**Decisions taken in the 62nd Meeting of the Genetic Engineering Approval Committee (GEAC) held on 13th January 2006.**

The 62nd Meeting of the Genetic Engineering Approval Committee was held on 13th January 2006 in the Ministry of Environment and Forests under the Chairmanship of Dr Amit Ghosh, Co-Chairman GEAC.

**Decisions**

**1.0: Permission for import of EPREX R(Epoetin alpha) from M/s. Fisher Clinical Services, Singapore for conducting phase III clinical trials in India by M/s Synchron Research Services Pvt Ltd. Ahemdabad**

1.1 During the deliberations, one of the Members pointed out that the need for conduct of Phase-III clinical trials is not clear since the product Eprex (Epoetin alpha) is already marketed in India by Johnson and Johnson. The Member Secretary, GEAC clarified that the product has not been approved by the GEAC. The representative of DCGI informed the Committee that the product has been approved by the DCGI. The possibility of the product being approved by DCGI prior to 1990 i.e before the Rules 1989 was implemented was also noted by the Committee. After detailed deliberations it was decided to obtain the following information/clarifications:-

a. The source from where Eprex is being procured.

b. Details of the approval granted by DCGI in respect of EPREX. DCGI to also clarify whether phase-III clinical trials have been conducted in India prior to market authorization.

c. A format legal notice to be issued to Johnson and Johnson seeking justification for not obtaining the approval of GEAC prior to marketing EPREX in India after obtaining the confirmation from DCGI.

**2.0: Permission for manufacture & marketing of r Hepatitis B by Human Biological Immunological, Hyderabad.**

2.1 The Committee noted that the Company has completed the conduct of Phase-III clinical trials in accordance with the approvals granted by the GEAC and DCGI. The Committee considered the present request for manufacture and marketing of r-human Hepatitis B vaccine in India and noted the recommendations received from the Experts.

2.2 On the issue of the containment facility, the Committee noted that the IBSC has not made any specific recommendation on this issue in the minutes of the IBSC meeting dated 21.11.2005. The Member Secretary, RCGM informed the Committee, that subsequently, observations of IBSC on the adequacy of the containment facility were called for by the RCGM. In the RCGM meeting held on 26.12.2005, the report of the IBSC was considered wherein it was concluded that the containment facility at R & D and production premises are adequate to meet the environmental safety regulation for production of r-Hepatitis B vaccine.

2.3 After detailed deliberations and taking into consideration the recommendation of RCGM and the Expert members, the Committee approved the manufacture & marketing of r Hepatitis B by Human Biological Immunological, Hyderabad subject to DCGI clearance.

**3.0: Permission for conduct of clinical trials of r-Mutant Tissue plasminogen Activator (TNK-t- PA) by M/s Emcure Biotech Ltd, Pune.**

3.1 The Committee noted that the Company proposes to conduct open label multi-centric non-comparative clinical trials to assess the efficacy and tolerability of TNK-TPA in the treatment of Acute Myocardial infraction at 6 centers with atleast 5 patients from each centre.

3.2 The Committee also noted that the pre-clinical toxicity data generated in laboratory animal system was examined by the RCGM in its meeting held on 21.9.2005 wherein it was concluded that the product was found to be safe for conduct of clinical trials.

3.3 To a query from one of the Experts regarding details about the mutants and data to show that the new variant is atleast as effective as the native t-PA. it was clarified that the Tenecteplase is the product name for TNK-t-PA and the same has been approved by USFDA.

3.4 After detailed deliberations and taking into consideration the recommendation of RCGM and the Expert members, the Committee approved the conduct of clinical trials with r-Mutant Tissue plasminogen Activator (TNK-t- PA) by M/s Emcure Biotech Ltd. Pune subject to DCGI clearance.

**4.0: Permission for conduct of clinical trials of Recombinant Human Granulocyte Macrophage Colony Stimulating Factor (r-GM-CSF) by M/s Emcure Biotech Ltd. Pune.**

4.1 The Committee noted that the Company proposes to conduct open non-comparative clinical trials to assess the efficacy and tolerability of r- GM-CSF in the treatment of Acute Myelogenous leukemia (AML) at three centers. About 30 patients will be enrolled for the study.

4.2 The Committee also noted that the pre-clinical toxicity data generated in laboratory animal system was examined by the RCGM in its meeting held on 27.10.2005 wherein it was concluded that the product was found to be safe for conduct of human clinical trials. The Committee further noted that r-GM-CSF is a drug approved for marketing in India.

4.3 After detailed deliberations and taking into consideration the recommendation of RCGM and the Expert members, the Committee approved the conduct of clinical trials with recombinant Human Granulocyte Macrophage Colony Stimulating Factor (r-GM-CSF) developed by the Company subject to DCGI clearance.

**5.0: Permission for conduct of clinical trials of r-erythropoietin by M/s Serum Institute of India, Pune.**

5.1 The Committee noted that the Company proposes to conduct a multi –Centric, randomized, single-blinded comparative two arm clinical trials to assess the efficacy and tolerability of r-erythropoietin at three 3 centers. About 30 patients per center will be enrolled in the study.

5.2 The Committee also noted that the pre-clinical toxicity data generated in laboratory animal system was examined by the RCGM in its meeting held on 25.5.2004 wherein it was concluded that the product was found to be safe for conduct of human clinical trials. The Committee further noted that r-erythropoietin is a drug approved for marketing in India.

5.3 After detailed deliberations and taking into consideration the recommendation of RCGM and the Expert members, the Committee approved the conduct of clinical trials with r-erythropoietin developed by the Company subject to DCGI clearance.

**6.0: Permission for conduct of clinical trials of Human Granulocyte Colony Stimulating Factor (r-G-CSF) and PEG-GCSF by Serum Institute of India, Pune**.

6.1 The Committee noted that the Company proposes to conduct multi-centric, comparative, non inferiority, three arm superiority clinical studies in three different centers with total of 135

patients having 45 patients per group. It was also noted that the Investigator and Centers where the clinical trials would be conducted has not been indicated.

6.2 The Committee also noted that the pre-clinical toxicity data generated in laboratory animal system was examined by the RCGM in its meeting held on 29.6.2005 wherein it was concluded that the product was found to be safe for conduct of human clinical trials. The Committee further noted that Human Granulocyte Colony Stimulating Factor (r-G-CSF) and PEG-GCSF is a drug approved for marketing in India.

6.3 After detailed deliberations and taking into consideration the recommendation of RCGM and the Expert members, the Committee approved the conduct of clinical trials with Human Granulocyte Colony Stimulating Factor( r-G-CSF) and PEG-GCSF developed by the Company subject to DCGI clearance after the Company identifies the Centers and Investigators for conduct of clinical trials.

**7.0: Approval for Installation of 300 L Fermentor / Bio-reactor of r-DNA Rituximab at Dr. Reddy's manufacturing unit for R& D purpose by Dr Reddy laboratories, Hyderabad**.

7.1 The Committee noted that the present application received on 13.12..2005 is for up-scaling the fermentor capacity to 300 L as the fermentation volume involved at R& D purpose are much more than the current installed capacity. /

7.2 After detailed deliberations and taking into consideration that the proposed activity has been approved by the IBSC and RCGM, the Committee approved the installation of 300 L Fermentor / Bio-reactor of r-DNA Rituximab by Dr Reddy's Laboratories Ltd for R&D purpose.

**8.0: Revalidation of permission for import & marketing of r-human interferon beta 1 a from M/s Industria Farmaceutica, Serono, S. P. A Italy by Serum Institute of India, Pune**.

8.1 The Member Secretary informed the Committee that the GEAC in its 27$^{th}$ meeting held on 8.8.2001 had approved the import & marketing of the above product from M/s Industria Farmaceutica, Serono, S.P.A Italy. As per the requirement of Rule 13 (2) of the 1989 Rules, the firm has requested for revalidation of the GEAC permission dated 22.8.2001 for a further period of two years.

8.2 The Committee conveyed their 'no objection' for revalidation of the GEAC clearance for a period of two years.

**9.0: Revalidation permission for import & marketing of r-human Insulin by Sun Pharmaceuticals Industries Ltd. Mumbai**.

9.1 The GEAC in its 9$^{th}$ Meeting held on 25.7.94 had approved the import of r human insulin injection in bulk from Eli Lilly, USA for further formulations in India for a period of four years. As per Rule 13(2) of the 1989 Rules approval of GEAC is valid for a period of four years at the first juncture and renewable for two years at a time.

9.2 In accordance with the above provisions, the approval was revalidated for a period of two years by the GEAC in the 39$^{th}$ Meeting of GEAC held on 3$^{rd}$ February 2004. Since the GEAC clearance expires on 2 February 2006, the Company has requested for revalidation of GEAC for two more years.

9.3 The Committee also noted that the GEAC permission was earlier accorded to M.J. Pharmaceuticals, Mumbai whose pharmaceutical business has now been taken over by Sun Pharmaceuticals India Ltd.

9.4 During the deliberations, one of the Members pointed out that the information submitted by the Company does not confirm the source from where r-human insulin is being procured. It was also noted that the applicant has not submitted information regarding the types of formulations produced and the quantity of the drug marketed by the Company in India at present and during the last 3 years.

9.5 Decision on the proposal was therefore deferred

**10.0: Permission to conduct clinical trials of r-human interferon alpha 2b (Reliferon) tm and to manufacture batches for proposed clinical trials by Reliance life Sciences Mumbai.**

10.1 The Committee considered the comments received and noted that DCGI, DBT and Experts have recommended the proposal.

10.2 The Committee also noted that the RCGM has recommended the product for human clinical trials based on the evaluation of pre-clinical animal toxicity studies i.e. acute and sub-acute toxicity studies in pregnant rats, allergencity studies in guinea pig and detection of antibodies in mice etc.

10.3 After detailed deliberations and taking into consideration the recommendation of RCGM, DBT, DCGI and the Expert members, the Committee approved the conduct of clinical trials with r-human interferon alpha 2b (Reliferon) tm and manufacture batches for proposed clinical trials by M/s Reliance life Sciences Mumbai subject to DCGI clearance.

**11.0: Request for manufacture and marketing of r-insulin from M/s Biocon by the following companies:-**

- **M/s. Ranbaxy, Gurgaon.**
- **M/s. Lupin Ltd. Mumbai**
- **M/s. Cadilla Pharmaceuticals Ahmedabad**

11.1 The Committee considered the revised information submitted by M/s Biocon and noted that the proposed supply of bulk insulin to the three companies mentioned above will be met from the existing installed capacity.

11.2 In view of the above and taking into consideration that the r-human insulin developed by M/s Biocon has been approved for manufacture and marketing by the GEAC and DCGI, the Committee approved the request of M/s Ranbaxy, M/s Lupin Ltd. and M/s Cadilla Pharmaceuticals for procurement of bulk insulin from M/s Biocon for further formulation and marketing in India.

**12.0: Permission for import of r-human granulocyte colony stimulating factor (rhg-CSF) from China for conduct of Phase III Clinical trials in India by M/s Sun Pharmaceuticals Industries Ltd. Mumbai.**

12.1 The Committee considered the clarifications given by the Company and noted that the information submitted is satisfactory.

12.2 The Member Secretary informed the Committee that the product has been approved by the GEAC for conduct of phase III clinical trials by Cadilla Pharmaceuticals. But subsequently Cadilla Pharmaceuticals have withdrawn their proposal as their request for waver of phase III clinical trials was not approved by the GEAC/ DCGI.

12.3 In view of the above and taking into consideration the recommendations of the Expert members, the Committee approved the import of r-human granulocyte colony stimulating factor (rhg-CSF) from China for conduct of Phase-III clinical trials in India.

**13.0 Permission for import and conduct of Phase II clinical trials of Chimerivax$^{tm}$ –JE an Japanese Encephalitis Inactivated Mouse Brain Vaccine in children of descending age and assessment of possible interaction with concomitant Measles Vaccine by M/s. Quintiles.**

13.1 The Committee noted that the GEAC in its 60$^{th}$ meeting held on 23$^{rd}$ November 2005 had considered the request of the Company for conducting Phase II clinical trials of Chimerivax$^{tm}$ –JE , a Japanese Encephalitis Inactivated Mouse Brain Vaccine in children of descending age and assessment of possible interaction with concomitant Measles Vaccine in India wherein it was decided that views of medical experts from All India Institute of Medical Science, National Institute of Immunology, New Delhi, National Institute of Virology, Pune and Indian Council of Medical Research would be obtained in the first instance.

13.2 The Committee noted the observations made by the Experts from National Institute of Immunology, ICMR and National Institute of Virology, Pune and discussed several issues of concern. During the deliberations the following points emerged:

a. The unintentional transmission of Chimerivax –JE by a mosquito feeding on a veraemic individual cannot be ruled out. In this regard it was pointed out by one of the Members that the company has generated data on the transmaybility of infection and replication of Chimerivax in the cell lines of three mosquito species A. aegypti, A.albopictus and C. tritaeniorhynchus and on this basis has opined that it will be restricted in C. Vishnui, the primary species responsible for JE transmission in India, also.
b. The vaccine Chimerivax$^{tm}$ –JE has not been tested in children anywhere in the world and would be tested for the first time in Indian children.
c. The vaccine is not recommended for infants younger than nine months.
d. Only phase I clinical trials have been conducted in adults in Australia and USA. Therefore it would be advisable to conduct phase I clinical trial of descending age before proceeding with the phase II clinical trials.

13.3 In view of the above and taking into consideration that Chimerivax_JE, a live GMO is to be introduced into the population, the Committee was of the view that the company need to provide the following information:

a. Detailed justification on conduct of phase II clinical trials in children since the safety of the vaccine for use in children has so far not been established anywhere in the world.
**b.** What is the probability of transfer of infection and replication of Chimerivax from the native mosquito species into the environment?
**c.** Whether the company would like to test the vaccine only in adults if approval for testing in children is not granted presently?

13.4 After detailed deliberation it was decided that the Company may be advised to make a presentation on the proposal as well give as their views on the various concerns raised above. The Committee further requested Member Secretary to invite the concerned experts from NII (Dr S Vrati) and ICMR (Dr V Muthuswamy) in the next GEAC Meeting for presenting their views on the proposal. Decision on the proposal was therefore deferred.

**14.0 Report of the Sub-Committee on Bt cotton and related issues.**

14.1 The Member Secretary, GEAC informed the Committee that the recommendation of the Sub Committee constituted by MoEF under the Chairmanship of Dr S Nagarajan, Director IARI and presently Chairman, Protection of Plant Varieties and Farmers Rights (PPVFR) Authority was placed on MoEF website for inviting stakeholder response. She briefed the Committee on the comments received from the following organizations.

a. All India Crop Life Association
b. Seedsmen Association
c. Nath Seeds ltd
d. Green Gold Seeds Ltd
e. Zuari Seeds Ltd
f. Uniphos Enterprises Ltd
g. Navkar Hybrid Seeds Pvt Ltd
h. Safal Seeds and Biotech ltd.

14.2 The Committee considered the following suggestions received from various stakeholders:

a. More number of locations and 1 year of LST is preferable rather than less number of locations and 2 yrs LST. The prescribed 80 locations per zone may therefore continue.
b. The number of locations for H x H hybrids can be reduced to 20 trials in south zone, 40 trials in central zone and 20 trials in north zone
c. 1 year LST for a gene which has completed all Biosafety and other requirements is enough. 1 yr additional LST will encourages monopoly and thus expensive seeds for farmer.
d. LST should be uniform for all cases and there should be no concession for CVRC notified hybrids.
e. There is no scientific logic that a new transgenic Bt cotton encoding a Cry 1Ac ' micro-variant' needs 1 yr LST whereas another new transgenic cotton encoding Cry 1Ab or Cry1Aa must go through 2 yrs of LST.
f. 1year of MLT, 2 years of ICAR and 1 year of extensive LST is adequate.
g. Non bt counter parts of the new bt hybrids may not be required as companies are developing new hybrids where the parental line contains the Bt gene. Therefore there will be no non Bt counter part.
h. The policy of including a national and local check in MLT/LST may be reviewed.

14.3 The Committee noted that the number of locations proposed by the Sub-Committee is rational as it takes into consideration the agro-climatic zones and area under cotton cultivation in each zone. Views were expressed that the Company should provide a detailed justification for the selected locations.

14.4 The Committee further noted that GEAC is following a case-by-case approval of each hybrid and therefore the Sub-Committee's recommendation in respect of GEAC released gene/event needs reconsideration.

14.5 The Committee also considered the three – protocols for field testing of Bt cotton and noted that the procedure outlined in Protocol- III which stipulates. 1 year MLT followed by years of LST and 2 years of ICAR testing in tandem should be applicable in all cases as interpretation of data based on 1 year LST will not provide any scientific conclusion. However, some Members were of the view that a CVRC notified hybrid/variety has been extensively field tested for agronomic performance and its suitability for a particular zone and therefore 1 year of LST and 1 year of ICAR testing is adequately provided, the Company is able to submit documentary

evidence through DNA finger printing that the transgenic Bt cotton hybrid / variety is equivalent to its non-Bt counter part.

14.6 After a brief discussion on the above issues, it was decided to re-consider the matter in the next GEAC meeting.

**15.0 Alternate Mechanism for Multi-location and Large-scale field trials of transgenic crops by the State Agricultural Universities**.

15.1 The Committee considered the views received from the State Departments of Agriculture and SAU's in respect of the 'Alternate Monitoring Mechanism' to evaluate the field trials of Bt Cotton and noted that the State Governments and SAU's have 'in principal' agreed with the concept of evaluating the field trials through the SAU's provided adequate financial mechanism is put in place. The Committee also considered some suggestions on the composition of the monitoring team, frequency of monitoring and parameters to be monitored.

15.2 The Committee was of the view that the proposed monitoring Mechanism can be made effective only if there is a representation from the Central Government/GEAC to coordinate and harmonise between different monitoring teams spread over the State. It was suggested that two experts (representatives of the GEAC/RCGM) should be included in the Monitoring team and one of the Experts should be appointed as the 'Head' of the Monitoring team. The representative of SAU should be the convener.

15.3 Regarding the financial mechanism, the Committee was of the view that is not advisable for the Company to pay directly to the SAU's for evaluating the field trials. It was agreed that a Central agency may be identified to institute the financial mechanism and co-ordination of the fields trials through the SAU's. The Committee requested DBT to consider the above suggestions and submit a revised proposal for consideration of the GEAC in the next meeting.

15.4 In view of the above, decision on the proposed 'Alternate Monitoring Mechanism' was deferred.

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