MINUTES OF THE 16th MEETING OF THE APEX COMMITTEE HELD ON 08-08-2014 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 Lov Verma,
   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 K.L Sharma
   Joint Secretary, Ministry of Health & Family Welfare

Special Invitee:

1. Shri R.K. Jain,
   Addl. Secretary & DG (CGHS)
   Ministry of Health and Family Welfare
2. Dr. G.N.Singh
   DCG (I), FDA Bhawan, New Delhi

Agenda item 1

1. The Apex Committee adopted the minutes of its 15th meeting.

Agenda item 2

Proposals of Clinical Trials recommended by Technical Committee after recommendations by NDACs/IND Committee

2. The Apex Committee was apprised that the 17th meeting of the Technical Committee has been held on 04.08.14, under the Chairmanship of DGHS, in which the Committee deliberated on the following issues:
   I. Evaluation of 23 clinical trial proposals; and
   II. Correction of typographical error in the minutes of the 14th Apex Committee held on 17.06.2014

3. The minutes of the meeting of the Technical Committee were circulated to the members of the Apex Committee during the meeting. A copy of the minutes of the Technical Committee is at **Annexure-A**. The Apex Committee directed that in future, the agenda papers should be circulated to the Chairman, members and special invitees before the meeting to enable them to peruse the same.

4. The details of the deliberations and recommendations made by the Technical Committee placed before the Apex Committee are as under:

(i) **Evaluation of 23 clinical trial proposals:**

The Technical Committee had deliberated upon the 23 proposals relating to clinical trials which had already been recommended by the NDACs.

(ii) Out of those 23 cases, 13 cases related to global clinical trials/ clinical trials of NCEs and remaining 10 cases related to clinical trials for approval of the New Drugs including fixed dose combination, subsequent new drugs and biological (09 cases of fresh proposal and 01 case of re-deliberation of clinical trial of Subsequent New Drug in which there was no Pharmacologist in the NDAC meetings).

(iii) The Technical Committee had noted that there were several clinical trial proposals concerning the field of Oncology. Since Dr. Raju Titus Chacko who is an oncologist, and some other members were absent due to unavoidable circumstances, the Committee deferred 12 proposals (07 from GCTs/clinical trials of NCEs [proposal No: 01,02,04,08, 09,10 &11 at Annexure–I of the

minutes of the Technical Committee] and 05 from other than GCTs/ clinical trials of NCEs [proposal No: 01,04, 05,06 & 07 at Annexure –II of the minutes]) to next Technical Committee meeting.

(iv) The Technical Committee had evaluated the remaining cases one by one and made recommendations. The Technical Committee evaluated 06 out of the13 cases of global clinical trials/ clinical trials of NCEs considering all aspects of safety and efficacy especially in terms of the three parameters viz. risk versus benefit to the patients, innovation *vis-a-vis* existing therapeutic option and unmet medical needs in the country. After detailed deliberations, out of 06 cases, the Technical Committee had recommended 05 cases for approval. In the remaining case, the Technical Committee had sought certain additional data/ information.

(v) The recommendations of the Technical Committee in respect of these 06 cases are mentioned at proposal No:03,05,06,07,12 &13 of the Annexure-I to the minutes of the Technical Committee**.**

(vi) The Technical Committee also evaluated the 05 out of 10 cases of clinical trial proposals [proposal No: 02,03,08,09 &10 of the Annexure-II of the Technical Committee Minutes] which were other than GCTs/clinical trial of NCEs. After detailed deliberations, out of these 05 cases, the Technical Committee recommended approval of 04 cases as per the recommendation of the NDAC. In the remaining cases, the Technical Committee had sought certain additional data/ information. The recommendations of the Technical Committee in respect of these 05 cases are mentioned at proposal No: 02,03,08,09 &10 of the Annexure-II of the minutes of the Technical Committee**.**

(vii) Thus, Out of total 11 cases, the Technical Committee recommended for approval of 09 cases as per recommendations of the NDAC. In remaining 2 cases, the Technical Committee had sought certain additional data/ information.

5. The Apex Committee after detailed deliberations approved the above recommendations of the Technical Committee.

Agenda item 3

Correction of typographical error in the minutes of the 14th Technical Committee held on 28.04.2014 with respect to proposal of Bevacizumab of M/s Biocon Ltd, protocol No: M100-CC-03-I01 (other than GCT/ NCEs)

6. The Technical Committee in its 14th Meeting held on 28.04.2014 had reviewed the proposal of Bevacizumab of M/s Biocon Ltd, protocol No: M100-CC-03-I01 (other than GCT/ NCEs) and as mentioned in Annexure-II to the aforesaid minutes, it was stated that "The Technical Committee agreed with NDAC opinion. However, the names of the sites where the "Pk-Pd" study will be conducted should be submitted and the PIs in the sites should be medical oncologist".

7. The Apex Committee was informed that inclusion of "Pk-Pd" was a typographical error and had been written inadvertently. It was also informed that the matter had been placed before the Technical Committee which recommended that the word "Pk-Pd" stands deleted from the recommendations from the above referred Annexure to the minutes of the 14th Technical Committee meeting and stands corrected accordingly.

8. The Apex Committee noted this correction and approved the recommendation of the Technical Committee.

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

****

Annexure-A

MINUTES OF 17th MEETING OF THE TECHNICAL COMMITTEE HELD ON 04.08.2014 UNDER THE 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.Nandini Kumar, Former Dy. Director (Sr. Grade) National Institute of Epidemiology, ICMR, Delhi	Member
3.	Dr. B. L Sherwal , DDG (M) & Director – Professor, Dept. Of Microbiology, LHMC & Associate Hospitals, New Delhi	Member
4.	Dr. S.N. Gaur, Prof. & Head, Dept. of Respiratory Medicine, V.P. Chest Institute, New Delhi	Member
5.	Dr. Kamalakar Tripathi Prof. Dept of Medicine, Sciences, BHU, Varanasi	Member
6.	Dr.Nikhil Tandon Prof & Head Dept of Endocrinology and Metabolism, AIIMS, New Delhi	Member

From CDSCO:

1. Dr. G.N. Singh,
   Drugs Controller General (India)
2. Dr.V.G.Somani,
   Joint Drugs Controller (India)
3. Sh. R. Chandrashekar
   Deputy Drugs Controller (India)

1. **Proposals of Clinical Trials recommended by NDAC / IND and earlier proposals where opinion of pharmacologist / expert was needed.**

The Committee deliberated the 23 cases of proposals of clinical trials. These cases have already been recommended by the NDACs.

Out of these 23 cases, 13 cases were proposals of global clinical trials/ clinical trials of NCEs, remaining 10 cases were related to clinical trials for approval of New Drugs including fixed dose combination, subsequent new drugs and biological (09 cases of fresh proposal and 01 cases of re-deliberation of Subsequent New Drugs in which there was no pharmacologist in the NDAC meetings).

The Committee noted that there are several clinical trial proposals pertaining to the field of Oncology. Since Dr. Raju Titus Chacko who is an oncologist and other members were absent due to unavoidable circumstances, the Committee deferred 12 proposals (07 from GCT/NCEs [proposal No: 01,02,04,08, 09,10 &11] and 05 from other than GCT/NCEs [proposal No: 01,04, 05,06 & 07]) to next Technical Committee.

Thereafter, the Committee evaluated the remaining cases one by one and made recommendations. The Committee evaluated the 06 cases of global clinical trials/ clinical trials of NCEs [proposal No: 03,05,06,07,12 &13] considering all aspect of safety efficacy especially in terms of the three parameter viz. risk versus benefit to the patients, innovation *vis-a-vis* existing therapeutic option and unmet medical need in the country. After detailed deliberation, out of 06 cases, the Technical Committee recommended for approval of 05 cases as per recommendations of the NDACs. In the remaining case, the Committee sought certain additional data/ information.

The recommendations of the Committee in respect of these 06 cases [proposal No: 03,05,06,07,12 &13] is enclosed as **Annexure-I.**

The Committee also evaluated the remaining 05 cases [proposal No: 02,03,08,09 &10] which were other than GCT/clinical trial of NCEs. After detailed deliberation, out of these 05 cases, the Technical Committee recommended for approval of 04 cases as per recommendations of the NDACs. In the remaining case, the Committee sought certain additional data/ information.

The recommendations of the Committee in respect of other 05 cases [proposal No: 02,03,08,09 &10] is enclosed as **Annexure-II.**

Out of total 11 cases, the Committee recommended for approval of 09 cases as per recommendations of the NDACs. In remaining 2 cases the Committee sought certain additional data/ information.

2. <u>Proposal for approval of New Drugs Aflibercept and Trastuzumab emtansine with waiver of local clinical trials.</u>

As per the D&C Rules, for new drugs substance 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.

It would be thus observed that there are certain conditions specified in the Drugs & Cosmetics Rules under which the licensing authority may grant permission to manufacture / import of new drugs without local clinical trials.

However, Parliamentary Standing Committee in its 59th report 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 chairmanship of Prof. Ranjit Roy Chaudhury, the Committee submitted its report. The action to be taken on the recommendations of the Expert Committee has been finalized by the Ministry of Health & Family Welfare.

As per the action, “The waiver of Clinical Trial in Indian population for approval of new drugs, which have already been approved outside India, 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 Apex Committee in its meeting held on **24.01.2014** has recommended that waiver of local clinical trial of 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 along with the recommendations of the Technical Committee.

The following 02 new drugs have been recommended by the NDACs for their approval for manufacture/ import for marketing in the country without local clinical trial. Details of recommendations of NDAC for these drugs are as under

Sr. no.	Drug Name	Indication	Recommendations
1.	Aflibercept	For patients with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin containing regimen.	Firm presented that there is an unmet need for this drug. The committee reviewed the presentation made in light of the Action taken report on Prof Ranjit Roy Committee Report and reiterate its previous observations which are as follows: There is an unmet need as a second-linetherapy for metastatic colorectal cancer. The firm has conducted clinical trial in other indications as part of Global clinical trial which showed no difference in the pharmacokinetic parameters in 14 Indian patients and there was no safety issue. Pharmacokinetic data in Indian patients shows that there is no pharmacokinetic difference when compared to Caucasians. The Drug has been found to be effective for the proposed indication as per the data generated in other countries. Committee recommended for import and market subject to condition that firm should conduct a structured India specific Phase IV trial after getting approval by this office
2.	Trastuzumab emtansine	For the treatment of patients with HER2-Positive, unresectable locally advanced or metastatic breast cancer who have received prior treatment with Trastuzumab and a	The proposal for the import and market the Trastuzumab Emtansine has been submitted for NDAC approval with Clinical Trial waiver. TDM 1 is a novel drug indicated for treatment of patients with HER2-Positive, unresectable locally advanced or metastatic breast cancer who have received prior treatment with Trastuzumab and a taxane” which is an

		taxane	unmet need. This drug is approved in 52 countries including countries such as US, Switzerland, Australia, Canada, Japan, Ecuador, Uruguay. Currently there is no standard of care for this condition and there is genuine unmet need. Overall 3000 patients have been exposed to the drug in various clinical trials globally. It shows significant improvement in overall survival. In addition to improving the Progression Free Survival, it also improves the overall survival based on the presentation made by firm. In view of the fact there is no therapy available for this condition and in the interest of public.Committee recommended for the permission to import and market for the subject drug may be given subject to conduct of adequately powdered phase IV clinical trial with a review of data in 2 years. The phase IV protocol should be duly approved by the CDSCO.

The Chairman observed that both the drugs are indicated for the treatment of different types of Cancer. However no Oncologist was present in the meeting. Hence, the Committee deferred the proposal to next Technical Committee.

3. <u>Request from Dr. Sunil M. Jain to revise the essential need of 50 bedded hospitals and consideration of his site, TOTALL diabetes Hormone Institute, Indore, Madhya Pradesh to conduct clinical trials.</u>

Dr. Sunil M. Jain, Managing Director of TOTALL diabetes Hormone Institute, Indore, Madhya Pradesh has requested to revise the essential need of 50 bedded hospitals to conduct a clinical trial and to grant permission for the conduct of clinical trials at their 20 bedded facilities.

The applications for inclusion of the above mentioned site i.e. TOTALL diabetes Hormone Institute, Indore, Madhya Pradesh, was submitted by M/s Novo nordisk india Ltd (the sponsor) to CDSCO for two Global Clinical trials in subjects with Type II Diabetes i.e.

CT/76/13: A trial comparing cardiovascular safety of insulin degludec versus insulin glargagine in subjects with type 2 diabetes at high risk of cardiovascular events.

CT/69/13: Efficacy and safety of Semaglutide once weekly versus Sitagliptin once daily as add on to Metformin and/or TZD in subjects with Type 2 dibetes.

Site details: TOTALL Diabetes Research Hormone Institute, A unit of Diabetes Thyroid Hormone Research Institute Pvt. Ltd, BCM Health Island, PU4, Scheme 54, Behind Prestige Management Institute, Near Bombay Hospital, Indore-452010 (Madhya Pradesh)

The Technical and Apex committee in its meetings dated **23.08.2013 & 30.08.2013** respectively have recommended that for all clinical trials the sites should be multispecialty hospitals with emergency services and having institutional ethics committees.

In compliance with the said requirement CDSCO has included this as one of the conditions of the clinical trial –NOC's and is approving only such sites for the conduct of Global clinical trials, New drug clinical trials, Subsequent new drug trials, FDC clinical trials etc. Sites that are not multi-specialty and that do not have emergency services of their own are not being approved by CDSCO for conducting clinical trial.

In view of the representations made by Dr. Sunil M. Jain, Managing Director of TOTALL diabetes Hormone Institute, Indore, Madhya Pradesh, the matter was put forth to the technical committee experts in the 14th meeting dated **28.04.2014**. The committee after due deliberation did not recommend for the addition of this site under the said studies as the site is having only 20 beds. (Minutes of the meeting attached).

The committee further recommended that the clinical trial sites should have minimum 50 number of beds in the institute/hospital with emergency medical care facility.

Now, Dr. Sunil M. Jain has once again requested to reconsider the proposal.

The Committee recommended that in present circumstances, the status quo shall be maintained with respect to the requirement of 50 bedded hospital with emergency medical care facilities for conducting clinical trial. However, the Committee recommended that an expert Committee comprising of experts from various therapeutic areas viz. two experts each from Medicine, Pharmacology, Oncology, Cardiology, Nephrology and one expert each from Ophthalmology, Dermatology and Endocrinology needs to be constituted to re-examine the issue as to whether, depending on nature of clinical trial in a particular therapeutic area, clinical trial can be allowed to be conducted in Hospitals/Institutes having less than 50 beds with/without emergency facilities. The Committee also opined that the proposed expert Committee may co-opt suitable expert(s) from other discipline as per requirement.

4. <u>Issue of waiver of local clinical trial for the new drugs used in serious & life threatening diseases and diseases of special relevance to Indian health scenario which is already approved in the well developed regulatory countries viz. USA, UK, Canada, Japan & Australia.</u>

In light of observations / recommendations of Parliamentary Standing Committee in its 59threport on approval of certain new drugs in the country without local clinical trials, Ministry of Health and Family Welfare constituted a Committee under Chairmanship of Prof. Ranjit Roy Chaudhury to formulate policy, guidelines on approval of new drugs and clinical trials. The Committee submitted its report to the Ministry in August, 2013.

With regard to the requirement of local clinical trial, the Committee recommended that drugs which are already in the market in well-regulated countries with a good PMS for more than four years, and which have a satisfactory report, may be permitted for direct marketing in India, subject to strict PMS for four to six years or after bridging studies, on a case-by-case basis.

The various actions to be taken on the recommendations of the Ranjit Roy Chaudhury Committee has been finalized by the Ministry. In respect of waiver of local clinical trial for approval of new drugs, which have already been approved outside India, the Ministry has 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**.

In this regard, it is pertinent to mention that in cases of life threatening diseases like Cancer, AIDS etc, where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, it is desirable to expedite the development, evaluation, and marketing of new therapies intended to treat persons especially where no satisfactory alternative therapy exists. In such cases patients / clinicians are generally willing to accept greater risks or side effects from products that treat life-threatening / serious diseases, than they would accept from products that treat less serious illnesses. Further, in such cases, conduct of clinical trial is also a complex, time consuming and costly affairs as such patients requires multiple therapy to manage the disease conditions.

Conducting local clinical trial with new drugs indicated for serious/life threatening diseases like Cancer, AIDS etc which are already approved in other country will not only delay its introduction, but also increase the cost of the new drugs which may not be in the interest of the patients suffering from such diseases especially where no satisfactory alternative therapy exists. Similarly, in case of New Drug indicated for diseases which have special relevance to Indian Health scenario, which are

approved in other country like USA, UK etc conducting local clinical trials will delay the introduction of drug and cost of the drug.

In view of above, CDSCO requested the Ministry of Health & Family Welfare to consider waiver of local clinical trial in case of new drugs indicated for serious/life-threatening diseases and diseases of special relevance to Indian health scenario in addition to the 5 criteria already decided by the Ministry.

In this regard, the Ministry has made following observation:

"DCG (I) has raised a very valid concern affecting the interest of patients at large in the country. With such a cumbersome process of clinical trials on the drugs which are already in use for years in the countries with highly developed regulatory system. We may not achieve anything substantially different from that already achieved in those countries. In light of this, we may consider approving the above proposal. However, the matter being technical, this needs to be discussed in the Technical Committee".

Accordingly, the proposal was placed before theTechnical Committee. The Committee deliberated the issue and agreed with the proposal stating that, this is already provided in the Drugs & Cosmetics rule. However, Committee stated that instead of accepting it, in general, the list of such serious /life threatening diseases and the diseases of special relevance to the Indian Health Scenario, where waiver of local clinical trial for approval of new drugs can be considered, may be developed by the experts.

5. <u>Conversion of status of registered independent ethics committees to institutional for review and approval of Clinical Trials- reg.</u>

CDSCO has registered so far around 790 ethics committees. Around 620 ethics committees are registered as Institutional and around 170 Ethics committees are registered as Independent.

The ethics committees which are constituted by following institutes are registered as Institutional Ethics Committees.

a. Hospital/Medical facilities having emergency management services/ICU
b. Dental Hospital
c. Medical Colleges
d. Research organization such as ICMR, National Labs of the Govt.

The Ethics committees which are not constituted by institutes mentioned above are registered as the Independent Ethics Committees i.e. Ethics committees constituted

by Clinics/OPD facilities/nursing homes having no emergency facilities & private research organizations are registered as Independent Ethics Committees.
Institutional ethics committees are allowed to review and accord its approval to clinical trial protocols.
Independent ethics committees are allowed to review and approve only protocols for Bioavailability/Bioequivalence (BA/BE) studies of approved drug molecules only.

Certain Ethics committees including, Deepak Foundation, CRD Ethics Committee, Manav Independent Ethics Committee, Jyothidev Ethics Committee, FOGS etc which were already registered as Independent Ethics Committees represented to convert their status to Institutional Ethics Committee. In view of various representations, whether the ethics committees constituted by following types of institutes can be given institutional status.

a. EC constituted by institutes like foundations/educational societies/trusts/NGO'S/ pharmacy colleges/ Private research organizations etc. having no medical facilities.
b. EC constituted by diagnostic labs, Pvt. Ltd. /Limited companies. having no medical facilities.
c. Ethics committees constituted by clinics/OPD centres/Day care units/ hospitals having less than 50 beds without multispecialty and emergency facilities but having MOU with other multi-speciality hospitals.

The Committee deliberated the matter in detail and reiterated its earlier recommendations made during its 2nd, 4th , 7th, 14th & 15th meetings**.**

6. <u>Correction in typographical error in the minutes of the 14th Technical Committee held on 28.04.2014 with respect to proposal of Bevacizumab of M/s Biocon Ltd, protocol No: M100-CC-03-I01 (other than GCT/ NCEs)</u>

The Technical Committee in its 14th Meeting held on 28.04.2014 reviewed the proposal of Bevacizumab of M/s Biocon Ltd, protocol No: M100-CC-03-I01 (other than GCT/ NCEs) and as stated in Annexure-II to the aforesaid minutes had recommended that "The Technical Committee agreed with NDAC opinion. However, the names of the sites where the "Pk-Pd" study will be conducted should be submitted and the PI's in the sites should be medical oncologist". In this case "Pk-Pd" was a typographical error and written inadvertently. The matter was placed before the Technical Committee and it was recommended that the word "Pk-Pd" stands deleted from the recommendation and minutes of the 14th Technical Committee meeting stands corrected accordingly.

The Meeting ended with vote of thanks to Chair.

****

Annexure-I

List of 13 cases of global clinical trials/ clinical trials of NCEs along with their evaluations and recommendations of the Technical Committee in its 17th Meeting.

Sr. No.	Drug	Applicant Name	Protocol No	Parameters 1. risk versus benefit to the patients 2. innovation vis-a-vis existing therapeutic option 3. unmet medical need in the country	Recommendations
1.	CT-P10 (Biosimilar Rituximab	PPD	CT-P10 3.3 (Version 1.1)		**Technical Committee Recommendation :** Deferred
2.	CT-P6 (Trastuzumab)	PPD	CT-P6 3.2 (Version 2.0)		**Technical Committee Recommendation :** Deferred

3.	Coagulation Factor VIII Concentrate	CMC Vellore	MUSFIH PRO (Version 1)	**Risk Versus Benefit To The Patients** In light of the fact that this product is already approved for replacement of factor VIII in severe to moderate Haemophilia, the risk vs benefit profile of the drug justifies the conduct of this phase III study. **Innovation Vis-A-Vis Existing Therapeutic Option** The purpose of the study is to assess the effectiveness of prophylactic replacement of lower than 'standard' doses of clotting factor concentrates in children with severe haemophilia A. **Unmet Medical Need In The Country** The study will provide data on prophylactic reduction of bleeding frequency in children with severe hemophilia compared to on demand treatment.	**Recommendation:** The investigator has applied for permission to conduct the clinical trial entitled: an Assessment of the effectiveness of prophylactic replacement of lower than „standard" doses of Coagulation Factor VIII Concentrates (EMOCLOT -1000 IU powder) for infusion in children with severe haemophilia and also to correlate this outcome with the dose of CFC used and evaluate if there is a dose response relationship at these doses. 100 subjects are planned to be enrolled. Patients will be classified into two categories according to age (3-5 and 5-7 years) and also into different groups according to the amount of factor replacement IU/kg/week (<20 iu/kg, 20-40 iu/kg and >40 iu/kg for >45. weeks in a year) and IU/kg/year (500-1000 iu/kg; 1000-1500 iu/kg; 1500-2000 iu/kg; > 2000iu/kg). The study is planned to be conducted in 7 countries which includes Brazil, Malaysia, Iran, Egypt, South Africa, Venenzeula and India NDAC has examined the proposal and recommends approval of the trial subject to fixation of the lower dose / dose range, for each of the groups of EMOCLOT (Factor VIII) for the prophylactic treatment and that the trial is not observational but involves intervention. The revised protocol including the above change to be submitted to CDSCO for approval. **Technical Committee Recommendation :** Recommended for approval as per recommendations of NDAC.

4.	Bosutinib	Wyeth	B1871040 (Dated 25 Feb 2013)		**Technical Committee Recommendation :** Deferred
5.	LY2605541 (Insulin Basal Analog)	Eli Lilly	12R-MC-BIDB (Dated 14-Oct-2013	**Risk Versus Benefit To The Patients** The risk vs benefit profile of the test drug from various preclinical toxicity studies including repeated dose, reproductive toxicity studies, phase I, II clinical studies justify the conduct of the study. **Innovation Vis-A-Vis Existing Therapeutic Option** The test drug has longer half life compared to the existing long acting insulin and its pharmacokinetic profile is not to be influenced by chronic kidney disease and also has low variability in glucose control. The purpose of the study is to compare LY2605541 with insulin glargine as basal insulin treatment in combination with oral anti-hyperglycemia medications in insulin-naïve patients with type 2 diabetes mellitus **Unmet Medical Need In The Country** The test drug may potentially provide an alternate choice for long acting insulin.	**Recommendation:** The risk vs benefit profile of the test drug from various preclinical toxicity studies including repeated dose, reproductive toxicity studies, phase I, II clinical studies justify the conduct of the study. The test drug has longer half life compared to the existing long acting insulin and its pharmacokinetic profile is not to be influenced by chronic kidney disease and also has low variability in glucose control. The test drug may potentially provide an alternate choice for long acting insulin. NDAC Recommended for the conduct of the proposed Clinical Trial Protocol **Technical Committee Recommendation :** Recommended for approval as per recommendations of NDAC.

6.	Semaglutide	Novo Nordisk	NN9535-3625 (Version 2.0)	**Risk Versus Benefit To The Patients** The risk versus benefit profile of the test drug from various preclinical toxicity studies including single- and repeat-dose toxicity, genotoxicity, carcinogenicity, developmental toxicity and phase I, II clinical studies justify the conduct of the study. **Innovation Vis-A-Vis Existing Therapeutic Option** The once weekly administration is expected to improve the treatment compliance significantly and to maintain the optimal glycemic levels. The purpose of the study is to compare efficacy and safety of semaglutide once weekly versus insulin glargine once daily as add on to metformin with or without sulphonyl urea in insulin-naïve subjects with type 2 diabetes." **Unmet Medical Need In The Country** The study drug may provide an alternate option for long acting insulins in patients with Type II diabetes mellitus.	**Recommendation:** The risk versus benefit profile of the test drug from various preclinical toxicity studies including single- and repeat-dose toxicity, phase I, II clinical studies justify the conduct of the study. The purpose of the study is to compare efficacy and safety of semaglutide once weekly versus insulin glargine once daily as add on to metformin with or without sulphonyl urea in insulin-naïve subjects with type 2 diabetes Semaglutide with once weekly dosing may potentially provides an add on therapy for type 2 diabetes mellitus patients. NDAC recommended for the conduct of the trial **Technical Committee Recommendation :** Recommended for approval as per recommendations of NDAC.

7.	MK-3102	MSD	MK-3102-018	**Risk Versus Benefit To The Patients** The risk vs benefit profile of the test drug from various preclinical toxicity studies including repeated dose toxicity studies, phase I, II clinical studies justify the conduct of the study. **Innovation Vis-A-Vis Existing Therapeutic Option** The test drug is a selective DPP-4 inhibitor with pharmacokinetic profile amenable for once weekly human doses. The purpose of the study is to assess cardiovascular outcomes following treatment with the test drug in subjects with type 2 diabetes mellitus. **Unmet Medical Need In The Country** The test drug may potentially benefit type 2 diabetes mellitus patients with cardiovascular complications.	**Recommendation:** The risk vs benefit profile of the test drug from various preclinical toxicity studies including repeated dose toxicity studies, phase I, II clinical studies justify the conduct of the study. The test drug is a selective DPP-4 inhibitor with pharmacokinetic profile amenable for once weekly human doses. The purpose of the study is to assess cardiovascular outcomes following treatment with the test drug in subjects with type 2 diabetes mellitus. The test drug may be more potent than other class of drugs in type 2 diabetes mellitus patients with cardiovascular complications. After detailed deliberation the NDAC opined that the conditions regarding HbA1c, BMI and monitoring of serum calcitonin levels in view of the rational now presented justified. The Committee recommended the conduct of the study with conditions previously recommended regarding 50% govt sites, undertaking to market the drug in India, the Firm also presented the protocol version 5 and 6 , the same were reviewed by NDAC and found to be acceptable except that SAE reporting should meet the requirements of the provisions of D & C act. **Technical Committee Recommendation :** Recommended for approval as per recommendations of NDAC subject to condition that the parameters to be assessed for the cardiovascular outcome are specified under the protocol.
8.	Dasatinib	BMS	CA180226		**Technical Committee Recommendation :** Deferred

9.	BIBW2992(Afatinib)	Boehringer	1200.98		**Technical Committee Recommendation :** Deferred
10.	Trastuzumab emtansine	Roche	TDM4997G/BO25734		**Technical Committee Recommendation :** Deferred
11.	Axitinib	Pfizer	A4061051		**Technical Committee Recommendation :** Deferred

12.	Rifapentine, Isoniazid	BJ Med, YRG, NARI	A5279	**Risk Versus Benefit To The Patients** In light of the fact that the test drugs are already approved for treatment of tuberculosis, the risk vs benefit profiles of the drugs justify the conduct of the study. **Innovation Vis-A-Vis Existing Therapeutic Option** The purpose of the study is to assess ultra-short-course rifapentine/isoniazid for the prevention of active tuberculosis in HIV-infected individuals with latent tuberculosis infection. **Unmet Medical Need In The Country** The study will potentially provide new regimen for treatment of latent tuberculosis infection in HIV-infected individuals.	**NDAC recommendation dated 11.02.2012:-** Proposed study is to compare 4 weeks daily rifapentine/isoniazid regimen to a standard 9 months daily isoniazid for prevention of TB in HIV infected patients without active TB. Committee desires sound justification for thw proposed regimen of Rifapentine/isoniazid in view of recently published articles in NEJM showing efficacy of weekly rifapentine/NH 900mg doses equivalent to 9 months efficacy of daily dose of INH. Compliance issue and post trial cost implementation should also be submitted. **NDAC Recommendation dated 28.092012:-** Data submitted is not adequate to address the following issues:- i) The possibility of increased serious adverse effects of daily dose of Rifapentine vs. once weekly use. ii) PK study has shown that peak conc of rifapentine is associated with better efficacy than increased AUC in daily dose schedule. This also raises doubt about the efficacy of daily dose. Hence committee did not recommend for giving permission to conduct the proposed study. **Technical Committee Recommendation :** The committee opined that the proposal be discussed in the presence of experts Dr. Sarin , Dr. S K Sharma (AIIMS) and Central TB Division. Hence these experts may be invited in the next TC meeting

13.	Octafibrin	M/s Max Neeman Medical Internatio nal Limited	FORMA -02	**Risk Versus Benefit To The Patients** The risk vs benefit profile of the test drug from preclinical single dose toxicity studies and reproductive toxicity study justify the conduct of this study. **Innovation Vis-A-Vis Existing Therapeutic Option** The purpose of the study is to assess the efficacy and safety of test drug in subjects with congenital fibrinogen deficiency Currently available treatments include large volumes of plasma or cryoprecipitant for serious and emergency bleeds as well as in the management of surgical case. **Unmet Medical Need In The Country** Fibrinogen concentrates availability may help in decreasing the volumes to be infused in emergency and serious bleeds	**Recommendation** The risk vs benefit profile of the test drug from preclinical single dose toxicity studies and reproductive toxicity study justify the conduct of this study. The purpose of the study is to assess the efficacy and safety of test drug in subjects with congenital fibrinogen deficiency Currently available treatments include large volumes of plasma or cryoprecipitate for serious and emergency bleeds as well as in the management of surgical case. Fibrinogen concentrates availability may help in decreasing the volumes to be infused in emergency and serious bleeds. NDAC recommended the conduct of phase III study. **Technical Committee Recommendation :** Recommended for approval as per recommendations of NDAC.

Annexure-II

A. List of 10 cases of clinical trial proposals other than GCT/NCE along with evaluations and recommendations of the Technical Committee in 17th Meeting.

Sl No	Drug	Applicant Name	Protocol No	Recommendation
1.	Bevacizumab	M/s Reliance Life Sciences Pvt Ltd		Deferred
2.	Somatropin	M/s Reliance Life Sciences Pvt Ltd	RLS/TP/2012/02	The matter has been deliberated in the Technical Committee and the members agreed to the NDAC recommendation
3.	Glucagon (Synthetic origin) vs Glucagon (r-DNA origin)	M/s Sun Pharmaceutical	GLG_113572_12	The matter has been deliberated in the Technical Committee and the members agreed to the proposal However the Committee recommended that the Exclusion Criteria viz. The subject receiving ACE inhibitors or ARBs should be omitted. Accordingly the revised protocol should be submitted.
4.	Brinzolamide + Timolol	M/s Ajanta Pharma limited		The Committee deferred the proposal and desired to have an opinion of Ophthalmologist.
5.	Brinzolamide + Brimonidine Tartrate	M/s Ajanta Pharma limited		The Committee deferred the proposal and desired to have an opinion of Ophthalmologist.
6.	Rebamipide	Ajanta Pharma Ltd.		The Committee deferred the proposal and desired to have an opinion of Ophthalmologist.

7.	Poly Lactide-co-Glycolic Acid (PLGA)biodegradable, synthetic carrier membrane / LECPLGA50:50P1	M/s LV Prasad Eye Institute	LVPEI-2012-11	The Committee deferred the proposal and desired to have an opinion of Ophthalmologist.
8.	Azilsartan Medoxomil Tablets 40 mg & 80mg.	M/s. MSN Laboratories Pvt. Limited		The Committee recommended for the conduct of the clinical trial subject to the condition that the patients with severe renal impairment should be excluded on the criteria of eGFR instead of Serum Creatinine as proposed in the protocol.
9.	Fenticonazole Nitrate Vaginal Capsules 600 mg	M/s. Glenmark Pharmaceuticals Ltd., 7-D, Atma Ram House,1,, TolstoyMarg, New Delhi,		Recommended for approval as per recommendations of NDAC.
10.	Tioconazole Vaginal Tab. 100 mg.	Precise Chemi pharma Pvt. Ltd.		Recommended for approval as per recommendations of NDAC.