Summary Record of 39th Meeting of the Genetic Engineering Approval Committee (GEAC) held on 3rd February, 2004.

The 39th Meeting of the Genetic Engineering Approval Committee was held on 3rd February, 2004 at 10.30 AM in the Ministry of Environment and Forests under the Chairmanship of Ms. Veena Chhotray, Additional Secretary, Ministry of Environment and Forests. List of participants is annexed.

1.0 Opening Remarks of the Chairman

1.1 The members of the GEAC welcomed the newly appointed Chairperson Ms. Veena Chhotray, Additional Secretary, Ministry of Environment and Forests. The Chairperson addressed the members of the Committee and welcomed them along with the special invitees from Dept. of Animal Husbandry and Dairying (Ministry of Agriculture), Director, IVRI, Izatnagar and Director, NDRI, Karnal. She emphasized that the GEAC was a multidisciplinary group with representative from different Ministries and technical experts. Therefore it didn't represent the view point of any one department. The GEAC was entrusted with the highly sensitive and technological progress in the fields of agriculture and pharmaceuticals and the environmental concerns. The responsibility becomes all the more onerous because biotechnology is still an evolving field.

1.2 She further announced that henceforth the GEAC meeting would be held on second Wednesday of every month at 10.30 AM in the Ministry of Environment & Forests. In the eventuality of the fixed date being a Gazetted holiday, the meeting would be held on the successive working day. Accordingly it was agreed that the next GEAC meeting would be held on 10th March 2004. After a brief introduction of all the members present, the Agenda Items were taken up for discussion.

2.0 Confirmation of the Minutes of the 38th Meeting of the GEAC held on 27th November, 2003

The minutes of the 38th Meeting of the GEAC held on 27th November, 2003 were circulated on 5th December 2003. Only one comment has been received from DBT in respect of agenda item pertaining to Shantha Biotechnics. These comments were being considered separately along with the relevant Agenda Item No. 4.1 in this meeting. Subject to this the minutes were confirmed.

3.0 Follow up on the decision taken in the 38th GEAC Meeting.

3.1 The Member Secretary briefed the Committee on the follow up action taken by the Ministry. It was pointed out that in the earlier GEAC meeting it was decided to set up a Sub-Committee to carry out a site inspection for on the spot verification of the existing facilities for manufacture to carry out a site inspection for on the spot verification of the existing facilities for manufacture of r-Hepatitis-B vaccine finished product by M/s Biological E. Ltd. the Committee comprising of the following members has been constituted.

1. Dr. T.V. Ramanaiah, Director, DBT
2. Dr. S.K. Mahajan, Member
3. Representative of DCGI

3.2 The above Members were requested to visit the above unit and submit their report on priority basis. The Members informed the Committee that the tentative date for the site visit has been scheduled for 14th February 2004. On the issue of nomination of a representative from DCGI, Dr. A.B. Ramteke, Asst. DCGI informed that Mr. A.P. Sharma, Assistant Drugs Controller, Zonal Office, Hyderabad has been nominated as a member of teh Sub-Committee for participation in the site visit.

3.3 Regarding the decision of the GEAC in the 37th GEAC Meeting which was subsequently endorsed by the GEAC in the 38th Meeting to set up a sub-committee to prepare general guideline on the minimum numbers of locations, zones, seasons, checks for conducting large scale trials, it was clarified that the streamlining of regulatory procedures is currently under review wherein there have been suggestions to merge ICAR and large scale trials with suitable modifications in the protocol. Therefore, it is proposed that the guidelines for the large scale trials may be prepared once the streamlining procedures have been firmed up. The Committee agreed with the above suggestion.

4.0 Consideration of new proposals

4.1 Manufacture and Marketing of recombinant Streptokinase by M/s Shantha Biotechnics Pvt. Ltd., Hyderabad.

4.1.1 M/s Shantha Biotechnics, had earlier submitted a proposal for Manufacture and Marketing of recombinant Streptokinase at Hyderabad. The GEAC in its last meeting on 27th November 2003 had rejected the company's request on the ground that the applicant had conducted Phase-III human clinical trials without the approval of the GEAC and this violated prescribed procedures. Besides, the following decisions were taken:

a) DCGI to investigate the NGO's complaint and submit a factual report to GEAC. A Bangalore based NGO, Anikethan has complained that Shantha Biotechnics has manufactured and tested the medicine r-Streptokinase on poor people at Osmania General Hospital, Hyderabad and other hospitals. It is reported that the about 8 persons died at Care Hospital, Hyderabad. No compensation was paid to the poor patient's families. It is also reported that the company has shifted its trials to Jayadev Institute of Cardiology, Bangalore.
b) DBT was advised to consult both RCGM and GEAC before finalizing any guidelines.
c) DBT was also directed to withdraw the revised procedure hosted on its website with immediate effect.

4.1.2 The Member Secretary briefed the Committee on the developments subsequent to the GEAC decision. **In view of the facts of the case placed before the GEAC, the Chairperson GEAC requested the Committee to take a final view with specific reference to the following issues:**

i. The proposal of Shantha Biotechnics based on the DCGI investigation report.
ii. Whether approval of GEAC is required for Phase-III human clinical trials. It may be noted that Ministry has received similar complaints regarding violation of procedures by other companies also.
iii. If approval of GEAC is required, whether the procedural lapse by Shantha Biotechnics can be condoned and ex-post facto approval can be given (either with warning or penalty) based on the examination of the data generated from the

human clinical trials, adequacy of facilities existing to ensure environmental safety, on site emergency plan, and track record of the company with respect to environmental compliance.

iv. Consideration of the issue regarding change in approval procedures.

4.1.3 The Committee considered at length the representation dated 1.12.2003 received from ABLE (Association of Biotechnology Led Enterprises) regarding the urgent need to streamline the regulatory process and clearly define the roles of GEAC, RCGM and DCGI to avoid inordinate delay. Issues raised by Dr. T.V. Ramanaiah, Director, DBT and Secretary, DBT (vide communication dated 12.12.2003 and 29.12.2003) with specific reference to the Shantha Biotechnics case and the DCGI investigation report dated 24.12.2003 were also discussed. The communication dated 2.1.2004 from the company requesting the GEAC to reconsider the earlier decision and grant them necessary approval for marketing and manufacturing of r-Streptokinase and their request for ex-post facto permission for the Phase-III human clinical trials were also considered.

4.1.4 Director, DBT, referring to the minutes of the 38th GEAC meeting and the Agenda Notes of this meeting pointed out the following:

- He expressed reservation on the GEAC decisions to reject the above proposal. He pointed out that the decision to reject the proposal and at the same time requesting DCGI to submit the investigation report on the complaint received from Anikethan a Bangalore based NGO are in contradiction. Taking note of the reservation made by DBT, it was clarified that the decisions of the GEAC to reject the proposal was on the grounds of non-compliance of procedural norms whereas the decisions to seek the investigation report was with specific reference to the complaint received that 8 persons had died during the human clinical trials at CARE Hospital, Hyderabad.

- RCGM only examines the toxicology and allergenicity data generated from Phase-I and Phase-II clinical trials and approval for Phase-I and Phase-II trials is not given by DBT.

- The revised procedure (deletion of GEAC approval for Phase-III trials) was made operational by DBT only after the consultative meeting held on 29.11.2001 and prior to that, the DBT guidelines of 1999 were being followed. As a case in point the Member Secretary pointed out that there has been variations in the approval issued by DBT event after 29.11.2001 which has led to confusion among the project proponent as to whether approval for Phase-III clinical trials is required or not.

- The Chairman, GEAC and Member Secretary of the GEAC were present in the consultative meetings held on 3.5.2000 and 29.11.2001. They had agreed to the suggestion made in the above meetings. The minutes of the meeting were also circulated to the Chairman, GEAC. On this issue the Chairperson GEAC pointed out:

- There is a procedure for formalizing the decisions taken in various meetings. While the Ministry and the GEAC appreciate and give full credit to the consultative meetings and suggestions made therein, any change proposed should be viewed in the context of the existing provisions of the EPA, 1986.
- Any change in the Rules under EPA can be initiated only by MoEF which is the Administrative Ministry.
- The proposed changes which would mean a modification in the stipulated mandate of GEAC under the 1989 Rules would necessitate amendments in 1989 Rules. This can only be done by following the prescribed procedures under the EPA 1986.

4.1.5 The Committee therefore advised DBT to follow the mandatory procedure before taking a final view/issuance of any revised procedure.

4.1.6 Making a reference to the mandate of the Task Force on Agriculture Biotechnology under the Chairmanship of Prof. M.S. Swaminathan and the presentation made by Secretary (E&F) to the Task Force, the Chairman, GEAC also informed the Committee that efforts for rationalization of various policy issues have been initiated in the Ministry with a view to streamline the regulatory process. This should take into account the concerns of the Pharma sector. With the above background, the Chairman requested the members to discuss the case under consideration.

4.1.7 The Committee noted that in the complaint, the NGO has made specific reference to the death of 8 persons at CARE Hospital, Hyderabad, during human clinical trials using r-Streptokinase. However, the DCGI's investigation report vide his letter dated 24.12.2003 is silent on this matter whereas the report confirms that allegations made by Anikethan that 9 patients died in Osmania General Hospital are unfounded. The Committee also took note of the fact that the mortality rate reported in the human clinical trials of r-Streptokinase conducted at six centres in India is about 4% which is much less than internationally reported mortality rate of 9%.

4.1.8 Dr. Ramteke clarified that the investigation report submitted by the Zonal Office includes the trials conducted at CARE Hospital and the allegations made by the complainant are unfounded and the mortality rate reported is based on the evaluation of the clinical trials conducted at six centres in India.

4.1.9 After detailed discussion the Committee requested DCGI to submit the following details to the Ministry on a priority basis:

a. Hospital wise reports on the clinical trials conducted using Streptokinase along with the total number of Patients on whom the trials were conducted, number of deaths that have occurred during the clinical trials and basis of death based on which the 4% mortality rate has been calculated.
b. Comments of DCGI with specific reference on the deaths occurred at CARE Hospital.
c. Confirmation of DCGI on the efficacy and purity of the product for safe and effective use in human beings.
d. Rate of overall mortality in the human clinical trials as per the International norms.

4.1.10 On the issue of the company's request to condone the procedural lapse and reconsider the earlier decision, the following points emerged:

a. There has been a clear procedural lapse on the part of Shantha Biotechnics in not obtaining the clearance of GEAC before conducting Phase-III human clinical trials. Vide their letter dated 7.5.2002, DBT had directed the company to obtain permission of the GEAC and DCGI before conducting such trials. After that there was not specific communication from the DBT revising their letter of 7.5.2002.
b. The extenuating factor however is the plea that, this procedural necessity had been obviated by the revised clearance procedure evolved by DBT and displayed on their website.
c. There is not evidence that there has been any deliberate attempt on the part of the company to short circuit the GEAC mandatory clearance. On the other hand, there is ground for a reasonable inference that the company could have been misled by the revised procedure proposed by DBT.

4.1.11 Therefore, taking into consideration that Streptokinase is a life saving drug, the GEAC decided to condone the procedural lapse by the company with a strict warning and recommend ex-post facto approval for Phase-III clinical trials. However, this should not be taken as a precedent.

4.1.12 The Committee also discussed the request of the company seeking approval of the GEAC for manufacture and marketing of the r-Streptokinase in India. The Committee noted that as intimated vide the DCGI's letter no. 12-21/92-DC dated 15th October 2003, the DCGI based on the Phase-III human clinical trials, has accorded approval for manufacturing and marketing of the product subject to approval of GEAC. The Committee was of the view that the product may be approved for manufacture and marketing subject to confirmation from DCGI regarding the product's efficacy, purity, safety and effectiveness. However, the Committee noted that information specific to containment facilities, treatment and disposal of contaminated effluent/solid waste, occupational health surveillance, on-site emergency plan needs to be furnished prior to giving approval for environmental release. Dr. Sushil Kumar, Co-Chairman, GEAC, pointed out that the report of the IBSC addressing the above issues is submitted to the RCGM for their approval. Accordingly, DBT was advised to forward a copy of the IBSC report and corresponding minutes of the RCGM.

4.1.13 The Committee was informed that Shantha Biotechnics was requested to be available for providing any clarification if considered necessary to the Committee. It was agreed that the representative may be invited to make a brief presentation on the containment facilities existing in the unit and other environmental related issues. Dr. Raman representative of the Shantha Biotechnics informed the Committee that he was a medical doctor and was not competent to address the issues raised by the Members. Prof. Subhash Chand suggested that henceforth all applications for manufacture and marketing of recombinant products should accompany specific information on containment facilities, treatment and disposal of contaminated effluent/solid waste, occupational health surveillance, on-site emergency plan etc. for which necessary directions may be issued.

4.1.14 The Committee also took a view that until the procedural changes proposed by DBT are formalized through necessary amendments in the existing 1989 Rules, approval of GEAC is mandatory for Phase-III clinical trials. The urgent necessity for the DBT to remove from its website the proposal modified procedure, till its finalization by due process was reiterated. This is necessary to stop sending any confusing signals to the applicants. This point has in fact been decided in the earlier meeting of the GEAC dated 27.11.2003 also.

4.1.15 In conclusion, the following decisions were taken by the GEAC:

a. To condone the procedural lapse by the company with a strict warning and recommend ex-post factor approval for Phase-III clinical trials. However, this should not taken as a precedent.
b. Obtain a copy of the IBSC report and corresponding minutes of the RCGM from DBT relating to the environmental safety aspects.
c. Obtain relevant information from DCGI as per para 4.1.9 (a to d) no page 4-5.
d. Until the procedural changes proposed by DBT are formalized through necessary amendments in the existing 1989 Rules, approval of GEAC is mandatory for Phase-III clinical trials.
e. DBT to remove from its website the proposed modified procedure, till its finalization by due process was reiterated.
f. All applications for manufacture and marketing of recombinant products should include specific information on containment facilities, treatment and disposal of contaminated effluent/solid waste, occupational health surveillance, on-site emergency plan etc.
g. The Committee authorized the Chairperson to take a decision on the above case on receipt of the requisite reports sought by the Committee from DCGI and RCGM.

4.2 Permission to import of r-human Lactoferrin (rhLF) and Placebo for Phase-II clinical trials studies by M/s Reliance Clinical Services, Mumbai from M/s Agennix Incorporated, Houstan, USA.

4.2.1 M/s Reliance Clinical Services had submitted a proposal for import and marketing of r-human Lactoferrin (rhLF) Placebo for Phase-II clinical trials studies in India as part of the Global clinical trial initiatives. The Committee noted that the present proposal is only for limited import of the drug for investigational use only and has not yet been approved in any country. The same drug product formulation has been used in a variety of clinical trials in the US, UK, Australia, Netherlands, Japan, Mexico, Belgium, Brazil, Argentina, and Chile. The intended use of the product in this clinical trial is in the field of Oncology as an anti tumor drug along with standard Paclitaxel/carboplatin in non small cell lung cancer.

4.2.2 In view of the comments received from the Experts, DCGI and DBT on the proposal, the GEAC accorded approval from environmental angle subject to compliance of statutory requirements under EPA and Drugs and Cosmetics Act.