MINUTES OF 20th MEETING OF THE TECHNICAL COMMITTEE HELD ON 19.12.2014 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. Ranjit Roy Chaudhury, National Professor Of Pharmacology, Former Member, BOG-MCI Y-85, Hauz Khas, New Delhi	Member
3.	Dr. Yash Paul, Prof. & Head, Dept. of Cardiology, PGIMER, Chandigarh.	Member
4.	Dr. Rajutitus Chacko Prof & Head, Dept. of Medical Oncology CMC Vellore	Member
5.	Dr. Ashok Kumar Das Director- Professor of Medicine & Endocrinology PIMS, Puduchery	Member
6.	Dr. Nikhil Tandon, Professor, Dept. of Endocrinology & Metabolism, AIIMS, New Delhi	Member

From CDSCO:

1. Dr. G.N Singh
   Drugs Controller General of India
2. Dr.V.G.Somani,
   Joint Drugs Controller (India)

3. Mrs. A Visala
   Deputy Drugs Controller (India)
4. Mrs. Rubina Bose
   Asst. Drugs Controller (India)
5. Mr. Sanjeev Kumar
   Asst. Drugs Controller (India)

Dr. V.G. Somani, JDC (I) welcomed the members on behalf of DCGI and with the permission of the Chairman, initiated the proceeding of the Committee as per the agenda.

The Committee then discussed the clinical trial proposals one by one as under.

1. <u>Proposals of Clinical Trials recommended by SEC / IND.</u>

The Committee deliberated 31 cases related to approval of clinical trials. Out of these 31 cases, 15 cases were related to global clinical trials (GCT) and clinical trials of NCEs. Remaining 16 cases were related to clinical trials for approval of New Drugs including fixed dose combination, subsequent new drugs, Medical Devices and biologicals. Out of these 16 cases, one case was for re-deliberation (S.No 14 of the Annexure-II).

The Committee evaluated the 15 cases related to global clinical trials and NCEs one by one and made recommendations considering all aspects of safety, 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 need in the country. After detailed deliberations, the Committee recommended approval for 14 out of 15 cases. In one case (S.No 12 of Annexure-I), the committee did not recommend for the conduct of the study. The recommendations of the Committee in respect of these 15 cases is enclosed as **Annexure-I.**

The Committee also evaluated the remaining 16 cases which were other than GCT/clinical trial of NCEs. After detailed deliberation, the Committee recommended for approval of 14 out of 16 cases. In one case (S.No 16 of Annexure-II), the Committee noted that it a request by applicant for withdrawal of their application and hence decided that such proposals shall not be placed before Committee and shall be appropriately processed by CDSCO before placing it to the Committee. In another case (S.No.14 of Annexure-II), the Committee has sought some additional information before considering the permission for clinical trial. The recommendations of the Committee in respect of these 16 cases is enclosed as **Annexure-II.**

Out of total 31 cases of clinical trial proposals, the Committee recommended for approval of 28 cases. In one of the remaining 03 cases (S. No. 14 of the Annexure-II), the Committee has sought some additional information. In another case (S. No. 12 of the Annexure-I), the Committee did not recommend for conduct of the study. In case of S. No. 16 of the Annexure-II**,** which is a case of withdrawal of application by the applicant, the Committee did not find the proposal to be appropriate for deliberation in the Technical Committee.

2. Waiver of Clinical Trial in Indian population for approval of new drugs, which have already been approved outside India

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.

Following 05 proposals (04 proposals from New Drug and 01 proposal from Biologicals) have been recommended by the SECs for their approval for manufacture/ import for marketing in the country without local clinical trial. The details of the same alongwith

recommendations of SEC were placed before the Committee for perusal and comments. The recommendations of the Technical Committee is as under:

Sr. no.	Drug Name	Indication	SEC Recommendations
1.	Sofosbuvir	Indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.	**Recommendation**: The Committee noted that Sofosbuvir is currently the only drug which can be safely used in patients with advanced fibrosis, cirrhosis, interferon ineligible and intolerant and an interferon free therapy with efficacy of 60-80%. After detailed deliberation, the Committee recommended for waiver of local clinical trial as per the recommendation of SEC. **SEC Recommendation:** The firm has applied for grant of permission for import and marketing of the drug Sofosbuvir indicated for the treatment of chronic Hepatitis C (CHC) infection as a component of a combination anti-viral treatment regimen with the request for local clinical trial waiver. The proposal was deliberated in a special expert committee meeting in which members of the SEC alongwith other invited experts participated. The Committee noted the following points: The firm presented the data on the efficacy, safety, pharmacokinetics, pharmacodynamic and also regulatory status of the drug in other countries 1. Sofosbuvir is reported to have been marketed in USA, Canada, European Union, Australia etc. 2. The drug is included in the treatment guidelines of USA, Europe, and WHO as a first line therapy. 3. On the whole about 80,000 patients have been treated so far world over. 4. More than 4000 patients have participated in several global clinical trials. 5. The firm informed that their request for break through therapy designation for Sofosbuvir tablet for the treatment of Genotype 1,2,3 chronically infected Hepatitis C virus subject has been considered and approved by USFDA. 6. The efficacy shown is higher than the current drugs used in India. 7. Sofosbuvir is currently the only drug which can be safely used in patients with advanced fibrosis, cirrhosis, interferon ineligible and intolerant and an interferon free therapy with efficacy of 60-80%. **The Committee also noted the following points:** 1. The sub-set analysis of Indian subjects of the 4000 patients participated in different countries is not available. 2. The PSUR report of the drug in the market

			globally was not available. 3. The drug has shown to have potential interaction with Poly-Glycoprotein(PGP) modulating drugs such as anti-tubercular like Rifampicin and anticonvulsants. In clinical trial, patients taking anti-tubercular and anticonvulsant drugs are excluded. The firm was asked to mention contraindication/ caution/ risk minimization plan, if available, when the drug is administered in patients with hepatitis C with tuberculosis and convulsive disorder. 4. The dose titration in subjects with poor renal function should be clearly stated. The Committee deliberated in detail on the above points and recommended that local clinical trial waiver may be granted and the drug may be approved for marketing in the country subject to the condition that a time bound PMS, Phase-IV study should be conducted by the firm for which a protocol etc., should be submitted to the DCG (I) for evaluation.
2.	Enzalutamide	Indicated for the treatment of adult men with metastatic castration resistant prostrate cancer whose disease has progressed on or after Docetaxel therapy.	**Recommendation**: The Committee noted that Enzalutamide 40mg capsule indicated for the treatment of adult men with metastatic castration resistant prostrate cancer whose disease has progressed on or after Docetaxel therapy and there is no similar drug available that act on androgen receptor signaling pathway. After detailed deliberation, the Committee recommended for waiver of local clinical trial as per recommendation of SEC as no other efficacious drug available in this category. **SEC Recommendation:** The firm applied for permission to import and market Enzalutamide 40 mg capsule indicated for the treatment of adult men with metastatic castration resistant prostrate cancer whose disease has progressed on or after Docetaxel therapy. After detailed deliberation, the Committee recommended that as the drug is an orphan drug for the proposed indication and in order not to delay access to a therapy that has been shown to have adequate efficacy and safety and the drug is already approved for marketing in USA, EU and 47 other countries, marketing authorization may be granted with local clinical trial waiver, subject to conduct of a Phase IV clinical trial in appropriate sample size which includes evaluation of the PK parameters in at least 12 patients. The firm should submit protocol for Phase-IV trial and PK study with appropriate sample size.

3.	Vorinostat	Indicated for the treatment of Cutaneous manifestations in patients with cutaneous T-cells lymphoma.	**Recommendation:** The Committee noted that the drug is indicated for the treatment of cutaneous manifestations in patients with cutaneous T-cell Lymphoma (CTCL) which is a serious and life threatening disease for which currently there is no satisfactory therapy. The drug also qualifies under the criteria of orphan drug as the drug is indicated for a rare disease. Therefore, the Committee recommended for waiver of local clinical trial as well as bioequivalence study in Indian subjects as recommended by SEC. **NDAC Recommendation dated 08.12.2012:** T-cell lymphoma is a serious and life threatening disease for which currently there is no satisfactory therapy. Therefore Committee opined that local clinical trial of the drug can be exempted in public interest. However a single dose bioequivalence study comparing Hetero's product with the innovator's product in patients with refractory cancer should be conducted getting protocol etc. approved from DCG (I). If BE result is satisfactory, permission can be granted by DCG (I). **Technical Committee Recommendation dated 15.01.2014** The Committee recommended that the proposal should be forwarded to the NDAC for reconsideration of waiver of local clinical trial in public interest. **SEC Recommendation dated 04.03.2014:** The Committee was informed that Vorinostat inhibits the enzyme activity of histone deacetylase HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II) at nonomolar concentrations (IC50<86 nM). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. In some cancer cells, there is an over expression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the association of acetyl group on the histone lysine residues in an open chromatin structure and transcriptional activation. The Proposal of the firm was placed earlier before the NDAC (Oncology &Hematology) Committee in its meeting held on 08.12.2012. The NDAC noted that T-cell lymphoma is a serious and life threatening disease for which currently there is no satisfactory therapy. Therefore NDAC opined that local clinical trial of the drug can be exempted in public interest. However a single dose

			bioequivalence study comparing Hetero's product with the innovator's product in patients with refractory cancer should be conducted. If BE result is satisfactory, permission can be granted. In view of this recommendation bioequivalence NOC was granted to the firm and the report of the same is awaited. Accordingly, the proposal was deliberated in Technical Committee and Apex Committee in its meeting held on 15.01.2014 and 24.01.2014 respectively. The Technical Committee recommended that the proposal should be forwarded to the NDAC for reconsideration of waiver of local clinical trial in public interest. The Apex Committee has also agreed to the recommendation of the Technical Committee. After deliberation, the Committee noted that the drug is indicated for the treatment of cutaneous manifestation in patients with cutaneous T-cell Lymphoma (CTCL) who have progressive persistent or recurrent disease on or following two systematic therapies which is an unmet need and no effective alternative therapy is available for this rare condition. The drug also qualifies under the criteria of orphan drug as the drug is indicated for a rare disease. In view of this the Committee recommended for the waiver of requirement of local clinical trial as well as bioequivalence study in Indian subjects.

4.	Bedaquiline Tablets 100 mg	Indicated in adults (≥18 years), as part of combination therapy of pulmonary tuberculosis (TB) due to multi-drug resistant (MDR) Mycobacterium tuberculosis	**Recommendation**: The Committee observed that Bedaquiline is approved in US, EU and other major countries. Bedaquiline is indicated for the treatment of pulmonary tuberculosis due to multi-drug resistant Mycobacterium tuberculosis, (MDRTB) for which presently no effective therapy is available in India. MDRTB is a serious life threatening condition with high mortality and it is disease of special relevance to Indian Health Scenario. Therefore, the Committee recommended waiver of local clinical trial at this stage and the approval of the drug Bedaquiline with restriction that it shall be approved for use under RNTCP framework for conditional access through the PMDT program for treatment of MDR-TB patients only. **SEC Recommendation:** The firm presented preclinical and clinical data on the safety and efficacy of the drug and requested for the waiver of requirement of phase-III clinical trial in India. The Committee noted that as part of global clinical trial only 5 patients were enrolled from India. The number of subjects from India was not considered adequate to address the safety concern. The committee therefore did not recommend for the waiver of clinical trial. A meeting was convened by DGHS alongwith TB division on this issue where firm's representatives were present and the firm presented the current status of approval of the drug in other countries based on phase-II data for consideration of approval. As per the minutes of the meeting, one of the action point recommended for early access to the drug was- "DCGI to provide drug approval for Bedaquiline for introduction under RNTCP framework for conditional access through the PMDT program only for treatment of MDR-TB patients, sighting appropriate reason such as unmet need – for lack of therapeutic options in this life threatening condition with high mortality. If need be, DGHS would authorize such special approval".
5.	Recombinant Factor IX concentrate (Rixubis)	Control and prevention of bleeding episodes in adults with Hemophilia B, Perioperative management in adults with Hemophilia B, routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with Hemophilia B. RIXUBIS is not indicated for induction of immune tolerance in patients with	**Recommendations**: The Technical Committee opined that the subject drug falls under the status of orphan drug and there is an unmet need in the country for recombinant Factor IX concentrate which is required for the treatment of Haemophillic patients, therefore marketing authorization may be granted to the firm with waiver of local clinical trial in line with the recommendations of SEC.

		Hemophilia B.	**SEC recommendations:** Committee opined that in view of the fact that there is adequate safety and efficacy data from global clinical trials as well as post marketing use in patients, this drug would qualify as an orphan drug in India and there is an unmet need in the country for Factor IX concentrate, marketing authorization may be given for the drug Recombinant anti Haemophilic Factor IX with a waiver for local clinical trial

3. Other:

a) Re-examination of condition imposed to manufacture the drug Clofarabine of M/s Sandoor in India, as a part of clinical trial waiver agreed for it in light of representation received from the firm.

The Technical Committee in its 11th meeting held on 15.01.2014 has examined the proposal of M/s Sandoor for waiver of local clinical trial for Clofarabine.

After deliberation, the Technical Committee noted that the drug Clofarabine which is indicated for the treatment of patients with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens could be appropriate current third line treatment for the indication. The Committee recommended for giving approval to market the drug in the country subject to the condition that the drug should be manufactured in the country.

This Directorate has received an application where the firm stated that in line with the guidelines issued by Prof. Ranjit Roy Chaudhary Committee, Clofarabine is an appropriate candidate for clinical trial waiver. Since, Clofarabine can be clearly categorized as “orphan drug for rare disease and drug for conditions/disease for which there is no therapy”. Clofarabine has been granted an orphan drug designation for the treatment of pediatric acute lymphoblastic leukemia in US, EU, Australia, South Korea and Japan. Furthermore, the firm has also stated that since the product is an orphan drug and the consumption cannot be more than a few hundred vials a year, hence it is also not feasible to set up manufacturing of this product in India.

Recommendation: The Committee deliberated the issue in detail and opined that the condition to manufacture in India, while agreeing for waiver of local clinical trial, was a suggestive condition. As the consumption cannot be more than a few hundred vials a year, hence firm may be allowed to import and market the drug in the country.

b) Recommendation of Apex Committee regarding placing the proposals of clinical trial related to New Chemical Entities (NCE's) only, before the Technical and Apex Committee and about re-examination of criteria for waiver of local clinical trial by Technical Committee for approval of new Drugs already approved outside India.

In light of Hon'ble Supreme court order dated 03/01/13, wherein it was stated that "clinical trials of new chemical entity shall be conducted strictly in accord with the procedure prescribed in Schedule Y of Drugs & Cosmetics Act, 1940 under the direct supervision of the Secretary, Ministry of Health & Family Welfare, Government of India, the Technical Committee in its meeting dated 27/3/14 has recommended that "the proposals of clinical trials of new chemical entity shall only be placed before the Committee". However, the Apex Committee in its 13th meeting dated 15/4/14 has "opined to maintain status-quo in this regard".

Similarly, while reviewing the criteria for waiver of local clinical trial for the drugs already approved in other countries like USA, UK, Europe, Australia, Technical Committee in its meeting held on 4/8/14, stated that, "this is already provided in the Drugs & Cosmetics Rules. 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".

Now, the Apex Committee in its 18th meeting held on 25/11/14 has recommended regarding these issues as following.

"The Committee desired that the Technical Committee will re-examine the criteria for waiver of local clinical trials in Indian population for approval of new drugs, which have already been approved outside India. Recalling the Supreme Court direction whereunder Secretary, MoHFW was to supervise the clinical trial related to New Chemical Entities, the Committee directed that other cases that do not fall within the scope of the aforesaid directions of the Supreme Court but were being placed before the Technical and Apex Committee to ensure the consistency in decision making, now need not be placed before them in all cases. However, in specific cases, Licensing Authority may place the matter before DGHS for Technical Advice".

Recommendation: The Committee deliberated the issues for consideration of recommendations of Apex committee and suggested that:

1. 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 can be considered, as provided under Drugs and Cosmetics Rules for approval of new drug which are already approved outside India, shall be identified by the NDAC/subject expert committees (SEC) in their respective therapeutic areas, in their forthcoming meetings, in time bound manner. The special agenda for developing such list shall be circulated to all SECs within 7 days by CDSCO and all members shall be requested to finalise the list within 21 days. Thereafter, it shall be placed before technical committee for consideration and finalisation.
2. As regards placement of clinical trial proposals of only New Chemical Entities before Technical and Apex Committee on the basis of directions of Hon'ble Supreme Court , the Technical Committee while considering this recommendations opined that, since Technical Committee is currently reviewing the proposals of subject expert committees nominated as per the recommendations of Ranjit Roy Chaudhury Committee, as a Technical review Committee, the other proposals shall be placed before it as per Prof. Ranjit Roy Chaudhury Committees recommendations.

c) <u>Examination of the proposal of M/s. Edwards Life sciences Pvt. Ltd., Mumbai for the registration and import and market of product i.e., SAPIENT xt-Transcatheter Heart Valve with the Novaflex+ Transfemoral Kit.</u>

M/s. Edwards Life sciences Pvt. Ltd., Mumbai has applied for the Import registration and market of the device i.e., SAPIENT xt-Transcatheter Heart Valve with the Novaflex+ Transfemoral Kit. As similar product is not yet approved, the application of the firm was referred to MDAC Cardiovascular.

The application of the firm was discussed in the MDAC Cardiovascular meeting held on 21.10.2014, wherein the Committee noted that the device is already been approved in various countries i.e., USA, Japan, Canada, EU etc. The data submitted shows that the device is safe & effective for its intended use. However, the Committee recommended to prove the safety & effectiveness of the device in Indian Population, therefore a clinical trial study need to be conducted. The firm is required to submit the clinical trial protocol to DCG (I) for consideration and same would be placed before the Committee for further review and taking further necessary action in the matter.

The firm made representation with additional information and reports to the DGHS which was forwarded to the DCG(I) for further consideration in the Technical Committee. This agenda was forwarded separately by mail to all Committee members. The agenda is placed before the Committee for deliberation.

Recommendation:

The representation of the firm was deliberated by the Committee along with the recommendations of MDAC and the Committee observed that this Trans Catheter Heart Valve System is approved in major countries and such systems are also being used in India. The Committee reviewed the recommendation of the MDAC along with the representation of the applicant and specifically mentioned that the cardiologists and the cardiac surgeons are present today in the Committee and in their opinion this device system can be approved for import & marketing without the requirement of clinical trial in Indian Population , subject to the condition that it shall be used in the cases which are not fit for surgery and in morbid condition on the advice of cardiac surgeon and cardiologists. The Committee also opined that there is unmet need for such devices. However, the Committee recommended that systematic PMS data of first 100 patients shall be generated and submitted to CDSCO along with the periodic safety update review.

The Meeting ended with vote of thanks to Chair.

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Annexure-I

List of 15 cases of Global Clinical Trials/ clinical trials of NCEs along with their evaluations and recommendations of the Technical Committee in its 20th Meeting.

Sr No.	IP	Name of the Firm	PROTOCOL	Parameters 1. risk versus benefit to the patients 2. innovation vis-a-vis existing therapeutic option 3. unmet medical need in the country	Recommendation
1	CSOM230 (Pasireotide)	Novartis	CSOM230B2219	**Risk versus benefit to the patients:** The safety profile of the test drug from various pre-clinical toxicity including single dose, repeat dose, genotoxicity, carcinogenicity, reproductive toxicity and clinical phase I, II studies justify the conduct of the trial. **Innovation vis a vis existing therapeutic option-** The purpose of the study is to investigate the management of Pasireotide induced hyperglycemia with incretin based therapy or Insulin in adult patients with cushing's disease or acromegaly. **Unmet need**- The study may provide additional information on the management of hyperglycemia in Cushing's disease/Paseriotide induce hyperglycemia	**Recommendations**: The Technical Committee recommended for approval as per the recommendation of the SEC **SEC Recommendations:** The applicant has made presentation before the committee. After detailed deliberation the committee recommended the conduct of the trial.
2.	LCI699	Novartis	CLI699C2301	**Risk versus benefit to the patients:** The safety profile of the test drug from various pre-clinical toxicity including single dose, repeat dose, genotoxicity, reproductive toxicity and clinical phase I, II studies justify the conduct of the trial. **Innovation vis a vis existing therapeutic option-** The objective of the study is to evaluate the safety and efficacy of test drug for the treatment of patients with Cushing's disease. **Unmet need-** The test drug may potentially provide an alternative option for the treatment of Cushing's disease.	**Recommendations**: The Technical Committee recommended for approval as per the recommendation of the SEC **SEC Recommendations:** The applicant has made presentation before the committee. After detailed deliberation the committee recommended the conduct of the trial subject to the conditions that

					additional government sites shall be included. Accordingly list of additional govt. sites shall be submitted to this office before approval of the trial.
3.	CSOM230 (Pasireotide)	Novartis	CSOM230B2412	**Risk versus benefit to the patients:** The safety profile of the test drug from various pre-clinical toxicity including single dose, repeat dose, genotoxicity, reproductive toxicity and clinical phase I, II, III studies justify the conduct of the trial. **Innovation vis a vis existing therapeutic option-** This is a roll over phase IV study in patient of cushing's disease who have completed the previous study to assess the continued beneficial effect. **Unmet need-** the test drug may provide a better treatment option for those patients in India.	**Recommendations**: The Technical Committee recommended for approval as per the recommendation of the SEC **SEC Recommendations:** After detailed deliberation the committee recommended the conduct of the trial.
4.	Insulin Detemir (NN304)	Novo Nordisk	NN304-4093	**Risk versus benefit to the patients**: In light of the fact that the test drug is already marketed in India, the established safety profile of the test drug justify the conduct of the study. **Innovation vis a vis existing therapeutic option-** The objective of the study is to compare the efficacy and safety of Insulin Determir versus Insulin Neutral Protamine Hagedron in combination with Metformin and diet or exercise on glycemic control in children and adolescents with type 2 diabetes insufficiently controlled on metformin ± other anti-diabetic drug(s) ± basal insulin. **Unmet need**- The test drug is expected to have less adverse drug reactions.	**Recommendations**: The Technical Committee recommended for approval as per the recommendation of the SEC **SEC Recommendations:** The applicant has made presentation before the committee. After detailed deliberation the committee recommended the conduct of the trial.
5.	NNC0195-0092	Novo Nordisk	NN8640-4054	**Risk versus benefit to the patients:** The safety profile of the test drug from various pre-clinical toxicity including single dose,	**Recommendations**: The Technical Committee

				repeat dose, genotoxicity, reproductive toxicity and clinical phase I studies justify the conduct of the trial. **Innovation vis a vis existing therapeutic option-** The objective of the study is to compare the efficacy and safety of once weekly dosing of test drug with once weekly dosing of placebo and Norditropin Flexpro in adults with growth hormone deficiency for 35 weeks with 53 week extension period. **Unmet need-** The test drug may provide an alternate choice for the management of growth hormone disorder.	recommended for approval as per the recommendation of the SEC **SEC Recommendations:** The applicant has made presentation before the committee. After detailed deliberation the committee recommended the conduct of the trial subject to the conditions that the base line evaluations should be specific and the results are reconfirmed by the sponsor at their central laboratory. Accordingly the firm shall submit undertaking for compliance to the above said recommendations.
6.	Masitinib Mesylate	MAYA CLINICALS	AB12003	**Risk versus Benefit to the patients**- The safety profile of the test drug from various pre-clinical studies including single dose, repeat dose, reproduction and development toxicity, genotoxicity and clinical phase I, I, studies justify the conduct of the study. **Innovation vis a vis existing therapeutic option**- The purpose of the study is to compare efficacy and safety of Masitnib in combination with Docetaxel to placebo in combination with Docetaxel in first line metastatic resistant prostrate cancer. **Unmet need-** The test drug may be an alternative treatment option for treatment of metastatic resistant prostrate cancer.	**Recommendations**: The Technical Committee recommended for approval as per the recommendation of the SEC subject to condition that the oncologist should be part of study team at each of the clinical trial sites. **SEC Recommendations:** After detailed deliberation the Committee recommended that to conduct the trial with proposed protocol.

7.	Masitinib Mesylate	MAYA CLINICALS	AB12005	**Risk versus Benefit to the patients-** The safety profile of the test drug from various pre-clinical studies including single dose, repeat dose, reproduction and development toxicity, genotoxicity and clinical phase I, I, II studies justify the conduct of the study. **Innovation vis a vis existing therapeutic option-** The purpose of the study is to compare as first line therapy efficacy and safety of Masitnib in combination with Gemcitabine, to Gemcitabine in combination with placebo, followed as second line treatment by Masitnib in combination with Folfiri3 versus placebo in combination with Folfiri 3 in the treatment of patients with non resectable locally advanced or metastatic pancreatic cancer. **Unmet need-** The test drug may be an alternative treatment option for treatment of non resectable locally advanced or metastatic pancreatic cancer.	**Recommendations**: The Technical Committee recommended for approval as per the recommendation of the SEC subject to condition that the oncologist should be part of study team at each of the clinical trial sites. **SEC Recommendations:** After detailed deliberation the Committee recommended to conduct the trial with proposed protocol
8.	Masitinib Mesylate	MAYA CLINICALS	AB12006	**Risk versus Benefit to the patients**- The safety profile of the test drug from various pre-clinical studies including single dose, repeat dose, reproduction and development toxicity, genotoxicity and clinical phase I, I, II studies justifies the conduct of the study. **Innovation vis a vis existing therapeutic option**-The purpose of the study is to compare the efficacy and safety of Masitnib in combination with Folfiri (Irinotecan, 5-Fluorouracil and Folinic acid) to placebo in combination with Folfiri in second line treatment with metastatic colorectal cancer. **Unmet need**- The test drug may be an alternative treatment option for treatment of metastatic colorectal cancer.	**Recommendations**: The Technical Committee recommended for approval as per the recommendation of the SEC subject to condition that the oncologist should be part of study team at each of the clinical trial sites. **SEC Recommendations:** After detailed deliberation the Committee recommended to conduct the trial with proposed protocol.

9.	LY2963016 (Long-Acting Basal Insulin Analog)	Eli Lilly	I4L-MC-ABER	**Risk vs Benefit to the patients**: Risk Vs Benefits profile of the test drug from pre-clinical repeated dose toxicity studies and phase I, II clinical study justifies the conduct of study **Innovation vis a vis against existing therapy**: The purpose of the study is comparison of a long acting basal insulin analogue LY2963016 to Lantus in adult patients with type 2 diabetes mellitus. **Unmet need**: Availability of Long acting basal insulin analogue from multisource may potentially benefits Indian patients.	**Recommendations**: The Technical Committee recommended for approval as per the recommendation of the SEC **SEC Recommendations:** After detailed deliberation the committee recommended permission subject to condition that the number of government sites should be increased to 50% of the total number of proposed sites
10.	Labetalol , Nifedipine, Methyldopa	Shuchita Mundle, Government Medical College, Nagpur	4000	**Risk vs Benefit to the patients**: In light of the fact that the test drugs are already approved and marketed in India, justify the conduct of the study. **Innovation vis a vis against existing therapy;** The purpose of the study is to compare the efficacy of oral Labetalol, oral Nifedipine and oral Methyldopa for management of severe hypertension in pregnancy. **Unmet need-** The test drugs may be an alternative option for the management of severe hypertension in pregnancy. The applicant presented that females with severe hypertension and who have not been on antihypertensive therapy for past 24hrs only, will be included in the study.	**Recommendations**: The Technical Committee recommended for approval as per the recommendation of the SEC **SEC Recommendations:** After detailed deliberation committee recommended for the conduct of trial subject to the condition that the hypertensive emergencies should be excluded from the study (i.e. signs of heart failure, CNS complications, no dissection of the aorta.) with the inclusion criteria now presented by the applicant.

11.	Mifepristone and Misoprostol	1) Dr. Suneeta Mittal and 2)Dr Lakhbir Dhaliwal		**Risk vs Benefit to the patients**: In light of the fact that the test drugs are already approved and marketed in India, justify the conduct of the study. **Innovation vis a vis against existing therapy:** The proposed protocol is with Mifepristone and Misoprostol for the termination of pregnancy at 64-140 days of LMP having the primary objective to collect data for registration of a medical abortion regimen, specifically, to investigate whether both 24h and 48h intervals between Mifepristone and Misoprostol give similar expulsion rates, accepting a difference of up to 5% at 24h, to justify the use of both intervals in clinical practice. **Unmet need:** The result of the study may demonstrate that the sequential treatment was significantly better regimen for the termination of pregnancy.	**Recommendations**: The Technical Committee recommended for approval as per the recommendations of the SEC **SEC Recommendations:** The proposed protocol is with Mifepristone and Misoprostol for the termination of pregnancy at 64-140 days of LMP having the primary objective to collect data for registration of a medical abortion regimen, specifically, to investigate whether both 24h and 48h intervals between Mifepristone and Misoprostol give similar expulsion rates, accepting a difference of up to 5% at 24h, to justify the use of both intervals in clinical practice. The study is being sponsored by Concept Foundation. An India specific study of similar medication was conducted previously by investigator (Dr.Lakhbir Dhaliwal). The objective was although different, the result of the study demonstrated that the sequential treatment was significantly better. The committee reviewed the data and

					observed that there was no safety concern when sequential medication was given up to 20 weeks of gestation. **Dr. Lakhbir Dhaliwal and Dr. Suneeta Mittal did not participate in the decision making process**. The other experts agreed with the protocol and recommended to conduct the trial with condition that the investigator (Dr. Lakhbir Dhaliwal) shall submit the authenticated data of previous trial to DCGI office

12	**RP5063**	Accutest	**ARL/14/139 Version 6**	**1. Risk vs. Benefit to the patients** **2. Innovation vis a vis against existing therapy** **3. Unmet need:** The Technical Committee observed that this drug is an NCE being developed for schizophrenia and not approved anywhere in the world. Uptil the applicant has carried out phase-I and phase-II study in capsule formulation. Phase-II study was carried out only in India. Now the proposed study is projected as relative bioavailability (Phase-III) study and going to be carried out only in India on healthy volunteers.	**Recommendations**: The Technical Committee observed that this drug is an NCE being developed for schizophrenia and not approved anywhere in the world. Uptil the applicant has carried out phase-I and phase-II study in capsule formulation. Phase-II study was carried out only in India. Now the proposed study is projected as relative bioavailability (Phase-III) study and going to be carried out only in India on healthy volunteers. Therefore the Committee recommended that the safety and efficacy of tablet dosage form in phase-I and Phase-II is not established. More so it does not appear to be a study for therapeutic equivalence. Therefore directly going to relative bioavailability (Phase-III) studies is not considered rational and appropriate. Hence the proposed relative bioavailability study (Phase-III) in healthy volunteers is not recommended. **SEC Recommendations:**

					During the deliberation the firm clarified that sponsor has carried out phase II study with capsule dosage form however the firm intends to carry out bio-equivalence studies with tablet(15 mg) Vs. two capsules of 10 mg & 5 mg. The objective of tablets is that most of anti-psychotic drug administered as tablet dosage form and this data and the tablet formulation shall be useful for phase III study. Accordingly the firm presented their proposal for BE/BA study and after detailed deliberation the committee recommended to conduct the study, earlier the NDAC has accorded approval of the phase II study with the same drug. However being a NCE this directorate will further seek its approval as whether as new molecule or IND.

13.	Endoxifen, 4-OH-*N*-Desmethyl Tamoxifen	Intas Pharmaceuticals Ltd		**Risk versus benefit to the patients**- Risk versus benefit of the test drug from various preclinical toxicity study including single dose, repeat dose, genotoxicity, fertility & embryo foetal studies, clinical phase I/ II studies justify the conduct of this study. **Innovation vis-à-vis existing therapeutic option-** Endoxifen is an active metabolite of Tamoxifen and reported to be 100-fold more potent than Tamoxifen. Endoxifen is non-cytotoxic agent that has shown to be safe in single and multiple dose studies in human and is bioavailable at therapeutic drug levels when administered orally. **Unmet Need:** The bioavailability of Endoxifen is not dependent upon metabolic pathway and is expected to act in the body in more efficient and potent manner than the parent compound. Endoxifen is likely to address the unmet need of the sizable population of metastatic breast cancer (MBC) patients unable to convert Tamoxifen due to deficiency of CYP2D6 (widely employed both for chemoprophylaxis as well as active treatment) in the body.	**Recommendation**: The Technical Committee recommended for proposal as per the recommendations of the IND **IND Recommendation** The IND Committee after detailed deliberation recommended for granting permission for the study as per submitted protocol.

14.	Evogliptin (DA-1229) tablets 5mg	Alkem Lab		**Risk versus benefit to the patients**- Various preclinical toxicity study including single dose, repeat dose, genotoxicity, etc., clinical phase I (Single Ascending Dose and Multiple Ascending Dose), phase II and the ongoing phase III clinical studies in South Korea justify the conduct of this study. No reports of serious drug reaction reported with this drug during phase-I and phase-II clinical studies reported. **Innovation vis-à-vis existing therapeutic option-** Evogliptin is a DPP-IV inhibitor claimed to show higher potency and more selectivity towards DPP-IV enzyme. Animal and human studies have demonstrated the safety and efficacy of Evogliptin. In animal models the drug has shown the potential to prevent and improve NAFLD & body fat which is highly desirable for any anti-diabetic drug. **Unmet Need:** The test drug may potentially be good anti-diabetic drug and a treatment option for patients who require mono-therapy or combination therapy with no risk of hypoglycemia, the drug may not require modifying the dosage in renal impairment.	**Recommendation**: The Technical Committee recommended for proposal as per the recommendations of the IND. The Committee opined that firm should conduct Phase-II clinical trial in the country. Based on Phase-II clinical trial data permission to conduct Phase-III clinical trial may be granted to the firm. After detailed deliberation, the Committee recommended for giving permission to conduct Phase-II clinical trial in the country subject to following conditions: 1. The study sites should be medical colleges or multispecialty hospitals geographically distributed across the country with emergency facilities, beds more than 50 and Institutional Ethics Committee should be registered with the CDSCO. 2. The dose of phase-II clinical trial should be Evogliptin 5 mg and patients enrolled in the study should be between 18-65 years

					of age. Accordingly revised protocol etc. of phase-II should be submitted to the DCGI. The firm has submitted the revised protocol.

15.	Rabimab	M/s Cadila Healthcare Ltd	Protocol No: Rabimab 1001, version 02 dated28th March 2014.	**Risk vs Benefits ratio the patients** As this is a first in human trial, safety and tolerability yet to be defined for test product, though considered safe on basis of pre-clinical results. The data generated for the safety and tolerability data on this new chemical entity will be helpful for many other people in future. **Innovation *vis-a vis* existing therapeutic options** Rabies in human is characterised by anxiety, hydrophobia, aerophobia, seizures, paresis or paralysis, ultimately followed by coma and death. Once clinical signs manifest the disease is almost i2nvariably 100% fatal. Currently HRIG (Human rabies immune globulin) and ERIG (Equine rabies immune globulin) are widely used. While HRIG is in short supply, ERIG is on the way to be phased out due to reasons associated with good animal ethics. Moreover both products, being of a serum based origin, carry a serious risk of being contaminated with infectious agents. The anti-rabies monoclonal antibody cocktail drug being developed by the firm M/s Zydus Research Center, Cadila Healthcare Ltd. is a unique combination of two murine anti-G monoclonal antibodies (MAbs) selected from a panel of five MAbs shortlisted by WHO from collaborating research centres around the world, that bind to two different epitopes on the G protein expressed on the surface of Rabies virus. From panels of anti-rabies Mabs available through its collaborating centers, WHO had initially selected a smaller panel of five murine anti-G MAbs on the basis of their ability to neutralise a broad range of rabies viruses and their heavy chain isotype, selected to be either IgG1 or IgG2a. From this shortlisted panel of WHO, Zydus selected two monoclonals primarily on the basis of their ability to bind two different epitopes on the G protein, and secondarily on the basis of the phenotypic stability of the clone, ability to grow in bioreactors, ability for scalability of the clone, expression levels of the clone etc. The Zydus cocktail of two MAb was developed with MAb 62-713, targeting the	**Recommendations of SEC:** The Technical Committee recommended for the proposal as per the recommendation of the SEC **Recommendations of NDAC/IND Committee** After detailed delibration the Committee recommended for conduct of part 2 of phase-I/II of the already approved study as per the amended protocol No. Rabimab 1001, version 02, dated 28th March 2014.

				site (III), and M777-16-3 targeting site (II). **Unmet Medical need in the country** Rabies is an acute fatal encephalomyelitis and remains one of the most feared and dreadful zoonotic diseases in the world. According to WHO estimate, Rabies occurs in more than 150 countries and territories. More than 55000 people die off Rabies every year. 40% of people who are beaten by suspected rabid animals are children under 15 years of age. More than 3 billion live in areas in which the disease is an enzootic. Once the clinical signs and symptoms develop, rabies is almost invariably fatal. Zydus will work phase I study in India with primary objective of investigating the safety and tolerability of Zydus Anti-rabies Monoclonal Antibodies (RABIMABS) in healthy adult subjects.	

Annexure-II

List of 16 cases of clinical trial proposals other than GCT/NCE along with evaluations and recommendations of the Technical Committee in 20th Meeting.

Sl No	Name of the Drug	Firm Name	Recommendation
1.	Bepotastine Besilate Tablet 10 mg	M/s. Lupin Limited, Mumbai	The Technical Committee recommended for proposal as per the recommendations of the SEC
2.	Apixaban	Bristol-Myers Squibb India Pvt. Ltd	The Technical Committee recommended for proposal as per the recommendations of the SEC
3.	Botulinum Toxin Type A	Allergan Healthcare India Private Limited	The Technical Committee recommended for conducting Phase-IV clinical trial proposal as per the recommendations of the SEC.
4.	MeRes™ Sirolimus Eluting Bioresorbable Vascular Scaffold System	Meril Life Sciences Pvt. Ltd.	The Technical Committee recommended for proposal as per the recommendations of the SEC
5.	Micra Transcatheter Pacing System	India Medtronic Pvt. Ltd.,	The Technical Committee recommended for proposal as per the recommendations of the SEC.
6.	Ti- 6Al- 4V Grade V Titanium alloy	Prof (Dr.) Mahesh Verma MAMC, Prof (Dr.) Naresh Bhatnagar, IIT, Hauz Khas	The Technical Committee recommended for proposal as per the recommendations of the SEC
7.	SIIL Recombinant Human Erythropoietin (REPOITIN)	Serum Institute of India Limited, Pune	The Technical Committee recommended for proposal as per the recommendations of the SEC.
8.	Adalimumab	Reliance Life Sciences Pvt. Ltd.	The Technical Committee recommended for proposal as per the recommendations of the SEC
9.	Interferon beta-1a	Reliance Life Sciences Pvt. Ltd.	The Technical Committee recommended for proposal as per the recommendations of the SEC

10.	Pegfilgrastim	Reliance Life Sciences Pvt. Ltd.	The Technical Committee recommended for proposal as per the recommendations of the SEC
11.	PEG-EPO (Pegylated Erythropoietin)	Cadila Healthcare Ltd. Ahmedabad	In compliance to the recommendations of SEC deliberation, the firm has submitted the report of the phase I clinical trial (part A) of the study and it was observed that there were no clinically relevant findings from clinical examination and vital signs attributed to the PEGEPO up to1.2 mcg/kg. No death was reported during the study. The firm concluded that PEGEPO has been found safe and well tolerated when administered as single dose up to 1.2mcg/kg in healthy male subjects. This conclusion was found to be acceptable by the technical committee. Therefore the Technical Committee recommended for conducting Part-B of the study as per the recommendations of the SEC.
12.	Teriparatide Injection 0.25 mg/mL	Cliantha Research Ltd, Ahmedabad	The Technical Committee recommended for proposal as per the recommendations of the SEC
13.	Saroglitazar Phase IV Clinical Trial	Cadila Healthcare Ltd. Ahmedabad	The Technical Committee recommended for proposal as per the recommendations of the SEC
14.	Phentermine Hydrochloride (Redeliberation)	Cadila Healthcare Ltd. Ahmedabad	After detailed deliberation, the Technical Committee recommended that the firm should submit the regulatory status of the drug in other countries and names of the countries where the drug is banned with the reasons for banning.
15.	Saroglitazar in Type 2 Diabetes Mellitus Phase III Clinical Trial	Cadila Healthcare Ltd. Ahmedabad	The Technical Committee recommended for proposal as per the recommendations of the SEC.

16.	R-STE-009 (Autologous Cultured Myoblasts)	Reliance Life Sciences Pvt. Ltd.	The committee noted that this is a case of re-deliberation on the conditions imposed by the Technical & Apex committee vide its meeting dated 28-02-2014 & 07-03-2014 respectively, where the firm was asked to submit the details of specialty of investigators involved in the study and also should ensure that there is equal geographic distribution of the centers and the investigators should be from Urology and Gynecology. However the firm has expressed inability to recruit the patients across the country and stated that they are withdrawing the study and requested to Directorate not to process the proposal further. As, in present case, the applicant is requesting for withdrawal of their application, the Committee after deliberation, observed that the proposal is not clear as what for it is placed before Technical Committee. Based on the inputs provided by the CDSCO officials that the applicant is unable to appoint Gynecologist and conduct multi-centric trial, Committee recommended to bring only clear proposal seeking permission for conduct of the trial before the Technical Committee and not the cases of withdrawal of application. It was also opined that the proposals shall be properly processed at CDSCO prior to placing before the Committee.