

**FORM C3a: APPLICATION TO RCGM TO CONDUCT PRECLINICAL AND/OR SAFETY STUDIES OF SIMILAR BIOLOGIC DEVELOPED USING GENETICALLY MODIFIED ORGANISMS (GMOs)/ LIVING MODIFIED ORGANISMS (LMOs) FOR HEALTHCARE AND INDUSTRIAL USE**

**1. Applicant Details :**

**Instructions to follow**

Name of Applicant :

Designation :

Address/Line - 1 :

Address/Line - 2 :

State / UT :

District :

Village / Town / City :

Pin Code :

Office Phone Number :

With STD Code

Mobile No :

Email :

**2. Application for :**

**3. Product Code :**

Choose/ generate the CODE, which explicitly conveys the essence of the proposed work. Kindly note that the same code might be used for generation of future references.

**4. Objective(s) of the proposal :**

Furnish details of key objectives and scientific background of the projects as bullet points.

## 5. Status of the Project :



Revised Submission



New Submission

## 6. Chronology of approval(s) accorded so far by the IBSC for the Similar Biologic under investigation :

- Mention the date(s) of IBSC meeting wherein various considerations pertaining to the product under investigation were deliberated and approved
- Enclose colored photocopy(ies) of the minutes of the relevant IBSC meeting(s)

Upload

Please upload only 2.0 MB File .pdf,.doc,.png,.jpg and .docx file.

## 7. Chronology of approval(s) accorded so far by the RCGM for the Similar Biologic under investigation :

- Mention the date of permission(s) issued previously by the RCGM for the product under investigation
- Enclose colored photocopy(ies) of permit(s) issued earlier

Upload

Please upload only 4.0 MB File.pdf,.doc,.png,.jpg and .docx file.

## 8. Background about the Reference Biologic(s) :

### 8.1 Product scientific name/INN:

Write international nonproprietary name (INN) of the molecule/ product

### 8.2 Trade name and its proprietary :

### 8.3 Type :

8.4 Source:

8.5 Therapeutic indication(s):

To be submitted as bullet points

8.6 Active Ingredient(s):

8.7 Target molecule(s):

8.8 Mode of Action :

8.9 Formulation :

	S.No.	Active Ingredient(s) and Excipient(s)	
		Reference Biologic 1	Reference Biologic 2, as applicable
	01		

8.10 Strength(s) :

8.11 Storage condition(s) and stability:

8.12 Dosages :

8.13 Number & route(s) of administrations per day/ per week/ per month :

8.14 Known side effects, if any :

8.15 Known toxicity both in animals and humans, if any :

8.16 Country of Origin:

INDIA

8.17 Host cell line :

Provide details of host cell line(s) used for the production of Reference Biologic

8.18 Status of approval & marketing history in India, country of origin and worldwide:

Upload

please upload only 0.5 MB File .pdf,.doc,.png,.gif and .docx file.

8.19 Existing treatments for the proposed indications:

Have you used/ planning to use more than one 'Reference Biologic' while assessing the similarity of proposed 'Similar Biologic'? If so, Please tick the checkbox:

☐

9. Indication(s) for which applied for :

To be submitted as bullet points

10. Details of Molecular Characterization:

10.1: Description of host organism(s) characteristics :

If the provided space is insufficient to furnish complete details, please enclose the relevant information as annexure

a) Taxonomy of host(s) or the host(s) carrying the vector(s)/target gene(s)

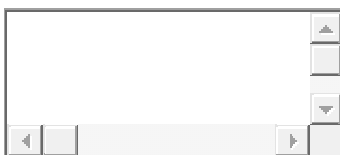
b) Morphology & Physiology :

c) Belonging to Risk Group(s)/ Risk Category(ies) before genetic modification, if any :

d) Belonging to Risk Group(s)/ Risk Category(ies) after genetic modification, if any :

As per DNA Safety Guidelines, 1990

e) History of use :



.Provide the details on its environmental stability; toxicity; allergenicity; virulence/ pathogenicity; host range; transmissibility and treatment options

.If the provided space is insufficient to furnish complete details, please enclose the relevant information as annexure



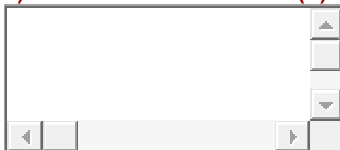
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please upload only 1 MB File.pdf,.doc,.png,.gif and .docx file.

## 10.2: Origin of gene(s) of a molecule under investigation:

If the provided space is insufficient to furnish complete details, please enclose the relevant information as annexure

### a) Source of nucleic acid(s) :



### b) Whether any modification(s) have been made in nucleotide sequence(s) of gene(s) encoding desired molecule compared to the nucleotide

sequence(s) of the Reference Biologic or to the nucleotide sequence(s) of the naïve WT gene(s)?

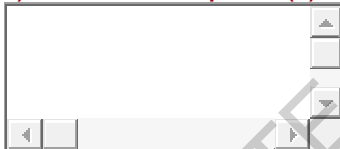
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Yes

☒

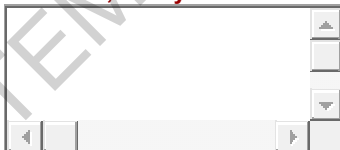
No

### c) Amino acid sequence(s) of the molecule under investigation :

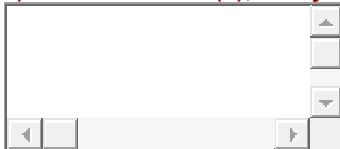


Please enclose sequence alignment of translated amino acid sequence(s) of the molecule under investigation and its alignment with reported amino acid sequence(s) of Reference Biologic or with the naïve WT sequence(s) reported in International Nucleotide Sequence Database in FASTA format with accession number, if any

### d) Description of the other gene(s) (such as marker, reporter gene, etc) inserted, deleted or modified, if any :



### e) Gene construct(s), if any :



Provide annotated restriction maps of the gene expression/ transfer construct(s) defining start & end positions of each gene along with salient features of key gene(s)

**f) Stepwise details on clone development and confirmation of target gene expression :**

**g) Copy number and stability of the plasmid(s)/ gene(s)/ gene construct(s) in expressing host :**

Upload

please upload only 1.7 MB File .pdf,.doc,.png,.gif and .docx file.

**11. Standardization of Fermentation/ Production Procedures**

please upload only .pdf,.doc,.png,.gif and .docx file.

If the provided space is insufficient to furnish complete details, please enclose the relevant information as annexure

**11.1: Media composition for pre-inoculum, inoculum and production process:**

Mention wherever commercial media used with its source, catalog number and its concentration used (V/V% of W/v%, g/L etc.)

**11.2: Feed composition and feeding rate of media affecting cell growth or product formation:**

Composition of feed medium (in case of commercial culture feed media, V/V% of W/V%, g/L etc.) and its rate of feeding along with feeding of critical nutrients in g of nutrient/h/L of initial fermentation broth

**11.3: Plasmid stability/ gene copy number in inoculums and production batches:**

Before induction and at the time of harvest or any other time having implications on product yield

**11.4: Details of batch size :**

Batch size adequate to give after purification enough purified product to generate preclinical data

#### 11.5: Consolidated trend of different parameters controlled during fermentation:

Parameters such as cell growth, product formation, pH, temperature, dissolved oxygen, nutrients consumption, agitation rate, oxygen supplementation, CO<sub>2</sub>, etc, as applicable

#### 11.6: Concentration of product(g/L), yield, volumetric productivity (g product formed/ L/ h) and specific productivity (g product formed/ cell/ day):

Provide details to show that the specific protein yield (amount of protein per unit cell mass) remains more or less constant at different cell concentration during fermentation

#### 11.7: Details of process parameters & % efficiency of in vitro post-translational modification, as applicable

e.g. pegylation, polysialylation, etc.

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please upload only 3 MB File .pdf,.doc,.png,.gif and .docx file.

### 12. Downstream Process for Purification:

Provide details of all unit operations

If the provided space is insufficient to furnish complete details, please enclose the relevant information as annexure

#### 12.1: Batch size for Downstream Process:

Batch size adequate to provide sufficient purified product to perform preclinical toxicology study

#### 12.2: List of reagents, chemicals and biochemicals, resins, membrane material or any other substance that comes in contact with target protein during purification and processing with properties :



**12.3: Process flow chart detailing each unit operations during purification :**

**12.4: Consolidated SDS-PAGE, and Western blot analysis/ ELISA/ Bioassay, as applicable representing each purification step:**

**12.5: Chromatographic analysis:**

**12.6: Consistency of refolding process and product quality :**

In case of inclusion bodies, details of refolding process, specific activity at different doses, dose response curve, stability data and quality of refolded protein in terms of confirmation of solubility and absence of aggregation

**12.7: Summary table indicating consistent recovery of drug substance, after each purification step:**

Yield at each stage of purification, overall product yield etc.

Upload

please upload only 3 MB File .pdf,.doc,.png,.gif and .docx file.

**13. Quality of Drug Substance and Recovery efficiency :**

If the provided space is insufficient to furnish complete details, please enclose the relevant information as annexure

**13.1: Size Exclusion Chromatograms of Drug Substance (DS) by HPLC :**

With three different, uniform concentrations (low, mid and high) of DS

### 13.2: Reverse Phase/ Ion Exchange chromatograms, as applicable:

With three different, uniform concentrations (low, mid and high) of DS

### 13.3: SDS-PAGE analysis of Drug Substance (DS) :

- With loading of three different, uniform quantities (low, mid and high) of DS in  $\mu\text{g}$ / well, under reduced and non-reduced conditions
- Preferably silver stained

### 13.4: Western blot analysis of Drug Substance (DS) :

With loading of three different, uniform quantities (low, mid and high) of DS in  $\mu\text{g}$ / well, under reduced and non-reduced condition

Upload

please upload only 2 MB File.pdf,.doc,.png,.gif and .docx file.

## 14. Physico-chemical characterization of Protein/ Product, as applicable

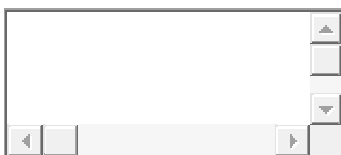
To be submitted for two, uniform & representative consistency batch

If the provided space is insufficient to furnish complete details, please enclose the relevant information as annexure

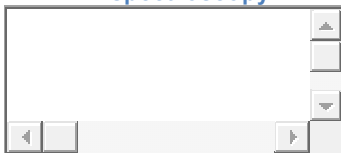
### 14.1: Intact mass analysis:

### 14.2: N and/ or C-terminus sequencing:

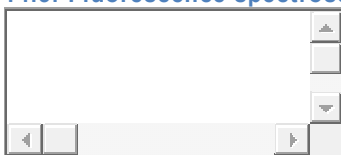
### 14.3: Peptide mapping :



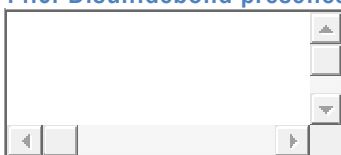
**14.4: CD spectroscopy:**



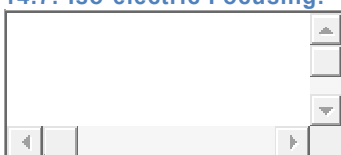
**14.5: Fluorescence spectroscopy :**



**14.6: Disulfidebond presence:**

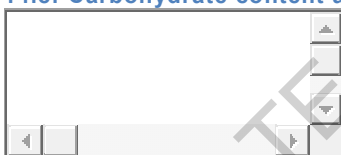


**14.7: Iso-electric Focusing:**



To be submitted in alignment with Isoelectric point based Marker

**14.8: Carbohydrate content and details of components:**



Sialic acid content, glycan analysis etc..

**14.9: Other studies, if any**



Furnish relevant details, which may facilitate assessment of this submission



Upload

please upload only 3 MB File .pdf,.doc,.png,.gif and .docx file.

**15. Product Formulation**

	S.No.	Active Ingredient(s) and Excipient(s)	Final Concentration		
			Reference Biologic 1	Reference Biologic 2 as applicable	Similar Biologic
<input type="checkbox"/>	01				

**16. Consolidated batch information, as applicable**

S.No.	Batch No	Batch Size	Details of Upstream Process		Details of Downstream Process		Details of Formulation		Details of Drug Substance Stability Studies		Details of Drug Product Stability Studies		
			Date of initiation	Date of Completion	Date of initiation	Date of Completion	Date of initiation	Date of Completion	Date of initiation of Real Time-Real Storage Condition studies	Date of initiation of Stress Studies (25°C ±2°C, 60% ±5% R.H )	Date of initiation of Real Time-Real Storage Condition studies	Date of initiation of Stress Studies (25°C ±2°C, 60% ±5% R.H )	Date of initiation of Stress Studies (25°C ±2°C, 60% ±5% R.H )
<input type="checkbox"/>	01												

**17. Product and Process related impurities**

S.No.	Batch No	Pyrogen content:	Host Cell Protein:	Residual DNA:	Residual, Process Component - 1	Residual, Process Component - 2	Residual, Process Component - 3	Residual, Process Component - 4	Residual, Process Component - 5
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## 18. Efficacy studies of the product, as applicable

If the provided space is insufficient to furnish complete details, please enclose the relevant information as annexure

### 18.1: Activity assay(s) such as Receptor binding; Cellular proliferation ; Signal transduction pathways; Tissue specific activity; In vivo studies in animal models, etc.

### 18.2: Sero-conversion and potency studies in case of vaccines:

Mention the reference for the selected protocol

Upload

please upload only 2 MB File .pdf,.doc,.png,.gif and .docx file.

## 19. Stability studies of Drug Substance (DS) and Drug Product (DP) batches, as applicable

- To be performed real time with real storage conditions for at least three months (0, 1, 3 months)
- In case of DS 'stress studies' to be performed at (i) 5°C ±3°C for 0, 1, 3 months and at (ii) 25°C ±2°C, 60% ±5% R.H for 0, 2, 4 weeks
- In case of DP 'stress studies' to be performed at (i) 25°C ±2°C, 60% ±5% R.H for 0, 1, 3 months and at 40°C ±2°C, 75% ±5% R.H for 0, 2, 4 weeks
- All the assessment must be performed in alignment with Reference Biologic (without undergoing stability studies) as a control • If the provided space is insufficient to furnish complete details, please enclose the relevant information as annexure

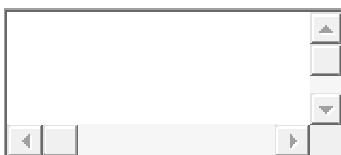
### 19.1: Physical Appearance, pH, Active Ingredient Concentration, etc:

Samples representing various stability time-points for a particular batch must be analyzed and represented

### 19.2: SDS-PAGE analysis:

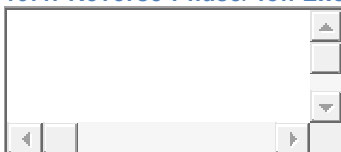
- Samples with uniform quantity (µg/well) representing various stability time-points for a particular batch must be resolved and analyzed under reduced and non-reduced conditions
- Preferably silver stained

### 19.3: Size Exclusion Chromatography analysis:



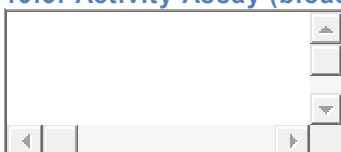
Samples with uniform concentration representing various stability time-points for a particular batch must be represented and analyzed as an overlay chromatogram

#### 19.4: Reverse Phase/ Ion Exchange chromatograms, as applicable:



Samples with uniform concentration representing various stability time-points for a particular batch must be represented and analyzed as an overlay chromatogram

#### 19.5: Activity Assay (bioassay):



Samples representing various stability time-points for a particular batch must be analyzed and represented as an overlay graphical representation

Upload

please upload only 3 MB File .pdf,.doc,.png,.gif and .docx file.

### 20. Acceptability criteria/ Certificate of Analysis (as specified in pharmacopeia or equivalent regulation)

Upload

please upload only 0.5 MB File.pdf,.doc,.png,.gif and .docx file.  
Please enclose the relevant information as annexure

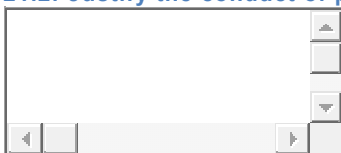
### 21. Proposed work plan for preclinical or other safety studies

#### 21.1: List of studies to be conducted:



- Please refer 'Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization, 2016' to decide upon studies to be conducted
- To be submitted as bullet points

#### 21.2: Justify the conduct of proposed studies and, selection & relevance of animal test system:



### 21.3: Protocol for Immunogenicity studies:

- To be performed as sequence specific, non-specific to other proteins and with adjuvant(s)/ excipient(s), as applicable
- Provide complete study design including parameters to be measured; monitoring schedules, etc.

Upload

please upload only 1 MB File .pdf,.doc,.png,.gif and .docx file.  
Please enclose the relevant information as annexure

### 21.4: Protocols for preclinical or other safety studies:

- Provide details of dose(s) to be tested, dose calculation (w.r.t. human equivalent dose) & basis of dose calculation, dose preparation; vehicle; route(s), mode(s) & number of administration(s) per day/ per week/ per month, in each study
- Provide complete study design including test species, age, body weight, control groups, comparator group, recovery groups; details of biochemical, histopathological and other parameters to be measured; organs to be weight; monitoring schedule etc.

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please upload only 1 MB File .pdf,.doc,.png,.gif and .docx file.  
Please enclose the relevant information as annexure

### 21.5: Address and accreditation status of the facility where studies are proposed to be conducted :

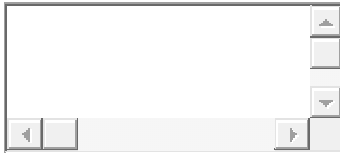
## 22. Safety compliance during pre-clinical studies

### 22.1: Status of functional existence of IBSC and IAEC of the facility where studies are proposed to be conducted:

### 22.2: Safety norms & containment measures to be observed during studies:

### 22.3: Proposed decontamination & disposal mechanisms :

**22.4: Contingency plan and risk management measures in case of an unintentional release of the HMOs, GMOs/LMOs and product(s) thereof :**



**23. Appropriate references and any other relevant information:**



Upload

please upload only 25.0 MB File .pdf,.doc,.png,.gif and .docx file.  
Please enclose the relevant information as annexure

**24. Confidential information?**

☐ YES ☒ NO

**25. Whether the HMOs, GMOs/LMOs and product(s) thereof under consideration, have been deliberated earlier by the RCGM? If so, provide relevant 'Unique Application Code (UAC)' assigned for each of those deliberations**

	S.No.	Unique Application Code (UAC)
	<input type="text" value="01"/>	<input type="text"/>

**26. Declaration By The Applicant:**

- I declare that I am familiar with, and agree to comply with all the provisions mentioned in the regulations and Guidelines on Biosafety of recombinant DNA Research and Biocontainment,2017 and Guidelines & Handbook for Institutional Biosafety Committee(IBSC),2011 and other applicable Guidelines, as modified time to time by the Government of India.
- I would ensure that all investigators/ researchers and staff working in the area of HMOs, recombinant DNA, GMOs/LMOs and product(s) thereof understand and follow the aforesaid biosafety guidelines.
- I assure that adequate training would be conducted to create awareness about compliance requirements while working with biorisk inherent microorganisms and/ or recombinant organisms.
- The HMOs, GMOs/LMOs and product (s) thereof (transferred material), if any, will be utilized for RCGM approved purpose(s) only.
- I also assure that deviations to the above provisions, if any; arising out of the experiments would be brought to the notice of the Chairman-IBSC and the Member Secretary-RCGM immediately.



- I am aware that making false or misleading statements may attract penalty under the Environment (Protection) Act, 1986.

**Name :**

**Designation :**

**Signature with stamp & Date:**

- To be signed in original by hand. (Electronic/ scanned signatures not acceptable)

**27. Certified & Forwarded By the Chairman of the IBSC:**

Submission of Minutes of the IBSC meeting is obligatory. Kindly note that minutes older than two years are void. Please refer FAQs for submission of minutes of the IBSC meeting

- I certify that the information contained in this form has been checked by the Institutional Biosafety Committee (IBSC) and found to be complete.
- I further certify that investigator(s), researcher(s) and staff intended to work with HMOs, recombinant DNA, GMOs/LMOs and product (s) thereof have adequate training and experience for the proposed dealings.
- I undertake that liability of IP issues, if any, on the product under investigation, such as infringement of intellectual property shall be borne by the organization.
- The proposal set out above has been considered and approved by the IBSC in its meeting held on  as the agenda item no.  and is forwarded to RCGM for further necessary action (Copy of the duly signed minutes of relevant meeting is enclosed).

**Name :**

**Designation :**Chairman

**Signature with stamp & Date:**

- To be signed in original by hand. (Electronic/ scanned signatures not acceptable)