Decisions taken in the 63rd Meeting of the Genetic Engineering Approval Committee (GEAC) held on 8th February 2006.

The 63rd Meeting of the Genetic Engineering Approval Committee was held on 8th February 2006 in the Ministry of Environment and Forests under the Chairmanship of Shri B S Parsheera Additional Secretary, MoEF and Chairman GEAC.

Decisions

1.0 Permission for import of Cervarix™ human Papilloma virus vaccine from M/s GlaxoSmithkline (GKS) Biologicals, Belgium for conduct of phase III B clinical trials by M/s GlaxoSmithkline (GKS) Asia Pvt. Ltd. Mumbai.

1.1 The Committee noted that the Company proposes to conduct a double blind-randomized, controlled study to evaluate the immunogenicity and safety of the product in Indian females aged between 18-35 years.

1.2 The Committee considered the comments received from DBT and CPCB. In response to the issues raised by CPCB, the Member Secretary clarified that the present request is for import of the drug for conduct of clinical trials.

1.3 During the deliberations one of the Expert Members pointed out that Schedule Y under the Drugs and Cosmetic Act, 1940 has been recently amended. While the amended Schedule Y does not make a reference to the number of patients to be tested for phase-III clinical trials, the original schedule Y indicated that the number of patients to be tested as around 100. The Committee opined that this matter may be brought to the notice of DCGI and requested representative of DCGI to provide necessary clarification to the GEAC in this regard as this matter would be applicable to other proposal as well which are referred to the GEAC.

1.4 After detailed deliberations and taking into consideration the views of the members and DCGI, the Committee accorded approval for conduct of Phase-III B clinical trials with Cervarix™ human Papilloma virus vaccine in India subject to DCGI clearance.

2.0: **Permission for import and marketing of purified Rabies Vaccine for human use (Vero cell) from M/s Liaoning Cheng da Biotechnology Co. Ltd., China by M/s May (India) Laboratories Pvt. Ltd. Chennai.**

2.1 The Committee noted that comments of Director, IVRI, Lucknow and Dr. S. K. Srivastava, Director, Department of Animal Husbandry and Dairying, MOA, DBT, ICMR, DCGI etc are awaited. One of the members informed that the proposal has not been received by him.

2.2 After detailed deliberations, the Committee decided to await the comments of the Experts before a final view is taken. Decision on the proposal was therefore deferred.

3.0: Permission for conduct of phase III Clinical trials of PEGINFERON (r-Peg Interferon alpha 2b) indigenously developed by M/s Virchow Biotech Pvt. Ltd. Hyderabad.

3.1 The Committee 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 clinical trials.

3.2 After detailed deliberations and taking into consideration the recommendation of RCGM, the Committee approved the conduct of clinical trials with PEGINFERON (r-Peg Interferon alpha 2b)

indigenously developed by the Company subject to DCGI clearance. The Committee also recommended that the phase III clinical study should include a comparative bioequivalence study with the commercialized international product.

4.0: Permission for import of formulations of r-Golimumab (CNTO 148Ig G Monoclonal Antibody Final Vialed Product) from Fisher Clinical Services, UK for conducting Phase III Clinical trials by M/s Synchron Research Services Pvt. Ltd. Ahmedabad

4.1 The Committee noted that the Company proposes to conduct clinical trials on two formulations C0524T05 and C0524T06. The primary objective of the study is to assess the efficacy of the drug in subjects with active Rhematoid Arthristis despite Methotrexate therapy. The proposed clinical trials are part of the global clinical trials and India would be among the 35 other countries participating in the clinical trials. Total number of patients anticipated to be recruited in India for Protocol C0524T05 is 100 and for C0524T06 are 80 patients.

4.2 The Committee also noted that comments from DBT, ICMR, DCGI etc are awaited. One of the members informed the proposal has not been received by him.

4.3 After detailed deliberations, the Committee decided to await the comments of the Experts before a final view is taken. Decision on the proposal was therefore deferred.

5.0: Permission for manufacture and marketing of recombinant –interferon alfa 2b by M/s Intas Pharmaceuticals Ltd. Ahmedabad.

5.1 The Committee noted that the Company has completed phase –III clinical trials in India with recombinant –interferon alfa 2b in India in accordance with the approval granted by DCGI, GEAC and Human Ethics Committee. The Committee considered the request for manufacture and marketing in India and noted that comments of Director, Indian Institute of Sciences, Bangalore and Director, ITRC, Lucknow, ICMR, DCGI and other experts are awaited. The Committee also considered the comments received from DBT regarding the need to conduct comparative bioequivalence with the already commercialized international biogenerics therapeutics during phase III clinical trials.

5.2 On the issue of containment facility, Member Secretary, RCGM informed that RCGM has examined the matter in its meeting held on 26.12.2005 wherein the Committee concluded that the containment facility at R & D and production premises are adequate to meet the environmental safety regulation for production of recombinant –interferon alfa 2b.

5.3 After detailed deliberations, the Committee decided to await the comments of the Experts. Decision on the proposal was therefore deferred.

6.0: Permission for manufacture and marketing of recombinant –Granulocyte Colony stimulating Factor (GCSF) by M/s Zenotech Laboratories Ltd. Hyderabad.

6.1 The Committee noted that the Company has completed phase –III clinical trials in India with recombinant –Granulocyte Colony stimulating Factor (GCSF) in accordance with the approval granted by DCGI, GEAC and Human Ethics Committee. The Committee considered the request for manufacture and marketing of the drug in India and noted that comments of Director, Indian Institute of Sciences, Bangalore and Director, CDRI, Lucknow, ICMR, DCGI and other experts are awaited. The Committee also noted that the proposal has been recommended by DBT.

6.2 On the issue of the containment facility, Member Secretary, RCGM informed that RCGM has examined the matter in its meeting held on 27.1.2006 wherein the Committee concluded that the

containment facility at R & D and production premises are adequate to meet the environmental safety regulation for production of recombinant –Granulocyte Colony stimulating Factor (GCSF).

6.3 After detailed deliberations, the Committee decided to await the comments of the Experts before a final view is taken. Decision on the proposal was therefore deferred.

7.0: Permission for manufacture and marketing of recombinant –Granulocyte Macrophage Colony stimulating Factor (GM-CSF) by M/s Zenotech Laboratories Ltd. Hyderabad.

7.1 The Committee noted that the Company has completed phase –III clinical trials in India with of recombinant –Granulocyte Macrophage Colony stimulating Factor (GM-CSF) in accordance with the approval granted by DCGI, GEAC and Human Ethics Committee. The Committee considered the request for manufacture and marketing of the drug in India and noted that comments of Director, Indian Institute of Sciences, Bangalore and Director, CDRI, Lucknow, ICMR, DCGI and other experts are awaited. The Committee also noted that the proposal has been recommended by DBT.

7.2 On the issue of the containment facility, Member Secretary, RCGM informed that RCGM has examined the matter in its meeting held on 27.1.2006 wherein the Committee concluded that the containment facility at R & D and production premises are adequate to meet the environmental safety regulation for production of recombinant – Granulocyte Macrophage Colony stimulating Factor (GM-CSF)..

7.3 After detailed deliberations, the Committee decided to await the comments of the Experts before a final view is taken. Decision on the proposal was therefore deferred.

8.0: Permission for import and marketing of recombinant –human Erythropoietin from M/s. Shenzhen SPEC-Bio-Pharmaceuticals Industry Co. Ltd. China by M/s VHB Life Sciences Inc. Mumbai

8.1 The Committee considered the request for import and marketing of the drug in India and noted that comments of Director, Indian Institute of Sciences, Bangalore and Director, CDRI, Lucknow, ICMR, DCGI and other experts are awaited. One of the members also pointed out that the data submitted is inadequate to claim its efficacy without showing bioequivalence in the clinical trials.

8.2 After detailed deliberations, the Committee decided to await the comments of the Experts. Decision on the proposal was therefore deferred.

9.0: Permission for import and conduct of Phase II clinical trials of Chimerivax^{tm} –JE in children of descending age from USA by M/s. Quintiles.

9.1 The Committee noted that the proposal was considered in the meeting held on 13.1.2006 wherein the following areas of concern was identified:-

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.

9.2 The Committee invited the Experts to present their views on the proposal. The following points were noted:-

- The vaccine is produced from an infectioUs clone of attenuated YF 17D vaccine virus modified by replacing the structural protein with those of JE virus (attenuated SA 14/14-2 strain)

- The vaccine is used in countries like USA and Australia as a vaccine for military personal and travelers who are already vaccinated for yellow fewer.

- The yellow fever virus does not exist in India. Therefore the introduction of a new virus is an area of environmental concern which needs to be addressed by the Committee.

- Both JEV and Chimerivax-JE are RNA viruses. Due to the transfer of RNA polymerase between the viral genomes during RNA synthesis, RNA viruses are known to recombine within and between species. An example is the appearance of Western equine encephalitis virus from recombination between two alpha viruses. Thus, risk associated with the emergence of a pathogenic virus following a recombination between Chimerivax-JE and another flavivirus, however small, cannot be ignored. Besides, potential of RNA viruses to mutate and become pathogenice is exemplified in the 1994 incidents wherein a strain isolated from a fatal 17D vaccine-associated case of encephalitis was shown to have sequence differences compared with the parent vaccine virus, and was associated with increased virulence for mice and monkeys. Another example relating to the virulence reversion of the live poliovirus vaccine strain in a child leading to poliomyelitis was also mentioned.

- The currently available JE inactivated mouse brain vaccine produced by Central Drug and Research Institute (CDRI) is considered safe and efficacious. The side effects are negligible and no published reports seem to be available in India on its adverse effects. Efficacy of the vaccine has also been proven. The limitation on its extensive use because the multiple dose schedules and requirement of boosters every year in addition to production capacity, availability and cost of the vaccine. In view of existence of such an alternative, it is a matter of debate whether newer vaccine(s) should be introduced whose risks are still not known.

- Live virus vaccines offer considerable promise in terms of efficacy and cost. Unfortunately, the risks of recombinants between vaccine virus and other wild-type flaviviruses resulting in recombinants with novel properties cannot be estimated. It was also pointed out that plenty of flavivirus activity is prevalent in our country in the form of JEV and Dengue viruses which are endemic to various parts.

During the deliberations it was pointed out that DCGI has permitted the import of the Chinese Encephalitis vaccine even without conducting phase-II clinical trials. The Chinese attenuated virus vaccine SA-14 14-2 could multiply in JE vector mosquitoes and showed titers up to 5.4 to 7.3 log / pfu mosquito. Other studies carried out in monkeys for neuro-virulence and safety is sufficiently satisfactory and has shown no recombination or back mutation. It was noted that the Chinese Encephalitis vaccine is not a recombinant product. It was however pointed out by one of the Members that Rules 1989 covers not only recombinant product but also hazardous micro-organism and as such the DCGI should have referred the matter to the GEAC in view of the associated environmental risks. The committee requested DCGI to clarify whether the concerns being raised in respect of Chimerivax_JE have been taken into consideration by the DCGI while according approval for import of the Chinese Encephalitis vaccine

9.3 The Committee subsequently gave an opportunity to the Company representatives to present their views on the concerns raised by the Company. The following points were noted:-

- Chimerivax_JE has been developed in a more acceptable cell substrate and requires only a single dose for immunization.

- Phase 3 trials in adults are underway (~1000 subjects) in USA and Australia. To a query on whether the Company would like to conduct clinical trials in adults in India since it has not been tested anywhere in the World in children, it was clarified that JE is mainly a disease in children in India and recent epidemic in India highlights unmet medical need. Since adequate data on adults are already available, it would serve no purpose to repeat the trials inn adults. Further, additional data in Indian adults would not be relevant to flavi-naïve children.

- The remote and theoretical risk of recombination should not prevent development of new vaccines that provide public health benefit.

- Flaviviruses have no sub-genomic RNA therefore inter-speci9fic recombination between flaviviridae has not been seen despite examination of a large number of flavivirus sequences including strains of four dengue serotypes which circulate in the same vectors and hosts n endemic regions.

- Flavivirus evolution has been driven by mutation of genetic sequences and not en bloc recombination between homologous and non-homologous genetic regions.

- No recombination event has resulted in a pathogenic phenotype change i.e. increase in virulence or replication efficiency.

- It is estimated that the possibility of hypothetical recombination approximates 1 per 300 million.

- For many flavivirus diseases, a live, attenuated virus strategy remains the best means to develop a suitable vaccine because control of endemics requires rapid immunization with a single dose. This is supported by the fact that out of 16 viral vaccines approved by US FDA, 10 are live attenuated viral vaccines.

9.4 During the deliberation, the availability of the indigenous JE inactivated mouse brain vaccine developed by CDRI was also discussed. It was clarified by one of the Members that CRI is in the process of expanding their facilities and the vaccine will be available at a cheaper cost within a year or two. In addition two more companies have shown interest in developing the inactivate mouse brain vaccine for JE. It was also noted that the shelf life of the vaccine developed by CDRI is four years.

9.5 After a detailed deliberation on the issues mentioned above, the Committee was of the view that adequate data is not available to rule out the possibility of introducing a new virus (yellow fever virus). Therefore available alternate options need to be explored. It was therefore decided that requisite clarifications, in this regard should be obtained from MoH, DCGI and CDRI. The Committee also advised the Company to submit additional information, if any to prove that the risk of introducing Yellow fever virus from the use of Chimerivax – JE is minimal. Decision on the proposal was deferred.

10.0: Report of the Sub-Committee on Bt cotton and related issues.

10.1 The Member Secretary briefed the Committee on the views expressed by Members on this matter in the previous GEAC meeting and placed the recommendation of the sub-Committee on Bt cotton and related issues for reconsideration of the Committee. The Committee reiterated the following points:-

- 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. However, the Company should provide a detailed justification for the selected locations.
- The 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.
- One view was that once the biosafety studies have been completed and approved by RCGM all hybrids should be treated on par for LST.
- It was also opined by some members that 1 year MLT followed by two years of LST and two years of ICAR testing in tandem should be applicable in all cases as interpretation of data based on 1 year LST may not provide any scientific conclusion.
- While 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.
- The new policy and procedure should be applicable only in prospective for new cases only and not retrospectively. The new cases would mean those hybrids that are refereed to the GEAC for the first time for LST during Kharif 2006.

10.2 The Committee also gave an opportunity to M/s Nath Seeds for presenting their views and concerns on the sub-committee's recommendations. The Company expressed concern regarding the new policies recommended by the sub-committee in respect of two years of LST for 'new gene/event'. They requested the GEAC to consider their case based on one year LST on the following grounds:-

- All the Bt cotton hybrids approved by the GEAC are either those of Mahyco-Monsanto (Monsanto's technology) or their sub-licensees. Because of the sole monopoly of a multi-national, the price of Bt cotton seed being charged remains exorbitantly high.
- Nath Seeds have ventured to come up with alternative Bt cotton technology, through indigenous efforts. Through 4 years of various testing, they have completed all the mandatory requirements of biosafety studies, one year MLT, two year ICAR trials and one year LST under GEAC as per prescribed regulatory procedures.
- About 16 such Bt hybrids were approved last year (2005), after one year of Large Scale Trials.
- It is difficult to comprehend as to what exactly is meant by the term 'micro-variants' (Cry 1 Ac-1, Cry 1 Ac-2, etc). Scientific literature does not recognize any such genetic nomenclature and the Sub-Committee has not elaborated upon except to say that "they do not have complete DNA homology, but have some base pair differences and hence may have some variation in the protein system". It is very important to specify as to what that 'some variation' would be.

10.3 During the deliberations, the members were of the views that there is merit in the Company's argument regarding the term 'micro-variants' (Cry 1 Ac-1, Cry 1 Ac-2, etc) and therefore Protocol –II recommended by the sub-Committee in respect of 'micro-variant' needs reconsideration. After detailed deliberation on the various issues mentioned above, the Committee concluded that the matter may be referred back to the sub-Committee for its reconsideration in the light of the views expressed by the members of the GEAC and also representations given from time to time by the industry representatives. The Committee further recommended that two more members (Dr R P Sharma and Dr Sushil Kumar) may be co-opted in the Sub-Committee in view of their expertise on the subject matter. It was also decided that the new policy and procedures would be applicable in prospective for new cases only and not retrospectively. It was also agreed that the new cases would mean those hybrids which have not been approved by the GEAC for large scale trials.

11.0: Representations received from NGOs in respect of Bt Cotton field trials.

11.1 The Member Secretary, GEAC briefed the Committee on the representation received from the Centre for Sustainable Agriculture, Greenpeace and other NGOs regarding the performance of Bt cotton as well as regarding alleged irregularities during large scale trials of Bt cotton approved by GEAC. She further informed that the representations have been forwarded to the respective State Dept of Agriculture and MOA for verification and submission of a factual report. Since the evaluation of the Bt cotton trials under RCGM / GEAC and AICCIP trials under ICAR are also in progress, the reports have also been forwarded to Member Secretary RCGM and AICCIP project co-coordinator. The reports received from Member Secretary RCGM and AICCIP project co-coordinator in respect of the complaint received from Centre for Sustainable Agriculture was also placed before the committee.

11.2 The Committee opined that the representations received need to be addressed in proper perspective. The Committee was of the view that a separate meeting to discuss the above issue may be convened by the Chairman GEAC to which the respective State Govts and other agencies associated with the monitoring of Bt cotton may also be invited for facilitating scientific discussion.

Date of the next GEAC Meeting: 8th March 2006

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