

“Rapid Response Regulatory Framework for COVID 19”

Compilation of Notifications



Department of Biotechnology
Ministry of Science & Technology
Government of India

June 2020



No. BT/03/27/2020-PID

Dated 20.3.2020

OFFICE MEMORANDUM

Subject: Rapid Response Regulatory Framework for COVID-19 to deal with applications for development of vaccines, diagnostics, prophylactics and therapeutics - reg.

Taking into account the rapid spread of COVID-19 in various countries and the need for immediate research and product development, it has been decided to fast track the regulatory approval process in consultation with DCGI to deal with the applications for development of vaccines, diagnostics, prophylactics and therapeutics for COVID-19 as per following:

- i. Permission for Import/ exchange: Review Committee on Genetic Manipulation (RCGM) will approve the application fulfilling all essential criteria within 7 days from the date of receipt of application along with IBSC recommendation on IBKP Portal.
- ii. Permission for initiating research work- RCGM will approve the application fulfilling all essential criteria within 7 days from the date of receipt of application along with IBSC recommendation on IBKP Portal.
- iii. Examination of physico chemical & molecular characterisation data and approval of the Animal Toxicity Protocol- 10 days after submission of all essential data, PCT protocol and IBSC recommendations on IBKP portal.
- iv. Recommendation of RCGM for appropriate phase of clinical trial – 10 days after submission of all essential Preclinical Toxicity Data.
- v. Approval of Form 29 / test licence/NOC to manufacturer by CDSCO within 10 days from the receipt of application.
- vi. CDSCO shall make a CORONA unit to address queries on development of diagnostics, prophylactics and therapeutics for COVID- 19 and will also provide a link at CDSCO portal in this regard.

2. For this purpose, an Empowered Committee of RCGM and CDSCO has been constituted to examine the applications and to recommend the applications for approvals as per the agreed timeframe.

This issues with the approval of the Secretary, Department of Biotechnology

(Nitin K. Jain)
Scientist F & Member Secretary, RCGM

To
NIC-Department of Biotechnology and CDSCO for uploading on websites



No. BT/BS/17/635/2015

Date: 8.4.2020

OFFICE MEMORANDUM

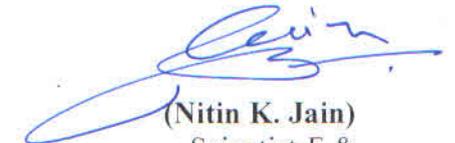
Subject: Regulations & Guidelines for Recombinant DNA Research & Biocontainment- Interim Guidelines on laboratory biosafety to handle COVID-19 specimen for R&D purpose

In continuation of this Department Office Memorandum of even No. dated 1.4.2018 and the powers conferred through the Sections 6, 8 and 25 of Environment Protection Act (EPA), 1986 and based on the recommendations of Review Committee on Genetic Manipulation (RCGM) in its meeting held on 7.4.2020, Department of Biotechnology hereby notify attached interim guidelines to handle COVID-19 specimens for R&D purpose. The guidelines include a whole range of basic minimal procedure to be followed, risk assessment & mitigation measures, routine laboratory procedure, specimen & nucleic acid storage, viral isolation, disinfectants & lab waste management, specimen packaging and shipment procedure etc.

2. As per the provisions of Rule 1989, all IBSCs and host institutions involved in research, development and handling of COVID-19 specimens are required to comply with these interim guidelines with immediate effect. Non-compliance shall attract the provisions of Section 15, 16 and 17 of Environment Protection Act (EPA), 1986.

3. For further information, IBSCs may also refer to interim guidelines issued by WHO and CDC on handling of COVID-19 specimens.

4. The interim guidelines on laboratory biosafety to handle COVID-19 specimens are notified at www.dbtindia.nic.in.


(Nitin K. Jain)
Scientist-F &
Member Secretary- RCGM

To:

- I. All Ministries and Departments of Govt. of India
- II. All IBSCs
- III. Communication Cell, DBT

Interim Guidance Document on Laboratory Biosafety to Handle COVID-19 Specimens

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), commonly known as 2019 novel coronavirus (COVID-19) has been declared as pandemic by the World Health Organization. With little scientifically validated information on this novel virus as well as the absence of vaccine and medications to treat or limit the spread, the laboratories planning for R & D work on suspected/confirmed positive COVID-19 samples should follow the precautions as enlisted for the Risk Group 3/4 organisms in the “*Regulations and Guidelines for Recombinant DNA Research and Biocontainment, 2017*”.

The purpose of this document is to provide an interim guideline on laboratory biosafety (in tune with the international norms) to be followed in handling and processing clinical samples/infectious virus for diagnostic testing and R&D work to develop new diagnostics / therapeutics for COVID-19. All virus-related manipulations should be performed in a BSL2/3 laboratory depending on the nature of the work and only by laboratory staff trained in the relevant technical and safety procedures with strict adherence to sample inventory, Personal Protective Equipments and Waste Management SoPs.

The basic minimal procedures to be followed are:

All Institutional Biosafety Committee’s (IBSCs) must assess the available facilities, trained manpower in handling high risk group (RG3 and above) hazardous microorganisms, personal protection equipment (PPE) and waste disposal mechanism to meet all the requirements prior to initiation of work involving COVID-19. Prior to the initiation of R&D work involving COVID-19, proposals should be submitted online at IBKP portal along with IBSC recommendation for the approval by the Review Committee on Genetic Manipulation (RCGM). All applications for the development of vaccines, diagnostics, prophylactics and therapeutics will be considered under Rapid Response Regulatory Framework for COVID-19 by RCGM and CDSCO as per DBT OM No. BT/03/27/2020-PID, dated 20.03.2020.

- i. Appropriate personal protective equipment (PPE) as determined by a detailed risk assessment, should be worn by all laboratory personnel handling these specimens.
- ii. All procedures must be performed based on risk assessment and only by personnel with demonstrated capability in strict observance to any relevant protocols at all times.
- iii. Where the work involves the use of only the viral components and not the live SARS-CoV-2 virus, patient specimens collected in the COVID treatment ward in collection tubes, sealed properly and containing virus inactivation reagents that denature the viral envelope, and inactivate the virus may be transported from the

Department of Biotechnology

hospital wards to respective Laboratories, similar to transportation of biomedical samples from the hospital wards to laboratory.

- iv. Patient specimens from suspected or confirmed cases should be transported as UN3373, “Biological Substance Category B”; Viral cultures or isolates should be transported as Category A, UN2814, “infectious substance, affecting humans” respectively and transported as per the WHO “**Guidance on regulations for the transport of infectious substances 2017–2018**”. As a first step, it is imperative that periodical recording of inventory of sample collection, storage, authorization of use, transfer and disposal of all materials are adhered to.
- v. Initial processing (before inactivation) of all suspected specimens should take place in a validated biological safety cabinet (BSC) or primary containment device.
- vi. Non-propagative diagnostic laboratory work (e.g. nucleic acids, sequencing, NAAT, PCR, isolation of antibodies, serum proteins) should be conducted in laboratories with facilities and procedures equivalent to BSL-2. Further, infective agent should be inactivated in BSL-2 cabinet under suitable PPE before any laboratory procedure. Based on the biological material required, if sample collected in inactivation medium, such procedure could be adopted.
- vii. All propagative work (e.g. virus culture, isolation or neutralization assays) should be performed only by properly trained and competent personnel in laboratories capable of meeting additional essential containment requirements and practices (BSL-3).
- viii. Appropriate disinfectants with proven activity against enveloped viruses should be used (e.g. hypochlorite (bleach), alcohol, hydrogen peroxide, quaternary ammonium compounds and phenolic compounds).
- ix. All technical procedures should be performed with standard operating protocols that minimize the generation of aerosols and droplets.
- x. IBSC should quarterly update status of such work in the organization along with details of inventory and biosecurity information.
- xi. Periodic reports of the staff handling the work and their medical surveillance reports duly certified by a medical doctor should be complied with.
- xii. For work related to COVID-19, RCGM may constitute an empowered Committee, if necessary to visit the laboratory to ensure due diligence to protocols and other requirements
- xiii. To prevent spread of disease in animals, if any, tested animals should be properly isolated and taken care.

Risk assessment and mitigation measures

Risk assessment and mitigation measures are dependent on the procedures performed and the competency level of the personnel performing the procedures in addition to identification of the hazards involved in the process and/or procedures, the laboratory equipment and facility, and

Department of Biotechnology

the resources available. It is highly recommended to start by performing a local risk assessment for each of the process step, i.e. starting from sample collection, to the different processes that are planned in the laboratory) and for each of the process step the potential hazards (e.g., aerosol exposure, potential spillage etc.,) have to be considered and assessed with a grade of risk. Appropriate risk control measures are to be identified and implemented to mitigate the risk identified to an acceptable level.

Routine laboratory procedures

Clinical samples being processed for non-culture-based laboratory diagnostic procedures and PCR analysis from patients suspected or confirmed to be infected with the novel coronavirus should adopt procedures and practices routine to a clinical and microbiology laboratory. A validated biosafety cabinet (BSC) to be strictly used for all manipulations that might potentially result in droplets or aerosol (e.g. loading and unloading of sealed centrifuge cups, grinding, blending, vigorous shaking or mixing, sonic disruption, opening of containers of infectious materials whose internal pressure may be different from the ambient pressure), from infectious COVID-19 samples.

Specimen and nucleic acid storage

Suspected or confirmed COVID-19 specimens, with appropriate identification labeling, should be stored at a designated place with controlled access to authorized personnel only at 2-8 °C or at -70°C depending on the nature of the experiment(s). Extracted nucleic acid samples should be stored at -70 °C or lower. All diagnostic laboratories should strictly follow the retention period as per standard guidelines for the samples submitted to them for testing.

Viral isolation

Viral isolation from clinical specimens suspected or confirmed to be infected with the novel coronavirus (COVID-19) should be performed only in Biosafety level 3 (BSL3) and above facilities.

Disinfectants and Laboratory waste management

For the selection of appropriate decontamination and disinfection strategies for biomedical waste treatment and disposal should be in accordance to those mentioned in the “**Revised Guidelines for Common Bio-medical Waste Treatment and Disposal Facilities**” (2016) developed by Central Pollution Control Board (CPCB). In the light of the comparable genetic characteristics with SARS-CoV and COVID-19, COVID-19 is likely to be susceptible to

Department of Biotechnology

disinfectants with proven activity against enveloped viruses, including sodium hypochlorite (bleach) (e.g. 1,000 ppm (0.1%) for general surface disinfection and 10,000 ppm (1%) for disinfection of blood spills), 62-71% ethanol, 0.5% hydrogen peroxide, quaternary ammonium compounds and phenolic compounds and used as per manufacturer's recommendations. The contact time for disinfection, dilution/concentration of the active ingredient and its shelf life should also be considered. The waste generated in the laboratory handling live virus be incinerated. The laboratory waste should be handled like other biohazardous waste as per the DBT notified "**Regulations and Guidelines on Biosafety of Recombinant DNA Research and Biocontainment, 2017**".

Specimen packaging and shipment

All specimens being transported should have appropriate packaging, labeling and documentation. For details, follow WHO's "**Guidance on regulations for the transport of infectious substances 2017–2018**". This document provides practical guidance to facilitate compliance with applicable international regulations for the transport of infectious substances by all modes of transport, both nationally and internationally, and include the changes that apply from 01 January 2017.

- i. All materials to be transported should be placed in a leak proof unbreakable primary container followed by a leak proof, watertight secondary packaging with absorbent material and a rigid outer packaging to minimize the potential for breakage or spillage.
- ii. Patient specimens from suspected or confirmed cases to be transported for diagnostic or investigational purposes - as UN3373, "Biological Substance, Category B"
- iii. Transporting viral cultures or isolates - as Category A, UN2814, "infectious substance, affecting humans".
- iv. Transport of specimens within national borders should comply national regulations.
- v. For cross boundary transport of novel coronavirus specimens should follow the UN Model Regulations, Technical Instructions by the International Civil Aviation Organization and other applicable regulations depending on the mode of transport being used.

Note: For further information, the IBSCs are advised to refer to the following two Interim Laboratory Biosafety Guidelines.

1. **WHO interim guidelines: Laboratory biosafety guidance related to the novel coronavirus (COVID-19) (as on 19 March 2020)**
2. **CDC Interim Laboratory Biosafety Guidelines for Handling and Processing Specimens Associated with Coronavirus Disease 2019 (COVID-19) (as on March 31, 2020).**



No. BT/BS/17/635/2015

Dated: 20th April, 2020

ORDER

Due to the prevailing COVID 19 situations, the IBSCs are allowed to conduct their meetings through video conferencing up to 3rd May, 2020 with the following conditions to be fulfilled:

- 1) The participation of the DBT nominee, the Biosafety Officer and at least one outside expert is mandatory.
- 2) The views of the DBT nominee and other members on every proposal considered in the meeting should be clearly recorded in the minutes.
- 3) The Video conferencing based meetings would be applicable to the reviewing of the ongoing proposals as well as new proposals requiring upto BSL 2 facilities.
- 4) The IBSC may demand presentations and videos from the applicants wherever physical inspection is required.

These are interim guidelines applicable during the lockdown period only.

(Dr. Nitin Kumar Jain)
Scientist 'F' and Member Secretary, RCGM

To
All IBSCs



No. BT/BS/17/635/2015

Dated : 13th May, 2020

ORDER

In continuation to this Department order no. even dated 20th April, 2020, it is informed that the IBSCs are now allowed to conduct their meetings through video conferencing upto 30th June, 2020 with the following conditions to be fulfilled :

- 1) The participation of the DBT nominee, the Biosafety Officer and at least one outside expert is mandatory.
- 2) The view of the DBT nominee and other members on every proposal considered in the meeting should be clearly recorded in the minutes.
- 3) The video conferencing based meetings would be applicable to the reviewing of the ongoing proposals as well as new proposals requiring upto BSL 2 facilities.
- 4) The IBSC may demand presentations and videos from the applicants wherever physical inspection is required.

(Nitin K. Jain)

Scientist 'F' and Member Secretary, RCGM

To

All IBSCs,



No. BT/03/27/2020-PID

Dated: 26th May, 2020

OFFICE MEMORANDUM

Sub: Rapid Response Regulatory Framework for COVID-19 Vaccine development -reg.

In pursuance of the recommendation of Empowered Committee of RCGM and CDSCO constituted by this Department OM of even No. dated 20.03.2020 to deal with applications for development of vaccines, diagnostics, prophylactics and therapeutics under Rapid Response Regulatory Framework for COVID-19, the Rapid regulatory framework for fast track processing of applications relating to recombinant vaccines for COVID 19 has been developed, which is attached herewith for information and necessary action by all the stakeholders.

(Dr. Nitin K. Jain)

Scientist-F &
Member Secretary, RCGM

To:

1. All IBSCs
2. NIC to upload on DBT website, IBKP Portal and CDSCO Portal.

Rapid Response Regulatory Framework to deal with applications for COVID 19 Vaccine Development

To facilitate the COVID-19 vaccines development, the following guidance note is issued for the COVID-19 Vaccines Rapid Regulatory pathways. This guidance document is recommendatory and dynamic in nature without prejudice to statutory provisions. Individual application will be examined based on the type of vaccines candidate and their data requirement.

Individual applications will be examined and considered depending on their completeness for approval under the Rapid Response Regulatory Framework. The applicants and regulators shall engage on regular basis to ensure the requisite progress in the development.

Following guidance note is hereby issued:

1. The checklist for application to conduct pre-clinical toxicity (PCT) studies for recombinant vaccine development for COVID-19 as per appendix – I.
2. **Consideration of preclinical data generated outside India:** Considering the research collaboration of Indian enterprises with foreign research organizations the preclinical studies already done outside India may be considered in regulatory submission and individual application will be examined based on quality of data generated and conduct of limited preclinical study may be asked for after examination, if required.
3. The applicant may submit parallel application for conducting appropriate phase of clinical trial to CDSCO for consideration at the time of conduct of PCT studies based on proof of concept. However, the application for clinical trial will be approved subject to NOC from RCGM after examination of data of pre-clinical studies.
4. **Consideration of data on clinical studies:** Data generated outside India will be considered and examined and an abbreviated pathway may be considered for COVID 19 vaccine based on scientific rationale and level of completeness of data in human trials in addition to satisfactory preclinical data. Phase I/II or phase III multicentric study on statistically significant sample size may be considered based on, initial safety studies, proof of concept and dose finding data.

Appendix-1

**Checklist for application to conduct Pre-Clinical Toxicity (PCT) studies
for recombinant vaccine for COVID-19.**

S. No.	Parameters	Remarks	Provided Yes/No (Page no.)
A	General The Vaccine production platform (live viral vector, DNA, Yeast/ cell line expression, etc.) and the anticipated end product (DS)* substantiated with published literature regarding its quality attributes, safety and immunogenicity. Substantiation can be with unpublished literature as well (inhouse research, patent needs, etc.). In such cases there should be substantial documentation like manuscripts, inhouse documents, etc.	-	
A1	The application to contain Table of contents, all pages serially numbered, and all cited annexure(s) included in the final application.	Required	
A2	Approval(s) accorded so far for the product under development by IBSC, RCGM, IAEC, etc. approved by CPCSEA, etc. (approvals as per proforma and guidelines may be provided later when COVID-19 situation improves)	Firm should apply for the appropriate approvals. Rolling submission allowed.	
A3	Describe source of material (isolate, lab, country)	Required	
B	Molecular Characterization		
B1	Describe origin of gene(s) coding the molecule under consideration (isolate, lab, organization country)	Required	
B2	Provide Nucleotide and translated protein sequences	Required	
B3	Information about the vector (Include restriction map, Promoter and Terminator used for the expression of recombinant gene, method of transformation, selection agent used, etc.)/	Required	
B4	Description of host organism characteristics/ / Cell type to be used for expression and method of recombinant gene delivery	Required	

B5	Safety of the host organism (indicate Risk Group#).	Required	
B6	Copy number and stability of plasmid in expressing host cell for microbial fermentation before induction and at the time of harvest.	Can be submitted later with toxicity report.	
B7	Provide information on the expression levels of protein	Can be submitted later with toxicity report.	
B8	Provide brief note on containment level adopted and biosafety procedures followed during the study.	Required	
B9	Describe waste disposal SOP	Required	
C	Standardization of fermentation/production procedures**,##		
C1	Detailed media composition for pre-inoculum, inoculum and production process (Indicate wherever commercial media used), feeding rate of media (in grams of nutrient/h/L of initial fermentation broth)	Brief information required	
C2	Information on three batches of fermentation and batch size (in terms of liters). Batches to be non-sequential, preferably 48hrs-1 week apart.	Three batches to establish consistency of the process required.	
C3	Consolidated trend of different parameters from three representative batches (such as cell growth, product formation, pH, temperature, dissolved oxygen, nutrient consumption, agitation rate, aeration rate, CO2supplementation) during fermentation.	Three batches to establish consistency of the process required	
C4	Time dependent product profile: 1). Concentration of product/L, yield and volumetric productivity (titre in case of recombinant virus). 2. Consistency of specific protein yield (amount of protein per unit cell mass at different cell concentration during fermentation). 3) In case of multiple antigenic targets – consistency for all the targets	Key profiles of three batches required	
C5	Describe waste disposal SOP	Required	
D	Downstream process for purification**,##		
D1	Purification process (flow chart detailing all major steps involved).	Required	
D2	List of reagents, resins, membranes used in the purification process along with their properties.	Required in short	

D3	Description of each unit of operation step (batch size) during purification. Chromatograms of three consistency batches.	Required in short	
D4	Quality of the product at each step of purification SDS-PAGE, reducing and non-reducing gels (include suitable MW Marker, Mention loading of DS in µg (e.g., 1µg, 3µg, 5µg etc.) Chromatographic analysis for each purification step (include an overlay of all batches). Batch consistency in terms (1) active component(s) (2) in case of multiple antigens or extracts or DNA or RNA constructs or VLPs or polysome/ liposomes/ microsomes or heat inactivated virus, etc., where multiple virus-associated antigens will be used for immunization. Batch consistency of product profile including different antigen ratios, wherever applicable, should be provided with supporting data in the form of silver stained gels or HPLCs profile, etc Data on downstream purification process shall include presence of any impurities such as host cell derived proteins/DNA/RNA, depending on the nature of the candidate vaccine and reagents/materials used in the downstream process. Biological activity for three batches should be compared to show they are within the permitted range. As above batches to be non-sequential.	Required	
D5	Stepwise and Overall recovery of the product (for each batch) in a tabulated form	Required	
D6	Summary table showing consistent recovery of drug substance (yield at each stage of purification, overall product yield, specific activity etc.)	Required	
E	Physico-chemical characterization**,###		
E1	Intact mass analysis Confirming the identity of the expressed gene product.	An overall plan of characterization be provided for PCT studies.	
E2	Peptide mapping (overlay results of all batches) and N-terminus amino acids sequencing data		
E3	Secondary structure data by CD spectroscopy/Near and far UV visible spectra (overlay results of all batches)	The basic CMC data should be submitted for RCGM approval of PCT study protocol. Complete CMC data should be submitted along with PCT reports.	
E4	Fluorescence spectroscopy to provide evidence for similarity at high order structure (overlay results)		
E5	Data on disulfide bond presence (when applicable)		
E6	Charge heterogeneity (Data from Ion exchange chromatography, Isoelectrofocusing, etc.)	Note; The data requirement vary	

E7	Carbohydrate/glycan content analysis and details of components, as applicable	depending on the type of vaccine. In case of DNA vaccine, sequence information of vector and target gene(s), host cell DNA contamination, etc. will be important.	
E8	Presence of aggregates (using any suitable method e.g. Size Exclusion Chromatography (SEC), Dynamic Light Scattering (DLS) etc.)	In case of subunit vaccine, expressed SARS CoV-2 virus protein(s), glycan analysis, CHO content, DS purity, aggregates will be important	
E9	Endotoxin/Pyrogen content (<i>for each consistency batch</i>)		
E10	Host Cell Protein content (<i>for each consistency batch</i>)		
E11	Host Cell DNA content (<i>for each consistency batch</i>)	Stability of the DP and its effective (efficacy) dose is a primary requirement for PCT studies.	
F	Immune response / Biological activity		
F1	Specify Adjuvant and dose formulation. Specify laboratory animal model used for assessing the immunogenicity (number, age, gender, strain), Vaccination protocol (site/dosage) concentration of antigen used, the immune response profile, antibody titers, etc. describe method of measuring antibody profile, antibody titres, etc. Provide data on antibody profile, antibody titre.	Required. This is critical for a vaccine candidate	
F2	Assessment of neutralizing antibodies, if any. Describe method for assessment of neutralization antibodies, provided data on neutralization efficiency/specificity, etc.		
F3	Report any adverse effect in animals	Required	
F4	Polyclonal or monoclonal antibody product? If poly clonal, batch consistency data and if monoclonal, clone data and other sib clones availability	Required	
G	Formulation and Stability studies of Drug Substance (DS) and Drug Product (DP), proposed done*		
G1	Submit consolidated three batch data	Required for three batches	

G2	SDS-PAGE analysis (preferably silver stained & in alignment with MW Marker) and confirming the identity by western blotting	Basic characterization for the Vaccine drug product.	
G3	Overlay of Size Exclusion Chromatography analysis	Detailed can be given with Tox. Report	
G4	Data on bioactivity/bioassays		
G5	Stability data on real time***, accelerated and stress studies of all batches of drug substance (DS) and drug product (DP) at defined time points for DS and depending on the proposed shelf life for DP .	Stability Program / Protocol should be given in PCT application and with the proof of start of stability for DS and DP. The stability data can be submitted in rolling submission for special COVID 19 situations as stability of the compound is a primary requirement for PCT studies)	
	Storage temp. of DS and DP	Required	
	Stability studies results should be submitted along with C3b form.	With Toxicity report	
	Should include Real time, Accelerated stability and Stress stability data.	Plan should be for all three	
G6	Define the composition of DP. Specify the adjuvant, excipients/stabilizers used in the formulation. In the case of multiple antigenic targets in the DP indicate the ratio of the different targets	Required	
H	Acceptability criteria of the formulated material for preclinical safety studies (<i>Acceptance limits should be set based on Indian pharmacopoeia for vaccines or equivalent regulation for general test parameters and in house criteria.</i>)		
H1	Specifications for DS and DP should be established around critical quality attributes.	Required	
I	Proposed study plan for preclinical toxicity studies		

I1	Whether the representative toxicology batch of DP is one of the RCGM approved consistency batch. If not, generate complete comparative data of this batch with that of the consistency batch approved earlier by RCGM.	Submit the batch size which should be sufficient enough to conduct characterization and PCT studies. Submit the profile of batch and COA after the batch is taken for PCT within a week of the testing is completed.	
I2	List of preclinical toxicity and immunogenicity studies to be conducted. (including protocol/guidelines/standards to be followed)	Required	
I3	Selection criteria for animals selected and numbers to be used in each group. Justification for the selection of animal model/numbers)	Required	
I4	Submit detailed Pre-clinical toxicity & Immunogenicity (sequence specific, non-specific to other proteins and with adjuvant, as applicable) study protocols. Protocols should include route of administration, dosage to be tested (based on effective dose), basis of dose calculation, vehicle, mode of administration, volume of administration (single or multiple administration).	Required	
I5	Provide address and accreditation status of the facility where studies are to be conducted.	Required	
I6	Explain compliance of containment facility measures.	Required	
I7	Specify decontamination and disposal mechanisms.	Required	
I8	Explain plans in case of any Emergency.	Required	
I9	Attach copies of IBSC approvals of the Sponsor and CRO(s) (Photocopy of IBSC/ minutes wherein proposed studies were approved).	Required (Online meetings are allowed)	
J	Undertaking/ Declaration Letter Signatures To be signed in original by hand (<u>Electronic/ scanned signatures not acceptable</u>).	Required (all legal signatures to be accepted)	

Follow the link below to determine Risk Group of host cell/organism and containment level to be followed. (<http://www.dbtindia.nic.in/wp-content/uploads/Regulations->

Guidelines-for-Recombinant-DNA-Research-and-Biocontainment-2017.pdf). For SARS CoV-2 follow the Interim Guidance Document on Laboratory Biosafety to Handle COVID-19 Specimens available at IBKP portal.

* The end product (DS) from the chosen production platform to be supported with appropriate documents (regulatory/ published reports / Clinical trials) for its quality attributes and safety

**Original Data (Tables, figures in colour wherever appropriate & graphs) with proper labelling and appropriate interpretation must be submitted. Figures with overlay data should be submitted for to facilitate direct comparison, if and applicable.

*** Up to one month Real time stability data of DS and DP required at the time of submission (if not a plan and weekly report of studies result may be submitted after application), applicant is required to submit a minimum one month data at the time of Form C3b submission, both with undertaking of commitment statement to continue studies for remaining period as per plan, and the remaining data at the time of toxicity report (Form C5) submission.

Data: (i.e. batch size, date of initiation & completion of fermentation, purification, formulation and stability studies) and formulation details along with excipients. Number of samples analyzed at each data point should sufficient enough to reveal statistically significant differences among the batches and assay points. To be adhered if planned for multiple antigenic targets

Gross pictures should be taken with sufficient shadow less white light and printed on photo quality, glossy , color ink jet paper and there should be a dimension marker (scale) included in the picture below the organ.

Histopathology pictures (high resolution pictures showing magnification used) shall be submitted. In addition, the stain used and the magnification at which the picture was taken should also be given in the photograph.

Historical data of haematology, clinical chemistry, histopathology should be mentioned in the report, including the normal range.

Evaluation criteria should be in terms of both statistical significance and biological response of the test system

Test system (animals) to be used for the toxicity/immune response studies should be characterized appropriately to generate reliable and reproducible data.

**Department of Biotechnology
Ministry of Science & Technology
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