Request for Proposals (RFP) for

A. Biosimilars Development
B. Shared Facilities Development of Biotherapeutics
C. Novel Cell Line Development

Under

Industry - Academia Collaborative Mission For Accelerating

Discovery Research to Early Development of Bio-pharmaceuticals

Innovate in India (i3) Empowering Biotech Entrepreneurs & Accelerating Inclusive Innovation.

Funded by

Department of Biotechnology, Ministry of Science & Technology,

Government of India

Co-funded through World Bank Loan Assistance

(Innovate in India for Inclusiveness Project)

through

Implementing Agency

Biotechnology Industry Research Assistance Council (BIRAC)

(A Government of India Enterprises)

Table of Contents

Section I - Program Overview - NBM

Industry-Academia Collaborative Mission For Accelerating Discovery Research To Early Development For Biopharmaceuticals - "Innovate in India (i3) Empowering biotech entrepreneurs & accelerating inclusive innovation", also referred to as National Biopharma Mission (NBM).

Funding agency

Department of Biotechnology (DBT) (Program co-funded by World Bank loan)

Implementing agency

Biotechnology Industry Research Assistance Council (BIRAC)

Background [1]

Towards strengthening the emerging biotechnology enterprise in India, Department of Biotechnology (DBT), Ministry of Science & Technology, has initiated the Mission Program entitled - An Industry-Academia Collaborative Mission for Accelerating Discovery Research to Early Development for Biopharmaceuticals – *"**Innovate in India (i3) Empowering biotech entrepreneurs & accelerating inclusive innovation**" ("Program").* Biotechnology Industry Research Assistance Council (BIRAC) setup by DBT is the Implementing Agency of *i3* Program (Program co-funded by World Bank loan) managed through a dedicated Program Management Unit (PMU).

The vision of the Program is to enable and nurture an ecosystem for preparing India's technological and product development capabilities in biopharmaceuticals including vaccines, biologics, medical devices and diagnostics to a level that will be globally competitive over the next decade.

This Request for Proposal (RFP) is to seek applications for the following:

A. Biosimilar Product Development

Applications are invited for development of Biosimilar Products and Biosimilar Clone Development.

B. Shared Facilities for Biotherapeutics Development

Applications are invited to set up facilities to address the needs of Biotherapeutic development.

C. Scientific Research: Novel Cell Line Development (Cell line engineering and Cell line development)

Applications are invited to establish a platform technology for production of Biopharmaceuticals

[1] *For further details of the Program, see the National Biopharma Mission Document*

Section II – Application process, Instructions, Applicant eligibility criteria and other processes for the RFPs at Section III and Section IV

1. Application Timelines

Key Dates

Call Opens	**30th December 2018**
Last Date of Submission	**15th February 2019 (5:00 PM)**

2. Application Guidelines and Process

The Proposal can be submitted online as per the required format. The call for the Proposal will be open for 06 weeks. The website will provide detailed user guide to facilitate the online proposal submission.

Process for submitting the proposals online is detailed below:

a. Go to BIRAC's website or Go the URL: http://birac.nic.in/nationalbiopharmamission.php
b. Click on the RFP on NBM link under Programs and the active call would be highlighted.
c. Click on the active call against which you wish to submit the proposal.
d. Further details on 'How to Submit a Proposal' would be available in the User Guide available on the website.
e. Log on to BIRAC website http://www.birac.nic.in
f. If you are a registered user, log-in using the credentials, else you need to register your company/organization by clicking on New User Registration.
g. In case of new user registration, a computer generated link will be sent to the email-id provided at the time of registration to generate a password.
h. Once you login, you will be navigated to the proposal submission page under NBM link.

Instructions:

a. Applicants are advised to fill-up and submit their applications early without waiting for the last date in order to avoid any last minute contingencies. The system stops accepting applications automatically after **5:00 PM** of the last date of submission.
b. Applicants are advised to provide sufficient details in their applications to allow for an informed and fair evaluation/review. Applicants are advised to provide self-contained proposals with essential supporting materials provided as uploads.
c. Requests for changes in the proposal once submitted will not be encouraged.
d. Providing incorrect information intentionally is viewed adversely.
e. Please read through this RFP in its entirety and ensure that your application, budget and organization are in compliance with the eligibility criteria provided. Proposals for projects that do not meet the eligibility criteria and/or do not directly respond to the call area will not be reviewed, regardless of their quality. You are strongly encouraged to contact BIRAC if you are unsure about the eligibility or responsiveness of your project.
f. Proposed budget shall be made inclusive of all applicable taxes and shall be considered accordingly.
g. Information on all relevant pre-existing agreements/ MoUs in connection to the proposed technology, background IP, collaborations, outsourcing, consultancy, joint

ventures, consortium partnerships, IP licensing, technology transfer, material transfer etc. should be provided at the time of proposal submission.

h. Risk management proposal for the project should be submitted after scrutiny of the execution aspects of the project.

3. Evaluation Methodology

a. PMU-NBM, BIRAC will screen the proposals for responsiveness to all the specified administrative and procedural provisions required in the RFP. If the application is found to be incomplete or unresponsive to the provisions described in the RFP, the application will be considered ineligible.
b. Proposals that meet the eligibility criteria will be submitted for peer-review by national and international reviewers to assess the proposal merit (and other review criteria as specified above). Reviewers will be checked for conflicts of interest and will sign confidentiality agreements. Information may also be shared with selected third parties for the purposes of independent audit, evaluation and assessment of activities.
c. The Scientific Advisory Group will collate the results of the reviews, make their own assessments and recommend shortlisted applications for further screening to the Technical Advisory Group.
d. Grantees may also be invited for interaction or sought written clarifications when it is felt beneficial to ensure that any outstanding questions are resolved prior to concluding the full review.
e. Technical and financial due diligence process (site visits) of the shortlisted applications would be carried out by PMU-NBM, BIRAC as part of the review process.
f. A final decision on applications to be funded will be made by the Technical Advisory Group.

All personal data will be stored and used by or on behalf of DBT/BIRAC in accordance with the Acts and confidentiality norms.

DBT/BIRAC reserves the right not to process your proposal should you be ineligible to be a proponent or should the subject of your proposal not fall within the RFPs' remit. Mere consideration of the Proposal in no way implies that sanction of Grant-in Aid will be forthcoming unless other legal requirements are fulfilled.

4. Eligibility Criteria

Who may apply?

The proposals can be submitted:

- Solely by Indian Company / LLP / Non-profit organizations / Society/ Trusts/ Foundation/ Associations/ Government entities/ Institutes/ R&D Organizations/ Bioincubator/ Industrial Zones which is a legal entity OR
- Jointly by Non-profit organizations / Society/ Trusts/ Foundation/ Associations/ Government entities/ Institutes/ R&D Organizations/ Bioincubator OR
- Jointly by an Indian Company and Non-profit organizations/ Government entities/ Institutes/ R&D Organizations / Bioincubator

Criteria Particulars for the Proponent entities

Indian companies

An Indian Company is defined as one which is registered under the Indian Companies Act, 2013 and minimum 51% of the shares of the Company should be held by Indian Citizens holding Indian passport [Indian Citizens do not include Person of Indian Origin (PIO) and Overseas Citizenship of India (OCI) holders].

Non-profit organizations/ Government entities/ Institutes/ R&D Organizations

This will include Academic Research Institutes, Universities, Research Foundation, Medical Colleges and Institutes – both public and private who are valid legal entities such as Trust, Society or established under central or state statute.

Incubation centres

Incubation centres registered as a legal entity and recognised under different ministries of the Govt. of India and having SIRO certification/ DSIR registration.

Relevant documents for submission in the application:

Applicant being an Indian academic scientist and researcher:-

a. Copy of passport (from academic scientists & researchers) or self-declaration of Citizenship attested by a gazetted officer
b. Either incubation agreement; or letter of intent in favour of applicant, issued by Incubation centre (which states that the incubation centre is willing to give facilities to applicant for the project applied for)

Companies:-

a. Incorporation certificate
b. Latest Share holding pattern as per BIRAC format only (For formats go to http://www.birac.nic.in/nationalbiopharmamission.php and click Formats), certified by external CA and verified from MCA/ ROC records
c. Details regarding in-house R&D facility, if any, or Incubation agreement
d. Audited financial details of last three financial years (i.e. 2015-16, 2016-17, 2017-18), if applicable
e. Copy of passports of the shareholders (in support of 51% eligibility criteria) or self-declaration of citizenship attested by a gazetted officer

Limited Liability Partnership:-

a. Incorporation/Registration certificate.
b. Partnership deed; or list of subscribers which states that minimum half of the partners are Indian citizens.
c. Copy of passports of Indian partners/subscribers or self-declaration of citizenship attested by a gazetted officer.
d. Research mandate/ details regarding in-house R&D facility, if any, or Incubation agreement.
e. Audited financial details of last three financial years (i.e. 2015-16, 2016-17, 2017-18), if applicable.

Indian institution/ universities/ public research organization:-

a. Affiliation/registration certificate or statute reference for establishment.
b. Details regarding in-house R&D facility, if any, or Incubation agreement.
c. If the institution/public research organization are registered under/as Society or Trust, then they have to submit the documents as mentioned in the case of Society/Trust.

Society/ Trust/ NGO/ Foundation/ Association:-

Society

a. Society registration certificate.
b. Details regarding in-house R&D facility, if any, or Incubation agreement.
c. CA certificate (supporting the fact that half of the members of the society are Indian citizens)

Trust

a. Trust deed.
b. Details regarding in-house R&D facility, if any / Incubation agreement.
c. CA certificate (supporting the fact that half of the members of the trustees are Indian citizens)

NGO/ Foundation/ Association

a. Registration details/ certificate.
b. Details regarding in-house R&D facility, if any / Incubation agreement.
c. If the NGO/ Foundation/ Association are registered under/as Society or Trust, then they have to submit the documents as mentioned in the case of Society/ Trust

5. Requisites for Funding

Decision to fund will be as per sanction of the competent authority. Successful proponents shall enter into necessary funding agreements. The fund disbursement will be subject to completion of required formalities. The disbursement will be by way of Grant-in-aid assistance. The fund recipient shall be accountable for fund utilization as per the sanction. Re-appropriation of funds can be undertaken only after approval of BIRAC, within the same Budget Head.

In addition to signing of agreement between all the concerned parties, following requirements need to be completed before the first instalment can be released:

a. A letter of authorization by the Head of the Academia and/or A Board Resolution from the Company Partner for acceptance of the Grant-in-Aid under NBM
b. Opening up a No-Lien Account with a scheduled/nationalized Bank
c. MoU with collaborator(s) (if applicable)/letter of support from contributors

d. Commitment to comply with Clinical Research Validation and Management Framework (CRVMF)
e. Commitment to obtain all applicable environmental authorizations, prior to the commencement of product development activities
f. Inclusion of qualified environmental / EHS engineer in the team for implementation of Environment and Health Risk Management Plan (EHRMP) and comply with Environmental Management Framework (EMF) requirements during all stages. Requirements on Environmental aspects may be found at http://www.birac.nic.in/webcontent/emf.pdf
g. Adhere to the Project Risk Management Plan during all stages of execution
h. Submission of documents related to conveyance of interests in the background technology/IP

6. Program Monitoring Mechanism

Project Monitoring Committee (PMC)

All funded projects must have their own Internal Monitoring Committee/Internal Project Review Committee.

The projects shall also be monitored and mentored regularly by a Project Monitoring Committee (PMC) constituted by PMU-NBM, BIRAC for each project. The PMC is responsible to monitor the progress of the Project in conformity with the outputs, milestones, targets and objectives contained in the Agreement.

Based on the foregoing PMC will assess and recommend:

a. Release of next instalment or part release thereof by the BIRAC
b. Revision of project duration
c. Closing or dropping or modifying any of the components of the Project within the overall approved objectives, budget and time-frame
d. Mentor(s) to overcome any technological problem faced in the Project implementation
e. To advise on issues related to securing of IPR
f. 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 proposed Scheme

7. Reporting of Progress

a. On Successful completion of each Milestone, the applicant will be required to submit a detailed Milestone Completion Report (MCR) as per the prescribed format
b. The MCR will be assessed by the PMC for its completion. On recommendation of the PMC, the next Milestone budget will be released
c. The Applicant will have to submit a duly certified Statement of Expenditure for every 30th September and 31st March
d. Format for MCR, Utilization Certificate and Statement of Expenditure will be made available as per requirement
e. Compliance to the Project Risk Management plan

8. Funding Mechanisms

Project must be budgeted on a milestone basis. Funding will be awarded for maximum upto 4 years depending on the objectives. Fund disbursements will be subject to the project team attaining the proposed milestones. The primary applicant and the proposed collaborators should specify their quantum percentage and their corresponding milestones. The funds will be disbursed to them separately subject to the achievement of milestone and reporting of progress

a. ***allowable costs include***

- *Personnel*: All personnel working for the development of the product *only* are allowed to claim costs. Researchers and PIs who receive a salary from the host institution as permanent or fixed term staff members may NOT claim salary reimbursement from BIRAC grants
- *Technology Consultants*: These may include both national and/or foreign consultants who provide a service and capability that is not available among the project partners. Preference should be given to national service providers
- Supplies and consumables for the equipment to be engaged for the project
- Travel & accommodation: Must be directly related to the execution of the project or travel related to seeking technology transfer
- Institutional overheads (maximum 5% of recurring budget)
- IP protection (Project related) – Upto Rs 2 Lakhs

b. ***Non-allowable costs include***

- Fundamental or basic research work (except in case of Biosimilar clone development and Novel cell line development RFPs)
- Purchase or construction of a building/ space/ land
- Rental costs for space
- Recruitment costs for staff
- Attendance at conferences
- Legal fees

9. Evaluation and Decision Making Criteria (For Products)

a. **Proposal Merit:**

- Does the proposal's approach align with the objective of RFP?
- Does the proposal demonstrate preliminary work of the identified product which will be useful for the proposed scope of work?
- Has the Primary applicant provided an adequate description of the existing manpower and infrastructure to understand their present capabilities?
- Are the objectives, activities and milestones well defined?
- Does the proposal identify project objectives with the Mission's mandate?

b. **Team/Applicant:**

- Is the Primary applicant competent to ensure effective conduct of the proposed work?
- Does the team have relevant capabilities and appropriate experience for the same?
- Does the applicant have any prior regulatory experience?
- Has the applicant provided letters of support/agreements with any third party they would like to engage with during the different stages of product development?

c. **Implementation:**

- Has the implementation methodology and work plan adequately detailed and realistic?
- Has the applicant provided clear metrics for monitoring project progress including milestones, and outputs expected timelines, budget and benchmarks? Do they seem feasible in the given time frame?
- Have the resources (technical and management people, equipment, collaboration, outsourcing needs etc.) required over the time frame been comprehensively mapped?
- Has the applicant anticipated difficulties/risks that may be encountered? Have alternative tactics and mitigation plans been considered in case of failure?

d. **Business Strategy:**

- Has the applicant provided any market surveillance details for the said product?
- Has the applicant provided any details on cost effectiveness of the product vis-à-vis existing products in the market?
- Has the applicant considered affordability on account of availing the Mission's funding?
- Has the applicant identified any specific clients or business opportunity for the product after development?

e. **Budget Estimates:**

- Is the proposed budget reasonable in light of the defined scope of work? Have reliable references been provided for justification?
- Is the resource allocation across various stages sufficient and appropriate?

10. Evaluation and Decision Making Criteria (Facilities)

a. **Proposal merit**

- Is the proposed facility aligned with the RFP's objective?
- Has the applicant provided adequate description of the existing facility to understand their present capabilities?
- Does the proposal demonstrate adequate prior activities of the identified scope which will be useful for the proposed scope of work?
- What is the state of readiness of the applicant's laboratory for the proposed work?
- Does the proposal describes prior experience in providing services?

b. **Team/Applicant**:

- Is the applicant competent to ensure effective conduct of the proposed work?
- Does the team have relevant capabilities and appropriate experience for the same?
- Are the team roles and responsibilities, governance and organizational structure clearly defined?

c. Implementation and Infrastructure:

- Has the implementation methodology and work plan adequately detailed and realistic?
- Have the resources (technical and management people, equipment, collaboration, outsourcing needs etc.) required over the time frame been comprehensively mapped?

- Has the applicant anticipated difficulties/challenges that may be encountered?
- Have alternative tactics and mitigation plans been considered in case of failure?

d**. Sustainability and revenue generation plan for the facility**:

- Has the applicant submitted any business plan for the sustenance/ maintenance of the facility?
- Has the applicant provided any differential pricing model for services they will render to established industry and/or start-ups?
- Are the plans for training and knowledge transfer well-articulated?

e**. Budget Estimates**:

- Is the proposed budget reasonable in light of the defined scope of work in terms of milestones and activities? Have reliable references been provided for justification?
- Is the resource allocation across various stages sufficient and appropriate?

Note: We welcome potential applicants contacting the mission before submitting applications to clarify any questions or discuss their ideas with us. Kindly submit the application at least a few days before the deadline to avoid proposal rejection due to non-alignment with the scope of RFP.

Contact Information

Further information can be obtained at BIRAC website. **BIRAC Website:** www.birac.nic.in

Contact Person:

Dr. Kavita Singh, Mission Director, PMU- National Biopharma Mission

Email: technical.birac@gov.in

Dr. Madhvi Rao, Senior Programme Manager, PMU- National Biopharma Mission

Email: nbm1.birac@nic.in

SECTION III - Details of the RFP

RFP AREA: AFFORDABLE PRODUCTS

RFP for Biosimilars

This Request for Proposal (RFP) is to seek applications for the following:

Background: One of the key areas of focus of the mission is to increase the present market share/ output of biosimilars in the country, for instance doubling it in the next 3-5 years. India has proven capabilities in this sector (more than 50 biosimilars being developed by 27 manufactures). Within the 10-year time (2015-2025), ~22 monoclonal antibodies and ~6 therapeutic proteins are going off patent that have not yet been marketed in India. Focusing on developing biosimilars for these in India is an opportunity to capture the global market and increase Indian biosimilar global market share from 3% to 5% in next 5 years.

RFP 1: Biosimilars Product Development

Applications are invited for development of Biosimilars (monoclonal antibodies and other therapeutic proteins) based on patent expiry of original biotherapeutic between 2015-2020 (US/ EU) and beyond or not patent protected in India.

RFP 2: Biosimilar Clone Development

Applications are invited for development of Biosimilar (therapeutic proteins and monoclonal antibodies not yet been marketed in India) expressing clones and with patent expiry between 2020-2025.

RFP 1: Biosimilar Product Development

A. Objective

To accelerate development of cost effective, safe and efficacious biosimilars of monoclonal antibodies and other therapeutic proteins that have high market scope, addresses India's disease burden and are feasible for development based on patent expiry of original biotherapeutic.

Example of list of molecules (but not limited to) that could be supported through this call, based on patent expiry of original biotherapeutic (2015-2020US/EU) or not patent protected in India:

- Infliximab
- Etanercept
- Abatacept
- Tocilizumab
- Palivizumab
- Peginterferon alfa-2a
- Peginterferon alfa-2b
- Ranibizumab
- Panitumumab
- Human Insulins

B. Scope of the RFP

1. This call seeks proposals for development of biosimilars from applicants who have an existing biosimilar expressing clone available in a commercial grade cell line (i.e. is GMP compliant and could be used for commercial production) with high yield, product quality and reproducible results.
2. The Call will fund activities related to:
    - Master Cell Bank (MCB) and Working Cell Bank (WCB) preparation and characterization
    - Process Optimization for Pilot Scale and further scale-up
    - Analytical characterization for biosimilarity analysis
    - Preclinical Studies including toxicology
    - Clinical Trials
3. The Call will **NOT** fund activities related to:
    - Fundamental or basic research
    - In-licensing of a Clone(s)
    - Filing of Registration to CDSCO/RCGM
    - Commercialization
    - Setting up large scale manufacturing facilities

C. Expectations from the Applicant

1. The Applicant must provide substantial justification for the Biosimilar(s) being considered (including but not limited to) :

- Need for the Biosimilar in the Indian market
- Market potential of the biosimilar supported with data (including any potentially competing development programmes already in place)
- The calculated cost reduction of the target Biosimilar compared to the innovator molecule (Impact on treatment costs)

2. Applications with indigenously developed Biosimilar clones and a product not launched by more than 2 Indian companies will be preferred. Such applicants are particularly encouraged to apply.

3. Applicants should provide all the relevant data that provides evidence of current stage of development of the Biosimilar (including but not limited to):

- Details of the cell line used and clone attributes
- Details of fermentation and purification processes, quality and yield of recovered protein
- Product characterization and bio-comparability data with respect to the reference molecule
- Stability data of drug substance and drug product
- Preclinical and initial toxicology studies' data (if available)
- Clinical development plan
- Marketing/commercialisation development plan

4. Applicants should provide a workplan with details of the scientific activities across all stages of development. Go/No-Go criteria, milestones and deliverables should be clearly defined to evaluate progress during the different stages of development. Anticipated risk and risk mitigation strategies should be identified and described

5. Applicants should provide letters of support/agreements with any third party they would like to engage with during the different stages of product development for which support is being sought under this call
6. The data generated as an outcome of this awarded grant through this call should be in compliance with ICH guidelines and follow general FDA principles for biosimilar development and suitable for submission to RCGM for seeking relevant approvals

D. Intellectual Property (IP) :

Applicants should have freedom to operate with relation to IP, including consent from others where applicable. Intellectual property developed under BIRAC funding through award of any grant will be owned by, and the responsibility of, the Principle Investigator (PI) (unless stated otherwise).

E. Sharing Research Results and Global Access objectives

Grantees are required to conduct and manage their research results and any clones and other material developed by BIRAC funding in a manner that enables (a) the knowledge gained during the project to be promptly and broadly disseminated, and (b) the intended product(s) or technology is made available and accessible at reasonable licensing fee/royalty terms to manufacturers who intend to develop affordable products within India.

Note: The proposals are not for early, pre-competitive research but for development of processes towards commercialization and for clinical trials (in India). Therefore, applications if submitted with academia / industrial collaborations should demonstrate that the partnership will move rapidly forward towards the proposed end goals and clearly articulate the role of the collaborators in attaining the end goals/deliverables.

RFP 2 Biosimilar Clone Development

A. Objective

To enhance India's biosimilar market and support indigenous development of biosimilars (therapeutic proteins and monoclonal antibodies) through development of clones preferably for those biosimilars with patent expiry (US/EU) between 2020-2025.

B. Scope of RFP

This call seeks proposals for development of clones that express biosimilar monoclonal antibodies that:

1. Belong preferentially to the list of mAbs with patent expiry between 2020-2025, with no biosimilar launched yet in the Indian market. This may include but is not limited to:

    - Eculizumab
    - Alemtuzumab
    - Certolizumab pegol
    - Ipilimumab
    - Ramucirumab
    - Golimumab
    - Uztekinumab
    - Denosumab
    - Pertuzumab

2. The Call will fund activities related to biosimilar clone development and characterization

3. The Call will **NOT** fund activities related to:
    - In-licensing of clone(s)
    - Filing of registration to RCGM/CDSCO
    - Toxicology studies and clinical Trials
    - Manufacturing
    - Commercialization
    - Setting up manufacturing facilities

C. Expectations from the Applicant

1. The Applicant must have relevant experience in development of a clone for protein production, preferably biosimilars
2. Applicants to be preferably from industry where institutes/ research organizations/ academia are outsourced for specific activities. Or academia having prior history of transferring Biosimilar clones to Industry and may submit this application along with an industry partner
3. The clone developed as an outcome of the awarded grant should be evaluated based on relevant attributes and found to be suitable for further development for a commercial product

4. Applicants should provide letters of support/agreements with any third party they would like to engage with during the different stages of product development for which support is being sought under this call
5. Applicants should provide a workplan with details of the scientific activities across all stages of development. Go/No-Go criteria, milestones and deliverables should be clearly defined to evaluate progress during the different stages of development. Anticipated risk and risk mitigation strategies should be identified and articulated.

D. Intellectual Property

1. The Applicant should have freedom to operate as related to IP, including consent from others where applicable including cell lines, protein sequence, media etc.
2. Intellectual Property developed under the BIRAC funding through this grant will be owned by and will be the responsibility of the PI (unless stated otherwise).

E. Sharing Research Results and Global Access objectives

Grantees are required to conduct and manage their research results and any clones and other material developed by BIRAC funding in a manner that enables (a) the knowledge gained during the project to be promptly and broadly disseminated, and (b) the intended product(s) or technology is made available and accessible at reasonable licensing fee/royalty terms to manufacturers who intend to develop affordable products within India.

RFP AREA – SHARED FACILITIES

RFP 3: Cell Line Repository

A. Background

The pharmaceuticals industry is one of the most rapidly growing sectors of the Indian biotechnology sector. In the bio-pharma industry, biologics, regenerative medicine and antibodies are considered as the key areas of focus of leading pharma/biotech companies. The growing pipeline of biological drugs has resulted in a continuous increase in the demand for different types of cell lines. Access to well characterized cell-lines is one of the prominent issues faced by manufacturers and entrepreneurs developing biopharmaceuticals products. Currently cell lines for use in India 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 cell repository of global standard that specializes in the authentication, production, preservation, and secure distribution of biological materials.

B. Objective

To create a GMP-compliant Cell Line Repository for providing access of cell lines (mammalian and microbial) and expression systems that are tested and well-characterized. These will be made available at differential pricing structure for R&D and commercialization purpose.

C. Scope

This call seeks proposals from applicants who are interested in establishment of a GMP compliant Cell Line Repository. The repository shall be responsible for:

1. Acquiring, authenticating, maintaining and storing cell lines and expression systems that could be used for assay development and manufacturing of products. The repository should have the cell lines and expression systems that include (but not limited to) either mammalian or microbial culture systems like:
    - Mammalian host system e.g. Chinese hamster ovary (CHO) cells, mouse myeloma Sp2/0 and NS0, Human embryonic kidney epithelial cells (HEK), or new cell lines like PER.C6)
    - Microbial host system (e.g. *E. coli* (BL21), *S. cerevisiae, Pichia pastoris*)
    - Improved Expression systems (e.g. using selective markers like DHFR or GS or strong promoter like CMV)
2. Conduct of quality control testing and characterization of the cell lines/expression systems and cell banks in compliance to ICH (ICH Q5A, ICH Q5B and ICH Q5D) and other relevant guidelines
3. Cataloguing and providing regulatory compliant documentation of each stored cell line/expression system (including information but not limited to name, typology, karyology, morphology, origin, properties, culture characteristics, immunological profile, cytogenetic analysis etc.)
4. Train personnel for conducting authentication, phenotypic characterization and purity of cell lines

D. Expectations from the Facility

The Applicant to fulfil or clearly articulate plans to fulfil the following criteria prior to submitting the Proposal:

1. Preferably have an existing ISO 9001/2015 certified facility and ISO 14001 certification
2. Preferably demonstrate steps for establishing linkages for acquisition of cell lines from International facilities
3. They must have knowledge in regulatory compliant acquisition, handling, authenticating, testing and characterization of cell lines and expression systems
4. They must have requisite space for supporting infrastructure such as:
    - Multiple freezers for storage with temperature monitoring and recording systems (vapor-phase liquid nitrogen freezers, mechanical freezers, cold rooms etc.)
    - Back-up for Freezer failure
    - Separate Laboratory space
    - Space for storing mammalian and microbial cell lines
    - Lyophilizer
5. Commitment for developing cataloguing and data management capabilities
6. Should demonstrate capabilities of being a service provider by having/ proposing an institutional fee-for-service governance model
7. The applicant must have trained human resource in management of a GMP environment
8. The applicant must delineate discrete goals, milestones, and criteria that can be used to evaluate the facility workplan during the grant period and sustainability post grant
9. The applicant should provide a framework of strategy so as to make the cell lines available at a differential pricing for R&D and commercialization purpose

RFP 4: Process Development Lab and GMP Manufacturing (CMC Facility)

A. Background

With the introduction of a new regulatory policy in India and increased affordability that biosimilars offer, the domestic market is predicted to grow at an accelerated pace. The challenges faced by small size industries and public institutions in biologicals development are, access to technology and huge manufacturing costs involved. A Process Development Lab (PDL) which can scale-up the process from lab scale to a pilot scale (batch size adequate to give enough purified product to generate preclinical data) maintaining same process economics is a highly challenging task.

With all pharmaceutical products, the chemistry, manufacturing, and controls (CMC) dossier is an essential part of the regulatory submission package for a clinical trial and in later stages, an application for market authorization.

To maintain consistency in manufacturing and seamless movement through the stages of process development till dossier generation, an end to end process development and cGMP certified CMC facility will be most useful. A well-defined manufacturing process with its associated process controls assures that an acceptable product is produced on consistent basis in accordance with Good Manufacturing Practice (GMP). An integrated PDL- GMP mfg. (CMC facility) will de-risk the scale-up of a Biological and save huge costs and time.

B. Objective

The objective of this RFP is to establish an end to end facility with an ability to develop a process in a non-GMP environment and further to manufacture a GMP grade material of a Biological (biotherapeutics and vaccines).

A PDL should develop and optimize the process to develop biologics. This lab should have capability to develop upstream and downstream processes to produce a non-cGMP grade drug substance with in-process Quality Controls. In addition to Process development, it should establish a cGMP certified CMC facility for manufacturing clinical trial lots in the same facility or should have an industry/CRO as a collaborator for manufacturing GMP grade material. In latter case, the PDL lab should have a technology transfer team or capability.

C. Scope

The combined scope of the facility or the collaborators will be:
For a PDL:

1. Assess the 'Develop-ability' or perform 'feasibility assessment' for process development of the Biological
2. The ability to develop stable Cell lines/ Cell banks and maintain the Cell bank/stable Cell line for the biological to be produced
3. The ability to optimize Process Development (upstream and downstream) at a minimum of at least 10 Litres working volume
4. Should also have scale-down models for process development
5. The ability to develop Analytical Methods for in-process QC and finished product
6. Production of material for Pre-clinical studies in a Non-GMP environment and support with stability studies for dossier submission to RCGM

For a GMP Manufacturing (CMC) facility:

1. During GMP manufacturing, ensure the Production Process, In-process QC testing, release and stability data which complies to relevant guidelines (RCGM/CDSCO/WHO/ICH) (mammalian and/or microbial cell line fermentation)
2. A Fill-finish line for formulation packaging (or evidence of collaboration with a fill-finish facility.
3. Proposing specifications and define the regulatory compliant release criteria and critical quality attributes (CQA)
4. Support development of a regulatory strategy and support preparation of related dossiers and regulatory filings.

D. Expectations from the Applicants

1. Academia/Research Institute application for establishing PDL should be in collaboration with an existing CMC facility of a company / Institute for similar product development (microbial/mammalian) through a Memorandum of Understanding (MoU). The collaborative proposal together should be able to provide the complete scope of responsibilities as mentioned above for PDL and GMP mfg (CMC facility).
2. .Companies with the following options will be eligible to apply:
    - Have an existing PDL and proposing establishment of GMP mfg CMC facility
    - Have an existing GMP mfg CMC facility and proposing establishment of PDL for similar product development (microbial/mammalian)
    - Propose to strengthen the existing facilities and make it an integrated PDL-CMC facility
3. Should have the required built-up infrastructure for establishing the facility
4. Applicant must be proficient with relevant upstream and downstream manufacturing technologies including the quality process parameters
5. As evidence of Process Development Lab experience, applicant should demonstrate capabilities in ability for media and process optimization, performing scale-up and development of analytical methods
6. As evidence of a GMP experience, applicant should have a know-how of Regulatory compliance and should have proven experience in documentation and preparation of regulatory dossiers for submission to RCGM/CDSCO/other regulatory agencies as per the client requirement
7. The applicant/organization should have demonstrated capabilities of being a service provider, ability to manage multiple clients and develop linkages
8. As a service provider, the applicant will be expected to have a fee-for-service governance model in place. Detailed governance model and differential pricing fee structure to be submitted
9. The applicant must delineate discrete goals, milestones, and criteria that can be used to evaluate the facility work plan and sustainability.
10. The services at differential pricing should continue for the period to match the BIRAC fund amount.
11. The applicant should provide letters of support/agreements with any third party they would like to engage for the purposes of the work under this call.

RFP 5: GLP compliant analytical facility

A. Background

Regulatory approval of complex biological molecules involves extensive state-of-the-art advanced analytics including assessment of physiochemical characteristics, efficacy, immunogenicity (antidrug antibody, ADA), contamination, strength etc., which need to be performed in a GLP compliant analytical facility.

To fulfil the regulatory requirements, the industry players are outsourcing majority of these tests with high fee of analysis and hurdles of sample shipment across the country. Alternatively, samples have to be shipped to several different facilities in India, where there is expertise, to complete the full spectrum of tests required.

A state-of-the-art instrumentation, validated protocols and expert data analysis on biologicals with huge costs involved in all of these is the critical gap that needs to be addressed. Having a GLP compliant analytical facility in an academic or a public institution which can offer services at a discounted pricing will be a big boost to the development of biosimilar industry.

B. Objective of the Facility

The aim of this program is to establish a GLP compliant analytical facility

C. Scope of the facility

Analytical characterization of Biologicals in compliance to regulatory guidelines (RCGM/CDSCO/WHO/ICH) so as to ensure data on:

1. Structure and Physicochemical properties (including but not limited to primary, secondary and higher order structures, post-translational modifications, molecular mass determination and intentional chemical modifications)
2. Biological Properties
3. Immunological properties
4. Analysis of in-process contaminants/impurities and extractables
5. USP/EP compendial test methods which can be applied across platforms/products

D. Expectations from the facility

The applicant can be an academic institute or a laboratory at an institute/University/ not-for-profit company. The Applicant must fulfill the following criteria prior to submitting the Proposal:

The Applicant must fulfil or clearly articulate plans to fulfil the following criteria prior to submitting the proposal:

1. Demonstrated prior capabilities of Bioanalytical characterization and Functional assessment of biologicals
2. Applicant should have the required built-up infrastructure (~ 2000 sq.ft) for establishing the facility
3. The team should have capabilities of data management and analysis

4. There should be human resources trained in establishing and in operational management of a GLP compliant environment
5. Applicant should demonstrate capabilities of being a service provider by having/ proposing an institutional fee-for-service governance model
6. Applicant may be asked to submit a detailed plan for the proposed facility
   - Business opportunity (target market, competition)
   - Execution (marketing, customers, metrices)
   - Technical challenges
   - Financial plan and the extent of differential pricing based on BIRAC financial support
7. The applicant must delineate discrete goals, milestones, and criteria that can be used to evaluate the facility work plan and sustainability.
8. The services at differential pricing should continue for the period to match the BIRAC fund amount.
9. The applicant should provide letters of support/agreements with any third party they would like to engage for the purposes of the work under this call.
10. Once the funded facility is functional, the data generated from this lab should be in a format which can be included in regulatory dossiers.

RFP AREA: SCIENTIFIC RESEARCH

RFP 6: Novel Cell Line Development (Cell line engineering / Cell line Development)

A. Background

A key factor in reducing the production costs of biopharmaceuticals is the development of cell lines that produce a high yield of product with the desired critical quality attributes. Selecting the right cell line early in the production process enables significant time and cost savings in later stages of development.

Although many systems have been developed to generate biologics over the past 25 years, Chinese hamster ovary (CHO) cells have become the predominant expression system for manufacturing complex glycoproteins such as monoclonal antibodies. Despite 100-folds increase in the yield of protein achieved with CHO cells, advances in cell line technology are still limited by the biology of these cells. To increase the potential of host systems, fundamental improvements to CHO cell lines or research for generating economical alternatives of human or mammalian cell lines are needed which are reliable, safe and scalable. This is particularly so for many of the new format molecules in development that are not natural protein molecules and in many cases are proving more difficult to express. Though CHO is the predominantly used system, *E.coli* is still an organism of choice to express heterologous proteins for therapeutic use in many cases, particularly for non-glycosylated, single chain products, with around 30% of all approved therapeutic proteins being produced in this host.

B. Objective

Improvement in existing CHO cell line using vector engineering or cell line engineering technologies or development of novel engineered *E.coli* strains that can solve a problem with the expression of relevant target biotherapeutic proteins. In case of CHO cell line, this is to be demonstrated by generation of a stable clone with two to three fold increase in the titre of a particular recombinant protein or an antibody or a biosimilar above those reported in the patent or scientific literature in a system that is amenable to commercial manufacturing (e.g. must demonstrate at appropriate scale and under industrially relevant condition that the product titre is enhanced and product quality is appropriate). In case of *E. coli*, similar fold-increase in the expression of desired protein or engineering that results in desired post-translational modifications in a well-folded protein. The methodology should be made available as a platform technology on negotiable licensing/royalty terms to Indian companies

C. Scope of RFP

This call seeks proposals from applicants who are interested in developing novel strategies for cell line development or improvement. The scope of activities under this call can be the following though not limited to:

1. Modulation of the transcriptional activity via expression vector engineering to improve the expression of desired genes of a therapeutic target protein or antibody: The applicant will be expected to construct a novel expression vector and screen for selection of the high producing (suspension-adapted) clones that demonstrate high viability, genetic stability and scalability to growth in bioreactor conditions.
2. Cell Line Engineering of CHO cells to genetically engineer production host cells to improve or modify the product quality or improve host cell robustness: The applicant will

be expected to detail the scientific approach or mechanism that will be used, e.g., Glycosylation control, novel gene editing or silencing methods or any other novel strategy.

3. New vector technologies that allow for 'targeted insertion' of gene or interest for higher productivity, increased stability of clone and reduce timeline of clone selection. Adaption of such clones suspension culture up to shake flask level so that the stable product expression at high cell density, desired genetic stability and high viability is maintained, and scalability to bioreactor can be assessed.
4. Engineering of therapeutic proteins production in *E. coli*: Technologies to overcome missing post-translational modifications and through novel strategy obtaining correctly folded biologically active protein.

D. Expectations from the Applicant

1. The applicant(s) should have a strong base in Molecular Biology, Chemical Engineering, Cell Culture techniques and has in depth knowledge in Mammalian or Microbial Cell Culture Process development through appropriate collaborations.
2. They must submit a brief concept and proposed modifications in CHO cells with :
    - Expression of the desired protein
    - Proof-of-concept studies from pooled stable transfectants
    - Single cell Clonal expansion up to shake flask
    - Stability of clone and product quality (titre, purity) of the insert
    - Comparative analysis of the product of parent cell line and of novel cell line demonstrating no impact on the quality and associated purity of the product
    - The improvement through Novel cell line should be demonstrated under Industrially relevant conditions
    - Demonstrate that the host cell protein (HCP) profile is not unduly impacted by the modifications to the cell
3. The mission particularly encourages applications with
    - Preliminary data showing the details of aforementioned methods with preliminary data on early product-specific titres.
    - Use of novel technologies for improved recombinant protein expression from mammalian cells by
    - miRNA or SiRNA technology
    - Novel gene editing tools
    - Novel vector elements and selection markers
    - Implementation of high throughput screening methodologies
    - Automated expansion of cell lines
    - FACS based screening of high-producing stable transfectants
    - Microfluidics or any other technology for faster screening of stable clones
    - For recombinant complex glycoprotein, the basal cell line/strain having expression levels of ~ 0.2g/L (this does not apply to standard monoclonal antibodies where appropriate technologies are already available), two to three fold improvement over the existing titre should be considered as the minimum relevant goal. For novel antibodies or biosimilar (antibody), the basal cell line having expression levels of 1g/L, further advances in yield to >2 g/L should be considered as a relevant goal. For expression of a *de novo* protein, for which a previous cell line does not exist, the same goal remain: (i) for recombinant complex glycoprotein, a titre of ≥0.3g/L should be considered a relevant goal, and (ii) for novel antibody or biosimilar (antibody), a titre of ≥2 g/L should be considered a relevant goal.

- Established linkages with other labs with capacity to scale-up and characterize the expressed product.
- Applicants from academia can collaborate with industry to validate the technology and those from industry can outsource specific activities to academia.
- Experience and understanding the requirements of cGMP manufacturing.

4. Applicants should provide a detailed work plan, with milestones and deliverables and a definition of success with appropriate letters of support/agreements with any third party they would like to engage with during the different stages of Cell Line development.
5. Applications, if submitted with an academia/industrial collaborator, should demonstrate how the partnership will rapidly move the proposal towards the end goals/deliverables and what each party will contribute to achieving the set milestones/deliverables.

E. Intellectual Property:

Applicants should have freedom to operate with relation to IP, including consent from others where applicable. Intellectual property developed under BIRAC funding through award of any grant will be owned by, and the responsibility of, the PI (unless stated otherwise).