Decisions taken in the 59th Meeting of the Genetic Engineering Approval Committee (GEAC) held on 10th October 2005.

The 59th Meeting of the Genetic Engineering Approval Committee was held on 10th October 2005 at 1.30 PM in the Ministry of Environment and Forests under the Chairmanship of Shri Suresh Chandra, Special Secretary & Chairman GEAC. List of participants is annexed.

Decisions

1.0 Permission for import and marketing of recombinant humanized anti –IgE antibody (murine monoclonal antibody) Xolair (omalizumab) in finished formulations from USA by M/s. Novartis India Ltd. Mumbai.

1.1 The Committee noted that M/s Novartis India Ltd. Mumbai intends to import Xolair (omalizumab) in finished formulations for marketing in India. It is a recombinant humananised monoclonal antibody (protein) indicated for the treatment of asthma and is administered via subcutaneous injection.

1.2 The Committee noted that, while clinical trials have been done in over 4000 patients in 20 countries including USA, UK, Australia, Germany, Canada, France, and Switzerland, the product is said to have been approved for marketing in Australia, Brazil, Chile, Colombia, Dominican Republic, Guatemala, Israel, New Zealand, Pakistan, Palestine, United States and Venezuela.

1.3 DCGI representative informed that the formal market authorization for import and use of the drug in India is under issue. It was also clarified that DCGI approval is initially only for a period of two years during which the applicant has to generate adequate data on safety and efficacy of the product.

1.4 The need for conducting phase III clinical trials in India prior to market authorization was discussed by the members of the GEAC. It was pointed out that as per the prevailing policy, clinical trials in India are mandatory and in quite a few cases, GEAC has insisted for phase-III clinical trials in India even though such trials have taken place in other countries and drug has been approved for sale there. However, there have been some exceptions to this requirement in cases where the drug is approved for use in many countries and its safety and efficacy has been well established.

1.5 Views were also expressed that the drug in question is very effective in treatment of Asthma and is basically a protein and not an LMO, which degrades rapidly in the environment. It was observed that the drug may not therefore pose any environmental risk.

1.6 After detailed deliberations it was decided to seek the following information:-

a. The status of approvals in the countries mentioned in Para 1.2 where clinical trials have been conducted but no information regarding their approval is available

b. Details of the clinical trials with type and categories of patients tested in other countries.

c. Status of issue of market authorization by DCGI.

1.7 Decision on the proposal was deferred.

2.0 Permission for conducting Clinical trials for indigenously developed VIRKINASE- recombinant Streptokinase by M/s. Virchow Biotech Pvt. Limited, Hyderabad.

2.1 The Committee noted that the present request is for conduct of clinical trials of VIRKINASE- recombinant Streptokinase indigenously developed by the Company in India. The Company proposes to conduct a multi-centric Randomized Double- blind Study in a total number of 75-100 subjects aged between 18-75 years with acute myocardial infraction fulfilling the eligibility criteria. The clinical trials will be conducted at five – CARE Hospitals in Hyderabad.

2.2 It was also noted that RCGM has recommended the product for Phase –III clinical trials in its meeting held on 25.5.2005 based on the pre-clinical toxicity data generated in rats and rabbits. The Committee also noted that the product r-Streptokinase is a drug approved for marketing in India.

2.3 After detailed deliberations and taking into consideration the recommendation of RCGM, DCGI and the Expert members, the Committee approved the conduct of clinical trials with VIRKINASE in India.

3.0 Permission to conduct large scale process optimization studies (R& D purpose only) of oral insulin IN –105 precursor, for the production of oral formulation of recombinant human Insulin by M/s. Biocon Ltd Banglore.

3.1 The Committee noted that the present request is for large-scale process optimization studies of 'oral insulin IN –105 precursor' for the purpose of R & D only in order to ensure that the process developed in the laboratory is valid for large scale manufacture (up to 30,000L).

3.2 During the deliberation it was noted that the company has not provided any details regarding the containment conditions nor have they provided any details about the chemical disinfections protocol they propose to use. It was decided to obtain the above information from the Company.

3.3 Decision on the proposal was deferred.

B. Reconsideration cases

4.0 Permission to conduct a phase 2 b study with Natrecor R (nesiritide) for management of patient with heart failure by M/s Quintiles, Mumbai.

4.1 The Committee noted that the GEAC in its 54th meeting held on 8.6.2005 had considered the request submitted by M/s. Syncron Research Services Pvt. Ltd. for conduct of phase 2 b trials. The proposal was rejected on the grounds that the product is not meant for use within the country and that there have been several adverse reports about

the product. Subsequently Synchron vide their letter dated 30th August have informed that M/s. Scios Inc. USA, the sponsor of the above mentioned clinical trials, has decided to transfer the responsibilities of conducting clinical trials from Synchron to Quintiles Research Centre.

4.2 Quintiles Research Centre vide their letter dated 14.9.2005 have clarified that the drug will be marketed in India.

4.3 The Committee also considered the response of the Company on the adverse reports and the effect of Natrecor on Renal Safety and mortality.

4.4 It was also noted that the Fusion II trial (Phase II (b) trial), is part of the global clinical trials and will be conducted in 12 countries (US, Canada, Mexico, Brazil, Argentina, Chile, Singapore, Hong Kong, Australia and New Zealand, India, South Africa). The clinical trial application has been approved by the health authorities in the US, Canada, Mexico, Argentina, Singapore, Hong Kong, Australia, and New Zealand. To date about 380 patients have been enrolled in the clinical trial worldwide. Clinical trial applications are in review in India, South Africa, Brazil, and Chile.

4.5 The representative of DCGI informed that the Directorate has approved the conduct of the fusion II trials (phase 2 b) in India vide their letter dated 23rd September 2005.

4.6 During the deliberations, it was pointed out that the meta-analysis publication which appeared in the Journal of the American Medical Association (JAMA) in April 2005 clearly indicates that, compared with noninotrope-based control therapy, nesiritide may be associated with an increased risk of death after treatment for acutely decompensated heart failure. This Meta-analysis is based on primary reports of completed clinical trials as of December 2004, which were obtained from the US, FDA, the study sponsor (Scios Inc), a PubMed literature search using the keywords-nesiritide, clinical trials, and humans, and a manual search of annual meetings of 3-heart associations 2005 issue of the "Circulation". However there has been no rebuttal on adverse effects as has been indicated in various publications on the drug.

4.7 The Committee gave an opportunity to the representatives of the Company to present their case. It was clarified by them that the short-term risk of death as reported in JAMA was reviewed by Panel of Cardiologists (Dr Sackner- Bernstein and colleagues) and their findings have been made public by the company. Also, a response to the said reporting in April, 2005 issue of JAMA have been published in August 2005 issue of JAMA. It was also clarified that the adverse reporting in JAMA is based on the retrospect data, which was not designed to evaluate either mortality or morbidity. To a query on whether the proposed clinical trials are with a view to test the efficacy and safety of the drug for people with diverse genetic/ethnic background, it was clarified that the genetic trend will be one of the parameters monitored under the clinical trials.

4.8 After detailed deliberations and taking into consideration the views of the Experts and clarifications submitted by the Company, the Committee approved the conduct of Fusion II trial (Phase II (b) trial) with Natrecor R (Nesiritide) in India. It was also decided that the proposal along with the observations of DBT be forwarded to three eminent Cardiologist namely Dr Srinath Reddy from AIIMS, Dr P L Tiwari from Bombay Hospital and Dr Trehan from Escorts for their comments. The Member Secretary was advised to forward the comments of the Experts to the investigators of the clinical trials so that necessary precaution, if any may be kept in mind while conducting the clinical trials.

5.0 Permission for manufacture and marketing of r-human interferon alpha (r-DNA Origin) by M/s. Wockhardt, Mumbai.

5.1 The Committee considered the explanation given by the Company and noted that the case is similar to some other cases where procedural lapse was condoned. It was therefore decided to condone the procedural lapse in this case as well.

5.2 On the substantive issue the Committee noted that the documents submitted by the Company are haphazard and not serialized and also the recommendation of RCGM on the containment facility is awaited.

5.3 After detailed deliberation, it was decided that a final view on the proposal may be taken after review of the RCGM recommendation on the containment facility. The Committee also advised that the views of the Experts on the various lacunae in the information furnished may be communicated to the Company for submission of revised information.

5.4 Decision on the proposal was accordingly deferred.

6.0 Permission for import & marketing of Recombinant Bovine somatrotropin from M/s L G. Chemicals, Korea by M/s L G. Chemicals Pvt. Ltd., New Delhi.

6.1 The Committee noted that the above proposal was considered by the GEAC in its meeting held on 3rd February 2004 wherein the following decisions were taken:

a. It would not be appropriate for the GEAC to take any decision that would be divergent from the general policy followed by the Animal Husbandry Department in the case. Therefore, the Animal Husbandry Department was requested to give a deliberate consideration to this issue and take a considered view.

b. The policy of the Dept. of Animal Husbandry and Dairying regarding adequate supply of feed and fodder also needs to be taken into consideration while evaluating the above proposal.

c. Since the present trials are only on crossbred cows, the effect of this product on the indigenous cows was also to be seen.

6.2 The Committee also considered the views of the Dept. of Animal Husbandry and noted that the Department has recommended the restrictive use of r-BST in two organized dairy farms in India, either in government or private sector, for two years subject to the following conditions:-

a. The farms would maintain proper records of its dairy farm operations including breeding history, marketing of products and health issues as directed by Department.

b. r BST is to be used only in high yielding elite animals with an option of using for a specific period of lactation. The user of the r BST must be enlightened about likelihood of export restrictions before using the product.

c. The data from these organized farms be submitted annually to the Department of evaluation of its performance vis-à-vis ill effects, if any. The Department may at any time inspect the farm through its representative.

6.3 The Committee noted that comments of the Dept of Animal Husbandry are silent on the issue of adequate provision of feed and fodder to animals during administration of the drug. The Committee requested the representative of the Dept of Animal Husbandry to clarify on the number of animals to be used and parameters to be monitored. It was clarified that the department has recommended restrictive use and therefore, there is no limitation on the number of animals to be treated with r BST under these trials.

6.4 After detailed deliberations, it was decided to obtain the following additional information from the department of Animal Husbandry:

a. The recommendation of the Dept. of Animal Husbandry and Dairying regarding adequate supply of feed and fodder.
b. Meaning and purpose of the restrictive use as against the trials.
c. Number of animals to be treated with r BST.
d. Parameters to be monitored and protocols to be followed.
e. The department has recommended that only high yielding elite animals should be used- whether it would suffice, as the effect of this product on indigenous cows also needs to be seen.

6.5 Decision on the proposal was accordingly deferred.

7.0 Permission for manufacture and marketing of r-insulin by M/s. Ranbaxy, Gurgaon from M/s. Biocon.

7.1 The Member Secretary informed the Committee that the above request is similar to the requests from M/s Lupin and M/s Cadilla to procure bulk r-human Insulin from M/s. Biocon for further formulation and marketing in India. It was noted that in these two cases, the Committee was of the view that information regarding the existing installed capacity from M/s. Biocon first needs to be obtained. The Committee therefore advised the Member Secretary to put up this case as well after requisite information from M/s Biocon is received.

Date of the Next GEAC Meeting

The next GEAC meeting is scheduled for 23rd November 2005 at 10.30 AM.

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