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INDIA'S BIOTECHNOLOGY POLICIES AND BIOSAFETY REGULATIONS

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ABSTRACT

Biotechnology is an already established phenomenon in India's research and technology implementation programmes. This paper discusses the scope of biotechnological developments in India and the status of recombinant DNA (rDNA) biosafety guidelines aimed at protecting the environment against release of hazardous genetic engineering products. The structure of the biosafety regulations implementation committees and their functions are described. The need to harmonise national biosafety regulatory policies with other countries of particular regions is underscored.

Key Words: **Biosafety guidelines, India, rDNA**

RÉSUMÉ

La biotechnologie est une activité déjà établie dans les programmes indiens de recherches et d'applications technologiques. Ce papier discute l'envergure des développements biotechnologiques en Inde et l'état des directives de la biosécurité rADN visant à protéger l'environnement contre la libération de produits dangereux de l'ingénierie génétique. La structure des comités de réglementation de la biosécurité et leurs fonctions sont décrites. Le besoin d'harmoniser les politiques nationales de réglementation de la biosécurité avec les autres pays de certaines régions est souligné.

Mots Clés: **Des directives de la biosécurité, Inde, rDNA**

INTRODUCTION

Biotechnology holds enormous potential for helping to fulfill some of the needs of humanity, from increasing food and energy supplies to improving health. Political will, careful planning, prioritisation, and execution of programmes with large scale support form government and private entrepreneurs, can provide social and national benefits in health, agriculture, industry, population control, energy production, animal population husbandry and environment improvement among others. It requires concerted effort on the part of developing countries to develop adequately trained, highly skilled personnel to support programmes in the multidisciplinary areas of biotechnology. Other factors facilitating biotechnology research and its application include well developed scientific and technological infrastructure and promotion of better interaction between academia, industry and the government.

In light of the requirements of developing countries to improve their capacity in science and technology, to enhance capabilities in food

production, and to manage and control population and provide health care for all, there is a need for collective effort on the parts of these countries to identify specific project proposals based on the priorities of each country. Policy options for developing countries needs may be outlined with reference to the experience of some of the developing countries which have embarked upon biotechnology programmes, a case in point being Mexico (Alvarez-Morales, 1995). There is no escape from indigenous capability building in research and development, especially after the enactment of the World Trade Organisation, WTO. The world is becoming highly competitive and capability oriented and no nation is willing to part with its local capability without a handsome compensation. Thus, besides in-country effort, collaborative work through South-South-Cooperation and co-operation with international organisations and other such bodies, such as International Agricultural Research Centres (IARC) with the Consultative Group on International Agricultural Research (CGIAR), would be beneficial for development. Through this, it would be possible to select appropriate research for different developing countries, as they vary greatly with respect to their food and agricultural needs.

A major issue affecting the role and application of biotechnology is the safety of genetically modified organisms (GMOs) and the regulatory measures for research, field testing and commercialisation of GMOs. Fears have been expressed that uncontrolled release of GMOs might cause changes in ecological or genetic equilibria. However, limited studies and field tests carried out in the USA have led to the belief that careful design of transgenic organisms, along with proper planning and regulation of environmental releases, is perhaps adequate to ensure that GMOs pose little risk to the environment. However, many scientific questions are yet unanswered. Taking note of the enormous relevance of this field for national development, a separate Department of Biotechnology (DBT) was set up in 1986 in the Central Ministry of Science and Technology (DST) of India.

RESEARCH AND DEVELOPMENT ACTIVITIES IN INDIA'S DEPARTMENT OF BIOTECHNOLOGY

The DBT was set up with a mandate to act as a focal point in the administrative structure of the government for planning, promotion and coordination of biotechnological programmes in order to provide a systematic impetus for the development of a strong research and development (R&D) base and for process and product development and their application in important socio-economic sectors. The DBT functions with the advice of two major committees, namely the Scientific Advisory Committee (SAC-DBT) comprising eminent scientists and technologists, and the Standing Advisory Committee (Overseas) (SAC-O) with non-resident Indian scientists as members who interact very closely with the Indian scientific community. The department has also set up a venture company called Biotech Consortium India Ltd. (BCIL) which provides interface between R&D, academia, research and industry by bringing financial institutions and industry together. In this endeavour, the DBT, without spending any government funds, has mobilised the financial institutions and several industries to provide a core grant. BCIL has been very effective in helping the scientists in upscaling their technological innovations, setting up pilot plants, preparing feasibility reports and bringing industries together with research laboratories for commercial ventures.

The main responsibilities entrusted to the DBT are: (1) to evolve integrated plans and programmes in biotechnology; (2) to identify specific R&D programmes and biotechnology related manufacturing; (3) to establish infrastructural support at the national level; (4) to act as an agent of government for importation of new recombinant DNA (rDNA) based biotechnological processes, products and technology; (5) to evolve biosafety guidelines for laboratory research and product application; (6) to initiate scientific and technical efforts related to biotechnology; (7) to initiate programmes of human resource development in

the areas of biotechnology; and (8) to establish the International Centre for Genetic Engineering and Biotechnology.

The DBT has made concerted efforts for generating basic know-how and carrying out fundamental research in front-line areas, and in developing biotechnology based products having immediate relevance to national needs. The priority areas in which the DBT runs programmes and projects of high national relevance include: (1) plant molecular and agricultural biotechnology; (2) biological control of plant pests, diseases and weeds; (3) plant tissue culture; (4) environmental biotechnology; (5) aquaculture and marine biotechnology; (6) animal biotechnology; (7) medical biotechnology; (8) biochemical engineering, downstream processing and instrumentation; (9) microbial biotechnology; (10) industrial biotechnology; (11) informatics; and (12) integrated manpower development. In view of the expansion of biotechnology, the department has already initiated activities in other areas such as biotechnology for silk worms and host plants; medicinal and aromatic plants; food biotechnology; and human genetics (DBT, 1994b).

SAFETY GUIDELINES AND REGULATIONS IN BIOTECHNOLOGY

Genetic engineering and rDNA technology holds enormous potential in delivering economically important, life saving products and technologies. At the same time, this area has the inherent probability of delivering unintended products through wrong expressions which could pose environmental risks and hazards to human and animals. It was, therefore, felt necessary to formulate safety guidelines and ensure their effective implementation to maintain safety in relation to the environment. In India, with the safety consideration in view, the DBT was mandated to evolve rDNA safety guidelines. The DBT has set up the rDNA Advisory Committee (RDAC) for this purpose. On the basis of current scientific information a document, on *Recombinant DNA Safety Guidelines* was published in January 1990 on the use of these techniques in the area of research, manufacture and application (DBT, 1990). The guidelines took into account local factors such as resistance to infection (immunity), host and parasite burden in the community, laboratory environment and chances of survival and growth of altered organisms under tropical conditions. As the biotechnology safety needs are likely to change with time due to ever expanding committee knowledge, the committee is supposed to modify the guidelines from time to time, based on the scientific information and experience gained locally and outside the country on the use of genetic engineering and rDNA research.

During the last decade, India has made noteworthy progress in the handling and manipulation of plasmids, construction of vectors and, through them, transformation of various hosts ranging from bacteria to yeast, animal and plant cell lines as well as transformed plants. Taking note of the GMOs, the DBT has revised the guidelines with the advise of an Expert Group as well as the Ministry of Environment and Forests, the Indian Council of Medical Research (ICMR) and the Indian Council of Agricultural Research (ICAR). The revised guidelines published in May 1994 incorporate the consolidated view of all the user ministries and organisations as well as the R&D and academic institutions. The revised guidelines include the procedures to be followed for the field trials of transgenic plants and their release to the environment (DBT, 1994a).

Scope of safety guidelines. The current guidelines cover areas of research involving genetically engineered organisms, genetic transformation of plants, rDNA technology in vaccine and diagnostics development and on large scale production, and deliberate or accidental release of organisms, plants, animals and products derived by rDNA technology into the environment, and also the import and shipment of GMOs/transgenics for laboratory research and large scale use.

Mechanism of implementation of safety guidelines. In order to ensure the compliance of requisite safeguards at various levels, an institutional mechanism was evolved for the implementation of the guidelines, which mainly consists of the following four committees; (1) the RDAC; (2) Institutional Biosafety Committee (IBSC); (3) Review Committee on Genetic

Manipulation (RCGM); and (4) Genetic Engineering Approval Committee (GEAC).

The RDAC takes note of development in biotechnology at national and international levels in assessing the safety regulations for India on recombinant research, use and applications. The RDAC meets once every six months or less for this purpose. The RDAC's main mandate is: (i) to evolve long term policy for research and development in rDNA; (ii) to formulate safety guidelines for rDNA research to be followed in India and; (iii) to recommend training programmes for technicians and Research Fellows to make them adequately aware of hazards and risks involved in rDNA research.

The IBSC is the nodal point for interaction within the institution for implementation of the guidelines. As such it is necessary that the institutions/universities/industries intending to carry out research activities involving genetic manipulation of micro-organisms, plants or animals should constitute the IBSC. Presently, IBSC has been constituted in nearly 60 Institutions, including industries, in the country. The IBSC should be notified of any research project which is likely to have biohazard potential during the execution stage. The IBSC has to meet at least twice a year and provide at least two half yearly reports on ongoing projects to RCGM. In addition, the activities of IBSC include training personnel on biosafety and instituting health monitoring programmes for laboratory personnel. Medical checkups, including pathological tests, are done periodically.

The RCGM functions under the DBT with the following mandates: (i) to establish a procedural guidance manual that outlines any activity involving genetically engineered organisms in research, production and applications related to environmental safety; (ii) to review the reports in all approved ongoing research projects and controlled field experiments; (iii) to visit sites of experimental facilities involving a high risk category periodically where projects with biohazards potential are being pursued; (iv) to recommend all types of containment facilities and the special containment conditions to be followed for experimental trials and for certain experiments; (v) to issue clearance for import/export of etiological agents and vectors, germplasms, organelle, etc. needed for experimental work/ training and research and; (vi) to assist the Bureau of Indian Standards to evolve standards for biologicals produced by rDNA technology.

The RCGM was reconstituted in 1994 with the representatives of ICMR, ICAR, Department of Science and Technology (DST), Council of Scientific and Industrial Research (CSIR), DBT, and three experts in their individual capacities. The RCGM meets at least twice a year.

The GEAC functions under the Ministry of Environment and Forests to examine and issue clearance from the view point of environmental safety on a case by case basis for; (i) activities involving large scale use of hazardous microorganisms and recombinants in research and industrial production; (ii) proposals relating to the release of genetically engineered organisms and products into the environment; (iii) production, sale, import or use of substances and products such as food stuffs and additives, including processing aids containing genetically engineered organisms/cells/microorganisms; (iv) import, export, transport, manufacture, process use or sale of any hazardous microorganisms or genetically engineered organisms/substances or cells and; (v) scale up or pilot operations for facilities using genetically engineered organisms/ microorganisms.

The GEAC is mandated to give directions to the occupier to take measures concerning discharge of the GMOs mentioned in the schedule from laboratories and hospitals, etc. The GEAC also supervises the implementation of the terms and conditions laid down in connection with the approvals accorded through the State Biotechnology Co-ordination Committee (SBCC) or the State Pollution Control Boards/District Level Committees (DLC) or through any person authorised on its behalf. The DLCs regularly submit their reports to the SBCC.

CATEGORIES OF GENETIC ENGINEERING EXPERIMENTS

As per the guidelines, the research activities are broadly classified into three categories mandating different levels of containment on the basis of risk involved therein. Category 1 requires prior intimation to IBSC, which in turn would inform

RCGM, while submitting half yearly reports to the latter as required under the procedure. The main concerns are that the permitted experiments involve the manipulation of organisms belonging to the same exchange group or involves DNA from organelles such as chloroplasts and mitochondria and/or host-vector systems either of non-viral origin or using defective viral genome. This category is exempted from information and approval of the competent authority.

In category 2, approval of IBSC and intimation to RCGM is needed before implementation of the experiments. Such experiments involve relatively low levels of risk: (i) transfer of genomes from organisms other than viruses to non-human vertebrates or any invertebrate; (ii) experiments involving non-pathogen DNA vector systems and regeneration from single cells and; (iii) large scale use of recombinants, constructed by self-cloning in systems belonging to exempt category such as *Escherichia coli, Saccharomyces* and *Bacillus subtilis.*

Category 3 requires prior intimation as well as clearance from RCGM. This category pertains to high-risk experiments, for example, toxin genes, cloning of genes for vaccine production (e.g. rinder-pest and leprosy vaccines), cloning experiments involving mosquito and tick DNA, transfer of antibiotic resistance gene to pathogenic organisms, manipulation involving animal and plant viruses, gene transfer to whole plants and animals, etc. The experiments in this category are periodically reviewed by RCGM.

LARGE SCALE INDUSTRIAL PROCESSES AND OPERATIONS

All operations requiring a handling capacity of 20 litres or more are deemed large scale and some additional safety precautions have to be stringently observed: (a) approval of the competent authority (e.g. GEAC) should be sought in all cases. The fundamental design of the process and operational details, as well as the methods for proper disposal of the potential harmful byproducts, should be submitted for prior review; (b) regular monitoring both by in-house and outside agencies for the control measures and safety equipment to the operation should be conducted; (c) proper training should be imparted to personnel in the safety execution of the process, as well as the disposal of the primary and by-products; (d) regular monitoring of viable process organisms in outside environment is necessary; (e) ideally, the host organisms should not be a pathogen and, although optimised for survival under bioreactor conditions, should not be able to survive in the harsh environment for extended periods of time; (f) monitoring of health status of the personnel involved in the process should be carried out periodically and; (g) pathogenic organisms and experimental animals, etc., should be destroyed.

FIELD TRIALS OF TRANSGENIC PLANTS AND THEIR RELEASE INTO THE ENVIRONMENT

Planned release of recombinant organisms should be carried out only after a stepwise evaluation of up-scaling of the GMOs from laboratory scale to a growth chamber and then to greenhouse conditions. Model experiments should be carried out with prior permission of RCGM in order to ascertain data on this aspect. Data should be provided to GEAC with a request for approval for release into the environment. Appropriate containment facilities must be provided to ensure safety and to prevent unwanted release in the environment. Bio-wastes resulting from laboratory experiments and industrial operations should be properly treated and carefully destroyed before their disposal into the environment.

For field testing of transgenic plants, the following criteria should be followed: (a) the minimum isolation distance recommended for raising "Foundation Seed" all around the transgenic plants be maintained; (b) in the isolation distance a non-compatible crop be grown; (c) beyond the isolation distance, a few rows of the non-transgenic plants of the same crop be grown so as to serve as a pollen trap; (d) analyse the seed progeny from the plants used as pollen trap for assessing pollen escapes and verifying the effectiveness of the isolation distance; and (e) pre-release tests of GMOs in agricultural application should include elucidation of genetic

markers, host range, requirements for vegetative growth and stability in small plots and experimental field trials for two years.

POST-HARVEST HANDLING OF THE TRANSGENIC PLANTS

From the safety point of view, post harvest handling of the transgenic plants may be done in the following ways: (a) by burning all the vegetative parts and left over seeds; (b) leave the land free for the next year and destruction of the plants if any, emerging form the seeds of the previous year in the soil and; (c) testing of samples for the absence of viable cells before disposal into the environment.

The GEAC may initially clear a project for limited trials with a view to generating data for assessing the environmental impact in cases where it is necessary. In cases where environmental impact studies are not required, GEAC may give permission for large scale trials.

RISK ASSESSMENT

Recombinant DNA techniques include the following three components: (1) the selected sequence of DNA of the donor (any living species or even synthetic sequence); (2) the vector, usually a virus or plasmid that carries the ligated donor sequences into the recipient host and; (3) a host, invariably a microbial cell or a cultured cell. To achieve the required biotechnological potential, manipulation of all the three components is essential. Therefore, any guidelines drawn up should take into account hazards/risks posed by all the three components, i.e., the donor, the vector and the host. Therefore, the guidelines are framed after considering the risks involved due to all the three components.

The guidelines prescribe four levels of risks while carrying out experiments with micro-organisms. Classification of pathogenic micro-organisms within these levels is based on pathogenicity and local prevalence of disease and epidemic causing strains in India. As the application and release of GMOs into the environment could lead to ecological consequences and potential risks, the guidelines also prescribe the criteria for assessment of the ecological aspects on a case by case basis for planned introduction of rDNA organisms into the environment. According to the revised guidelines of India, the following aspects are to be considered for risk assessment: (1) geographical location, size and nature of the site of release, and physical and biological proximity to man and other significant biota. In the case of plants, proximity to plants which might be cross pollinated is considered; (2) details of the target ecosystem, and the predicted effects of release on that ecosystem; (3) method and amount of release, rate or frequency and duration of application; (4) monitoring capabilities and intentions of how many novel organisms can be traced, e.g., to measure effectiveness of applications; (5) on-site worker safety procedures and facilities; (6) contingency plans on the event of unanticipated effects of the novel organism; (7) the nature of the organism or the agent to be released, its host range and pathogenicity (if any) to man, animals, plants or micro-organisms; (8) the procedures used to introduce the genetic modification; (9) the nature of any altered nucleic acid and its source, its intended function/purpose and the extent to which it has been characterised; (10) verification of the genetic structure of the novel organism to form long-term survival forms, (e.g. spores, seeds) and the effect that altered nucleic acid may have on this ability; (12) details of any target biota (e.g. pest in the case of a pest control agent), known effects of non-manipulated organism and predicted effects of manipulated organism; (13) effect of manipulation on the growth and survival characteristics of the host organism; (14) susceptibility to abiotic stresses; (15) potential for transfer of inserted DNA to other organisms including methods for monitoring survival and transfer and; (16) methods to control any superfluous organism or nucleic acid surviving in the environment or possibly in a product.

IMPORT AND SHIPMENT

The import of etiological agents and vectors of human and animal diseases or their carriers is subject to quarantine regulations. Permits authorising the import of regulated materials for research (such as toxin genes, hybridomas, cell cultures or organelle) and specifying conditions

under which the agent or vector is shipped, handled and used are issued by the RCGM, while large scale imports for industrial use are regulated by GEAC. The inter-state shipment of indigenous etiological agents, diagnostic specimen and biological products need the clearance of IBSC under intimation to RCGM.

QUALITY CONTROL OF BIOLOGICALS PRODUCED BY rDNA TECHNOLOGY

The general regulations normally applicable for biologicals are also applicable to rDNA products. A new license would be required on products created through rDNA technology, even if the product is chemically and physically similar to the naturally occurring substance. An rDNA product produced in the same host and demonstrated to be identical to a normally occurring substance would not require toxicological and pharmacological data if the information is already available at dose levels of intended use, but fresh clinical trials on a relatively limited basis will be necessary on all such products.

CONCLUSION

Biotechnology facilities are being established in most developing countries. Among developing countries, the status of biotechnology varies considerably. A few countries, such as Brazil, China, India, Mexico, and the Republic of Korea have sought to gain full scientific and technological capacity, especially in agriculture biotechnology; others, such as Indonesia, Malaysia, the Philippines, Thailand and a few countries of Latin America, have built the capacity to apply biotechniques and to develop biotechnologies useful for the agriculture and food industries. More detailed description of the status of biotechnology in India is given by Ghosh (1991, 1993).

In India, efforts for developing biotechnologies have aimed at two main aspects: meeting development requirements and making India internationally competitive. The DBT has provided the necessary support for the execution of the programmes by creating several national facilities and strengthening institutional infrastructure already existing at various national institutes/universities and research organisations. In this endeavour, industry has been made a partner through collaborative arrangements with R&D institutes and universities. In view of the multidisciplinary and knowledge-intensive field of biotechnology, special attention has been paid by the decision makers to the formation and generation of specialised skills with a long range perspective. Teaching and research programmes in biotechnology have been introduced at post graduate level in nearly 25 universities and centres of excellence in India. Also, orientation given to planning, coordination and execution of biotechnology development programmes towards meeting the country's development requirement is perceptible in the areas covered by R&D (DBT, 1994b).

In certain areas, biotechnologies are at the threshold of commercialisation (Ghosh 1992, 1994). Achievement in terms of demonstration of technologies developed through R&D programmes have been notable in the areas of biological pest control, biofertilizers, aquaculture, embryo transfer, etc. (Ghosh and Wahab, 1994). Research in biotechnology has also demonstrated enhanced productivity through elite high yielding tissue culture (Ramachandran and Wahab, 1992).

While the genetic engineering and rDNA technology holds potential for multifarious beneficial applications, it has also raised concerns about possible risks to humans, animals, and the environment. As such, in handling GMOs, it is necessary to comply with certain precautionary measures for ensuring safety in research, industrial production and environmental protection. In view of safety consideration, DBT issued the Recombinant DNA Safety Guidelines in 1990 which were revised in 1994. These guidelines are being enforced through the existing laws and enactment of new legislation wherever necessary. Appropriate containment facilities, practices and equipment are recommended for necessary safeguards in handling microorganisms, plants and animals in various risk groups. The institutional mechanism set up for the implementation of guidelines consist of four committees. The follow up of these measures is effected through the microorganisms and gene technology rules under the Environmental

Protection Act of 1986. The guidelines of the rules have since been approved and appropriately notified by the Government of India.

However, the biosafety aspects are primarily a matter for national decision. National governments and regional programmes should act to safeguard their own ecosystems, genetic resources and the health and well being of their citizens from any possible risks associated with the release of GMOs and the commercialisation of genetically engineered food and other products. For this purpose, national governments should establish appropriate policies, laws, regulations and enforcement mechanisms for the control of potentially problematic introductions, whether for testing, export and import or release on a commercial scale. In most of the industrialised countries, laws, regulations and guidelines on research release, containment and monitoring of GMOs and on food safety assessment are available and feasible to implement. In most of the developing countries such measures are not being established and to aid this process, the scientific expertise and resources for adequate assessment of the risks and implication must be strengthened. However, national and international efforts are needed to develop, hormonise and implement procedures and standards based on sound and comprehensive scientific assessment, so that all countries may follow internationally agreed biosafety procedures and regional decision making processes.

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