MINUTES OF 30th MEETING OF THE TECHNICAL COMMITTEE HELD ON 26.11.2015 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. Kamlakar Tripathi, Prof., Dept. of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi – 221005.	Member
5.	Dr. S.N. Gaur, Professor & Head, Dept. of Respiratory, Medicine, VP Chest Institute, New Delhi.	Member

From CDSCO:

1. Dr. V. G. Somani,
   Joint Drugs Controller (I)
2. Mrs. Annam Visala
   Deputy Drugs Controller (I)
3. Mrs. Rubina Bose
   Deputy Drugs Controller (I)
4. Mr. Asheem Sahu
   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 20 cases related to approval of clinical trials. Out of these 20 cases, 03 cases were related to clinical trials of NCEs, 08 cases were related to global clinical trials (GCT) remaining 09 cases were related to clinical trials for approval of New Drugs and Biologicals.

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

The Committee evaluated the 03 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. For remaining one case (S. No 03 of Annexure-I), the Committee has sought certain clarifications. The recommendation of the Committee is enclosed as **Annexure-I.**

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

Thereafter, the Committee evaluated 08 cases related to global clinical trial. After detailed deliberation, the Committee recommended all 08 cases. The recommendation of the Committee is enclosed as **Annexure-II.**

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

The Committee evaluated the 09 cases of other than GCT/clinical trial of NCEs. After detailed deliberation, the Committee recommended for approval of all 09 cases, out of which for one case (S. No: 02 of the **Annexure-III),** the Committee recommended subject to certain condition.
The recommendation of the Committee is enclosed as **Annexure-III.**

Thus, the Committee recommended for approval of 19 cases, out of total 20 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:**

05 proposals from Medical Device were placed before the Committee for consideration of permission for manufacture/ import for marketing in the country without local clinical trial. The details of recommendations of the Committee along with recommendation of the SEC were annexed at **Annexure-IV.**

5. Others:

a) Appeal by M/s Novartis to waiver on the Clinical Trial condition imposed by Technical Committee in its 28th meeting dated 21-08-2015.

Study title: "A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to Valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction"

It may please be informed that the proposal was deliberated in Technical Committee in its 28th meeting dated 21-08-2015 and CT NOC has been issued on 30-09-2015 as per the recommendations of Technical Committee.

The details of the deliberations are given below:-

1. Deliberation of proposal by SEC:-

The proposal was deliberated in the meeting of SEC held on 16-07-2015

The Committee after deliberation recommended as under:-

After the detailed deliberation the committee recommended the conduct of the study subject to the following condition

1. Serum potassium levels should be assessed at 1 week post dose escalation to 160 mg BD.
2. Ejection fraction assessment should be performed by 2D volumetric methods.

2. Deliberation of proposal in 21st Technical Committee (TC):-

The proposal was placed before the Technical Committee along with the recommendations of the SEC in the 28th Technical Committee meeting held on 21-08-2015.

The Committee after deliberation recommended as under:-

After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation with the condition that the patients who have eGRF less than 45 ml/min should be excluded from the study.

3. Appeal by M/s Novartis for waiver on the condition imposed under CT NOC:-

There after the applicant represented the matter to DCG (I) for waiver on the condition imposed under CT NOC based upon following justifications;

I. US FDA approved prescribing information of LCZ696 (Brand Name-Entresto (Sacubitril/Valsartan)] recommends no dosage adjustment for patients with mild to moderate renal impairment (eGFR 30-90 ml/min.) Further, a starting dose of 24/26 mg twice-daily is recommended for patients with severe renal impairment (eGFR<30mL/min/1.73 $m^{2)}$ which can be doubled every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient. The current study protocol more than complies with the approved information of LCZ696 and excludes patients with severe renal impairment i.e., eGFR<30ml/min (Kindly refer page no. 35 of Protocol version 02 dated 6 May 15.

II. The consequence of inhibiting the rennin-angiotensin-aldosterone system (RAAS), decrease in renal function may be anticipated in susceptible individuals treated with

LCZ696. The study subjects would be randomized to receive either LCZ696 or Valsartan. The study protocol excludes any subject who requires simultaneous administration of two RAAS blockers, thereby mitigating the risk of renal dysfunction.

III. The approved prescribing information of LCZ696 in US recommends close monitoring of serum creatinine and down-titration or interruption of LCZ696 in patients who develop a clinically significant decrease in renal function. The current protocol complies with this recommendation and has adequate provisions in place to monitor renal function of study subjects.

IV. During the run-in period, patient's serum creatinine and eGFR is being closely monitored and any patient with >35% reduction in eGFR from baseline will not be randomized into the study.

V. Even after randomization, serum creatinine and eGFR is being closely monitored at all scheduled site visits. Appendix 5 of the protocol provides Guidelines to the investigators for management of renal dysfunction.

If, at any time after randomization, eGFR degreases by >25% from baseline (Visit 1) or if serum creatinine concentration increase to 2.5mg/dL [221 µmol/L), the investigator will check for potentially reversible causes of renal dysfunction (as above). The investigator may consider down-titration of study drug. He/she may stop the study drug after contacting the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable value.

In view of the above, the current protocol has adequate precautionary measures to monitor renal function of study subjects and it also provides guidelines to the investigators for management of renal dysfunction. Further, the protocol complies with the approved prescribing information of LCZ696 in US. Thus, no additional measures are really required.
Accordingly, the proposal was placed to the Technical Committee.

Recommendation of the Technical Committee:
After examining the justification furnished by firm in detail, the committee opined that patients with severe diabetes, hypertension with diastolic blood pressure ≥ 85 mmHg, patient on high dose of insulin should be excluded from the study. If eGFR decrease by ≥ 25% from baseline, subject should not be randomized into the study

Annexure-I

List of 03 cases of clinical trial of NCEs along with their evaluations and recommendations of the Technical Committee in its 30th Meeting.

Proposal No	Details of the proposal	Assessment of the Proposal *vis –a vis* specified Parameters	Recommendation 1. Technical Committee 2. Subject Expert Committee /IND Committee
1.	**Name of the Drug:** Alpelisib (BYL719) **Protocol No** : CBYL719C2301 **Phase of the Study:** Phase III **Name of the Applicant:** Novartis Healthcare Private Limited **Name of the Sponsor:** Same as above **Name of the Manufacturer:** Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel, Switzerland **Title:** SOLAR-1: A phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative	**Risk Versus Benefit to the Patients:** The safety profile of the test drug from preclinical repeated dose toxicity studies and clinical phases I study, justify the conduct of this study. **Innovation vis-a-vis Existing Therapeutic Option:** The objective of the study is to determine whether treatment with Alpelisib in combination with fulvestrant prolongs PFS compared to treatment with placebo in men and postmenopausal women with HR+HER2- negative advanced breast cancer which progressed on or after aromatase inhibitor treatment for the following cohorts i) patients with PIK3CA mutant status ii) patients with PIK3CA non-mutant status. **Unmet Medical Need in the Country:** The test drug may potentially provide alternative treatment option in patients with HR+ HER2- negative advanced breast cancer.	**1. Recommendation of SEC** After detailed deliberation the committee recommended conduct of the study subject to the following conditions, 1. In view of the significant number of patients developing hyperglycemia while on the drug, monitoring of glycemic control (Blood sugar fasting and 2 hrs post prandial) 2 times every cycle for all cycles and estimation of HbA1C every three cycles. 2. The Site study team should include a medical oncologist as PI or Co-I. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.

	advanced breast cancer which progressed on or after aromatase inhibitor treatment.		
2.	**Name of the Drug:** LEE011 **Protocol No:** CLEE011F2301 **Phase:** III **Name of the Applicant:** Novartis Healthcare Private Limited **Name of the Sponsor:** Same as above **Name of the Manufacturer:** Novartis Pharma AG Lichtstrasse 35 CH-4056 Basel, Switzerland **Title:** **"**A randomized double-blind, placebo controlled study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment".	**Risk Versus Benefit to the Patients:** The safety profile of the test drug from preclinical single dose, repeated dose and genotoxicity studies and clinical phase I & II studies, justify the conduct of this study. **Innovation vis-a-vis Existing Therapeutic Option:** The objective of the study is to determine whether treatment with fulvestrant+ ribociclib prolongs PFS compared to treatment with fulvestrant + ribociclib placebo in postmenopausal women with HR+, HER2-advanced breast cancer who received no or only 1 line of prior hormonal therapy for advanced breast cancer. **Unmet Medical Need in the Country:** The test drug may potentially provide alternative treatment option in patients with HR+, HER2- negative advanced breast cancer.	**1. Recommendation of the SEC:** After detailed deliberation the committee recommended conduct of the study subject to the following conditions 1. In view of the significant number of patients developing neutropenia while on the drug, monitoring of blood count (CBC + DLC) 2 times every cycle for all cycles. 2. The Site study team should include a medical oncologist as PI or Co-I. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.
3.	**Name of the Drug:** Genopep -1 **Protocol No** : Issar/2012/01 **Phase of the Study:** Phase II	**Assessment of risk vs benefit to the patient:** There was minimal risk to any patient on the phase 1 study. Since the study group is advanced refractory or resistant cancers, any response to treatment or reduction in symptomatology	**1. Recommendation of the IND Committee:** After detailed deliberation, the Committee recommended for giving permission for the proposed study subject to condition that haemolytic

	Name of the Applicant: ISSAR Pharmaceuticals pvt.ltd Serene chambers,3rd floor , Road no.5, Banjara hills,Hyderabad-500 034,India **Name of the Sponsor:** Same as above **Name of the Manufacturer:** Same as above **Title:** A Phase II Clinical Study to Assess the Efficacy and Safety of the Genopep 1 (Issar 1) in a Non-Randomized, Open-Label, Single-Arm, Multi-Centre Design in Indian Adult Patients with Relapsed/ Recurrent/ Resistant Solid Tumours	will be of great benefit to the lives of cancer patients. **Innovation vis-à-vis existing therapeutic option:** There is no drug in this class of compounds in clinical use.Hence, it is truly innovative. The mechanism of action being different, the drug may have high activity in patients who have failed multiple lines of cancer therapy. **Unmet medical need in the country:** Relapsed refractory cancer patients often suffer emotionally and physically from severe symptoms from advanced cancer. Very few avenues of treatment except palliative and symptomatic treatment are presently available. A drug from a new class of agents (membrane lytic peptides), would therefore be a welcome addition to the treatment armamentarium.	anemia should be monitored during the study. **2. Recommendation of the Technical Committee:** The Committee deliberated the proposal and opined that the firm may be asked to clarify the following for further deliberation: ➢ The firm shall specify the types of patients and the types of tumor. ➢ Whether the proposed treatment is post surgical, monotherapy or as an adjuvant therapy. ➢ Proof of efficacy of the drug in tumor reduction in animal model.

Annexure-II

List of 08 cases of Clinical Trial proposals of GCT along with evaluations and recommendations of the Technical Committee in 30th 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:** CT-P10 (Rituximab) **Protocol No** : **CT-P10 3.4** **Phase of the Study:** Phase III **Name of the Applicant:** PPD Pharmaceutical Development India Private Limited, 01-Dynasty B-Wing (Kanakia Spaces), Andheri-Kurla Road, Andheri East, Mumbai-400059, India **Name of the Sponsor:** CELLTRION, Inc. 23, Academy ro, Yeonsu-Gu, Incheon, 22014, South Korea **Name of the Manufacturer:** Same as above **Title:** A Phase 3, Randomised, Parallel-Group, Active-Controlled, Double Blind Study to Compare Efficacy and Safety between CT P10 and Rituxan in Patients with Low Tumour Burden Follicular Lymphoma	**Risk versus Benefit to the patients**- The safety profile of the test drug from preclinical repeat dose toxicity study, and clinical phase I PK study in RA patients, justify the conduct of the study. **Innovation vis a vis existing therapeutic option**- The purpose of the study is Compare Efficacy and Safety between CT-P10 and Rituxan in Patients with Low Tumour Burden Follicular Lymphoma. **Unmet need**-Availability of bio-similar products from multiple companies will be helpful in controlling pharmacoeconomic scenario due to fair market competition and will result in benefit to patient	**1. Recommendation of the SEC:** After detailed deliberation the committee recommended conduct of the study. **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:** Nintedanib **Protocol No** : **1199.214** **Phase of the Study:** Phase III **Name of the Applicant:** Boehringer Ingelheim India Private Limited, 1102, 11th Floor, Hallmark Business Plaza, Gurunanak Hospital Road Near Gurunanak Hospital, Bandra East, Mumbai – 400 051, INDIA **Name of the Sponsor:** Boehringer Ingelheim India Private Limited on behalf of Boehringer Ingelheim International GmbH **Name of the Manufacturer:** Catalent Germany Eberbach GmbH, Gammelsbacher Strasse 2,69412 Eberbach, Germany **Title**: A double blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD)	**Risk versus Benefit to the patients**- The safety profile of the test drug from preclinical studies single dose toxicity, repeat dose toxicity, Genotoxicity, reproductive and developmental toxicity including and Clinical Phase I, II & III studies in IPF, Justify the conduct of this study. **Innovation vis a vis existing therapeutic option-** The purpose of the study is to evaluate efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD). **Unmet need**- The test drug may be an better treatment option for Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD).	**1. Recommendation of the SEC:** After detailed deliberation the committee recommended the conduct of the trial with the following conditions; 1. Standard of care treatment must be provided free of cost 2. DLCO must be done at accredited Lab. 3. DLCO to be done at baseline and at the end of 52 weeks of study. The undertaking for sending samples for biomarker testing outside country should be submitted. 2. **Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.
3.	**Name of the Drug:** Carbetocin RTS **Protocol No** : **A65870** **Phase of the Study:**	**Risk versus Benefit to the patients**- The safety profile of the test drug from preclinical local tolerance studies in rabbits and in vitro	**1. Recommendation of the SEC:** After detailed deliberation the committee recommended the conduct of the trial with the

	Phase III **Name of the Applicant:** Dr. Shivaprasad S. Goudar, Professor, Department of Physiology & Research Coordinator, Women's and Children's Health Research Unit, J N Medical College, Belgaum 590 010, Karnataka, India **Name of the Sponsor:** World Health Organization, Department of Reproductive Health & Research Avenue Appia 20, 1211 Geneva 27, Switzerland **Name of the Manufacturer:** Ferring Pharmaceuticals A/S, Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark. **Title**: A phase III, randomized, double-blind, active, controlled, multinational, multicentre, non-inferiority trial using carbetocin room temperature stable (RTS) for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally.	hemolysis and coagulation tests, pharmacokinetic and bioavailability studies in health and non pregnant women and efficacy and safety study in women at the risk of PPH following vaginal delivery, justify the conduct of the study. **Innovation vis a vis existing therapeutic option**- The objectives of the study are to evaluate non-inferiority of carbetocin RTS 100 µg IM versus oxytocin 10 IU IM after vaginal delivery in the prevention of the composite endpoint "blood loss of 500 mL or more or the use of additional uterotonics" at one hour and up to two hours for women who continue to bleed after one hour and to evaluate noninferiority of carbetocin RTS 100 µg IM versus oxytocin 10 IU IM in the prevention of severe PPH (≥1000 mL blood loss) at one hour and up to two hours for women who continue to bleed after one hour. **Unmet need**- The test drug may be a alternative option in the treatment for the prevention of postpartum haemorrhage during the third stage of labor in women delivering vaginally	following, 1. Modifications of the exclusion criteria in which all medical diseases should be excluded. 2. Provide evidence justifying use of carbetocin in patients with pre-eclampsia. 3. It was suggested that study should include wider geographical distributions across the country. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.
4.	**Name of the Drug:** Alirocumab **Protocol No** : **EFC13889**	**Assessment of Risk vs. Benefit to the patients:** The safety profile of the study drug	**1. Recommendation of the SEC:** After deliberation the

	Phase of the Study: Phase III **Name of the Applicant:** Sanofi-Synthelabo (India) Private Limited, Sanofi House, CTS No.117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai 400 072, India **Name of the Sponsor:** Sanofi-aventis recherché & developpement, 1, Avenue Pierre Brosso lette, 91380 Chilly-Mazarin, France **Name of the Manufacturer:** Sanofi-Winthrop Industrie Le Trait, Boulevard Industriel ,76580 Le Trait, France **Title**: A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab (SAR236553/ REGN727) Versus Ezetimibe in Asia in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy.	from preclinical pharmacology, repeat dose toxicity, reproductive and embryo fetal toxicity, juvenile toxicity studies and phase I, II, and III clinical studies justify the conduct of the trial. **Innovation vis-à-vis Existing Therapeutic Option:** The purpose of the study is to evaluate efficacy and safety of Alirocumab versus Ezetimibe in Asia in high cardiovascular risk patients with hypercholestroma not adequately controlled with their statin therapy **Unmet Medical Need in the country:** The test drug may potentially provide alternative treatment option in high cardiovascular risk patients with hypercholestroma not adequately controlled with their statin therapy.	committee agreed with the justification now presented and recommended conduct of the study as per protocol no. EFC13889 submitted. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.
5.	**Name of the Drug:** Pregabalin **Protocol No** : **A0081106** **Phase of the Study:**	**Risk versus benefit to the patients**: In light of the fact that the test drug is already marketed in India, the safety	**Recommendation of the SEC:** After detailed deliberation, the committee recommended conduct of this extension study

	Phase III **Name of the Applicant:** Sanofi-Synthelabo (India) Private Limited, Sanofi House, CTS No.117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai 400 072, India **Name of the Sponsor:** Sanofi-aventis recherché & developpement, 1, Avenue Pierre Brosso lette, 91380 Chilly-Mazarin, France **Name of the Manufacturer:** Sanofi-Winthrop Industrie Le Trait, Boulevard Industriel ,76580 Le Trait, France **Title**: A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab (SAR236553/ REGN727) Versus Ezetimibe in Asia in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy.	profile of the test drug, justify the conduct of the trial. **Innovation vis-a-vis existing therapeutic option-** The purpose of the study is to evaluate the safety and tolerability of Pregabalin as adjunctive therapy in pediatric subjects 1 month to 16 years of age with partial onset seizures and pediatric and adult subjects 5 to 65 years of age with primary generalized tonic-clonic seizures. **Unmet medical need in the country-** The test drug may be an alternative treatment option as adjunctive therapy in pediatric subjects 1 month to 16 years of age with partial onset seizures and pediatric and adult subjects 5 to 65 years of age with primary generalized tonic-clonic seizures.	protocol No. A0081106. The committee also noted that protocol No. A0081042 is not approved in India. Therefore this proposed extension study is not applicable for A0081042. 2. **Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.
6.	**Name of the Drug:** Bevacizumab **Protocol No** : **B7391003** **Phase of the Study:** Phase III	**Risk versus Benefit to the patients-** The safety profile of the test drug from preclinical repeat dose toxicity study, and clinical phase I PK study, justify the conduct of the	**1. Recommendation of the SEC:** After detailed deliberation the committee recommended conduct of the study. It is reiterated that if the proposed

	Name of the Applicant: Pfizer Limited, Pfizer Center, Patel Estate, Off S. V. Road, Jogeshwari (W), Mumbai 400102, Maharashtra, India **Name of the Sponsor:** Pfizer Inc, 235 East 42nd Street, New York, NY 10017, United States of America **Name of the Manufacturer:** Pharmacia & Upjohn Company 7000 Portage Road, Kalamazoo, MI 49001, USA **Title**: A phase 3 randomized, double-blind study of PF-06439535 plus Paclitaxel-Carboplatin and Bevacizumab plus Paclitaxel-Carboplatin for the first-line treatment of patients with advanced Non-Squamous Non-Small Cell Lung Cancer.	study. **Innovation vis a vis existing therapeutic option-** The propose of the study is to compare the confirmed objective response rate (ORR) by Week 19 following treatment with bevacizumab-Pfizer in combination with paclitaxel and carboplatin to bevacizumab-EU plus paclitaxel and carboplatin in patients who have not received previous treatment for advanced NSCLC **Unmet need-** Availability of bio-similar products from multiple companies will be helpful in controlling pharmacoeconomic scenario due to fair market competition and will result in benefit to patient	PI is not a medical oncologist there should be a fully trained medical oncologist from same institute. 2. **Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.
7.	**Name of the Drug:** Semaglutide **Protocol No** : NN9535-4216 **Phase of the Study:** Phase IIIb **Name of the Applicant:** Novo Nordisk India Private Ltd., Plot No.32, 47 - 50,EPIP Area,	**Risk versus Benefit to the patients-** The safety profile of the test drug from preclinical studies including single dose toxicity, repeat dose toxicity, reproductive and developmental toxicity and Clinical Phase I, II & IIIa studies, justify the conduct of the study.	**Recommendation of the SEC:** After detailed deliberation the committee recommended conduct of the trial subject to the following conditions 1. Dose titration with dulaglutide in line with the approved prescribing information. Accordingly the protocol should be suitably modified.

	Whitefield,Bangalore - 560 066 **Name of the Sponsor:** Same as above **Name of the Manufacturer:** Novo Nordisk A/S, NovoAlle, Bagsvaerd, Denmark, MI 49001, USA **Title**: Efficacy and Safety of Semaglutide versus Dulaglutide as add-on to Metformin in subject with type 2 diabetes.	**Innovation vis a vis existing therapeutic option-** The purpose of the study is to evaluate the efficacy and safety of semaglutide versus dulaglutide as add-on to metformin in subjects with type 2 diabetes. **Unmet need-** The test drug may be an alternative treatment option in subjects with type 2 diabetes.	2. 50 % trial sites must be govt. sites. 2. **Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.
8.	**Name of the Drug:** YLB113 **Protocol No** : YLB113-002 **Phase of the Study:** Phase IIIb **Name of the Applicant:** INC Research CDS services Pvt. Ltd., Building No. 14, Tower B, 14th Floor DLF Cyber City, Phase III, Gurgaon – 122001 Haryana , India **Name of the Sponsor:** YL Biologicals Ltd. 2-31-1, Nihonbashi-Hamacho, Chao-Ku, Tokyo, 103-007, Japan **Name of the Manufacturer:** AY Pharmaceuticals Co. Ltd. 6-8, Hachiman, Kawajima-mach, Hiki-	**Risk versus Benefit to the patients-** The safety profile of the test drug from preclinical studies including single dose toxicity, repeat dose toxicity, and Clinical Phase I study, justify the conduct of the study. **Innovation vis a vis existing therapeutic option-** The purpose of the study is to evaluate the Efficacy, Safety and Immunogenicity of YLB113 (Etanercept) and Enbrel (Etanercept) [Pfizer] for the Treatment of Rheumatoid Arthritis. **Unmet need-** Availability of bio- similar products from multiple companies will be helpful in controlling pharmacoeconomic scenario due to fair market competition	**1. Recommendation of the SEC:** After detailed deliberation the committee recommended conduct of the study subject to the conditions that 1. 50% of the trial sites should be from Govt. sites. 2. Methotrexate dose should be 15-25mg/week for Indian subjects. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation.

	gun, Saitama 350-0151 Japan **Title**: A Comparative Study to Assess the Efficacy, Safety and Immunogenicity of YLB113 and Enbrel for the Treatment of Rheumatoid Arthritis.	and will result in benefit to patient	

Annexure III

List of 09 cases of clinical trial proposals other than GCT/NCEs along with evaluations and recommendations of the Technical Committee in 30th Meeting.

Sl No	Name of the Drug	Firm Name	Recommendations: 1. Subject Expert Committee 2. Technical Committee
1.	Adalimumab	M/s Biocon Research Limited- SEZ Unit	1. **Recommendation of the SEC :** After detailed deliberation committee recommended for the phase III trial subject to the following conditions • The study site should be geographically distributed • Latent TB patients are to be excluded from the trial • If PPD skin test is negative Qunatiferon TB Gold test should be done to rule out latent TB • The follow up period of 2 month after last dose of the trial drug to be included **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
2.	Dengue Tetravalent Vaccine, Live Attenuated– Recombinant (Lyophilized)	Panacea Biotec Ltd	1. **Recommendation of the SEC** The committee deliberated the proposal in detail and recommended for conduct Phase I/II trial with following conditions: 1. The firm shall conduct cohort I study (Adult subjects) initially and submit the safety report to DSMB 2. The firm will start Cohort II (2 to 18 years) only after clearance of safety data by DSMB **2. Recommendation of the Technical Committee:**

			The Technical Committee recommended the proposal subject to the inclusion of investigators with specialization in medicine instead of pediatrician as the study population included adults in first phase. Also to include specialist in medicine as an investigator in one of the study site where pharmacologist is proposed as an investigator.
3.	HBI Pentavalent (DTwP-Hb-Hib[Liquid]) Combination Vaccine	Human Biologicals Institute	**1. Recommendation of the SEC:** The Committee deliberated the proposal in detail and recommended for approval with the condition that only those babies who has received birth dose of Hepatitis B vaccine will be included. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
4.	Pneumococcal Conjugate Vaccine (SIILPCV10)	Serum Institute of India Ltd	**1. Recommendation of the SEC:** The Committee deliberated the proposal in detail and recommended for the conduct of Phase II trial. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
5.	Test vaccine: Rabies G protein Vaccine (Dose: 10 µg/0.5 ml, Day 0,3)	M/s Cadila Pharmaceuticals Limited	**1. Recommendation of the SEC:** The committee deliberated the proposal in detail and recommended for conduct of Phase III trial.

			2. Recommendation of the Technical Committee: After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
6.	Fixed dose combination of Minoxidil 5 % and Finasteride 0.1 % Lipid Solution for Topical Application	M/s Intas Pharmaceuticals Ltd	**1. Recommendation of the SEC:** The committee noted that the FDC is already approved by CDSCO and after detailed deliberation, committee recommended for conducting the trial with following conditions : 1. Age criteria for enrolling the patients shall be kept from 18 to 45 years. 2. Area of application shall be clearly defined as per the standard text books. 3. Only patients of Alopecia Hamilton grading II to IV shall be enrolled. 4. The investigators must possess MD (Dermatology) qualification. 5. The sample size shall be minimum of 160 patients. Accordingly, the firm shall submit the revised protocol to CDSCO for grant of permission to conduct the proposed trial. The amended protocol has been submitted to CDSCO for consideration. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
7.	Capecitabine and Cyclophosphamide	M/s Sanofi-Synthelabo (India) Private Limited	**1. Recommendation of the SEC:** The Committee recommended the inclusion criteria to be following. • Recurrence of the disease following at least two lines of Chemotherapy for metastatic triple negative Breast cancer. • In ER/PR positive Breast cancer,

			recurrence of the disease following at least one line of chemotherapy and failure of at least two lines of hormonal therapy. • Accordingly, the Exclusion criteria to be modified. The committee recommended for conducting phase II study with above changes and accordingly revised protocol should be submitted for grant of permission. The amended protocol has been submitted to CDSCO for consideration. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
8.	Cisplatin	Dr. Hemanth Raj .E	**1. Recommendation of the SEC:** The PI presented the investigator initiated study which was deliberated and recommended by the Committee as submitted. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended to conduct the study as per the SEC recommendation.
9.	Oxaliplatin	Dr. Hemanth Raj .E	**1. Recommendation of the SEC:** The PI presented the investigator initiated study which was deliberated and recommended by the Committee as submitted. **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 05 cases of Clinical trial waiver in Indian populations:

Sr. no.	Drug Name	Name of the Firm	Indication	1. Recommendations of the SEC 2. Recommendations of the Technical Committee
1.	Spectranetics Laser Sheath	M/s. Clairvoyance Consulting	These are intended for use as adjuncts to conventional lead extraction tools in patients suitable for transvenous removal of chronically implanted pacing or defibrillator leads constructed with silicone or polyurethane outer insulation in patients suitable for transvenous removal of chronically implanted pacing or defibrillator leads constructed with silicone or polyurethane outer insulation	**1. Recommendations of the SEC:** The committee after deliberation recommended that the product is not yet approved for use in Indian patients. Hence, a clinical study needs to be conducted to establish the safety and efficacy on Indian population, with statistically significant sample size. Firm may be directed to submit protocol for further consideration by the experts. However, the firm has applied for Clinical Trial waiver for the subject mentioned products and the case again deliberated SEC – Cardiology on 30.10.2015 and the committee opined that, the permission for the import of **Spectranetics Laser Sheath** may be granted because there is an unmet need for lead extraction and there is no established safe therapy available. This approval is subject to condition that the firm shall submit sub analysis of Post marketing surveillance data for 2 years at the interval of every six months. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended for waiver of local clinical trial as per the SEC recommendation.
2.	Tracheo-bronchial Silicone Stent	M/s. Shreyass Healthcare	The GSS intended to maintain opened airways, after dilatation of the Stenosis or	**1. Recommendations of the SEC:** The experts opined that, the product is already being used in the clinical practices freely more

			resection of the obstruction. For maintain opened airways, after dilatation of the Stenosis or resection of the obstruction, in particular in case of, • Trachea-bronchial tumors. • Tracheal stenoses with scarring. • Stenoses following surgical anastomosis, resection or pulmonary transplantation. • In general after any diminuation of the diameter by inner or outer compression.	than 10 years in India. Hence, a clinical trial on Indian population is not required. The product is also available globally. The committee recommended that import permission may be granted for Tracheo-Bronchial silicon stents with the condition that the firm shall submit PMS data every six months for 2 years. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended for waiver of local clinical trial as per the SEC recommendation.
3.	Implantable Balloon	M/s. Encarta Pharma Pvt. Ltd	The In Space biodegradable implantable balloon (spacer) is used as a spacer to reduce friction between the acromion and the humeral head or Rotator Cuff to allow smooth gliding of the humeral head against the acromion. The indications for the InSpace include: • Scarred or torn tendon due to trauma or degradation, • Absence of tendon /muscle or non-functional tendon/ muscle • Ruptured tendon	**1. Recommendations of the SEC:** The committee after deliberation opined that the applicant presented their case but failed to submit published data on efficacy of the product as desired by the committee. No randomized trials have been done so far. The Committee therefore, recommended that published data on randomized control trials need to be submitted for further review by the Committee. The firm has submitted the above asked data and deliberated by SEC – Orthopaedics in its meeting held on 05.11.2015. The Committee recommended that the firm shall conduct the clinical trial to generate data on Indian population; accordingly clinical trial protocol shall be submitted to the Committee for further review.

				2. Recommendation of the Technical Committee: The firm has represented to Directorate General of Health Services for consideration of their proposal for grant of import and marketing of the device in the country based on the Global clinical data generated on the product. The product is approved in European countries (the Netherland), Israel, South Africa and South Korea. After detailed deliberation, the Committee noted that the device is already approved and being used in European and other countries as mentioned above and as such there is no further requirement of conduct of clinical trial in Indian population for such medical device. Therefore, the Committee desired to call the subject expert in Orthopedics for deliberation in the next Technical Committee meeting and also desired to call the firm to present the proposal before the Committee.
4.	Pulsecath Ivac3l	M/s. Meril Life Sciences India Pvt. Ltd	It is indicated for use in patients with impaired left ventricular function which require left ventricular mechanical circulatory support for upto 24 hours. It can be positioned in the left ventricular cavity through the subclavian/ axillary artery, or through the aortic wall during open-chest surgery. The iVAC3L-ST (Short Tip) has a shorter tip part and can only be used in case of direct insertion in the	**MDAC recommendation on 30/06/2014:** The Committee after deliberation recommended that the firm is need to conduct Clinical Trial on Indian Population on minimum of 30 patients as there is no latest human clinical data. Accordingly, this office has requested to the firm to submit the clinical trial protocol vide letter dated 14.07.2014 for MDAC further review. In response to that, the firm has requested to this office for clinical trial waiver of and the same has

			aortic arch, during open-chest surgery. The iVAC3L-ST is especially indicated in case the insertion site is located close to the aortic valve	been again discussed in MDAC Cardiovascular held on 21.10.2014 . **Recommendation on 21.10.2014:** The committee deliberated and recommended that the firm's application for waiver of clinical trial of said product may not be considered and this office informed to the firm vide letter dated 03.11.2014 to submit the protocol as per letter dated 11.07.2014. The firm represented to Directorate General of Health Services vide letter dated 05.08.2015 for the clinical trial waive off based on the Unmet need and based on similar case of M/s. Edward Life Sciences Pvt Ltd., Mumbai discussed in the 19th Apex Committee held on 24.12.2014 and the same is placed before the Committee. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee noted that the device is already approved and being used in countries like Netherland, Austria, Germany and as such there is no further requirement of conduct of clinical trial in Indian population for such medical device. Therefore, the Committee desired to call the subject expert in Cardiology for deliberation in the next Technical Committee meeting and also desired to call the firm to present the proposal before the Committee.

5.	Talcum	M/s. Shreyass Healthcare	It is intended to be used in patients with mainly malignant but sometimes also benign pleural effusions or spontaneous pneumothorax for which the treating physician decides that pleurodesis is appropriate	**1. Recommendations of the SEC:** The Committee after deliberation opined that the firm should submit the detailed evidence of safety & efficacy of the product in Indian patients so far used in the country and the year wise sale data of the product from all over the country. The firm has submitted the documents as asked vide above dated meeting and the case has been deliberated by SEC – Pulmonary on 29.10.2015, the firm has presented the testimonials in clinical use in Indian population. The experts opined that, the product is already being used in the clinical practices freely more than 10 years in India. Hence, a clinical trial on Indian population is not required. The product is also available globally. The committee recommended that import permission may be granted with the condition that the firm shall submit PMS data every six months for 2 years. **2. Recommendation of the Technical Committee:** After detailed deliberation, the Committee recommended for waiver of local clinical trial as per SEC recommendation.

ADDITIONAL AGENDA

S. No: 01

This office has received an application from M/s Stempeutics Research Pvt. Ltd., Bangalore for grant of permission to manufacture and market Adult Human Bone Marrow derived, Cultured, Pooled, Allogenic Mesenchymal Stromal Cells (Brand name Stempeucel®) for IM Injection.

The proposal of M/s Stempeutics Research Pvt. Ltd., Bangalore was deliberated in the meeting held on 03/02/2015 for clarification of MOM of 7th CBBTDEC meeting. The committee studied the regulatory perspective of Pharmaceuticals & Medical Devices agency (PMDA), Japan and recommended that the company be given conditional approval. They should increase the no. to 200 with 2 million dose to be conducted in period not exceeding two years before seeking marketing authorization.

The said proposal was further discussed in the 27th meeting of Technical Committee held on 23.07.2015 under the chairmanship of DGHS and the committee is seeking CBBTDEC's view as what is meant by "conditional approval" as per PMDA model, in how many patients it shall prove major/significant improvements efficacy and what further condition shall be put with respect to further studies and charging the patients.

The recommendation of Technical Committee was forwarded to the CBBTDEC experts on 19/08/2015 to give their opinion/ comments in this regard.

The CBBTDEC in their meeting held on 29/10/2015 has deliberated on the issues raised by the Technical Committee. The following clarification has been submitted by the CBBTDEC.

a) What is meant by "Conditional Approval" as per PMDA model?

PMDA Japan has implemented a new regulatory frame work in November 2014 for regenerative medicine products (RMP) considering the importance of earlier access of these products by the patients for unmet medical needs. PMDA has revised Pharmaceutical Affairs Law for RMP and the Japan's parliament has enacted the Bill. The Bill allows the Japanese Government to give conditional approval to such products if their safety is confirmed and expectable efficacy trends are demonstrated in early stage of clinical trials, as may occur on completion of Phase II.

CBBTDEC in their last meeting held in Feb 2015 under the chairmanship of Dr. V M Katoch, opined that Stempeutics has demonstrated enough safety and efficacy of their product in the Phase I and Phase II clinical trials and hence recommended conditional approval of Stempeucel for manufacturing and marketing as per PMDA model. It was felt that this will provide clinical benefit to the patients over and above the existing treatment. During the conditional approval period, the company is obliged to conduct post marketing clinical studies in compliance with Good Post Marketing Study Practice (GPSP) and Good Vigilance Practice (GVP).

b) How many patients can be treated during the conditional approval period?

Revised PMDA Act is silent regarding the number of the patients it shall prove significant improvement/efficacy. It may be decided from case to case basis.

During 7th CBBTDEC meeting held on 9th December 2014, the members deliberated on the data/application presented by the Stempeutics Research Pvt. Ltd. and arrived at the decision that Stempeutics has demonstrated the safety and efficacy of their product in the Phase I and Phase II clinical trials with substantial improvement in 36 patients of CLI with Burger's Disease in 2 million cells per kg body weight dose and hence recommended conditional approval of Stempeucel for manufacturing and marketing as per PMDA model.

CBBTDEC felt that considering the phase II data and the disease prevalence of Critical Limb Ischemia due to Buerger's Disease in India, the company should increase the number of patients in the effective arm i.e. 2 million cells per kg body weight to 200. The company was advised to submit the data of cumulative 200 patients before seeking full marketing authorization. This should be completed within the next two years.

c) What price the company can charge for the product during the conditional approval period?

The committee felt as per the PMDA model, the company may levy reasonable service charges during the conditional approval period. Since it is a new drug and the approval is being given at the earlier stage, the company may be recommended to supply the product at its cost. The company may intimate the cost to the regulatory authorities before starting the treatment. After negotiations, it was finalized as 1.5 lakhs and further breakup details need to be submitted by the company.
Accordingly, the proposal was discussed in the Technical Committee.

Recommendation of the Committee:

After deliberation, the Committee recommended that in the patients who are given this product during the conditional approval, the firm shall provide the detailed list of existing standard/ current medical care that the patients will be receiving and recommended the proposal as per the CBBTDEC recommendation

S. No 02

This office has received an application from M/s APAC Biotech Pvt. Ltd, Gurgaon for Marketing Authorization of APCEDEN™ [Dendritic Cell (DC) product].

The proposal of M/s APAC Biotech Pvt. Ltd, Gurgaon was deliberated in the meeting held on 03/02/2015 for clarification of MOM of 7th CBBTDEC meeting. The Committee studied the regulatory perspective of Pharmaceuticals & Medical Devices agency (PMDA), Japan and recommended that the company be given conditional approval. They should increase the number of patients to 439 to be conducted in period not exceeding two years before seeking marketing authorization.
Further the proposal has been deliberated in the 27th Technical Committee meeting held on 23.07.2015 in which the committee opined that the data presented by the firm is more presumptive about approval. The recommendations of the CBBTDEC are not supported with the basis of approval as:-

1. In how many patients major improvement noted and in how many it is required in one particular indication;

2. What is the criteria for approval of indication in such "already in the practice" cell based product for "conditional approval" (either based on PMDA or CBBTDEC's guidelines).

However, Committee acknowledged that if it is 19% improvement in the various tumors, it is considered as a major improvement. Therefore, the proposal may be referred back to CBBTDEC for review.
Similarly, a general comments or CBBTDEC's view as what is meant by "Conditional approval" as per PMDA model and in how many patients it shall prove major/ significant improvements/ efficacy and what further condition shall be put with respect to further studies and charging the patients, may be obtained.

The CBBTDEC in their meeting held on 29/10/2015 has deliberated on the issues raised by the Technical Committee. The following clarification has been submitted by the CBBTDEC.

1. In how many patients major improvement noted and in how many it is required in one particular indication:
    - The committee was informed by the firm that improvement was noted on an average in 5 subjects in each condition of Ovarian, Prostrate, Colorectal, Lungs cancers.
    - As cancer is largely an unmet need, it was suggested to consider 15-20% improvement as substantial efficacy.
    - The committee opined that as a general principle, the significant and remarkable clinical improvement shall be observed in 5 to 10 patients in life threatening indication for consideration of conditional approval.

2. What are the criteria for approval of indication in such "already in the practice" cell based product for "conditional approval" (either based on PMDA or CBBTDEC's guidelines).

- PMDA Japan has implemented a new regulatory frame work in November 2014 for regenerative medicine products (RMP) considering the importance of earlier access of these products by the patients for unmet medical needs. PMDA has revised Pharmaceutical Affairs Law for RMP and the Japan's parliament has enacted the Bill. The Bill allows the Japanese Government to give conditional approval to such products if their safety is confirmed and expectable efficacy trends are demonstrated in early stage of clinical trials, as may occur on completion of Phase II.

Similarly, a general comments or CBBTDEC's view as what is meant by "Conditional approval" as per PMDA model and in how many patients it shall prove major/ significant improvements/ efficacy and what further condition shall be put with respect to further studies and charging the patients, may be obtained.

- APAC need to include only those cancer conditions in which substantial safety and efficacy has been demonstrated. Hence, the committee recommended conditional approval for enhancing the number to 200 including 50 numbers in each of ovarian, Prostate, Lung and Colorectal Cancer patients. The company was advised to submit the data of 200 patients before seeking full marketing authorization. This should be completed within one year duration.
- For rest of the cancer types, APAC needs to conduct well designed clinical trial including appropriate controls after obtaining approval from DCG(I)

The committee felt as per the PMDA model, the company may levy reasonable service charges during the conditional approval period. Since it is a new drug and the approval is being given at the earlier stage, the company may be recommended to supply the product at its cost. After negotiations, it was finalized as Rs 87500 per dose (of six dose treatment) excluding hospital charges and further breakup details need to be submitted by the firm.

Accordingly the proposal was discussed in the Technical Committee.

Recommendation of the Committee:

The Committee deliberated the issue and required explanation and presentation from the applicant regarding the specific cancer condition that are to be considered as proven treatable indications based on result of clinical trials in general and specifically with regard to lung cancer. The Committee also sought the details of such product's approval status in other countries,

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