"**Product development of in-house developed Insulin Glargine towards commercialization**

M/s. Stelis Biopharma Private Limited

Environmental and Health Risk Management Plan

1. Institutional Arrangements

Requirements	Current Status	Mitigation Steps
Institutional Bio-Safety Committee (IBSC)	Having valid IBSC constitution membership approved by RCGM (Stelis Unit-I). IBSC approval valid up to 31.08.2019. Applied for renewal with extension to Stelis Unit-II.	Any incident occurs in the facility shall be communicated to IBSC and further intimated to RCGM. Periodic biosafety audits are conducted by IBSC as per current biosafety guidelines.
EHS Team	Having dedicated EHS department to look after all EHS related compliances and activities.	EHS team provides training on all safety aspects to employees and mock drills are conducted in regular intervals.
Documentation and Record Keeping in reference to the risks mentioned below and quantifiable records of generated waste and compliance measures.	Documents and records are well maintained for compliance of EHS activities.	Maintaining records for biomedical waste segregation and waste disposal carried out by third party approved by KSPCB. Maintaining records for hazardous waste segregation and waste disposal carried out by third party approved by KSPCB. Monthly and annual returns are submitted to KSPCB.
SOPs related to Environment Compliance e.g Chemical spillage handling, waste segregation etc.	SOP's and Manuals are in-place.	➢ SOP available on "Procedure for collecting, handling, storage and disposal of the biomedical DQA/002". ➢ SOP available on "Management and handling of spillage – EHS/004". ➢ Laboratory Biosafety Manual - SBP/BSM/001, rev.: 02 is

Requirements	Current Status	Mitigation Steps
		available. ➢ Trainings are given frequently to all personnel working in labs.
General Safety and Storage	Procedures and equipment's are in-place.	➢ Laboratory Biosafety Manual - SBP/BSM/001, rev.: 02 is available. ➢ Personal Protection Equipment such as gloves, coats, gowns, shoe covers, boots, respirators, face shields, safety glasses or goggles are provided. ➢ Conducting annual medical surveillance program as per SOP HRA/011. ➢ First aid kits & Spill kits are available. ➢ Provided biosafety cabinets for protection to persons and product. ➢ Displayed warnings and sign boards in all areas. ➢ Displayed emergency contact numbers in all relevant areas. ➢ Providing fire proof racks for chemical storage. ➢ Providing external training on first aid & fire fighting.

2. Environmental Impact and risk mitigation

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
Air Pollution	Moderate Risk	Air pollutants from DG sets causes respiratory illness to the exposed persons. Fumes generation while handling of chemicals may leads to allergic reactions.	Monitoring of ambient air quality and stack monitoring for the chimney attached to 125 & 600 KVA DG are done on monthly basis, reports are submitted to KSPCB. Fume hoods and PPE are provided to minimize the

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
			effect.
Water Pollution and Waste water treatment	Project implementation may result in Water contamination	Improper treatment of water may lead to water pollution and illness to the people exposed.	In-house Common Effluent Treatment Plant was available to treat the Effluent & Sewage waste generated in the facility. ("Procedure for operation of effluent treatment plant and sewage treatment plant – EHS/001"). Dedicated staff are employed to perform the functions with proper training. The sludge generated in the cETP is handed over to the KSPCB approved vendor for further processing. Decontamination and inactivation procedures are available. All hazardous waste generated in the facility are stored in a dedicated area and handed over to the KSPCB authorized vendor.
Chemical waste	Project implementation may result in Contamination of water or land.	Contamination of water or land will inhibits the growth of other organisms.	
Biological Waste	Project implementation may result in Microbiological or biotechnological waste.	Improper segregation and disposal leads to infections.	SOP is available on "Procedure for collecting, handling, storage and disposal of the biomedical DQA/002". Biological waste is handed over to KSPCB approved vendor after doing initial treatment (decontamination) for further processing.
Heavy metals	Most of the heavy metals which are considered potentially hazardous not related to our manufacturing process.	Most of the heavy metals which are considered potentially hazardous not related to our manufacturing process. .	Trade effluent analysis was done to monitor total dissolved solids and submitted reports to KSPCB.
Radiation Waste	Minimal Risk	project implementation may	project implementation may not cause any adverse

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
		not cause any adverse radiation waste.	radiation waste.
Electronic Waste	Minimal Risk	Project implementation may not cause any adverse electronic waste.	Project implementation may not cause any adverse electronic waste
Hazardous and C&D Waste	Project implementation may result in occupational Injuries among workers	Injuries to personnel working in the areas.	Procedure for work permit (EHS/005) system is available for clearances of the waste generated during construction and demolition. All safety procedures and equipment's are available, trained and displayed in construction sites.
Destruction/alteration of surrounding ecosystem	Minimal Risk	Project implementation may not cause any adverse destruction/alteration of surrounding ecosystem	Project implementation may not cause 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	. Minimal Risk	Project implementation will not create any adverse heat hazards.	Dedicated HVAC Systems are available for each rooms with temperature and humidity controls.
Chemical hazards, including fire and explosions	Moderate Risk.	Health hazards to the persons handling (skin irritation or corrosion)	We are having SOP on "Chemical handling, storage, safety and emergency procedure" (QAD/025) and training given to all personnel working in the labs. Material Safety Data Sheet

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
			(MSDS) are displayed in the chemical storage area. Engineering controls and PPE's are provided to prevent harmful exposures.
Pathogenic and biological hazards	There will be moderate risk due to cross contamination and Increase in Bioburden	There will be Infection and allergies to the persons handling and threat to controlled environment.	Stelis facility is designed to handle containment upto Biosafety level – 2. SOP is available on "Procedure for collecting, handling, storage and disposal of the biomedical DQA/002". Decontamination procedure are available to inactivate the biological hazards before sending for disposal. Procedures are available for lab fumigation on periodical basis to prevent bioburden. Biosafety training is provided to all personnel working in the labs. Display of warnings and sign boards in respective labs. Display of emergency contact numbers in all relevant areas.
Radiological hazards	Minimal Risk	Project implementation may not cause any adverse radiological hazards	Project implementation may not cause any adverse radiological hazards
Electronic Waste	Minimal Risk	Project implementation may not cause any adverse electronic waste	Project implementation may not cause any adverse electronic waste
Hazardous and C&D Waste	Project implementation may	Injuries to personnel	Procedure for work permit (EHS/005) system is available

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
	result in occupational Injuries among workers	working in the areas.	for clearances of the waste generated during construction and demolition.
			All safety procedures and equipment's are available, trained and displayed in construction sites.
Noise	Occupational Injuries among personnel.	Damage to ear and sensitive tissues.	Noise monitoring is conducted once in a month to measure the sound levels of premises. Ear protective equipment's were provided for the personnel working in specified area.
Process safety	Process activities including any use, storage, manufacturing, handling or the on-site movement of hazardous chemicals	There will be Injuries to the user.	Having Standard Operating Procedures in-place. Having skilled employees and trained for operations. Facility is designed to minimize process risks. Regular monitoring on daily basis for the activities carried out during operation by quality assurance.

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)	Accident or damage to vehicle and accidental spillage Improper segregation and packing of waste.	May cause illness to the exposed persons and environment pollution.	The condition of the vehicles used for transportation of biological and hazardous waste are thoroughly checked by Stelis. Decontamination procedure are available to inactivate the biological hazards before sending for disposal.

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
			SOP is available on "Procedure for collecting, handling, storage and disposal of the biomedical waste DQA/002".
Emergency preparedness and participation of local authorities and potentially affected communities	Fire accident	Damage to property and persons. Shut down of operations.	Onsite emergency plan approved by department of factories and boilers, Karnataka is available. Fire alarms, smoke detectors, fire extinguishers and trained firefighting teams are available. Emergency assembly point is also available. Emergency escape/exit procedures are available. All regulatory approval for product and statutory approvals for facility are available.

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**.**

We at Stelis, are committed to achieve world class Environment Health and Safety (EHS) Standards. It is the responsibility of each and every one to ensure for reaching this goal by continually performance improvement. Stelis adopt pollution free environment and prevent work place accidents, promote employee health and well-being and reduce the environmental impact of what we produce, in every aspect of our business. Stelis comply with all the applicable laws and regulations related to EHS.

Stelis biopharma aim to use natural resources efficiently and by constant monitoring and preventive actions, minimize the environmental impacts on activities and products during production. We ensure this through well designed systematic storage and use of chemicals, safe disposal of effluent material, control of gas emissions. Providing & ensuring safety for all the personnel's in the facility- employees, visitors & contractors. Regular safety training are given (on job & off job training) to all the employees.

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
Standard operating procedures area available for Environment Health and Safety at Stelis and listed below. 1. Procedure for operation of effluent treatment plant and sewage treatment plant – EHS/001. 2. Procedure for waste management – EHS /002. 3. Management and handling of spillage – EHS/004. 4. Procedure for work permit system – EHS/005 5. Mock drill - EHS/007. 6. Procedure for operation and maintenance of wind sock - EHS/009. 7. Procedure for collecting, handling, storage and disposal of the waste - DQA/002. 8. Chemical handling, storage, safety and emergency procedure - QAD/025			

Notwithstanding the above other risk (relevant to the project activities) that will be identified in the course shall be addressed as per standard mitigation monitoring parameters and manner of records keeping shall be in accordance to the recommendations of the project monitoring committee on subject experts engaged by BIRAC.

Clinical Trial Risk Management Plan (if applicable)

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
Production of CT material	• Enhanced monitoring during technology transfer can provide preliminary indication of process performance and product quality.	• Efficient systems for knowledge transfer from R&D to Manufacturing are available. • Pre-defined procedures to manufacture CT material are in place.
Protocol design and scientific validity ensuring Favourable risk-benefit ratio	• Objective of the planned clinical studies to be defined properly • The inclusion and exclusion criteria of the subjects defined properly • The clinical end points of the studies to defined carefully to meet the study objective • The analytical methods to be sensitive enough for measurement of study end point markers	• The available literature on Insulin Glargine and clinical studies conducted by other pharmaceutical companies has been followed to design the study objective to ensure that the scientific validity and risk-benefit ration analysis is done properly • All the planned clinical studies will be initiated only after approval from DCGI • All applicable analytical methods to be used in the study will be validated before use in the study • Standard diagnostic methods will be used for determination of safety parameters like Haematology, Biochemistry, etc. Only NABL accredited diagnostic laboratories will be used in the study.
Regulatory approvals	Receipt of approval from DCGI	• All the proposed clinical study protocol along with other required documents will be submitted to DCGI's office for their review and approval of the study.

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
		• No clinical study site will be initiated without getting the approval or clearance from DCGI's office.
Ethics approvals	Approval of Site Specific Ethics Committee before site initiation	• Clinical study sites with a registered Ethics committee only will be selected for conducting the clinical studies • All the study protocols and related documents will be submitted to the Ethics Committee for their review and approval • No study related activities will be initiated without approval from the site specific Ethics Committee
Ensuring appropriate informed consent process and respect for human subjects	Approval from Ethics Committee	• The Informed consent forms will be generated in all applicable regional languages and are simple to understand as required by the clinical study site • The Informed Consent for will be submitted to the Ethics Committee for their review and approval • No consent form will be used in the study without approval from the Ethics Committee
Capacity of the sponsor	Availability of Designated Clinical Team To manage the clinical studies	• Sponsor is having adequate number of qualified personnel in it's disposal to manage the clinical studies and to take medical decision • Sponsor will ensure that at any point of time adequate number of people are available to clarify any query or concern raised by the clinical study sites, Ethics Committee and Regulatory Agencies
Staff at the trial site and	Selection of qualified	• Sponsor will select a qualified

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
Investigator responsibilities	clinical study sites	Contract Research Organization (CRO) to identify, and select qualified study sites. • The selection of the CRO will be done as per the SOP of the organization. • Sponsor will ensure that proper feasibility assessment is done by the CRO while selecting the study sites and wherever required Sponsor clinical team will be part of feasibility assessment and selection of the clinical study sites. • All the sites will be trained on the protocol as well as will be explained about their responsibilities during the site initiation. The site initiation related documents will be made part of the study files.
Recruitment of study subjects and fair subject selection	Selection of qualified clinical study sites and training of the sites	• Selection of sites will be done as per the SOP of the selected CRO and sponsor will be involved in the process of selection of sites. • Sponsor will ensure that the PI and the study staff at the clinical sites are properly trained for selection of the subjects and conducting the study as per protocol • All the documents related to training of the clinical study sites will be properly documented and made part of the clinical trial master files
Safety Management (AE and SAE)	Monitoring of the adverse events during the study	• Sponsor has a dedicated team of pharmacovigilance to monitor and report any kind of adverse events to the regulatory agencies as per the

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
		applicable regulations. • The clinical study protocol will have a proper section of monitoring and reporting of adverse events and all the study site staffs will be trained on the same. • The training records will be documented properly • The sponsor will report all AEs/SAEs to the regulatory agencies, Ethics Committee and study sites as per the regulation. • Sponsor has the safety database in place to record and report the SAEs to all regulatory agencies throughout the globe. • Sponsor in association with the CRO will make a Safety Management Plan and keep it ready before start of the study.
Costs and reimbursements to subjects	To ensure that the compensation and reimbursements done to subjects are recorded	• Any payment to be done to the subjects as compensation towards their participation in the study will be approved by the Ethics Committee of the clinical study site. • All the payments done to the subjects participating in the study should be recorded in the study site master files. • The clinical study monitor will ensure that all the records of payments done to the subjects are recorded properly during the monitoring visits. • The clinical study manager will ensure that proper contingency plan is in place in the clinical study budget to make the payments to the subjects.
Compensation and	Subjects and sites are	• Sponsor has the policy to have

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
Insurance	compensated for any kind of expenses towards the medical management of adverse event due to the study	Clinical Trial Insurance in place before any subject is recruited into any study • The copy of the Clinical Trail Insurance will be provided to all the participating clinical study sites and to the Ethics Committee of the sites wherever applicable • Sponsor follows the GCP guidelines in the medical management of adverse events occurred during the study till it's not established that the event is not related to the clinical study process, procedure or the drug under investigation • Sponsor will do the proper investigation of the adverse events to find the root cause of the events and to establish the causal relationship of the event with the clinical study process, procedure and/or drug. All the investigations done will be reported to the clinical study investigators, Ethics Committee and Regulatory Agencies as applicable.
Breach of confidentiality and protocol violations	Recording and reporting of protocol deviations	• Sponsor has the policy of having confidentiality agreement (CDA) with all the vendors and/or service provide before any technical discussion or disclosure is done to them on any project. We already have the CDA in place with the CROs with which the discussion to conduct the clinical studies are ongoing. • As per the regulations the

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
		sponsor will ensure that the Clinical Trail Agreement (CTA) with all the investigator is signed before any study related activity is initiated at the site. • The CTA will be provided to the Ethics Committee and the regulatory agencies as and when required. • The copy of the CTA will be made part of the Study Master File.
Audit and independent reviews	Regular monitoring of the clinical study site	• Sponsor will develop a clinical monitoring plan before start of the study to ensure that the activities at the clinical study site is being monitored by the CRA • The protocol will have the section in it regarding Audit and inspection of the facility • The CTA signed with the investigators also will have the section for audit and inspection • All the sites will be informed during the training to keep themselves open for audit and inspections by independent auditors or sponsor auditors or regulatory agencies or Ethic Committee
Logistics and Data quality	Real Time verification of the progress	• For the long term (Phase-III) studies, sponsor will use the clinical trial management system to review the recruitment, treatment progress at different sites on real time basis. • On basis of use of the products at different sites sponsor will make the arrangement of shipment of products to the

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
		sites well in advance (managed through centralized depot system) • For the long term (Phase-III) studies, Sponsor will be using the electronic data capturing system (eCRF) for capturing of all the data related to the trial. • For the Phase-I study (single site) all the products required at the study site will be shipped well in advance to the site • All the shipment of the products will be done after getting approval from Ethics Committee of the site. • No site will be initiated to start study related activities without available of the study products at the site • Statistical Analysis Plan will be kept in place before any data is unblended and analysed for the evaluation of the primary objective of the study
Serology / efficacy	Real Time Evaluation	• Sponsor will be using qualified and accredited diagnostic facility for testing of biological samples for evaluation of safety of the subject and efficacy of the product in Phase-III studies • In Phase-I and Phase-III studies for the PK and Immunogenicity evaluation will be qualified and/or validated before it's used.
Post- trial access issues (if applicable)	Long term Storage	• All sites will be advised to archive the data and documents related to the study for long term as per regulatory expectations. • Provision will be made for the

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
		same in the protocol and/or in the CTA as applicable. • Sponsor will keep the study related documents in the Trial Master File (TMF) and archive the same for longer duration of time as required by the regulatory agencies. • No site will be closed until unless all data and documents from the site is collected and kept in the TMF. • The TMF will not be closed and sent to archival by the sponsor till it's reviewed by the Quality team and approved for archival.

Notwithstanding the above other risk (relevant to the project activities) that will be identified in the course shall be addressed as per standard mitigation monitoring parameters and manner of records keeping shall be in accordance to the recommendations of the project monitoring committee on subject experts engaged by BIRAC.

We will abide by the guidelines of CRVMF of National Biopharma Mission, BIRAC.