules to be followed by the Investigator, Sponsor, Ethics Committee, Independent Expert Committee & the DCG(I) should be placed before the next meeting of Drug Technical Advisory Board for further consideration and recommendation in the matter. Further, committee also recommended that in case of clinical trial related deaths, after establishment of causality analysis by the Independent Expert Committee and DCG(I), such cases shall be placed from time to time before the Technical Committee as well as Apex Committee for further consideration.

Meeting ended with the vote of thanks to the Chair.