MINUTES OF THE 4th MEETING OF TECHNICAL COMMITTEE HELD ON 30-05-2013 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, Chairman
   Director General of Health Services.

2. Dr. Ranjit Roy Chaudhury, Member
   National Professor of Pharmacology,
   Former Member, BOG – MCI,
   Y-85, Hauz Khas, New Delhi-110016

3. Dr. KamlakarTripathi, Member
   Prof., Dept. of Medicine,
   Institute of Medical Sciences, Banaras Hindu University,
   Varanasi – 221005.

4. Dr. Ashok Kumar Das, Member
   Director – Professor of Medicine & Medical Superintendent,
   JIPMER, Puduchery-605006.

5. Dr. P.K. Dalal, Member
   HOD, Dept. of Psychiatry,
   CSMU Medical College, Lucknow.

6. Dr. B.L. Sherwal, Member
   Director-Professor,
   Dept. of Microbiology,
   LHMC & Associated Hospitals, New Delhi.

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 third meeting of the Technical Committee which was held on 29.04.13. The minutes of the third meeting approved by the Chairman were already circulated to the members.

As regards to registration of Independent Ethics Committee, DCG(I) informed that the Apex Committee in its third meeting held on 29.04.13 had agreed to the recommendation of Technical Committee for registration of Independent Ethics Committee subject to the condition that these Independent Ethics Committees should be allowed to review and approve only protocols for Bioavailability/ Bioequivalence (BA/BE) studies of approved drug molecules. Accordingly, office of DCG(I) has started registration of Independent Ethics Committees also.

However, one of the member of the Technical Committee has passed a comment from a legal expert stating that even though there is no distinction between Institutional and Independent Ethics Committees in the D&C Act or Rules, the DCGI in its own wisdom classified the applications for registration into two categories on the basis of the names and started giving registrations separately by inserting a condition that the Independent Ethics Committees shall review only BA/BE study protocols. On the other hand, the DCGI has not clarified what will be the status of the ongoing Phase II, Phase III, and Phase IV trials under review of the Independent Ethics Committees and who will review those protocols in future. It is further stated that whatever may be its title/name, the ethics committees should be treated as one category and their role should be the same. Political/Administrative expediency should not be the sole factor to be taken into account by government/authorities in introducing and enforcing rules in specialized areas where decision making calls for managerial skills with problem-solving approach.

Therefore, the member has opined that the independent ECs should be allowed for continuing review of the ongoing Phase II, III and IV trials till completion because patients being suddenly deprived of the intervention is unethical and the study also goes waste because the plan has been interrupted which could have negative result on the body of the participant and also the results of the study.

The committee deliberated the above issue and recommended that Independent Ethics Committees should be allowed to make periodic review of the clinical trials already approved by them. However, no new clinical trials shall be reviewed and approved by such independent Ethics Committees.

As regards to approval of clinical trials the Committee was apprised that in its third meeting held on 29.04.13 has recommended for 33 global clinical trials which were already recommended by NDACs for approval but yet to be approved by CDSCO. However, Apex Committee in its third meeting held on 29.04.13 and the Apex Committee recommended that details of Investigators and study sites, no. of subjects involved along with details of exemption of requirements as per Drugs & Cosmetics Rules, if any, considered for these 33 cases, should be placed before the Apex Committee for further consideration in the matter. The details of investigator sites, no. of subjects were placed before the committee.

In addition to the above cases the committee was informed that IND Committee in its meeting held on 25.04.13 after deliberation have also recommended for giving approval of 8 clinical trials of INDs subject to certain conditions. The details of recommendations of IND Committee were placed before the Technical Committee.

After deliberation the committee opined that office of DCG(I) should make a format in consultation of the committee members to capture basic information of all clinical trials including global clinical trials, clinical trials of new drugs, biologicals, medical devices, INDs, recommended by NDACs / IND Committee. The format should be made in order to capture the details like name of the drug, therapeutic category, brief of pre-clinical, clinical information, study title, study design, sample size, study site details etc. along with the details of the experts recommended for approval of these trials. Details of all such clinical trials as per the format along with the recommendation of NDACs/ IND Committee shall be placed before the Technical Committee for further action.

With regard to concerns on certain regulatory provisions related to the examination of SAEs and payment of compensation, the Committee was informed that these concerns have been considered and deliberated in the meeting of DTAB held on 16.05.2013. The recommendations of the DTAB would be forwarded to the Ministry of H&F.W. for further necessary action.

The committee was further informed that, the independent Expert Committees constituted for examination of SAEs of death, in their two meetings held on 23.04.2013 and 07.05.2013 have deliberated in details regarding the criteria to be considered for deciding the quantum of compensation in case of clinical trial related deaths and devised a general formula for the purpose.

The Draft Formulae to decide the Quantum of Compensation was deliberated by the Committee as under:-

- That base Amount of Rs.**4 lakhs** may be considered as the compensation for related deaths occurred during Clinical Trial based upon Railway Accident and Untoward Incidences (Compensation) Rules 1990 wherein compensation for death or 100% permanent disability is Rs. 4 Lakhs.

- For Healthy volunteer the compensation in case clinical trial related death, an amount of **Five times of base amount** shall be paid i.e. 4 lakhs x 5 = 20 lakhs.

- For subjects of High Risk, the compensation shall be **half of the base amount** as the life expectancy of subject is less (4 lakhs x 0.5 = 2 lakhs).The high risk group will include those cases where the chance of death is high.

- In case of SAE (death) occurred during clinical trial due to negligence/scientific misconduct/ protocol violation, various options were discussed for deciding the amount of additional compensation to be paid. In case of death of any patients due to administration of spurious/adulterated/substandard, there is a provision of a fine of not less than Rs. 10 lakhs which is paid to the relative of the deceased. Based on similar lines, an additional amount of compensation of not less than Rs. 10 lakhs in case of death of a subject occurs due to negligence/ scientific misconduct/ protocol violation in clinical trial

Accordingly a formula for deciding the quantum of compensation for related deaths occurred during the clinical trial were prepared as under:-

Base Amount		**Healthy Volunteer**		**High risk Subjects/ terminally ill subjects**		**In case of Negligence/mis conduct/protoc ol violation**
4 lakhs	**x**	5 x 4 lakhs of Base Amount =. 20 Lakhs	**x**	0.5 x4 lakhs of base amount = 2 lakhs	**+**	Additional compensation of not less than 10 lakhs

It was considered by the Independent Expert Committee that the above formula is a general guideline and provisionally final for the time being, However the Expert Committee will examine cases of SAEs of deaths and decide the final quantum of compensation after due diligence and application of mind and recommend the same to DCG(I) on case to case basis. However, the final recommendations of the expert committee giving details of the formula are yet to be received.

The Technical committee while agreeing to the formula in general opined that the base amount should be 6 lakhs instead of 4 lakhs. Accordingly, in case of high risk subjects the compensation amount should be 3 lakhs even if a subject dies because of the disease. Therefore, necessary regulatory provisions should be made under the Drugs & Cosmetics Rules so that in case of death of any high risk subject in clinical trial even for the disease itself , compensation of 3 lakhs is paid by the sponsor or his representative conducting the clinical trial in the country.

DCGI informed the committee that with the approval of Ministry of Health & Family Welfare, power has been delegated to DDC(I)s to approve and sign certain licenses / approvals like clinical trial NOCs, import registration, import license, bioequivalence permissions, subsequent new drug approvals etc. Powers for grant of license / approval in respect of other regulatory activities are also being delegated to the next level officers of CDSCO. The Committee opined that if such delegations are allowed under the provision of Drugs & Cosmetics Act and Rules, DCGI may delegate the power to the officers of CDSCO as per the rules. However, DCGI should provide checklists to be followed for reviewing applications for grant of various approvals / licenses under the provisions of Drugs & Cosmetics Act and Rules.

The committee was also apprised about the updated status of evaluation of various applications of new drugs and clinical trials by the twelve New Drugs Advisory Committees (NDACs), payment of compensation in cases of trial related deaths, status of registration of ethics committees, clinical trials site inspection as under:-

- Out of total 1065 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 814 applications in 68 meetings. Out of these 814 applications, 288 were related to approval of Global Clinical Trials (GCTs) including clinical trials of new chemical entities. Of these 288 applications, NDACs after deliberation have recommended for approval of 248 applications and have not recommended for approval in case of the remaining 40 applications.

  Since 03.01.2013, CDSCO has received a total of 119 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 21 times and have evaluated 311 proposals of clinical trials and New Drugs. Out of which 57 applications pertain to global clinical trials. Out of these 57 applications of global clinical trials, NDAC has recommended for approval in 50 cases.

- As regards to status of applications for EC registration it is mentioned that so far a total of 808 applications for registration of Ethics Committees have been received which includes applications from both Institutional as well as Independent ethics committee. Out of this, CDSCO has processed 578 applications, of which registration has been granted to 386 Ethics Committees, rejected in one case and remaining 192 committees have been asked to submit further information.

- Clearance of a total of 203 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 were granted by CDSCO.

- The committee was informed that zonal offices of CDSCO have conducted inspections at various clinical trial sites in the country and submitted the inspection reports to CDSCO. A total of 530 inspection reports have been received by CDSCO which are under examination. So far show cause notices have been issued in 140 cases.

- As regards to payment of compensation in cases of clinical trials related deaths, the committee was informed that out of 89 cases of SAEs of related deaths occurred during clinical trials between January, 2005 to December 2012, payment of compensation has already been made by the companies in 72 cases. In 10 cases, amount has been decided and payments are being made by the companies. Matter is being further pursued with the companies in remaining cases.

Meeting ended with the vote of thanks to the Chair.