Decisions taken in the 42nd Meeting of the Genetic Engineering Approval Committee (GEAC) held on 12th May 2004.

GENERAL POLICY DECISIONS

1. It was noted by the Committee that in a number of cases Phase-III clinical trials have been conducted without prior approval of GEAC. Some such request had also been received for ex-post facto approval and the GEAC has been considering this matter on a case-to-case basis. While emphasizing the need to observe prescribed procedures the GEAC noted that the procedural lapse in most of the cases, appeared to be circumstanced by the amended procedure displayed on DBT website during 2003-2004. The Committee requested the DBT representative to furnish a list of such cases with relevant particulars, which was approved by RCGM during that period.

2. Regarding the decision of GEAC to seek a report from RCGM on the adequacy of containment facilities and other biosafety aspects involved in manufacture of r-Pharma products, the DBT representative suggested that on this subject the GEAC could take its view on the basis of IBSC report without routing it through the RCGM. During discussions it was highlighted by various members that RCGM is responsible for bringing out bio-safety guidelines as well as evaluation of safety requirements in the manufacturing units even though implementation of the Protocols and Guidelines are directly under the supervision of IBSC. Ordinarily, the report of the IBSC, which has a nominee of the DBT and has the advantage of on site supervision, should be adequate. However, the need for a review by an impartial technical body after recommendation of IBSC, which is primarily a company outfit, was also emphasized. After deliberation, the view taken was that, the report of IBSC could be considered by RCGM on a case-to-case basis and after due consideration the RCGM may make its recommendation to GEAC for a final clearance.

3. The Committee also considered the need for a report from RCGM regarding the biosafety aspects including containment facilities for subsequent products manufactured within the same premises. On this matter the Committee's view was that after taking into consideration the type of product to be manufactured and type of containment facilities installed by the company the RCGM may make its recommendation to GEAC in every case.

4. The issue of delay in decision-making due to delay in obtaining opinion of experts (who were not members of GEAC) was also discussed. The Member Secretary apprised the Committee that as per prevailing practice expert opinion was sought at the initial stage of receipt of a proposal before conducting Phase-III clinical trials. After deliberation the Committee concluded:

- Noting that Phase-III clinical trials are conducted to establish safety and efficacy of the product, the proposals may be referred to outside experts along with clinical trials data at the manufacturing stage. However, this would be applicable to approved products. In the case of new products, experts' opinion may be obtained prior to Phase-III clinical trials.
- The Co-Chairman GEAC informed the Committee that in the light of the new policy taken by the Ministry to hold the GEAC meeting every month, the time given to experts for review of the proposals is not adequate. He suggested that a minimum of 30 days should be given to the experts for review of proposals. This was agreed by the Committee.

5. The representative of DBT suggested that since the pre–clinical trials data are evaluated and approved by RCGM prior to DBT recommending the proposal for Phase-III clinical trials, there is no need to refer the case to DBT at this stage. This was also accepted by the Committee.

6. The Member Secretary briefed the Committee on the request from M/s Nuziveedu Seeds Limited & M/s J. K. Agri Genetics for conducting, large-scale trials simultaneously with the contained field trials under RCGM and ICAR trials. The Committee invited representatives of both these companies to present their case before the Committee. The Committee noted the following:

a. M/s Nuziveedu Seeds Limited has transferred the Cry 1 AC Gene (earlier approved by the GEAC) through traditional back crossing method into the parental lines of the hybrids NCS-145 ("Bunny") and NCS – 207 (Mallika). Both these non-Bt hybrids are notified hybrids and is extensively cultivated in the Central & South zones.

b. M/s J. K. Agri Genetics has developed indigenous Bt Cotton technology in collaboration with IIT BREF BIOTECH, Kharagpur and University of Delhi, South Campus. In this Programme, Cry IAC Gene was incorporated in some of J. K. Cotton parental lines (J K Durga, JK 666, JK Vanur and JK99). The company explained that bio-safety trials in progress and the results would be submitted by December 2004.

c. The hybrids developed by the companies have been given clearance by RCGM for conducting contained field trials under RCGM & ICAR-AICCIP trials only during Kharif 2004. It was submitted by the representative of M/s Nuziveedu Seeds that their request for reducing the duration of AICCIP trials to one years for notified hybrids is pending consideration of ICAR.

The Committee concluded that the request of the companies involve policy issues and need further discussion which may be taken up in the next GEAC meeting.

DECISIONS ON PHARMA PROPOSALS

1. Permission for manufacture and marketing or r-Streptokinase by M/s Shantha Biotechnics, Hyderabad.

1.1 The above proposal was discussed in the context of the decisions taken in the last GEAC meeting held on 15th April 2004. The Committee noted that requisite clarifications from the company regarding Phase-III clinical trials have been received vide DCGI's letter dated 28th April 2004.

1.2 In the above meeting RCGM was also requested to give their report regarding adequacy of the containment facilities at Shantha Biotechnics to meet the environmental safety regulations. The Member Secretary informed the Committee that the meeting of RCGM scheduled for 3rd May 2004 had to be deferred since it was declared as a public holiday and the meeting has been rescheduled for 13th May 2004. The representative of DBT confirmed that the above issue has been placed in the Agenda for discussion in the RCGM meeting on 13th May 2004.

1.3 The Committee noted that the proposal r has been considered in several GEAC meetings held on 27th November 2003, 3rd February 2004, 31st March 2004 & 15th April 2004. Considering the clarifications received regarding Phase-III clinical trials are in order, the Committee decided to accord approval for manufacture & marketing of r-Streptokinase by M/s Shantha Biotechnics subject to confirmatory report from RCGM regarding the adequacy of containment facilities to ensure compliance of environmental safety as per prescribed guidelines.

2. Permission for manufacture and marketing or r- Erythropoietin & conducting Phase-III clinical trials by M/s Shantha Biotechnics, Hyderabad.

2.1 The Committee considered the explanation submitted by the company for not obtaining the approval of GEAC prior to conducting Phase-III clinical trials. The Committee noted that RCGM in its meeting held on 29.1.2003, examined the pre clinical data submitted by the company and DBT vide their letter dated 10th March 2003 had directed the company to undertake human clinical trials with the approval of DCGI and under intimation to the GEAC. As per the information submitted by the company they had conducted Phase-III clinical trials after obtaining approval of DCGI vide letter dated 4.4.2003. Further, as directed by DCGI, the company has obtained the approval of Ethical Committee before initiating human clinical trials at Manipal Hospital, Bangalore, Maulana Azad Medical College and Apollo Hospital, Hyderabad, Kamineni Hospital Hyderabad and Sanjay Gandhi Post Graduate Institute, Lucknow.

2.2 Since the request is for manufacturing of recombinant product the Committee decided to await the recommendation of RCGM and views of the experts before taking a final view on the above matter.

3. Permission for conducting Phase-III clinical trials on human Erythropoietin by M/s Intas Pharmaceuticals, Ahmedabad.

3.1 The Committee noted that the company has carried out pre-clinical animal toxicity studies of the product which was approved by the IBSC in its meeting held on 5th January 2004. Subsequently the pre clinical data was approved by the RCGM in the meeting held on 21.1.2004. DCGI vide their letter dated 28.4.2004 has also recommended the proposal.

3.2 Further, taking note of the recommendation made by the expert regarding the review of the Protocol for clinical trials by a different referee with related expertise, the Committee concluded that the company should follow the Protocol prescribed by DCGI as per the Drugs and Cosmetics Act. Hence the need for a separate review in this case was not felt necessary.

3.3 Based on the facts of the case and the recommendation made by RCGM, DCGI and CCMB expert and taking into consideration that it is an approved drug, the Committee accorded approval for conducting Phase-III clinical trials using r-Erythropoitien developed by the company subject to statutory requirements under EPA and Drugs and Cosmetics Act.

4. Permission for conducting Phase-III clinical trials on r-interferon by M/s Intas Pharmaceuticals, Ahmedabad.

4.1 The Committee noted that the company has carried out pre clinical animal toxicity studies of the product as per the approval granted by RCGM through the letter dated 3.6.2003. The pre clinical animal toxicity data studies was also approved by the IBSC in its meeting held on 5th January 2004. Subsequently, the pre clinical data was approved by RCGM on 21.1.2004. The DCGI vide their letter dated 28.4.2004 has also approved the proposal.

4.3 Taking note of the recommendations made by RCGM, DCGI and taking into consideration that it is an approved drug, the Committee accorded approval for conducting Phase-III clinical trials using r-interferon developed by the company subject to statutory requirements under EPA and Drugs and Cosmetics Act.

5. Permission for manufacture and marketing of r-Hu-G-CSF by M/s Intas Pharmaceuticals, Ahmedabad.

5.1 The Committee considered relevant facts in the light of the letter received from the company and took note of the following facts:

- The pre clinical data was examined by RCGM in the meeting held on 23.4.2003 wherein RCGM observed that the product was found to be safe. Accordingly, DBT vide their letter dated 28.5.2003 has directed the company to approach DCGI for permission to conduct Phase-III clinical trials.

- Phase III Clinical studies of the product have been carried out as per the approval granted by DCGI through their letter dated 28.5.2003. The report of the Phase-III clinical trials has been approved by r-DNA Committee on 12.4.2004.

- The report on clinical trials was approved by the IBSC on 8th March 2004.

5.2 After deliberations, the view taken was that it would be desirable to await the recommendations of RCGM regarding the biosafety aspects including the adequacy of the containment facilities and views of experts before taking a final decision in this case.

6. Permission for manufacture and marketing of insulin by M/s Biocon India Ltd., Banglore.

6.1 The Committee considered the explanation submitted by the company for not obtaining the approval of GEAC prior to conducting Phase-III clinical trials.

6.2 Based on the facts of the case, the Committee concluded that further clarifications from the company on the following are necessary before taking a final view:

a) Reasons for non-compliance of the directions issued vide DCGI letter dated 2.9.2003 in which it was stipulated that the clinical trials were not to be initiated before RCGM clearance.

b) Reasons for non-compliance of directions issued by DBT vide letter dated 12.12.2003 directing the company to obtain the approval of competent authority for conducting Phase-III clinical trials. As per the prevailing practice the procedures outlined in the "Guidelines for generating pre-clinical and clinical data for r-DNA vaccines, diagnostics and other biological, 1999" mandate that approval of GEAC for conducting Phase-III clinical trials is mandatory.

7. NOC for use of enzyme from GMM (Genetically modified microorganisms) by M/s. Zytex Corp. Mumbai.

7.1 The above proposal was discussed in the light of the decisions taken in the 40th meeting of GEAC held on **31st** March 2004.

7.2 The information submitted by the company vides letters dated 5th April 2004 & 16th April 2004 and comments received from M/o Food Processing Industries were considered at length by the Committee. The Committee noted that the enzymes are approved for manufacture and marketing in Denmark and has been cleared by the Codex Committee. The US FDA also lists the enzymes as GRAS.

7.3 The Committee also noted that Ministry of Food Processing & Industries has recommended that such products should be cleared and tested for adverse health impacts in the Indian context. Taking note of the above recommendation and taking into consideration the absence of labeling law in India, the Committee concluded that there was a need for conducting safety trials on adverse health impacts in India. It was further recommend that the company should carry out safety trials as per the Protocol approved by Ministry of Health. The safety trials should be evaluated and cleared by Ministry of Health. In view of the above, decision on the proposal was deferred.

8. Permission for import and marketing or r-Human Interlukin-2 (rhuIL-2) from Laboratories Pablo Cassara Argentina by Glenmark Laboratories Pvt. Ltd.

8.1 The request of the company for waiver of the requirement for Phase-III clinical trials was discussed in the light of the decisions taken in the 41st meeting of GEAC held on 15.4.2004.

8.2 14.2 The Committee took note of the various documents furnished by the company and information on international practice in the use of this drug.

8.3 It was noted the drug has not been extensively tested in the international market. The Member Secretary informed the Committee that GEAC had previously considered similar request for this product. The GEAC requested the Member Secretary to provide details of decision taken by GEAC for import/manufacture of r-human Interlukin-2 and in such cases how these companies have addressed the issue of Phase-III clinical trials. Decision on the proposal was deferred.

9. Permission for Import and marketing of r-human Granulocyte colony stimulating factor rhG-CSF from M/S. Shanghai Sunway Biotech, China by M/s Emcure Biotech Ltd. Pune.

9.1 As per the decisions taken by the GEAC in its 37th meeting held on 16th June 2003 the company has conducted Phase-III clinical trials in India for establishing safety of the product. The Committee noted that decision on the request of the company for import and marketing of the above product was deferred in the GEAC meeting on 31st March 2004 in the absence of specific comments from DCGI regarding the purity and efficacy of the product.

9.2 The Member Secretary briefed the Committee that DCGI vide their letter dated 29.4.2004 has confirmed that the phase III data generated on safety and efficacy in respect of r-HuGCSF imported by Emcure Biotech Ltd. Pune has been found to be in order.

9.3 Considering the recommendation of DBT and DCGI and noting that the present product has been evaluated for its safety and efficacy, the GEAC approved the import and marketing of the product subject to statutory requirements under EPA and Drugs and Cosmetic Act.

10. Permission for Manufacture and marketing of r-human pentavalent vaccine by M/s. Panacea Biotech Ltd., New Delhi.

10.1 As per the decisions taken by the GEAC in its 33rd meeting held on 5th July 2002 the company has conducted Phase-III clinical trials in India for establishing safety of the product. The Committee noted that decision on the request of the company for import and marketing of the above product was deferred in the GEAC meeting on 31st March 2004 in the absence of specific comments from DCGI regarding the purity and efficacy of the product.

10.2 The Member Secretary briefed the Committee that DCGI vide their letter dated 29.4.2004 has confirmed that the phase III data generated on safety and efficacy in respect of r-human pentavalent vaccine has been found to be in order.

10.3 Considering the recommendation of DBT and DCGI and noting that the present product has been evaluated for its safety and efficacy, the GEAC approved the import and marketing of the product subject to statutory requirements under EPA and Drugs and Cosmetic Act.

11. Permission for Import and marketing of r-human Insulin from M/s. Bioton Co. Ltd, Warszawa, Poland by M/s Shreya life Sciences Pvt. Ltd. Bangalore.

11.1 As per the decisions taken by the GEAC in its 35th meeting held on 6th March 2003 the company has conducted Phase-III clinical trials in India for establishing safety of the product. The Committee noted that decision on the request of the company for import and marketing of the above product was deferred in the GEAC meeting on 31st March 2004 in the absence of specific comments from DCGI regarding the purity and efficacy of the product.

11.2 The Member Secretary briefed the Committee that DCGI vide their letter dated 29.4.2004 has confirmed that the phase III data generated on safety and efficacy in respect of r-human Insulin has been found to be in order.

11.3 Considering the recommendation of DBT and DCGI and noting that the present product has been evaluated for its safety and efficacy, the GEAC approved the import and marketing of the product subject to statutory requirements under EPA and Drugs and Cosmetic Act.

12. Permission for Import and marketing of Recombinant Human Erythropoitein (EPOSINO) Manufactured by M/s Sandong Kexing Pharmaceuticals Co. Ltd; People of China by M/s Hindustan Bio-Sciences Ltd. Hyderabad.

12.1 The Committee noted that the proposal was discussed in the 40th GEAC meeting held on 31.3.2004 wherein it was decided to await specific comments from DCGI on the safety and efficacy of the product and views of experts on the additional information submitted by the company.

12.2 The Member Secretary informed the Committee that both DCGI and Director IMTECH have recommended the proposal. Based on the facts of the case and comments received from DBT, DCGI and IMTECH, the GEAC accorded approval for limited import of the product for conducting Phase-III clinical trials as recommended by DBT subject to statutory requirements under EPA and Drugs and Cosmetic Act.

13. Permission for import and marketing of Interlukin-2 (rIL-II) from M/s Beijing Four Rings Bio-Engineering Product Factory China by M/s Kee Pharma Ltd. New Delhi.

13.1 The above proposal was considered in the 40th GEAC meeting held on 31.3.2004 wherein it was decided to await the specific comments of DCGI on the safety and efficacy of the product. The Member Secretary informed the Committee that DCGI vide their letter dated 28.4.2004 has conveyed their no objection.

13.2 Based on the facts of the case and comments received from DBT & DCGI, the GEAC accorded approval for limited import of the product for conducting Phase-III clinical trials as recommended by DBT subject to statutory requirements under EPA and Drugs and Cosmetic Act.

14. Permission for import and marketing of r-human Erythropoietin (rhEPO) manufactured by Shenzhen SPEC- Bio- Pharmaceuticals Industry Co. Ltd. China by M/s V.H. Bhagat Co, Mumbai.

14.1 The request of the company for waiver of the requirement for Phase-III clinical trial was discussed in the light of the decisions taken in the 41st meeting of GEAC held on 15.4.2004.

14.2 The Committee took note of the various documents furnished by the company and information on international practice in the use of this drug.

14.3 It was noted that the drug has not been extensively tested in the international market. The Member Secretary informed the Committee that GEAC had previously considered similar request for this product. The GEAC requested the Member Secretary to provide details of decision taken by GEAC for import/manufacture of r-human Erythropoietin and in such cases how these companies addressed the issue of Phase-III clinical trials. Decision on the proposal was deferred.

15. Permission for manufacture and marketing of r- Hepatitis B Vaccine by M/s Biological E. Ltd., Hyderabad.

15.1 Discussion on the above proposal was deferred due to constraint of time. It has been decided to consider the proposal in the next GEAC meeting.

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