MINUTES OF 29th MEETING OF THE TECHNICAL COMMITTEE HELD ON 12.10.2015 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, Nirman Bhawan, New Delhi	Chairman
2.	Dr.Rajutitus Chacko, Prof. & Head, Dept. of Medical Oncology, CMC, Vellore	Member
3.	Dr. Yash Paul, Prof. & Head, Dept. of Cardiology, PGIMER, Chandigarh.	Member
4.	Dr. Nandini Kumar, Former Dy. Dire. Gen. Sr. Grade, Adjunct Professor, KMC, Manipal, 5/1 (New) Padmalaye Apt. Chennai.	Member
5.	Dr. B.L. Sherwal, Director, Rajendra Institute of Medical Sciences, Ranchi.	Member

From CDSCO:

1. Dr. V. G. Somani,
   Joint Drugs Controller (I)
2. R. Chandrashekar
   Deputy Drugs Controller (I),
3. Mrs. Annam Visala
   Deputy Drugs Controller (I)
4. Mrs. Rubina Bose
   Deputy Drugs Controller (I)

The Chairman welcomed the members of the meeting and Dr. V. G. Somani, JDC (I) initiated the proceedings of the Committee. Thereafter, the Committee discussed the clinical trial proposals one by one as under:

The Committee deliberated 15 cases related to approval of clinical trials. Out of these 15 cases, 02 cases were related to clinical trials of NCEs, 06 cases were related to global clinical trials (GCT) remaining 7 cases were related to clinical trials for approval of New Drugs, Medical Devices and Biologicals.

1. **Proposals of Clinical Trials of NCEs recommended by SECs / IND.**

The Committee evaluated the 02 cases related to clinical trial of NCEs 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 deliberation, the Committee recommended 02 cases of NCEs. The recommendation of the Committee is enclosed as **Annexure-I.**

2. **Proposals of Clinical Trials of GCT recommended by SECs / IND.**

Thereafter, the Committee evaluated 06 cases related to global clinical trial. After detailed deliberation, the Committee recommended 02 cases and for 02 cases (Sr. No 02 and 04 of **Annexure-II**) the Committee recommended subject to certain condition. Out of remaining 02 cases, one case (Sr. No 03 of **Annexure-II**) the Committee has sought certain clarification and one case (Sr. No 06 of **Annexure-II**), the Committee referred back to the SEC to re-examine the recommendation.
The recommendation of the Committee is enclosed as **Annexure-II.**

3. **Proposals of Clinical Trials other than GCT/ NCEs recommended by SECs / IND.**

The Committee evaluated the 07 cases of other than GCT/clinical trial of NCEs. After detailed deliberation, the Committee recommended for approval of 06 cases out of 07 cases. The remaining case (S. No: 06 of the **Annexure-III),** the Committee deferred the proposal for certain information.
The recommendation of the Committee is enclosed as **Annexure-III.**

Thus, the Committee recommended for approval of 12 cases, out of total 15 cases of clinical trial proposals.

4. **Waiver of Clinical Trial in Indian population for approval of New Drugs and Drugs falling under the category of Medical Devices which have already been approved outside India:**

07 proposals (04 from New Drugs Division, 02 from Biological and 01 from Medical Device) were placed before the Committee for consideration of permission for manufacture/ import for marketing in the country without local clinical trial. Out of these 06 proposals, 02 proposals (S. No 04 and 05 of **Annexure-IV**) have not been recommended by the SEC. However various representations have been received through e-mail from the stakeholders and associations to reconsider the proposal for approval of the drug for import/manufacturing and marketing with waiver of local clinical trial.
The details of recommendations of the Committee along with recommendation of the SEC are annexed at **Annexure-IV.**

5. Others:

a) Re-deliberation of the proposals based on the recommendation of the Committee

a) <u>Name of the Drug</u> : Ulinastatin Injection (50,000 IU/1,00,000 IU)
Name of the Applicant: M/s Lupin ltd.

M/s Lupin Ltd has submitted an application to conduct phase IV clinical trial of the drug Ulinastatin Injection as per the condition imposed by this Directorate while granting permission for manufacturing and marketing of the drug Ulinastatin Injection indicated for the treatment of Sever Sepsis.

Study title: "**A Phase IV, Prospective, Multi-centric, Double-blind, Comparative, Clinical Study To Compare the Efficacy and Safety of Intravenous Ulinastatin versus Placebo adjunct To Standard Supportive Care In Subjects With Severe Sepsis"**

Recommendation of the Technical Committee dated 06.05.2015

The proposal was deliberated upon by the technical Committee in its meeting held on 06.05.2015. After detailed deliberation, the Committee noted that it is not clear in the protocol as what is meant by standard supportive care. Therefore, the Committee recommended that the firm shall clarify it and provide a proper protocol within 15 days from receipt of letter, failing which the marketing authorization which was granted subject to the conduct of phase-IV trial in 200 patients shall be made invalid. Further, whether standard care of treatment will be provided in Placebo arm needs to be clarified. Hence the Committee did not recommend the trial as per protocol submitted.

Accordingly, the firm has submitted the reply in respect of the recommendation of the Technical Committee as follows:

Meaning of standard supportive care: Standard supportive care would be as per recommendations of 'Surviving Sepsis Campaign International Guidelines for Management of Sever Sepsis and Septic Shock: 2012 to which the Indian Society of critical care Medicine is also a signatory. On the basis of this guideline, the firm has included the details in the protocol.
Revised version of protocol: 100 subjects in Group A Ulinastatin will be administered in a dose of 200,000 IU (diluted in 100 ml of 0.9% saline or 5% dextrose) given IV over one hours every 12 hours for 5 days along with standard supportive care
100 subjects in Group B placebo will be administered identical appearing placebo (diluted in 100 ml of 0.9% saline or 5% dextrose) given IV over one hour every 12 hours for 5 days along with standard supportive care

Standard supportive care would be as per recommendations of surviving sepsis campaign international Guidelines for Management of severe sepsis and septic shock: 2012 and standard treatment protocols of individual hospitals

Whether standard care of treatment will be provided in Placebo arm: The firm has confirmed that Standard supportive care will be provided to placebo arm and it will be same as that provided to Ulinastatin arm.

Recommendation of the SEC dated 04.09.2015

The reply of the firm was deliberated upon by the SEC on 04.09.2015 wherein the Committee recommended as under:

" As desired by Technical Committee in its meeting held on 1-5-2015, firm presented the clarification with respect to the concerns raised by Technical Committee . The firm clarified that standard care treatment will be given in both the arms as per guideline: surviving sepsis campaign international Guidelines for Management of severe sepsis and septic shock 2012. Hence the committee recommended for the proposed trial".

Recommendation of the Committee: After detailed deliberation, the Committee recommended the study subject to condition that the phase-IV study should give reasonable evidence of being comparable with phase-III situation.

b) Re-deliberation of the proposal of M/s. Sun Pharma Laboratories Ltd based on the recommendation of the committee.

Name of the drug: Glibenclamide, metformin hydrochloride and voglibose tablets (5 mg + 500 mg + 0.2 mg) and (5 mg + 500 mg + 0.3 mg).

Name and address of the applicant: Sun Pharma Laboratories Limited,
Acme Plaza, Andheri Kurla Road,
Andheri (E), Mumbai – 400059.

The Committee noted that M/s. Sun Pharma Laboratories Ltd. has submitted an application to conduct:-

1) Phase III clinical trial study of FDC Glibenclamide, metformin hydrochloride and voglibose tablets (5 mg + 500 mg + 0.2 mg) and (5 mg + 500 mg + 0.3 mg).

2) Comparative bioavailability study of FDC Glibenclamide, metformin hydrochloride and voglibose tablets (5 mg + 500 mg + 0.3 mg).

Study title: Safety and Efficacy Study of Fixed Dose Combination of Three Antidiabetic Drugs in Comparison to Two Antidiabetic Drugs in Patients with Type 2 Diabetes.

Recommendation of the SEC Dated: SEC (Endocrinology) 19th March 2015.

Firm presented the Phase III clinical trial protocol before the committee. The committee noted that the firm already holds permission to conduct clinical trial with glimepiride + Metformin+ Voglibose. The committee discussed the proposed FDC and opined that the firm may be permitted to conduct proposed CT with the conditions

1. HbA1C level shall be less than 9%
2. The patients with the history of serious hypoglycemia shall be excluded
3. The report of the study shall be presented before the committee before considering for manufacturing and marketing approval."

The above data are as per the revised protocol submitted by applicant (as per SEC recommendations).

Recommendation of the Technical Committee Dated: 23.07.2015.

After detailed deliberation, the Committee was not convinced about the 3 drugs combination. The Committee opined that the firm may be requested to make a detailed presentation before the Committee for further consideration.

Accordingly the firm was requested for detailed presentation before the committee for further consideration.

Recommendation of the Committee: Accordingly the firm gave presentation before the Committee and gave justification for the 3 drugs combinations. After deliberation, the Committee recommended the conduct of the study.

c) Re-deliberation of the proposal of M/s. Cadila Healthcare Limited based on the recommendation of the committee.

M/s Cadila Healthcare Limited has submitted an application for conducting Phase-I clinical trial of the drug **ZYAN1.**

Study Title: A randomized, double-blind, placebo-controlled Phase I clinical study to evaluate the safety, tolerability and pharmacokinetics of ZYAN1, a novel PHD-2 Inhibitor, following oral administration in healthy volunteers. **Protocol No. ZYAN1 1001 Ver. 3.0**

The proposal was deliberated upon by the IND Committee in its meeting held on 06.05.2015. The recommendation of the Committee is as under:

The Committee noted from the firm's presentation that the proposed study is multicentric in Australia and India and the firm has received permission from the regulatory authorities of Australia to conduct the study. After detailed deliberation the Committee recommended the proposed study subject to the following conditions:-

- Study should be conducted under the full time monitoring of a Cardiologist.
- Upper limit of Haemoglobin should be less than 15 g/dL.

- Complete chemical structure should be submitted to CDSCO.
- DSMB should be constituted to monitor the study.

Accordingly, revised protocol etc. should be revised and submitted to DCGI.

Thereafter the firm had submitted the revised protocol and the proposal was deliberated in the 28th Technical Committee meeting held on 23.08.2015.

Recommendation of the Technical Committee: After detailed deliberation, the Committee sought the clarification and presentation on following observation.

1. Animal details indicating the pharmacology and mechanism of action of the NCE are not explained clearly. The details of proof of pharmacological action in the given therapeutic indication, which justify further trials in human, are not given.

2. The hypoxia related disorder which is mentioned as one of the proposed indication is too general and needs to be specified.

Based on the recommendation of the Committee, the firm was asked to present the proposal before the Committee.

Recommendation of the Committee: Accordingly the firm gave presentation before the Committee. After deliberation, the Committee recommended the conduct of the study.

b) Appeal by M/s Sanofi for approval of protocol amendment 2 dated 17th Jan 2014 (Protocol No- MIPO3801011)

1. This Directorate granted permission for "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients with Familial Hypercholesterolemia and Inadequately Controlled Low-Density Lipoprotein Cholesterol" vide CTNOC **dt.19 Sep 2012** to M/s. Sanofi Synthelabo India Ltd., Mumbai-400 093.

2. Application for approval of Protocol Amendment 01 dt.18.07.2013 was submitted to this office on 06.09.2013 which mainly included the **addition of 12 month open label continuation period option for all patients who complete the 60 week blinded treatment period and primary endpoint assessment.**

NDAC Recommendation: The proposal was deliberated on NDAC meeting (Cardiology and Renal) held on 28.05.2014. The committee reviewed and opined that there is an unmet need for this condition and recommended the approval of the said amendment 01.

Technical and Apex Committee Recommendation: The proposal was further deliberated in 16th Technical Committee meeting held on 10.07.2014 and 15th Apex Committee held on 15.07.2014 wherein the proposed amendment was approved with a condition that if the

subjects in the placebo arm are found refractory to standard of care after 03 months, they should be withdrawn.

The Protocol Amendment 01 dt.18.07.2013 was approved with the above condition vide letter dt.13.08.2014.

3. Application for approval of Protocol Amendment 02 dated 17 Jan 2014 was submitted to this office on 25.08.2014 which mainly included the **reduction in open label continuation period from 12 months (52 weeks) to 6 months (26 weeks).**

   Rationale: Reducing the duration of the open label extension from 12 months to 6 months continues to allow patients the opportunity for open label treatment.

   SEC recommendation: The proposal was deliberated in SEC (16th Cardiology and Renal) on 25/11/2014. The committee after detailed deliberation opined that the trial duration can be modified only when overwhelming efficacy has been proven or the safety profile is in doubt. Since no such data was furnished the open label phase should be continued for the 52 week period that was previously approved.

   M/s Sanofi Synthelab India Ltd., Mumbai was intimated the above SEC recommendation, vide letter dt.15/12/14.

4. The firm again requested this office to review application for reducing the open label continuation (OLC) phase from 12 months to 6 months with the following justification:
   Protocol Amendment 2 has been accepted by NRA of all the other 24 countries participating in the open label phase of this study except India. Without further evidence, the sponsor cannot state with confidence that ongoing treatment with Mipomersen after the 6 month open label continuation period is in patient's best interest. Furthermore, these patients have other therapeutic options available by the time they complete participation in the open label continuation study. Further firm clarified that the purpose of the OLC phase is to provide additional data regarding safety and efficacy in patients with familial hypercholesterolemia (FH) who have completed the blinded treatment period. The OLC phase for 12 months (amendment 1) being changed to 6 months is also sufficient to collect safety and efficacy data. The objectives of the OLC phase are not changed by reducing duration of OLC phase.

   SEC Recommendation: The Protocol Amendment 02 was again re-deliberated in 22nd SEC (Cardiology and Renal) on 04-06-2015 by the experts and it was opined that the firm failed to furnish any justification for the reduction in trial duration of the open label phase. Hence the committee did not recommend for the approval of protocol amendment 02.

   As per the recommendation of the SEC, the rejection letter for protocol amendment 02 was issued to the firm on 16.06.2015.

5. Now, the firm has appealed to deliberate the matter in the upcoming Technical committee meeting to allow them close the study in India in compliance with the Global protocol amendment 02 and then continue to provide the study medication to the subject under **name patient program (NPP)**with the following justifications:

   A. Genzyme's decision to amend the MIPO3801011 protocol to shorten the open label extension from 12 to 6 months was not based on any safety data or any safety concern. The decision allowed for a more timely completion of the overall clinical trial, while effectively and efficiently allowing patients access to open label drug. From prior studies, 6 months has been demonstrated to be sufficient time for LDL-C lowering; therefore, placebo patients rolling into this 6 month open label phase would have sufficient time to show effect.

   B. Throughout the duration of theMIPO3801011 study, the Data Monitoring Committee (DMC) has routinely met to review the benefit-risk profile of Mipomersen by assessing unblinded safety and efficacy data and to date, the DMC has not identified any safety risk nor recommended changing the study design for any safety reason. The investigator sites have routinely been sent documentation of the overall DMC deliberation assessments. The DMC continues to monitor safety and efficacy data until the end of the study (defined as the last patient last visit after the 6 month safety monitoring phase). The DMC had been informed of the sponsor's decision to amend the trial protocol to limit the open-label continuation to 6 months and have not raised any concerns.

   C. The amendment to reduce the open-label treatment from 12 to 6 months has been approved in all countries where this study was enrolling patients with the exception of India.

   D. In order to abide by the Indian SEC request to provide treatment for the full 12 months in the open-label treatment phase, Genzyme has proposed to continue to supply the mipomersen study drug to the 1-3 eligible trial patients in India on a named patient program (NPP) for the subsequent 6 months. The NPP SOP and other requested information are provided as enclosures to this letter.

	CT Route	NPP **Route**
Complexity of process	complicated process	Simpler process
Patient access to 6 months drug	Will be delayed thus defeating the purpose	No delays; It is the fastest and most efficient way to provide drug access.
Oversight by PI and safety-data collection	Visits as per the CT protocol (stringent), safety	PI determined visits (practical and convenient).

	data is collected.	Safety data is collected.
AE reporting	Will be as per protocol	PI determined AE reporting
Re-amendment of global protocol	Will need to re-amend the global protocol (even for India specific protocol), that will take weeks for necessary approval.	No Need
clinical database/EDC	Will need to revise the whole clinical database in EDC, that will further delay the drug access to patients	Not applicable
CRO contract	Will need to revise contract with CRO	Not applicable
Any cost implication to patient	No	No

Using the NPP process will ensure that the eligible clinical trial patients in India continue to receive Mipomersen for the additional 6 months without disrupting the global data analysis, while Genzyme also fulfils the requirements of the SEC.

Using NPP process the eligible CT patients in India continue to receive Mipomersen free of cost for additional 06 months without disrupting the global data analysis, while the firm also fulfills the requirement of the SEC.

As per the status of study in India:

Total **5 patients** who rolled over to OLC phase:

a) **02 patients** discontinued
b) **02patients** completed OLC phase (these are eligible for NPP program if they are willing)
c) **01 patient** is not willing for NPP

Recommendation of the Committee: In view of the justification furnished by the firm, the Committee recommended the reduction in open label period from 12 months (52 weeks) to 6 months (26 weeks)

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Annexure-I

List of 02 cases of clinical trial of NCEs along with their evaluations and recommendations of the Technical Committee in its 29th Meeting.

Proposal No	Details of the proposal	Assessment of the Proposal *vis –a vis* specified Parameters	Recommendation 1. Subject Expert Committee /IND Committee 2. Technical Committee
1.	**Name of the Drug:** CPL-2009-0031 Film coated tablets (35mg, 70mg & 140mg) **Protocol No** : CRSC12015 **Phase of the Study:** Phase I/II **Name of the Applicant:** Cadila Pharmaceuticals Limited, 1389-Trasad Road, Dholka – 387810, Dist – Ahmedabad, Gujarat. **Name of the Sponsor:** Same as above **Name of the Manufacturer:** Same as above **Title:** A safety, pharmacokinetics and pharmacodynamics study of CPL-2009-0031 in healthy volunteers and patients with Type 2 Diabetes mellitus (T2DM)"manufactured indigenously by Cadila Pharmaceuticals Limited.	**Assessment of Risk vs. Benefit to the patients**: DPP-IV inhibitors have been suggested as drug candidates for the treatment of impaired glucose tolerance and T2DM. Sitagliptin, Saxagliptin and Vildagliptin which act by inhibiting DPP-IV, are currently used clinically for the treatment of T2DM with good safety and efficacy profile. The test drug used in the study is a pro drug of Sitagliptin. **Innovation *vis-à-vis* Existing Therapeutic Option**: The test drug is a prodrug of Sitagliptin which may have better safety profile than Sitagliptin. **Unmet Medical Need in the country**: Despite the availability of various antidiabetic treatments, the majority of the subjects fail to attain or maintain optimum glycemic control over time, increasing their risk for serious microvascular and macrovascular complications, majorly being cardiovascular outcomes.	**1. IND Recommendation on 06-08-15:** After detailed deliberation the Committee recommended to conduct Phase-I clinical trial in healthy volunteers as per stage-I of the protocol, based on the 28 days repeat dose toxicity study report and comparative pK study conducted with the Investigational product vs Sitagliptin in rats. Further toxicity studies of duration as prescribed in Schedule-Y need to be carried out as the molecule will go in further clinical developmental stages. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the IND Committee recommendation.

2.	**Name of the Drug: QGE031** **Protocol No:** CQGE031B2204 **Phase:** IIb **Name of the Applicant:** Novartis Healthcare Private Limited, Sandoz House, Shivsagar Estate, Dr. Annie Besant Road, Worli Mumbai - 400 018. **Name of the Sponsor:** Same as above **Name of the Manufacturer:** Novartis Pharma AG, Schaffhauserstrasse 101, CH-4332 Stein, Switzerland **Title:** A multi-center, randomized, double-blind, placebo controlled study to investigate the efficacy and safety of 52 weeks treatment with QGE031 s.c. in asthma patients not adequately controlled by medium- or high-dose ICS plus LABA with or without OCS".	**Risk versus benefit to the patients**: The safety profile of the test drug from various pre clinical studies including repeat dose, reproductive and development toxicity, juvenile toxicity and clinical phase I, II studies justify the conduct of the study. **Innovation vis a vis existing therapeutic option-** The propose of the study is to investigate the efficacy and safety of 52 weeks treatment with subcutaneous QGE031 in asthma patients not adequately controlled with medium or high-dose inhaled corticosteroids and long acting β2-agonists with or without OCS. **Unmet need**- The test drug may be an alternative treatment option in asthma patients.	1. **Recommendation of the SEC:** After detailed deliberation the committee recommended the conduct of the study subject to the following conditions. 1. Patient with tropical pulmonary eosinophilia should be excluded. 2. Adrenaline should be provided for the management of hypersensitivity at the trial site. 3. Trial site should be selected from Eastern part of the country. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.

Annexure-II

List of 06 cases of Clinical Trial proposals of GCT along with evaluations and recommendations of the Technical Committee in 29th Meeting.

Proposal No.	Details of the proposal	Assessment of the Proposal *vis –a vis* specified Parameters	Recommendation 1. Subject Expert Committee 2. Technical Committee
1.	**Name of the Drug:** Human-cl rhFVIII **Protocol No** : GENA15 **Phase of the Study: IIB** **Name of the Applicant :** Max Neeman Medical International Limited, Max House, First Floor,1 Dr. Jha Marg, Okhla Phase-III, New Delhi-110020, India **Name of the Sponsor:** Octapharma Pharmazeutika Produktionsges.m.b.H., Oberlaaer Strasse 235, A-1100 Vienna, Austria **Name of the Manufacturer:** Octapharma, SE-11275 Stockholm, Sweden **Title:** Extension Study for Patients who completed GENA-05 (NuProtect) – to Investigate Immunogenicity, Efficacy and Safety of Treatment with *Human-cl rhFVIII*. .	**Risk versus benefit to the patients-** The risk versus benefit of the test drug from safety and efficacy in pre-clinical, repeat dose toxicity and clinical study in Hemophilia A. justify the proposed clinical trial. **Innovation vis-a-vis existing therapeutic option-** The purpose of this extension study is to assess immunogenicity, efficacy and safety of the test drug in severe haemophilia A patients **Unmet medical need in the country-** Multisource availability of recombinant factor VIII in the country will benefit Indian patients.	**1. Recommendation of the SEC:** After detailed deliberation the committee opined that the extension of core study GENA 05 is justified and the protocol may be approved as such. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.
2.	**Name of the Drug:** Secukinumab (AIN457) **Protocol No** : CAIN457F2342 **Phase of the Study: III** **Name of the Applicant :** Novartis Healthcare Private Limited, Sandoz House, Dr. Annie Besant Road, Worli, Mumbai - 400 018.	**Risk versus Benefit to the patients-** The safety profile of the test drug from various pre-clinical toxicity studies including single dose, repeat dose, immunogenicity, reproduction and development toxicity and clinical phase I, II studies justify the conduct of the study. **Innovation vis a vis existing**	**1. Recommendation of the SEC:** After detailed deliberation the committee recommended the conduct of the study subject to the following conditions 1. If PPD skin test is negative Quantiferon TB Gold test should

	Name of the Sponsor: Novartis Healthcare Private Limited, Sandoz House, Dr. Annie Besant Road, Worli, Mumbai - 400 018. **Name of the Manufacturer:** Novartis Pharma Stein AG, Schaffhauserstrasse, 4332 Stein, Switzerland **Title:** A Phase III, randomized, double-blind, placebo controlled multi-center study of subcutaneous secukinumab (150 mg and 300 mg) in prefilled syringe to demonstrate efficacy (including inhibition of structural damage), safety, and tolerability up to 2 years in subjects with active psoriatic arthritis (FUTURE 5).	**therapeutic option-** The primary objective of the study is to demonstrate that the efficacy of secukinumab 150 mg s.c. (With or without loading regimen), or 300 mg s.c. with loading regimen, at Week 24 is superior to placebo based on proportion of subjects with active PsA achieving American College of Rheumatology 20 (ACR20) response. **Unmet need-** The test drug may be a better treatment option in subjects with active psoriatic arthritis.	be done to rule out Latent TB. 2. The trial site should be geographically distributed across the country including representation from North and East part. Dr. Uma Kumar did not participate in decision making process. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study subject to the condition that exclusion criteria should specify that the patients with LV dysfunction (Ejection Fraction less than 40%), malnourishment and other immune compromised patients shall be excluded from the study.
3.	**Name of the Drug:** Carvedilol **Protocol No** : LB1109 **Phase of the Study:** Phase III **Name of the Applicant :** Accutest Research Lab (I) Pvt. Ltd. (Unit-II) Opposite The Grand Bhagwati Hotel, Sarkhej – Gandhinagar Highway, Bodakdev, Ahmedabad – 380 054, Gujarat – INDIA. Tel.: +91 (79) 4023 1600; Fax: +91 (79) 40029317 **Name of the Sponsor:** Libbs Farmacêutica Ltda., Rua Alberto Correa Frankfort, 88. Postal Code: 06807-461. Barra Funda. Embu-SP.	**Assessment of Risk vs. Benefit to the patients:** In light of the fact that the test drug is already old drug and marketed in India, the safety profile of the test drug justify the conduct of the trial. **Innovation vis-à-vis Existing Therapeutic Option:** The purpose of the study is to evaluate efficacy, safety and tolerability of carvedilol controlled release tablets, compared to Coreg (Carvedilol Immediate release tablets) of in Patients of stable systolic heart failure. **Unmet Medical Need in the country:** The test drug may potentially provide alternative	**Recommendation of the SEC: 25/08/15** The proposal was deliberated in SEC on 04/06/15, after deliberation, the committee observed that 10, 20, 40, 80 mg CR formulations of Carvedilol are available in India. The committee also observed there is no distinct advantage of the proposed formulations (Carvedilol CR tablets) of 8, 16, 32 and 64 mg. The proposed study is to compare 8, 16, 32 and 64 mg (OD) of Carvedilol CR tablets with the 3.125mg, 6.25 mg, 12.5 mg and 25 mg (BD) of Carvedilol immediate release formulation. The committee opined that the firm should

	Name of the Manufacturer: Same as above **Title:** A Prospective, randomized, double-blind, double-dummy, parallel group, multi- center comparative clinical trial, to evaluate efficacy, safety and tolerability of Carvedilol controlled release tablets of Libbs Farmacêutica, Brazil, compared to Coreg ® (Carvedilol Immediate release tablets) of Roche Químicos e Farmacêuticos S.A., Brazil in patients of stable systolic heart failure.	treatment option in stable systolic heart failure patient.	submit proper justification for comparing Carvedilol CR with Carvedilol immediate release formulation. The applicant has now presented the justification in respect of previous recommendation, after detailed deliberation the committee recommended the conduct of the comparative study. **2.Recommendation of the Technical Committee:** The Committee noted the unequal distribution of the study subjects amongst the participating countries and asked for justification for inclusion of 100 subjects from India and 40 subjects from other countries for further deliberation in the matter.
4.	**Name of the Drug:** Dydrogesterone **Protocol No** : M13-625 **Phase of the Study:** III **Name of the Applicant :** Abbott India Limited, 2nd Floor, Unit No. 3, Corporate Park, SionTrombay Road, Chembur, Mumbai 400 071 **Name of the Sponsor:** Abbott Laboratories GmbH, Freundallee9A, D30173Hannover **Name of the Manufacturer:** Abbott BiologicalsB. V. Veerweg 128121AA Olst The Netherlands	**Risk versus Benefit to the patients-** In light of the fact that the test drugs are old drug and marketed in India, the safety profile of the test drugs justify the conduct of the trial. **Innovation vis a vis existing therapeutic option-** The purpose of the study is to compare the efficacy, safety and tolerability of Oral Dydrogesterone 30 mg daily versus Crinone 8% intravaginal progesterone gel 90 mg daily for luteal support in In-Vitro Fertilization. **Unmet need-** The test drug may be a alternative option in the treatment of luteal support in In-Vitro Fertilization.	**1. Recommendation of the SEC:** After detailed deliberation, the committee recommended conduct of the trial. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.

	Title: A Randomized, Open-label, Two-arm, Multicenter Study Efficacy, Safety and Tolerability of Oral Dydrogesterone 30mg daily versus Crinone 8%intravaginal progesterone gel 90 mg daily for Luteal Supportin. In-Vitro Fertilization (LOTUSII)		
5.	**Name of the Drug:** Clindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5% **Protocol No** : **AM-CBG-001** **Phase of the Study:** Clinical Bioequivalence **Name of the Applicant :** Amneal Pharmaceuticals LLC 85 Adams Avenue Hauppauge, NY 11788 **Name of the Sponsor:** Amneal Pharmaceuticals Pvt. Ltd., Corporate Headquarters) 508-514, 5th floor, Venus Atlantis, Nr. Safal Pegasus Prahladnagar, Ahmedabad - 380 015 **Name of the Manufacturer:** : 1 New England Ave. Piscataway, NJ 08854 **Title:** A Double-Blind, Randomized, Parallel-Group,Vehicle-Controlled, Multicenter Study ComparingClindamycin Phosphate and Benzoyl Peroxide Gel, 1%/5%and BenzaClin® (Clindamycin and Benzoyl Peroxide) Gel 1%/5% and Both Active Treatments to a Vehicle	**Risk versus benefit to the patients**- In light of the fact that the FDC is already approved, the safety profile of the test drugs justify the conduct of the trial. **Innovation vis a vis existing therapeutic option**- The purpose of the study is to assess the efficacy and safety of test drug with reference product in patients with Acne Vulgaris. **Unmet need-** The test drug may potentially be an additional option to the existing formulation in the market.	**Recommendation of the SEC:** After detailed deliberation the committee recommended the conduct of the study subject to the condition that only non-medicated moisturizer and cleanser should be used as per OGD Guidelines. **2.Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study subject to the condition that the indication for use of rescue medication and type of rescue medication/ standard care must be specified in the protocol.

	Control inthe Treatment of Acne Vulgaris.		
6.	**Name of the Drug:** Insulin degludec/insulin aspart **Protocol No** : NN5401-4243 **Phase of the Study:** IIIb **Name of the Applicant :** Novo Nordisk India Private Ltd, Plot No. 32, 47 - 50, EPIP Area, Whitefield, Bangalore -560 066, Karnataka, India. **Name of the Sponsor:** **Same as above** **Name of the Manufacturer:** Novo Nordisk A/S, Novo Allé DK-2880, Bagsværd, Denmark **Title:** A trial comparing efficacy and safety of insulin degludec/insulin aspart twice daily and biphasic insulin aspart twice daily in subjects with type 2 diabetes mellitus before, during and after Ramadan.	**Assessment of Risk vs. Benefit to the patients**: In light of the fact that the test drug is already approved and marketed in India, the safety profile of the test drug justify the conduct of the trial. **Innovation vis-à-vis Existing-Therapeutic Option:** The purpose of the study is to compare the efficacy and safety of insulin degludec/insulin aspart twice daily and biphasic insulin aspart twice daily in subjects with type 2 diabetes mellitus before, during and after Ramadan. **Unmet Medical Need in the country:** The data generated from the study may provide optimal second line therapy when first line therapy fails to provide adequate glycaemia control.	**1. Recommendation of the SEC:** After detailed deliberation, the committee recommended the conduct of the trial with the following conditions- 1. The minimum gap between two injections should be 8 hrs and it should be clearly mentioned in study protocol. 2. Standard procedure for the management of hypoglycaemia during Ramadan should be clearly mentioned in ICF as well as study protocol. **2.Recommendation of the Technical Committee:** The Committee opined that the practical feasibility of minimum 8 hrs gap between two injections (as recommended by SEC) during Ramadan must be re-examined by the SEC Committee with consideration of the interval between two meals during the Ramadan. After re-examination, the matter may be placed before the Technical Committee for further deliberation.

Annexure III

List of 07 cases of clinical trial proposals other than GCT/NCE along with evaluations and recommendations of the Technical Committee in 29th Meeting.

Sl No	Name of the Drug	Firm Name	Recommendations: 1. Subject Expert Committee 2. Technical Committee
1.	Darbepoetin Alfa Injection	M/s Hetero Drugs Limited	1. **Recommendation of the SEC** After discussion on the revised study protocol, Committee recommended for the conduct of the phase IIIb clinical study. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
2.	Liquid Formulation of Bovine Rota virus Pentavalent Vaccine (LBRV-PV)	M/s Serum Institute of India Ltd	1. **Recommendation of the SEC** The Committee deliberated the proposal and recommended the proposal subject to following changes: 1. The firm shall remove the placebo group 2. Study will be open label, to be conducted in at least 20 subjects. Accordingly, firm shall submit revised protocol to DCG (I) office for approval of protocol. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
3.	Measles Vaccine Live, Attenuated (Freeze-dried).	M/s Biological E. Limited	1. **Recommendation of the SEC** After detailed deliberation the committee recommended the study with the following changes in the protocol: 1. Age group- 4-5 years instead of 9-12 months 2. Only safety assessment to be done 3. Only single arm i.e. Test vaccine to be used.

			4. No. of subjects to be 24 only Accordingly, the firm should submit the revised protocol to the office of DCG (I). **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
4.	Measles and Rubella Vaccine Live, Attenuated (Freeze-dried).	M/s Biological E. Limited	1. **Recommendation of the SEC** After detailed deliberation the committee recommended the study with the following changes in the protocol: 1. Age group- 4-5 years instead of 9-12 months 2. Only safety assessment to be done 3. Only single arm i.e. Test vaccine to be used 4. No. of subjects to be 24 only Accordingly, the firm should submit the revised protocol to the office of DCG (I). **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
5.	Coated Copper T	M/S HLL Life care Ltd	1. **Recommendation of the SEC** The case has been reviewed by SEC – Reproductive & Urology meeting held on 05/08/2015 whereby the Committee recommended that the permission for conducting Phase-II Clinical trial is accepted. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendations.
6.	Hydra Aortic Valve and Delivery System	M/s Vascular Concepts Ltd	1. **Recommendation of the SEC** The firm has submitted the preclinical data as per earlier recommendation which has been examined by this committee and committee recommended for the grant of

			the clinical trial permission. However, the study should be carried out in a Hospital having Hybrid OT and the device shall be used by cardiologist in presence of Anesthesiologist and Cardiac Surgeons. **2. Recommendation of the Technical Committee:** The Committee observed that the objective of the study is to assess the safety and performance of the HYDRA TAVI system in the treatment of severe aortic stenosis **in high risk patients. Therefore the Committee opined that** high risk patients need to be defined and to be monitored by team comprising of Cardiologist, Cardiac surgeon and Anesthetist for further review by the Technical Committee.
7.	Cadexomer Iodine Powder and Ointment	M/s Virchow Biotech Private Limited	1. **Recommendation of the SEC** The firm presented its proposal. After detailed deliberation, the Committee recommended the study subject to the following amendment in the Protocol: 1. The claim of the ointment/powder should be appropriate. 2. The application of investigational product on the wound must be done by the Investigator by the competent paramedic, trained for dressing the wound as per the protocol. 3. All subjects should be provided with the diary to record any adverse effect. The diary should also have symptoms checklist. 4. In no case, the standard care should be compromised. In case where the wound requires Iodine application, it must not be put on simple saline dressing at any stage of the study. 5. The informed consent must include the information about the need of option of saline and Iodine. 6. The number of subjects mentioned in the protocol should be followed for both powder and ointment separate.

			7. The informed consent should be corrected. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.

Annexure-IV

Recommendations of the 07 cases of Clinical trial waiver in Indian populations:

Sr. no.	Drug Name	Name of the Firm	Indication	1. Recommendations of the Technical Committee: 2. Recommendations of the SEC
1.	Nintedanib Capsules	M/s. Boehringer Ingelheim India Pvt. Ltd	Indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF)	**1. Recommendations of the Technical Committee:** The Committee deliberated the proposal and noted that the drug is already approved as orphan drug by USFDA and also approved in EU. Therefore, the Committee recommended for waiver of local clinical trial as per recommendation of the SEC. However, the Committee opined that it is required to clearly explain active surveillance and what is required to be submitted by the firm for doing active surveillance shall be clearly mentioned in the regulatory approval. **2. Recommendations of the SEC:** The firm has made an application for grant of permission to import & market Nintedanib soft gelatin 100/150 mg capsules indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF) and to slow disease progression. The firm presented data on 20 Indian patients who participated in the Global clinical trial of the drug and submitted that safety and efficacy results of the Indian subset is comparable with the Global data & requested for waiver of local clinical trial as IPF is an orphan disease and also there is an unmet need of the drug for the disease. The Committee deliberated the proposal in detail and observed the following: 1. For IPF patients in India there is only limited treatment option. 2. This drug was approved as orphan drug by USFDA and also approved in EU in 2015.

				The Committee recommended for approval of Import and marketing of the drug with waiver of local clinical trial subject to the condition that- 1. Marketing approval initially shall be given only for two years. 2. The firm will conduct an active surveillance of all the patients who will be prescribed for a period of two years and protocol etc. should be submitted for evaluation. 3. The continued marketing of the drug beyond two years shall be based on the favorable risk benefit ratio on the data in the Indian population.
2.	Dabrafenib Mesylate capsule 50/75mg	M/s. Glaxo Smith Kline Pharmaceuticals Limited	Indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	**1. Recommendations of the Technical Committee:** The Committee deliberated the proposal and noted that the drug is already approved as orphan drug by USFDA and also approved in EU. Therefore, the Committee recommended for waiver of local clinical trial as per recommendation of the SEC. **2. Recommendations of the SEC** The firm made an application for grant of permission to import and market Dabrafenib mesylate capsules 50mg/ 75mg indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The proposal was deliberated in the SEC meeting held on 28.01.2014 where the Committee had asked to obtain data of BRAF V600 mutation in Indian patients. The firm presented the presence of this mutation in 20 patients in the present SEC meeting. The Committee deliberated the proposal in detail and felt that : 1. There is no other option for these patients, who have a life-threatening disease. 2. The drug has been granted Orphan drug designation in the USA.

				Hence the drug may be granted permission for import and marketing without clinical trial subject to the condition that the firm shall submit safety data in first 20 patients post marketing to the Committee for continued marketing of the product. The firm shall also submit the detail BRAF V600 mutational data on the 20 melanoma patients.
3.	"Celox Gauze and Celox Z Fold Gauze"	M/s. Emergo India Consulting Pvt. Ltd.,	Indicated to be used to achieve hemostasis in emergency situations for the temporary control of severe topical bleeding	**1. Recommendations of the Technical Committee:** After detailed deliberation, the Committee noted that the product is used in emergency situations. Further the product is marketed in USA, Europe, and Canada for more than 5 years with no safety concerns and as such there is no requirement of clinical trial for such product. Therefore, the Committee agreed with SEC recommendations. **2. Recommendations of the SEC** The case has been reviewed by SEC – Oncology & Haematology in its meeting held on 21.07.2015. The committee has deliberated upon the proposal and recommended that the product may be granted marketing approval for the indication of temporary external use to control moderate to severe bleeding. The committee also felt that it would not be feasible or practical to conduct a trial on the product as it's use is in an emergency situation. The committee also noted that the product is approved in USA, Europe and Canada and that it is in global market for more than 5 years with no safety concerns. The firm is required to submit PSUR after 6-months which will be reviewed by the committee.
4.	Sofosbuvir (400 mg) + Ledipasvir (90 mg)	M/s Mylan, M/s Hetero	**For M/s Mylan:** Indicated for the treatment of chronic hepatitis C (CHC) in adults	**1. Recommendations of the Technical Committee:** The Committee deliberated the proposal in details and noted that there is no therapy for the treatment of genotype 1 HCV infection patients with renal failure, prior organ

			For M/s Hetero & M/s Natco: Indicated for the treatment of Chronic Hepatitis C virus (HCV) genotype 1 infection in adults.	transplantation, decompensated liver disease and cirrhotic condition where Interferon in combination with other HCV drugs is not useful. As the drug is already approved by USFDA, therefore, the Committee recommended that the application for new drug approval without local clinical trial can be considered provided that; the firm shall conduct BA/BE study in Indian population if the product is manufactured "as different" than the one approved in country of origin. Further, the product shall be approved for the indication for which it is approved in USA subject to condition of conduct of phase-IV study. It was also decided by the Committee to further get the matter examined by experts including , 1. One expert from Institute of Liver and Biliary Sciences (ILBS). 2. One expert from PGI, Chandigarh. 3. One expert from GB pant Hospital. **2. Recommendations of the SEC** **i) Recommendation for M/s Mylan:** The firm presented the proposal for permission to manufacture and market, with waiver of local clinical trial for a fixed-drug combination of Sofosbuvir and Ledipasvir, for "treatment of chronic hepatitis C (CHC) in adults". During the presentation, the company informed that the combination is already approved for the treatment of "chronic hepatitis C". A perusal of the documents provided indicates that the above fixed-drug combination is approved by US FDA and Health Canada for "treatment of chronic hepatitis C virus (CHC) genotype 1 infection in adults". Hence, the permission requested is for an indication that extends beyond the indication for which it is approved in

				other countries. Hence, the committee did not recommend marketing of the drug with waiver of local clinical trial. **ii) Recommendation for M/s Hetero:** The firm presented the proposal for permission to manufacture and market, with waiver of local clinical trial for a fixed-drug combination of Sofosbuvir and Ledipasvir, for "treatment of chronic hepatitis C (CHC) genotype 1 in adults". A perusal of the documents provided indicates that the above fixed-drug combination is approved by US FDA and Health Canada for "treatment of chronic hepatitis C virus (CHC) genotype 1 infection in adults". The permission requested is for an indication for which it is already approved in other countries. The currently available treatments for genotype 1 HCV infection (Interferon-ribavirin combination, or Sofosbuvir-Interferon-Ribavirin combination) are not effective in some such patients, and their use is not possible in some subgroups of patients, such as those with renal failure, prior organ transplantation, decompensated liver disease. In these patients, there is a need for this combination. Hence, the Committee felt that there may be a point in permitting marketing of the drug with waiver of local clinical trial subject to the following conditions: a) That a bioequivalence study will be carried out. b) The prescribing information, patient information sheet and all the material used for marketing will clearly indicate that the drug combination is not approved for treatment of infection with non-1 HCV

				genotypes. c) The firm will undertake a phase IV clinical trial, the protocol of which should be submitted. However, the Committee took cognizance of the order dated July 3, 2014, that "waiver of clinical trial in Indian population for approval of new drug, which have already been approved outside India, can presently be considered only in cases of national emergency, extreme urgency, and epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy'. The drug does not meet any of the situations listed above. Hence the Committee did not recommend waiver of the need for a local trial.
5.	Daclatasvir 30 mg and 60 mg Tablet	M/s Natco	Indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.	**1. Recommendations of the Technical Committee:** The Committee deliberated the proposal in details and noted that the drug in combination with other medicinal product becomes imperative to expedite the treatment of all types of Hepatitis C. Hence, the Committee recommended that the application for approval Daclatasvir without local clinical trial can be considered subject to the following condition: 1. The innovator has certified that there is technology transfer of the manufacturing process to the Indian manufacturer. 2. The firm shall conduct BA/BE study in Indian population. Accordingly the firm shall be asked to submit BA/BE protocol for approval. In the meantime the proposal may be got examined by an experts including , 1. One expert from Institute of Liver and Biliary Sciences (ILBS) 2. One expert from PGI, Chandigarh 3. One expert from GB pant Hospital **2. Recommendations of the SEC** The firm presented the proposal for

				permission to manufacture and market Daclatasvir, with waiver of local clinical trial for "treatment of chronic hepatitis C (CHC) in adults, in combination with other medicinal products". The drug is already approved "in combination with other medicinal products for the treatment of chronic hepatitis C infection in adults". The available data show that the drug has activity against various genotypes of HCV, and is safe, except severe bradycardia when administered along with Amiodarone. The Committee felt that there may be a point in permitting marketing of the drug with waiver of local clinical trial subject to the following conditions: a. That a bioequivalence study will be carried out. b. The firm will undertake a phase IV clinical trial, the protocol of which should be submitted. However, the committee took cognizance of the order dated July 3, 2014, that "waiver of clinical trial in Indian population for approval of new drug, which have already been approved outside India, can presently be considered only in cases of national emergency, extreme urgency, and epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy'. The drug does not meet any of the situations listed above. Hence the Committee did not recommend waiver of the need for a local trial.
6.	Siltuximab	M/s Johnson & Johnson Private Limited	Indicated for the treatment of patients with Multicentric Castleman's Disease (MCD) who are human immunodeficiency virus (HIV) negative and Human Herpesvirus-8 (HHV-8) negative.	**1. Recommendations of the Technical Committee:** After detailed deliberation, the Committee recommended waiver of local clinical trial as per SEC recommendation. **2. Recommendations of the SEC** After detailed deliberation the committee has recommended clinical trial waiver in respect of Siltuximab due to following reasons:

				1. MCD is rare disease with no standard treatment at present, therefore it is a clear unmet need 2. It has orphan drugs status in USA and Europe. 3. It is approved in USA and Europe 4. The drug has a favorable risk benefit profile.
7.	Inactivated Polio Vaccine	M/s Serum Institute India, Pune	Indicated for active immunization for the prevention of poliomyelitis caused by poliovirus Types 1, 2, and 3.	**1. Recommendations of the Technical Committee:** After detailed deliberation, the Committee recommended waiver of local clinical trial as per SEC recommendation. **2. Recommendations of the SEC** The committee deliberated the proposal in detail and noted that firm has requested for fast track approval of the vaccine without clinical trial in India since the vaccine is intended to be included in the National Immunization Programme and large quantity will be required. The firm is already importing the bulk from the same source and the formulation is exactly the same. Therefore, the Committee has recommended for Marketing Authorization (Form 45) of IPV in single dose and multi-dose (5 doses) presentations.

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