NOTIFICATION REGARDING ADOPTION OF THE RECOMMENDATIONS OF THE TASK FORCE ON R-PHARMA UNDER THE CHAIRMENSHIP OF DR R A MASHELKAR, DG-CSIR WITH EFFECT FROM 1.4.2006

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1. The Ministry of Environment & Forests (MoEF) under 'Rules for the Manufacture, Use, Import, And Export And Storage Of Hazardous Micro Organisms Genetically Engineered Organisms or Cells, 1989', framed under the provisions of the Environment (Protection) Act, 1986 is concerned with the environmental clearances of genetically modified food/crops/pharmaceuticals. To streamline the regulatory process in respect of the r-Pharma Sector under the above mentioned rules, the MoEF had constituted a Task Force on Recombinant Pharma Sector under the Chairmanship of Dr R A Mashelkar, DGCSIR with a vide OM No 12/7/2004-CS dated 20.4.2004. The mandate of the Task Force was to review the current framework and recommend a transparent and streamlined regulatory mechanism and process for the use of living Modified Organisms (LMOs) in the pharmaceutical industry during the various stages of R & D, testing, manufacture and import of LMOs as drugs.

2.0 The Task Force held five meetings during the period April 2004 to June 2005. The review and recommendations of the Task Force are based on a consultative approach involving a large number of stakeholders spanning diverse interests. The draft final report was posted on the MoEF website for a period of 6 weeks for further stakeholder consultation. Based on the recommendations and comments received, the report was adopted by the members of the Task Force on 13th June 2005.

3.0 The Chairman of the Task Force, Dr R A Mashelkar, DG-CSIR presented this report to Hon'ble Union Minister for Environment & Forests, Thiru A Raja on 13.9.2005 for consideration of the Government. The recommendations were subsequently adopted by the Ministry Of Environment And Forests, Department Of Biotechnology, Drugs Controller General of India And Ministry Of Health in the inter-ministerial held on 23rd January 2006.

4.0 **The recommendations and procedures outlined by the Task Force have been adopted by the Government of India and shall be in force from 1st April 2006.** Accordingly, the following recommendations and procedures under 'Rules for the Manufacture, Use, Import, And Export and Storage of Hazardous Micro Organisms Genetically Engineered Organisms or Cells, 1989' of EPA, 1986 shall be applicable in respect of recombinant Pharma products under Rules 1989. All applicants seeking the approval of

IBSC/RCGM/GEAC/DCGI are hereby directed to strictly follow the step-wise procedures outlined in the five protocols as applicable in the respective cases.

A. Definition of LMOs:

The definition of LMOs will include only those organisms modified by r-DNA techniques through human interventions where the end product is living modified organism.

B. Step –wise regulatory procedure for use of LMOs as drugs:

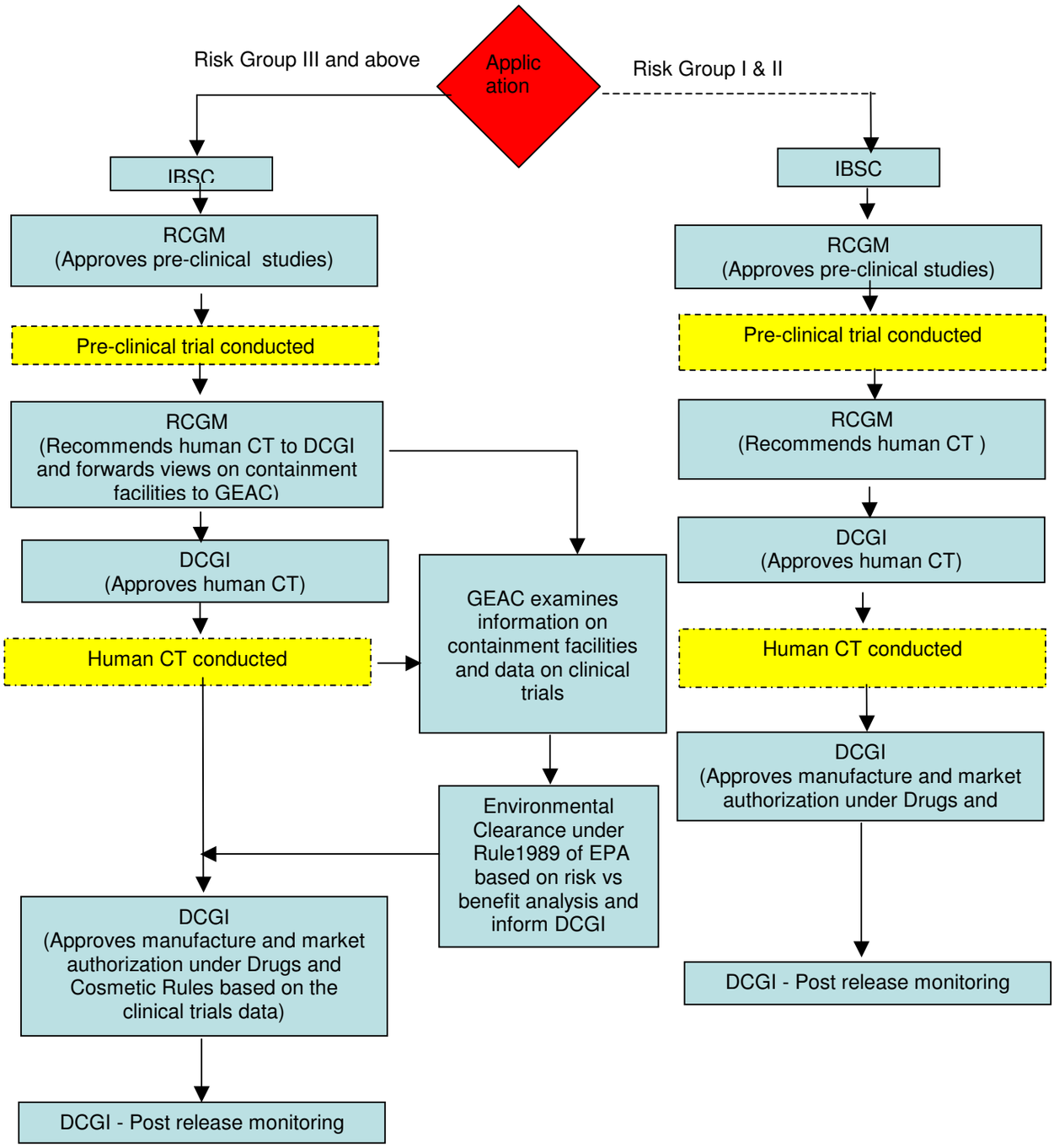
The product where the end product is a LMO has the potential for propagating/replicating in the environment and therefore needs a higher level of regulation as compared to products derived from LMOs where the end product is not a LMO. Further the magnitude and probability of environmental risk depends 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 import of therapeutic proteins in finished form. Further taking into consideration the regulatory objective of RCGM, GEAC and DCGI and the risks involved in the use of LMOs during the research & product development, manufacture and import from the environmental angle, the Task Force has rationalized the regulatory procedure for five categories.

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 pharmaceutical products where the end product is a LMO:
c. Import and marketing of *LMOs* as Drugs/Pharmaceuticals in finished formulations where the end product is a LMO:
d. Import and marketing of LMOs as Drugs/Pharmaceuticals in bulk for making finished formulation where the end product is a LMO: .
e. Import and marketing of products derived from *LMOs* as Drugs/Pharmaceuticals in bulk and/or finished formulations where the end product is not a LMO.

The step-wise regulatory procedure for each category is indicated in the five protocols mentioned below:

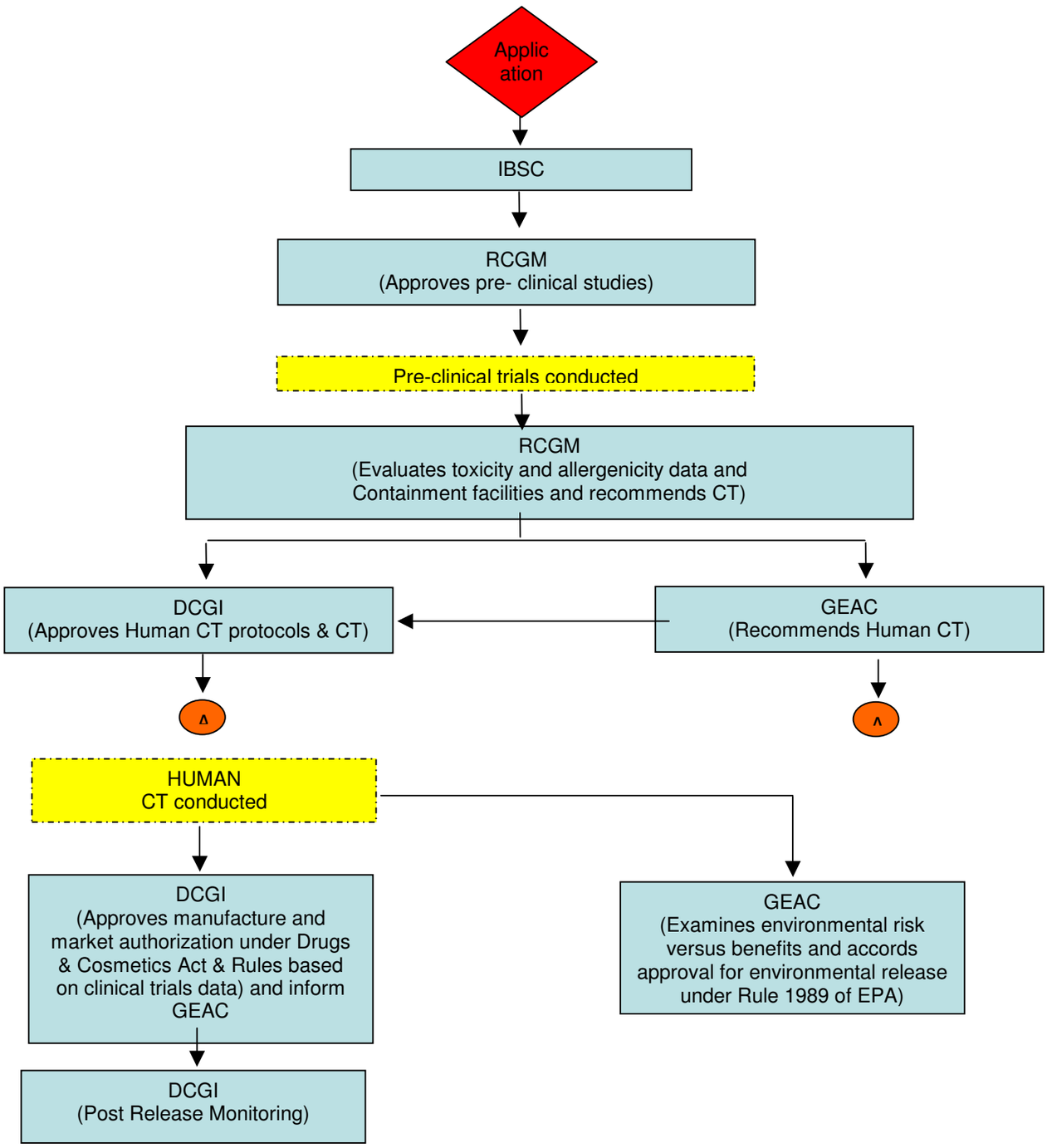
PROTOCOL - I

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



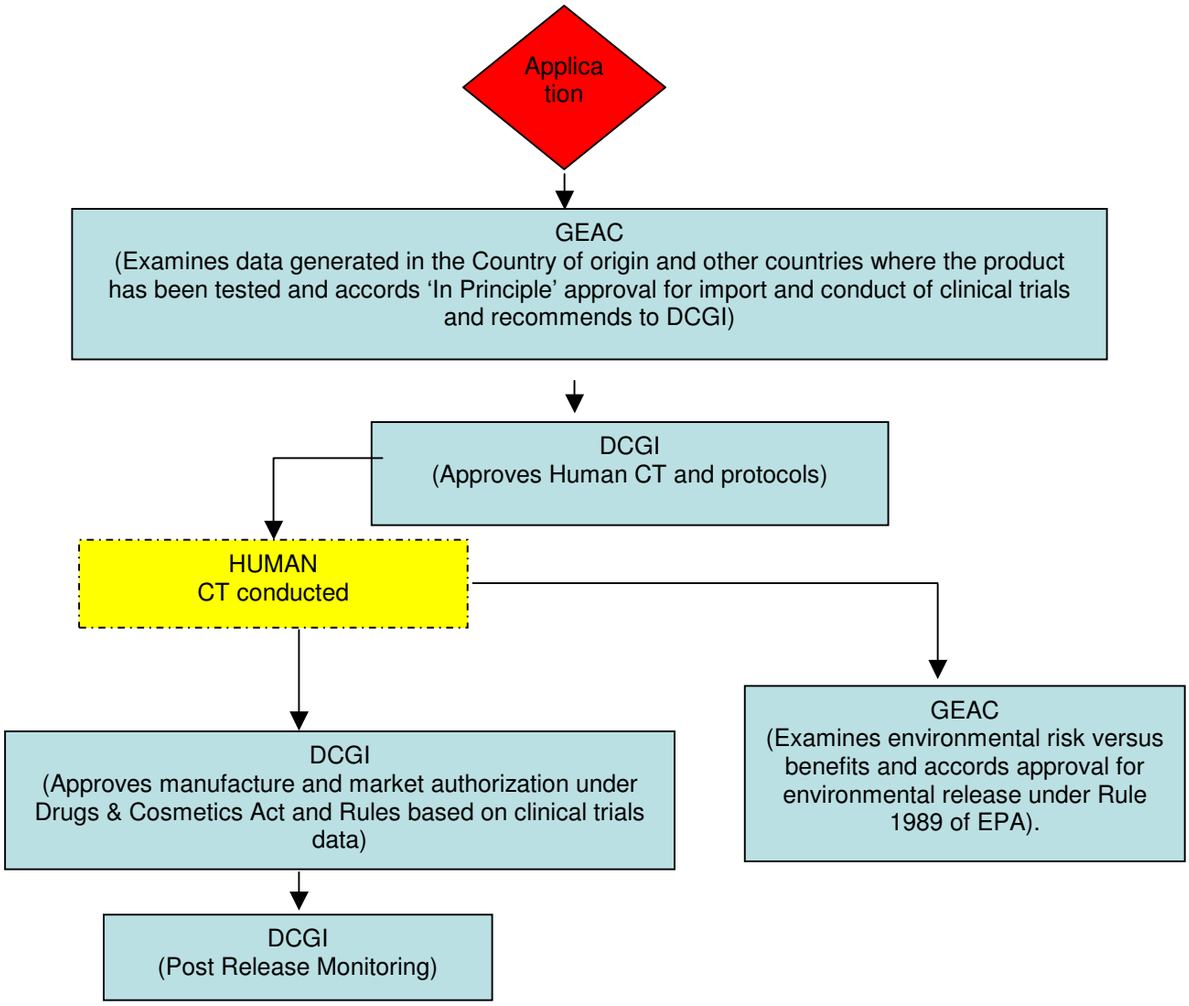
PROTOCOL – II

Indigenous product development, manufacture and marketing pharmaceutical products where the end product is a LMO



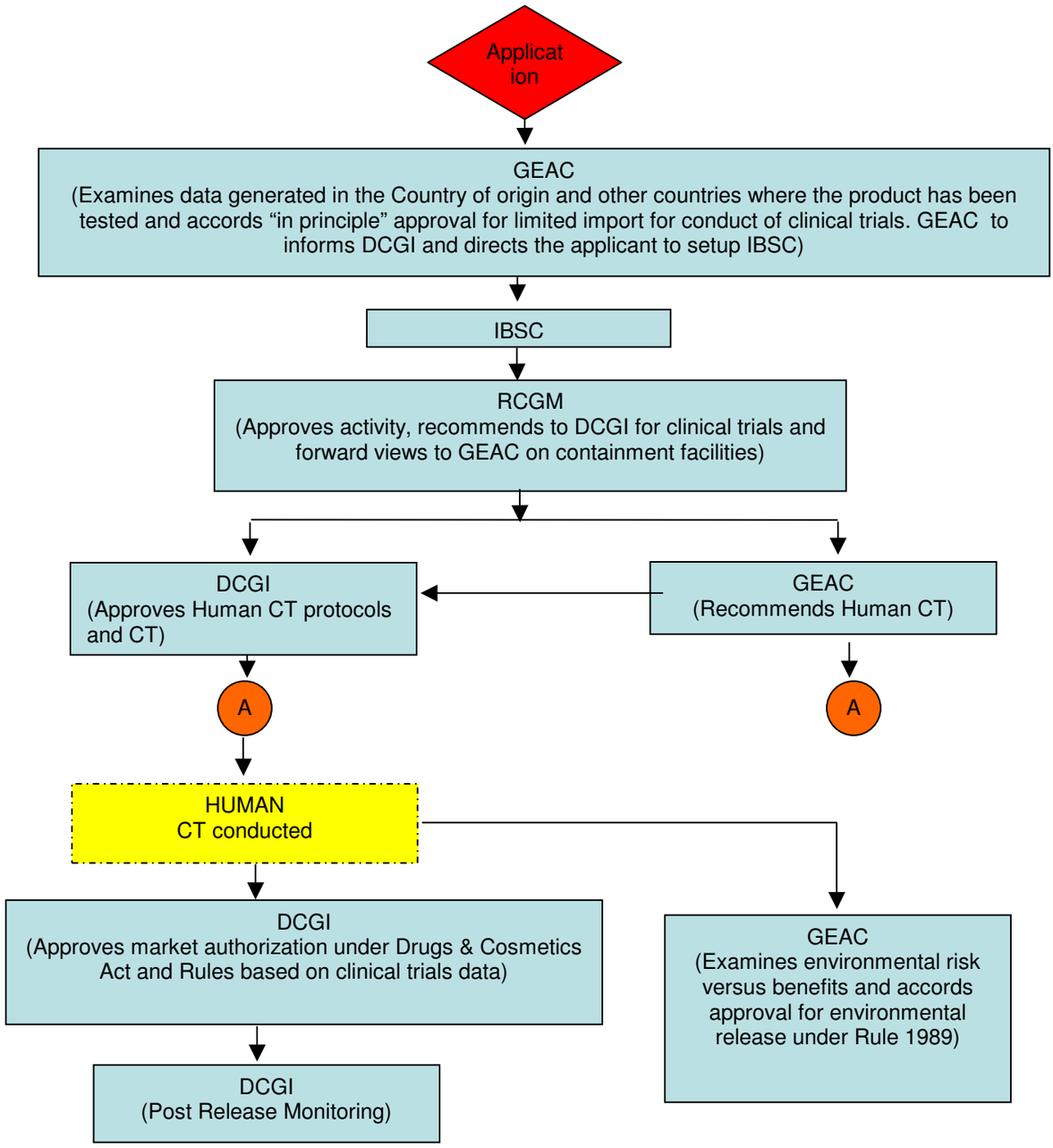
PROTOCOL – III

Import and marketing of Pharma Products in Finished Formulations where the End Product is a LMO



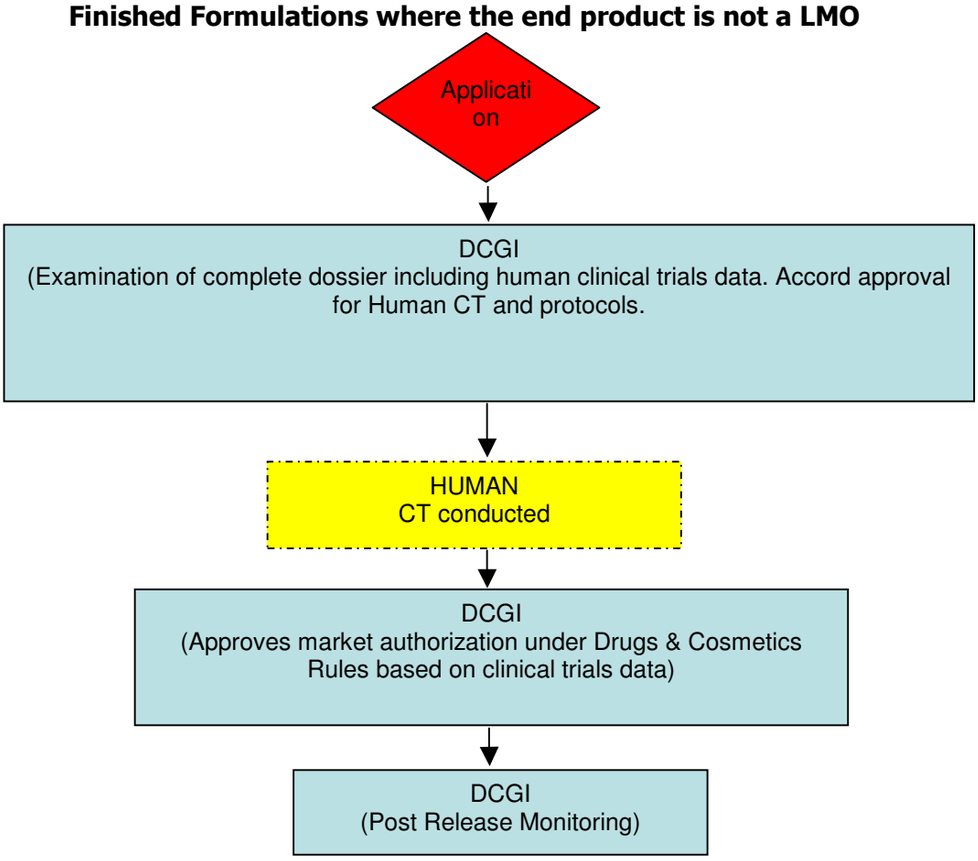
PROTOCOL – IV

Import and marketing of Pharma Products in Bulk for making Finished Formulation where the End Product is a LMO



PROTOCOL – V

Import and marketing of Pharma Products derived from *LMOs* in bulk and/or Finished Formulations where the end product is not a LMO



C. Time Lines for decisions by the regulatory Committees / Competent authorities.

- RCGM approval for pre-clinical animal studies: 45 days
- DCGI approval for Human Clinical Trials protocol: 45 days
- DCGI examination of clinical trial data and response: 90 days
- DCGI & GEAC decisions (simultaneous) 45 days

(GEAC clearance to be harmonized with the best practices guidelines for regulatory approvals adopted by MoEF)

D. Other Linked Recommendations:

i 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.

ii. 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.

iii. 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.

iv. 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.

v. 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.

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

(xvi) 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.

E. Constitution of a Standing Technical Advisory Committee on Biotechnology Regulation (STACBR) : The Task Force recommends the Constitution of a Standing Technical Advisory Committee on Biotechnology Regulation under the Chairmanship of an eminent scientist to redress and look into various regulatory aspects and make issue-based recommendations on case-by-case basis prior to any deviation from the regulatory mechanism. The MoEF is in the process of constituting **the STACBR**

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