

**Environment, Occupational Health and Safety Management
Framework (EMF)**

FOR

**Industry-Academia Collaborative Mission For Accelerating
Early Development For Biopharmaceuticals - “Innovate in India
(i3) Empowering biotech entrepreneurs & accelerating inclusive
innovation”**



Funded by

**Department of Biotechnology
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Implementing Agency:

Biotechnology Industry Research Assistance Council (BIRAC)

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Chapter 1.0 Introduction

Guidance to Occupational Health, Safety and Environmental Policy (EMF)

This framework Document is aimed at providing guidance to the Implementing agencies of Industry-Academia Collaborative Mission for “Accelerating Discovery Research to Early Development for Biopharmaceuticals - Innovate in India (I-3/ “Programme”)

Based on the Programme objectives the relevant Occupational Health, Safety and Environmental (EMF) aspects have been collated as stated herein this Framework.

HOW TO USE THIS DOCUMENT

This framework is to assist the implementation officers in identification, assessment, monitoring, evaluation and compliance to the Occupational Health, Safety and Environmental aspects generally associated with various components of the Programme. It suggests practical ways to integrate sustainability management into the internal operations of I-3 Programme.

Based on the different Programme components, the relevant EMF parameters can be considered by the implementing officers from this document.

Programme Description aspect outlines the cardinal components and the expected deliverables of Accelerating Discovery Research to Early Development for Biopharmaceuticals - “Innovate in India (I-3) .

Environment, Occupational Health and Safety Management Framework (EMF) outlines the essentials for the Programme components and the specific management parameters

Legal and Regulatory Requirement provides the consolidated framework on the Product development and Occupational Health, Safety and Environmental requirements as relevant for the Programme components including the World Bank Safety and Environmental Safeguards.

Programme Cycle outlines the general implementation process in practice for the Programme and the crucial principles to be considered in order to ensure compliance related to EMF.

The suggestions received through Stakeholder meetings in order to implement the practices for programme are stated there under the Stakeholder Consultations

Environmental, Safety and Health aspects under the Programme specifies the issues Identified under the Programme through site visits to representative locations relevant to the programme components through corresponding feedbacks and evaluation. The Management Framework accordingly provides for the mitigation measures to be included for the programme components based on the identified issues.

Institutional arrangements outlines the aspects of structural framework defined the structures put in place in order to implement safeguard parameters. The monitoring strategy and grievance redressal mechanism defines the methods for periodical review and monitoring of the

management strategy and the mode for addressing the concerns and grievances if any that may be brought into the fore by any stakeholder under the Programme.

Training Plan provides for the definite means to build the Environmental management capacity through tailor made training modules structures as a part of the broader Programme Training Component followed by applicable budget specifications under I-3Programme Description

Chapter 2.0

Programme Description

2.1 Background

The National Biotechnology Development Strategy 2015-2020 announced by the Department of Biotechnology (DBT) lays emphasis on Making India ready to meet the challenge of achieving US\$100 billion biotech industry by 2025. The focus is on generation of biotech products, processes and technologies for affordable and accessible health care, promoting innovation R&D, establishing India as world class bio-manufacturing hub, and building the required skilled workforce. To achieve this it is important to promote industry – academia interface and enable the start-ups and small and medium enterprises to build translational innovation research capacities for affordable healthcare product development.

In the public health arena in India, there is an enormous burden of communicable and non-communicable diseases which reflect the necessity to develop tailored solutions towards addressing health needs specific to the disease burden. Vaccines have emerged as the most effective solution for prevention of communicable disease but there are diseases in India for which efficacious vaccines are yet not available. Additionally, development of biosimilars and novel biologics has also become essential for designing affordable solutions against high burden non-communicable disease. Also to address the disease burden development of medical devices and diagnostic tools are a necessity.

The India biopharmaceutical market accounts for 2% of global market. The Indian vaccine market is 3.5% of the total global vaccine market. Current CAGR is at about 18%, but it is estimated that introduction of newer vaccines would enhance this current growth rate. The Indian biosimilar market is 2% of the total global biosimilar market. Strengthening of this sector could lead to capture 4% of the global bio similar market by 2020 if the growth rate is accelerated at 26% CAGR. Indian medical device market is worth US\$10.30 billion. The sector is expected to continue witnessing double-digit growth with an estimation to grow at about 28% CAGR and reach US\$50 billion by 2025 if the current ecosystem is sustained.

The Indian biopharmaceutical industry faces stiff competition from China, Korea in respect to innovation. The challenge today is not only ensuring a rapid industrial growth for domestic and global market, but developing innovative, affordable and accessible products for public health needs. Innovation is one of the key driving forces behind the sustainable growth of the biopharmaceutical industry and an important determinant of a nation's potential for economic growth and global competitiveness.

The success of biopharmaceutical innovation programs require strengthening of biotechnological sub-disciplines such as translational research (including discovery and validation), early development and clinical development capacities and manufacturing capabilities. There is a need for establishing accessible bio-manufacturing or CMC units, which are Good Manufacturing Practices (cGMP) and Good Laboratory Practices (cGLP) compliant, are product-agnostic, have varied capabilities for modern enabling technologies,

and are modelled to operate in a non-competitive phase for the sustainable growth of the biopharmaceutical industry.

To achieve the desired goals the need was felt for an integrated Mission Programme addressing key challenges of the sector involving all stakeholders. For designing the Mission Programme an assessment of key strengths and gaps was essential. A Detailed Mapping was done and three landscape documents were prepared– ‘Analytical Report for Accelerating Biopharmaceutical innovation in India’ a mapping report of the Intellectual Property - “Situational Analysis of the Early Stage Discovery Landscape in the Indian Bio-pharma Sector” and a report on Human Resource gaps and needs “Talent Mapping: BioPharma R&D”. Based on these feasibility reports, challenges, gaps and needs were identified.

2.2 Program Overview:

2.1.1 Mission

Enable and nurture an ecosystem for preparing India’s technological and product development capabilities in biopharmaceuticals to a level that will be globally competitive over the next decade, and transform the health standards of India’s population.

2.1.2 Goal

The Mission Programme would be a PAN-India Programme with the main aim of enabling and nurturing the ecosystem for Innovation Research and Product Development capabilities in Bio-pharmaceuticals to enable the sector to be globally competitive over the next decade and transform the health of Indian population. Through these efforts it is proposed that India would work towards achieving its target of US\$100 billion Biotech Industry by 2025 and also capturing 5% of the Global Biopharmaceutical market share. This Mission is designed in a manner in which it addresses the key components of the Vision outlined in the National Missions -Make in India and Start up India and also aims to take forward the commitments made by DBT in the National Biotechnology Development Strategy.

The mission will focus on:

- Development of product leads that are at advanced stages of the product development lifecycle and relevant to the public health need by focusing on managed partnerships
- Establishing and strengthening shared infrastructure facilities and product discovery/validation and manufacturing
- Developing human capital by providing specific trainings to address the critical skills gap among nascent biotech companies across the product development value chain, including in business plan development, and market penetration.
- Creating and enhancing technology transfer and intellectual property management capacities and capabilities in public and private sector.

2.1.3 Objectives

- i. Foster PDPs for the acceleration of the discovery-to-product commercialization process
- ii. Strengthen shared infrastructure facilities for research and manufacturing
- iii. Build and strengthen domain-specific knowledge, skills, and management
- iv. Provide technical assistance for actors in the industry ecosystem and program Management.

Specific objectives and activities are:

i. Development of specific affordable products:

Development of affordable and accessible biopharmaceuticals (vaccines and biosimilars) and medical devices & diagnostics relevant to public health needs of India by supporting Public and Private institutions researchers and startups and entrepreneurs that have established proof of concept and are on the path of product development.

ii. Establishment and strengthening of shared infrastructure:

Creating an enabling environment by strengthening existing infrastructure, building effective collaborative partnerships for development of cutting-edge technologies, enhancing clinical expertise and accelerating translational research that would aid in current product development and future pipeline development and enhanced outsourcing capabilities. Components of this section are:

- A. Establishing shared facilities that are accessible, equipped with state-of-the-art infrastructure and relevant talent:
 - GLP Validation and Reference Laboratory for standardized bio-analytical and biological characterization
 - CMC Facilities for Early Development for manufacturing of pilot lots of biopharmaceuticals
 - Med-Tech Validation Facility for prototyping and validation of medical devices and diagnostics during early stages of development and testing.
 - Cell Line repository for storage and maintenance of well characterized cell lines and expression systems
- B. Building a consortium of partners, in-country & global network of research entities, for development of innovative technologies and platforms:
 - Network of laboratories for:
 - i. Translational & interdisciplinary research for developing and validating novel assays/technologies/biomarkers
 - ii. Development of cell lines and expression systems
 - Process Development Laboratory
 - Clinical Trial Network

iii. Building and strengthening domain specific knowledge and management skills:

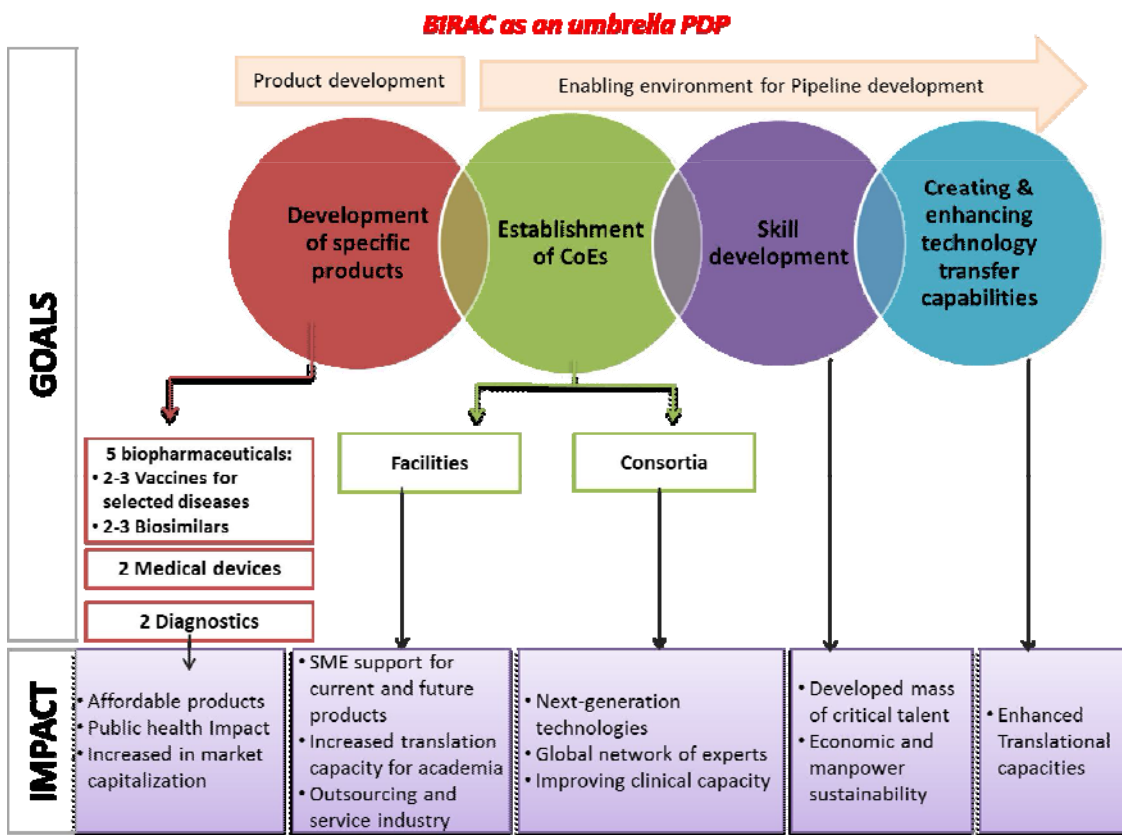
The program would facilitate skill development in vital areas of skills gap towards building an effective workforce and next generation leaders in following areas:

- Technical skill (e.g. next generation skills like genomics, NGS, Proteomics, high throughput screening, assay development, bioanalytical development, PK-PD studies etc.)
- Non-technical skill (e.g. technology transfer and licensing, compliance in GLP, GMP and GCP norms, regulatory knowledge, IP reading and legal expertise, project management and business development etc.)

iv. Creating and enhancing technology transfer capabilities in public and private sector including Intellectual Property Management:

The program would enhance academia-industry interlinking and provide increased opportunities for academia to translate knowledge into products and technologies through the following activities:

- Setup of Technology transfer offices;
- Training of technology transfer and Intellectual Property Management professionals;
- Providing assistance for acquisition and adaptation of technologies.



2.1.4 Implementation Modality

The Mission Programme of Department of Biotechnology, Ministry of Science & Technology, proposed to be partially financed by The World Bank, will be implemented by Biotechnology Industry Research Assistance Council a Public Sector Undertaking of the Department. For this a Programme Management Unit will be set up at BIRAC which has the experience of managing the Department of Biotechnology (DBT) - Bill & Melinda Gates Foundation (BMGF) partnership and based on its excellent performance and strength Welcome Trust and U.S. Agency for International Development (USAID) have also now joined as its partner. For the implementation of various components public and private sector researchers, institutes and industries, startups and entrepreneurs would be supported who will be selected through a competitive system based on defined selection criteria.

Biotechnology Industry Research Assistance Council (BIRAC) was setup by the Department of Biotechnology to act as an interface to serve emerging biotech industries. Its core philosophy is to foster innovation by enabling biotech start-ups in translating innovative research to affordable and need based technologies and products with the purpose of catalyzing innovation driven biotech enterprise and create a true “Indian Bio-economy”. BIRAC has so far supported nearly 500 Biotech companies and public sector researchers including start-ups and entrepreneurs. Nearly 50 products and technologies are at an advanced stage of development and over 100 new IP have been generated. These schemes and the leads from these will be the basis of further study and research under the Mission.

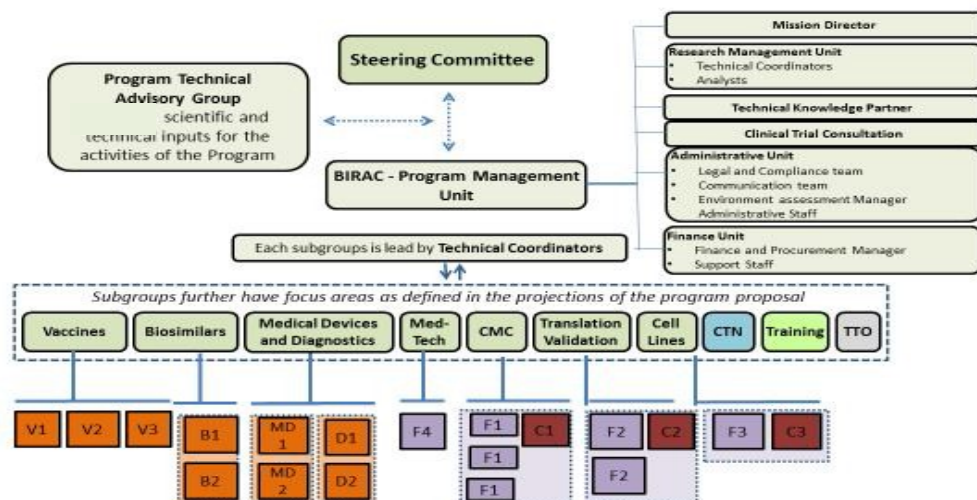
BIRAC being well-woven into the basic, clinical and translational research networks in the country; makes it relevant that the proposed Mission Program be structured to function in a PDP mode. BIRAC playing the central role as a PDP would be responsible for bringing together partners through existing frameworks for specific programmatic goals and would facilitate this program by:

- Engaging with multiple partners (in-country & global network of research entities) and aligning their goals with the common interest;
- Providing access to experts/mentor/advisors (global and Indian) at different stages of product development;
- Utilization existing indigenous potential, resources and infrastructure;
- Development of technical and non-technical skills for product innovation;
- Ensuring next-generation technology acquisition and adaptation;
- Building a non-competitive environment promoting industry-academia collaboration accelerating translational research;
- Engaging with regulatory authorities;
- Safeguarding IPR and technology management policies for all the parties involved.

Efficient conduct of the program could be further facilitated by involving established organization(s) with relevant expertise in product development to act as the Product Development Management arm for the PMU, supported by the Research Management Team consisting of Technical Coordinators and Analysts; the Administrative Unit consisting of legal and compliance personnel, communications team, environment assessment manager and other administrative staff; and a Finance Unit comprising of financial and procurement manager.

The PMU will also engage Technical Knowledge Partner to provide assistance for technical consultations and for preparing scientific documents to facilitate Scientific and Technical Advisory Committee in decision making.

A Clinical Trial consultant will also be engaged for all Clinical Trial activity guidance and oversight.



Chapter 3

Environmental, Occupational Health and Safety Management Framework (EMF)

DBT/BIRAC with the mission to promote innovation and self-sufficiency in the biotechnology sector, strives to reduce any social and environmental risks in its activities. As the Product developments and related components for creation of robust innovation ecosystem in the biotech sector is the primary focus of I-3 Program, the following elements become inevitable such as compliance to corresponding legislations, good practices in research and development methods, enhanced awareness on social and environmental risk management procedures, adherence to bioethics principles, capacity building of key stakeholders. Sections below, outline these elements of EMF to be followed during the implementation of I-3 Program.

3.1 EMF integration into I-3 Programme

DBT and BIRAC are committed to environmental sustainability by upholding numerous good practices throughout their pursuit of fulfilling their mandate including:

- Protect the environment and to continual improvement in the management of Programme activities;
- Ensure better compliance with applicable regulations, and reducing adverse impacts on people and the environment from the Programme operations;
- Promote adoption of Good Industry Practices (GIP), Good Laboratory Practices (GLP) and best practices in I-3 Programme activities;
- Integrate economic and environmental considerations in the decision-making process;
- Capacity Building of the Biotechnology stakeholders towards sustainability consciousness;
- Exercising monitoring as a quality control tool for determining whether study activities are being carried out as planned, so that deficiencies can be identified and corrected; and
- Pursue environmental goals in a cost effective manner and to preserve culture of sustainability.

In line with these commitments, due risk assessment and mitigation strategies have been proposed for the I-3 Programme that will be integrated into the entire implementation chain. The Product Development grantees will be required to abide by the environmental health principles by establishing mechanisms that enable those best placed to maximize benefits or minimize costs to develop their own solutions and responses to environmental problems under the I-3 Programme.

3.2 Objectives of EMF

- (i) To endeavor for minimizing/ mitigating adverse environmental and social impacts/risks;
- (ii) To ensure that minimization or mitigation of environmental and social impacts and risks meet the requirements of laws and regulations of GOI and states, and responsive towards environmental and social safeguards requirements of BIRAC;

- (iii) To sensitize various stakeholders involved in Infrastructure development about safeguard issues, and in monitoring, reporting, and in undertaking corrective actions, if any;
- (iv) To ensure that mechanisms are in place for Safeguard compliance during project implementation

3.3 Approach to the Development of EMF

The approach adopted for the development of EMF for the I-3 Programme, to achieve the above objectives comprised the following.

- A quick assessment of possible environmental and health risks associated with the proposed components of I-3 Program, through visits to facilities carrying out activities similar to I-3 Programme and discussions with key stake holders;
- A review of legal and regulatory requirements of GoI and environmental safeguard policies of the World Bank, related to the activities envisaged in I-3 Programme;
- Development of draft EMF addressing risks identified and regulatory requirements, along with appropriate monitoring mechanisms;
- Consultations with stakeholders on the elements of EMF; and
- Final EMF incorporating feedback from the stakeholder consultations.

3.4 Environmental and Health Risks from the activities of I-3 Program

In order to understand the likely environmental and health risks associated with the bio-tech / bio-pharma activities of the proposed I-3 Programme, visits to facilities carrying out similar activities such as development of vaccines, biosimilars, devices and diagnostics were conducted. Visits to shared infrastructure facilities were also carried out. During these visits, the product development centers, laboratory and research facilities were studied and detailed discussions were also held with key technical and managerial staff on environmental and health risks. Based on these visits, discussions and a review of secondary information on bio-tech/bio-pharma sector, it can be concluded that the activities of the Programme are not expected to cause significant, irreversible impacts on environment. However, the following low to moderate environmental and health risks are expected from the program activities and requires attention.

- Air emissions
- Wastewater
- Solid and hazardous wastes
- Hazardous materials
- Threats to biodiversity
- Bioethics

3.4.1 Air Emissions

Volatile organic compounds (VOCs) and particulates may be emitted from development processes of biotech / biopharma products from point sources and fugitive emissions. While VoCs are expected from filtration systems, reactor vents, etc. fugitive emissions are expected from centrifuge, pumps and other equipment, used in the development of vaccines, biosimilars, devices and diagnostics.

Small combustion source emissions are also expected pumps and other engines for power and heat generation. Product development activities are also expected to cause odor nuisance both to the people working within and outside product development area.

3.4.2 Wastewater

I-3 Programme activities such as development of vaccines, bio-similar, medical devices, etc. and operation of CMC facilities are expected generate wastewater from laboratory processes, chemical streams, sterilization and strippers and facility wash water, etc. The quantity and characteristics of wastewater generated from these activities will vary from the actual process followed by a particular product development agency. The typical pollutants, however include BOD, COD, TSS, solvents, organic and inorganic acids.

3.4.3 Solid and Hazardous Wastes

The sources of solid and hazardous wastes from the I-3 Programme supported activities include residual waste and byproducts from the product development processes, solid and slurry wastes, etc. The other sources of hazardous wastes also include, laboratory waste, sludge from wastewater treatment plant and other sources.

3.4.4 Hazardous Materials

The product development activities of the I-3 Programme, could also involve handling of hazardous materials including those of radioactive substances, depending the processes adopted by the respective agencies. In the event of use of such hazardous substances, the agencies should conduct Hazard Assessment and implement management plans for prevention and emergency response to release of hazardous substances.

3.4.5 Threats to Bio-diversity

The process of collection of genetic resources (bioprospecting), which may be part of certain biotechnology activities, may include access to different types of habitats. In addition to the potential for negative impacts to the biodiversity of these habitats, which may also depend on the physical nature of the collection activities and the types of genetic material involved, bioprospecting may also raise issues about the rights of local communities to consent in the use or to a share in the benefits of the commercialization of their cultural heritage or the genetic resources extracted. The proposed I-3 Programme will not involve bio-prospecting and hence doesn't impact bio-diversity.

However, the product development activities could involve production, handling, storage, transport, and use of organisms and could cause threats to biological diversity due to the controlled or uncontrolled release of the organisms into the environment.

Risk-based approach to identify key control points in the process cycle, including in-plant handling, off-site transport, and use of modified organisms, shall be developed in line with the Cartagena Protocol on Biosafety of the Convention on Biological Diversity and also taking into account risks to human health.

3.4.6 Bio-ethics

Similar to the various other issues, the ethical issues, will vary for each product supported through the program and depend significantly on the activity. As per Government of India regulations, the bio-technology institutions in India, comply to,

- Well established ethics mechanisms including management commitment; dedicated internal ethics personnel;
- Adhere to internationally accepted ethical principles applicable to genetic research, clinical trials involving human participants, and any other activities with critical bioethical issues;
- Follow industry good practices in the use of animals for experimental and scientific purposes, including design and operation of animal breeding, husbandry, and care facilities.

3.4.7 Occupational Health and Safety

The occupational health and safety issues that may occur during product development and research stage of biotechnology products are similar to those of other laboratory research activities. While some of the relevant occupational health and safety hazards that occur during the development of biotechnology products are highlighted below, the actual hazards however shall be assessed by the product development agency, specific to the product being supported by the I-3 Program.

- Heat hazards
- Chemical hazards including fire and explosions
- Pathogenic and biological hazards
- Radiological hazards
- Noise
- Process safety

Heat hazards in bio-technology operations are expected, when large volumes of pressurized steam and hot water is used for fermentation and / or compounding operations. This could cause burns due to exposure to steam or direct contact with hot surfaces as well as heat exhaustion. Measures such as insulation of steam and thermal fluid pipelines, aligning them away from areas of worker access and screening of high temperature areas, etc. shall be implemented to avoid heat hazards.

The risk of occupational **exposure to chemicals** in biotechnology manufacturing activities can occur due to inhalation of VOCs from recovery, isolation, and extraction activities; and from fugitive emissions for leaking pumps, valves, and manifold stations (e.g. during extraction and

purification steps). Additional sources of inhalation exposures include extraction operations and sterilization activities, as well as exposure to synthetic hormones and other endocrine disruptors. To avoid such hazards, preventive measures such as workers training, use of personal protective equipment (PPE), and toxic gas detection systems with alarms, etc. shall be implemented.

Fire and explosion hazards may arise during laboratory activities involving inflammable substances, hazardous materials, etc. and should be controlled through process safety engineering and controls.

Similarly, exposure to pathogens may occur during isolation and growth of micro-organisms in laboratory and in fermentation processes and radiological hazards may occur if radiological materials are used in product development chain. Both these hazards should be managed to prevent and control worker exposures, according to standard regulatory protocols.

High noise levels may be expected in due to compressed air, vacuum sources, and ventilation systems, during the biotechnology activities. Specific mitigation and management measures including use of PPEs, shall be adopted to address the issue of high noise levels.

3.5 Applicable environmental regulations of GoI for I-3 Program

Activities related to development of drugs, biosimilars and vaccines are governed by number of sectoral regulations and environmental laws. The Department of Biotechnology (DBT) constituted under the Ministry of Science and Technology is the nodal agency for policy, promotion of R&D, international cooperation and manufacturing activities in India. A brief review of some relevant regulations is presented in the following sections.

3.5.1 Rules for Manufacture, Use/Import/ Export & Storage of Hazardous Micro Organisms/ Genetically Engineered Organisms or Cells, 1989

These are umbrella rules notified by the Ministry of Environment, Forest & Climate Change (MoEFCC), Government of India, with a view to protecting environment, nature and health in connection with application of gene technology and micro-organisms. Commonly referred as 'Rules 1989', these rules cover areas of research as well as large scale applications of GMOs and their products including experimental field trials and seed production. Rules 1989 are further supported by the bio-safety guidelines which have been developed through a consultative approach and following the international norms.

The Rules 1989 also define the following six competent authorities and composition of such authorities for handling of various aspects of the Rules.

- Recombinant DNA Advisory Committee (RDAC): The functions are of an advisory nature and involve review of developments in biotechnology at national and international levels and recommend suitable and appropriate safety regulations for India in recombinant research, use and applications from time to time.
- Review Committee on Genetic Manipulation (RCGM) established DBT to monitor the safety related aspects in respect of on-going research projects and activities (including small scale field trials) and bring out manuals and guidelines specifying

procedure for regulatory process with respect to activities involving genetically engineered organisms in research, use and applications including industry with a view to ensure environmental safety.

- Genetic Engineering Appraisal Committee (GEAC) established under MoEFCC is the apex body to accord notified under Rules 1989. For approval of activities involving large scale use of hazardous microorganisms and recombinants in research and industrial production from the environmental angle. The GEAC is also responsible for approval of proposals relating to release of genetically engineered organisms and products into the environment including experimental field trials (Biosafety Research Level trial-I and II known as BRL-I and BRL-II).
- State Biotechnology Coordination Committee (SBCC's) have a major role in monitoring. It also has powers to inspect, investigate and take punitive action in case or violations of statutory provisions.
- District Level Committees (DLCs) have a major role in monitoring the safety regulations in installations engaged in the use of genetically modified organisms/hazardous microorganisms and its applications in the environment.
- Institutional Biosafety Committee (IBSC) is established under the institution engaged in GMO research to oversee such research and to interface with the RCGM in regulating it.

3.5.2 Other applicable environmental regulations

The Biotechnology industry in India is governed by the following enactments depending upon their relevance/applicability on case to case basis. A summary of relevant regulations along with their applicability I-3 Program is provided in table 1 below.

No.	Act/ Rule/ Notification	Brief	Applicability for I-3 Program
1	Water (Prevention & Control of Pollution) Act, 1974 and Water (Prevention & Control of Pollution) Rules, 1975	It provides for the prevention and control of water pollution. All activities that are being developed, implemented, established, and/or operational, that would lead to generation, treatment of sewage or effluent and further discharge into a stream or well or sewer or land should take consent to establish or operate from the State Pollution Control Board/Committee.	Project grantees shall obtain consent from respective PCB for the discharge of wastewater from its activities.
2	Air (Prevention & Control of Pollution) Act, 1981	All activities that are being developed, established, and/or operational, that emit any air pollutant should take consent to establish/operate from the State Pollution Control Board/Committee.	Project grantees shall obtain consent from respective PCB, for discharge of air emissions lab operations, DG Sets, etc.

No.	Act/ Rule/ Notification	Brief	Applicability for I-3 Program
3	The Environment Protection Act, 1986 and The Environment Protection Rules, 1986	Umbrella Act for the protection and improvement of environment and the prevention of hazards to human beings, other living creatures, plants and property.	<u>Applicable in general</u>
4	The Hazardous Wastes (Management, Handling and Transboundary Movement) Rules, 2008	Regulation and control of indiscriminate disposal of Hazardous waste; and its sound management to reduce risks to environmental and human health	<u>Authorization shall be obtained from PCBs, if the project grantees use hazardous substances for its activities.</u>
5	The Manufacture, Storage & Import of Hazardous Chemicals Rules, 1989	Regulations and controls to reduce environmental, safety and health risks while manufacturing, handling and storage of hazardous chemicals.	<u>Authorization shall be obtained from PCBs, if the project grantees use hazardous chemicals for its activities.</u>
6	Municipal Solid Waste (Management and Handling) Rules, 2016	Regulations on procedures to be undertaken for proper management, handling, processing and safe disposal of municipal solid waste generated in Urban areas	Solid waste generated by the project grantees shall comply with these rules.
7	The Noise Pollution (Regulation and Control) Rules, 2000	Regulations to control ambient noise levels in public places from sources such as industries and other activities.	Activities of the project grantees shall comply to these rules
8.	E-Waste Management and Handling Rules, 2016	Regulations and controls to reduce environmental, safety and health risks while manufacturing, handling and storage of hazardous chemicals.	Activities of the project grantees shall comply to these rules
9.	Bio-medical Waste Management and Handling Rules, 2016	Regulations and controls to reduce environmental, safety and health risks while manufacturing, handling and storage of hazardous chemicals.	Activities of the project grantees shall comply to these rules

3.5.3 Environmental safeguard policies of the World Bank

Based on the anticipated impacts summarized in the earlier sections, World Bank's Operations Policy 4.01 on Environmental Assessment and Environment, Health and Safety Guidelines of World Bank Group, will be applicable for I-3 program. The objective of this policy is to ensure that Bank financed projects are environmentally sound and sustainable and all relevant environmental safeguard issues are appropriately addressed in advance. Based on this policy, the

project can be categorized as 'Category B Project' with its activities having moderate and temporary impacts on the environment. This EMF has been developed primarily to address this requirement of OP 4.01. The EMF further provides guidance to integrate key environmental issues related to the I-3 program activities during the implementation by project grantees.

3.6 Environment due diligence for the sub-activities of I-3 Program

As detailed out in program overview section of this EMF, the I-3 Program envisages four main activities. Of these four, most of the environmental issues identified in the earlier sections are applicable for Activity 1 on development of specific affordable products and Activity 2 on establishment and strengthening shared infrastructure. In order to address these issues and integrate Good Environmental Management Practices (GEMPs) in the project activities, the EMF proposes the following due diligence process.

- i. In addition to complying with Biotechnology, environment and Safety regulations of GoI and World Bank Group, all activities of I-3 program will follow Good Laboratory Practices (GLP), Good Industry Practices (GIP) and Good Manufacturing Practices (GMP). This will be committed by the potential grantees, during the submission of proposals for availing funds through I-3 Program.
- ii. Along with the proposals for various product development and / shared infrastructure facilities, the potential grantees shall submit an 'Environmental and Health Risk Management Plan (EHRMP) specific to the activity, for which grant is being sought. The EHRMP shall be prepared based on a review of the proposed activity vis-à-vis environmental issues highlighted in Section 3.4 of the EMF and the guide lines provided in Annex 1 of the EMF.
- iii. The EHRMP shall comprise of (i) a brief description of the proposed activity (ii) an analysis of environmental and health risks issues that associated with the activity (iii) various environment related regulatory clearances required for the activity, and (iv) a management plan to be implemented during the design and implementation phase of the activity
- iv. The EHRMP will be reviewed by the domain experts committee of I-3 Program during the evaluation of proposals. The review will focus on the adequacy of EHRMP, in relation to the proposed activity and significant risks (if any).
- v. The EHRMP of the successful grantee, shall be included in the grant agreement for implementation by the grantee.
- vi. EHRMP of the successful grantee shall be disclosed in the website of the grantee and BIRAC / DBT.
- vii. The grantee shall obtain all applicable environmental authorizations, prior to the commencement of product development activities.
- viii. The grantee shall be responsible for overall implementation of EHRMP with the help of a qualified environmental / EHS engineer and BIRAC with the help of a qualified Environmental engineer, shall monitor the implementation.

Chapter 4 Stakeholder Consultations

Five different stakeholder meetings were conducted by DBT/BIRAC, while designing overall program and provided herein below are the minutes of the Stakeholder Consultation Meetings. While these consultations focused on overall program design, issues around environmental management and risks were also briefly discussed in these consultations.

Minutes of the Stakeholder Consultation Meetings

1. 2nd July, 2013, Meeting Minutes

On 2nd July, 2013, BIRAC organized a multi-stakeholder interaction to help prepare a blueprint for building of an Industry Academia Collaborative Mission for Accelerating Discovery Research to Early Development of Biologicals. The meeting summarized recent developments in interdisciplinary science, emerging technologies and the likely influence on biopharmaceuticals and vaccine development. The stakeholders at the meeting reinforced the need for a developing such a mission for India which would have the involvement of all stakeholders from the Government Ministries / Departments, National Laboratories, Universities and Industries - Large, small and medium, startups, entrepreneurs in the research, scale up and manufacturing space.

It was agreed that to help develop a detailed proposal for a setting up a new technology led innovation based Industry Academia Collaborative Mission for Accelerating Discovery Research to Early Development - Vaccines and Biologicals, it was necessary first to have salient inputs through performing an analysis of the current “art of the possible in India”. This is important to plan the key components of the mission and also address other important elements like development of a diverse pool of human resources, role and need for global partners etc.

Based on these recommendations a “Situational Analysis” exercise has been initiated to map the existing capacities and capabilities in academia and industry related to technology, infrastructure and human resources, including existing effective institutional mechanism and consortia for new technology development. It is also now felt necessary to have a focused discussion on how we proceed further. Taken together, the preliminary analysis data, experience of stakeholders involved deeply in the sector for many years and the International Experience in successfully launching and implementing similar Missions would provide a good understanding on the next steps and help guide us in framing a clear action plan.

With this objective a Round Table Discussion on Accelerating Discovery Research to Early Development for Biopharmaceuticals”2013 was organized by BIRAC on 18th December, New Delhi.

2. 18th December, 2013, Meeting Minutes

Round table discussion on “Accelerating Discovery Research to Early Development for Biopharmaceuticals” gave rise to the proposal that a National Biopharmaceutical Acceleration Program could be conceived to identify the possible areas of need for early discovery and development for effective un fragmented excellence. The stakeholders who participated in the meeting were innovators, innovation funding agencies, innovation intermediaries and users (academic, CROs etc.). The following components were hence ascertained as cardinal for a suitable program:

- Early discovery & translational groups
- Multiuser Technology Platforms
- Multidisciplinary Collaborative Institutions
- Effective workforce & leaders
- Models of Cooperation - Precompetitive phase
- Clear Roles and Responsibilities
- Mechanisms for Knowledge and Resource Sharing
- Rules of Engagement
- IPR
- Tech transfer
- Commercialization
- Resources

Initiation of a mapping exercise with following aspects-

- Existing Capacity and Capability of Human resources and training needs
- Existing R&D capacity and capability in academia and industry
- Existing CMC capacity and Capability with special focus to early development
- Existing institutional framework to connect Industry and Public Institutions

The stakeholders stressed the need to form groups to establish the sectoral champions;-

At Precompetitive Phase the following considerations were recommended by the stakeholders-

- Define the Technical and Operational components
- Identify and engage key stakeholders
- Form strategic partnerships
- Define Rules of engagement
- Establish the leadership & management

During the meeting it was emphasized that radical new targets should emerge. Tools that improve success are needed and investors need to be assured of some chance of success before they put in money. The barriers between discovery research and early development should be done away with. For this, sharing of knowledge and resources between industry and academia becomes vital.

The following elements should be encouraged;

- a. Partnering with others within the country and globally.
- b. New capabilities should be built in academia and industry.

- c. New targets should be accessed and new assays should be developed.
- d. Clinical Trial adherence to good practices should be ensured
- e. A comprehensive mapping analysis of barriers and our own achievements should be done.
- f. Access to tech transfer is very important.
- g. Technology developed in institutions can be made available to Indian industries. This should be put in context of affordable pricing.
- h. Industry view of public research organizations are to be changed.
- i. There should be focus on targeted research.
- j. A mechanism to group different institutions needs to be formulated the consortia based models based on specific skills and platforms should be created.
- k. Mapping of disease priority areas will determine the type of consortia. Institutional mechanisms are important.
- l. It is important to create new mechanisms for government and consortia interactions. Biogenerics is the medium term opportunities. New biological entities can be developed using the disease burden data and from natural products.
- m. There should be an open call for entrepreneurship development.
- n. Mapping of recent global financing experiences should be used as case studies to develop our own models.
- o. The element of translation should be embedded in an academic project.
- p. A technical program for the acceleration can be established. The key problems should be defined with the appropriate partner; for this an enabling mechanism of free interaction needs to be developed.
- q. For the industry to take part in such consortia, the product should be viable with appropriate price control mechanisms.
- r. A scientific attitude should be developed within the consortia along with consensus building. The enterprise approach has to be comprehensive and holistic.

3. **Summary of the Roundtable discussion on Strategy for Affordable Product Development in India for Biopharmaceuticals dated 20th January 2015**

Date: 20th January 2015

Time: 10:00am

Venue: BIRAC Office, MTNL Building, 1st Floor, 9 CGO Complex, New Delhi

Meeting participants

The participants of the meeting were as follows:

Prof. K. Vijayraghavan, Secretary, DBT/DST (Chairman)

Prof. G. Padmanaban, IISc

Dr. Renu Swarup, Sr. Advisor, DBT & MD, BIRAC

Dr. Amit Mishra, Principal Scientist & In charge, Pharmaceutics Division, CDRI, Lucknow

Dr. Amulya K. Panda, Scientist, NII, Delhi

Dr. Robin Mukhopadhyaya, Independent Biotechnology Professional, Ex-Principal Investigator, ACTREC

Dr. Sandeep Kale, Assistant Professor of Bioprocess technology at DBT-ICT-CEB, Mumbai

Dr. Uday Kumar Ranga, Professor, Molecular Biology and Genetics Unit, JNCASR, Bangalore

Dr. P.N. Rangarajan, IISc, Bangalore

Dr. Amit Ghosh, NICED, Kolkata

Dr. Anurag Rathore, IIT-Delhi

Mr. Vinay Konaje, Navya Biologicals

Dr. Umesh Shaligram, Serum Institute of India, Pune

Dr. Arun Chandrasekhar, Bhat Biotech

Dr. Dhananjay Patankar, Syngene, Head – Pharmaceutical and Biopharmaceutical Development

Dr. Sanjay Singh, Genova

Dr. Rajat Goyal, Country Director, IAVI

Dr. PKS Sarma, Head Technical, BIRAC

Dr. Jyoti Shukla, Manager Technical, BIRAC

Dr. Dhiraj Kumar, Manager Technical, BIRAC

Dr. Nikhil Singla, Manager- Vaccine R&D Program, IAVI

Ms. Pritha Aggarwal, Consultant PPMU

Ms. Rajeshwari Sinha, Consultant PPMU

Dr. Shweta Chatrath, Consultant PPMU

Dr. Mousumi PaulChakrabarti, Consultant IAVI.

The specific focus of the meeting was to discuss the major technical and operational needs and shortcomings relevant to formulating this initiative by deliberating the various processes relevant to bio-manufacturing and related cost structures.

The Mission Program on Biopharmaceutical Acceleration was introduced, which is aimed at accelerating the process of preparing India's capabilities in life science translational research such that India emerges as a hub for design and development of novel, affordable and effective biopharmaceutical products and solutions. A summary of the efforts made towards the planning of this Program, including the mapping exercises that have been concluded to generate an understanding of the current landscape of the biopharmaceutical sector in India; establishment of

a Program Proposal Management Unit in collaboration with IAVI India and its purpose, among others was also provided.

The stakeholders emphasized that

- a. India currently lacks a public-sector support for manufacturing of important biologics, particularly for those biologics, which are socially relevant but not commercially profitable.
- b. Pilot-scale manufacturing facilities are also not easily available or accessible in the country today
- c. there is a lack of appropriately trained scientists currently involved in product development in India, and hence
- d. there is a crucial need for providing appropriate training and human resource development. He also suggested that we need to identify a category of products which will help in strategizing the next steps.

The first session was focused on deliberating the technical modalities (i.e., identification of needs, gaps and focus areas based on current processes, cost structures for the same and prioritization criteria) for this initiative.

- This session was on the need to focus on affordability of biologics and the challenges in the biopharmaceutical industry related to reduction of cost of goods without compromising on quality Regulatory issues, identification of specific modules or areas in product development value chain, which are most susceptible to cost reduction and developing and incorporating novel innovative technologies, which will aid cost reduction in the manufacturing processes were also discussed.
- The following are the major issues that were highlighted: *the need to incorporate and develop indigenous innovations in manufacturing; addressing the lack of facilities for validation and pilot scale production; the lack of skilled human resource; and resolving regulatory hurdles.*
- The participants identified the following modules in product development that can be target of product development: upstream processes such as fermentation of mammalian cells and import of media components; and other equipment required in downstream process including columns, buffers, resins and filters. It was recommended that novel innovations like new cell lines, serum free media components, indigenously made columns, buffers, resins, filters need to be integrated in industry. Other new trends in manufacturing such as use of disposable bioreactors, efficient storage of product and establishing continuous manufacturing could also be incorporated.
- Further, the need for one or more accessible centralized manufacturing facility to support small companies who do not have their own manufacturing facilities was highlighted by the participants. The participants suggested that acceptance of new products is much higher if various processes such as pre-clinical toxicology testing, product validation, and pre-clinical and phase-1 manufacturing have been established. Hence, there was a need for a facility for facilitating phase-1 pilot scale manufacturing and validation.
- Emphasis was laid for the need of development and training of skilled human resource who have relevant experience in the whole process in translation of a product from lab to

manufacturing stage are critical in reduction of time and cost factors. Moreover, the participants highlighted that regulatory issues are yet another roadblock which contributes to increase in cost of production, but suggested that for products developed in India to remain internationally relevant, the manufacturers in the country will have to adhere to international quality and safety standards.

The second session was focused on discussing various operational issues such as business models; IPR issues; funding mechanisms; training and collaboration models, among others that would need to be addressed for implementing the solutions for filling-in the current gaps and needs.

- This session was led by Dr Rajat Goyal (presentation enclosed). He outlined the summary of the discussions from the previous session, and highlighted the need for charting out the focus area prioritization (i.e., product(s), related technologies and facilities- and criteria for the same). He further outlined the need to that business/operational models and BIRAC's role in the implementation of the solutions.
Preliminary data from the mapping analysis being conducted towards the Mission Program was also presented, which conveyed the presence of suitable entities in India with relevant infrastructure and talent to aid in this initiative. In conclusion, he emphasized the need for collaboration between academia, industry and government entities in a consortium model to address the issues pertaining to affordable biopharmaceutical product development.
- Post the presentation, the floor was left open to participants to express their views and opinions. The following are the major issues that were highlighted: *criteria for prioritization of product areas; modalities for setting-up accessible product development facilities; and new funding mechanisms.*
- For the focus area prioritization various suggestions were discussed, including based on addressing the public health needs, based on products (i.e., product class or specific products) and related technologies. It was suggested that the focus could be initially on a class of products like mAb's or vaccines since the technologies to manufacture them would be similar, and can therefore be later modified and adopted for other classes.
- The participants further focused on the operational modalities, including accessible facilities supporting the entire product development value chain including the clinical trials. It was suggested that the focus should be on leveraging current facilities in the country by making them more accessible, rather than building new facilities. Participants from industry were agreeable to sharing their facilities based on the certain modalities that would need to be ironed out (e.g., subsidized support to users from BIRAC; exploring business models for these facilities). Compliance to all applicable clinical trial statutes and guidelines should be emphasized.

Additionally, the participants discussed the funding mechanisms for this initiative. In this direction, Dr. VijayRaghavan stated that there was a need to establish high end technology platforms and put appropriate regulatory structures in place, which would promote biotech investment in the country and result in product innovation. Moreover, he suggested that based on such initiatives, novel funding mechanisms need to be explored, e.g., venture capital and biotech banks (based on the NABARD model).

Summary:

Based on the above, there was agreement among the participants that there is a critical need to facilitate development of affordable and high quality products in India, which addresses the public health and commercial needs of the domestic as well as the international markets. Some of the key elements that would be crucial in enabling this process that were discussed by the participants are outlined below:

- The participants discussed various critical technical and operational issues, which would facilitate and support the entire ecosystem of biopharmaceutical product development in the country;
- The technical aspects of the discussion covered:
 - The need to incorporate and develop new innovations in manufacturing technologies across different processes required in biopharmaceutical product development for cost-cutting and improving efficiency and quality;
 - Providing accessible facilities for supporting the entire ecosystem of biopharmaceutical product development by leveraging on current facilities and filling the gaps in these facilities to meet the needs of SMEs and academicians;
 - Address the lack of skilled and productive technical workforce.
- The operational aspects of the discussion highlighted the need for:
 - Understanding various prioritization criteria such as public health need, commercial prospects, affordability, product-independent innovation or product-class/product-specific innovation;
 - Appropriate business models and areas where BIRAC would facilitate and enable the requisite solutions (e.g., IPR management, training support, acquisition/adaptation of technologies, funding mechanisms, management models);
 - Innovation funding for addressing India's needs in accelerating biopharmaceutical product development, and exploring new funding mechanisms (e.g., venture funding, biotech bank models based on NABARD).
- Other issues such as catalysing industry-academia collaboration and setting-up of appropriate regulatory structures were also discussed to facilitate credible product innovation and platform technologies.

Action Points:

- Organize prioritization workshop (for products and other general areas) comprising of a small group of relevant stakeholders from industry, academia and government.
- Identification of major biopharmaceutical products currently in development in the country. Also, outlining areas/technologies to facilitate development of such products to facilitate prioritization.
- Proposals should be invited for the prioritized product(s) development, and also for innovative technologies required for enabling affordable and effective biopharmaceutical product development.
- Organize workshop for addressing operational issues such as identification and selection of industry players for possible set-up of accessible facilities with appropriate business models.
- The workshop should also help in addressing other issues such as funding mechanisms, IPR management and establishing requisite training modules and any relevant collaboration for the same.

1. **Minutes of the Second Advisory Group Meeting for the Mission program for Biopharmaceutical Accelerator dated 3rd June 2015**

Date: 3rd June 2015

Time: 2:00 pm

Venue: BIRAC Office, MTNL Building, 1st Floor, 9 CGO Complex, New Delhi

Meeting participants

The participants of the meeting were as follows:

Prof. K. VijayRaghavan, Secretary, DBT and Chairman BIRAC

Dr. M. K. Bhan, Ex Secretary, DBT

Dr. V. M. Katoch, Ex DG, ICMR

Dr. Renu Swarup, Sr. Advisor, DBT & MD, BIRAC

Dr. Satyajit Rath, NII

Dr. Ajit Kamath, Head-Strategic Research Partnerships, Pfizer

Dr. Ramaswamy, CEO, C-CAMP (on Skype)

Dr. Rajat Goyal, Country Director, IAVI

Dr. PKS Sarma, Head Technical, BIRAC

Dr. Jyoti Shukla, Manager Technical, BIRAC

Dr. Dhiraj Kumar, Manager Technical, BIRAC

Mr. Amit Katiyar, Project Manager IP and Technology Transfer

Dr. Nikhil Singla, Manager, Vaccine R&D Program, IAVI

Ms. Pritha Aggarwal, Consultant PPMU

Dr. Rajeshwari Sinha, Consultant PPMU

Dr. Shweta Chatrath, Consultant PPMU

Objective

The objective of the second Advisory Group (AG) meeting was to provide a preview of the landscaping exercise and seeking inputs and guidance from the AG on the same. The meeting was intended to understand how to move forward based on the findings and outline what could be the next steps towards accelerating the establishment of this national Program.

Summary of Discussion

There was a general consensus among the AG members in terms of the usefulness of the data and the overall concept i.e. the consortia network model, the proposed setting up of validation and biomanufacturing units focused on incremental/non-incremental phases of work. However, the AG suggested that further clarity needs to be generated with regards to understanding the following:

1. ***Prioritizing the focus of this mission driven program by BIRAC***

Considering that it would now be helpful to relook at the landscaping mapping around a proposal, use of specific *filtering mechanisms* to decide what products could be incrementally or non-incrementally developed based on disease priority and probability of success was recommended. The filtering mechanism must be applied from point of

view of being able to decide the yardstick of success, the current roadblocks, strategy to overcome them and investment/ timelines involved therein.

2. Articulated proposal outlining specific product development and product pipeline agreeable to the proposed consortia model comprising of validation and biomanufacturing units

Based on use of specific filtering approaches, the following was suggested:

- *Identification of low-hanging fruits* for e.g. 2-3 vaccines (for which early work has been done and which were relevant to public health needs) to take them ahead;
- *Increasing the present output of biosimilars in the country*, for instance doubling it in the next 5 years; identification of gaps and roadblocks in their development, primary stakeholders who could be involved and understanding how they could help doing it (short term initiatives);
- Development of a *product pipeline* or novel tools/technologies/platform development (medium-to-long term initiative).

Towards the above:

- Specific meetings with domain expert groups could be conducted for understanding the feasibility/ viability of specific leads. Experts from organizations like NIH, BMGF or Wellcome Trust who are already partnering with BIRAC could be engaged for access to deeper expertise;
- A more focused analysis based on disease (focusing on communicable, non-communicable diseases as well as metabolic disorders), product and technology related (product development or product pipeline creation) or based on industry/academia interaction (development of bulk products, routinely required for biotech and pharma industry or linking up existing bioclusters for effective innovation work) was desired;
- An understanding of the budgeting required, the financial details and timelines involved was also deemed essential.

Based on the above, it was suggested to have a possible list of priorities and start engaging in regional consultations to assess the feasibility of a proposal. Specific stakeholder meetings (possibly in Delhi, Bangalore or Pune) within regional sub-clusters could be conducted from the perspective of understanding what kind of cluster strengthening or non-cluster strengthening strategy would be involved; modalities of collaboration and ownership; available capacities/capabilities, strengths, gaps, areas of comfort, prioritization they would prefer to usefully initiate work, acceptance of and willingness to actively be a part of the consortia network model and how they could help in taking ahead such prioritized projects.

Based on outputs from the consultations and prioritization achieved, drafting of a specific, goal-driven, practical and rational proposal which befits the mission and the role of BIRAC should be drafted. The proposal should be agreeable to and embed well within the validation and bio-manufacturing units as proposed in the consortia network model and also outline the required tools, capacity and capability needed and the necessary budget and timelines. It would also be appropriate to understand from the proposal how

BIRAC could play the specific role and how other inter-ministerial departments (ICMR etc.) can be involved.

3. *IPR and regulatory issues*

In biosimilar development, the necessity for regulatory consciousness and further understanding of regulatory skill sets, for e.g IPR reading skills was highlighted. It was suggested that skills pertaining to IP and regulatory issues related to biosimilar business are equally essential tools in biosimilar development and therefore it was pertinent that development of relevant training modules be considered for the same.

Action points

- The current landscaping data should be submitted in the form of an interim report to BIRAC;
- The present landscaping to be relooked at from a proposal perspective; application of filtering mechanisms to decide what could be incrementally or non-incrementally developed and why, and come up with 4-5 projects based on disease priority and probability of success;
- Meeting/consultations within regional sub-clusters to be conducted to assess the feasibility of a proposal
- Drafting of a specific, goal-driven, articulated proposal which befits the mandate of BIRAC;
- Development of relevant training modules towards regulatory consciousness and skills pertaining to IP and regulatory issues involved in bio similar development.

Chapter 5 Institutional Arrangements

The Mission Programme of Department of Biotechnology, Ministry of Science & Technology will be implemented by Biotechnology Industry Research Assistance Council (BIRAC), Public Sector Undertaking of the Department.

For this a Programme Management Unit (PMU) will be set up at BIRAC. For the implementation of various components the Technical Development Unit will be supported at identified centre / location. The Selection of Technical Units would be through a competitive process depending on the eligibility and selection criteria as identified by the Technical Advisory Group (TAG)/ Steering Committee. The Programme Governance structure is as below (Fig 3):

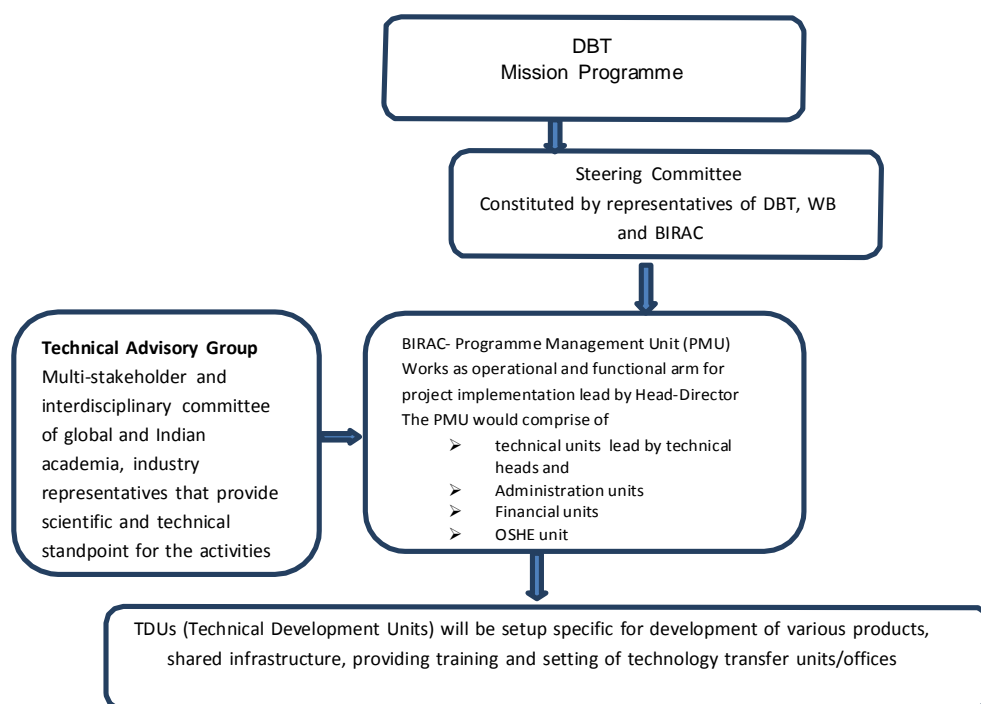


Figure-3

Structural Framework

Considering the global success factor of PDPs where to date PDPs have contributed to the development and introduction of 42 products for use by affected populations and BIRAC being well-woven into the basic, clinical and translational research networks in the country, it becomes relevant that the proposed Mission Program be structured to function in a PDP mode with BIRAC playing the central role. *BIRAC as an umbrella PDP* would be responsible for bringing together partners through existing frameworks (as outlined in the Figure4) for specific programmatic goals and would facilitate this program by:

- Selecting and Engaging with multiple partners (in-country & global network of research entities) and aligning their goals with the common interest;
- Providing access to experts/mentor/advisors (global and Indian) at different stages of product development;
- Utilization of existing indigenous, potential, resources and infrastructure;
- Development of technical and non-technical skills for product innovation;
- Ensuring next-generation technology acquisition and adaptation;
- Building a non-competitive environment promoting industry-academia collaboration accelerating translational research;
- Engaging with regulatory authorities;
- Safeguarding IPR and technology management policies for all the parties involved.

A manufacturer led Product Development Unit (PDU) would be formed towards development of each selected component candidate.

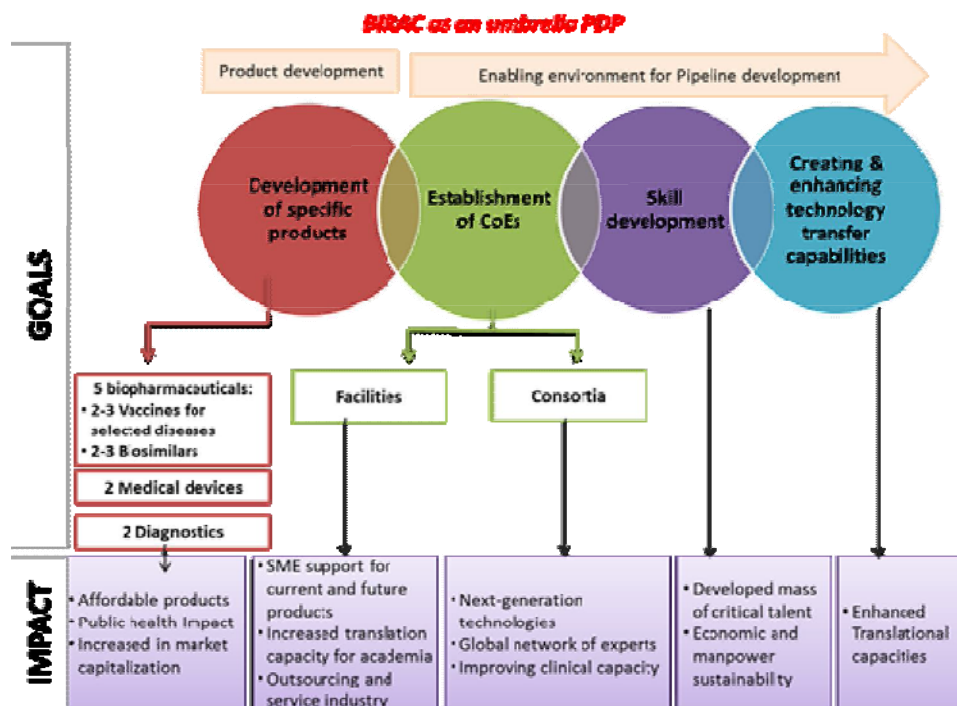


Figure-4

The details of the administrative structure and their roles have been defined below:

- A Steering committee (SC) would be constituted for management and oversight of the Program and be supported by the Technical Advisory Group (TAG) for providing specific and timely technical insights on various aspects of the Program.
- It shall be supported by the Program Management Unit (PMU) that would be led by a CEO/Program Manager and constituted of technical coordinators, analysts, legal and compliance team, communication team, quality control and administrative staff.

- PMU shall have one coordinator who would oversee the implementation of this EMF during the selection, sanction and execution stages.
- PDU would be created around each element of the Program (vaccines –V1/2/3, biosimilars- B1/2, medical devices-MD1/2 & diagnostics-D1/2, shared facilities-F1/2/3/4, consortia-C1/2, clinical trial units, trainings and TTOs) with an implementer as the central pillar supported by global/national experts and coordinated by technical coordinators that are part of the PMU. (functionality of these have been described in Implementation Methodologies section)
- Role of the technical coordinators would be to :
 - Link with implementers i.e. manufactures, facility owners, scientific leaders, training partners, academic centers etc. of each functional unit
 - Ensure linkages amongst the various units formed.
 - Convene with global experts for various units for ably supporting the implementers.
- Overall role of the PMU will be to:
 - Engage with global expertise to build a strategy involving the implementers
 - Develop a work plan for implementation and provide administrative and functional support
 - Provide linkage mechanism by engaging with multiple stakeholders and conduct suitable meeting/consultations for the same
 - Ensure suitable information is available for the TAG and SC towards overall efficient governance, management, implementation and oversight of the Program.

Enable funds disbursement to various units against the defined milestones and timelines

In all the Clinical Trial Projects, expert organizations such as Clinical Development Services Agency (CDSA) shall be part of the Functional Units. The monitoring/auditing by the Functional Units shall cover all the five basic bioethics aspects of the clinical trial Projects:

1. Initiation
2. Planning
3. Execution
4. Data safety Monitoring and controlling deviations
5. Analysis and reporting

PDU level

Every PDU under the Program will constitute a core committee having a designated person for implementation of this EMF from among the investigators. The quarterly Project report shall have a separate compliance status on EMF.

Monitoring strategy

A Project Monitoring Committee (PMC) comprising of eminent experts from the relevant field(s) will be constituted by BIRAC to monitor the progress of the objective(s) of the Project. BIRAC shall have at least one representative in the PMC who will monitor the EMF parameters.

The functions of the PMC shall be as follows:

- a. To monitor the progress of the Project in conformity with the outputs, milestones, targets objectives and other terms and conditions as contained in the funding agreement
- b. To assess the global developments impacting the domain of the Project.
- c. Based on the foregoing, to assess and recommend:
 - i. the release of next installment or part release thereof by the BIRAC.
 - ii. revision of Project Duration
 - iii. closing, dropping or modifying any of the components of the Project, within the overall approved objectives, budget and time-frame,
 - iv. inclusion of additional industrial/institutional partner(s), if the Company and the Institutes requests involvement of such partner(s), in the overall interest of the Project; and
 - v. revision of the financial assistance.
- d. To advise on issues related to securing of EMF compliance and mentor to overcome any technological problem faced in the Project implementation; and
- e. To advise on any other matter as referred to it by BIRAC and/or otherwise reasonably necessary for effective discharge of its duties and/or achievement of aims and objectives of the Program.

Training elements

Required training with regard to EMF will be made as integral part of the broader training component under the Program. The initial training on EMF will be imparted soon after the sanction of the Program and periodic training will be conducted to the designated PDU personnel.

The relevant component is termed hereunder;

Building and strengthening domain specific knowledge and management skills	I. Skill development through international exposure in vital areas of skill gap II. Investment in existing training centers III. Content and courseware development that can be delivered by designated training partners
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Training for EMF elements will be enabled through a separate module as part of the activities of skill developments.

Activity Skill development through international exposure and designated training partners in vital areas of skill gap – (scientists, budding entrepreneurs, industry representatives)

- Areas of Skill development include-
 - Onsite training for validation skills (bioanalytical development, PK-PD studies, assay development etc)
 - Onsite training for biomanufacturing skills (upstream/downstream and quality assurance)
 - Training in other interdisciplinary areas required for development of new technologies (e.g. development of novel assays, manufacturing tools & technologies, and cell lines & expression systems)
 - Clinical trial capabilities on site
 - Compliance in GLP, GMP and GCP norms
 - Regulatory knowledge including EMF
 - Intellectual property reading and legal expertise
 - Onsite training in the area of technology transfer and licensing
 - Project management
 - Business development

Environmental, Health, and Safety Guidelines for Pharmaceuticals and Biotechnology Manufacturing

Introduction

The Environmental, Health, and Safety (EHS) Guidelines are technical reference documents with general and industry specific examples of Good International Industry Practice (GIIP)¹. When one or more members of the World Bank Group are involved in a project, these EHS Guidelines are applied as required by their respective policies and standards. These industry sector EHS guidelines are designed to be used together with the **General EHS Guidelines** document, which provides guidance to users on common EHS issues potentially applicable to all industry sectors. For complex projects, use of multiple industry-sector guidelines may be necessary. A complete list of industry-sector guidelines can be found at: www.ifc.org/ifcext/enviro.nsf/Content/EnvironmentalGuidelines

The EHS Guidelines contain the performance levels and measures that are generally considered to be achievable in new facilities by existing technology at reasonable costs. Application of the EHS Guidelines to existing facilities may involve the establishment of site-specific targets, with an appropriate timetable for achieving them.

The applicability of the EHS Guidelines should be tailored to the hazards and risks established for each project on the basis of the results of an environmental assessment in which site specific variables, such as host country context, assimilative capacity of the environment, and other project factors, are taken into account. The applicability of specific technical

recommendations should be based on the professional opinion of qualified and experienced persons.

When host country regulations differ from the levels and measures presented in the EHS Guidelines, projects are expected to achieve whichever is more stringent. If less stringent levels or measures than those provided in these EHS Guidelines are appropriate, in view of specific project circumstances, a full and detailed justification for any proposed alternatives is needed as part of the site-specific environmental assessment. This justification should demonstrate that the choice for any alternate performance levels is protective of human health and the environment.

Applicability

The EHS Guidelines for Pharmaceuticals and Biotechnology Manufacturing include information relevant to pharmaceuticals and biotechnology manufacturing facilities. They cover the production of active pharmaceutical ingredients and secondary processing, including intermediates, formulation, blending, and packaging, and related activities research, including biotechnology research and production.

This document is organized according to the following sections:

Section 1.0 — Industry-Specific Impacts and Management
Section 2.0 — Performance Indicators and Monitoring

Section 3.0 — References 2007

Annex A — General Description of Industry Activities

¹ Defined as the exercise of professional skill, diligence, prudence and foresight that would be reasonably expected from skilled and experienced professionals engaged in the same type of undertaking under the same or similar circumstances globally. The circumstances that skilled and experienced professionals may find when evaluating the range of pollution prevention and control techniques available to a project may include, but are not limited to, varying levels of environmental degradation and environmental assimilative capacity as well as varying levels of financial and technical feasibility.

1.0 Industry-Specific Impacts and Management

The following section provides a summary of EHS issues associated with pharmaceuticals and biotechnology manufacturing, along with recommendations for their management. Recommendations for the management of EHS issues common to most large industrial facilities during the construction and decommissioning phase(s) are provided in the **General EHS Guidelines**.

1.1 Environmental

The following environmental issues should be considered as part of a comprehensive assessment and management program that addresses project-specific risks and potential impacts. Potential environmental issues associated with pharmaceuticals and biotechnology manufacturing projects include the following:

- Air emissions
- Wastewater
- Solid and hazardous wastes
- Hazardous materials
- Threats to biodiversity
- Bioethics

Air Emissions

Volatile organic compounds, acid gases, and particulates may be emitted during pharmaceuticals and biotechnology manufacturing facilities from both point sources and fugitive emissions. Greenhouse gas emissions are also of significance.

Volatile Organic Compounds

Chemical synthesis and extraction are the manufacturing phases responsible for significant emissions of volatile organic compounds (VOCs). In primary pharmaceutical manufacturing, VOC emissions

are generated from reactor vents, filtering systems in the separation process, solvent vapors from purification tanks and dryers (including loading and unloading operations), fugitive emissions from valves, tanks, pumps, and other equipment (e.g., centrifuges), solvents and other VOCs related to extraction chemicals in natural product extraction, prefermentation and fermentation solvents, and wastewater collection and treatment units.

VOC emissions from secondary pharmaceutical manufacturing may be generated from mixing, compounding, granulation, and formulation (e.g. use of ethanol or isopropyl alcohol), from operations involving the use of solvents (e.g. granulation) or alcoholic solutions (e.g. tablet coating), and from aerosol manufacturing processes.

Solvent and VOC emission prevention and minimization measures include the following:

- Reducing or substituting the use of solvents and other materials which have a high VOC content, and substitution with products that have lower volatilities, and switching to aqueous-based coating films and aqueous-based cleaning solutions²;
- Implementation of VOC leak prevention and control strategies from operating equipment as described in the **General EHS Guidelines** (Air Emissions and Ambient Air Quality: Fugitive Sources);
- Implementation of VOC loss prevention and control strategies in open vats and mixing processes as described in the **General EHS Guidelines**, including installation of process condensers after the process equipment to support a vapor-to-liquid phase change and

² Solvent selection is a key consideration in process development. For instance, ethyl acetate, alcohols and acetone are preferable to more toxic solvents such as benzene, chloroform and trichloroethylene. An example of a solvent selection guide is provided in the EU IPPC BREF on Organic Fine Chemicals (Section 4.1.3). Solvent substitution may be the subject of strict regulatory requirements.

to recover solvents. Process condensers include distillation and reflux condensers, condensers before vacuum sources, and condensers used in stripping and flashing operations;

- Reduction of equipment operating temperatures, where possible;
- For drying operations, adoption of closed circuits under a nitrogen atmosphere;
- Use of closed-loop liquid and gas collection equipment for cleaning of reactors and other equipment.

VOCs should be collected in local exhaust ventilation hoods for subsequent control of point and fugitive emissions. VOC emissions extraction and controls, especially from fermentation processes, may also reduce nuisance odors. Recommended VOC emissions control measures include the following:

- Venting of emissions from sterilization chambers into control devices such as carbon adsorption or catalytic converters;
- Condensation and distillation of solvents emitted from reactors or distillation units. Possible installation of cryogenic condensers, reducing the gas stream temperature below dew point to achieve higher VOC recovery efficiencies;³
- Installation of wet scrubbers (or gas absorbers), which may remove VOCs as well as other gaseous pollutants from a gas stream,⁴ and addition of hypochlorite to the

³ Cryogenic condensers allow higher removal efficiency (up to 99 percent) than traditional condensers, but they have higher energy requirements. ⁴ Scrubbers may consist of packed towers, plate or tray towers, venturi scrubbers and spray towers. These options are best applied to highly watersoluble VOCs (e.g., alcohols). Water, caustic, and acidic scrubbers are widely used for organic and inorganic gas emission abatement. Acid gas emissions are controlled through water and caustic scrubbing systems (often several scrubbers in series). Scrubbers create a wastewater stream requiring further treatment.

scrubber in order to reduce emissions of nuisance odors;

- Installation of activated carbon adsorption or destructive control devices such as thermal oxidation / incineration, catalytic incinerators, enclosed oxidizing flares, or other methods described in further detail in the **General EHS Guidelines**.

Particulate Matter

Particulates consisting of manufactured or in-process product can be emitted from bulk (e.g. fermentation) and secondary manufacturing. The most common sources of particulates include milling, mixing, compounding, formulation, tableting, and packaging. Recommended particulate matter management strategies include:

- Collection with air filtration units and recycling of particulate matter into the formulation process (e.g. tablet dust), depending on batch record requirements and on process characteristics;
- Installation of dedicated filtration systems (sometimes double stages of filtration) in granulation equipment. An abatement room should be also provided where the particulate is removed from the air, decreasing flow speed;
- Installation of high efficiency particulate air (HEPA) filters in the heating, ventilating and air conditioning (HVAC) systems to control particulate matter emissions internally and externally as well as to prevent indoor crosscontamination. Air ducts should be segregated to prevent air cross-contamination from different processes and to ease the air stream treatment;
- Collection of particulates through air filtration units, typically baghouse / fabric filters;
- Depending on the volume of emissions and prevailing size of particulate matter,

additional particulate emissions control methods should be considered, such as wet scrubbing and wet electrostatic precipitators, especially after combustion / thermal oxidation treatments.

Combustion Source Emissions

Exhaust gas emissions produced by the combustion of gas or diesel in turbines, boilers, compressors, pumps and other engines for power and heat generation, are a significant source of air emissions from pharmaceuticals and biotechnology manufacturing facilities. Guidance for the management of small combustion source emissions with a capacity of up to 50 megawatt thermal (MWth), including air emission standards for exhaust emissions, is provided in the **General EHS Guidelines**.

Odors

The main source of odor emissions is typically associated with fermentation activities. Recommended odor management strategies include:

- Considering the location of new facilities, taking into account proper distances to neighbors and the propagation of odors;
- Post-combustion of venting gases;
- Use of exhaust stack heights that are consistent with practices as described in the **General EHS Guidelines**;
- Use of wet scrubbers to remove odors with a high affinity to water;
- Condensation of vapors combined with scrubbers.

Wastewater

Industrial Process Wastewater

Wastewater streams in pharmaceuticals and biotechnology manufacturing depend on the specific process and may include: chemical reactions streams; product wash water; spent acid and caustic streams; condensed steam from sterilization and strippers; air pollution control

scrubber blowdowns; equipment and facility wash water; and clean-in-place wastewater.

The main conventional pollutants of concern in these wastewater streams from primary manufacturing (e.g. fermentation, chemical synthesis, crystallization, purification, and biological / natural extraction) are parameters such as biochemical oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids (TSS), ammonia, toxicity, biodegradability, and pH. Other chemical compounds may also be present including, but not limited to, solvents (e.g. methanol, ethanol, acetone, isopropanol, and methyl-ethyl ketone), organic acids (e.g. acetic acid, formic acid), organic halides, inorganic acids, ammonia, cyanide, toluene, and active pharmaceutical ingredients (API).

Recommended source reduction measures include:

- Material substitution, especially adoption of biodegradable water-based materials for organic solvent based materials (e.g. in tablet coating);
- Condensation and separation processes to recover used solvents and aqueous ammonia, including:
 - Low-boiling compounds from wastewater stream by fractioned distillation
 - Volatile compounds from wastewater stream by inert gas stripping and condensation
 - Solvent extraction of organic compounds (e.g. high or refractory halogenated compounds and high COD loads)
- Combination of solvent waste streams to optimize treatment.

Process Wastewater Treatment

Techniques for treating industrial process wastewater in this sector include source segregation and pretreatment of concentrated

wastewater streams, especially those associated with active ingredients. Typical wastewater treatment steps include: grease traps, skimmers, dissolved air floatation or oil water separators for separation of oils and floatable solids; filtration for separation of filterable solids; flow and load equalization; sedimentation for suspended solids reduction using clarifiers; biological treatment, typically aerobic treatment, for reduction of soluble organic matter (BOD); biological nutrient removal for reduction in nitrogen and phosphorus; chlorination of effluent when disinfection is required; dewatering and disposal of residuals in designated hazardous waste landfills. Additional engineering controls may be required for (i) containment and treatment of volatile organics stripped from various unit operations in the wastewater treatment system, (ii) advanced metals removal using membrane filtration or other physical/chemical treatment technologies, (iii) removal of recalcitrant organics and active ingredients using activated carbon or advanced chemical oxidation, (iii) residual color removal using adsorption or chemical oxidation, (iv) reduction in effluent toxicity using appropriate technology (such as reverse osmosis, ion exchange, activated carbon, etc.), (v) reduction in

TDS in the effluent using reverse osmosis or evaporation, and (vi) containment and neutralization of nuisance odors.

Management of industrial wastewater and examples of treatment approaches are discussed in the **General EHS Guidelines**. Through use of these technologies and good practice techniques for wastewater management, facilities should meet the Guideline Values for wastewater discharge as indicated in the relevant table of Section 2 of this industry sector document.

Other Wastewater Streams & Water Consumption

Guidance on the management of non-contaminated wastewater from utility operations, non-contaminated stormwater, and sanitary sewage is provided in the **General EHS Guidelines**. Contaminated streams should be routed to the treatment system for industrial process wastewater. Recommendations to reduce water consumption, especially where it may be a limited natural resource, are provided in the **General EHS Guidelines**.

Solid and Hazardous Wastes

Hazardous Waste

Bulk manufacturing processes in the pharmaceutical industry are typically characterized by a low ratio of finished products to raw material resulting in significant quantities of residual waste, especially during fermentation and natural product extraction. Chemical synthesis processing generates wastes containing spent solvents, reactants, spent acids, bases, aqueous or solvent liquors, still bottoms, cyanides and metal wastes in liquid or slurry form, as well as filter cakes which may contain inorganic salts, organic by-products and metal complexes. Fermentation processes may generate spent solids, intermediates, residual products and filter cakes containing mycelia, filter media, and small amounts of nutrients. Other sources of hazardous or potentially hazardous wastes may include raw materials packaging waste, used air filter media, offspec and expired products, laboratory wastes, sludge from the wastewater treatment process, and collected particulate from air pollution control systems.

Recommended pollution prevention and control measures include:

- Waste reduction by material substitution (e.g. use of water based solvents, etc.);

- Process modifications (e.g. continuous rather than batch operations to reduce spillage and other material losses);
- Spent solvent recycling and reuse, through distillation, evaporation, decantation, centrifugation and filtration;
- Other potential recovery options should be investigated, including inorganic salts recovery from chemical liquors produced during organic synthesis operations, high organic matter materials from biological extraction, and filter cakes from fermentation⁵;
- Potentially pathogenic waste from biotechnology manufacturing should be inactivated through sterilization or chemical treatment before final disposal.

5 Solid wastes from fermentation (e.g., mycelia) may be added to animal feeds as a nutritional supplement or as soil conditioners and fertilizers. Hazardous and non-hazardous industrial wastes should be stored, transported, and managed as described in the relevant sections of the **General EHS Guidelines**.

Hazardous Materials Management

Pharmaceutical and biotechnology manufacturing plants should assess the risks associated with the use and handling of hazardous materials and implement practices to prevent and minimize such risks. As indicated in the **General EHS Guidelines**, the application of these management practices should be documented in a written Hazardous Materials Management Plan. The purpose of this plan is to establish and implement a systematic set of preventive actions against accidental releases of substances that can cause serious harm to the environment, and to health and safety of workers and the public from short-term exposures and to mitigate the severity of releases that do occur.

In establishing the hazardous material management plan⁴, facilities should:

- Conduct a Hazard Assessment considering accident history in the last five years, worst case scenario, and alternative release analysis;
- Identify and implement management procedures including process safety, training, management of change, incident investigation, employee participation, contractor training and oversight;
- Implement prevention measures including process hazard analysis, operating procedures, mechanical integrity, prestart review, work permit, and compliance audits;
- Develop and implement an Emergency Response Program including emergency response procedures, emergency equipment, training, review and updates.

Threats to Biodiversity

Bioprospecting

The process of collection of genetic resources (bioprospecting), which may be part of certain pharmaceutical or biotechnology projects, may include access to different types of habitats. In addition to the potential for negative impacts to the biodiversity of these habitats, which may also depend on the physical nature of the collection activities and the types of genetic material involved, bioprospecting may also raise issue about the rights of local communities to consent in the use or to a share in the benefits of the commercialization of their cultural heritage or the genetic resources extracted.

Recommended management practices include:

- Avoiding or minimizing harm to biodiversity in compliance with applicable legal requirements;
- Development and application of bioprospecting procedures that are

⁴ See IFC Hazardous Waste Management Manual.

consistent with internationally recognized standards and guidelines, including aspects of:⁵,⁶ oCoordination with representatives from the National Focal Point⁹ prior to the undertaking of bioprospecting activities to identify national and local requirements, Obtaining Prior Informed Consent (PIC) from the State which is party to the Convention on Biological Diversity (CBD) in material screened for genetic use according to the basic principle of the CBD, and oDevelopment and implementation of contracting agreements for the sharing of benefits arising from the development and commercialization of genetic resources.

Biosafety

For projects or facilities involved in research, manufacture, or trading of living modified organisms, the risks associated with their production, handling, storage, transport, and use may include threats to biological diversity due to the controlled or uncontrolled release of the organism into the environment.

Recommended biosafety management practices include:

- Development of a risk-based approach to the identification of key control points in the process cycle, including in-plant handling, off-site transport, and use of modified organisms.¹⁰ The assessment should cover the processes used and potential releases (including living modified organisms as discussed in Annex III of the Cartagena

Protocol on Biosafety to the Convention on Biological Diversity) on the conservation and sustainable use of biological diversity, taking also into account risks to human health;¹¹

- Implementation of in-plant and transport safety measures including specialized training of personnel, primary containment (e.g. containment barriers) and secondary containment (e.g. airlocks, differential pressure, exhaust air filters and treatment of contaminated material and wastes)¹², and equipment and personnel decontamination procedures;

¹⁰ Examples of risk assessment methodologies include Annex III of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity; the UNEP International Technical Guidelines for Safety in Biotechnology; and the United States Department of Agriculture, Animal and Plant Health Inspection Service (APHIS) and the related International Biosafety Protocol website, available at :http://www.aphis.usda.gov/brs/international_biosafety.html as well as the Biotechnology Regulatory Services website, available at: <http://www.aphis.usda.gov/biotechnology/about.shtml> and <http://www.aphis.usda.gov/brs/biosafety.html>

¹¹ The risk assessment should consider the controlled or potentially accidental nature of the environmental release of an organism.

¹² Classification and description of biosafety containment levels are provided by international organizations, such as the World Health Organization (WHO), and

- Preparation and implementation of Transportation Safety Plans specific to the type of organism being handled and consistent with the objectives of applicable international conventions and treaties;^{13,14}

⁵ Examples of internationally recognized guidelines include the Bonn Guidelines on Access to Genetic Resources and Fair and Equitable Sharing of the Benefits Arising out of their Utilization published by the Secretariat of the Convention on Biological Diversity (CBD, 2002) and the Akwe: Kon Guidelines applicable to the conduct of cultural, environmental, and social assessments (also published by the Secretariat of the CBD, 2004).

⁶ Examples of procedures developed by the private sector include the

Guidelines for BIO Members Engaging in Bioprospecting published by the Biotechnology Industry Organization (BIO), Washington DC. (2006).⁹ As per Convention on Biological Diversity.

- Implementation of risk-management measures for controlled releases applicable to the specific organism including, as appropriate, training of those involved, monitoring of the activity, controlling access to the site, and application of isolation methods.¹⁵

Bioethics

The ethical issues faced by the pharmaceutical or biotechnology industry are potentially complex and depend significantly on the activity of the company. These issues may include the development of genetically modified foods; gene therapy experiments and stem cell research; human participant trials; animal testing; handling of genetic information; sale of genetic and biological samples; and the creation of transgenic animals, among others.¹⁶ Recommended bioethics management approaches include:

- Well established ethics mechanisms including management commitment; dedicated internal ethics personnel; access and use of external expertise (e.g. consultants and advisory boards); internal training and accountability mechanisms; communications programs to engage with suppliers and external stakeholders; and evaluation and reporting mechanisms;¹⁷

national institutes, such as the US Centers for Disease Control and Prevention (CDC) and US National Institutes of Health (NIH).

¹³ Cartagena Protocol on Biosafety to the UN Convention on Biological Diversity. ¹⁴

Examples of biosafety good practices can be found in the UN Recommendation on the Transport of Dangerous Goods (Orange Book).

¹⁵ Examples of management practices applicable to controlled releases of plants, animals, and micro-organisms can be found in Annex 5 of the

UNEP International Technical Guidelines for Safety in Biotechnology.

¹⁶ Mackie, et al. (2006) ¹⁷

Ibid.

- Adherence to internationally accepted ethical principles applicable to genetic research, clinical trials involving human participants, and any other activities with critical bioethical issues;⁷
- The use of animals for experimental and scientific purposes should be conducted according to industry good practice which includes reduction of the numbers of animals used in each study to the absolute minimum necessary to obtain valid results and refinement of the use of research animals to use less painful or the least invasive procedures whenever possible.^{8,9} Animal breeding, husbandry, and care facilities of the company or its suppliers should be designed and operated according to internationally certifiable methodologies.¹⁰

⁷ Examples include the Universal Declaration on Bioethics and Human Rights and more specifically publications by specialized entities such as the International Bioethics Committee (IBC, <http://portal.unesco.org>); US National Bioethics Advisory Commission (<http://www.bioethics.gov/>); and the Biotechnology Industry Organization Statement of Ethical Principles (<http://www.bio.org/>).

⁸ An example of this approach is the United States Department of Agriculture's

Three R Concept, which includes "Reduction, Refinement, and Replacement"

(National Agricultural Library (<http://awic.nal.usda.gov/>)). It should be noted that "replacement" (consisting of the replacement of animal experiments with nonanimal experiments such as mathematical models, computer simulations, and in vitro biological systems) is often considered a long term goal given the current lack of technological feasibility.

⁹ See also European Union Directive 86/609/EC on protection of animals used for experimental and other scientific purposes as well as the Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Research, 1996).

¹⁰ Animal handling methods should be certifiable according to requirements of international accreditation bodies such as Association for Assessment and

1.2 Occupational Health and Safety

Facility-specific occupational health and safety hazards should be identified based on job safety analysis or comprehensive hazard or risk assessment using established methodologies such as a hazard identification study [HAZID], hazard and operability study [HAZOP], or a scenario-based risk assessment [QRA].

As a general approach, health and safety management planning should include the adoption of a systematic and structured system for prevention and control of physical, chemical, biological, and radiological health and safety hazards described in the **General EHS Guidelines**.

The occupational health and safety issues that may occur during the construction and decommissioning pharmaceutical and biotechnology manufacturing facilities are similar to those of other industrial facilities, and their management is discussed in the **General EHS Guidelines**. The most significant occupational health and safety hazards occur during the operational phase of pharmaceutical and biotechnology facilities and primarily include the following:

- Heat hazards
- Chemical hazards including fire and explosions
- Pathogenic and biological hazards
- Radiological hazards
- Noise
- Process safety

Heat

The use of large volumes of pressurized steam and hot water are typically associated with fermentation and with compounding operations

representing potential for burns due to exposure to steam or direct contact with hot surfaces as well as heat exhaustion. Recommended management practices include:

- Steam and thermal fluid pipelines should be insulated, marked, and regularly inspected;
- Steam vents and pressure release valves should be directed away from areas where workers have access;
- High temperature areas of presses should be screened to prevent ingress of body parts.

Recommended management practices to avoid heat exhaustion are presented in the **General EHS Guidelines** (Occupational Health and Safety).

Chemicals

The risk of occupational exposure to chemicals in pharmaceutical and biotechnology manufacturing activities are potentially complex. Among the most common types of chemicals and exposure routes is the inhalation of volatile organic compounds (VOCs) from recovery, isolation, and extraction activities; from handling of wet cakes in drying operations; during wet granulation, compounding, and coating operations; from uncontained filtration equipment; and from fugitive emissions for leaking pumps, valves, and manifold stations (e.g. during extraction and purification steps). Additional sources of inhalation exposures include chemical synthesis and extraction operations and sterilization activities (e.g. germicides such as formaldehyde and glutaraldehyde, and sterilization gases such as ethylene oxide) as well as exposure to synthetic hormones and other endocrine disrupters. In secondary pharmaceuticals manufacturing, workers may be exposed to airborne dusts during dispensing, drying, milling, and mixing operations.

Potential inhalation exposures to chemicals emissions during routine plant operations should be managed based on the results of a job safety analysis and industrial hygiene survey and according to the occupational health and safety guidance provided in the **General EHS Guidelines**. Protection measures include worker training, work permit systems, use of personal protective equipment (PPE), and toxic gas detection systems with alarms. Additional recommended measures include:

- Use of partitioned workplace areas with good dilution ventilation and / or differential air pressures;
- When toxic materials are handled, laminar ventilation hoods or isolation devices should be installed;
- Manufacturing areas should be equipped with suitable heating ventilation and air conditioning (HVAC) ¹¹ systems designed according to current Good Manufacturing Practice (cGMP) protocols, including use of high efficiency particulate air (HEPA) filters in ventilation systems, particularly in sterile product manufacturing areas;
- Use of gravity charging from enclosed containers and vacuum, pressure, and pumping systems during charging and discharging operations to minimize fugitive emissions;
- Use of local exhaust ventilation (LEV) with flanged inlets to capture fugitive dusts and vapors released at open transfer points;
- Conducting liquid transfer, liquid separation, solid and liquid filtration, granulation, drying, milling, blending, and compression in work areas with good dilution and LEV;
- Enclosing of granulators, dryers, mills, and blenders, and venting to air-control devices;

¹¹ HVAC systems should be designed to meet product protection, occupational health and safety, and environmental protection needs. Air conditioning systems should be designed to include filtration of air.

- Use of dust and solvent containment systems in tablet presses, tablet-coating equipment, and capsule-filling machines. Tablet-coating equipment should be vented to VOC emission control devices;
- Whenever possible, less hazardous agents should be selected in all processes (e.g. alcohols and ammonium compounds in sterilization processes);
- Sterilization vessels should be located in separate areas with remote instrument and control systems, nonrecirculated air, and LEV to extract toxic gas emissions. Gas sterilization chambers should be evacuated under vacuum and purged with air to minimize fugitive workplace emissions before sterilized goods are removed;
- Use vacuuming equipment with HEPA filters and wet mopping instead of dry sweeping and blowing of solids with compressed air.

Fire and Explosions

Fire and explosion hazards may arise during solvent extractions. Organic synthesis reactions may also create major process safety risks from highly hazardous materials, fire, explosion, or uncontrolled chemical reactions, which should be controlled through process safety engineering and control.

Secondary pharmaceuticals manufacturing operations (e.g. granulation, mixing, compounding and drying) also use flammable liquids, with the potential to create flammable or explosive atmospheres. In addition, some pharmaceutical dusts are highly explosive. Recommended management practices are presented in the **General EHS Guidelines**.

Pathogenic and Biological Hazards

Exposure to pathogens may occur during isolation and growth of micro-organisms in laboratory and in fermentation processes.

Recommended management practices are presented in the **General EHS Guidelines**.

Radiological Hazards

Research and development operations may include the use of radiological materials which should be managed to prevent and control worker exposures according to licensing requirements. Additional guidance on the management of radiological hazards is provided in the **General EHS Guidelines**.

Noise

High noise levels may be reached in some pharmaceuticals and biotechnology manufacturing areas (e.g. chemical synthesis facilities). High sound levels may be generated by manufacturing equipment and utilities (e.g. compressed air, vacuum sources, and ventilation systems). Industry-specific hazards are related to the typical enclosed design of pharmaceutical and biotechnology workplace modules, where personnel are often operating close to equipment during manufacturing and packaging operations. Recommended management practices to prevent and control occupational exposures to noise are presented in the **General EHS Guidelines**.

Process Safety

Process safety programs should be implemented, due to industry-specific characteristics, including complex chemical reactions, use of hazardous materials (e.g., toxic and reactive materials, and flammable or explosive compounds) and multistep reactions. Process safety management includes the following actions:

- Physical hazard testing of materials and reactions;
- Hazard analysis studies to review the process chemistry and engineering practices, including thermodynamics and kinetics;

- Examination of preventive maintenance and mechanical integrity of the process equipment and utilities;
- Worker training; and
- Development of operating instructions and emergency response procedures.

1.3 Community Health and Safety

The most significant community health and safety hazards associated with pharmaceutical and biotechnology manufacturing facilities occur during the operation phase and may include the threat from major accidents related to the aforementioned fires and explosions at the facility and potential accidental releases of finished products during their transport outside of the processing facility. Guidance for the management of these issues is presented under Major Hazards below and in the **General EHS Guidelines** including the sections on: Traffic Safety; Transport of Hazardous Materials; and Emergency Preparedness and Response.

Major Hazards

The most significant safety impacts are related to the handling and storage of solid, liquid, and gaseous substances described above. Impacts may include significant exposures to workers and, potentially, to surrounding communities, depending on the quantities and types of accidentally released chemicals and the conditions for reactive or catastrophic events, such as fire and explosion.

Major hazards should be prevented through the implementation of a Process Safety Management Program that includes all of the minimum elements outlined in the respective section of the **General EHS Guidelines** including:

- Facility-wide risk analysis, including a detailed consequence analysis for events with a likelihood above 10⁻⁶/year (e.g. HAZOP, HAZID, or QRA);
- Employee training on operational hazards;
- Procedures for management of change in operations, process hazard analysis, maintenance of mechanical integrity, pre-start review, hot work permits, and other essential aspects of process safety included in the **General EHS Guidelines**;
- Safety Transportation Management System as noted in the **General EHS Guidelines**, if the project includes a transportation component for raw or processed materials;
- Procedures for handling and storage of hazardous materials;
- Emergency planning, which should include, at a minimum, the preparation and implementation of an Emergency Management Plan prepared with the participation of local authorities and potentially affected communities.