MINUTES OF THE 26th MEETING OF THE APEX COMMITTEE HELD ON 10-12-2015 UNDER THE CHAIRMANSHIP OF SECRETARY, HEALTH AND FAMILY WELFARE FOR SUPERVISING CLINICAL TRIALS ON NEW CHEMICAL ENTITIES IN THE LIGHT OF THE DIRECTIONS OF THE HON'BLE SUPREME COURT OF INDIA DATED 03.01.2013.

Present:

1. Shri B. P. Sharma,
   Secretary, Department of Health and Family Welfare
   and Chairman, Apex Committee

2. Dr Soumya Swaminathan,
   Secretary, Department of Health Research and
   DG, ICMR.

3. Dr. Jagdish Prasad,
   Director General of Health Services,New Delhi

Special Invitee:

1 Shri K. B. Aggrawal
  Addl. Secretary (Food and Drugs)
  Department of Health and Family Welfare, New Delhi

2 Dr G N Singh ,
  Drugs Controller General(I)

3 Dr. V.G. Somani,
  Joint Drugs Controller (I), FDA Bhawan, New Delhi

Initiating the discussion, the Chairman, Apex Committee welcomed the members of the Committee and special invitees to the meeting. Thereafter, the Committee deliberated upon each of the agenda items and recommended as following-

Item No. 1. Proposals of Clinical Trials related to New Chemical Entities (NCEs) recommended by Technical Committee.

(i) 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 advanced breast cancer which progressed on or after aromatase inhibitor treatment.

The Apex Committee after detailed deliberations, concurred with the recommendations of Technical Committee for approval of clinical trial protocol for conduct of the study, as detailed in agenda notes annexed herewith as **Annexure-I.**

(2) 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.

The Apex Committee after detailed deliberations, concurred with the recommendations of Technical Committee for approval of clinical trial protocol for conduct of the study, as detailed in agenda notes annexed herewith as **Annexure-I.**

Item No. 2. Waiver of Clinical Trial in Indian population for approval of New Drugs and Devices falling under the category of Drugs, which have already been approved outside India.

(1) Tracheo-bronchial Silicone Stent of M/s. Shreyass Healthcare.

The Apex Committee after detailed deliberations concurred with the recommendations of Technical Committee for approval of waiver of local clinical trial, as detailed in agenda notes annexed herewith as **Annexure-II.**

(2) Talcum of M/s. Shreyass Healthcare

The Apex Committee after detailed deliberations concurred with the recommendations of Technical Committee for approval of waiver of local clinical trial, as detailed in agenda notes annexed herewith as **Annexure-II.**

(3) Spectranetics Laser Sheath of M/s Clairvoyance Consulting.

The Apex Committee after detailed deliberations concurred with the recommendations of Technical Committee for approval of waiver of local clinical trial, as detailed in agenda notes annexed herewith as **Annexure-II.**

An agenda note for giving waiver to medical devices approved by the regulators of ICH countries with necessary safeguards be brought before the next meeting.

Item No. 3. Deliberation on proposal of M/s Stempeutics Research Pvt. Ltd., Bangalore for conditional approval of Adult Human Bone Marrow derived, Cultured, Pooled, Allogenic Mesenchymal Stromal Cells (Brand name Stempeucel®) for IM Injection for Critical Limb Ischemia due to Buerger's

Disease in India based on the recommendation of the CBBTDEC and Technical Committee.

The committee did not approve the proposal in view of PMDA model not having legal framework support in the country, but gave flexibility for continued clinical study in 200 patients on cost recovery basis, limited to Rs 1.5 lakh per patient in consultation with ICMR, as per the recommendation of CBBTDEC with condition that outcome of study shall be submitted to CDSCO for further evaluation.

The meeting ended with vote of thanks to & from the Chairman.

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Agenda Notes

26th Meeting of Apex Committee

Agenda

1. Proposals of Clinical Trials related to New Chemical Entities (NCEs) recommended by Technical Committee.
2. Waiver of Clinical Trial in Indian population for approval of New Drugs and Devices falling under the category of Drugs, which have already been approved outside India.
3. Deliberation on proposal of M/s Stempeutics Research Pvt. Ltd., Bangalore for conditional approval of Adult Human Bone Marrow derived, Cultured, Pooled, Allogenic Mesenchymal Stromal Cells (Brand name Stempeucel®) for IM Injection for Critical Limb Ischemia due to Buerger's Disease in India based on the recommendation of the CBBTDEC and Technical Committee.

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Item No: 01

Proposals of Clinical Trials related to NCEs recommended by Technical Committee.

The Technical Committee evaluated the 03 cases related to clinical trial of NCEs 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 recommendations of the Technical Committee in respect of these 02 cases related to clinical trial of NCEs which were recommended by the Technical Committee are enclosed as **Annexure-I.**

The details of these 02 proposals and recommendations of the Technical Committee and SEC are as given below for consideration of Apex Committee:

1) Proposal No: 01

Phase III study of the drug Alpelisib (BYL719) is a Global Clinical trial which will be carried out in Germany besides India vide Protocol No: CBYL719C2301, details of which are as following:

Protocol title of the Clinical trial:	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 advanced breast cancer which progressed on or after aromatase inhibitor treatment.
Name of the Drug:	Alpelisib (BYL719)
Name of the Applicant	Novartis Healthcare Private Limited, India
Name of the Sponsor:	Same as above
Name of the Manufacturer:	Novartis Pharma AG, Lichtstrasse 35, CH-4056 Basel, Switzerland
Type of Clinical Trial:	Global
Phase of the study:	Phase-III

Consideration by Subject Expert Committee:

The proposal was deliberated upon by 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 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 Principal Investigator or Co-Investigator.

Recommendations of the SEC are at **Annexure –I.**

Consideration by Technical Committee

After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation. Recommendations of the Technical Committee are at **Annexure –I**

The Committee may deliberate the proposal and give its recommendations.

Proposal No: 02

Phase III study of the drug LEE011 is a Global Clinical trial which will be carried out in USA, Canada, Germany, Denmark and Sweden besides India vide Protocol No: CLEE011F2301, details of which are as following:

Protocol title of the Clinical trial:	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.
Name of the Drug:	LEE011
Name of the Applicant	Novartis Healthcare Private Limited, India
Name of the Sponsor:	Same as above
Name of the Manufacturer:	Novartis Pharma AG, Lichtstrasse 35, CH-4056 Basel, Switzerland.
Type of Clinical Trial:	Global
Phase of the study:	Phase-III

Consideration by SEC Committee:

The proposal was deliberated upon by 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 Principal Investigator or Co-Investigator.

Recommendations of the SEC are at **Annexure –I.**

Consideration by Technical Committee

After detailed deliberation, the Committee recommended the conduct of the study as per the SEC recommendation. Recommendations of the Technical Committee are at **Annexure –I**

The Committee may deliberate the proposal and give its recommendations.

Item No: 02

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

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

The Committee may deliberate the proposals and give its recommendation.

Item No: 03

Deliberation on proposal of M/s Stempeutics Research Pvt. Ltd., Bangalore for conditional approval of Adult Human Bone Marrow derived, Cultured, Pooled, Allogenic Mesenchymal Stromal Cells (Brand name Stempeucel®) for IM Injection for Critical Limb Ischemia due to Buerger's Disease in India based on the recommendation of the CBBTDEC and Technical Committee.

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 Minutes of Meeting 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 to 200 with 2 million doses 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 where 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 Technical Committee:
After deliberation, the Technical 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

The Committee may discuss the matter and give its recommendation.

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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 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 advanced breast cancer which progressed on or after aromatase inhibitor treatment.	**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.

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 3. 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. 4. 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.

Annexure-II

Recommendations of the 03 cases of Clinical trial waiver in Indian populations:

Sr. no.	Details of the proposals	Name of the Firm holding permission outside the country	Indication	1.Recommendation of the Technical Committee 2. Recommendation of the SEC
1.	Tracheo-bronchial Silicone Stent **Name of the Applicant:** M/s. Shreyass Healthcare **Composition:** Barium Sulphate filled studs for radiology, Gold Filled Studs. **Regulatory status:** Approved for marketing in France, Australia, European Union, Switzerland, Peru, Thailand, Chile and Venezuela.	**M/s. Novatech SA,** Z.I.A thelia III-1058, Voie Antippe, 13705 La Ciotat Cedex, France.	The GSS intended to maintain opened airways, after dilatation of the Stenosis or 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.	**1. Recommendations of the SEC:** 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 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.
2.	Talcum **Name of the Applicant:** M/s. Shreyass Healthcare **Composition:** Chemical formula for STERITALC is $Mg_3Si_4O_{10}(OH)_2$. **Regulatory Status:** Approved in France, Australia, European Union, Peru, Thailand, Chile and Singapore	**M/s. Novatech SA,** Z.I.A thelia III-1058, Voie Antippe, 13705 La Ciotat Cedex, France.	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.
3.	Spectranetics Laser Sheath Name of the Applicant: M/s. Clairvoyance Consulting. Composition: Polyimide fiber coating, cyanoacrylate, PVP coating reagent, Isopropyl alcohol, Plaitnum 90% & Iridium 10%; white Pebax, Stainless Steel. Regulatory Status: Approved for marketing in USA, European Union, Australia, Russia, Taiwan, Thailand, Costa Rica and many more.	**M/s. Spectranetics Corporation, 9965 Federal Drive, Colorado Springs, Colorado 80921**	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.