

MINUTES OF THE 5th MEETING OF TECHNICAL COMMITTEE HELD ON 01-07-2013 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:

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| 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. Yashpaul Sharma,
Prof. & Head, Dept. of Cardiology,
PGIMER, Chandigarh. | Member |
| 4. | Dr. Rajutitus Chacko,
Prof. & Head, Dept. of Medical Oncology, CMC,
Vellore. | Member |
| 5. | Dr. P.K. Dalal,
HOD, Dept. of Psychiatry,
CSMU Medical College, Lucknow. | Member |
| 6. | Dr. B.L. Sherwal,
Director-Professor,
Dept. of Microbiology,
LHMC & Associated Hospitals, New Delhi. | Member |
| 7. | Dr. Nandini Kumar,
Former Deputy Director General Sr. Grade,
ICMR. | 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 fourth meeting of the Technical Committee which was held on 30.05.13. The minutes of the fourth meeting approved by the Chairman were already circulated to the members.

The details of 49 proposals of clinical trials of new drugs (including INDs, fixed dose combinations, subsequent new drugs, biological), medical devices and global clinical trials as per the format approved by the committee in its fourth meeting were already circulated to the members through e-mail. Further 5 proposals of institutional clinical trials which have also been recommended by the NDAC were also placed before the committee for deliberation. Out of these 54 proposals there were 8 proposals of IND, 27 cases of Global Clinical trials and remaining were clinical trial proposals related to fixed dose combinations, subsequent new drugs, biological and medical devices. List of these proposals is as under:

S.No.	Drug	Applicant	Category
1.	GRC 17536	Glenmark Pharma	IND
2.	Human Monoclonal Antibody on rabies (SIIR Mab)	Serum Institute	IND
3.	Rabies G Protein Vaccine	Cadila Pharma	IND
4.	S0597	Sun Pharma	IND
5.	DRL-17822	Dr. Reddy's Labs	IND
6.	PMZ-2010	Pharmazz India	IND
7.	Endoxifen	Intas Pharma	IND
8.	RBx11160 + PQP	Ranbaxy Labs	IND
9.	Transtuzumab	Roche Scientific	GCT
10.	MV25599 (PegBase)	Roche Scientific	GCT
11.	Exenatide	Parexel	GCT
12.	Belimumab	Parexel	GCT
13.	LY2127399	Parexel	GCT
14.	Mometasone Furoate/Formoterol Fumarate MDI	Covance	GCT
15.	Ceftazidime Avibactam	PPD Pharmaceutical	GCT
16.	Fluticasone + Salmeterol MDI	Parexel	GCT
17.	Tenofovir Disoproxil	KlinEra	GCT
18.	RAD001 (Everolimus)	PPD Pharmaceutical	GCT
19.	Lixisenatide	Sanofi Synthelabo	GCT
20.	Solifenacin Succinate	PPD Pharmaceutical	GCT
21.	Tofacitinib	Pfizer Ltd.	GCT
22.	Fesoterodine	Pfizer Ltd.	GCT
23.	Liraglutide	Novo Nordisk	GCT
24.	AMG 145	Amgen Technology	GCT
25.	Lanthanum Carbonate	ICON	GCT
26.	Vildagliptin	Novartis	GCT
27.	MK 8457	MSD Pharma	GCT
28.	Delamanid	Jubliant	GCT
29.	ART-123	Asiatic Clinical	GCT

		Research	
30.	Human Cell Line Recombinant Factor	Max Neeman	GCT
31.	Octafibrin	Max Neeman	GCT
32.	Evacetrapib	Covance	GCT
33.	Sebelipase Alfa	Clintec (India) International	GCT
34.	Semaglutide	Novo Nordisk	GCT
35.	MK 3415	MSD Pharma	GCT
36.	Pegylated Recobinant Human Erythropoeitin	Intas Pharma	Biological (Recombinant)
37.	Etanercept	Intas Pharma	Biological (Recombinant)
38.	Adalimumab	Cadila Healthcare	Biological (Recombinant)
39.	Tetanus Toxoid Vaccine	Cadila Healthcare	Biological (Vaccine)
40.	Diphtheria & Tetanus Vaccine	Cadila Healthcare	Biological (Vaccine)
41.	Diphtheria, Tetanus and Pertussis Vaccine	Cadila Healthcare	Biological (Vaccine)
42.	Diphtheria, Tetanus Pertussis and Haemophilus Type B conjugate Vaccine	Cadila Healthcare	Biological (Vaccine)
43.	Diltiazem + Lignocaine	Themis Medicare	FDC
44.	Artesunate + Piperaquine Phosphate	Ipca Labs	FDC
45.	Naftopidil + Dutasteride	Intas Pharma	FDC
46.	Tapentadol Hydrochloride Nasal Spray	Torrent Pharma	SND
47.	Lubiprostone	Sun Pharma	SND
48.	On X mechanical heart versus SJM mechanical heart	iProcess Clinical	Medical Device
49.	Simplicity Renal Denervation System	India Medtronic	Medical Device
50.	Levamisole	Dr. H.K. Kar, RML Hospital	Institutional Clinical Trial
51.	Rebamipide	Dr. Radhika Tandon, AIIMS	Institutional Clinical Trial
52.	Primaquine	NIMR	Institutional Clinical Trial
53.	Platelet rich plasma	Dr. Vijay Kumar Jain, RML Hospital	Institutional Clinical Trial
54.	Platelet rich plasma	Dr. P.P. Kotwal, AIIMS	Institutional Clinical Trial

The committee members opined that there are no issues for approval of these proposals. However in some cases only two NDAC members participated in the meeting and recommended for approval. The committee recommended for grant approval of these proposals subject to concurrence of the Apex Committee except those cases which were recommended by two NDAC members only. The committee recommended that the cases recommended by only two members shall be further deliberated by concerned NDACs in their meetings with a proper representation of members during the meeting. Committee also recommended that as and when approval is granted, details of these proposals as per the format should be uploaded on the CDSCO website except those information which the concerned applicant / companies would not like to be disclosed.

The committee further discussed about functioning of NDACs including process of referring the proposals and examination by the NDAC. After discussion the committee recommended that NDACs should be updated as follows:

1. There should be more than one NDAC committee for each of twelve therapeutic areas.
2. Each committee should consist of 15 members including 3 pharmacologists and 12 subject experts.
3. The members to be included in NDAC may be Professor / Associate Prof. / Asstt. Prof. working in government medical colleges / institutions as well as experts from reputed private medical colleges like CMC Vellore, St. John's Medical College known for their integrity.
4. Quorum for NDAC meeting shall be at least 5 members, out of which one should be a pharmacologist.

The committee further recommended that the list of medical college / institutes as above from across the country should be prepared by CDSCO and list of experts from these institutes therapeutic areawise shall also be prepared by CDSCO and forwarded to the Chairman for his consideration. After concurrence of the Chairman the list shall be forwarded to the members of the committee. It was also decided in the meeting that the members shall also forward the list of experts for this purpose.

As regards to the timelines for approval of clinical trials, concerns were raised regarding delay in approval of clinical trials specifically clinical trials of NCEs. The committee recommended that the process of evaluation of clinical trial proposals by NDAC should be streamlined. It should be completed within 6 weeks from the date of receipt of any application.

DCG(I) apprised the members that recently manufacture and marketing of four drugs namely, Dextropropoxyphene, Analgin, Pioglitazone and FDC of Flupenthixol + Melitracen have been suspended in light of the safety and efficacy issues reported and regulatory actions taken by overseas regulatory agencies. The committee

opined that these drugs should be referred to DTAB for examining their safety and efficacy issues. The committee also recommended that the DTAB while examining these drugs may invite subject experts for each drug. For Pioglitazone the committee recommended that DTAB may invite the following experts for deliberation:

1. Dr. Nikhil Tandon, AIIMS, New Delhi
2. Dr. Anoop Mishra, Fortis Hospital, Vasant Kunj, Delhi
3. Dr. V. Mohan, Diabetes Speciality Centre, Hyderabad
4. Dr. M.V. Jali, KLES Prabhakar Kore Hospital, Belgaum

As regards to the draft formulae for compensation, the draft Formula for determining the compensation in case of clinical trial related deaths suggested earlier by the Independent Expert Committee in its meeting held on 07/05/2013 was discussed by the Technical Committee in its 4th Meeting held on 30/05/2013 under the chairmanship of DGHS as well as in the APEX committee meeting held on 31-05-2013 under the Chairmanship of Secretary, Health and Family Welfare.

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 the 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 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.

The apex committee opined that the issue under consideration is the payment of compensation in the case of death related to clinical trial of a subject while death because of disease is a separate issue. The criteria for deciding the compensation in case of trial related deaths should be defined with logical input. The committee however opined that the issue may be further deliberated after receiving the final decision from the independent expert committee in this regards. Committee also desired that guidelines / criteria , if any , followed by other countries for deciding the quantum of compensation in case of the clinical trial related deaths may be looked into while preparing the guidelines in this regards.

In view of above, the criteria for deciding the quantum of compensation is under discussion by the independent Expert Committee and systems/procedures followed in other countries are also being discussed. It was observed that in most of the countries like Belgium, Brazil, France, Italy, Russia, Spain, Czech Republic, Poland, Romania etc. compensation in cases of clinical trial related injury or death is covered through insurance. Before conducting clinical trial in such countries, sponsors are required to take insurance coverage for the trial subjects as per their regulations. However as per the provisions of Drugs & Cosmetics Rules any death related to

clinical trial is entitled for compensation which must be paid by the sponsor or his representative whosoever had obtained permission from DCG (I).The payment of compensation shall be made within the prescribed time line whether it is through sponsor or through any insurance.

Following aspects are under discussion by the independent Expert Committee for framing formula for determining the quantum of compensation:

1. It may be appropriate to consider the age and risk with respect to disease condition of the trial subject.
2. It is noted that The Workmen Compensation Act prescribes the factors (based on age) for calculation of the lump sum amount of compensation to be paid by the employer in case of permanent disablement and death depending upon age of the injured. The factor ranges from 99.37 (for age of 65 or more) to 228.54(of age not more than 16) depending upon the age of the injured. After deliberating the above it was suggested that the same factor may be applied for considering the age of the subject while calculating the amount of compensation in case of clinical trial related death. The base amount of 6 lacs shall be considered for the age of 65 and above and the amount will increase depending on the age as per the factors above.
3. As regards to the risk factor of the subject it was considered that, while deciding for the quantum of compensation a scale of 1, 2, 3 and 4 shall be used for determining the risk factor depending on the seriousness and severity of the disease of the subject at the time of enrollment in the trial. 1 represents high risk (i.e. terminally ill subjects) whereas 4 represent no risk (i.e healthy volunteers).

Accordingly the following formula is being suggested:

$$\text{Compensation} = \frac{B \times F \times R}{99.37}$$

Where,

B = Base amount (i.e. 6 lacs)

F = Factor depending on the age of the subject as per Annexure-A(based on Workmen Compensation Act)

R = Risk Factor depending on the seriousness and severity of the disease of the subject between a scale of 1 to 4 [1 represents high risk (i.e. terminally ill subjects) whereas 4 represent no risk (i.e healthy volunteers).]

The Technical committee took note of the above formula and opined that the base amount should be increased to 10 lakhs so that in most of the cases the compensation amount may vary between 10 to 20/25 lakhs. Further the members also suggested that the risk factors 1, 2, 3 & 4 should be defined in appropriate manner.

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 75 cases. In 9 cases, the amount has been decided and payments by the companies are under process. The matter is being pursued further with the companies in remaining cases for payment of compensation. The committee was further informed that in one case where the whereabouts of the subject could not be traced and the payments could not be made by the company, the Apex Committee in its last meeting has recommended that in such cases the compensation amount should be kept with the institution involved in the clinical trial and not with the company. Accordingly, the company has been directed by DCG(I) to transfer the amount of compensation to the institution.

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 1070 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 124 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 841 applications for registration of Ethics Committees have been

received which includes 650 applications from Institutional and 191 applications from Independent ethics committee. Out of this, CDSCO has granted registration to 413 Institutional Ethics Committees and 76 Independent Ethics Committees. Further, rejection has been issued in 11 cases and 243 ethics committees (150 institutional and 93 independent) have been asked to submit further information.

- Clearance of a total of 223 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 further informed that since 03.01.2013, CDSCO has granted approval for conducting clinical trials in 8 institutional clinical trials applications. These clinical trials are of approved drugs and not new chemical entities.

- 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 574 inspection reports have been received by CDSCO which are under examination. So far show cause notices have been issued in 156 cases. The committee however desired that only those cases where there is major irregularities / discrepancies with respect to subjects rights, safety and well-being should be brought to notice of the committee.

The committee noted the above status report and opined that the above information with respect to approval of institutional clinical trials which are not of any new chemical entities, number of applications and their evaluation by NDAC, number of licenses / protocol amendments etc. granted by CDSCO are general in nature and it may not be required to update the committee every month with respect to the above information.

Meeting ended with the vote of thanks to the Chair.