To develop low cost and affordable Biosimilar Herceptin

Serum Institute of India Ltd.

Environmental and Health Risk Management Plan

1. Environmental Impact and risk mitigation

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
Air Pollution	1. Escape of microorganisms to environment 2. Air pollution from boiler and DG flue gas emission	1. Health hazard. 2. Air pollution	1. All the exhaust air should be 0.2 micron filtered. 2. AHU's are installed to filter the contaminated air and exchange with fresh filtered air. 3. Provided stack with sufficient height. 4. Provided the bag filters/ cyclone separator for briquette boiler. 5. Replaced boiler fuel from furnace oil to environmental friendly clean fuel CNG.
Water Pollution and Waste water treatment	1. Mixing of waste water to environment	1. Contaminate water source	1. Waste water treatment plant having Primary, secondary, and tertiary treatment is provided. 2. Treated water used for the gardening purpose.
Chemical waste	1. Contamination of water source and soil. 2. Disposal of expired and off-specification of products.	1. Contaminate water and soil. 2. Health hazard	1. Neutralization of chemical waste before release into environment. 2. MSDS are available for proper disposables of chemical waste. 3. Spill control procedures are available. 4. Disposable of waster through pollution control board authorised facility.

Biological Waste	1. Live genetically modified organism released into environment. 2. Biological waste generated from animal house.	1. Contaminate environment. 2. Health hazard to operator and persons comes in contact.	1. Deactivation procedures are available e.g. Acid/Alkali treatment, Autoclavation, Incineration.
Heavy metals	1. Heavy metals are not used in the process	Not applicable	Not applicable
Radiation Waste	1. Radiation based materials are not used in process	Not applicable	Not applicable
Destruction /alteration of surrounding ecosystem	1. Disposal of biological, chemical waste	1.Alteration and destruction of surrounding ecosystem	1. Solid and liquid waste treated prior to disposal. 2. ETP and incinerators are available for disposable of waste.
others	Not Applicable	Not Applicable	Not Applicable

2. Occupational Health and Safety and risk mitigation

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
Heat Hazards	1. Hot surfaces in manufacturing area.	1. Operator may be injured if exposed to hot surfaces.	1. Insulations are provided; instructions and signage boards are displayed. 2. Safety gears are available to handle high temperature materials. 3. Equipments are comes with Interlock system to avoid direct exposure of heat to operators.
Chemical hazards, including fire and explosions	1. Exposure to acid and alkali. 2. Handling of chemicals.	1. Operator may be injured if exposed.	1. Fire hydrant, fire alarm and fire detection systems are in place. 2. Spill control procedures are available 3. Safety gears are available to avoid exposures. 4. In case of emergency fire extinguishers are kept at suitable points in facility. 5. Solvents are used in very low volume and in diluted form.
Pathogenic and biological hazards	1. Live genetically modified organism released into environment	3. Contaminate environment. Health hazard to operator and	1. Decontamination procedures are available e.g. Acid/Alkali treatment,

		persons comes in contact	Autoclavation, Incineration. 2. Use of PPE like gloves, goggles, safety shoes, etc.
Radiological hazards	1. Radiation based materials are not used in process	Not applicable	Not applicable
Noise	1. High noising equipments.	1. Impair hearing ability of operator over the time	1. Equipments are selected as per factory act to meet the noise requirement specifications. 2. Engineering controls are in place like acoustic enclosures for DG sets 3. PPE e.g. ear plugs, ear muffs are available on site.
Process safety	1. Exposure to live organism or chemicals.	1. Health hazard to operator	1. All the processes are conducted in closed environments. 2. Most of the equipments are single use. 3. PPE are available. 4. Solid and liquid waste handling procedures are available.
others	Not Applicable	Not Applicable	Not Applicable

3. Community Health and Safety and risk mitigation

Risks	Project Specific Risk	Potential Impact	Mitigation Steps
Safety Transportation Management System (for transport of hazardous material)	1. Spillage of hazardous material in case of accident/incident 2. As transmission of blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and processing of blood, and shipping and handling of all specimens for this study. 3. Accidental spillage and wastage of blood samples. 4. Risk of temperature excursion.	1. On environment. 2. Transmission of blood-borne infections to healthy population 3. Wastage of blood sample may lead to unavailability of key immunogenicity results. 4. Temperature excursion may lead to poor quality immunogenicity results.	1. Quantities are low than that of threshold limit. 2. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. 3. Bio hazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations. 4. All laboratory personnel should be adequately trained on GLPs or accreditation standards and laboratories should be approved at GLP level and/or accredited.
Emergency preparedness and participation of local authorities and potentially affected communities	1. Spillage of hazardous material within the factory	1. Impact on human health. 2. Impact on environment	1. Procedures of handling of hazardous waste in place. 2. On site emergency plan is in place. 3. Training provided to the employees.
If not, please describe the impact because of hazardous material, release of chemicals, biologicals, management of catastrophic events like fire/explosion**.**			

Annexure 3 (if applicable)

Clinical Trial Risk Management Plan

Clinical and Regulatory		
Area of Risk	**Monitoring Parameters**	**Mitigation Measures**
Production of CT material	1. Central Drugs Laboratory (CDL, Kasauli) release certificate 2. Certificate of Analysis (COA)	Ensure availability of these certificates before initiating the clinical trial.
Protocol design and scientific validity ensuring Favourable risk-benefit ratio	1. Protocol must be as per ICH-GCP and National Regulatory Guidelines. 2. Design includes Hypothesis, Objectives and Endpoints 3. Preferably RCT design should include blinding strategy, multiples centres, phase of trial, sample size and statistical considerations, Inclusion/Exclusion criteria, IP, Comparator, Dosage and routes of administration, Safety monitoring, Immunogenicity/Efficacy assessment 4. Accreditated and validated safety and immunogenicity labs should be considered 5. Throw light on favourable risk-benefit ratio in the protocol.	1. Design and finalization of the protocol by Sponsor and its review at multiple levels by Sponsor team, Principal Investigators, Contract Research Organization and external international agencies. 2. To mitigate unexpected changes which may arise during trial conduct, protocol can be amended and notification can be made to regulatory agencies. 3. Technical Committee and Subject Expert Committee (SEC) review (CDSCO, DCGI) 4. Scientific committee of the site and IEC review.
Regulatory approvals	1. Seek DCGI approval letter 2. CTRI registration 3. Export NOC for biological samples 4. Local FDA License for labelling and packaging	1. Post submission of final protocol to DCGI, it will be discussed during SEC meeting and committee may provide suggestions and minutes of meeting regarding protocol modifications for resubmission. 2. Ensure DCGI approval copy 3. Ensure CTRI registration number 4. Ensure Export NOC

		5. Ensure Local FDA License
Ethics approvals	1. Institutional Ethics Committee/ Institutional Review Board (IEC/IRB) must be registered with DCGI. 2. Seek IEC approval letters from respective study sites. 3. Few sites may have additional scientific committee meetings prior to EC meetings	1. Ensure IEC registration number and approval letters. 2. IEC may provide their suggestions and MOM, accordingly sponsor modify the protocol and other relevant documents.
Ensuring appropriate informed consent process and respect for human subjects	1. Written Informed Consent Form (ICF) and Audio-Visual (AV) ICF as per Schedule Y guideline 2. ICF and AV-ICF translation and back-translation 3. ICF should be duly signed by subject and PI.	1. Ensure equipments and infrastructure is adequate to support ICF process. 2. Ensure study staff is adequately trained for counselling of ICF recording. 3. Ensure translation certificates are available for ICF and AV-ICF translation and back-translation. 4. Ensure subject has voluntarily agreed to participate in the study by signing the ICF.
Capacity of the sponsor	1. Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). 2. Supplying and Handling Investigational Product(s) 3. Participating in DCGI and WHO regulatory meetings. 4. Clinical Trial Application (CTA) dossier notification/submission to Regulatory Authority(ies) 5. Identification and selection of CRO, Sites and Labs	1. Development and adherence to SOPs. 2. Selection of competent vendors for supply, packaging and labelling. 3. Sponsor dedicated regulatory team performs CTA submission on SUGAM portal. 4. Sponsor conducts bid-defence meeting for CRO selection. 5. Dedicated CRO data management team and advanced Electronic Data Capture (EDC) system.

	6. Data Handling, and Record Keeping 7. Manufacturing, Packaging, Labelling, and Coding Investigational Product(s) 8. Clinical Study Reports (CSR) are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s)	
Staff at the trial site and Investigator responsibilities	1. Staff should be qualified and well trained on ICH-GCP, human subject protection, protocol specific procedure and maintain qualification/certification and training documentation throughout the study. 2. Investigator should be qualified, experienced, well trained on ICH-GCP 3. Investigator should be willing and accountable to conduct clinical trial and compliant to study protocol. 4. PI must identify safety signals and should be responsible for timely and appropriate medical management of the subject.	1. Provide ICH-GCP and protocol specific trainings to site staff as needed (Site Initiation, retraining, protocol amendment training, etc). 2. Collection of Curriculum Vitae (CVs) and Medical Registration Certificate (MRCs) of PI. 3. Site identification and feasibility visit 4. If required, Periodic Protocol Safety Review Team (PSRT) during trial period.
Recruitment of study subjects and fair subject selection	1. PI, Co-PI and study staff should be efficient in the recruitment of the subject to maintain adequate recruitment rate at site. 2. Site must adhere to Inclusion/Exclusion criteria of the protocol for fair ethical and scientific selection of subjects.	1. Sponsor ensure recruitment potential and monitor recruitment rate of the site by site visits, teleconference and email communications. 2. Sponsor must conduct investigator meetings, site initiation visits and interim trainings to address recruitment and subject selection related issues.
Safety Management (AE and SAE)	1. PI is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as per provided in the protocol for the duration of the study.	1. Ensure PI, Co-PI and study staff is available 24x7 to deal with safety problems.

	2. Subject should be aware of signs and symptoms, and must contact site where study staff should be available 24x7. 3. Sponsor and CRO must review eCRF database and conduct regular monitoring visits to identify safety issues 4. Sponsor and CRO should be in loop with site for occurrence of AE,SAE and medical emergencies 24x7 5. Safety recording, reporting and management should be as per Schedule Y guidelines and internal SOPs.	2. Ensure site and CRO SOPs for safety management. 3. Prepare PSRT and Data Safety Monitoring Board (DSMB) quorum and periodic meetings for safety management. 4. All SAEs should be immediately (within 24 hours of knowledge of the event) reported by the PI to the Licensing Authority, Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, PSRT, and the Ethics Committee that accorded approval to the study protocol, by sending a completed SAE form.
Costs and reimbursements to subjects	Travel cost and medical management reimbursement	1. Ensure financial transactions have been done. 2. Reply to DCGI communication regarding SAE medical management reimbursement.
Compensation and Insurance	In the event that a subject suffers injury or death, appropriate treatment and/or compensation will be provided by and/or paid to the subject by the Sponsor in accordance with applicable national laws and/or guidelines.	Ensure Clinical Trial Insurance Policy.
Breach of confidentiality and protocol violations	1. Clinical Trial Agreements (CTA) between Sponsor, CRO and Site. 2. Notification of protocol deviations and violations to IEC.	1. Ensure signed, sealed and stamped CTA. 2. Ensure notification letter to IEC. 3. Timely training to avoid further protocol deviations and violations.
Audit and independent reviews	1. Sponsor/CRO may audit the study to ensure that study procedures and data collected	1. Ensure site preparedness for audit. 2. Development of SOPs.

	comply with the protocol and applicable SOPs of the site and the CRO, and that data are correct and complete. 2. Regulatory agencies audits. 3. External independent agencies like DSMB reviews and meetings prior to and at the end of the study.	3. Internal QC audit by CRO 4. Regular monitoring visits by Sponsor and CRO. 5. Reply to audit findings.
Logistics and Data quality	1. IP shipment in cold-chain to study sites. 2. Blood sample transportation (cold-chain) to CRO lab and Central immunogenicity lab. 3. Provision of stationary, equipments and study related operational documents. 4. Perform source data verification (SDV) of the data recorded in the EDC system against the source documents available at the site to ensure consistency between the source data and the data present in the EDC systems. 5. Standard Good Clinical Practice (GCP) will be followed to ensure accurate, reliable and consistent data collection.	1. Ensure capable Vendor and IP shipment along with temperature monitoring device as per SOPs. 2. To avoid accidental loss of blood sample during transportation, Sponsor/CRO can divide sample into multiple shipments and in addition to this, Sponsor/CRO can consider dummy run before actual shipment. 3. Electronic edit check programs and resolution of discrepancies. 4. Study monitors will closely evaluate pre-screening data, inclusion/exclusion criteria, informed consents, data entry timeliness, and visit window capture to ensure integrity of the study is maintained.
Serology / efficacy	1. Construct serology/immunogenicity/efficacy study endpoints as per standard WHO Guidelines/Scientific literature 2. Immunogenicity tests will be conducted at immunogenicity lab. 3. Efficacy will evaluated by selected PIs.	1. Review of final endpoints by Sponsor, national and international subject experts. 2. The immunogenicity lab should be reputed, accredited and validated lab assays. 3. Lab HOD should be qualified, experienced, national/international faculty with scientific publication.

		4. The PI should be competent clinician to evaluate efficacy based on standard clinical criteria, radiological/pathological investigations laid down by national/international/WHO reference guidelines.
Post-trial access issues (if applicable)	Not applicable	Not applicable