MINUTES OF THE 11th MEETING OF THE APEX COMMITTEE HELD ON 24-01-2014 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

The Apex Committee was apprised that 11th meeting of the Technical Committee was held on 15.01.2014 under the Chairmanship of DGHS and the Committee deliberated various issues related to clinical trials. The minutes of the 11th meeting of the Technical Committee were circulated to the members.

The details of the deliberations and recommendations made by the Committee are as under:

1. **Evaluation of 157 Global Clinical Trials as per order of theHon'ble Supreme Court**

   The Committee was informed that out of these 157 cases, 65 trials are ongoing,13 trials have not yet been initiated by the applicants and 39 already completed. Out of the remaining 40 cases, 25 trials have been withdrawn/ discontinued by the respective applicants without any patient enrolment while 15 trials have been terminated /suspended by the respective applicants prematurely, after patient enrolment due to various reasons.

Out of the 157 cases, 50 cases of ongoing trials were evaluated by the Technical Committee in its 10th meeting held on 28.11.13 and Apex Committee in its meeting held on 6.12.13. List of the remaining 107 cases is annexed as **Annexure-I.**

The Apex Committee observed that the Technical Committee has evaluated the remaining 15 cases of the ongoing trials (Sr. No. 1 to 15 in the **Annexure-I**) in detail and recommended that 14 of these 15 cases meet all the requirements of safety and efficacy aspects especially in terms of risk versus benefits to the patients, innovation *vis-a-vis* existing therapeutic options and unmet medical need in the country and these studies should continue. In respect of one case mentioned at Sr. No. 9 in the **Annexure-I,** the Technical Committee has opined that prophylactic anti TB treatment is acceptable. However, empiric treatment with anti-TB drugs in HIV patients may not be justified, given the risk *vs.* benefit to the patients. Therefore, theTechnical Committee has recommended that the report of the Data Safety Monitoring Board (DSMB) for this trial shall be submitted to the Technical Committee for evaluation. Till such time the DSMB report is evaluated by the Committee, there should be no further enrolment of any new subject in this trial. However, the trial should continue with the subjects already recruited in the study.

The Apex Committee agreed to the above recommendations of the Technical Committee. The Committee further recommended that the applicant should also be asked to submit evidence to show that the empiric TB treatment in patients with advanced HIV disease with no probable or confirmed TB will reduce the early mortality of such patients and information that the post mortem reports of such patients who died, have shown that the deaths have occurred due to extensive TB.

The Committee also noted that the Technical Committee has evaluated the 13 cases which have not yet been initiated by the respective applicants (Cases mentioned at Sr. No. 70 to 82 of the **Annexure-I**) and recommended that except one case mentioned at Sr. No. 76, all other 12 cases meet all the requirements of safety and efficacy particularly in terms of assessment of risk versus benefit to the patients, innovation vis-a-vis existing therapeutic option and unmet medical need in the country. The case at Sr. No. 76 is the same study as mentioned in Sr. No. 9 of annexure-I, permitted to different applicant. The recommendation made by the committee in respect case at Sr. No. 09 above is applicable for the case mentioned at Sr. No. 76 also.

The Committee agreed to the above recommendations of the Technical Committee.

The Committee also noted that remaining 79 cases, of which 39 are already completed, 15 are terminated/ suspended by the applicants and 25 cases are those which have been withdrawn/discontinued by the respective applicants without any patient enrolment have also been evaluated by the Technical Committee. No specific action has been recommended by the Technical Committee for these cases. However, the Committee after detailed deliberation recommended that the respective applicants of the15 terminated/suspended and 25 withdrawn/discontinued cases should be informed by DCGI that the permissions granted to conduct these clinical trials stand "withdrawn" and these studies should not be initiated without prior permission from DCGI.

2. **Evaluation of 36 cases of fresh proposals of clinical trials**

The Committee observed that the Technical Committee in its 11th meeting has evaluated 36 cases of fresh proposals of clinical trials keeping in view the risk versus benefit to the patients, innovation *vis-a-vis* existing therapeutic option and unmet medical need in the country. These cases have already been recommended by the NDACs. The lists of these cases are annexed as **Annexure II.** The recommendations of the Technical Committee in respect of these 36 proposals are as under:

- In cases of proposals at Sr. No. 1, 2, 7, 8, 9, 10, 12, 15, 17, 30, 31 & 36, the Committee observed that there was no Pharmacologist present during NDAC meetings when these proposals were evaluated. The Committee, therefore, recommended that these proposals should be evaluated by the NDACs in their meetings with proper representation of members including at least one Pharmacologist in each meeting.

- In case of the proposal at Sr. No. 14, the Committee noted that there is no Govt. clinical trial site included in the study. Therefore, the Committee recommended that there shall be at least 25% Govt. sites in the study.

- For proposal at Sr. No. 16, the Committee recommended that only the reference product should be provided to the patients under the compassionate use stage of the trial and not the test drug.

- In case of proposal at Sr. No. 27 the Committee observed that the trial is proposed to be conducted in children with cerebral palsy. However, there was neither any Pediatrician nor Neurologist, present during the NDAC deliberation. The Committee, therefore, recommended that this proposal shall be again deliberated by the NDAC in its meeting with a proper representation of its members alongwith Pediatrician and Neurologist.

- For remaining 21 cases mentioned at Sr. No. 3, 4, 5, 6, 11, 13, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 32, 33, 34 and 35, the Committee recommended for giving permission to conduct the trials.

The Committee agreed to the above recommendations of the Technical Committee.

3. **Recommendations of the Technical Committee for further strengthening of clinical trials**

The Committee noted that the Technical Committee has recommended certain actions as under to further improve the transparency and accountability in clinical trials.

i) Number of NDACs should be increased from existing 12 to about 50 Committees.
ii) The number of cases that should be evaluated by NDACs in a meeting should not be more then 8 to 10.
iii) As and when required the Chairman of theTechnical Committee shall invite the outside subject experts.

iv) The Sponsor/CRO should put all details of clinical trials being conducted in the public domain.
v) CDSCO should further strengthen the "clinical trial monitoring cell" in its headquarter as well as in Zonal offices.

The Committee while agreeing to the above recommendations in general, opined that NDACs should be gradually increased from existing 12 to 50 and number of cases that should be evaluated by NDACs in a meeting should not be more then 10.

4. <u>Requirements of local clinical trials for approval of New Drugs already approved in other countries</u>

The Committee noted that the Technical Committee in its 11th meeting has discussed the issues related to proposals of approval of new drugs (already approved in other countries) without local clinical trials in the country. There are certain provisions under Drugs and Cosmetics Rules under which requirements of local clinical trials for approval of such new drugs in the country can be waived off. Details are as under:

For new drugs approved in other countries, phase III clinical trial is required before granting permission to manufacture / import of finished formulation of the new drug.

However, requirements of local Clinical Trial may be waived off / relaxed under certain conditions as per Drugs & Cosmetics Rules 122 A (2) ,122 B (3) & clause 1 (3) of schedule-Y as mentioned above depending on nature of drugs and diseases for which it is indicated.

Under Rule-122A(2) & Rule-122B(3) of Drugs & Cosmetics Rules, the requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest, decide to grant such permission on the basis of data available from other countries. Further, the submission of requirements relating to animal toxicology data may also be modified or relaxed under the same Rules in case of new drugs approved and marketed for several years in other countries and adequate published evidence regarding the safety of the drug is available.

As per Clause 1(3) of Schedule Y to Drugs & Cosmetics Rules, for drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.

Parliamentary Standing Committee in its 59threport has raised concerns on approval of certain new drugs in the country without local clinical trials. In light of the same, the Ministry constituted a Committee under the chairmanship of Prof. Ranjit Roy Chaudhury. The Committee has submitted its report. The various

actions to be taken on the recommendations of the Ranjit Roy Chaudhury Committee have been finalized by the Ministry of Health & Family Welfare and the same has already been posted in the CDSCO website. With regard to the waiver of local clinical trial for approval of new drugs, which have already been approved outside India, the Ministry has already decided that such waiver can be considered only in cases of national emergency, extreme urgency, epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy.

The Technical Committee has opined that waiver of local clinical trial for approval of new drugs which have already been approved in other countries can be considered under the above criteria as decided by the Ministry. However, such proposals should be evaluated carefully on case by case basis. If considered necessary by the expert committee in light of risk versus benefits to the patients, innovation *vis-a-vis* existing therapeutic options and unmet medical need in the country, such cases of new drugs may be considered for approval in the country without going through local clinical trials in larger interest of the patients as per these three criteria.

The Committee deliberated on the matter and recommended that waiver of local clinical trial in such cases, should be granted only under the criteria as already decided by the Ministry viz .national emergency, extreme urgency, epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy. In case local clinical trial waiver is required for any other category, the matter should be brought before the Committee for consideration alongwith the recommendations of the Technical Committee.

5. <u>Audio-visual recording of the informed consent process</u>

As regards to audio-visual recording of the informed consent process, the Committee was informed that as per the observation / direction of the Hon'ble Supreme Court on 5 cases of Global Clinical Trials for which approvals were given by DCGI between 03.01.13 to 31.08.13, DCGI vide its order dated 19.11.13, with the approval of the Ministry of Health and Family Welfare, issued directions making audio-visual recording of the informed consent process mandatory in all clinical trials. As per the direction, in addition to the requirements of obtaining written informed consent, audio-visual recording of the informed consent process of each trial subjects, including the procedure of providing the information to the subjects & his/her understanding on such consent is required to be done while adhering to the principles of confidentiality. This is applicable to the new subjects to be enrolled in all clinical trials including Global Clinical Trials. Such audio-visual recording and related documentation would be preserved.

As recommended by the Committee in its 10th meeting held on 06.12.13, draft guidelines were prepared and uploaded on CDSCO website for comments from the stakeholders. A copy of the draft guideline was also placed before the 11th meeting of the Technical Committee held on 15.01.14. The members of the Technical Committee were of the opinion that audio-visual recording of giving detailed information to the subjects as per the elements specified in Appendix-V of Schedule-Y may be a cumbersome procedure. Therefore, the members were of the opinion that, the patients' understanding on the informed consent should be recorded through audio-visual means instead of recording the whole procedure of giving detailed information as well as patients' understanding on the informed consent. However, the Technical Committee recommended that the guidelines should be finalized taking the suggestions/opinions of the stakeholders into consideration.

The Apex Committee noted that audio-visual recording of the informed consent process, for which there are directions of Hon'ble Supreme Court also, has to be undertaken. However, procedure for audio-video recording will be prescribed in the guidelines. Accordingly, the Apex Committee after deliberation recommended that the suggestions/opinions of the stakeholders received on the draft guidelines should be examined by the Technical Committee. The recommendations of the Technical Committee for any changes, if required in the guidelines, should be placed before the Apex Committee for consideration.

6. **To make public the information in respect of financial support, fees, honorarium, payments in kind etc. paid by the Sponsors to the Investigators:**

The Committee was informed that through administrative order vide letter no. DCGI/MISC/2013(107) dated 03.04.13, it has already been decided that the sponsor or his representatives making an application to the office of DCGI for undertaking clinical trial shall also furnish the details of the contract entered by the sponsor with investigator / institutions with regard to financial support, fees, honorarium, payments in kind etc. to be paid to the Investigator. The Committee was informed that proposal for making necessary amendments in the Rules in this regard is under consideration of DTAB.

The Committee after deliberation recommended that to make these information public, these should be posted in the CDSCO website.

The meeting ended with a vote of thanks to and from the Chair.

ANNEXURE- I

S.No.	Drug	Applicant
1.	FST-100 (0.1 %Dexamethasone and 0.6% PVP- Iodine)	Excel life sciences
2.	DE-109 (Sirolimusintraverial formulation)	Excel life sciences
3.	Valacyclovir hydrochloride	Smita N Despande
4.	Vandetanib	Quintiles
5.	BAX326 (Recombinant Factor IX)	Baxter
6.	Polycap [FDC of Simvastatin (40mg) + Ramipril (10mg) + Atenolol (100mg) + Hydrochlorothiazide (25mg) Capsule], low dose aspirin and vitamin D	Cadila
7.	Raltegravir+Lopinavir/Retinovir	YRG
8.	Riyataz+Stocrin+ Truvada+Combivir+Laetra/Aluvia+Norvir+Epzicom+Prezista	YRG
9.	Atripla+Truvada+Emtriva+Vierad+Stocrin	YRG
10.	AMG-785 (Anti-sclerostin monoclonal antibody)	Amgen Technology Pvt. Ltd
11.	CF101	Karmic
12.	Vemurafenib	Roche
13.	nabiximols	PRA
14.	Rindopepimut	Novotech
15.	MEDI-546	Kendle
16.	BUSPIRONE HYDROCHLORIDE TABLETS 5 MG AND 10 MG (App. In INDIA)	Accutest Research Lab
17.	RP5063	Sristek Clinical Research
18.	LA-EP2006 (Pegfilgrastim) and Neulasta	inVentiv
19.	LA-EP2006 (Pegfilgrastim) and Neulasta	inVentiv
20.	Netupitant and Palonosetron	PAREXEL
21.	Trastuzumabemtansine	Roche
22.	NVA237 (Glycopyrronium bromide)	Novartis
23.	NVA237 (Glycopyrronium bromide)	Novartis
24.	QAW039	Novartis
25.	MOMETASONE FUROATE	Novartis
26.	SAR153191(SARILUMAB)	SANOFI
27.	TenofovirDisoproxilFumarate (TDF)	Klinera
28.	AR-12286	MAX NEEMAN
29.	Glimepiride and Metformin	SANOFI
30.	LINAGLIPTIN	Boehringer
31.	Linagliptin and Metformin	Boehringer
32.	Bosentan	Clintec
33.	A-623 (Blisibimod)	Kendle
34.	Fluticasone Propionate/FormoterolFumarate	Kendle

35.	CXA-201 (Ceftolazone) and metronidazole	PRA
36.	Insulin deglutide/Liraglutide	Novonordisk
37.	Biphasic insulin aspart (BIAsp)	Novonordisk
38.	Insulin Degludec/Liraglutide	Novonordisk
39.	LIRAGLUTIDE (Approved in INDIA)	Novonordisk
40.	USL255 (Topiramateexetended release tablet)	PPD
41.	Sitagliptin	MSD
42.	Tafenoquine	GSK
43.	Macitentan	Clintec
44.	PF-04937319	Pfizer
45.	Fesoterodinefumarate (PF-00695838)	Pfizer
46.	PF-04937319	Pfizer
47.	PH 797804	Pfizer
48.	Ranolazine	Klinera
49.	BAX326 (recombinant factor IX)	Baxter
50.	Brinzolamide 10 mg/mL / Brimonidine 2 mg/mL Eye Drops, Suspension	Alcon lab
51.	Starplus™Starch acetate (high amylose maize starch 6% acetate)	Christian Medical College
52.	CD0271 (Adapalene)	CIPD
53.	AUS-131 (S –Equol)	Novotech
54.	BCD-020 (Rituximab)	SMO
55.	DEB025 (Alisporivir)	Novartis
56.	AZD4547	AstraZeneca
57.	Palifosfamide-tris	PPD
58.	Lucanthone	OncoRxPharmaPvt. Ltd
59.	Lurasidone	Quintiles
60.	OPT-822	Clinigene
61.	Preladenant	Fulford
62.	Vernakalant Hydrochloride (MK-6621	MSD
63.	Extended Release Niacin/Laropiprant	Covance
64.	Niacin/Laropiprant	Covance
65.	Tamibarotene	Veeda
66.	BMS-820836 (Liafensine)	BMS
67.	BMS-820836 (Liafensine)	BMS
68.	Teriparatide	Eli Lilly
69.	YKP3089	Quintiles
70.	Kedrion Factor VIII concentrate (EMOCLOT)	MAX Neeman
71.	Sevuparin / DF02	MAX NEEMAN
72.	AR-12286 Ophthalmic Solution,0.5%	MAX NEEMAN
73.	EGT0001442	MAX NEEMAN
74.	Esmolol hydrochloride (Galnobax®)	SIRO
75.	BAX 326 (Recombinant Factor IX)	Baxter
76.	Atripla (r) Drug: EfavirenzDrug: Truvada Drug: Rifampin/isoniazid/pyrazinamide/ethambutol FDC Drug: Rifampin/isoniazid FDC	NARI
77.	SeeMoreTM(EVP 1001-1 Injection)	Kentron

78.	Tenofovir + Emtricitabine + Efavirenz	YRG
79.	Gentian Violet	BJ Medical college/NARI
80.	THR-18 (Tissue plasminogen activator)	Infinitus
81.	nabiximols	PRA
82.	Sitagliptin + Metformin	MSD
83.	CP690,550 F C (Tofacitinib) Tablet	Pizer
84.	CP,690,550 TOFACITINIB	Pizer
85.	Tofacitinib	Pizer
86.	CP-690,550	Pizer
87.	CP-690,550(Tofacitinib)	Pizer
88.	CP-690,550 (Tofacitinib)	Pizer
89.	Oxycodone/Naloxone	Kendle
90.	SOLIFENACIN (approved in INDIA)	PPD
91.	Eltrombopag	GSK
92.	Ofatumumab	GSK
93.	OPC-34712 (Brexspipraezole)	Quintiles
94.	EN3348 (Mycobacterial cell wall DNA complex)	Diagnosearch
95.	Armodafinil (CEP-10953)	inVentiv
96.	Armodafinil (CEP-10953) 50mg uncoated tablet	inVentiv
97.	Recombinant Human Coagulation Factor IX Fusion Protein (rFIXFc)	Biogen Idec
98.	Etanercept	Pfizer
99.	Teriparatide (rDNAorgin) Injection (LY333334)	Eli Lilly
100.	V212 Inactivated Varizella Zoster Virus Vaccine	MSD
101.	Aripiprazole	Covance
102.	Aripiprazole	Covance
103.	BA058 (Teriparatide) for injection 80μg	Pharmanet
104.	BIBW 2992(Afatinib)-20/30/40 mg	Boehringer
105.	BI10773 (Empagliflozin)	Boehringer
106.	DALCETRAPIB	Quintiles
107.	Eprotirome	MED PACE

Annexure-II

Sr. No.	Drug	Names of the Applicant	Division
1.	Treprostinil	PRA. India	GCT
2.	Treprostinil	PRA. India	GCT
3.	SB4 (Proposed Etanercptbiosimilar) or EU Sourced Enbrel	Quintiles Pvt. Ltd	GCT
4.	SB2 (PropsedBiosimilar of Remicade)	Quintiles Pvt. Ltd	GCT
5.	Belimumab	Quintiles Pvt. Ltd	GCT
6.	AIN457 (Secukinumab)	Novartis Healthcare	GCT
7.	Rituximab	Cliantha Research Limited,Ahmedabad	GCT
8.	Afatinib (BIBW 2992)	BoehringerIngelheim India Pvt Ltd.	GCT
9.	Afatinib	BoehringerIngelheim India Pvt Ltd.	GCT
10.	LDK378	Novartis Healthcare	GCT
11.	MasitinibMesylate	Maya Clinicals	GCT
12.	MasitinibMesylate	Maya Clinicals	GCT
13.	BCD-020	CJSC BIOCAD	GCT
14.	Linagliptin	ManipalAcunova limited	GCT
15.	Biochaperone	Virchow Biotech Pvt.	Biological (Recombinant)
16.	Trastuzumab	Cadila Healthcare Limited,	Biological (Recombinant)
17.	Ranibizumab	Novartis Healthcare	Biological (Recombinant)
18.	Albumin	Dr. Kapildevsoni	Biological
19.	Typhoid Vi Capsular polysaccharide- tetanus toxoid conjugative vaccine(TYPBAR-TCV)	Bharat biotech International Ltd.	Biological (Vaccine)
20.	Varicella Vaccine, Live (I.P.)	Bio-Med Private Limited	Biological (Vaccine)
21.	Monovalent Oral Poliovirus Vaccine type 3 (mOPV3) and Azithromycin	Christian Medical College	Biological (Vaccine)
22.	Cyclophosphamide	Dr. Lalit Kumar, AIIMS,	Institutional CT
23.	Bisphosphonate	Dr. SiddharthDubey, AIIMS	Institutional CT

24.	Transarterial Chemoembolization	Dr. Madhusudhan KS	Institutional CT
25.	Probiotic VSL#3	Dr. ArvindSaili, Lady Hardinge Medical College	Institutional CT
26.	Chlorhexidine	Dr. Vinod Kumar Paul, AIIMS	Institutional CT
27.	Tizanidine	Dr. Pratibha.D.Singhi, P.G.I.M.E.R.	Institutional CT
28.	Guaifenesin 600mg Extended Release Bi- layer Tablets.	ManipalAcunova Ltd	SND
29.	Clindamycin phosphate 1.2% and Benzoyl peroxide 5%, topical gel	Cliantha Research Limited	GCT
30.	BepotastineBesilate Ophthalmic Solution	Ajanta Pharma Limited	NDA
31.	Phentermine hydrochloride	Cadila Healthcare Ltd.	NDA
32.	On X Mechanical heart versus SJM Mechanical valve	IProcess Clinical Marketing process Pvt. Ltd	Medical Device
33.	BKM120	Novartis	GCT
34.	Trastuzumab	Biocad	GCT
35.	Bevacizumab	Biocad	GCT
36.	Cyclosporine Ophthalmic Emulsion 0.05 %	AurobindoPharma Ltd.	GCT