Environmental Health Risk Management Plan (EHRMP)

Intas Pharmaceuticals Limited

Proposal entitled: "Development of recombinant adeno-associated virus [rAAV] based genetic vaccine for COVID-19"

(i) Brief description of the proposed activity

rAAV have been established for its safety and efficacy in human subjects and rAAV-based gene therapy products Zolgensma and Luxturnahave already been approved by US-FDA / EMEA for the treatment of spinal muscular atrophy and retinal disorders, respectively. Therefore, current project aims to develop rAAV-based COVID-19 genetic vaccine by triple-transfection of HEK293T cells using packaging plasmid, helper plasmid and transfer plasmid.

Plasmid production

The competent *E. coli* cells are transformed with individual plasmids encoding therAAV packaging (rep and cap gene of AAV), helper (E1, E2a, E4 and VA genes of adenovirus) and transfer (antigenic variants of spike protein of SARS-CoV-2 flanked by 5'- and 3-'ITR) vectors. The master microbial cell banks are prepared and characterized. The characterized microbial banks are used for large scale endotoxin-free plasmid preparation. QC for identity, purity and sterility will be done and the produced plasmids will be used for the generation of rAAV.

rAAV generation

Triple-plasmid transfection are used to generate rAAV-COVID-19 vaccines in HEK293T cells.In brief, the HEK293 cells are seeded two day before transfection. On the day of transfection, high quality endotoxin free plasmids and the transfection reagent will mixed at an optimal ratio and added to the cells. After incubation, the supernatant with un-transfected plasmids is removed and a fresh culture medium is added to the cells for rAAV production. Culture is harvested 72 hours post transfection and rAAV is purified using affinity chromatography, ultracentrifugation and buffer exchange. The purified rAAV are stored at -80°C till further usage.

rAAV characterization

A functional titer of the rAAV vector is determined by a cell-based assay. A host cell line is used for evaluation of the rAAV's ability to transduce a cell line under specific conditions (transduction units). The titration is performed using the limiting dilution method to transduce the host cells and the titer is measured by real-time polymerase chain reaction (qPCR) quantification of viral genomes in host cell DNA from transduced cells. In brief, the host cells are seeded into 24 well plate and a series of diluted rAAVparticles are added to the cells for transduction. Total host cell DNA from each transduced well is extracted and gene specific qPCRare performed to determine the copy number of transfer plasmid in transduced cells. Additionally, purified transfer plasmid alone are used to run standards for the assay. rAAV preparations are also characterized for integrity (SDS-PAGE) and endotoxin. The titer of $5 * 10^9$ TU/ml are used for the QC testing and release criteria.

(ii) List of environment related regulatory clearances required for the activity.

1. Review Committee on Genetic Manipulation (RCGM)
2. Institutional Biosafety Committee (IBSC)

3. Consent/ authorization from respective PCB for following:
   - Water (Prevention & Control of Pollution) Act, 1974 and Water (Prevention & Control of Pollution) Rules, 1975.
   - Air (Prevention & Control of Pollution) Act, 1981.
   - The Environment Protection Act, 1986 and The Environment Protection Rules, 1986.
   - Municipal Solid Waste (Management and Handling) Rules, 2016.
   - The Noise Pollution (Regulation and Control) Rules, 2000.
   - E-Waste Management and Handling Rules, 2016.
   - Bio-medical Waste Management and Handling Rules, 2016.

Institutional Arrangement

	Area of Risk	**Yes**	**No**	**Details**	**Proposed Plan**
1.	Is there a designated full-time staff for Environment Health and Safety (EHS) issues?	X		EHS Org Chart in place	The concerned staff will be trained on the Environment Health and Safety (EHS) and will comply with the norms and requirements of the Pollution Control Committee.
2.	Does the EHS staff handle the following?				Currently Intas Biopharma handles the following. EOHS, Waste management, Consents and regulatory clearances, record keeping of accidents and procedures and EHS training. We will comply to Environment Management Framework compliance for Innovate in India Project.
	Occupational Health and Safety	X			
	Waste Management	X			
	List of consents and regulatory clearances	X			
	Record keeping of accidents and procedures	X			
	EHS trainings for staff	X			
	Environment Management Framework compliance for Innovate in India Project	X		Environment, Occupational Health and Safety Management Framework (EMF) FOR Industry-Academia Collaborative Mission For Accelerating Early Development For Biopharmaceuticals - “Innovate in India (i3) Empowering biotech entrepreneurs & accelerating	

				inclusive innovation" under review	
3.	Is there a reporting structure in place regarding EHS issues?	X		Describe: As per EOHS Policy EHS/PY/002-02.	The reporting structures is in place and shall be updated and maintained.
4.	Are regular EHS trainings provided to staff?	X		Frequency: Fire Drill: Every two months EHS awareness training to staff: Annual. Other Safety Trainings: As per training matrix	Training records will be provided upon request and further training will be conducted as per the schedule.
5.	Institutional Bio-Safety Committee (IBSC)	X		IBSC is already in place for site.	Periodic review meetings will be scheduled and proper approvals will be taken from the IBSC Committee.
6.	Ethics Committee (EC)		X	Not available at Intas premises.	The CRO that will be involved in animal studies, would have Institutional Ethics Committee to conduct the study.
General Occupational Health and Safety					
	Area of Risk	**Yes**	**No**	**Details**	**Proposed Plan**
7.	Are there Standard Operating Procedures for accidents, hazards, and other emergencies (chemical spills, heat hazards, fire hazards, radioactive hazards etc.)?	X		EHS policy (EHS/PY/002-02) available	Already in place and will follow SOP's.
8.	Are the following in place?			Chemical spill kits Eye wash Shower stations First Aid Kit Fire Extinguishers Register of accidents and injuries are available at the premises.	Already in place and this safety measure will be maintained in working condition.
	Chemical spill kits	X			
	Eye wash	X			
	Shower stations	X			
	First Aid Kit	X			
	Fire Extinguishers	X			
	Register of accidents and injuries	X			

9.	Are proper signage and storage system in place?	X		Bio-safety manual Proper signage and storage system are available at Intas Biopharma premises. Display of Material Safety Data Sheet (MSDS) where relevant is available. Display of emergency numbers and procedures are displayed at all critical places. Signage across the facility (labs, storage, hazardous areas, etc.) are displayed. Flammable materials are appropriately stored to prevent fire hazards	These would be regularly updated/ replaced.
	Display of Material Safety Data Sheet (MSDS) where relevant	X			
	Display of emergency numbers and procedures (Person to Contact, Doctor, Ambulance, Fire Emergency, Police) displayed in all critical Places	X			
	Signage across the facility (labs, storage, hazardous areas, etc.)	X			
	Are flammable materials appropriately stored to prevent fire hazards?	X			
10.	Are smoke detectors, fire alarms, automatic safety/shut off systems, overflow preventors, etc. in place and regularly maintained?	X		Smoke detectors, fire alarms, automatic safety/shutoff systems, overflow preventers are available at Intas Biopharma premises.	Already in place and will ensure that they are properly maintained and in working condition.
11.	Are there control measures for VOC, air emissions, high operating temperatures, pathogens/vectors etc. in place?	X		Control measures for VOC, air emissions and high operating temperatures, pathogens/vectors are available at Intas manufacturing sites.	Already in place.
12.	Are regular mock drills conducted for emergency preparedness and safety?	X		Frequency (type wise): Fire Drills every six months	Records of mock drills available and the mock drills are being conducted regularly.
13.	Are staff provided with OHS training?	X		Describe: Annual OHS Training program is conducted for all the staff.	Records for training are available and will be produced upon request by any authority. Trainings will be continued.
	Biomedical Waste (BMW)				
	Area of Risk	**Yes**	**No**	**Details**	**Proposed Plan**

14.	Is there generation of biomedical waste (as described in Bio-Medical Waste Management Rules, 2016) in the grantee?	X		As per BMW authorization form – III (Rule 10, 2016 under the EPACT'86) GPCB has permitted Intas for handling BMW for the following (KG/Month) BMW Auth No. 349187, valid upto 31/12/2075 Yellow waste-480 Kg White waste (translucent) – 150 Kg Red waste – 10 Kg Blue waste – 120 Kg		We mostly produce biological waste that is immediately segregated at point of generation as liquid and solid waste. Liquid waste is treated with sodium hypochlorite/NaOH and drained to the kill tank. Solid biological wastes are treated with sodium hypochlorite/NaOH before collection in appropriate bags (Waste management SOP: SOP/GT/014 Disposal of waste). Similarly, in future any biomedical waste coming from animal origin like blood or tissue will be only opened in BSL-2 hood. Biomedical waste generated in the process will be treated as mentioned above for biological waste. The biomedical waste shall be segregated at point of generation in the facility and stored in suitable containers for disposal.
15.	Is there trained staff to handle biomedical waste in the grantee?	X		EHS team train staff annually as per training matrix		The trainings will be continued.
16.	Has the grantee obtained authorization from State Pollution Control Board /Pollution Control Committee?	X		Gujarat pollution control board consent number AWH-103574 date of issue -19 Aug 2019 and valid till 26 Aug 2024.		The provisions in the authorization will be adhered.
17.	Is the biomedical waste segregated at point of generation in the facility and stored in suitable containers?	X		Yellow	Yes	We mostly produce biological waste that is immediately segregated at point of generation as liquid and solid waste. Liquid waste is treated with sodium hypochlorite/NaOH and drained to the kill tank. Solid
				Red	Yes	
				White	No	
				Blue	No	

						biological wastes are treated with sodium hypochlorite/NaOH before collection in appropriate bags (Waste management SOP: SOP/GT/014 Disposal of waste). Similarly, in future any biomedical waste coming from animal origin like blood or tissue will be only opened in BSL-2 hood. Biomedical waste generated in the process will be treated as mentioned above for biological waste. The biomedical waste shall be segregated at point of generation in the facility and stored in suitable containers.
18.	Is the bar code system for the segregated waste in place?		X	The bar code system is not applicable Intas Biopharma site.		The bar code system is not applicable, because we do not handle biomedical waste. We handle biological waste. However it shall be implemented when required.

19.	Is the biomedical waste being sent to an **authorized** common BMW facility?	X		Name and address of CBMWF: Ecoli waste management PVT Ltd. Plot No. 14/1, Saket Industrial estate, Village Moraiya, Tal Sanand, Ahmedabad 382210 Distance from facility: 3 KM	Already in place for biological waste and will be followed for biomedical waste originated from animal samples as mentioned in point 17.

				Frequency and Mode of transport: Daily, Ecoli waste management PVT Ltd. authorized vehicle Who transports? Ecoli waste management PVT Ltd.	
20.	Does the grantee have an in-house BMW treatment facility?		X	Reason: Biological liquid waste treated at in-house water treatment facility. Authorization: GPCB Distance of nearest CBWM from facility: 10 Km Types of treatment: autoclave, incinerator, scrubber, microwave	BMW not available since we do not generate biomedical waste.
	Is the treatment facility own (individual)?	X			
	Is the treatment facility a shared facility in an industrial park?	X			
21.	Are lab waste, microbiological waste and chemical liquid waste pre-treated before storing and sending to treatment facilities according to guidelines prescribed in BWM, 2016 regulations?	X		Types of treatment: SP-PR-044-Handling of Biomedical Waste Materials. IBPL-M-QA-001 Biosafety module	The waste treatment as per guidelines prescribed in BWM, 2016 regulations and the Biosafety manual are followed at the current facility. Compliance calendar shall be maintained.
22.	Is the liquid waste checked for active cells before sending to treatment plant?	X		SOP: SOP/GT/014 – Disposal of waste (Intas Gene therapy R&D lab)	Active cells are checked as per SOP SOP/GT/014
23.	Are necessary waste pre-treatment equipment in place?	X		List of equipment: autoclaves,	Standard equipment already in place and will be

	Do the equipment adhere to prescribed norms by State Pollution Control Board (SPCB)?	X		serological pipette holders with hypochlorite solution and essential equipment for ETP. Details of waste pre- treatment: chemical inactivation or steam sterilization, pH adjustment and finally ETP.	utilized effectively.
24.	Are chlorinated plastic gloves and bags phased out in the grantee?	X		Not under use	Usage of latex and nitrile gloves are the only practice followed at Intas Biopharma
25.	Are grantee's personnel involved in handling BMW provided with regular training?	X		Frequency: Once a Year Trainer: EHS Personnel	Training is being provided and will be provided regularly.

26.	Are medical examination provided to personnel involved in BMW waste handling and are they provided with relevant immunization like Hepatitis B and Tetanus?	X		Frequency of medical examination: Once a Year SP-EH-001: Routine (Post Employment) Medical Examination, Intas Biopharma. Practice in place to immunize all the personnel involved in the BMW.	Reports will be maintained.
27.	Is a daily register for biomedical waste maintained including accident reporting record?	X		Currently there is a register for biological waste maintained. Accident reporting is governed by EHS/PY/002-02 : Policy on Accident / Incident Management	Already in place and the register for biological waste shall be maintained.
28.	Are annual reports on BWM submitted to SPCB as per required form (see Bio-Medical Waste Rules 2016)?	X		Form 04 (form for filling annual returns by occupier or operator of facility) submitted annually	The annual submission will be continued.
Hazardous Waste (HW)					
	Area of Risk	**Yes**	**No**	**Details**	**Proposed Plan**
29.	Is there generation of hazardous waste (as per Hazardous Waste Rules, 2016) in the grantee?	X		If Yes, provide a list of hazardous waste produced in the facility Used oil from DG sets is treated in the in-house ETP plant. The ETP sludge is then transported to the approved TSDF site for further treatment and disposal. TSDF (Treatment Storage and Disposal Facility) Site	The hazardous waste generated is handed over to authorized hazardous waste recycler and hence there is no harm to environment and health. This process will be continued throughout the project.

				Phase II, GIDC, Vatva Ahmedabad 382445 Valid consent available at site for water, air, hazardous waste from GPCB	
30.	Is there trained staff in the facility to identify and handle hazardous waste?	X		There are trained EHS personnel who would identify and handle hazardous waste	The trained staff will ensure that the hazardous waste is handled in a safe manner.
31.	Does the grantee have authorization from SPCB for hazardous waste?	X		Valid consent available	Valid consent shall be made available upon request. Timely renewals will be made with proper approvals as and when required.
32.	Is there a secure location for storage of HW with proper signage?	X		The HW is immediately treated in the ETP and the sludge is stored at a secure location until transported to the registered TSDF site.	Well-ventilated area and separated room will be used for storing the Hazardous waste during the Project.
	Are hazardous waste stored for more than 90 days in the grantee's premises?		X		
33.	Is the hazardous being send to an **authorized** disposal facility or user?	X		Name and address of facility: TSDF (Treatment Storage and Disposal Facility) Site Phase II, GIDC, Vatva Ahmedabad 382445	All the hazardous waste generated is outsourced to an authorized TSDF.
	Is the disposal facility in house?		X		
	Is the disposal facility external/outsourced?	X			
34.	Is a register maintained on production and treatment, and a manifest system followed for transport of hazardous waste from the grantee to treatment facility?	X		Register is maintained on production and treatment, and a manifest system followed for transport of hazardous waste from Intas to treatment facility	Maintenance of register will be continued and manifest system will be followed.

E-Waste and Batteries

	Area of Risk	**Yes**	**No**	**Details**	**Proposed Plan**

35.	Does the grantee generate e-waste, produce or manufacture electrical and electronic equipment?	X		E-waste such as non working IT equipments are generated. No other electrical or electronic equipment is produced or manufactured	E-waste is recycled at Jagdamba scrap traders, Ahmedabad and this process will be followed throughout the project.
36.	Has the grantee obtained SPCB authorization on e-waste?		X	E-waste generated is scrapped to Jagdamba Traders and they are the registered recyclers	Not Applicable.
37.	Does the grantee channelize the e-waste to **authorized** recycling or disposal facility?	X		Name and address of disposal facility/ recycler: Jagdamba scrap traders, Ahmedabad In-house or outsourced Facility: outsourced	Practice already in place will be followed throughout the Project.
38.	Does the manufacturing grantee have Extended Producer Responsibility system and EPR-authorization in place?		X	Describe: Not required	Not Applicable
39.	Does the grantee practice reduction in the usage of hazardous substances in the manufacture of electrical and electronic equipment and its parts?		X	Not Applicable	Not Applicable
40.	Does the grantee provide detailed information on the constituents of the equipment and their components/spares and declaration of conformation to Reduction in Hazardous Substances in the product user documentation?		X	Not Applicable	Not Applicable
41.	Does the grantee maintain a record of collection, storage, sale and transport of e-waste?	X		As per SP-PA-012: Scrap Handling and Campus Solid waste Management, Intas Biopharma facility, records for e-waste is available.	Existing procedures, process and regulatory compliance will be extended and followed throughout the project.

42.	Does the grantee submit annual reports on e-waste to SPCB?		X	Scrap record is available at premises for e-waste and the registered recycler is audited by SPCB	Information shared with SPCB.
43.	Is there accident reporting and records in place?	X		Accident reporting and records in place	Practice already in place and records may be provided on request.
44.	Are PPEs available to staff?	X		SOP on Handling Solid waste talks about PPE	The stock status of PPE will be regularly monitored and procurement will be done in time to avoid any situation of stock out.
45.	Is the grantee involved in manufacture of batteries?		X	We don't manufacture any kind of batteries.	No proposed plan to manufacture batteries.
46.	Does the grantee generate battery waste?	X		Intas does generate battery waste from UPS. The used batteries are recycled as an exchange from the vendor who is supplying the new batteries. The batteries that are not fit for exchange are being sent to Jagdamba scrap traders, Ahmedabad	Existing procedures, process and regulatory compliance will be extended and followed throughout the project.
47.	Does the grantee deposit the battery waste to registered recycler/dealer/manufacturer/reconditioner/collection center?	X		Name and address of battery waste receiving entity: Jagdamba scrap traders, Ahmedabad	Proposed plan in place to handover the battery waste to registered recycler will be followed throughout.
48.	In case of manufacturing, does the grantee comply to Battery Management Rules 2000 and ensure collection of old batteries?	X		Registered Recycler: Jagdamba scrap traders, Ahmedabad	Existing procedures, process and regulatory compliance will be extended and followed throughout the project.

Community Health and Safety and risk mitigation					
		Yes	**No**	**Details**	**Proposed Plan**
49.	Safety Transportation Management System (for transport Of hazardous material)	X		Membership with Ecocare Infrastructure Pvt Ltd. For safe transportation & disposal of Hazardous waste. Membership with E-coli waste management for safe transportation & disposal of bio medical waste.	Existing procedures, process and regulatory compliance will be extended and followed throughout the project.
50.	Emergency preparedness and participation of local authorities and potentially affected communities	X		Emergency response plan available	Emergency response plan practice already in place which will be maintained

Other					
	Area of Risk	**Yes**	**No**	**Details**	**Proposed Plan**
51.	Does the grantee use any radioactive materials (isotopes, tracers, radiation equipment, etc)?		X	Not required as we don't use.	We don't use any radioactive material in our facilities and will not be used in the future also.
	Does the grantee have appropriate radioactive material and waste storage and disposal system in place?		X	Describe: Not required	
	Are radioactive warning signs in place?		X	Not required	
52.	Is the lab/room air regularly checked for microbial contamination?	X		Environmental monitoring program is not available for R&D at Intas Biopharma facility	Not Applicable
53	Are there any odor control measures in place?		X	Polyelectrolytes for damp ETP sludge and then lime is sprayed. Filter press and screw press process is carried out for dry sludge extraction. The dry sludge is filled in polyethylene bags and stored at a safe distance – HW storage area as per GPCP norms	Mentioned practice is in place.
54.	Are fume hoods and exhausts regularly checked and maintained?	X		SOP: SP-EN-155 (preventive maintenance of	Practice already in place.

				fume hood) at Intas Biopharma facility	
55.	Does the grantee use DG set > 15 KVA?	X		To Check: Inspection report/Certificate available. Consent for DG > 15 KVA available. The emissions from the boilers and DG sets are monitored and are within the prescribed norms.	Monitoring for air emissions will be continued.
	Does the grantee have consent for DG > 15 KVA?	X			
	Are emissions from boilers and DG sets regularly monitored to be within the prescribed norms?	X			
56.	Does the grantee have proper disposal process for solid and plastic waste in compliance to Solid Waste Management Rules, 2016 and Plastic Waste Management Rules, 2016?	X		Describe: SP-PA-012: Scrap Handling and Campus Solid waste Management, Intas Biopharma facility Municipal solid waste is treated in our ETP site and the sludge that is generated is further sent to the registered TSDF site for further processing and disposal. Plastic solid waste that are generated are all sent to the Jagdamba scrap traders, Ahmedabad for recycling.	Solid waste are segregated and sent to PCB Authorized Vendor.
57.	Is wastewater treated separately by the grantee? (Liquid waste from laboratory, chemicals, fluids, solvents, medium and cultures, coolants, etc.)	X		Types of wastewater: Liquid waste from laboratory, chemicals, fluids, solvents, medium and cultures, coolants Treatmentof wastewater: Treated in ETP Chemical management in wastewater treatment plants: all effluents from labs are treated in ETP. Coagulation and flocculation chemicals are used.	Periodic checks will be done and the treated water will be sent to ETP.

				EHS/PY/006-01 Policy on operation of effluent treatment plant.	
	Are there sludge management and cut off drains in place for wastewater?	X		EHS/PY/006-01 Policy on operation of effluent treatment plant.	The mentioned practice is already in place and will be followed.
58.	Are necessary provisions for noise cancellation in place?	X		Enclosure are built for loud noise escape. Use of PPE such as ear plugs and ear muff.	Mentioned practice is in place and proper checks and balances will be maintained.
59.	Are there any settlements, water bodies, cultivated land, or any other eco-sensitive areas near the grantee's premises?		X	Describe: NA Distance from premises: NA	Not Applicable
60.	Are there any buffers, fire vehicle routes in the grantee's premises?	X		As per the Intas layout, there are vehicle routes in and around the facility accessible to all the buildings within the premises to ensure buffers and safety.	Will ensure that the premise is well equipped with these essential services which are properly and regularly maintained.
COVID Precautions & Guidelines Implementation					
61	Guidelines of CPCB/SPCB/GoI for Handling, Treatment, and Disposal of COVID Waste Generated is whether being followed		X	Intas will not generate COVID waste. In the current project, Intas will produce rAAV(recombinant Adeno Associated Virus) encoding a segment of spike protein and outsource it to relevant facilities to evaluate its safety and efficacy. This will not involve any COVID strain or waste.	COVID waste not generated at Intas. In case any waste is being generated in future proper disposal as per guidelines of CPCB/SPCB/GoI will be followed.
62	SOP on preventive measures to contain spread of COVID-19 issued by ICMR/GoI from time to time is whether being followed	X		Intas follows general guide-line issued by ICMR/GoI to contain spread COVID-19 among employees.	Intas is not involved in generation of any COVID waste through any of its process.

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.