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.

BT/03/27/2020-PID   **Date: 23.05.2020**

**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 rational 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, CO_2 supplementation) 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 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	An overall plan of characterization be provided for PCT studies. The basic CMC data should be submitted for RCGM approval of PCT study protocol. Complete CMC data should be submitted along with PCT reports. **Note**; The data requirement vary	
	Confirming the identity of the expressed gene product.		
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)		
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.)		

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 CARS CoV-2 virus gene(s), host cell DNA contamination, etc. will be important. In case of subunit vaccine, expressed SARS CoV-2 virus protein(s), glycan analysis, CHO content, DS purity, aggregates will be important	
E8	Presence of aggregates (using any suitable method e.g. Size Exclusion Chromatography (SEC), Dynamic Light Scattering (**DLS**) etc.)		
E9	Endotoxin/Pyrogen content (*for each consistency batch*)		
E10	Host Cell Protein content (*for each consistency batch*)		
E11	Host Cell DNA content (*for each consistency batch*)		
		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***(Acceptance limits should be set based on Indian pharmacopoeia for vaccines or equivalent regulation for general test parameters and in house criteria.)*		
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 applicable0) 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 (**Electronic/ scanned signatures not acceptable**).*	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-Reocminant-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.