

**EIGHTH MEETING OF CELLULAR BIOLOGY BASED THERAPEUTIC DRUG
EVALUATION COMMITTEE (CBBTDEC), HELD ON 29 OCT. 2015 IN THE
CONFERENCE HALL, ICMR, NEW DELHI**

Ministry of Health & Family Welfare, Govt. of India constituted a Core IND panel of experts namely CBBTDEC vide order no. DCG(I)/Misc/2010/2010 (Pt. Stem Cells)/DFQC dated 01/09/2010. The Eighth meeting of the CBBTDEC was held on 29 Oct. 2015 at 11:00 A.M. in the Conference Hall, ICMR Headquarter, Ansari Nagar, New Delhi under the chairmanship of Dr. Soumya Swaminathan, Secretary, Department of Health Research & Director General, ICMR, New Delhi.

The following Expert panel members, ICMR members and CDSCO staff attended the meeting:

Expert Committee Members:

1. Dr. Soumya Swaminathan, Secretary & Director General, ICMR, New Delhi -110029.
2. Prof. N. K. Mehra, Dr C.G. Pandit National Chair and Former Dean (Research) and Ex-Head Dept. of Transplant Immunology & Immunogenetics, AIIMS, New Delhi.
3. Prof. D. Balasubramanian, Director (Research), L.V. Prasad Eye Institute Banajara Hills, Hyderabad 500034.
4. Dr. Rita Mulherkar, FNASc., ACTREC, Tata Memorial Centre, Navi Mumbai, 410210.

ICMR Members:

Dr. Vijay Kumar, Sr. Deputy Director General (Scientist G), ICMR, New Delhi.
Dr. Geeta Jotwani, Deputy Director General (Scientist 'E'), ICMR, New Delhi.

CDSCO Staff:

Dr. V. G. Somani, Joint Drugs Controller (I)
Dr. A. Ramkishan, Dy. Drugs Controller (I)
Mr. Shiv Kumar, Asst. Drugs Controller (I)
Mr. Rahul Panwar, Drugs Inspector

At the outset of the meeting, Dr. V. G. Somani, Dy. Drugs Controller (I) welcomed the expert members and briefed the Chair regarding issues tabled for the meeting. He said that the meeting was being held for the first time with Dr Swaminathan as the chair. He then invited the Secretary, DHR and DG, ICMR to chair the meeting and initiate the proceedings. The chairperson welcomed the members and thanked them for their time. She invited inputs from members on support and stimulate more Rand D in the field keeping in mind the ethics and the guidelines. She stressed that it is important to hold meetings of the committee at regular intervals so that all issues concerning cell based therapies are discussed without delay. She said we must take a pragmatic view of the scientific developments in the area of stem cell research and promote cell based therapies wherever applicable. Prof N.K. Mehra stated that the inter-agency meeting organized in July was very helpful in defining the role and jurisdiction of various committees associated with stem cell research. He expressed the need for organizing training and educational workshops for the benefit of researchers and physicians. Dr Balasubramaniam supported the views expressed and highlighted the current scenario including HSCT and the upcoming therapy using Limbal stem cells.

. On the basis of the discussions following recommendations were made:

General recommendations:

- The frequency of meeting needs to be increased and efforts should be made to hold quarterly meetings.

- The committee needs to be expanded by including experts in the field of clinical research and bio-statistics. Subject experts could be included as special invitees on the basis of the agenda tabled.
- CBBTDEC being the Technical Committee; therefore DCGI may consider taking the recommendations directly to the Apex committee for expediting the decisions.
- The recommendations of the committee should be detailed and well defined with the following components:
 - Evaluation of the proposals should be based on scientific strength of the proposal, available evidence and infrastructure available as per GMP, GLP guidelines.
 - The decision reached should be clear and without any ambiguity.
 - For inspection/ monitoring of clinical trial sites , the state FDAs need to be empowered for random/ periodic checks.

The representatives of the firms were then asked to make presentation of their respective proposals before the meeting for discussion and detailed deliberation.

The following proposals were considered and various questions raised by the member panel along with the opinion are as follows:

S.No.	Proposal	Recommendation
Agenda 1	<p>In continuation to the Fifth CBBTDEC meeting held 30/04/2014- Application from M/s Life Cell International Pvt. Ltd., Chennai for the issue of NOC for collection, processing and storage of Dental Stem Cells.</p> <p>The committee recommended to generate stability study data and to include certain safety tests and marker of storage in the protocol.</p>	After detailed deliberations, the committee opined that as of date, there is no scientific evidence and proof on the clinical utility of mesenchymal stem cells derived from the dental pulp of decidual teeth. Hence, NOC for collection, processing and storage of Dental Pulp Stem Cells was not recommended.
Agenda 2	<p>In continuation to the Fifth CBBTDEC meeting held on 30/04/2014 - Application from M/s Life Cell International Pvt Ltd, Chennai for New Drug Approval (NDA)- Autologous stem cell product bone marrow aspirate concentrate (BMAC) for No Option-Critical Limb Ischemia (CLI).</p> <p>The committee recommended for approval of the device only.</p> <p>The firm has again approached this office and stated that this was not the intent of application as their device is already registered with DCG(I) office and requested for New Drug Approval.</p>	After detailed deliberations, the committee opined that the firm must first substantiate the efficacy of BMAC for no option CLI. Accordingly, the firm needs to submit Phase III protocol with adequate numbers for statistical significance. They were also advised to submit clinical trial data of BMAC in CLI conducted by Harvest Technology Pvt. Ltd, in USA, Germany etc.
Agenda 3	<p>In continuation to the Third CBBTDEC meeting held on 07/08/2014- Application from M/s Life Cell International Pvt. Ltd., Chennai for collection and storage of Mesenchymal stem cells (MSC) from menstrual blood and umbilical cord.</p> <p>The committee recommended that the firm shall submit following documents:</p> <ol style="list-style-type: none"> 1. Separate application for collection, processing, expansion and storage and sale of Mesenchymal Stem cells from various human sources, and also inform whether the subject products are 	After detailed deliberations, the committee opined that as of date, there is no scientific evidence and proof on the clinical utility of mesenchymal stem cells derived from menstrual blood and umbilical cord. Hence, NOC for collection, processing, expansion and storage and sale of Mesenchymal Stem cells from various human sources was not recommended.

	<p>pharmacopoeial products.</p> <p>2. Pre-clinical report/data generated in India.</p> <p>3. Clarify, if Mesenchymal Stem Cell at some stage is minimally manipulated?</p>	
Agenda 4	<p>In continuation to the Fourth CBBTDEC meeting held on 21/05/2013- Application from M/s Frontier Life Line, Chennai regarding application for permission to develop and manufacture 1. Tissue Engineered Bovine Pericardium, 2. Tissue Engineered Bovine Jugular Vein, 3. Tissue Engineered Porcine Pulmonary Artery for treatment of unmet medical needs.</p> <p>The committee recommended to submit the following:</p> <ol style="list-style-type: none"> 1. Application for Phase III protocol as per the provisions of Drugs and Cosmetics Act and Rules. 2. An application should be made for the inspection and accreditations of the manufacturing sites under intimation to this office. 3. Special safeguards should be incorporated against xenogenic infections under intimation to this office. 	<p>After detailed deliberation and reviewing the retrospective data presented by Dr. K. M. Cherian, the committee opined that the proposal for phase III trial may be recommended subject to clarification on the following:-</p> <ol style="list-style-type: none"> 1. Facility audit for GMP consisting of one CBBTDEC/ ICMR expert, one representative from CDSCO(HQ), SLA, Tamilnadu and CDSCO(SZ), Chennai. 2. Protocol should be amended including comparison group as a control arm in the non-vascularised bed. 3. The protocol should be amended to include primary and secondary end points for all three xenografts. 4. For the export of biological materials, it is mandatory to obtain an NOC from HMSC, ICMR.
Agenda 5	<p>Application from M/s Regenerative Medical Services Pvt. Ltd., Mumbai for application for grant of permission to conduct Phase III clinical trial titled “ A prospective, open label, multi-centric study to assess the safety and efficacy of Autologous Adult Live Cultured Buccal Epithelial cells (MUKOCELL) in subjects with urethral strictures.” Protocol No. RMS/MU/UR/1502, version No. 1.0 dated 10/06/2015.</p>	<p>After detailed deliberation and reviewing the data presented by M/s RMS Pvt. Ltd, Mumbai, the committee recommended conducting Phase IIb clinical trial instead of Phase III clinical trial of Autologous Adult Live Cultured Buccal Epithelial cells (MUKOCELL) in subjects with urethral strictures. Accordingly, the firm should submit the revised protocol to the office of DCG(I).</p>
Agenda 6	<p>In continuation to the Sixth CBBTDEC meeting held on 09.09.2014 - Application from M/s Reliance Life Sciences Pvt. Ltd., Navi Mumbai for permission to conduct Phase I/II clinical trial titled “Prospective, randomized, open label, double arm, dose finding clinical study of <i>R-HSC-008</i> as an adjunct cell based therapy as a prophylaxis for aGvHD after allogeneic Hematopoietic Stem Cell Transplantation- Phase I/II (Protocol No.: RLS/RM/HSC/2012/04;</p>	<p>After detailed deliberations, the committee suggested to modify the protocol in view of the following:-</p> <ol style="list-style-type: none"> 1. The protocol should be amended to Phase IIa instead of Phase I/II. 2. The trial should be restricted to single dose i.e. 4 millions cells/kg body wt. Justification for the same along with published evidence to be submitted. 3. AEs and SAEs need to be defined and dealt with as per existing guidelines.

	version 02, dated 05.12.2014)”. The committee recommended that the firm shall submit justification for sample size calculation and IC-SCR approval need to be taken. The committee also recommended that the firm shall explain the type of cases to be evaluated and take target groups where a GvHD is high.	4. The protocol should be amended to include primary and secondary end points.
Agenda 7	Application from M/s Reliance Life Sciences Pvt. Ltd., Navi Mumbai for permission to conduct Phase I/II clinical trial titled “A Prospective, randomized, open label, double arm, controlled multi-centric, dose escalation clinical study to evaluate the safety and efficacy of R-HSC-010 in prevention of progression of chronic kidney disease stage III”, Protocol No.: RLS/RM/HSC/2012/06; version 01, dated 06.11.2013.	After detailed deliberation, the proposal to conduct Phase I/II clinical trial was not recommended due to the following concerns:- <ol style="list-style-type: none"> 1. Committee opined that the trial design is conceptually incorrect. 2. R-HSC-010 is a combination product of Umbilical Cord derived Mesenchymal Stem Cell and CD34+ cells from two mismatched/partially matched individuals, in effect the HLA match with the recipient will be jeopardised. 3. The route of administration of the investigational product was mis-conceptualized.
Agenda 8	Application from M/s Nexus Clinical Research (I), Ltd., Navi Mumbai for permission to conduct Phase II/III clinical trial titled “A Prospective, Phase II/III, open, single arm and multicentric clinical study to evaluate the safety and efficacy of fetal progenitor cell transplantation for treatment of Idiopathic Pulmonary Fibrosis (IPF). Protocol No.: NEX/EMP/IPF/CT-II/III/2014; version 1.0, dated 11/02/2015.	After detailed deliberations, the committee recommended to conduct Phase IIa clinical trial including appropriate control arm with the following suggestions:- <ol style="list-style-type: none"> 1. Include some Government Medical College/Hospitals as clinical trial sites. <p>Accordingly, the firm should submit the revised protocol to the office of DCG(I).</p> <ol style="list-style-type: none"> 2. Facility audit for GMP consisting of one CBBTDEC/ ICMR expert, one representative from CDSCO(HQ), SLA, Mumbai and CDSCO(WZ), Mumbai.
Agenda 9	Application from M/s Nexus Clinical Research (I), Ltd., Navi Mumbai for permission to conduct Phase II/III clinical trial titled “A multi-centric, Prospective, randomized, open label, parallel group, Phase II/III clinical trial study to evaluate efficacy and safety of fetal progenitor cells transplantation of EmProCell Clinical research Pvt. Ltd., India versus Granulocytes Colony –Stimulating Factor (G-CSF), in the treatment of Liver Cirrhosis.. Protocol No.:	After detailed deliberations, the committee recommended to conduct Phase IIa clinical trial with following suggestions:- <ol style="list-style-type: none"> 1. Include some Government Medical College/Hospital as clinical trial sites. <p>Accordingly, the firm should submit the revised protocol to the office of DCG(I).</p> <ol style="list-style-type: none"> 2. Facility audit for GMP consisting of one CBBTDEC/ ICMR expert, one

	NEX/EMP/PRO/CT-II/III/2014; version 1.0, dated 10/02/2015.	representative from CDSCO(HQ), SLA, Mumbai and CDSCO(WZ), Mumbai.
Agenda 10	Annual status update report of Phase II clinical trial in patients with osteoarthritis of knee from M/s Stempeutics Research Private Ltd., Bangalore.	The Annual status report of the trial presented by the group was accepted by the committee and recommended for continuation of the study.
Agenda 11	<p>In continuation to the Seventh CBBTDEC meeting held on 09.12.2014 & 03/02/2015 -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.</p> <p>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.</p> <p>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.</p>	<p>The committee deliberated on the issues raised by the Technical Committee , Following are the clarifications for the same:-</p> <p>a) What is meant by "Conditional Approval" as per PMDA model?</p> <p>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.</p> <p>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).</p> <p>b) How many patients can be treated during the conditional approval period?</p> <p>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.</p>

		<p>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.</p> <p>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.</p> <p>c) What price the company can charge for the product during the conditional approval period?</p> <p>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.</p>
Agenda 12	<p>In continuation to the Seventh CBBTDEC meeting held on 09.12.2014 & 03/02/2015- Application for Marketing Authorization from M/s APAC Biotech Pvt. Ltd, Gurgaon for APCEDEN™ [Dendritic Cell (DC) product].</p> <p>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 439 to be conducted in</p>	<p>The committee deliberated on the following issues as raised by the Technical Committee:-</p> <ol style="list-style-type: none"> 1. In how many patients major improvement noted and in how many it is required in one particular indication: <ul style="list-style-type: none"> • The committee was informed by the firm that improvement was noted on an average 5 subjects in each condition of

<p>period not exceeding two years before seeking marketing authorization. Further the proposal has been deliberated in the 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:-</p> <ol style="list-style-type: none"> 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). <p>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.</p>	<p>Ovarian, Prostrate, Colorectal, Lungs cancers.</p> <ul style="list-style-type: none"> • 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. <ol style="list-style-type: none"> 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). <ul style="list-style-type: none"> • 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. <p>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.</p> <ul style="list-style-type: none"> • APAC need to include only those cancer conditions in which substantial
---	--

		<p>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.</p> <ul style="list-style-type: none"> • For rest of the cancer types, APAC needs to conduct well designed clinical trial including appropriate controls after obtaining approval from DCG(I) <p>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.</p> <ul style="list-style-type: none"> • The DCG(I) was asked to share the outcome of inspection conducted by them at different sites of APAC on receiving complaints from Swasthya Adhikar Manch, Pune.
--	--	--