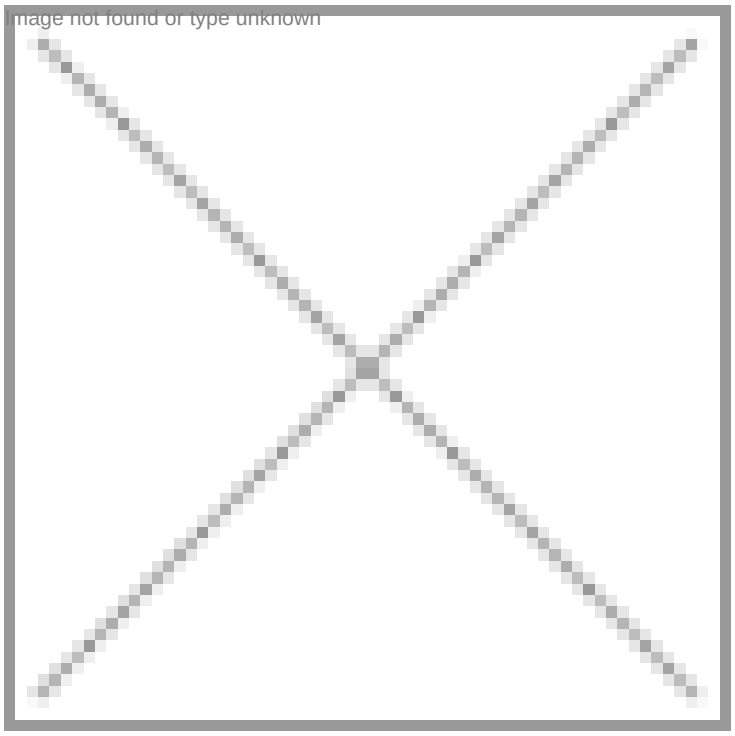
BioSpectrum
the business of | Bio & Health Sciences

The Mashelkar Report on Recombinant Pharma

11 October 2005 | News

Image not found or type unknown



The Mashelkar Report on Recombinant Pharma

Highlights

The report of the Task Force on Recombinant Pharma, headed by Dr R A Mashelkar, director-general, Council of Scientific and Industrial Research (CSIR), has been submitted to the Ministry of Environment and Forests (MoEF) for action. The Genetic Engineering Approval Committee (GEAC) under MoEF had been acting as the key biotech regulator, providing environmental clearance to all products using genetically modified organisms (GMOs).

- Task force takes 90 percent of LMOs out of GEAC purview
- National Biotech Regulatory Authority (NBRA) as unified regulatory suggested
- Timelines set for regulatory approvals
- DBT to play major role in biotech regulation

" My report will ensure that 90 percent of the organisms used by biotech companies which are from Category I and II will be out of the purview of GEAC," Dr Mashelkar told BioSpectrum immediately after submitting the report.

Officials at MoEF expect most of its recommendations to be implemented in the coming months. However, a ministry official cautioned that the industry should not jump to start implementing its suggestions and await the relevant notifications to be issued by relevant government agencies. Officials expect these processes to be done in the next three months and the industry could start getting the benefits of Mashelkar's recommendations from January 2006.

The Task Force was appointed by MoEF In March 2004 to suggest a new regulatory framework for recombinant pharma products. This followed a series of representations to the government from the industry to streamline the regulatory system for biotech products.

BioSpectrum presents here the highlights of the recommendations of the Mashelkar Task Force:

Analyzing the various issues and relevant suggestions made by biotech stakeholders regarding the streamlining of the current regulatory framework and procedures outlined in the DBT guidelines for implementation of Rules 1989 of EPA, the Task Force came to the conclusion that

(i) There is no overlapping of regulatory objectives up to the evaluation of pre-clinical study data generated by the applicant on the recombinant pharmaceutical products

(ii) The regulatory process can be expedited if the regulatory objectives of GEAC and DCGI are clearly defined. The Task Force recommends that the regulatory objective of GEAC should be confined to regulation of proposals which involve the large scale use of LMOs from environmental angle. Evaluation of the product safely, efficacy, clinical trials and market authorization is the mandate of the DCGI

(iii) The current regulatory procedure under 'Rules 1989' of EPA is applicable to all recombinant pharma products irrespective of the risk group of LMOs. Therefore, the current regulatory procedure and protocols for product development, clinical trials and market authorization should be elaborated to address various scenarios in the development and marketing of recombinant pharma products. The specific recommendations of the Task Force are stated below:

Recommended Procedure for Regulation of Recombinant Pharma Products derived from Living Modified Organisms (LMOs)

Taking into consideration the regulatory objective of GEAC, which, is confined to regulation of LMOs, two protocols are recommended: (i) products derived from LMOs but the end product is not a LMO and (ii) product derived from LMO where the end product is a LMO.

The product where the end product is a LMO has the potential for propagating/replicating in the environment and therefore needs a higher level of regulation as compared to products derived from LMOs where the end product is not a LMO.

Further the magnitude and probability of environmental risk depends on the extent of use of LMOs within the R&D and production units. In case of imports this risk is not there, especially in cases of therapeutic proteins in finished form.

Taking into consideration various aspects, the Task Force recommends that the regulatory procedure needs to be rationalized for the following five scenarios:

a) Indigenous product development, manufacture and marketing of pharmaceutical products derived from LMOs but the end product is not a LMO

b) Indigenous product development, manufacture and marketing of pharma products where the end product is a

LMO

c) Import and marketing of LMOs as drugs/pharmaceuticals in finished formulations

d) Import and marketing of LMOs as drugs/pharmaceuticals in bulk for making finished formulation

e) Import and marketing of products derived form LMOs as drugs/pharmaceuticals in bulk and/or finished formulations where the end product is not a LMO

The Task Force has detailed the procedures for each of these five scenarios.

The detailed procedures will be available on the BioSpectrum website (www.biospectrumindia.com)

Common Recommendations applicable to all five scenarios

1. Approval for import of recombinant organisms for the purpose of research and development is within the purview of RCGM

2. The regulatory agency to authorize human clinical trials would be the DCGI in all cases. However, approval of GEAC is necessary prior to conduct of Phase III clinical trials where applicable as outlined in Protocol II, III and IV.

3. In situations where approval of both DCGI & GEAC is mandatory, clearances from these regulatory agencies need be interlinked and both agencies can process their case concurrently.

Functions of the Regulatory Commitees/Competent Authorities under Rules 1989 of EPA and Drugs & Cosmetics Act, 1940 and Rules 1945.

a. IBSC (Institutional Bio Safety Committee) to examine proposals involving r-DNA work; to ensure adherence of Recombinant DNA Safety Guidelines of 1990 including preparation of emergency plans; examine product protocols for pre-clinical studies and inspection of containment facilities at R&D and production units. Throughout the product development, pre-clinical and clinical trials and manufacturing, the IBSC would act as a nodal point for interaction with statutory bodies.

As per the Recombinant DNA Safety Guidelines of 1990, IBSC can approve experiments utilizing organisms and genetic elements from Risk Group-I and II under intimation to RCGM. This practice would continue.

For experimental use of organisms falling in Risk Group III and above, IBSC would make its recommendations to RCGM. IBSC would also examine the protocols for toxicity/allergenicity studies as per national and international guidelines and make their recommendations to RCGM. IBSC to recommend to RCGM import/exchange of GMOs/LMOs, vectors, gene constructs, plasmids etc., for research purposes.

b. RCGM to approve experiments utilizing the organisms and genetic elements of all Risk Group organisms. This is as per the Recombinant DNA Safety Guidelines of 1990. RCGM to approve protocols for preclinical studies for all products. RCGM to submit its recommendations on the preclinical studies/data directly to the DCGI. For the products from the Risk Group III and above organisms, RCGM to examine the information on containment facilities at the R&D and production sites as well as the results of the preclinical studies and submit their recommendations both to the GEAC and DCGI. Approvals for import of recombinant organisms for the purpose of research is the mandate of RCGM.

c. GEAC to confine its regulatory role in terms of product approval if the proposals involve use of LMOs falling in Risk Group III and above as well as use of LMOs in open environment specifically when the end products are LMOs per se. In this context GEAC to approve activities involving large scale use of LMOs in industrial production and application; authorize large-scale production and release of LMOs into the environment; adopt procedures restricting or prohibiting production, sale, import and use of LMOs for applications under EPA; authorize agencies or persons to have powers to initiate punitive actions under EPA against defaulters.

d. DCGI to examine preclinical studies data on animal toxicity and allergenicity and Quality Control data and the

protocol for human clinical trial and approve production of trial batches. Prior to market authorization, DCGI to examine human clinical trial report, test reports from a laboratory designated by DCGI. The responsibility of post market surveillance is the mandate of DCGI. For products and processes involving Risk Group III and above organisms, DCGI will make available its decision on Phase III clinical trials to the GEAC.

The Timelines of decisions:

A consensus on the following timelines emerged for various approvals by the regulatory committees/competent authorities.

- RCGM approval for preclinical animal studies : 45 days
- RDAC approval for Human clinical trials protocol : 45 days
- RDAC (DCGI) examination of clinical trial
- Data and response : 90 days
- Simultaneous DCGI & GEAC decisions : 45 days

Documentations to be submitted by the applicant to the regulatory authorities for obtaining clearances.

The Task Force observed that formats for preparing documents to be submitted by the applicant to the IBSC, RCGM and GEAC have been evolved and is adequate for taking a view on the proposals. The proforma forms have been attached as annexures X, XI and XII.

The Task Force recommends that a format for submission of data to the DCGI by the applicant be evolved by the DCGI at the earliest.

Recommendations on other Linked Issues:

1. The definition of LMOs will include only those organisms modified by r-DNA techniques through human interventions. MoEF in this regard would issue necessary amendments to Rules1989 of EPA.

2. Since the responsibility of according market authorization for recombinant drugs is being entrusted to DCGI, there is an urgent need for strengthening the Committees under the Drugs & Cosmetics Act and Rules.

3. The expertise in the various regulatory agencies under Rules 1989 of EPA should be further strengthened.

4. There is a need for creation of an independent inspection facility to audit the manufacturing and containment facilities set up by the applicants involved in the production of recombinant drugs. This would also ensure acceptability of the Indian r-DNA pharmaceutical products in the global market. Since there is no single agency with adequate field level support system to carry out an independent inspection, the Task Force recommends that the Government may set up a separate agency for this purpose.

5. The products emanating from mono-clonals derived from rDNA technology in the form of therapeutic proteins/drugs would attract the provisions of Rule 1989 of EPA, and can be treated under Protocol I as Risk Category I & II.

6. Enzymes /industrial products from GMOs would attract the provisions of Rule 1989 of EPA. In such cases,

RCGM may be authorized to approve such proposals under intimation to GEAC.

7. If there is a change in the host organism or expression construct, fresh permission will be required to be sought from RCGM for the change by providing adequate data on bio-equivalence. If the data is found to be inadequate then RCGM may prescribe limited pre-clinical and/or clinical studies to be conducted to establish bio-equivalence. This would also be applicable to finished imported products intended for marketing.

8. No imported recombinant pharma product should be allowed to be introduced in the Indian market without adequate evaluation of clinical trial data or clinical evaluation in the country. The Task Force recommends that the efficacy and safety of the imported product should be evaluated for its efficacy on the Indian population before issue of market authorization.

9. For import of GMO / LMO for research/contract manufacturing or similar service, where the product (which is not an LMO) is to be exported out of India, a procedure should be laid down so that the companies can explore opportunities for this business while the safety aspect is also adequately addressed. A suggested procedure is: IBSC to examine proposal and recommend to RCGM; RCGM to approve if within Risk Group I and II. If organism is of Risk Group III or above, GEAC permission will be required. DCG(I) need not play any role.

10. On the issue of seeking approvals of PPA/DCGI/GEAC under Rules 1989 of EPA and PQO by Customs Authorities on the imports of microorganisms, GMOs/ LMOs for R&D purpose it is suggested that the earlier practice of permitting the import with the approval of RCGM should continue and PPA/DCGI to issue instructions to Custom Authorities to clear the consignment based on RCGM approval.

11. Regarding the constraints faced by the industry for import of non-GMOs, PPA may issue instruction to Customs Authorities to clear the consignment based on the declaration of the importer/exporter on certification of the nature of the non- GM organisms etc.

Standing Technical Advisory Committee on Biotechnology Regulation

1. Since several modifications have been made in the existing regulatory mechanism for recombinant pharma; during its implementation, several anomalies may become apparent.

To address these issues, the Task Force recommends, constitution of a Standing Technical Advisory Committee on Biotechnology Regulation to redress and look into various regulatory aspects and make issue based recommendations on case-by-case basis. Prior to any deviation from the proposed regulatory mechanism, which when comes in vogue, the views of this Committee should be obtained in the first instance.

2. The terms of reference of the proposed Standing Technical Advisory Committee should be to address the issues emanating from the overlapping/ conflicting Rules in various Acts applicable that are regulating biotechnology activities at R&D, import, export, trials, release, etc. and also to frame guidelines from time to time to facilitate the growth of biotechnology in the country.

Since the issues involved are highly technical and complex, the Task Force recommends that the Standing Technical Advisory Committee should comprise of an expert body instead of an inter-ministerial body.

An eminent Scientist should head the Standing Technical Advisory Committee and the members should include Chairman Genetic Engineering Approval Committee (GEAC), Chairman RCGM, Member-Secretary GEAC, Member-Secretary RCGM, DCGI and Experts on Immunobiologicals, Biogenerics, Plant Breeding, Molecular Biology, Environmental Sciences and other relevant areas.

3. The Committee can be administratively supported by any of the concerned agencies.

Proposed Independent Institutional Mechanism
National Biotechnology Regulatory Authority/Commission

1. The group believes that the creation of a professionally managed single authority would send a strong signal to the international community and promote trade and investment as well as ensure timely and effective regulation. While it is desirable to establish an independent professionally competent authority, if possible, for providing single window approvals, the Group also recognized the fact unless the existing relevant statutory requirements under EPA/Seeds Act/ DCGI are harmonized; setting up a NBRA may lead to "one more window clearance instead of a single window clearance". It is therefore recommended that such harmonization is an essential prerequisite for establishing the national biotechnology regulatory authority.

2. On the issue of the model for NBRA, the Group recommends that one of the models for National Biotechnology Regulatory Authority/Commission (NBRA), similar to the FDA system was proposed by Secretary DBT in the second meeting of the Task Force held on 15 June, 2004 may be considered by the Government. The proposed model recommends that the NBRA would comprise of four wings namely:

a) Agricultural products / Transgenic Crops

b) Pharmaceutical/ Drugs and Industrial Products

c) Transgenic Foods/Feed and

d) Transgenic Animals/ aquaculture.

Professionals who have been well trained in regulatory affairs would manage the four wings of the authority. This will facilitate more interactive regulatory process. A Vice Chairman would head the four wings of the Secretariat.

The recommendation of the Secretariat would be forwarded to Apex Committee with Statutory Powers. The members of the Apex Committee would comprise of representatives from all stakeholders Ministries/ Departments. The Apex Committee would report to the Chairman. The proposed model for NBRA is given at Annexure- XII.

3. Alternate models of how a National Biotechnology Regulatory Authority can be created also need to be examined.

4. In view of the complexities, the Task Force recommends that an inter-ministerial group be established to examine the model proposed by Secretary DBT among various others administrative Departments/ Ministries, for functioning of the proposed authority and make specific proposals with respect to the implementation including the budgetary requirements.