

**MINUTES OF THE SEVENTH MEETING OF THE APEX COMMITTEE
HELD ON 30-08-2013 UNDER THE CHAIRMANSHIP OF SECRETARY,
HEALTH AND FAMILY WELFARE FOR SUPERVISING CLINICAL
TRIALS ON NEW CHEMICAL ENTITIES IN THE LIGHT OF DIRECTIONS
OF THE HON'BLE SUPREME COURT OF INDIA DATED 03.01.2013**

Present:

1. Shri Keshav Desiraju,
Secretary,
Department of Health and Family Welfare.
2. Dr. V. M. Katoch,
Secretary, DHR & DG ICMR
New Delhi
3. Dr. Jagdish Prasad,
Director General of Health Services,
New Delhi
4. Shri R.K. Jain,
Addl. Secretary & DG (CGHS)
Ministry of Health and Family Welfare
5. Dr. Arun K.Panda
Joint Secretary,
Ministry of Health & Family Welfare
6. Dr. G.N. Singh,
Drugs Controller General (India)

The Apex Committee was apprised that the seventh meeting of the Technical Committee was held on 23.08.2013 under the Chairmanship of DGHS and the committee deliberated on various issues related to approval of various categories of Clinical Trials, formula prepared by the Independent Expert Committee to determine the quantum of compensation in case of clinical trial related death and other issues related to clinical trial.

The minutes of the seventh meeting of Technical Committee were circulated to the members.

The Apex Committee noted that the Technical Committee in its seventh meeting has deliberated the details of 29 proposals of clinical trials of new drugs (including fixed dose combinations, subsequent new drugs, biological), medical devices and global clinical trials. Out of these 29 proposals there were 4 cases of clinical trials of New drugs, 13 cases of Global Clinical trials and remaining were clinical trial proposals related to fixed dose combinations, new claims of approved drugs, biological, medical devices and institutional trial. Details of these 29 cases are placed at ANNEXURE I.

In the case of proposal of clinical trial with Azilasartan (case no. 21 & 22), the Technical Committee had pointed out that there is a washout period of 15 days, where the subjects will not be given any antihypertensive drug. The Technical Committee had recommended that the study should be conducted in first 20 patients in ICU setting. Based on results of 20 patients, the study can be extended on the subjects under OPD setting. The Apex Committee agreed to the recommendation.

The Technical Committee had also pointed out that the Ethics Committees for some of the proposed sites for the clinical trial proposals mentioned at item no. 1, 2, 3, 4, 7, 8, 12, 13 and 20 are Independent Ethics Committees. Clinical trial should not be allowed to be conducted at these sites. The clinical trial sites should be multispecialty hospitals/institutes having emergency facilities and Institutional Ethics Committees registered with CDSCO.

The Apex Committee agreed to the recommendation of the Technical Committee in respect of approval of the 20 cases of clinical trials except the nine proposals mentioned at item no. 1, 2, 3, 4, 7, 8, 12, 13 and 20 as Ethics Committees for some of the sites of these clinical trials are Independent Ethics Committees. For these nine proposals, the applicants should identify clinical trial sites which are multi-speciality hospitals / medical colleges having emergency facilities and Institutional Ethics Committee registered with CDSCO.

The Committee also agreed to the recommendation of the Technical Committee that in case in a meeting of Ethics Committee, if the Chairman is not available, there should be a mechanism of having a Vice-Chairman who can conduct the meeting and discharge the responsibilities of the Chairman. However, such mechanism should be defined by the Ethics Committees in their SOPs. The Apex Committee further recommended that in such a case, the Vice-Chairman should also be from outside the Institute and fulfil the other requirements as per Drugs & Cosmetics Rules.

The Apex Committee also considered the formula prepared by the Expert Committee for the purpose of determining the quantum of compensation to be paid by the Sponsor or his representative in cases of trial related deaths. The committee observed that the Independent Expert Committee under Chairmanship of Dr. Arun Agarwal has submitted the formula to be followed for determining the quantum of compensation in cases of clinical trial related deaths which is as under:

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

Where,

B = Base amount (i.e. 8 Lakh)

F = Factor depending on the age of the subject as per ANNEXURE II (based on Workmen Compensation Act)

R = Risk Factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:

1. 0.50 Terminally ill patient (expected survival not more than (NMT) 6 months)
2. 1.0 Patient with high risk (expected survival between 6 to 24 months)
3. 2.0 Patient with moderate risk
4. 3.0 Patient with mild risk
5. 4.0 Healthy Volunteers or subject of no risk

However, in case of patients whose expected mortality is 90% or more within 30 days, a fixed amount of Rs. 2 Lakh should be given.

The committee observed that while determining the base amount of Rs. 8 lakhs, the Independent Expert Committee has considered that base amount should be such that if the nominee of the subject keeps that amount of compensation in bank by way of fixed deposit, he or she will get an monthly interest amount which is at least approximately equivalent to the minimum wages (reference: Minimum wages of Delhi) of the unskilled workers. The minimum wages of unskilled workers in Delhi as on date is Rs. 7722.00 per month. Accordingly, a base amount (rounded) of Rs. 8.0 lakhs has been considered as appropriate by the Expert Committee. It has also been decided by the Independent Expert Committee that this base amount should refer to the subject's age of 65 years which corresponds to the factor of 99.37 of the table of Workmen Compensation Act. It is evident that the base amount will increase / change with the revision of minimum wage of unskilled workers.

The Committee noted that the Technical Committee has agreed to the above formula. However, the Technical Committee also recommended that amendment in certain clauses of Drugs & Cosmetics Rules related to the payment of compensation in case of injury/death occurring during clinical trial, as recommended by DTAB, should be made expeditiously, so that causality analysis of Serious Adverse Events is done following appropriate criteria and quantum of compensation is decided as per the above formula.

The Apex Committee after detailed discussions also agreed to the formula for determining the quantum of compensation in cases of clinical trial related deaths. The committee also recommended that a separate formula should also be worked out for determining the quantum of compensation in case of clinical trial related injury other than death.

The committee also noted status of various regulatory activities related to clinical trials as under:

1. 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 83 cases. In 2 cases, the amount has been decided and payments by the companies are under process.
2. Clearance of a total of 239 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.
3. 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 577 inspection reports have been received by CDSCO which are under examination. So far notices have been issued in 213 cases seeking clarification.
4. A total of 907 applications for registration of Ethics Committees have been received which includes 667 applications from Institutional and 200 applications from Independent ethics committee. Out of this, CDSCO has granted registration to 463 Institutional Ethics Committees and 95 Independent Ethics Committees. Rejection has been issued in 11 cases. 238 Ethics Committees (153 institutional and 85 independent) have been asked to submit further information.

As regards to the proposed amendments in certain clauses in Drugs & Cosmetics Rules related to examination of Serious Adverse Events in clinical trial and payment of compensation, a comparative table of existing provisions, recommendations of DTAB, recommendations of Ranjit Roy Chaudhary committee and suggested modifications were circulated to the members. It was decided that the said suggestions should be processed for further consideration.

Meeting ended with the vote of thanks to the Chair.

Annexure I

LIST OF 29 CASES OF CLINICAL TRIALS PROPOSALS

S.No.	Drug	Applicant	Category
1.	Empagliflozin	Boehringer	GCT
2.	Empagliflozin + Linagliptin	Boehringer	GCT
3.	Dapagliflozin	Bristol Myers	GCT
4.	MK-0859 (Anacetrapib)	MSD Pharma	GCT
5.	Empagliflozin + Linagliptin	Boehringer	GCT
6.	MK-3102	Parexel	GCT
7.	MK-3102	MSD Pharma	GCT
8.	MK-3102	Parexel	GCT
9.	SAR153191 (Sarilumab)	Sanofi Synthelabo	GCT
10.	SAR153191 (Sarilumab)	Sanofi Synthelabo	GCT
11.	Ixekizumab (LY2439821)	Eli Lilly	GCT
12.	Volasertib	Boehringer	GCT
13.	Nepadutant	Karmic Labs	GCT
14.	Inactivated Japanese Encephalitis Vaccine	Bharat Biotech	Biological (Vaccine)
15.	Measles Vaccine, (Live, Freeze Dried, Single and Multi Dose)	Cadila Healthcare	Biological (Vaccine)
16.	Measles Mumps and Rubella (MMR) vaccine, (Live, Freeze Dried, Single and Multi dose)	Cadila Healthcare	Biological (Vaccine)
17.	Suspension of heat killed (autoclaved) Mycobacterium W	Cadila Pharma	Biological (Vaccine)
18.	Typhoid Vi Polysaccharide –Diphtheria Toxoid conjugate vaccine	Shantha Biotech	Biological (Vaccine)
19.	Pneumococcal polysaccharide conjugate vaccine (adsorbed) 13-valent-Prevenar 13.	Wyeth Ltd.	Biological (Vaccine)
20.	FDC of Silver Sulfadiazine (Nanonized) 0.5%w/w/0.75% w/w + ChlorhexidineGluconate 0.2% w/w Topical Cream	Ranbaxy Labs	FDC
21.	Azilsartan Medoxomil	Synokem Pharma	NDA
22.	Azilsartan Kamedoxomil	Hetero Labs	NDA
23.	Vilazodone Hydrochloride	Hetero Labs	NDA
24.	Meclofenamate Sodium Capsule	Lupin Ltd.	NDA
25.	Combination of Moxifloxacin 400 mg + Rifampicin 600mg + Minocycline 200 mg (MRM)	Dr. H.K. Kar, RML Hospital, Delhi	Institutional
26.	Aceclofenac Gel 5%w/w	Inventia Healthcare	SND
27.	Salbutamol Pressurised Inhalation (100 mcg per actuation) CFC free pMDI.	Glenmark Pharma	SND
28.	Teriparatide	Lupin Ltd.	Biological (Recombinant)
29.	PEG-Filgrastim	GVK Biosciences	Biological (Recombinant)

ANNEXURE - II

Completed years of age on the last birthday of the workman immediately preceding the date on which the compensation fell due		Factor (F)
1	2	
Not more than 16		228.54
17		227.49
18		226.38
19		225.22
20		224.00
21		222.71
22		221.37
23		219.95
24		218.47
25		216.91
26		215.28
27		213.57
28		211.79
29		209.92
30		207.98
31		205.95
32		203.85
33		201.66
34		199.40
35		197.06
36		194.64
37		192.14
38		189.56

39	186.90
40	184.17
41	181.37
42	178.49
43	175.54
44	172.52
45	169.44
46	166.29
47	163.07
48	159.80
49	156.47
50	153.09
51	149.67
52	146.20
53	142.68
54	139.13
55	135.56
56	131.95
57	128.33
58	124.70
59	121.05
60	117.41
61	113.77
62	110.14
63	106.52
64	102.93
65 or more	99.37