High yielding cell line development of a Factor VIII Biosimilar with a novel purification strategy

Vellore Institute of Technology (VIT) Vellore

Environmental and Health Risk Management Plan

1. Institutional Arrangements

Requirements	Current Status	Mitigation Steps
Institutional Bio-Safety Committee (IBSC)	VIT has established BioSafety Committee headed by a nominee from DBT, Govt. of India nominee. *Dr. K. Sankaran* Professor of Eminence Former Director and HoD, Centre for Biotechnology Former Coordinator, NHHID, CEMA, UIC-B, BUILDER Anna University Chennai-600 025, India and supported by Doctors and Scientist from CMC Vellore and VIT Vellore.	IBSC suggestions and recommendations will be followed
EHS Team	Present	Recommendations of EHS will be followed
Documentation and Record Keeping in reference to the risks mentioned below and quantifiable records of generated waste and compliance measures.	Existing	IBSC recommendations are followed
SOPs related to Environment Compliance e.g Chemical spillage handling, waste segregation etc.	Existing	The SOPs are provided to researchers in the laboratory.
General Safety and Storage	Standard practise followed Project staff and students are provided adequate training and provided with a manual	Any inadequacy/accidents are reported to IBSC; appropriate measure are taken to avert further

	having standard operating procedures.	damages to individuals and for the property Individuals are provided adequate medical attention within University and if necessary taken to CMC Vellore for further treatment.

2. Environmental Impact and risk mitigation

Risks	**Project Specific Risk**	**Potential Impact**	**Mitigation Steps**
Air Pollution	Minimal Risk	Project implementation will not create any adverse air pollution.	Project implementation will not create any adverse air pollution.
Water Pollution and Waste water treatment	Minimal Risk	Project implementation will not create adverse water pollution.	Project implementation will not create adverse water pollution.
Chemical waste	Flammable chemicals are used with appropriate protection in the certified hood. All chemicals are disposed off as per the norms established by Centre for Disaster Management and Mitigation (CDMM) and School of Advanced Sciences, VIT Vellore	The risk will be minimum and adequate protection will be taken as solvents such as methanol, acetonitrile will be used in the work. The solvent waste bottles will be covered with caps and kept in certified hoods and handed over to solvent waste management team for disposal	VIT has established a Centre for Disaster Management (CDMM) and Mitigation which over sees any eventuality. Hazardous/flammable chemicals are used with appropriate protection in the certified hood. All flammable liquids are kept in certified closed cupboards below the chemical hood. Smoke detectors have been installed in the laboratories and fire alarms have been installed as well.

			Fire extinguishers placed near the entrance of the laboratory to dose off fire in case of fire accidents. All chemicals are disposed off as per the norms established by Centre for Disaster Management and Mitigation (CDMM), VIT Vellore and School of Advanced Sciences, VIT Vellore
Biological Waste	Biological wastes are mainly from bacteria, yeast and mammalian cells. All the biological plastic wares and tissue culture wares are collected in biohazard bags and autoclaved and discarded through Biolink Biohazard disposal vendors. While the spent media is treated with 4% Sodium hypochlorite and discarded in specified locations in VIT. All the biological wastes are managed as per the norms IBSC. All waste are disposed off by Biolink which is certified third party vendors to collect the biological wastes for disposal.	The impact is minimal as safety measures are in place as per IBSC regulations. All the biological wastes such as plastics or other materials autoclaved and disposed according Biosafety guidelines.	Biological wastes are mainly from bacteria, yeast and mammalian cells. All the biological plastic wares and tissue culture wares are collected in biohazard bags and autoclaved and discarded through Biolink Biohazard disposal vendors. While the spent media is treated with 4% Sodium hypochlorite and discarded in specified locations in VIT. All the biological wastes are managed as per the norms of IBSC. All waste are disposed off by Biolink which is certified third party vendors to collect the biological wastes for disposal.

Heavy metals	Minimal Risk	Project implementation will not create any adverse heavy metal waste.	Project implementation will not create adverse any heavy metal waste.
Radiation Waste	-Minimal Risk	Project implementation will not create any adverse radiation waste.	Project implementation will not create any adverse radiation waste.
Electronic Waste	Minimal Risk	Project implementation will not create any adverse electronic waste	Project implementation will not create any adverse electronic waste
Hazardous and C&D Waste	Minimal Risk	Chemicals which comes under the category of carcinogenic agents will be minimally used with appropriate protection including using masks, safety googles, protective dress etc.	Project personnel are trained to use chemicals in the certified hood with protective clothing, gloves, safety goggles, masks. The facilities are in place.
Destruction/alteration of surrounding ecosystem	Minimal Risk	Project implementation will not create any adverse Destruction/alteration of surrounding ecosystem	Project implementation will not create any adverse Destruction/alteration of surrounding ecosystem

3. Occupational Health and Safety and **risk mitigation**

Risks	**Project Specific Risk**	**Potential Impact**	**Mitigation Steps**
Heat Hazards	No direct contact with fire is done in the work. Autoclaves are used for sterilization purposes for both	Minimal; Periodically proper functioning of the autoclaves	Autoclaves are kept in an isolated and secured room. They are periodically inspected for the quality of gasket,

	experimental requirements and	and are monitored	pressure valves. Etc. Any accidents, security and safety personnel will be invited to assess the situation and assistance will be sought from medical practioners to provide immediate primary health care to affected indivuals. Estate office and to depute service maintenance staff to rectify any anomalies.
Chemical hazards, including fire and explosions	All the hazardous and flammable chemicals are handled in certified chemical hoods All chemicals are disposed off by certified third party vendors	Risk is minimal	In case of accidents; rooms/regions will be isolated and blocked. Any accidents, security and safety personnel will be invited to assess the situation and assistance will be sought from medical practioners to provide immediate primary health care to affected indivuals. Estate office and to depute service maintenance staff to rectify any anamolies.
Pathogenic and biological hazards	All waste are disposed off by certified third party vendors as per the norms of IBSC	Risk is minimal as pathogenic and infectious organisms are not used in the proposed work. Biological solid wastes will be autoclaved biohazard bags	IBSC SOPs are followed. They are displayed in the laboratory as a guideline. Researchers are also trained for BioSafety compliance as IBSC

		and disposed through Biolink Vendors. Liquid wastes are treated with 4% Sodium hypochlorite and discarded in specific meant for dispoal	
Radiological hazards	Not used in the work	Nil	Nil
Electronic Waste	Very minimal waste will produced	Minimal risk	Minimal risk
Hazardous and C&D Waste	Hazardous and C & D chemicals are kept in certified shelves and used in hood	Not Applicable	Not Applicable
Noise	The proposed work generates minimal noise.	Minimal impact	If any equipment found to be noisy,; Immediately, the equipment will be turned off. Authorized company service ppersonnel will be invited to rectify the problems.
Process safety	The process producing the rBDDFVIII molecule is done authorized rooms. The cabinets and incubators will be checked periodically. The maximum volume that will be used in the study is 0.5 Lits	Risk is minimal	IBSC protocol for cleaning and disposal will be followed which includes both solid and liquid wastes produced during the process
others	Nil	Nil	Nil

4. Community Health and Safety and risk mitigation

Risks	**Project Specific Risk**	**Potential Impact**	**Mitigation Steps**

Safety Transportation Management System (for transport of hazardous material)	Hazardous chemicals/reagents will not be transported. Biologicals samples will be transported which includes plasmid constructs, CHO cells, cell culture media expressing rBDDFVIII (10ml, 50ml, 100ml and 500 ml containers)and purified rBDDFVIII.	Hazardous chemicals/reagents will not be transported. Biological materials such as plasmid construct, CHO Cells, rBDDFVIII containing CHO cell media, purified factor VIII are not hazardous. Minimal impact due to spillage	The intended biological samples well packed and sealed containers or tubes according to volume. In addition, the samples will also be kept with cold packs or dry ice if necessary in appropriate cardboard boxes and covered and labelled as per the norms. They will be transported either in a car in secured manner or professional vendors who transport biological samples
Emergency preparedness and participation of local authorities and potentially affected communities	Emergency preparedness and participation of local authorities may not be required as No hazardous chemicals will be transported. Regarding biological samples, they are non-hazardous and in addition they will not harbour any pathogens or infectious agents which will affect the local communities Since, volume of the samples transported will be small (upto	Very minimal	The intended biological samples well packed in sealed containers or tubes according to volume (10 ml to 500 ml). In addition, the samples will also be kept with cold packs or dry ice if necessary in appropriate cardboard boxes and covered and labelled as per the norms. They will be transported either in a car in a secured manner. Alternatively, services of professional vendors who transports such

	500 ml) in sealed containers and packed boxes, the impact of any spillage will be very minimal. Moreover, the biological samples transported are for laboratory research purposes only .		materials will be utilized.

In case your organization already has **EHS guideline**, please summarise the same. Also, share details of the **EHS Officer/ Contact Person** of the organization. If not, please describe the impact because of hazardous material, release of chemicals, biologicals, management of catastrophic events like fire/explosion**.**

VIT Vellore has EHS guidelines and provides guidance and also monitors the compliance and periodic inspections are done as per the guidelines.

EHS Officer: Registrar, VIT Vellore
Contact details: registrar@vit.ac.in

Annexure - 3

Clinical Trial Risk Management Plan (if applicable)

(NOT APPLICABLE) as this project proposal does not involve any human clinical trial

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
Production of CT material	Nil	Nil
Protocol design and scientific validity ensuring Favourable risk-benefit ratio	Nil	Nil
Regulatory approvals	Nil	Nil
Ethics approvals	Nil	Nil
Ensuring appropriate informed consent process and respect for human subjects	Nil	Nil
Capacity of the sponsor	Nil	Nil
Staff at the trial site and Investigator responsibilities	Nil	Nil
Recruitment of study subjects and fair subject selection	Nil	Nil
Safety Management (AE and SAE)	Nil	Nil
Costs and reimbursements to subjects	Nil	Nil
Compensation and Insurance	Nil	Nil
Breach of confidentiality and protocol violations	Nil	Nil
Audit and independent reviews	Nil	Nil
Logistics and Data quality	Nil	Nil
Serology / efficacy	Nil	Nil
Post- trial access issues (if applicable)	Nil	Nil

Schedule 4

Results Governance Framework

1. SCOPE OF IP GENERATED DURING THE CONDUCT OF THE PROJECT

a) The New Intellectual Property (IP) rights belong to Fund Recipients

Provided, this Project is not determined as a "Nationally Important Project" to be governed through specific 'Order of BIRAC'. Such cases of "Nationally Important Project" shall have specific terms of licensing, pricing or March-in-rights for the purposes of public interest/ demand of Government of India.

b) It is the responsibility of the Fund Recipients to protect the New Intellectual Property (New IP). They shall bear the expenditure involved in protecting the New IP.

c) Sale in India may be subject to negotiation of price by BIRAC/Government of India to promote affordability on account of the grant-in-aid assistance under NBM.

2. GLOBAL ACCESS

The Fund Recipients agree to conduct and manage the Project and the resulting products, services, processes, technologies, materials, software, data or other innovations (collectively, "Product") and any IP that arises (New IP) in the manner that ensures " Global Access."

Global Access requires that

a) The knowledge and information gained from the Project be promptly and broadly disseminated or published.

b) Project Developments and/or New IP are made available and accessible at an affordable price to people most in need within developing countries.

c) In this regard, ensure Global Access in all present and future research and development agreements in a suitable form.

NOTE: For the purpose of this GLA, New IP means intellectual property generated during the conduct of the Project by the Fund Recipients, but excluding the intellectual property generated by the Fund Recipients before execution of this GLA and any IP generated outside the scope of this GLA even during the term of this GLA.

3. **The background Intellectual Property (IP) generated by the Fund Recipient before execution of this GLA are as provided hereunder**;

	Background IP of the Fund Recipient
There is NO Background IP existing from Amthera Life Sciences Pvt. Ltd. related to this project.	

Project Risk Management Plan

To comply with DBT, World Bank & BIRAC's mission to promote innovation and self-sufficiency in the biotechnology sector while striving to reduce any social and environmental risks in its activities, **AMTHERA Life Sciences Pvt. Ltd**, Bengaluru, Fund Recipients for the proposal entitled "**High yielding cell line development of a Factor VIII Biosimilar with a novel purification strategy"** has identified the following risks related to Project, Environment (including occupational health and community) and during conduct of clinical trials (if applicable). Risk mitigation measures are being taken by Amthera Life Sciences as defined in the following annexures:

i) Project Implementation Risk Management plan: identifies project monitoring mechanisms, complaint redressal mechanism and describes the mitigation measures being implemented for the programme components based on the identified risks. Institutional arrangements in order to implement safeguard parameters, methods for periodical review, monitoring strategy and grievance redressal mechanism are described in this annexure.

ii) Environmental and Health Risk Management Plan: Compliance to corresponding legislations, Good practices in research and development methods, including while use of animals will be followed. We have referred to the Environment, Occupational Health and Safety Management Framework (EMF) document while preparing this annexure. Facility-specific occupational health and safety hazards have been identified based on risk assessment using established methodologies. The Community health and safety impacts related to handling and storage of solid, liquid and gaseous substances have been evaluated and accordingly mitigation measures will be implemented during project implementation. Impacts due to significant exposures to workers and potentially to surrounding communities, depending on quantities and types of accidentally released chemicals and biologicals have been thoroughly evaluated and addressed.

iii) Clinical Trial Risk Management Plan: Ensures adherence to bioethics principles in conduct of clinical trial. The plan abides by the legal, regulatory and ethics requirements as per the national and global guidelines and the social safeguard policies.

Project Implementation Risk Management Plan

1. Project Risk Management:

Risk	Mitigation Measures	Monitoring parameters
Technical		
Breach of any license terms and termination of license agreement (if applicable)	Currently, there are no licence agreements with any party	NIL
Scientific failure that product will not reach the market.	Investigation into the cause of failure and corrective action will be taken up immediately.	We have internal progress monitoring and verification of technical procedures, design of experiments, equipment qualification and regular work reviews and necessary changes will be made by the technical team based on the indicators of failure.
Project Non-Progress	Key factors that may cause this involve supply chain delays as well as unexpected technical hurdles. Vellore Institute of Technology will revise its strategies and resources (materials, manpower and equipment) to mitigate project Non-Progress.	Constant monitoring of execution tasks is the way to monitor critical progress parameters. Progress reports and next activity plan will be discussed and proper action plan will be taken to overcome the problems coming in way of project progress. Project management line items at timed intervals
Manpower risk and backup plan and turnaround time to recruit an alternate person	Employ existing manpower with increasing responsibilities. Manpower will be hired for the duration of the project. If any project staff quit during the project time frame, then there will be Exchange of manpower between the CBSTVIT and AMTHERA Life Sciences	A three-month notice period is required from all employees. Therefore, enough buffer exists to monitor and address this risk and recruit additional appropriate manpower

	Pvt.Ltd (Collaborator of this project)	
Social		
Failure to meet affordability	Affordability plays the key role. We continuously identify and recruit experts who can assist us in this endeavour.	We continuously identify and recruit experts who can assist us in this endeavour. It will be only a stop-gap arrangement to compensate for time which we may lose, if a project personnel quits. Salaries will be paid as per the norms of the funding agency. Both teams will make arrangements for their stay with nominal daily allowance to cover living expenses. This is done only to continue the proposed project activities. Simultaneously, efforts undertaken to ensure new project staff is recruited in a short span of time without compromising the rules and regulations of funding agency and the host institute.
Gender non-representation	Attempt to equalize gender representation. AMTHERA is an equal opportunity employer does not discriminate individuals either based on gender or based on weaker section of the society.	All the staff recruitment will be done as per the guidelines. Proper advertisement, interview followed by the Minutes of selection process will be prepared.
Employment generation	AMTHERA is a start up company developing Biosimilars which is an emerging sector in the pharmaceutical industry. With growth AMTHERA will surely contribute to employment generation	Direct and indirect employment will be generated throughout this project. List can be provided

Financial		
Misutilization of funds	Strict follow up on use of funds is done through authorized procedures. Purchase of every item will be documented as per the norms of the Company and funding agency. Details will be provided to funding agency periodically	Audit will be done in regular interval. Utilization certificates and Statement of Expenditure will be provided
Non-repayment of existing loans. Risk of being listed as NPA.	AMTHERA is a start-up company built on the principles of best practices of corporate governance and the leadership has worked in reputed organizations in the USA as well as in India. Credibility loss is taken with utmost sincerity at Amthera and will be avoided all the time.	Internal audits at regular intervals with complete transparency
Adverse audit findings	Corrective measures will be taken after regular and frequent audits to mitigate impact if any correction within a stipulated time and comply to the norms of funding agency	Audited statements will be provided to the funding agency. Corrective measures will be implemented as per the norms of the funding agency.
Late disbursal of funds from NBM	UC/SoE's certificates, progress reports and all other necessary paperwork will be filed well in time to ensure that fund release is not delayed. Funds from internal accruals of the company will be utilized to meet the emergency and critical requirements with prior approval from NBM Revise strategy with available internal resources	Progress of the project can be monitored by the expert committee. Finance section will be constant touch with NBM officials for resolving any issue to avoid delays. Monthly review of budget to foresee the requirements
Data Management		
Loss of Data	2 times data storage: Lab Note Book (Hard Copy) and its soft	Dedicated data management team having a data management

	copy in the digital server. Adequate measures will be taken to protect the data and will be provided to the host institute and funding agency as and when required.	plan which includes data quality monitoring. Periodic reports will be maintained Review of LNBs and digital copies by authorized personnel.
Misutilization of Data	All data will be held securely with controlled access. Data protection and sharing policy will be strictly followed Implementing data accessibility only with appropriate authorization. Importance of maintaining the confidentiality is strictly imparted to young scientists	Review of LNBs and digital copies by authorized personnel. Data protection and sharing policy will be strictly followed.
Procurement		
Irregularity in procurement	Purchase and procurement are through internal transparent processes and committees that follow strictly follow procurement policy of the host organization and funding agency	There will be review of policy adherence by internal auditors.
Failures during vendor validations processes.	Avoid or terminate any business with the vendor. Already validated vendor list available with Purchase department	Number of validated vendors for each items are in place.
Lack of vendor databases	Already validated vendor list available with Purchase department	The process has set procedures for the vendor registration.
Others (if any)	NIL	NIL
Legal		
IP conflict regarding use of technology	Ensuring no IP conflict in the project	We frequently review IP landscape and constantly monitor for any relevant pending patent application which may be granted with subject matter that is relevant to us. IPR policy is in place.

Non-compliance to regulatory framework for conduct of study	Investigate the nature of non-compliance and take corrective measures to comply All the study protocols will be approved by the Institutional Human Ethics committee, animal ethics committee and the biosafety committee.	Approvals will be taken and annual reports will be submitted to the respective committees
Termination of license	There are no license terms directly concerning AMTHERA. Renewal of license, if applicable anytime.	There are no license terms directly concerning AMTHERA. Renewal of license, if applicable anytime.
Dispute with outsourcing agency	Investigate and take corrective measures. Qualify multiple outsourcing agency for the same job.	Investigate and take corrective measures. Qualify multiple outsourcing agency for the same job.
Change of entity status due to statutory non-compliance	Take all necessary steps to avoid change of entity status due to statutory non-compliance	Review by internal auditors to detect any statutory non-compliance and to take immediate corrective measures Immediate information to NBM in case of change in entity status occurs.
Preclinical and Regulatory **The Project dose not involve preclinical studies**		
Delay in approval by the competent authority (eg. IAEC, CPSCEA)	NIL	NIL
Unavailability of animals to conduct study.	NIL	NIL
GLP Compliance	NIL	NIL
Animal welfare/Loss of animal during the study period	NIL	NIL
Inconclusive study	NIL	NIL
Others (if any)	NIL	NIL

1. **Complaint Redressal:**

Internal Grievance/ Complaint Redressal	Mechanism/ Mitigation
Employees	All permanent employees of Amthera Life Sciences are paid as per the current industry standard. Currently Amthera does not have any Whistle Blower Policy in effect, and will create a policy in the future
Women Employees	Currently AMTHERA has 1 women employee. Amthera will constitute a Grievance Cell with increasing number of women employees
Vendors/ Partners	AMTHERA monitors the vendors for their promptness and integrity; business with troublesome vendors are terminated. In addition, informs investigators for any anomaly in prices of competitive products guides the investigators appropriately. Persistent and transparent communication channel is applied for addressing any grievance.
Customers	AMTHERA will create a Grievance redressal policy to address the Grievance pertaining to customer

2. **Project Monitoring Mechanism:**

	Monitoring Mechanism	Strategy
1	Financial Audit Reports on monitoring Fund utilization, Fund re-appropriation	Accounts and Finance maintains the records all the transactions of the projects through Purchase and Stores. A separate account is maintained for each project and fund utilization details can be provided as per norms of the funding agency. Fund re-appropriation is done only upon request by the investigators to the funding agency through the knowledge of the company administration followed by approval by the competent authorities in the funding agency. Essentially, the investigators can appropriate the funds for utilization upon obtaining permission from the funding agency.
2	Internal Technical Reviews	Technical review for each resource is conducted on a bi monthly basis

3. **Impact of the project:**

- **Affordability:**

  How funding from NBM will impact: affordability of the product(s) – cost of product with/without NBM funding, product availability/ affordability under National missions, technology licensing to MSMEs/ start-ups. Please share the cost sharing ratio,

BIRAC funding will definitely help in speeding up the process of obtaining the product and it hastens the affordability to develop the product envisaged in this proposal. Without BIRAC's funding, development of the product envisaged may get delayed further. To help in this endeavour BIRAC has come forward to fund the project proposal to have a focussed effort in realizing the product.

This project proposal will be ably supported by the collaborating partner Amthera Life Sciences Pvt.Ltd., Bengaluru (www.amthera.in). Amtehra Life Sciences Pvt.Ltd. is a biopharma company focusing on developing biotherapeutic and biosimilar products. In this project, Amthera team will contribute in clonal development which is an important component of the project. It has established a very good platform to produce biologicals needed for Indian and International market. It will contribute scientifically and technically for the clone development and to establish the biosimilarity of the product.

Amthera is developing Biosimilar products to cater to several therapeutic segments like Cancers, Inflammatory diseases, Diabetes, and Hematological disorders. It has a state of the art facility with R & D laboratories for cell line development, process development, product testing & characterization to achieve regulatory compliance. It has a dedicated inspired and highly experienced manpower to undertake the development of quality & affordable Biopharma Products. Amthera's vision is to become a global biosimilar player with a pipeline of products created with highest quality and most cost-effective technology platforms and ensure maximum access with very high affordability standards for these biosimilar products.

- **Social:**

Use of product/ technology, target population, public health programs, availability of product/ technology to MSMEs for further usage, generation of employment among local population.

The long term goal of this project is to develop a Factor VIII biosimilar which is required to treating blood clotting disorder Hemophilia A. Hemophilia A patients require life-long treatment in order to live normally. Patients without treatment die at very young age.

Currently, the FVIII product available in the market are very expensive and not affordable for people of developing countries such as India. Even for people of Western countries, the treatment costs exorbitant without health care

The project team has developed simple and efficient patented technologies to overcome the cost intensive production of FVIII molecules to treat Hemophilia A patients. It is collaborating with an industrial partner Amthera Life Sciences Private Ltd (a start up company) for the clone development and followed by development of the product with the ultimate aim providing the product at affordable prices to afflicted people. In addition meeting cGMP guidelines will also allow the product to be marketed in international marker upon clearances from appropriate agencies.

Employment generation: The current project employees will be absorbed in the Collaborator's organization for further development of the product for commercialization. Amthera has already employed trained professionals from biopharma/biotech background to work in their company. The successful development of the product would generate employment for Indian citizens both directly and indirectly. People with different skill sets which includes scientists, medical doctors, health care professionals, engineers, business management, intellectual property management, commerce, product packaging, advertising and marketing, legal, administrative background etc. will find job opportunities upon successful development of the product.

Annexure 2

Environmental and Health Risk Management Plan

5. Institutional Arrangements

Requirements	Current Status	Mitigation Steps
Institutional Bio-Safety Committee (IBSC)	AMTHERA is in the process of making the application to constitute the IBSC to DBT. *As a required first step, Company registration through the RCGM website & Consent Letters from 3 external experts is completed.*	IBSC suggestions and recommendations will be followed.
EHS Team	Not Existing	Recommendations of EHS will be followed
Documentation and Record Keeping in reference to the risks mentioned below and quantifiable records of generated waste and compliance measures.	Existing	IBSC recommendations are followed
SOPs related to Environment Compliance e.g Chemical spillage handling, waste segregation etc.	Existing *Handling& Storage of Chemicals Handling & Disposal of Hazardous Chemicals & Biological Waste*	The SOPs are provided to researchers in the laboratory.
General Safety and Storage	Standard practise followed Project staff and students are provided adequate training and provided with a manual having standard operating procedures.	Any inadequacy/accidents are reported to IBSC; appropriate measure are taken to avert further damages to individuals and for the property

6. Environmental Impact and risk mitigation

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
Air Pollution	-Minimal Risk	Project implementation will not create any adverse air pollution.	Project implementation will not create any adverse air pollution.
Water Pollution and Waste water treatment	Minimal Risk	Project implementation will not create adverse water pollution.	Project implementation will not create adverse water pollution.
Chemical waste	Flammable chemicals are used with appropriate protection in the certified hood. All chemicals are disposed off as per the norms established by by Pollution Control Board of Govt. Of Karnataka	The risk will be minimum and adequate protection will be taken as solvents such as methanol, acetonitrile will be used in the work. The solvent waste bottles will be covered with caps and kept in certified hoods and handed over to solvent waste management team for disposal	Hazardous/flammable chemicals are used with appropriate protection in the certified hood. Fire extinguishers placed near the entrance of the laboratory to dose off fire in case of fire accidents. All chemicals are disposed of as per the norms established by Pollution Control Board of Govt. Of Karnataka
Biological Waste	Biological wastes are mainly from bacteria, yeast and mammalian cells. All the biological plastic wares and tissue culture wares are collected in biohazard bags and autoclaved and discarded through	The impact is minimal as safety measures are in place as per IBSC regulations. All the biological wastes such as plastics or other materials autoclaved and disposed according to Biosafety guidelines.	Biological wastes are mainly from bacteria, yeast and mammalian cells. All the biological plastic wares and tissue culture wares are collected in biohazard bags and autoclaved and discarded through **Medicare Environmental Management Pvt. Ltd.** which is a certified third party vendor. While the spent media is treated with 4% Sodium

	Medicare Environmental Management Pvt. Ltd., Bengaluru, which is a certified third party vendor.While the spent media is treated with 4% Sodium hypochlorite and discarded in specified locations at AMTHERA. All the biological wastes are managed as per the norms IBSC. All waste of Amthera are disposed off by **Medicare Environmental Management Pvt. Ltd., Bengaluru,** which is a certified third party vendor to collect the biological wastes for disposal.		hypochlorite and discarded in specified locations AMTHERA. All the biological wastes are managed as per the norms of IBSC. All waste are disposed off by **Medicare Environmental Management Pvt. Ltd. Bengaluru,** which is a certified third party vendor to collect the biological wastes for disposal.
Heavy metals	Minimal Risk	Project implementation will not create any	Project implementation will not create any heavy metal waste.

		adverse heavy metal waste.	
Radiation Waste	-Minimal Risk	Project implementation will not create any adverse radiation waste.	Project implementation will not create any adverse radiation waste.
Electronic Waste	Minimal Risk	Project implementation will not create any adverse electronic waste	Project implementation will not create any adverse electronic waste
Hazardous and C&D Waste	Minimal Risk	Chemicals which comes under the category of carcinogenic agents will be minimally used with appropriate protection including using masks, safety googles, protective dress etc.	Project personnel are trained to use chemicals in the certified hood with protective clothing, gloves, safety goggles, masks. The facilities are in place.
Destruction/alteration of surrounding ecosystem	Minimal Risk	Project implementation will not create any adverse Destruction/alteration of surrounding ecosystem	Project implementation will not create any adverse Destruction/alteration of surrounding ecosystem

7. Occupational Health and Safety and **risk mitigation**

Risks	**Project Specific Risk**	**Potential Impact**	**Mitigation Steps**
Heat Hazards	No direct contact with fire is done in the work. Autoclaves are used for sterilization purposes for both experimental requirements and	Minimal; Periodically proper functioning of the autoclaves and are monitored	Autoclaves are kept in an isolated and secured room. They are periodically inspected for the quality of gasket, pressure valves. Etc. Any accidents, security and safety personnel will

	post experimental sterilizations		be invited to assess the situation and assistance will be sought from medical practioners to provide immediate primary health care to affected indivuals. Estate office and to depute service maintenance staff to rectify any anamolies.
Chemical hazards, including fire and explosions	All the hazardous and flammable chemicals will be handled in certified chemical hoods All chemicals are disposed off by certified third party vendors	Risk is Minimal	In case of accidents; rooms/regions will be isolated and blocked. Any accidents, security and safety personnel will be invited to assess the situation and assistance will be sought from medical practioners to provide immediate primary health care to affected individuals. Estate office and to depute service maintenance staff to rectify any anomalies.
Pathogenic and biological hazards	All waste are disposed off by certified third party vendors as per the norms of IBSC	Risk is minimal as pathogenic and infectious organisms are not used in the proposed work. Biological solid wastes will be autoclaved biohazard bags and disposed through Biolink Vendors. Liquid wastes are treated with 4% Sodium hypochlorite and discarded in	IBSC SOPs are followed. They are displayed in the laboratory as a guideline. Researchers are also trained for BioSafety compliance as IBSC

		specific meant for disposal	
Radiological hazards	Not used in work	NIL	NIL
Electronic Waste	Very minimal waste will produced	Minimal Risk	Minimal Risk
Hazardous and C&D Waste	Hazardous and C & D chemicals are kept in certified shelves and used in hood	NIL	NIL
Noise	The proposed work generates minimal noise.	Minimal impact	If any equipments found to be noisy,; Immediately, the equipments will be turned off. Authorized company service personnel will be invited to rectify the problems
Process safety	The process producing the rBDDFVIII molecule is done authorized rooms. The cabinets and incubators will be checked periodically. The maximum volume that will be used in the study is 0.5 Lits	Risk is minimal	IBSC protocol for cleaning and disposal will be followed which includes both solid and liquid wastes produced during the process
others	NIL	NIL	NIL

8. Community Health and Safety and risk mitigation

Risks	**Project Specific Risk**	**Potential Impact**	**Mitigation Steps**
Safety Transportation Management System (for transport of hazardous material)	Hazardous chemicals/reagents will not be transported. Biologicals samples will be transported	Hazardous chemicals/reagents will not be transported. Biological materials such as	The intended biological samples well packed and sealed containers or tubes according to volume. In addition, the samples will also be kept with

	which includes plasmid constructs, CHO cells, cell culture media expressing rBDDFVIII (10ml, 50ml, 100ml and 500 ml containers)and purified rBDDFVIII.	plasmid construct, CHO Cells, rBDDFVIII containing CHO cell media, purified factor VIII are not hazardous. Minimal impact due to spillage	cold packs or dry ice if necessary in appropriate cardboard boxes and covered and labelled as per the norms. They will be transported either in a car in secured manner or professional vendors who transport biological samples
Emergency preparedness and participation of local authorities and potentially affected communities	Emergency preparedness and participation of local authorities may not be required as No hazardous chemicals will be transported. Regarding biological samples, they are non-hazardous and in addition they will not harbour any pathogens or infectious agents which will affect the local communities Since, volume of the samples transported will be small (upto 500 ml) in sealed containers and packed boxes, the impact of any spillage will be very minimal. Moreover, the biological samples transported are for laboratory	Very Minimal Risk	The intended biological samples well packed in sealed containers or tubes according to volume (10 ml to 500 ml). In addition, the samples will also be kept with cold packs or dry ice if necessary in appropriate cardboard boxes and covered and labelled as per the norms. They will be transported either in a car in a secured manner. Alternatively, services of professional vendors who transports such materials will be utilized.

	research purposes only .		
In case your organization already has **EHS guideline**, please summarise the same. Also, share details of the **EHS Officer/ Contact Person** of the organization. If not, please describe the impact because of hazardous material, release of chemicals, biologicals, management of catastrophic events like fire/explosion**.**			

Annexure - 3

Clinical Trial Risk Management Plan (if applicable)

NOT APPLICABLE. As this project proposal does not involve any human clinical trial

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
Production of CT material	NIL	NIL
Protocol design and scientific validity ensuring Favourable risk-benefit ratio	NIL	NIL
Regulatory approvals	NIL	NIL
Ethics approvals	NIL	NIL
Ensuring appropriate informed consent process and respect for human subjects	NIL	NIL
Capacity of the sponsor	NIL	NIL
Staff at the trial site and Investigator responsibilities	NIL	NIL
Recruitment of study subjects and fair subject selection	NIL	NIL
Safety Management (AE and SAE)	NIL	NIL
Costs and reimbursements to subjects	NIL	NIL
Compensation and Insurance	NIL	NIL
Breach of confidentiality and protocol violations	NIL	NIL
Audit and independent reviews	NIL	NIL
Logistics and Data quality	NIL	NIL
Serology / efficacy	NIL	NIL
Post- trial access issues (if applicable)	NIL	NIL

Schedule 4

Project title: High yielding cell line development of a Factor VIII Biosimilar with a novel purification strategy

Ref proposal No.BT/NBM0181/04/19

Results Governance Framework

1. SCOPE OF IP GENERATED DURING THE CONDUCT OF THE PROJECT

a) The New Intellectual Property (IP) rights belong to Fund RecipientsProvided, this Project is not determined as a "Nationally Important Project" to be governed through specific 'Order of BIRAC'. Such cases of "Nationally Important Project" shall have specific terms of licensing, pricing or March-in-rights for the purposes of public interest/ demand of Government of India.

b) It is the responsibility of the Fund Recipients to protect the New Intellectual Property (New IP). They shall bear the expenditure involved in protecting the New IP.

c) Sale in India may be subject to negotiation of price by BIRAC/Government of India to promote affordability on account of the grant-in-aid assistance under NBM.

2. GLOBAL ACCESS

The Fund Recipients agree to conduct and manage the Project and the resulting products, services, processes, technologies, materials, software, data or other innovations (collectively, "Product") and any IP that arises (New IP) in the manner that ensures " Global Access."

Global Access requires that

a) The knowledge and information gained from the Project be promptly and broadly disseminated or published.

b) Project Developments and/or New IP are made available and accessible at an affordable price to people most in need within developing countries.

c) In this regard, ensure Global Access in all present and future research and development agreements in a suitable form.

NOTE: For the purpose of this GLA, New IP means intellectual property generated during the conduct of the Project by the Fund Recipients, but excluding the intellectual property generated by the Fund Recipients before execution of this GLA and any IP generated outside the scope of this GLA even during the term of this GLA.

3. **The background Intellectual Property (IP) generated by the Fund Recipient before execution of this GLA are as provided hereunder**;

CBSTVIT team	Background IP of the Fund Recipient
1. MONOLITH-BASED PSEUDO-BIOAFFINITY PURIFICATION METHODS FOR FACTOR VIII AND APPLICATIONS THEREOF Inventors: VIGNESH NARASIMHAN JANAKIRAMAN; RAJASEKAR RAJAGOPAL PRASANNA; AGAMUDI SIVASANKARAN KAMALANATHAN; MOOKAMBESWARAN ARUNACHALAM VIJAYALAKSHMI PCT Reference No. PCT/IB2013/060438 & PCT Status: Nationalized Indian patent Reference No. 5018/CHE/2012 & Indian patent Status: Pending European Patent Reference No.: Application No. 13857951.1-1120-292577 Granted (Dt.04.04.2019); and Validated (Dt.01-05-2019).	