



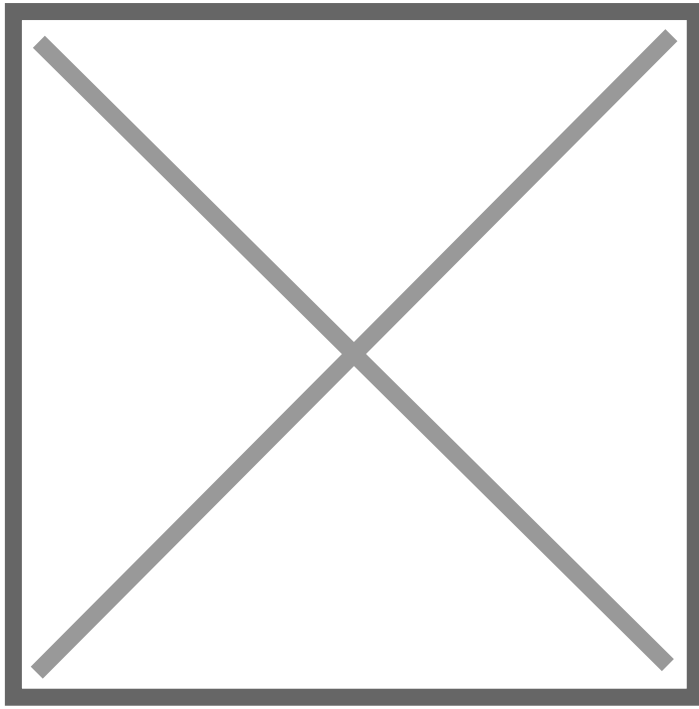
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Mashelkar Panel Draft Report Ready

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A national task force headed by CSIR chief Dr RA Mashelkar was set up in April 2004 to streamline the regulatory process involved in the approval of all recombinant DNA products. The Ministry of Environment and Forest (MoEF), which oversees the regulatory agency, Genetic Engineering Approval Committee (GEAC), had issued the notification for setting up the task force on April 20. The task force, which was asked to submit its report by May 2004, had the 12 members as part of the panel. The first meeting of the Task Force was held on May 12, 2004 and subsequently the task force met the industry and other stakeholders at several levels. The draft report of the Task Force on recombinant pharma is now ready.



On setting up the panel, industry leaders welcomed it and quickly evinced their suggestions to help the task force with the tasks ahead. Now that the draft will be circulated, industry has few quick comments to offer on the same.

Four great developments emanate from this report said the South Asia Office of The International Service for the Acquisition of Agri-biotech Applications (ISAAA).

- GEAC will not have a say if the final product doesn't involve LMOs. Most of the recombinant pharmaceuticals don't have living organism in their final products (only protein derived from LMOs/GMOs). It will be a savior for biotechnology industry. GEAC's role would be limited to inspection (if fermentation capacity is over 20l) only. Reversely, anything that involves LMOs/GMOs would come under the purview of GEAC irrespective of its risk categories. The report will have, if any, adverse impact on the growth of agricultural biotechnology.
- Constitution of Inter-ministerial Standing Committee on biotechnology regulation to address issues and anomalies concerning recombinant pharma that have never appeared before. It would strengthen coordination among different

ministries and smoothen the process for approval of innovative products to be come in the market.

- Task force vehemently recognizes the importance of an independent institutional mechanism called National Biotechnology Regulatory Authority. Since both Prof. Swaminathan and Dr Mashelkar recognize the need to develop strong institutional structure and scientific body i.e., NBRA, the government must evolve this process rapidly to give fillip to investments and trade in biotechnology products.
- Protocol V would be detrimental to Indian biotechnology industry and dumping of biotech products in India. Eventually, it would promote "trading" than "innovation" in our country.

Since the final recommendations have not been made public yet, the comments to each of the individual points in the recommendations is difficult to make said Dr Dhananjay Patankar, head, biotechnology, Intas Pharmaceuticals Ltd. However, he made some general comments.

- We are overall quite satisfied with the draft recommendations of the Mashelkar Task Force. The main concerns of the industry in the existing framework was that various committees were looking at the same data, often outside their area of expertise, thus causing duplication and redundancy and delays. Further, there was a problem of infrequent meetings of the committees. The draft recommendations have streamlined the procedure such that different committees examine the data that fall under their field of expertise and there is no unnecessary duplication. The different committees like RCGM, GEAC have also on their own already increased the frequency of their meetings and increased their communication with the companies.
- We are very happy about the way the government has really responded to the industry's concerns and brought about simplification of procedures without diluting the stringency of the regulatory scrutiny of the data before according approval to products.
- For registration of imported biotech products, however, we have one further suggestion to the DCGI (although this was not under the scope of the Mashelkar Task Force). We believe that the DCGI should insist on inspection of the manufacturing facilities and GMP aspects of the manufacturer whose product is to be imported. As of now there is no such provision, and thus we cannot be sure of the quality of the production system of the manufacturer. The expenses for carrying out inspections can be recovered through application fees charged to the importer. The domestic manufacturers adhere to strict GMP regulations as per Schedule M but there is no method for ensuring that the foreign manufacturers are adhering to such quality systems.



Dr Prasanta Kumar Ghosh, senior vice president, Cadila Pharmaceuticals Ltd, Ahmedabad, who had served in various key positions in the government and retired as advisor from the DBT in May 2002, in his personal capacity, observed that the Indian rules on GMOs were framed when the knowledge base on nucleotide sequences including the promoters, the enhancers, terminator sequences etc. were inadequate. Information on safety of complete coding construct and transformed host were also inadequate. With the advent of knowledge, review of the Rules has become imminent. In that context the work of the Task Force (TF) is very relevant.

He added: "The TF is mandated essentially to recommend a transparent and streamlined regulatory mechanism and a regulatory process including mechanism for the use of LMOs in the pharmaceuticals industries as also for import of LMOs by

the pharma sector. The analysis of the regulatory framework by the TF seems to be somewhat myopic and the essence of the strength of the current framework of the regulation has largely been missed out. Few problems identified in the analysis seem to be supposition and some of the conclusion appears to be inexact."

Ghosh pointed out:

- As regards the recommendations appearing on Para 5 of the draft report the existing system has been found to be workable and largely status quo has been maintained for the roles of IBSC and RCGM (Para 5.1a and 5.1b).
- For recommendation at Para 5.1c, it has been stated that for the review of LMOs, GEAC will take note of or approve only the containment facilities for the use of LMOs including more than 20 liter fermentation capacity where the end product is a purified material intended for commercialization. This recommendation does not seem to be scientifically consistent with LMO substances containing nucleotide sequences consisting of coding sequences with or without promoters and terminator sequences. Presence of such sequences in adequate quantities in the purified finished product could be potentially harmful. For this recommendation, I think it should be modified for LMO substances for which there is no pharmacopial specification and yet the nucleotide sequences are present in quantities less than 100 picogram per dose.
- In Para 5.1d, it has been stated that the DCGI would examine animal toxicity, allergenicity and QC data. Here too the recommendation needs to be modified to include only those LMO drug substances that have been incorporated in Indian Pharmacopoeia or in any other Pharmacopoeia accepted by the Indian authorities.
- In recommendation Para 5.2a, it has been stated that "It was agreed that... for conducting Phase III human trials". The conclusion seems to be inconsistent with the existing law the reason for the GEAC to state that it has no objection to the conduct of trials on human including Phase I or Phase II or Phase III or Phase IV when GEAC is satisfied that the animal safety data generated by the applicant indicates that the product is reasonably safe. GEAC works under EPA and it has been the responsibility of GEAC to examine whether a pharmaceutical product derived from LMO is safe to human and animal. Safety information emanating from the presence of Host DNA and Host nucleotide sequences as well as trans nucleotide sequences are within the purview of GEAC under Indian EPA.
- The recommendations at Para 5.2 a 2,3,4 seem to be okay and they are consistent with sound logic and good argument. These are also being generally followed presently.
- Recommendation at Para 5.2a 5 does not seem to be okay for new drugs derived from rDNA technology. These can be okay for Pharmacopial drugs only.
- The recommendations at Para 5.2b2 does not seem to be correct as the presence of large quantities of the coding sequences can be potentially dangerous to human health.
- The recommendation at Para 5.2b3 is consistent if it is a Pharmacopial drug. This recommendation is therefore not required for situations where LMO's are Pharmacopial drugs.
- Recommendation 5.2b4 is also inconsistent with LMO drug that are Pharmacopial
- The recommendation at Para 5.2c on import and marketing of recombinant Pharma products also needs to be revised and perhaps for recommendation on 5.2c1 it can be stated that for import of recombinant pharma products where the presence of Host DNA or the transgenic DNA is less than 100 picogram each per dose, GEAC approval is not required. Otherwise all such substances should require GEAC approval. Obviously, Pharmacopial LMO products will not require approval of GEAC.
- Para 5.2c2 can be modified to incorporate that LMOs approved in any acceptable Pharmacopial will not require GEAC approval.

- He suggested the report could have been made much more simplified by excluding:
- All substances produced by LMOs where the substances are so pure that the presence of transnucleotide sequences as well as Host related proteins and DNA are not detectable by standard scientific practices
- All Pharmacoepial drugs including LMOs and products thereof would not require the approval of GEAC.



GEAC could also publish a list of nucleotide sequences, pharmacoepial drugs produced by rDNA technology, as well as other GRAS organisms on which there is no known environmental risk as exempt from the GEAC provisions. These would simplify the situation substantially he noted.

Rajesh Jain, joint managing director, Panacea Biotec Ltd, has his share of suggestions for the draft report on specific issues.

Containment facilities

- Inspection and approval of containment facilities (less than 20 ltr) may be provided by IBSC.
- RCGM may be involved in inspection and approval of containment facilities with capacity of more than 20 liters.
- GEAC may not get involved in approval of containment facilities.
- Clearance of proposal using various risk category organism
- All proposals using a category risk II microorganism be examined and approved by IBSC. The organisms under category I risk are non-pathogen and are exempt for any clearance.
- The proposals using organisms belonging to category risk III, IV or higher risk be first examined by IBSC and recommendations may be made to RCGM for approval.

Pre-clinical toxicology protocol/data

- RCGM should restrict its role in examining the proposal relating to the specifications, characterizations and information on rDNA biologicals materials. The RCGM should consider providing permission for generation of preclinical toxicology data.
- The preclinical toxicology protocol to be used would vary depending upon the requirements and products and such protocols are usually designed after discussion with appropriate laboratory or center involved in conduction of clinical trials. Therefore the precise protocol to be used would ideal be left to the investigators.

- The preclinical toxicology data so generated be examined by "rDNA expert committee" located in the DCGI office.
- Strengthening of IBSC and rDNA expert committee
- In both of these committees, the nominee of GEAC may also be included as member, so that all aspects relating to environment could be addressed at the initiation of the proposal and during examination of the data so generated.

Nonetheless no one is disputing the fact that the Mashelkar report is a sincere attempt to examine various issues and find reasonably sound solutions given the mandates of different authorities involved. "It is good that importers of biotech products (rDNA not containing LMOs) need not seek GEAC approval. Indigenous manufacturers now have a structured process and will benefit from IBSC, RCGM, RDAC and DCGI as long as timelines for approval are met. There is need for a stricter mandate on meeting timelines. The intention to provide impetus to the Indian industry is seen in the report but actions have to match it specially the pace with which each independent authority operates. The inter-ministerial committee on BT regulation is forward looking and if the single window approach could become a reality through National Biotechnology Regulatory Authority (NBRA) similar to US FDA it would be a boon and indeed pave the way for a brighter future for the Indian industry," informed Rajiv Gulati, MD and Chairman, Eli Lilly India.

Srinivas Rao

Draft Report of The Task Force on Recombinant Pharma

Key Recommendations

5.1 Roles of regulatory authorities and decision-making criteria under Rules 1989 of EPA and Drugs & Cosmetics Act, 1945.

a. IBSC to note, examine and approve proposals involving r-DNA work; to ensure adherence of r-DNA safety guidelines 1990 of Government; inspection of containment facilities at R&D and production units and to inform the RCGM about the facilities; to prepare emergency plan according to guidelines; to approve experiments utilizing the organisms and genetic elements from Risk Group-I and II organisms up to laboratory fermentation 20 ltrs capacity with intimation to RCGM; for using organisms falling in Risk Group III and above, IBSC to recommend to RCGM for approval to conduct laboratory studies; to recommend for import/ exchange of GMOs/LMOs, vectors, gene constructs, plasmids, etc., for research purposes; to act as a nodal point for interaction with statutory bodies; to examine the description of the target gene and source; nucleotide sequence and amino acid sequence of target gene and the target protein; the composition of the vector used; schematic diagram of the expression cassette; restriction map of vector indicating the location of the target gene; cloning strategy; description of the host cell line including genera and species; risks involved in handling of cell line; methods of maintenance of cell line; classification of the host cell line as per the guidelines; to examine protocols for toxicity/allergenicity studies as per national and international guidelines and their recommendations to RCGM.

b. RCGM to examine information on preparation of MCB and WCB; QC tests conducted on the cell line; approaches adopted for expression of target gene in the host cell line; genetic analysis including copy number of inserts, stability; level of expression of target gene; description of production process; growth kinetics; fermentation parameters; in-process control measures; quality control & quality assurance data; approaches adopted for extraction and purification of the target gene product; examine data on physico-chemical, biochemical, immunological and pharmacological characterization of the bulk; characterization of the finished formulation; acceptability criteria for bulk and formulation as per IP, USP, BP or other national/international specifications etc; efficacy tests on the target product; trial batch fermentation data on the product; estimation of contaminants like DNA, RNA, lipids, carbohydrates, proteins etc, derived from the host organism and any toxic processing materials in the product; to approve the protocols for conducting animal toxicity and allergenicity studies and examination of in-process and final QC data on the product etc; inform and recommend to the GEAC about the containment facilities at R&D and production sites.

c. GEAC will take note of/approve only the containment facilities for the use of LMOs, including more than 20 ltrs fermentation capacity, if the end product is a purified product like antigens, proteins or any therapeutic/prophylactic product intended for commercialization. It will confine its regulatory role in terms of product approval only if the end products are living modified organisms (LMOs) per se in terms of risk vs. benefit analysis. In this context GEAC to approve activities involving large scale use of LMOs; industrial production and application; permit to use LMOs for commercial applications; authorize large-scale production and release of LMOs into the environment; adopt the procedures for restriction or prohibition, production, sale, import and use of LMOs for applications under EPA; authorize agencies or persons to have powers to initiate punitive actions under EPA on defaulters.

d. DCGI would examine animal toxicity and allergenicity and QC data; examine the protocol and recommends conduct of human clinical trial; examination and approval of clinical trial report; approve for production of trial batches; accept of Test Reports from CRI, Kasauli; final approval to manufacture and market.

5.2 Procedure Recommended in the biosafety regulations of LMOs and the products thereof for indigenous development as well as imported products.

a. Indigenous Product Development, Manufacture and Marketing of pharmaceutical products derived from LMOs:

1. There is no overlapping of regulatory objectives up to the pre-clinical evaluation of the data generated by the applicant on the recombinant pharmaceutical products derived from LMOs. It was agreed that there is no need for obtaining approval from GEAC for conducting phase III human clinical trials. The general consensus was that it is the mandate of DCGI to look into the pre-clinical and clinical data for assessing the efficacy and safety of the product. Therefore DCGI only may accord approval for conduct of human clinical trials.

2. RCGM to continue the practice of examining the protocols and pre-clinical data submitted by the applicant and forward their recommendation to DCGI for consideration of granting approvals for human clinical trials and simultaneously, endorse a copy to GEAC for information and record.

3. RCGM, based on the report of IBSC to send information to GEAC about the adequate containment facilities installed for handling LMOs during R&D and production by the applicant. GEAC in-turn takes cognizance of the information.

4. However, approval of GEAC would be required for the containment facility involving use of LMOs during the product development and manufacturing of recombinant pharma products utilizing more than 20 liters fermentation capacity.

5. RDAC in DGHS to approve the protocol and recommend to DCGI for conducting phase-I to phase-III human clinical trials; the clinical trial data is to be directly submitted to the DCGI by the applicant. DCGI is to examine the Human Clinical Trials data and approve the marketing of the product as per the Drugs and Cosmetics Act & Rules and endorse the information to GEAC for record.