Mission Document

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
Ministry of Science & Technology
Government of India

Implementing Agency:

Biotechnology Industry Research Assistance Council (BIRAC)

(A Government of India Enterprise)

Co-funded through World Bank Loan Assistance

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Abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
BIRAC	Biotechnology Industry Research Assistance Council
CAGR	Compound annual growth rate
CMC	Chemical Manufacturing and Controls
CMOs	Contract Manufacturing Organization
CRO	Contract Research Organization
CTN	Clinical Trial Network
DBT	Department of Biotechnology
DCVM	Developing Countries Vaccine Manufacturers
FDU	Facility Development Units
GCP	Good Clinical Practise
GDP	Gross Domestic Product
GLP	Good Laboratory Practise
GMP	Good Manufacturing Practise
GoI	Government of India
HPV	Human papillomavirus
IAP	Indian Academy of Paediatrics
IP	Intellectual Property
M&E	Monitoring & Evaluation
MoA	Memorandum of Agreement
MoU	Memorandum of Understanding
NTAGI	National Technical Advisory Group on Immunization
PDU	Product Development Unit
PK-PD	Pharmacokinetics-Pharmacodynamics
PMU	Program Management Unit
PTAG	Program Technical Advisory Group
R&D	Research & Development
RFP	Request for Proposal
SAG	Scientific Advisory Group
SC	Steering Committee
SMEs	Small Medium Sized Enterprise
TA	Travel Allowance
TAG	Technical Advisory Group
TB	Tuberculosis
TPP	Target Product Profile
TTO	Technology Transfer Offices

1. Program Overview

1.1. About the program

An Industry-Academia Collaborative Mission of Department of Biotechnology (DBT) for Accelerating Early Development for Biopharmaceuticals; to be implemented by Biotechnology Research Assistance Council (BIRAC)-a Public Sector Undertaking of DBT

The National Biopharma Mission was approved by the Cabinet for implementation in May 2017 with a total cost US$ 250 million which is co-funded World Bank 50%.

1.2. The Aim and Objectives:

The Mission Programme is a Pan-India Programme with the main aim of making India a hub for design and development of novel, affordable and effective biopharmaceutical products and solutions. This Program would aid in enhancing India's innovation research and product development capabilities, especially by focusing on development of vaccines, biologics and medical devices for combating public health concerns. The Program would aid academic researchers (through enhancing their translation capability); empower bio-entrepreneurs and SMEs (by decreased cost and risk during early stages of product development) and the industry (by elevating their innovation quotient). Anticipated long term impact would benefit the Indian population at large benefit due to availability of affordable solutions and products relevant to Indian health needs.

It would enable connecting the essential key components required for product development in a virtual manner and make availability-accessibility process easier. This network would leverage on unique strengths for building collaborations and cross-product platform technologies; creating a global network of experts/mentors/advisors; consolidating resources for building centers of excellence; strengthen existing infrastructure, capacities and technical know-how to enable development of specific products and aid in development of a pipeline for products

Through these efforts it is proposed that India would work towards achieving its target of $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.

1.3. Mission of the Programme :

To 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 through affordable product development

The mission is focusing on:

- Development of product leads that are at advanced stages of the product development lifecycle and relevant to the public health need in vaccine, biosimilar and medical devices & diagnostics
- Establishing and strengthening shared infrastructure facilities for product development and validation. These would be for all product being developed.
- Developing human capital by providing specific trainings to address the critical skills gap across the product development value chain.
- Creating and enhancing technology transfer and intellectual property management capacities and capabilities.

1.4. Program Strategy

Towards strengthening the ecosystem, the proposed strategy is thus to have a multipronged approach categorized into incremental and non-incremental approach to generate maximal impact in next 5 years.

The Program's goal is to support of development of specific products by de-risking and accelerating product development. Together with experts from around the world the most promising candidates through the pipeline would be selected based on scientific merit/technical feasibility, degree to which the priority health needs, stage of development (earlier projects may carry more risk but also greater promise) and alignment with the target product profiles. Through this detailed and rigorous assessment, the probability of the product being brought closer to the market within the Program timelines would be substantial. This would not only aid in decrease of development timelines, but also impact the uptake time by the public health agencies.

Industry developing the shortlisted products (vaccines, biosimilars and medical devices) would lead a Product Development Unit (PDU) that would be linked to a strong supportive and collaborative network of global and Indian experts to mentor and guide and a robust management support. Through the PDU structure, the candidate would be shepherd the early phases through the later phases[1] with the opportunity to access partner network and flexibility of choosing the best partner to link with at each phase.

Additionally, capabilities would be developed in parallel to provide support across all stages of product development (*Figure 1*). Providing access to infrastructure for product evaluation, characterization in preclinical and clinical stages; pilot scale manufacturing and building up a cell line bank would decrease development costs. Indian ecosystem does not have appropriate sites with a suitable infrastructure with access to well defined and characterized population for conducting clinical trials. The Program would enhance the institutional and organizational capacity needed to successfully conduct clinical trials and facilitate links for manufactures to test their products. *(Figure 1: Component 1-5)*

[1] Early stages implies preclinical development; process development and Phase 1 Clinical trials, while late stage implies beyond Phase 2 Clinical trials and large scale manufacturing

In parallel, the Program would create an enabling environment that would pave the way for the entire field, not just the Program supported products and establish a continuum foster future innovation. It would support development of novel assays for evaluation and discovery of products; technologies and platforms to enhance manufacturing capabilities, strengthen technology transfer capabilities and invest in building a task force of scientific leaders. (Figure 1: Component6-9)

Figure 1: Prioritized components to accelerate development of products that could be in different stages

1.5. Key Objectives & Deliverables and Milestones:

Specific objectives and activities are:

I. Development of 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, start-ups, entrepreneurs and companies that have established proof of concept and are on the path of product development. Shortlisted products are - vaccines for dengue, HPV and pneumococcal & a new and complex vaccine for emerging disease; biosimilars for cancer, rheumatoid arthritis, diabetes and critical technologies to develop medical devices. Additionally, novel product development for complex, emerging, high priority infections will also be considered.

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 / strengthening shared facilities that are accessible, equipped with state-of-the-art infrastructure and relevant talent:

- GLP Validation facility for conducting preclinical and clinical characterization and evaluation of bio therapeutics (therapeutic proteins and monoclonal antibodies)
- GCLP Validation facility for conducting preclinical and clinical characterization and evaluation of vaccines
- CMC units for with capabilities to provide analytical assays as per regulatory requirements and manufacturing of pre-clinical and early clinical lots
- Process Development Laboratory for enabling optimized, robust, streamlined and cost effective process development to aid manufacturing
- 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

B. Building a consortium of partners, in-country& global network of research entities, for development of innovative technologies and platforms:

- Translation Research Consortia for generating in-depth understanding of disease and immunity for identification of new targets and better evaluation of products biotherapeutics and vaccines
- Consortia for development of novel cell lines

C. Clinical trial units linked to network of clinical experts and sites for conducting standardized and reliable clinical trials.

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

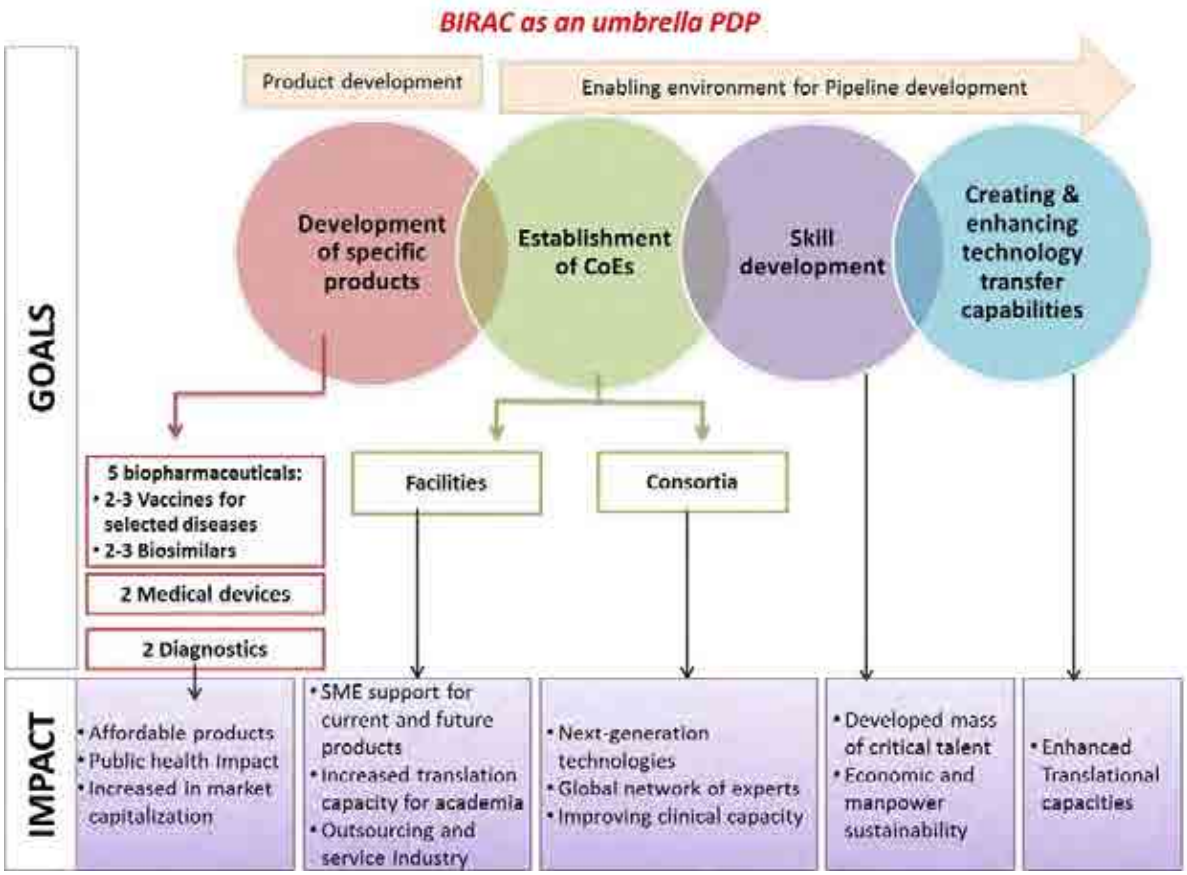
The program would facilitate skill development to build next generation inter-disciplinary skills for product innovation, knowledge of navigating regulatory policies, business development capabilities, better management of IPR systems and practices for building effective workforce and next generation leaders. Exemplary skills are:

- 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 officesin regions that are already established or are upcoming bio-clusters
- Training of technology transfer and Intellectual Property Management professionals;
- Providing assistance for acquisition and adaptation of technologies.
- Creating IP awareness



2. Program Description – For each of the Program components

2.1. Supporting Vaccine Development

2.1.1. Development of Specific Products

Background

Vaccines are one of the most cost-effective means available for managing infectious diseases. However, vaccines that are available for prevention or control of diseases with the greatest impact are often not designed with the developing country context in mind. These vaccines often confer short-lived immunity resulting in multiple re-vaccinations, display poor efficacy or safety profiles and have limited capacity to protect against multiple serotypes.

Additionally, novel vaccine discovery and development is plagued with challenges like lack of understanding of the precise antigens needed to elicit protective immunity due to genetic variation; inability to predict immunogenicity, efficacy, reactogenicity or safety and knowledge of factors that would enable generation of long-lived protective immune responses. Gaps in availability of validated assays, accessibility to well characterized cohorts for conducting clinical trials; unclear regulatory pathway for novel vaccines further contribute to delays in novel vaccine development.

Cervical cancer is the fifth most common cancer in humans, the second most common cancer in women worldwide and the most common cause of death due to cancer in the developing countries. With limitations of current screening and treatment procedures, vaccination is considered to be the best means of HPV Management.

Pneumonia remains a major killer of children under five with India having the greatest number of pneumococcal deaths in children aged 1–59 months.WHO and United Nations Children's Fund (UNICEF) have also prioritized reducing child mortality due to pneumonia by 2025.

WHO and the Indian Academy of Pediatrics Committee on Immunization (IAPCOI) has further recommends offering HPV and Pneumococcal vaccine to all who can afford the vaccine. Though there are vaccines currently available in the market, their high cost makes them unaffordable to large section of the Indian population. Hence there is a need to develop cost-effective indigenous vaccine against HPV and Pneumonia.

Emerging infections are a potent threat to public health security. Intriguingly most of these are viral in origin; thus highlighting the potency of viral threat in an ever-changing ecosystem of the world. Currently, half of the global population lives under dengue threat; and an estimated 390 million infections occur worldwide every year with ~100 million cases of clinical disease with over 25,000 deaths. India has one of the highest dengue disease burden with an estimated 20-40 million infections per year.

In addition to dengue, there are several others which have evolved at the turn of the 21st century. Avian influenza virus A H5N1 infection spiraled into a global pandemic in 2009, due to mutations in highly infectious H1N1 strain. The outbreak directly affected tourism, service sector, retail, trade, transport, entertainment, agriculture, pig farming and international economy. While chikungunya which was first recorded in Kolkata in 1963 remerged in 2006 after a gap of 32 years and caused an explosive outbreak affecting 13 states in India and

causes an annual economic loss of 391 million rupees. In 2002-03, severe acute respiratory syndrome (SARS) spread to 28 countries, and affected around 8500 people worldwide, claiming 800 lives (ref). In early 2015, a widespread epidemic of Zika fever, caused by the Zika virus in Brazil, created global panic as it spread to parts of Southern and Northern America. Similarly the Ebola Virus Disease (EVD) outbreak in West Africa in 2014-15 was one of the deadliest pandemic outbreaks in the recent history. The emergence of infections such as SARS, Ebola and Zika and global pandemics demonstrates our vulnerability to spread of infectious diseases in the era of transnational trade and increased mobility. The spread of the pandemic echoes the need for preventive measures, ensuring robust health care systems and development of effective biomedical tools e.g. vaccines which shall help to respond beyond the spatial and temporal limitations.

Objective:

The Program thus aims to facilitate early development of promising novel vaccine candidates for such high priority, complex infections by the Indian industry. The strategy is to accelerate product development by strengthening the ecosystem, enable de-risking and increase success rates by providing support across the product value chain and bring them closer to commercialization in 5 years of this grant. By ensuring that the product development is in alignment with Target Product Profile (TPP) specific for Indian needs, in addition to the product is brought closer to the market within the Program timelines, the uptake time by the public health agencies would also be accelerated.

This program would support acceleration of cost effective, safe and efficacious vaccines through direct funding of R&D activities and providing access to a group of experts from industry and academia with relevant expertise that would help define and streamline R&D pathway for efficient and quicker product development.

Product selection:

A multi-parametric filtration mechanism was embarked to screen out diseases for which vaccines can be supported. Parameters considered were Indian public health requirements – based on availability or/and high cost of current products in market; market interest and demand determined through - priorities of the Developing Countries Vaccine Manufacturers Network (DCVMN), procurement agencies like GAVI and recommendations by Indian Academy of Pediatrics (IAP) and National Technical Advisory Group on Immunization (NTAGI) and the availability of products in pipeline for these diseases. Further inputs from the Advisory Group aided in finalizing vaccines for**Dengue, Pneumococcal, HPV and other emerging infections where Indian vaccine manufacturers have candidate vaccines.**

Mapping of the vaccine candidates under development by Indian manufacturers showed that there are multiple products in pipeline for each of these diseases. Selection of final candidate for support for each of these diseases would be based on proximity to the Target Product Profile (TPP) of an India relevant vaccine for e.g. the vaccine composition, target population and required duration of protection would depend on prevalence, and strain diversity in India.

Program Strategy:

The proposed strategy is a multipronged approach that would support manufacturers with vaccine candidates at different stages of development through direct funding of R&D activities and providing access to a group of experts from industry and academia with relevant expertise that would help define and streamline R&D pathway for efficient and quicker product development.

Methodology of Support

- Direct Funding through the various stages of vaccine development including, preclinical development, early production of clinical grade material and early phase human clinical trials.
- Setting up of a Product Development Unit (PDU) that would bring together a group of experts and help set up a strong product management team by the manufacturer. In addition to provision of funds BIRAC shall also provide the applicant access to a group of experts from industry and academia with relevant expertise that would ensure completeness and feasibility of the product development plan, help define and streamline R&D pathway for efficient and quicker product development. This is akin to models such as the Malarial Vaccine Development Partnership and Rotavirus Vaccine development Program, the PDUs would bring together expertise to provide technical oversight for identification of anticipated challenges and suggesting specific areas support; and a strong product management team to provide technical and management support and enable vertical integration of multidisciplinary partners, both Indian and global, across the product development value chain
- Access to the following affordable services and solutions supported through the i3 program:
    - GcLP compliant facility for vaccine characterization, evaluation and validation in preclinical and clinical stages of development.
    - Facility for conduct of Challenge/protection studies in Transgenic/Humanized Mice and Non-Human Primate Models
    - Creation of strategies and plans for clinical trial plans/designs and engagement of an enriched study population towards intended product outcomes
    - Development of a regulatory strategy and support preparation of related filings
    - Development of Product Development Plan and Target Product Profile and provision of tools for monitoring of objectives vs. deliverables.

- This program will not support:

    - Projects focused on development of new adjuvants, formulations.
    - Projects lacking appropriate preliminary/immunogenicity data supporting the target candidate vaccine(s).

Success Parameters:

Given the above efforts, it is anticipated that at the end of five years, the following impact would be perceptible:

- Progress of two-three vaccine candidates would be accelerated along their development pathway, subject to their current stage of development, for e.g.: products that have proof of concept established and are currently in Pre-clinical stages of developmentwould be accelerated till late phase clinical trial and late stage manufacturing;
- Establishment of a continuum that spurred future innovation and assisted in development of pipeline of products;
- Identification of targets and antigens that have enabled manufacturers to develop novel vaccine;
- Development of regulatory assays that have transferred to GCLP/GLP lab
- Development of novel assays that enabled rapid evaluation of vaccines.

2.1.2. Building Shared Facilities

2.1.2.1. GCLP labs for Vaccines

Background:

Biopharmaceutical (mAbs and vaccines) development is a time taking and resource intensive process (8-10 years for a product to reach market and estimated cost of $800 million per NME product) with high rate of failure due to lack of efficacy and safety in later stages of development (FDA data shows 50% failure for Phase III products due to lack of efficacy and 30-40% due to safety). Therefore thorough assessment of these parameters in early stages of development becomes crucial.

To address this 'lagging science of product development' this Program will establish national service centers that would work with leading academic and industry partners to provide integrated solutions to enable proof of concept establishment, critical evaluation and validation of products (vaccines and mAbs) - that are in either early stages or in clinical stages of development, by bridging the gap between academic scientific research and commercial product discovery and development.

The centers will also address gaps in current infrastructure and skills by providing access to state-of-the-art high throughput equipment, technical support, and cross-training for the production and analysis of high-resolution data. In addition to the above, these facilities would be linked with global and national expertise to continuously upgrade technologies and expertise.

While these centers will offer equal-opportunity nationwide access to services through an open application process, they will be a "preferred provider" facility for the products in pipeline being supported through this Program.

The impact of the facility would enable lowering cost of development for products (monoclonal Abs and vaccines) in the pipeline by decreasing capital investment, aiding effective resource utilization and reducing risk of failure.

Hence by aiding in effective resource utilization, decrease in capital investment and reduction in risk of failure, the facility would enable lowering cost of development for products (monoclonal Abs and vaccines) in the pipeline.

Objective of the Facility:

The aim is to fill the current gaps in characterization, evaluation and validation of vaccines (supported through the i3program) by providing Indian industry and academia with a Vaccine Assay Core (GCLP) by establishing a regulatory compliant facility(s) that provides integrated solutions for validation of efficacy, and potency to support clinical trials of vaccine candidates.

Detailed Scope:

- ***Validate efficacy, and potency to support clinical trials of vaccine candidates***
  The facility would provide services to study clinical trial samples for:
  - Assessment of antibodies generated in response to vaccine:
    - Serum binding titers
    - Serum serotyping
    - Functional characterization of the antibodies generated by studying virus neutralization
    - Antibody effector function
  - Assessment of T-cell responses e.g.:
    - Antigen specific memory T cell differentiation and long term protective response by immuno-phenotyping and immunogenicity assays
    - Measuring T-cell proliferation
    - Identification of specific cytokines/chemokines in response to infection/vaccination as a measure of T cell response
    - Inhibition of viral replication
  - Detection of viral shedding and quantification

<u>Linkages with the Translation Research Consortia (TRC)</u>

The Translational Research Consortia and the GCLP Validation labs (for vaccine and other for antibodies) are Program components that would function independently and require different levels of investment, functional modalities and purpose, but also would feed into each other. The new technologies (novel products/assays/biomarkers) that are developed through the Interdisciplinary and Translation Research Consortia can be integrated and validated in the GCLP validation lab, while the honed infrastructure and expertise from the lab would support the consortia.

Proposed Impact

- Setup of a Global standard service facility that would have validated and established assays for product in pipeline, that are currently unavailable in the country
- Enabling quicker clinical validation and faster market reach by providing efficient validation of products
- Increase in chances of developing indigenous novel products by building and upgrading indigenous capabilities
- Affording lower cost of development for products vaccines in the pipeline by decreasing capital investment, aiding effective resource utilization and reducing risk of failure

2.1.3. Support New Technology / Platform Development and Product Development

2.1.3.1. Translational Research Consortium

Background:
Multiple scientific and clinical challenges obstruct the development of novel preventive and therapeutics solutions. Challenges in evaluation of novel vaccines are theinability to predict immunogenicity, efficacy, reactogenicity or safety and identification of the factors that would enable generation of long-lived protective immune responses. Additionally, with the emergence of new antibody discovery technologies, the rate of discovery of new antibody therapeutics is accelerating rapidly and there is growing need for discovery of rare antibodies with unique functions.
A strategic response to this would be to establish interdisciplinary and integrative approaches to address major problems in biomedical research would help in development of novel monoclonal Abs and assays for evaluation of viral vaccinesthrough a Translation Research Consortia.

Objective:
The aim is to fill the current gaps impeding discovery, development and evaluation of new products (vaccines and biotherapeutics), enable and provide the Indian industrywith the following:

1. Creation of a Network of partners that can engage in:
    a. Identification of targets on different viruses and to provide high-throughput assays to evaluate biologics that are effective against different viruses
    b. Enabling novel Ab discovery and preclinical evaluation for academia and industry
    c. Development of assays for evaluation of vaccines
2. Development of animal models and conduct of animal studies (not for safety studies)
3. Support and Advise for clinical development
4. Support and Advise for Product Licensure in Compliance with Indian and Global Regulations
5. Support and Advice in quality assurance and Project management through various stages of New Product Development
6. Support for Acquisition and Adaptation of New technologies that can be used by Industry and Network of Partners for point (a) above

Technical Scope of the Partnership Platform:

1. Creation of a Network of partners that can engage:

i. **Virology platform:** *Identification of targets on different viruses and to provide high-throughput assays to evaluate biologics that are effective against different viruses:*

- Viral quantification using various viral specific assays (plaque assays, foci formation assays and real time PCR)
- Viral genome sequencing studiesusing next generation sequencing
- Stock production of viruses (by making pseudo viruses / VLPs) for assessing the breadth of neutralization of the potential biologics.
- Viral Characterization
- Create inventory of primary virus panels for different infectious diseases (up to BSL3 containment).
- Development of regulatory and novel neutralization assays
- Target/antigen development

ii. **Antibody evaluation platform:** *Enabling novel Ab discovery and preclinical evaluation for academia and industry:*

- Antibody isolation*:* Using specific Ab isolation techniques (such as Memory B cell sorting, B cell activation)
- Functional characterization of the antibodies by studying binding affinity, virus neutralization and effector function
- Epitope mapping
- Bio-analytical characterization by structure determination, post translation modification e.g. glycosylation & disulphide bridges, aggregation, stability etc.
- Small animal model protection studies
- Non-human primate protection studies

iii. **Vaccine evaluation platform:** *Development of assays for evaluation of vaccines*

- Novel neutralization assays (e.g. Luciferase Reporter virus based neut assay; Fluorescent antibody cell sorter-based)
- Identification of various cytokines/chemokines in response to infection/vaccination through ELISPOT
- Intracellular cytokine staining by FACS
- Immuno-phenotyping
- MHC Tetramer staining

2. Animal Studies

- Develop new EPF free Transgenic/Humanized Mice models utilizing knock in and knock out (KO) methodologies through different technologies for gene editing Immunization studies for establishing proof of concept or understanding the

immunological characteristics of the product by assessing the relevant immune response, e.g. humoral and/or cell-mediated immune response
- Design, Manage and/or conduct Challenge/protection studies in Transgenic/Humanized Mice and Non-Human Primate Models as applicable

3. **Support and Advise for clinical development**
   - Guide and support clinical trial plans/designs
   - Develop strategies for engagement of an enriched study population towards intended product outcomes
   - Identify and Manage partners engaged in clinical development

4. **Support and Advise for Product Licensure in Compliance with Indian and Global Regulations**
   - Develop a regulatory strategy and support preparation of related filings, e.g. pre-IND, IND (India, USA and International)

5. **Support and Advice in quality assurance and Project management through various stages of New Product Development**
   - Aid in Product development planning, including supporting development of Product Development Plan and Target Product Profile and provision of tools for monitoring of objectives vs. deliverables.
   - Aid in development of plans for process development, manufacturing and product characterization

6. Provide Project Management support along with Advise and linkages with partners to support activities through different stages of product development

TRC shall have strong and integrated link with GcLP laboratories for transfer and validation of assays in regulatory compliant environment and linkages with the Clinical trial network would be established to seek input into clinical development plans and access to a well-studied and characterized population

Proposed Impact

- Enhancing early development capability, generating new ideas and technologies by building suitable networks of collaboration
- Establish a continuum to foster future innovation by building a translation ecosystem for taking the research forward to clinical development or at a stage of collaboration with industry.
- Additionally capabilities would be built for discovery novel mAbs for infectious diseases and developing assays for vaccine evaluation particularly to support current products in pipeline.

2.2. Supporting Bio-therapeutics (Novel and Biosimilar Antibodies and Therapeutic Proteins) Development

2.2.1. Specific Product Development

Background:

Global efforts to develop bio-therapeutics (therapeutic proteins and monoclonal antibodies) have given us many novel and effective products that have enormously improved human health with more than 135 bio-therapeutics being use in various indications. They offer an attractive solution in comparison to small molecule with longer circulating half-life, high target specificity and ability to induce the immune system thereby providing successful solutions against medical conditions that had no effective treatments till recently. Yet their exorbitant cost makes them inaccessible to the Indian population e.g. a full one-year course of Herceptin treatment for breast cancer costing about $70,000, advocating the need for cost effective solutions.

Biosimilars are a cost effective alternative to this, with a huge market potential (large number ofblockbuster biologics, mostly mAbs, worth $100 billion will be going off-patent by 2020). India with proven capabilities in this sector (more than 50 biosimilars being developed by 27 manufactures) has the business opportunity to capture the global market and increase its share from **3% to 5%** in next 5 years.

Yet challenges in the ecosystem such as exorbitant cost of attaining technology and cell line access from global players, inaccessible and/or unaffordable facilities for standard characterization and pilot-scale manufacturing ; lack of operational support for SME's; regulatory hurdles and delays; support for clinical trials contribute to delays and increased cost of product development. Hence there was a need realized to provide solutions to strengthen the biopharmaceutical industry to enable production of large quantities with cost and time efficiency without compromising on quality.

Objective:

The objective of the Program would support development of 2-3 biosimilars (therapeutic proteins and monoclonal antibodies)that are currently under development by the industry and bring them closer to the market in 5 years and simultaneously develop an ecosystem that would spur innovation to develop novel products.

Product selection:

Selection of candidates for support was carried out through a sequential mechanism. From an initial list of 135 bio therapeutics that could be developed as biosimilars in India, filtering was done based on various parameters including impact (public health, market feasibility), probability of success (scope for licensure, product leads available) and inputs from experts (industry, academia and Government representatives) that led to shortlisting of 5 bio therapeutics that address critical diseases of public health concern including cancer, diabetes and rheumatoid arthritis.

Selection of candidates for support for each of these diseases would be based on quality and risk assessment of the technology and the process being developed.

Program Strategy:

The proposed strategy is to create an environment that would enable design and development of affordable and effective bio therapeutics in the next 5 years. The multipronged approach is to:

- Direct funding to 2-3 biosimilarsthrough the various stages of biosimilar development including, preclinical development, early production of clinical grade material and early phase human clinical trials.
- Setting up of a Product Development Unit (PDU) that would bring together a group of experts and help set up a strong product management team by the manufacturer. In addition to provision of funds BIRAC shall also provide the applicant access to a group of experts from industry and academia with relevant expertise that would ensure completeness and feasibility of the product development plan, help define and streamline R&D pathway for efficient and quicker product development
- Access to the following affordable services and solutions supported through the i3 program:
    - A GMP-compliant Cell Line Repository for providing access to cell lines (mammalian, microbial) and expression systems that are tested, validated and well-characterized
    - A GcLP compliant facility for biosimilar characterization, evaluation and validation in preclinical and clinical stages of development.
    - A Process Development Laboratory that would enable manufacturing process of bio-therapeutic products (monoclonal antibody and therapeutic protein) with high titers, cost and time efficiency and desired quality standards.
    - A GMP compliant CMC facility for development of preclinical and clinical lots of biosimilar and novel monoclonal antibodies; generating relevant data (assays for product characterization and release, assays for in-process controls, stability testing) and provide support for regulatory documentation towards fulfilling the CMC requirements for IND submission (product release criteria, manufacturing facility details, product specifications, batch record review etc.)
    - Creation of strategies and plans for clinical trial plans/designs and engagement of an enriched study population towards intended product outcomes
    - Development of a regulatory strategy and support preparation of related filings
    - Development of Product Development Plan and Target Product Profile and provision of tools for monitoring of objectives vs. deliverables.
- Stimulate development of novel mAbs and & corresponding novel assays through setup of collaborations such as the Translational Research Consortia that would enable identification of new targets and immune factors.

Success Parameters:

Given the above efforts, it is anticipated that at the end of five years, the following impact would be perceptible:

- Progress of two-three biosimilars would be accelerated along their development pathway, subject to their current stage of development; for e.g.: products that have proof of concept established and are currently in Pre-clinical stages of developmentwould be accelerated till late phase clinical trial and late stage manufacturing;

- Establishment of a continuum that spurred future innovation and assisted in development of pipeline of products and lowering cost of product development;
- Identification of targets and antigens that have enabled manufacturers to develop novel mAbs;
- Development of novel technologies and assays that enabled efficient and effective characterization and production of biotherapeutics.

2.2.2. Building Shared Facilities

2.2.2.1. GLP labs for antibodies

Background

Monoclonal antibody development is a time taking and resource intensive with high rate of failure due to lack of efficacy and safety in later stages of development. While for biosimilars – the 'generic' version of novel bio therapeutics, establishing comparability to the original drug is a rate limiting step owing to the complexity of molecules. Major issues are:

- Since the biological activity is closely linked with structure, conformation, and chemical stability of the molecules, need for high end bioanalytical and biological characterization becomes critical, particularly for biosimilars, where clinical trials are not extensive
- Availability and accessibility of appropriate sites with a suitable infrastructure for early biotherapeutic development (including ability to conduct validated clinical assays, analytical support for establishing early proof of concept establishment)

To address this 'lagging science of product development' this Program will establish GLP/GCLP (like) validation facilities by bridging the gap between academic scientific research and commercial product discovery and development.

Objective

Establish regulatory compliant, affordable and accessible facilities that would work with leading academic and industry partners to provide integrated solutions to enable proof of concept establishment, critical evaluation and validation of mAbs (novel and biosimilar) by:

i. Providing access to validated assays for characterizing and establishing proof of concept of novel mAbs to Advance research and development of mAbs in preclinical stages and

ii. Conducting robust bio-analytical and functional characterization to prove comparability of biosimilars against reference drugs

The value proposition of this is to provide equal-opportunity nationwide access to state-of-the-art high throughput equipment, technical support, and cross-training for the production and analysis of high-resolution data.

The GCP Validation lab and the Translational Research Consortia would have strong and integrated link where the new technologies (novel products/assays/biomarkers) that are developed through the Translation Research Consortia would be integrated and validated as per regulatory standards in the GLP validation lab, while the honed infrastructure and

expertise from the lab would support the consortia. Additionally, it would assist the CMC facility in conducting analytical assays for product characterization.

Scope
The facility would conduct:

- Bio-analytical characterization using state-of-the-art technology to assess physicochemical characterization, purity, impurities and contaminants determination, aggregation studies and stability studies
- Appropriate studies for functional assessment like binding affinity estimation, breadth & potency assessment by antibody neutralization and effector function estimation

Proposed Impact
- Setup of a Global standard service facility that would have validated and established assays for product in pipeline, that are currently unavailable in the country
- Enabling quicker clinical validation and faster market reach by providing efficient validation of products
- Increase in chances of developing indigenous novel products by building and upgrading indigenous capabilities
- Affording lower cost of development for mAbs in the pipeline by decreasing capital investment, aiding effective resource utilization and reducing risk of failure

2.2.2.2. Chemistry, Manufacturing, Control Units

Background
Inherent challenges in advancing novel products from basic discovery through the preclinical-to-clinical translation process include a complex technological landscape requiring expensive specialized facilities and demanding regulatory requirements, withCMC related issues often being the root cause of clinical delays. Major issues are:

- Given that the quality of process defines the quality of product for biopharmaceutical, any process change significantly impacts clinical trial results leading to need for additional studies and delay
- Lack of integration between clinical and CMC development plans
- Clinical assays not performing robustly and/or not validated in later stages
- Availability and accessibility of appropriate sites with a suitable infrastructure for early biotherapeutic development (including ability to develop pilot/clinical trial lots, analytical support for establishing specifications and release criteria, performing feasibility assessments and aid for product development plan)

Chemistry, Manufacturing, and Controls (CMC)[2] help expedite early development by utilizing scientific and regulatory expertise to craft a streamlined program for the manufacturing and testing of novel products. In addition to providing the appropriate information to regulatory authorities, CMC oversight identifies and manages issues to reduce costly delays and setbacks and ensure development remains on track.
The CMC facility equipped with a robust understanding of the regulatory framework would provide end to end support to enable regulatory documentation towards fulfilling the CMC requirements.

Objective:
Establish a GMP compliant CMC facility to provide services for development of preclinical and clinical lots of biosimilar and novel monoclonal antibodies; generating relevant data (assays for product characterization and release, assays for in-process controls, stability testing) and provide support for regulatory documentation towards fulfilling the CMC requirements for IND submission (product release criteria, manufacturing facility details, product specifications, batch record review etc.)
The CMC facility would link with other i3 program components including the Process Development Lab for transfer of the production cell lines, the process for manufacturing and the analytical methods and the GLP validation lab that would assist in conducting analytical assays for product characterization.

Strategy
Technical and infrastructural support to bridge existing gaps impeding early development of monoclonal antibodies currently in pipeline in India with the following services:
I. Pilot Scale GMP Analysis and Manufacturing Core, including activities like:

- Process optimization and standardization
- Pilot batch manufacturing with appropriate in process testing for upstream processes (monitoring cell growth, harvesting etc.) and for downstream processes (inactivation, purification, stability processing and detoxification)
- Ensure quality of production through measuring yield and product quality during fermentation and harvest
- Conduct characterization of manufacturing processes in detail including the nature and performance of the specific equipment used for every step of the manufacturing process

II. Analytical Assay Core:

- Conduct method validation as per ICH guidelines (ICH Q2(R1))

[2]Chemistry, Manufacturing and Controls (CMC) asdefined by the USFDA includes activities related to chemistry (product characterization, product release andstability testing), manufacturing (manufacturing facility, utilities, process equipment and materials, manufacturing personnel, manufacturing process) and controls (in-process controls, product specifications, product expiration dating, documentation, batch record review, auditing).

- Conduct stability and safety studies for evaluating production cells (through gene copy number estimation, consistency of expression, stability of the genetic markers under the conditions of propagation; and ensuring cell lines are free from adventitious agents);
- Ensure robust product characterization, determination of specifications for product release testing and quality control of monoclonal antibodies and related substances.

III. Technical Management and Regulatory Support:

- Support and Advise for Product Licensure in Compliance with Indian and Global Regulations
    - Develop a regulatory strategy and support preparation of related filings, e.g. pre-IND, IND (India, USA and International)
- Aid in documentation and preparation of regulatory dossiers as per relevant ICH guidelines for CMC submission (ICH Q8, Q9, Q10)including:
    - Information to assure the identity, quality, purity, strength and stability of the drug product
    - Information on controls including process controls, consistency, and specifications, product expiration dating, documentation, batch record review
    - Information on manufacturing including details of manufacturing facility, utilities, process equipment and materials, manufacturing personnel and manufacturing process

Proposed impact

Given the above efforts, it is anticipated that at the end of five years, the following outcomes would be perceptible:

- Establishment of a Global standard service facility that would have effectively produced of clinical trial lots for one product
- Bringing down the associated costs and facilitating quicker initiation of clinical trials due to decrease in attrition rate in late-stage manufacturing as well hedge risk by deferring investment in in-house capabilities until the proof of concept is vigorously tested
- Availability of analytical toolkit that meets the qualification and validation expectations of regulatory authorities for researchers and manufacturers
- Establishment of a continuum that spurred future innovation and assisted in development of pipeline of products;
- Enhanced outsourcing capabilities

2.2.2.3. Cell line Repository

Background

Access to well characterized cell-lines is one of the prominent issues faced by manufacturers and entrepreneurs developing biopharmaceuticals products. Currently cell lines either have to be ordered from cell banks overseas (that have challenges like prohibitive shipping costs, time delays and customs issues); bought from companies (with high cost of licensing fees and

royalties) or are sourced from other academic labs (risk of misidentification and purity).Hence it becomes critical to establish a central cell repository of global standard that specialize in the authentication, production, preservation, and secure distribution of biological materials.

Objective

To create a GMP-compliant Cell Line Repository for providing access to cell lines (mammalian, microbial) and expression systems that are tested, validated and well-characterized for use in process development, evaluation, assay development and manufacturing of biosimilars, novel monoclonal antibodies and vaccines.

The repository would acquire cell samples from other globally recognized repository organizations or a commercial or research entities; and supply high-quality, uncontaminated, well characterized and well-documented cell lines at affordable cost to manufacturers for further product development. This unit would also link with other i3 program components - the Process development laboratory, CMC facility and the Consortia for Novel cell line development.

The repository is expected to stimulate biopharmaceutical product development by encouraging innovators and manufacturers, through the easy availability of high-quality, reliablecell lines to develop novel products that could otherwise not be done due to a lack of access, high cost and other legal and IPR issues.

Strategy

Cell Line Repository would be a GMP compliant that would:

1. Acquire cell lines such as:
    a. Mammalian cell lines (CHO cell based cell lines, NS0, HEK, Sp2/0, GS (---/---), Per.C6);
    b. Microbial cell lines (E. coli (BL21), S. cerevisiae, Pichia pastoris) and
    c. Expression systems (CMV promoter enhancer, DHFR negative cell lines, GPEX Technology)

2. Conduct quality control testing and characterizationin compliance ICH regulatory guidelines (ICH Q5D) such as:
    a. Authentication (STR profiling; isoenzyme analysis or sequence-based barcoding; cytogenetic analysis);
    b. Phenotypic characterization (viability, cell morphology, doubling time, receptor status, protein secretion);
    c. Purity (cells are free of adventitious agents primarily mycoplasma, bacteria, and viruses)

3. Maintain and store cells with capabilities for safeguarding, generating aliquots, storage of duplicates at a remote site, freezer failure back-up plan, and other contingencies.
4. Distribute cell lines at nominal charges and provide additional services (e.g. c*haracterization of cell lines)* as determined by the i3 Program management

5. Develop and provide relevant documentation with detailed information on each cell line and DNA sample (such as name, typology, karyology, morphology, origin, properties, culture characteristics, immunological profile, cytogenetic analysis etc.)

Impact

- Set up of fully regulatory compliant accessible and common facilities
- Providing access to well- characterized cell lines that would provide reliable qualified, and low-priced biological materials for advancement of basic research and process development & manufacturing of biopharmaceuticals
- Decreased dependence on global banks and private suppliers that would help in cost cutting by reducing cost of licensing fees and royalties

2.2.2.4. Process Development Laboratory

Background and Problem Statement:

The continuous increase in the number of approved biotherapeutics suggests that therapeutic proteins, mAbs, and their derivatives, will continue to be the focus of the biopharmaceutical industry for years to come. With longer circulating half-life, high target specificity and ability to induce the immune system,biotherapeutics offer an attractive solution in comparison to small molecules. Yet their exorbitant cost makes them inaccessible to the Indian population e.g. a full one-year course of Herceptin treatment for breast cancer costs about $70,000, advocating the need for cost effective solutions.

Although there have been vast improvements in capability to manufacture, characterize, and stabilize them, there are still challenges to be overcome. MAbs have high effective dose as compared to other drugs and require availability of large quantities of the product with quality, cost and time efficiency to meet market demand. Maintaining desired quality attributes as per regulatory standards, while reducing time to market and sustaining cost effectiveness is a critical hurdle.

Process development and optimization is hence a critical step to ensure that high titers are being achieved along with maintaining product quality and process consistency.

Objective:

Establish a Process Development Laboratory that would enable manufacturing process of bio-therapeutic products (monoclonal antibody and therapeutic protein) with high titers, cost and time efficiency and desired quality standards. It may develop, modify or adopt methodologies for improving and optimizing biological, technical, engineering aspects of the process to broaden the experimental design space and lower the cost of process development.

This unit would link with other i3 program components - the Cell Line Repository for access to well-characterized cell-lines and the CMC facility to transfer the process for manufacturing and the analytical methods for development of preclinical and clinical lots in GMP environment and regulatory documentation towards fulfilling the CMC requirements.

To establish the innovation continuum and be a link for researchers/innovators to connect with the manufacturing partners (CMOs/CMC facility), the lab would also provide support for feasibility/developability assessment, target product profile (TPP) development; identifying critical quality attributes (CQA) and critical process parameters (CPP) and formulating a robust process, analytical and regulatory strategy.

Program Strategy

Process Development Lab would support in developing cost effective, high titer and regulatory standard process for novel monoclonal antibodies and therapeutic proteins manufacturing through activities such as

i. **Cell line development -** Generation of a suitable genetically-modified, engineered cell line capable of producing a monoclonal antibody/therapeutic protein with sufficiently high productivity.

ii. **Preliminary Analytical Method Development -** Development of appropriate analytical methods to confirm that the right product is produced by the candidate cell lines and the final selected cell line; support cell culture and purification development and identifying any critical process parameters that should be monitored or controlled to ensure that the product is of the desired quality.

iii. **Process Development and Optimization –** Optimize and streamline various process steps that delivers reliable and efficient product yields (final up to 200L), and reduces the time and cost of production by improving yields, reducing upstream and downstream development times, minimizing risk of failure, ensuring consistency and curtailing wastage.

iv. **Technical Management and Product Leadership Support**

- Conduct robust 'Develop-ability Assessment' or 'feasibility assessment' for state of readiness for process development of molecules that have established proof of concept
- Develop a Process Development plan (outline of process to advance the candidate from the research stage to manufacturing for Phase 1/ early Phase 2 clinical evaluation) in collaboration with the selected CMO/industry-partner/CMC facility; define the Target Product Profile (TPP) of the candidate with researchers/innovators, define critical quality attributes (CQA) and critical process parameters (CPP) and propose specifications and define the release criteria at a later stages of manufacturing,
- Develop a quality assurance protocol and conduct analysis at all the stages of in alignment with regulatory requirements to meet the pre-defined specifications and ensure consistency and quality of the process and product
- Conduct on-site GMP audit of the CMOs/CMC Facility to assess their quality system and identify any non-compliance to aid in selection of appropriate manufacturing partners and ensuring regulatory compliance of the product.
- Enable linkages at early and late stages (Phase 1 and early Phase2) with CMOs/CMC Facility for manufacturing for pilot scale and/or large scale lots and provide technology transfer support.

Impact of the Unit

Given the above efforts, it is anticipated that at the end of five years, the following impact would be perceptible:

- Development and adoption of efficient bio-manufacturing process to aid manufacturing of novel mAbs.
- Reducing operating costs.
- Increasing efficiency of production (yield, minimizing loss in primary recovery and purification).
- Improved process consistency and robustness.

Success Parameters

- Development and successful transfer of a MCB and WCB and the manufacturing process for a bio-therapeutic.
- Provided support to manufacturing facilities
- Reducing cost and easing the product development pathway that has contributed to the accelerated development of biosimilars candidates supported for manufacturing for the i3 program.

2.3. Consortia for Novel Cell-line Development

Background:
The number of biologics produced using biotechnological procedures is growing continuously with the world market for biotherapeuticsbeing estimated at $80 billion per annum. Driven by production demands and unmet market needs, there is a need to engineer stable cell lines to produce increased yields for a range of biotherapeutics including recombinant proteins and monoclonal antibodies. Additionally exorbitant cost and difficulties of attaining technology access from global players add to the cost of product development. The science of cell line development is complex and requires balance of investments in platforms, technologies, and personnel to meet the increasing production demands within shortened development timelines.

The focus of the Program is to streamline workflows between research and manufacturing by strengthening the capabilities across the continuum starting from development novel cell lines, storing and maintaining the cell lines that can then by sourced for further manufacturing via developing working cell banks and process optimization.

Towards the above, the Program would hence develop consortia by consolidating current expertise for discovering novel cell lines, expressing system and phages.

Objective/Strategy:
Setup a consortia to enable discovery and incremental improvements in host cell lines, cell line engineering, expression systems, and vectors, promoters for improving titer and product quality and enhancing speed-to-market and cost reduction using next generation genome editing and –omics based technologies. This would assist in drug discovery, cell-based assays and manufacturing for a range of biotherapeutics including recombinant proteins and monoclonal antibodies. Exemplary methodologies are:

- Increasing expression of recombinant proteins through methods involving strong promoter/enhancers, selective markers, inducible expression systems, reduce lactate accumulation
- Enhancing viable cell density by targeting diverse cellular functions such as apoptosis, autophagy, proliferation, regulation of cell cycle, protein folding, protein secretion and metabolites production
- Enhancing product quality by glycoengineering technologies with enhanced ADCC activity

Characterization of the cell lines would be done by providing a set of information including source, purity, strain identity, genetic stability on which the quality assessment of the cell lines can be done successively.

The well-characterized novel cell lines generated would be transferred to a central cell repository for development as MCB and further procurement by manufactures, academia and other users. Linkages with other Program components would be established based on the purpose of the cell lines e.g. cell lines for assays can be taken up GCLP labs while cell lines

for production sourced by Process development lab for further transfection and process optimization.

Proposed Impact:

- Creation of consortia for developing novel indigenous cell lines and enhancing indigenous capabilities for improved process development for biopharmaceuticals
- Development of novel cell lines and expression vectors
- Decreased dependence on imported cell lines and development of indigenous capability that would help in cost cutting and reducing cost of product development by avoiding licensing fees and royalties.

2.4. Medical Device and Diagnostics

Background:

The Indian healthcare industry is growing at a tremendous rate and simultaneously going through transformation across the continuum. With the approval of National Health Policy 2017 by the Government of India, healthcare expenditure intends to increase to 2.5% of gross domestic product (GDP) and India embarks on a planned approach to bridge the healthcare divide while maintaining industry competitiveness.

The medical device sector represents 9% of the overall Indian healthcare industry. The Indian medical device sector is worth approximately USD 5.5 Billion and is growing at 15% CAGR. Indian medical devices market is the 4th largest in Asia and in the list of top 20 in the world. The global medical devices market has been growing exponentially and Indian companies have also been capitalizing on their indigenous capabilities. Despite significant progress, there are certain challenges such as import dependency and unsuitable devices that have been designed for use in industrialized countries. The medical device market is dominated by imported products, which comprise of around 75% of total sales.

This advocates for a critical need to channelize efforts towards promoting the medical device sector and focus on development of innovative and affordable medical devices and diagnostics relevant to the Indian public health needs, making it one of the key focus areas of the Program

Indian government is making serious efforts to uplift domestic manufacturing of medical devices, the i3 program can give boost to the efforts of BIRAC and GoI towards “Make in India” initiative.

Objective:

The objective of the Program is to develop Core Technologies in the medical device segment. Proposed innovations must be strategic, product oriented, application based and transformational which has potential to make a substantial and equitable impact on improving domestic manufacturing of associated medical products. The proposed innovations are expected to:

- Enable indigenous manufacturing of core technologies
- Improve compatibility with existing medical devices
- Are safer and/or cost effective replacements to current choices

Product selection:

A systematic approach is followed for the selection of critical technologies that will lead to developing complete know how of Core medical device Technologies that could support critical and/or multiple medical device product segments.

The first level of guidance is obtained by stakeholders meeting wherein a diverse group of experts in the medical device and diagnostics space in India, including players ranging from industry, SMEs and start-ups, experts from academia, funding agencies, incubators, regulators and Government representatives participated. On the basis of these, detailed

landscaping exercise is performed. The matrix approach followed for the landscaping considers disease burden of top five communicable and Non – communicable diseases in India. The general medical and diagnostic devices are mapped for these top five diseases. The priority list obtained from such mapping are than compared with the high import and low expert ratio of the Country.

The landscaping document was further validated by conducting technical consultation meetings which is attended by 50 industrial, research & start up representatives. The main objective of the consultation meeting is 1. Identification of core technologies and their respective product segments reflecting the burden of disease and trade economics of India and 2. Identification key technological barriers towards focused research & innovation (R&I) furthering their manufacturing in India.

Through the technical consultation meeting 108 core technologies across 15 product segments were identified and Component level technological barriers were identified along with facility needs to accelerate their research. These 108 core technologies are further narrowed down to 10 most critical medical devices to be included in the i3 program.

Program Strategy:

The proposed program strategy is to accelerate development of medical devices and diagnostics in the country which can be achieved incrementally by development of 4-6 core technologies, which will be platform technologies and can be used in various product segments leading to development of at least 10 -12 indigenously developed medical devices.

The current strategy is to support industry/academia/SMEs and start-ups across the development value chain (i.e., early product development, product validation, manufacturing, clinical development).

The Non-incremental approach towards the program strategy is addressing critical gaps that will aid in accelerating the development process like facilitating access to facilities (e.g. for pre-clinical and clinical validation) developing collaborations for technology development and providing trainings in areas of skill gaps. It also includes providing access to a group of experts from industry and academia with relevant expertise that would help define and streamline R&D pathway for efficient and quicker product development; pooling available resources and access to technologies.

The program will also facilitate collaborations such as with clinical Investigators and clinical partners to facilitate the clinical investigation / validation of the products. Connections with regulatory consultants and regulators to provide guidance on regulatory pathways will help to clear the regulatory hurdles and bringing the product to market ready level.

Success Parameters:

- Creation of a holistic ecosystem in the country for the sunrise sector of medical devices, thus enabling cost effective manufacturing also for developing futuristic and innovative products, processes and new technology with emphasis on indigenization. (Make in India).

- Providing turnkey and total solutions to industry to start manufacturing new products.
- New product development and sorting out technology related issues to enhance productivity and quality of products manufactured by the industry for exports.
- Development of 4-6 core technologies, which will be platform technologies and can be used in various product segments leading to development of at least 10 -12 indigenously developed medical devices
- Reduction in the import dependence for health care sector and facilitating manufacture for exports in the long run, by promoting development of necessary machinery/equipment related to the sector.
- Support for effective health care services to the common man and promoting manufacturing under make in India. Service Providers – enabling the growth of testing and manufacturing facilities not hitherto available in the country.

2.5. Clinical Trial Network

Background

As the Biotechnology market in India continues to grow and become more complex, their relationships with academia and universities continue to evolve. The industry in India, while is strong in manufacturing low cost goods of generic products, does not invest in resource intensive R&D. On the other hand, cutting-edge research being done in academia rarely gets translated into products due to lack of product-oriented discovery and translational capabilities

A major bottleneck, especially for entrepreneurs, small- and medium-scale enterprises and academic labs is translation of biopharmaceutical product candidates from discovery research through to preclinical and clinical development. Even for larger industries, development of biopharmaceuticals is a resource intensive process that requires huge amounts of investment and deters development of innovative products particularly to conduct clinical trials.

Issues hindering conduct of clinical development are:

- Access to healthy subjects, well defined and characterized geographically diverse patient population and communities (including disease incidence and transmission indices, subject recruitment and retention rates, behavioural and immunological characteristics of target populations etc.) necessary for design and implementation of efficient phase 2/IIb/III clinical trial designs.
- Competent and qualified Principal investi g a tors (PI's) and participating investigators registered with the CDSCO.
- Availability of appropriate sites with a suitable infrastructure for biotherapeutic studies (including ability to collect, process, store and ship laboratory specimens; handling of product that requires refrigerated storage; providing counselling and referrals to relevant community services; and comply with regulatory needs with regard to protection of human research subjects; and performing clinical assessments and documenting medical findings).
- Availability of a network of clinical research sites that can aid in enhancing the speed of implementation of clinical trials in a cooperative, transparent, and interactive environment.

Objective

Develop a coordinated a network of suitable clinical trial sites in India with a fair geographical distribution and devoid of public and private sector influence that can conduct regulated clinical trials of bio therapeutic products supported through the i3 Program. The goal is that each of the sites of the network under a competent PI has suitable infrastructure as per regulatory and product needs and access to a well-studied and characterized population for phase II/III studies.

The established network through this Program will function through effective linkages with institutions/industry where innovation related projects are implemented. It shall also have strong and integrated link to the translational research consortium and GcLP laboratories set up through the i3 program that would enable the manufacturers funded through the i3

program:

- Seek input into clinical development plans
- Design of clinical trial protocols
- Access to a well-studied and characterized population
- Development of standardized assays for monitoring product efficacy and suitability to the Indian population.

A Scientific Advisory Board set up under the i3 program for establishment of this network consisting of renowned global and national experts shall not only help in establishment of suitable sites within the network and coordination mechanisms but shall also guide in seek specialized expertise (e.g. clinicians, educators, and statistician) and global collaborations on a need basis.

Proposed Impact

- Creation of an accessible network of clinical experts and sites for conducting clinical trials (product dependent)
- Enabling efficient clinical trial design and implementation
- Ensuring of a reliable and robust clinical validation of products ensuring safety of Indian population.

2.6. Training and Skill Development

Background and Challenges

India has been an active player in the pharmaceutical industry, but accounting for only ~3% of the total $156B, India also has a lucrative opportunity to grow and capture the global biopharmaceutical market. The availability and quantity of skills and talent is seen as a key prerequisite to meet this demand and ensure global competitiveness, continued investments and sustainable employment in the sector.

The Biopharma sector in India has several key strengths including an international reputation based on low cost manufacturing capabilities - with industry skilled in bioprocess, analytical characterization and cell line development. While understandably, the academia has strong capabilities in discovery particular in areas of molecular biology, computational biology, and immunology, but the talent spread across the areas of next generation skills such as proteomics, systems biology, genomics, high throughput screening, and structural biology is accompanied by lack of availability of trained workforce who are well exposed and well versed with industrial skills. Critical gaps for both academia and industry lies in the translational space where lack of technical skills like peptide synthesis, assay development, NGS sequencing delay translation of novel molecules to clinical and manufacturing stages.

Global and domestic drivers of growth are impacting on Biopharmaceutical skills demand. These includes the general challenge of achieving innovation and operational excellence, maintaining global standards of product and process compliance, regulatory knowledge, intellectual property reading and legal expertiseand delivering on the specific skills required for both Pharma and Biologics manufacturing.

There is also both a challenge and an opportunity for the Biopharma academia and industry, working in collaboration with education and training providers and other stakeholders, to increase awareness of the range of careers available in the sector and attract a greater share of available graduates from the fields of science, engineering, and business studies. There is also scope to upskill jobseekers, continue the upskilling of those already working in the sector, and to attract international talent to India to increase the depth of experience in companies.

Objective

Through close engagement and collaboration of companies and academics in the design and delivery the training programs generating next-generation of trainers and leaders. By targeting young professionals (30-40 years), build proficiency in product design and develop, ensure a supply of talent for the facilities being developed through the i3 Program, particularly for translational research, manufacturing and discovery of novel molecules and simultaneously elevate India’s capabilities to a level that will make it globally competitive over the next decades.

The focus areas of trainings would be prioritized based on consultations with the Technical Advisory group involving national and global experts across industry and academia. Further, other specific training needs would be fulfilled for enabling different components of the

program (as may arise during the course of development of products, establishment of facilities, Clinical trial networks, consortia, TTOs).

Exemplary training areas are:

Stage of Product Development	Skill gaps
Discovery	Next generation skills like proteomics, genomics, High Throughput Screening, big-data analytics, systems biology, bioinformatics, structural biology, biophysics
Validation	Bioanalytical development, peptide synthesis, PK-PD studies, assay development, among others
Bio manufacturing	Upstream and downstream process development, cell line development, quality assurance, formulation
Clinical evaluation	Clinical trial study design and execution, on-site trial capabilities
Other Non-technical areas	Science communication and grant writing Compliance in GLP, GMP and GCP norms Regulatory knowledge Intellectual property reading and legal expertise Management skills : Project management, business development

Program Strategy

The functional unit responsible for ensuring implementation of trainings would comprise of training partners (industry and academia) that would structure training modules and provide relevant trainings. Existing national and international training institutes would be selected on the basis of institute's capability aligning with the training need.

The trainees would be selected through a thorough selection procedure to ensure that people who are competent and if supplemented with appropriate skills, could have a considerable impact on product design and development and improve their career prospects. In this regard, depending upon the area of training, the target populations could include the following:

- Academic researchers (PhDs and Post-docs)
- Academic pass-outs willing to join industry (post-graduates and PhDs)
- Industry employees involved in product development
- Facility staff
- Trial site investigators
- Entrepreneurs
- Training staff

Further, the training structure would also be dependent on the focus area of training and may include short-term classroom sessions, on-site trainings or a combination of both.

Proposed Impact

- Training ~100 people in key critical skill areas through various modalities
- Spurring next-generation of trainers
- Creation of high-end workforce for product development and able staffing of facilities
- Enabling innovative thinking & cross learning
- Empowering next generation entrepreneurs
  - Building scientific leadership
- Enabling proficiency in intellectual property support and management

2.7. Technology Transfer Offices

Objective

Enhance academia-industry inter-linkages, strengthen biocluster ecosystem and provide increased opportunities for academia to translate knowledge into products and technologies through the following activities:

- Developing linkages with academic centers for setup of TTOs
- Acquisition of professionals with knowledge of technology transfer
- Provide assistance for acquisition and adaptation of technologies
- Creation of IP awareness

Program Strategy

TTOs would be setup in regions that are already established or are upcoming bioclusters. They could be setup either as one office serving multiple institutions/universities in a region or one TTO within each selected university, depending on the quantum of technologies being developed. They would be strengthened so that they become self-sustainable through technology licensing, transferring technologies to industries and establishing new spinout ventures. The selected centres would be funded for acquisition of personnel skilled in following areas:

- Intellectual assets protection, technology transfer and licensing
- Legal expertise
- Expertise in outreach to industry for technology dissemination and post commercial monitoring for technology deployment

Proposed Impact

- Set-up of 8-10 TTOs equipped with skilled professionals at key biotech clusters
- Creation of a platform to academia for patenting and to industry to access new technologies and innovations
- Promoting industry-academia collaborations
- Enabling access to IPR data
- Strengthening existing biotech clusters

3. Program Implementation

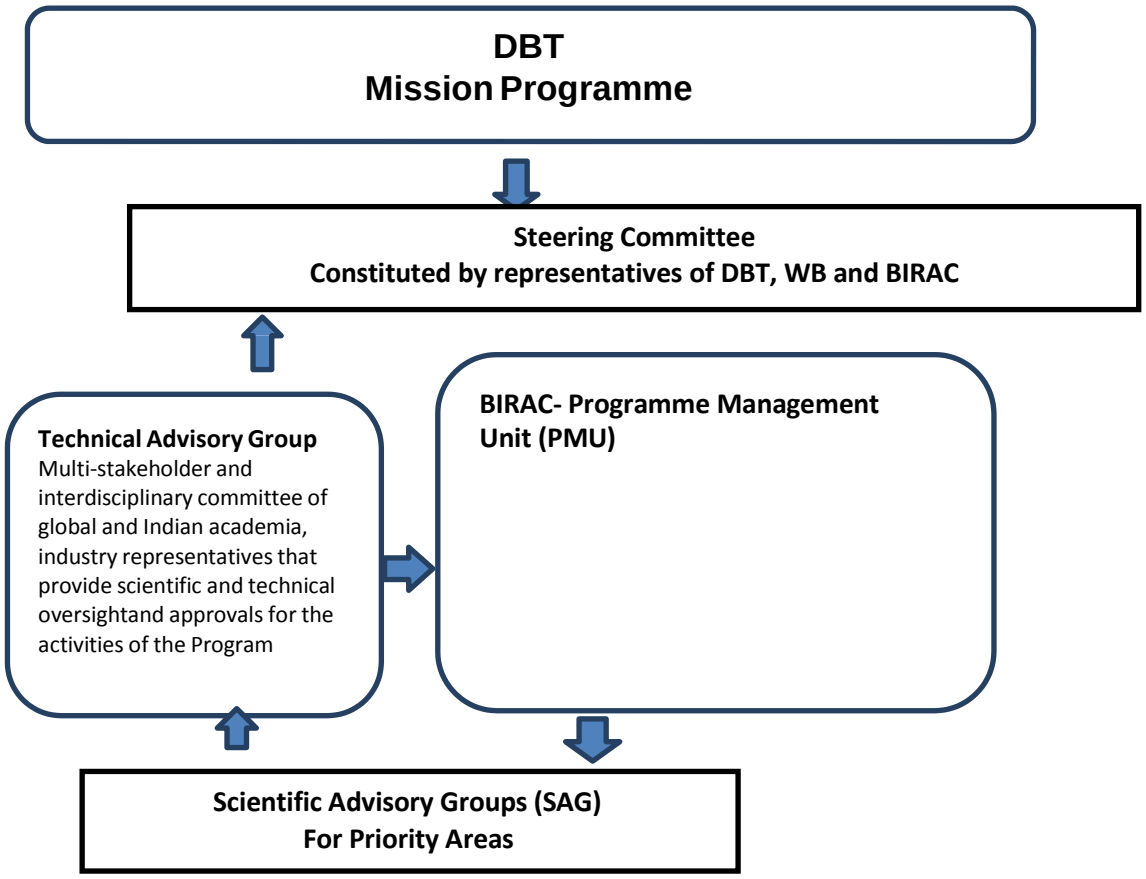
3.1. Implementation and Governance:

Mission of Department of Biotechnology Ministry of Science & Technology, Government of India; will be implemented by Biotechnology Industry Research Assistance Council (BIRAC) a Public Sector Undertaking of DBT at total cost of US$250 million over a period of 5 years. For this a Project Management Unit will be set up.

Oversight of the mission will be by the Steering Committee which would be an Apex level committee headed by Secretary, Department of Biotechnology as Chairman and with representation from Department of Biotechnology (DBT) and other concerned Ministries/Departments and Stakeholders. The Steering Committee (SC) will play an important role in ensuring successful delivery of the program in alignment with the overall vision and goal including maximizing the benefits and ensuring the effective and efficient management. Members of the Committee would provide cross-functional leadership and direction.

There would be Technical Advisory Group (TAG) chaired by an eminent scientist with participation of representatives of all concerned ministries / departments and stakeholders including World Bank and national and global experts. The TAG would provide scientific leadership to the mission drawing upon global expertise.

In addition a Scientific Advisory Group (SAG) will be constituted for each of the activities/product development partnerships. This will be a Multi-stakeholder and interdisciplinary committee of national and global experts and Key opinion leaders (KoL)including eminent scientists, industry representatives and other experts that have proficiency in product development and innovation sector will provide scientific oversight to the program and review scientific progress of its components; facilitate engagement with experienced, neutral, external facilitators to drive, monitor and advise on scientific strategies and solutions in alignment with the overall objectives; provide recommendations on priorities and facilitate acceptance of new strategies and solutions at any stage of the program.


DBT
Mission Programme
Steering Committee
Constituted by representatives of DBT, WB and BIRAC
Technical Advisory Group
Multi-stakeholder and interdisciplinary committee of global and Indian academia, industry representatives that provide scientific and technical oversightand approvals for the activities of the Program
BIRAC- Programme Management Unit (PMU)
Scientific Advisory Groups (SAG)
For Priority Areas

3.2. Governance Structure

The Program would be a scientifically driven enterprise, governed by a:

- *Steering committee (SC):*The SC is expected to play an important role in ensuring successful delivery of the Program by enabling effective and efficient management, in alignment with the overall vision and goals.
- *Technical Advisory Group (TAG):* A multi-stakeholder and interdisciplinary committee of national and global experts and Key opinion leaders (KoL) including eminent scientists, industry representatives and other experts to provide scientific approvals and oversight of the program and review scientific progress of its components.

  *Scientific Advisory Groups (SAG):*SAGs would be responsible for scientific decision making and provide the scientific and/or technical knowledge, judgment, scrutiny and oversight necessary TAGfor meeting the objective and ensuring successful implementation of the Program. Multiple SAGs, each anchored around a domain expertise would be responsible for specific Program components, and will be formed.

3.3. Decision Making Process And Parameters

The proposals will first be assessed for basic eligibility and compliance with the requirements of the RFP by the PMU. Further in-depth technical assessment in alignment with technical requirement of the RFP would be conducted by the PMU that along with the full proposals will be sent to the Scientific Advisory Group for final decision making. Each SAG member would rate the proposals on a pre-defined decision making matrix. The cumulative score from all the SAG members would decide the final grantee.

Grantees may also be invited for interviews or sought written clarifications when it is felt beneficial to ensure that any outstanding questions are resolved prior to concluding the full review.

Information (including “personal data”) provided in the Proposal will be used to process and evaluate the Proposals and to administer grant support, for the purposes of audit and evaluation and to monitor the fairness and trends in application decisions. Reviewers will be checked for conflicts of interest and sign confidentiality agreements. Information may also be shared with selected third parties for the purposes of independent audit, evaluation and assessment of activities. Some of the individuals, organizations and third parties with whom the information may be based outside of India. All personal data will be stored and used by or on behalf of DBT/BIRAC in accordance with the Acts and confidentiality norms.

Evaluation criteria

I. Screening and Preliminary review of the Proposal:
   - Completeness of the Proposal: All the components duly filled (details in section 9) with appropriate documentation
   - Basic eligibility:

- Legal requirements
- Aligned with the call objectives and requirements (detailed in Requirements in Section 3)

II. The Scientific Advisory Group will review based on the following parameters:

- **Approach and Methodology**

Ethical, scientific, scholarly, and financial standards in the promotion, design, conduct, evaluation and reporting of research.

1. Clarity of the research question.
    - Writing style that facilitates understanding of the plan
    - Objective/goals and reasoning clearly presented
2. Clarity of rationale for the research approach and methodology.
    - Appropriateness of the research design.
        - Best strategy chosen and alternative approaches considered
        - Well-integrated, well-reasoned
    - Appropriateness of the research methods
        - Consistent with the research design and best for achieving the desired research outcomes
    - Feasibility of the research approach
        - Project has clear and realistic plan, timeframe, work plan, budget, benchmarks
    - Literature review and preliminary data (If available) relevant to study design/research plan.
3. Anticipation of difficulties/risks that may be encountered in the research and plans for management.

- **Intellectual Property (if applicable)**
    1. Is there any background IP?
        - Relevance of the background IP for the proposed project
    2. Possibility of generating foreground IP
    3. Does the applicant have freedom to operate

- **Impact**

1. Potential for a significant contribution to the improvement of people's health in India and the world and/or to the development of more effective health services and products.
2. Appropriateness and adequacy of the proposed plan for knowledge dissemination and exchange - publication, dissemination amongst users , product related/commercialization

- **Organization credentials**

1. Qualifications of the applicant(s), including training, experience, demonstrated potential and independence (relative to career stage).
2. Experience of the applicant(s) in the proposed area of research and with the proposed methodology.
3. Expertise of the applicant(s), as demonstrated by scientific productivity over the years (publications, books, grants held, etc.). Productivity should be considered in the context of the norms for the research area, applicant experience
4. Appropriateness of the team of applicants (if more than one applicant) to carry out the proposed research, in terms of complementarity of expertise and synergistic potential.

Detailed Request for Proposal (RFPs) for projects will be issued by PMU, BIRAC.