Guidance for Industry: Chemistry, Manufacturing, and Controls (CMC) Documentation for Initial Investigational New Drug Application of Biosimilars

Center for Drug Evaluation, NMPA

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I. Introduction

In recent years, with the rapid development of the biopharmaceutical industry, the number of Investigational New Drug (IND) applications of biosimilars has continued to increase. In order to continuously deepen the reform of the drug review and approval system, improve the quality of CMC dossiers for IND applications of biosimilars, and better serve applicants, the Center for Drug Evaluation (CDE) has formulated the Guidelines in accordance with ICH M4Q (R1) guideline and in light of previous review practice experience.

The Guidelines are based on the overall framework of ICH M4Q (R1), and maintain consistent in format and style with it. With the framework, in combination with the CMC study characteristics of biosimilars, the requirements for CMC dossiers for IND applications have been refined, so as to provide guiding suggestions for the preparation of CMC dossiers for IND applications of such drugs.

The application dossiers should be provided in accordance with the requirements of relevant regulations and guidelines, such as the *Requirements for Registration Classification and Application Dossiers of Biological Products* and the *Guidelines for Acceptance and Review of Biological Product Registration*. This document is a guidance for the preparation of application dossiers. For technical requirements, reference should be made to relevant regulations and technical

guidelines that have been continuously updated at home and abroad. With the update of relevant ICH guidelines, relevant contents in the Guidelines will be continuously improved and updated.

II. Scope of Application

The Guidelines are mainly applicable to the preparation of CMC dossiers for initial IND applications of biosimilars.

The Guidelines maintain consistent in format and style with ICH M4Q (R1) and provide detailed specifications and suggestions for each section for applicants' reference. Applicants may evaluate the applicability of each item based on the characteristics of products under application and specific study conditions, and may adjust the contents and presentation forms when necessary. In addition, the Guidelines provide summary examples for reference. It is recommended that at the end of each section of the dossiers, corresponding contents be summarized in the format of the summary examples.

III. Main Contents

3.1 Table of Contents of Module 3

A Table of Contents for the filed application should be provided.

3.2 Body of Data

3.2.S Drug Substance[1]

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Provide information on the nomenclature of the drug substance, including but not limited to generic name (if applicable), company or laboratory code, etc.

3.2.S.1.2 Structure

Provide amino acid sequence,specify glycosylation sites or other major post-translational modifications (if any) and relative molecular mass, and provide molecular structure diagram.

3.2.S.1.3 General Properties

Provide the physical and chemical properties and other relevant properties of the drug substance, including appearance, pI value, extinction coefficient, biological properties (mechanism of action), etc.

[Summary Example-3.2.S.1 General Information]

Drug structure: The amino acid sequence of this product is consistent with that of the reference drug. It is an IgG1 lambda monoclonal antibody, consisting of 2 identical heavy chains and 2 identical light

[1]It is commonly referred to as bulk in biological products, but in order to maintain consistent with ICH M4Q (R1), the drug substance is used in the Guidelines.

chains through four inter-chain disulfide bonds, with the disulfide bond positions of CXXX-CXXX, CXXX-CXXX, CXXX-CXXX and CXXX-CXXX. Pyroglutamylation occurs 100% at the N-terminus of the peptide chain, and lysine deletion occurs more than 89.00% at the C-terminus. No deamidation sites are found, and the oxidation site is at methionine XXX. The glycosylation site is at asparagine XXX, and the main glycotypes are G0F and G1F. The structural schematic diagram is as follows.

Mechanism of action: The main mechanism of action of this product is to exert the XXX effect by targeted binding to XXX, thereby blocking the XXX process.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Provide a list of the manufacturers and testing facilities, including their names, addresses, and responsibilities. In case of contract manufacturing/contract analysis, it shall be indicated.

[Summary Example-3.2.S.2.1 Manufacturer(s)]

Manufacturer:

Name	Address	Responsibilities

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Provide manufacturing process information, and specify culture mode and culture scale. Provide the manufacturing process flow chart, describe each process step in detail, and clarify the process parameters of each step. The flow chart shall include all steps (such as unit operation) and intermediates. **[Summary Example-3.2.S.2.2 Description of Manufacturing Process and Process Controls]**

Process flow: cell recovery → shake flask culture → seed culture → 2000 L single-use bioreactor culture → affinity chromatography → virus inactivation and deep filtration → anion exchange chromatography → cation exchange chromatography → virus removal filtration → ultrafiltration/diafiltration → filtration, filling and storage.

3.2.S.2.3 Control of Materials

1. Upstream development and cell bank

Provide information on the source, modification sites and modification reasons of the target gene, as well as the target gene sequence and amino acid sequence. Make clear that the amino acid sequence of this product is consistent with that of the reference drug, and provide the sequence comparison information.

Describe in detail the development and screening process of the expression vector, and provide the functional elements of the expression vector, and the confirmation results and confirmation reports of target gene sequences (if any).

Specify the phenotype and genotype of host bacteria, and provide the source and historical information of host cells/host bacteria, including subculture, modification process, cell bank generation and testing information (if any), etc. Make clear whether the host cells/host bacteria for the candidate drug are consistent with those for the reference drug.

Describe in detail the generation and screening process of engineering cells/engineering bacteria, including gene transduction/transfection methods, screening conditions, monoclonal selection, preferred clone screening, etc.

Describe in detail the establishment process and testing results of the cell bank/test strain bank, including the name, batch number, passage number, culture medium component, cryopreservation solution component, passage conditions, cryopreserved cell density, storage conditions, etc., and provide the testing report of the cell bank/ test strain bank as an attachment. Describe in detail the stability study process and results of the cell bank/test strain bank (if any).

2. Other raw materials for production

Provide a list of raw materials for production, including culture media, additives, reagents, chromatography media, and filter membranes involved in the production process and their manufacturers, whether they comply with the pharmacopoeia standards, their use stages, etc. Provide the in-house specifications for major raw materials (if any), and provide COAs of critical raw materials as attachments. Make clear whether materials of human or animal origin are used in cell bank establishment and production processes. If any, specify the details of their use, including the stage of use and amount, and conduct a safety risk assessment. Provide TSE/BSE statements or supporting documents regarding supplier's control of adventitious agents.

If self-made raw materials are involved, make clear whether materials of human or animal origin are used, and provide information on the upstream development, manufacturing process, quality study and control, stability study, etc. If such materials are produced with eukaryotic cells such as CHO cells, the process should include a virus removal/inactivation unit, and the validation study protocol and results of virus clearance should be provided, and the validation report should be provided in the form of an attachment.

[Summary Example-3.2.S.2.3 Control of Materials]

Target gene: The amino acid sequence of this product is derived from XXX, which is completely consistent with that of the innovator drug.

The nucleotide sequence of this product has been designed based on the amino acid sequence, and XXX Company was entrusted to complete the codon optimization and gene synthesis.

Expression vector: The plasmid is derived from XXX, and the supporting documents regarding the source of plasmid XXX have been provided. The heavy chain gene and light chain gene were inserted into the expression vector via double enzyme digestion of XXX/XXX and XXX/XXX, respectively, to obtain expression vector XXX. The main functional elements include GS gene, hCMV promoter, KanR, etc. Enzyme digestion validation and sequence determination were performed on the expression vector. The enzyme digestion size was consistent with the theoretical one, and the sequence determination result was consistent with that of the reference drug, with the sequence determination report provided.

Host cells/host bacteria: Host cells/host bacteria XXX (the phenotype and genotype of host bacteria should be clarified) were purchased from XXX, after which the serum-free adaptation was performed, the XXX cell bank was generated, the cell bank was tested for XXX and the results met the pharmacopoeia requirements. The host cells/host bacteria of the candidate drug were consistent with those of the reference drug.

Engineering cells/bacteria: The expression vector was linearized after XXX enzyme digestion and transferred into host cells by

electrotransfection. After the cell is optimized by selection under MSX pressure, monoclonal screening was performed by the XXX method. After Fed-batch culture, the XXX cell strain was obtained by growth characteristics, expression quantity and product quality screening to be used for subsequent cell bank generation.

Cell bank: The MCB and WCB were generated under GMP conditions.

Cell bank name	Batch No.	Passage number	Culture medium	Cell density	Storage conditions

The cell bank generation process is as follows:

PCB: The XXX cell strain was recoveried into the subculture medium containing MSX (culture medium name/composition). Subculture amplification was performed every 2-3 days. After XXX passages, when the cell viability exceeded 99% and the total cell count reached above XXX, subculture was terminated. The cell suspension was then centrifuged to remove the supernatant, and the cell pellet resuspended in the subculture medium supplemented with 10% (v/v) DMSO, after which the suspension was dispensed into cell cryogenic vials. The cryogenic vials were placed in the programmed cooling box, then transferred to the -80□ refrigerator for storage, and after 24 hours, moved to a liquid nitrogen tank. A total of XXX vials were cryopreserved, each containing 1 mL, with a cell density being XXX, a

viability being XXX at cryopreservation, a PDL being XXX, a name being XXX and a batch number being XXX.

MCB: Same as PCB.

WCB: Same as PCB.

EOPC (if any): EOPC was prepared with clinical batch XXX.

Cell bank testing: The testing was entrusted to XXX company, and the test methods complied with ICH guidelines/pharmacopoeia requirements. The results are as follows, and the original testing report has been provided.

Item	**Analytical procedure**	**Criteria**	**Master cell bank**	**Working cell bank**	**EOPC**
Cell identification	Carry out the test according to the "Preparation and Quality Control of Animal Cell Matrices Used for Production of Biologics" in Volume III of the Chinese Pharmacopoeia (the XXX Edition).				
Sterility test	Carry out the test				

Item	Analytical procedure	Criteria	Master cell bank	Working cell bank	EOPC
	according to the "Preparation and Quality Control of Animal Cell Matrices Used for Production of Biologics" in Volume III of the Chinese Pharmacopoeia (XXX Edition) and General Chapter XXX.				
Test for mycobacteria	Carry out the test according to the "Preparation and Quality Control of Animal Cell Matrices Used for Production of Biologics" in Volume III of the Chinese Pharmacopoeia (XXX Edition) and General Chapter XXX.				
Test for mycoplasma	Carry out the test				

Item		Analytical procedure	Criteria	Master cell bank	Working cell bank	EOPC
		according to General Chapter XXX in Volume III of the Chinese Pharmacopoeia (the XXX Edition).				
Test for spiroplasma		Culture method/nucleic acid method				
Test for endogenous and exogenous viral contamination	*In vitro* culture method	*In vitro* inoculation and culture method using various indicator cells (X cells, X cells, and X cells, for a period of 28 days)				
	In vivo inoculation method in animals and chicken embryos	Suckling mice				
		Adult mice				
		Chicken embryos				
		……				
	Retroviral detection	Reverse transcriptase activity				
		Infectivity test				
		Transmission electron microscopy				

Item		Analytical procedure	Criteria	Master cell bank	Working cell bank	EOPC
	Species-specific virus test	(Specify the type of virus tested)				
		……				
	Detection of viruses of bovine origin	(Specify the type of virus tested)				
		……				
	Detection of viruses of porcine origin	(Specify the type of virus tested)				
		……				
	……					

Cell bank stability study (if any): Cell bank passage stability studies and storage stability studies were conducted.

Passage stability study (if any): One vial of the XXX cell strain was recoveried and sub-cultured in the XXX medium under XXX pressure/no pressure until the PDL reached XXX. Cells were cryopreserved at PDLXXX, PDLXXX, PDLXXX and PDLXXX, respectively. The cryopreserved cells were resuscitated and subjected to Fed-batch culture, respectively, and then tested for growth status, cell viability, expression level, product quality (binding activity, SEC purity, nrCE-SDS purity, rCE-SDS purity, charge variants, glycosylation, peptide map, etc.), and genetic stability (gene copy number, target gene sequence, etc.). The target gene sequence of cells of each passage was

consistent with the theoretical sequence, and no significant differences were observed in any of the test items. The preliminarily proposed limit passage number for WCB is XXX, which can meet the needs of production at a scale of XXX L or above.

Storage stability study (if any): The description format of the passage stability study can be referenced, and the description should be based on the actual storage stability study results.

Other raw materials for production

Name	**Manufacturer**	**Compliance with pharmacopoeia standards**	**Stage of use**	**COA**	**In-house specification (if any)**
		Complies with Chinese Pharmacopoeia standards		Provided/Not Provided	Provided/Not Provided

Whether materials of human or animal origin are used: Yes □ No □

3.2.S.2.4 Controls of Critical Steps and Intermediates

Provide the process parameters or critical process parameters for critical steps, as well as routine control items and acceptance criteria for intermediates or production processes.

[Summary Example-3.2.S.2.4 Controls of Critical Steps and Intermediates]

Main/critical process parameters

Process step	Process parameter	Parameter range
	……	
……		

Intermediate or in-process control

Process step	Item	Analytical procedure	Acceptance criteria
	……		
……			

3.2.S.2.5 Process Validation and/or Evaluation

If any, provide the process validation protocol and results, and provide the validation report in the form of an attachment.

3.2.S.2.6 Manufacturing Process Development

Provide the detailed process development data as well as the changes of each process version. Specify the relevant information of drug substance batches produced during development, such as process version, batch

number, production scale and purpose (e.g., stability, non-clinical and reference materials), and specify the corresponding drug substance batch information or process version information of batches that have been used for clinical studies (if any), batches intended for clinical studies in China, and toxicological batches.

Make clear whether the corresponding drug substance manufacturing processes of batches intended for clinical studies in China and toxicological batches have changed. If the manufacturing processes have changed, sufficient comparability study data shall be provided. For the products that have been used in clinical studies, describe in detail the differences and similarities in the corresponding drug substance manufacturing processes between batches intended for clinical studies in China and batches that have been used in clinical studies, and provide sufficient comparability study data.

[Summary Example -3.2.S.2.6 Manufacturing Process Development]

Key batch information:

Batch No.	**Production scale**	**Process version**	**Purpose (e.g., pharmacological and toxicological study, clinical study, stability study, reference product batch, etc.)**

The drug substance involves a total of X versions of manufacturing processes, namely Process A, Process B and Process C. Among them, the drug substance manufactured by Process B is used for toxicological studies, and the drug substance manufactured by Process C is intended for clinical studies in China.

The changes in Process B and Process C are as follows, while no other changes have occurred:

Change comparison		**Process B**	**Process C**
Cell bank			
Raw materials for production			
Manufacture	Manufacturer		
	Equipment		
	Scale		
	Process steps and parameters		
	……		
Container closure system			
……			

Process performance comparison (including controls of intermediates) and quality comparability studies were performed between Process B and Process C.

Process performance comparison: The process performance comparison between XXX batches manufactured by Process B and XXX batches manufactured by Process C was provided, including intermediate quality,

yield, etc. No significant differences were observed except for XXX. Differences were analyzed as follows: XXX.

Characterization comparability: Characterization comparability studies were performed between XXX batches manufactured by Process B and XXX batches manufactured by Process C. See the Characterization section for details. Differences were analyzed as follows: XXX.

Batch analysis comparability: Batch analysis comparability studies were performed between XXX batches manufactured by Process B and XXX batches manufactured by Process C. See the Batch Analyses section for details. Differences were analyzed as follows: XXX.

Stability comparability: Long-term, accelerated, influencing factor, and forced degradation comparability studies were performed between XXX batches manufactured by Process B and XXX batches manufactured by Process C. See the Stability section for details. Differences were analyzed as follows: XXX.

3.2.S.3 Characterization

3.2.S.3.1 Structure and Physicochemical Properties

Provide detailed information on primary, secondary, and higher-order structures, physicochemical properties, post-translational modifications,

biological activity, purity, and immunochemical properties (if applicable). Provide the original study reports as appendices.

3.2.S.3.2 Impurities

Provide studies on product-related impurities and process-related impurities, including the source of impurities, test methods, and test results or safety evaluation results of representative batches.

[Summary Example-3.2.S.3 Characterization]

Characterization	**Test item**		**Test method**	**Test result**		
				Batch No.	**Batch No.**	**Batch No.**
				Process version	**Same as that in the left column**	**Same as that in the left column**
Structure elucidation	Primary structure	Complete molecular weight				
		Deglycosylated molecular weight				
		Light chain molecular mass				
		Non-deglycosylated heavy chain molecular mass				
		Deglycosylated heavy chain molecular mass				
		Sequence First-order				

Characterization	**Test item**			**Test method**	**Test result**		
					Batch No.	**Batch No.**	**Batch No.**
					Process version	**Same as that in the left column**	**Same as that in the left column**
		coverage	mass spectrometry				
			Second-order mass spectrometry				
		Post-translational modification	Modification 1				
			Modification 2				
			……				
		Identification of CDR characteristic peptides					
		C/N-terminal amino acid sequence					
		Free thiol					
		Disulfide bond					
	Higher-order structure	Circular dichroism	Far UV				
			Near UV				

Characterization	Test item			Test method	Test result		
					Batch No.	Batch No.	Batch No.
					Process version	Same as that in the left column	Same as that in the left column
		spectroscopy					
		Fluorescence spectroscopy					
		Heat stability					
		……					
	Glycosylation	N-glycosylation sites					
		N-glycan type and proportion	G0F				
			G0				
			……				
		Sialic acid modification	NGNA				
			NANA				
Physicochemical properties	Molar extinction coefficient						
	Isoelectric point						
	Purity and impurities	Size exclusion chromatography	Polymer				
			Principal peak				
			Fragment				
		Reduced CE-SDS	Light chain + heavy chain				

Characterization	Test item		Test method	Test result		
				Batch No.	Batch No.	Batch No.
				Process version	Same as that in the left column	Same as that in the left column
		Fragment				
		Principal peak				
	Non-reduced CE-SDS	Fragment				
	Charge variant	Acidic region				
		Principal peak				
		Basic region				
Biological function	Binding activity					
	Biological activity					
	FcγRI binding affinity					
	FcγRIIa binding affinity					
	FcγRIIb binding affinity (KD, M)					
	FcγR□a binding affinity (KD, M)					
	FcRn binding affinity (KD,					

Characterization	Test item		Test method	Test result		
				Batch No.	Batch No.	Batch No.
				Process version	Same as that in the left column	Same as that in the left column
		M)				
		C1q binding affinity				
		ADCC				
		CDC				
		……				
Impurities	Product-related impurities	……				
	Process-related impurities	Residual Protein A				
		Residual adventitiousDNA				
		Residual host cell protein				
		……				

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification

Provide the specification for the drug substance in tabular form, including test items, acceptance criteria and analytical procedures.

3.2.S.4.2 Analytical Procedures

Provide the detailed analytical procedure for each test item of the drug substance.

3.2.S.4.3 Validation of Analytical Procedures

Provide analytical validation/verification information.

3.2.S.4.4 Batch Analyses

Provide the batch information and batch analysis results of representative batches.

3.2.S.4.5 Justification of Specification

Provide the justification of the specification.

[Summary Example-3.2.S.4 Control of Drug Substance]

Specification and batch analysis results:

Test item		**Test method**	**Acceptance criteria**	**Verification result**		
				Batch 1	**Batch 2**	**Batch 3**
Identification	Identification 1					
	Identification 2					
	……					
Glycosylation	N-glycan profile					
Physicochemical properties	Appearance					
	pH					
	……					

Test item		Test method	Acceptance criteria	Verification result		
				Batch 1	Batch 2	Batch 3
Purity and impurities	Size exclusion chromatography					
	Charge variant					
	Reduced CE-SDS					
	Non-reduced CE-SDS					
	Residual Protein A					
	Residual adventitious DNA					
	Residual host cell protein(HCP)					
	……					
Activity	Binding activity					
	Biological activity					
Assay						
Bacterial endotoxin						
Bioburden						

Validation/verification of analytical procedures

Test item		Methods	Validation/Verification content of analytical procedures							
			Specificity	Linearity	Precision	Accuracy	Limit of detection	Limit of quantitation	Range	Ruggedness
Identification	Peptide map	HPLC	+	-	+	-	-	-	-	+
Purity										

Test item		Methods	Validation/Verification content of analytical procedures							
			Specificity	Linearity	Precision	Accuracy	Limit of detection	Limit of quantitation	Range	Ruggedness
and impurities										
Activity										
Assay										
Safety										

Note: Mark “+” if the preliminary analytical validation is completed; otherwise, mark “-”.

3.2.S.5 Reference Standards or Materials

Provide information on the reference standards or reference materials used for testing of the drug substance, including the preparation processes and studies of the reference standards or reference materials, such as characterization, batch analyses, reference standard material calibration and stability.

[Summary Example-3.2.S.5 Reference Standards or Materials]

Name	Reference standard or material

Name	Reference standard or material
Batch No.	
Corresponding drug substance batch No.	
Packaging container	
Assay	
Formulation	
Storage conditions	
Useage	

Calibration of reference standards or materials: The processes and results of assay calibration and biological activity calibration were provided.

Assay calibration: The assay calibration of X samples was performed by X analysts, the total RSD was XXX, and the mean value was XXX.

Biological activity calibration: The biological activity calibration of batch XXX was performed with batch XXX as a reference, and the biological activity calibration of X samples was performed by X analysts, the total RSD was XXX, and the mean value was XXX.

Stability: The stability study protocol (including study conditions, study items, etc.) and study results (if any) were briefly described.

3.2.S.6 Container Closure System

Provide the information on the container closure system, including the name, specification, source and material of each component.

[Summary Example-3.2.S.6 Container Closure System]

Item	Container closure system
Name of packaging material	
Specification of packaging material	
Packaging material composition	
Manufacturer of packaging material	

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

The subsequent stability protocol shall be provided.

3.2.S.7.3 Stability Data

Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative.

[Summary Example-3.2.S.7 Stability]

Item	Storage conditions	Study time (completed)	Study item	Study batch (process version, and purpose)

Item		Storage conditions	Study time (completed)	Study item	Study batch (process version, and purpose)
Study container closure system		Consistent with the container closure system material under application or not: Yes □ No □ In case of inconsistency, the representativeness of the container closure system shall be assessed.			
Long-term					
Study result		The change trends and preliminary conclusions of the study items shall be briefly described. The study was performed for XXX months, and each test item showed no obvious change trend.			
Accelerated					
Study result		The change trends and preliminary conclusions of the study items shall be briefly described. If there is any significant change, the degradation pathway and rate shall be analyzed. For example: The study was performed for XXX months, the principal peaks of molecular size isoforms decreased (98.9%-99.2% → 96.6%-96.9%) and high molecular weight(HMW) impurities increased (0.8%-1.1% → 3.1%-3.4%); the principal peaks of charge variants decreased (68.3%-69.1% → 56.5%-57.4%), the acidic isoforms increased (25.8%-26.5% → 35.4%-36.3%), and other test items showed no significant change trend. No new impurity peak was found in the impurity profile comparison.			
Influencing factor testing	High temperature				
	Light				
	Freeze-thaw				
	……				
Study result		The change trends and preliminary conclusions of the study items shall be briefly described. If there is any significant change, the			

Item	Storage conditions	Study time (completed)	Study item	Study batch (process version, and purpose)
	degradation pathway and rate shall be analyzed. For example: The study was performed at high temperature for 30 days, the biological activity exceeded the acceptance criteria (65%, criteria: 70%~130%), and other test items met the proposed acceptance criteria. The principal peaks of molecular size isoforms decreased (99.7%→95.6%), and high molecular weight(HMW) impurities increased (0.3%→4.0%); other test items showed no significant change trend. No new impurity peak was found in the impurity profile comparison.			
Transportation stability (if any)				
Study result				
Storage conditions and expiration date				

3.2.P Drug Product

3.2.P.1 Description and Composition of the Drug Product

Provide a description of the drug product and its composition, including composition, strength, and type of container closure system for the drug product. Provide all components of the dosage form, and their amount on a per-unit basis, the function of the components, and a reference to their quality standards Provide a list for the formulation comparison between the candidate drug and the reference drug. If there is any difference, it should be fully explained with supporting data provided.

For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part “p”, as appropriate.

[Summary Example-3.2.P.1 Description and Composition of the Drug Product]

This product is a sterile injection made of CHO-K1 cell expressing recombinant anti-XXX humanized monoclonal antibody, and supplemented sucrose, disodium hydrogen phosphate, sodium dihydrogen phosphate, polysorbate 20 and water for injection. R&D Code (if any): XXX. Strength: XXX, route of administration: XXX. This product is a biosimilar with XXX (trade name: XXX) marketed at home and abroad by XXX Company as a reference drug.

The formulation of the drug product is as follows and the batch size is XXX.

Formulation of this product						**Formulation of reference drug**	
Component	**Content**	**Supplier**	**Specification**	**Registration No.**	**Function**	**Component**	**Content (if any)**

Whether there is an overage: Yes □ No □

Whether there is an overfilling: Yes □ No □

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

The compatibility of the drug substance with excipients should be preliminary demonstrated. For combination products, the compatibility of drug substances with each other should be preliminarily demonstrated.

3.2.P.2.2 Drug Product

The detailed formulation development process shall be provided, such as type and concentration screening of excipients, buffer salts and stabilizers, and pH screening. In case of overage, the supporting data shall be provided.

3.2.P.2.3 Manufacturing Process Development

Provide the detailed process development data as well as the changes of each process version (including the change of formulation). Specify the relevant information of drug product batches produced during development, such as process version, batch number, production scale and purpose (e.g., stability, non-clinical and reference materials), and specify the batch information or process version information of batches

that have been used for clinical studies (if any), batches intended for clinical studies in China, and toxicological batches.

If the manufacturing processes of study batches intended for clinical studies in China are different from those of toxicological batches, sufficient comparability study data shall be provided. For the products that have been used in clinical studies, describe in detail the differences and similarities in the drug product manufacturing processes between batches intended for clinical studies in China and batches that have been used in clinical studies, and provide sufficient comparability study data. For international multi-center clinical trial applications, specify the information on processes or batches to be used for clinical trials in China.

3.2.P.2.4 Container Closure System

The applicability of the container closure system shall be preliminarily demonstrated, and the compatibility of the product with the packaging materials may be evaluated based on the data on studies of the packaging materials completed by the container closure system supplier and the stability study results of the product.

3.2.P.2.5 Microbiological Attributes

The sterility of the product shall be preliminarily demonstrated, and the package integrity shall be evaluated.

3.2.P.2.6 Compatibility

The compatibility of the drug product with reconstitution diluent(s) and dosage devices should be addressed to support the intended use in the clinical protocol.

[Summary Example-3.2.P.2 Pharmaceutical Development]

Key batch information:

Batch No. (Corresponding drug substance batch No.)	**Production scale**	**Process version**	**Purpose**

The drug product involves a total of X versions of manufacturing processes, namely Process 1, Process 2 and Process 3. Among them, the drug product manufactured by Process 2 is used for toxicological studies, and the drug product manufactured by Process 3 is intended for clinical studies in China.

The changes in Process 2 and Process 3 are as follows, while no other changes have occurred:

Change comparison	**Process 2**	**Process 3**
Corresponding drug substance process version	**Process B**	**Process C**
Formulation composition		
Strength		

Change comparison		Process 2	Process 3
Corresponding drug substance process version		**Process B**	**Process C**
Manufacture	Manufacturer		
	Equipment		
	Scale		
	Process steps and parameters		
	……		
Container closure system			
……			

Process performance comparison (including controls of intermediates) and quality comparability studies were performed between Process 2 and Process 3.

Process performance comparison: The process performance comparison between XXX batches manufactured by Process 2 and XXX batches manufactured by Process 3 was provided, including intermediate quality, yield, etc. No significant differences were observed except for XXX. Differences were analyzed as follows: XXX.

Batch analysis comparability: Batch analysis comparability studies were performed between XXX batches manufactured by Process 2 and XXX batches manufactured by Process 3. See the Batch Analyses section for details. Differences were analyzed as follows: XXX.

Stability comparability: Long-term, accelerated, influencing factor, and forced degradation comparability studies were performed between XXX batches manufactured by Process 2 and XXX batches manufactured by Process 3. See the Stability section for details. Differences were analyzed as follows: XXX.

Compatibility evaluation: It could be seen from the data on studies of the packaging materials completed by the container closure system supplier and the stability study results of the product that the compatibility was favorable.

In-use stability study: With XXX as the compatibility solution, the drug product was diluted to XXX mg/mL, and the drug product was investigated in a syringe made of XXX under the conditions of XXX for XXX h, with the study item: XXX. Results: XXX. Conclusion: XXX.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Provide a list of the manufacturers and testing facilities, including their names, addresses, and responsibilities. In case of contract manufacturing/contract analysis, it shall be indicated.

[Summary Example-3.2.P.3.1 Manufacturer(s)]

Manufacturer:

Name	Address	Responsibilities

3.2.P.3.2 Batch Formula

A batch formula should be provided, including all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, and a reference to their quality standards. The overfilling should be specified.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

The manufacturing process information shall be provided, indicating the application scale and batch size (if any). Provide the flow diagram of the manufacturing process, with a detailed description of each process step, indicating process parameters for each step.

[Summary Example-3.2.P.3.3 Description of Manufacturing Process and Process Controls]

Drug substance thawing → Pooling → Sterile filtration → Filling → Capping → Visual inspection → Labeling and packaging → Drug product.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Provide the process parameters or critical process parameters for critical steps, as well as routine control items and acceptance criteria for intermediates or production processes.

[Summary Example-3.2.P.3.4 Controls of Critical Steps and Intermediates]

Main/critical process parameters

Process step	Process parameter	Parameter range
	……	
……		

Intermediate or in-process control

Process step	Item	Analytical procedure	Acceptance criteria
	……		
……			

3.2.P.3.5 Process Validation and/or Evaluation

If any, provide the process validation protocol and results, and provide the validation report in the form of an attachment.

3.2.P.4 Control of Excipients

The general information of excipients shall be provided, including the name, manufacturer, specification and registration number (if any). The test method for each excipient (if applicable), method validation results and report (if applicable), and justification of the specification for excipients (if applicable) shall be provided.

Make clear whether there are excipients of human or animal origin and novel excipients.

If self-made excipients are involved, make clear whether materials of human or animal origin are used, and briefly describe the upstream development, manufacturing process, quality study and control, stability study, etc. If such excipients are produced with eukaryotic cells such as CHO cells, the process should include a virus removal/inactivation unit, and the validation study protocol and results of virus clearance should be provided, and the validation report should be provided in the form of an attachment.

[Summary Example-3.2.P.4 Control of Excipients]

Name	Manufacturer	Specification	Registration No. (if any)
		Pharmacopoeia standard/Enterprise standard	

Whether excipients of human or animal origin are used: Yes □ No □

Whether novel excipients are used: Yes □ No □

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)

The specification for the drug product shall be provided, including study items, acceptance criteria and analytical procedures, and compared with the specification for the reference drug. If there is any difference, it shall be further explained.

3.2.P.5.2 Analytical Procedures

Provide the analytical procedure for each test item of the drug product.

3.2.P.5.3 Validation of Analytical Procedures

Provide analytical validation/verification information, with no need to repeatedly provide the validation contents the same as those of the drug substance.

3.2.P.5.4 Batch Analyses

Provide the batch information and batch analysis results of representative batches.

3.2.P.5.5 Characterisation of Impurities

The information on the characterisation of impurities shall be provided.

3.2.P.5.6 Justification of Specification(s)

Provide the justification of the specification.

[Summary Example-3.2.P.5 Control of Drug Product]

Specification comparison:

Test item		**Candidate drug**		**Reference drug**
		Test method	**Acceptance criteria**	**Acceptance criteria**
Identification	Identification 1			
	Identification 2			
Physicochemical properties	Color			
	Clarity			
	Visible particles			
	Particulate matter			
	Deliverable volume			
	pH			
	Osmolality (mOsmol/kg)			
Purity and impurities	Size exclusion chromatography			
	Charge variant			
	Reduced CE-SDS			
	Non-reduced CE-SDS			
Activity	Binding activity			
	Biological activity			
Assay				
Sterility test				

Test item	Candidate drug		Reference drug
	Test method	Acceptance criteria	Acceptance criteria
Bacterial endotoxin			
Undue toxicity			
Excipient requiring control			
……			

Batch analysis results of candidate drug:

Test item		Test method	Acceptance criteria	Verification result		
				Batch No. 1	Batch No. 2	Batch No. 3
Corresponding drug substance batch No.				Batch No. a	Batch No. b	Batch No. c
Identification	Identification 1					
	Identification 2					
Physicochemical properties	Color					
	Clarity					
	Visible particles					
	Particulate matter					
	Deliverable volume					
	pH					
	Osmolality (mOsmol/kg)					
Purity and impurities	Size exclusion chromatography					
	Charge variant					
	Reduced CE-SDS					
	Non-reduced CE-SDS					
Activity	Binding activity					
	Biological activity					

Test item	Test method	Acceptance criteria	Verification result		
			Batch No. 1	Batch No. 2	Batch No. 3
Corresponding drug substance batch No.			Batch No. a	Batch No. b	Batch No. c
Assay					
Sterility test					
Bacterial endotoxin					
Undue toxicity					
Excipient requiring control					
……					

Validation/verification of analytical procedures

Test item		Methods	Validation/Verification content of analytical procedures							
			Specificity	Linearity	Precision	Accuracy	Limit of detection	Limit of quantitation	Range	Ruggedness
Identification	Method 1	HPLC	+	-	+	-	-	-	-	+
Purity and impurities										
Activity										
Assay										

Test item		Methods	Validation/Verification content of analytical procedures							
			Specificity	Linearity	Precision	Accuracy	Limit of detection	Limit of quantitation	Range	Ruggedness
Safety										

Note: Mark "+" if the preliminary analytical validation is completed; otherwise, mark "-".

3.2.P.6 Reference Standards or Materials

The information on reference standards or reference materials used for testing of the drug product shall be provided, and the requirements for data preparation are the same as those for the drug substance. If the information is the same as that for the drug substance, such information is not necessary to be provided repeatedly, and it shall be indicated that the information is the same as that of the reference standards or reference materials for the drug substance.

3.2.P.7 Container Closure System

Provide the information on the container closure system, including the name, specification, source and material of each component.

[Summary Example-3.2.P.7 Container Closure System]

Item	Container closure system

Item	Container closure system		
Name of packaging material			
Specification of packaging material			
Packaging material composition			
Manufacturer of packaging material			
Registration No. of packaging materials (if any)			

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

The subsequent stability protocol shall be provided.

3.2.P.8.3 Stability Data

Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative.

[Summary Example-3.2.P.8 Stability]

Item	Storage conditions	Study time (completed)	Study item	Study batch (process version, and purpose)
Study container closure	Consistent with the container closure system material under			

Item		Storage conditions	Study time (completed)	Study item	Study batch (process version, and purpose)
system		application or not: Yes □ No □ In case of inconsistency, the representativeness of the container closure system shall be assessed.			
Long-term					
Study result		Same as those of the drug substance			
Accelerated					
Study result		Same as those of the drug substance			
Influencing factor testing	High temperature				
	Light				
	……				
Study result		Same as those of the drug substance			
Transportation stability (if any)		The drug product transportation stability study results shall be provided to assess whether the implementation of a clinical trial is supported.			
Study result					
Storage conditions and expiration date					

3.2.A Appendices

3.2.A.1 Facilities and Equipment

A diagram should be provided illustrating the manufacturing flow including movement of materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas.

A summary description of product-contact equipment, and its use (dedicated or multi-use) should be provided.

3.2.A.2 Adventitious Agents Safety Evaluation

Information assessing the risk with respect to potential contamination with adventitious agents should be provided, including non-viral adventitious agents and viral adventitious agents.

The control of viral adventitious agents shall be described in detail in terms of cell lines, materials of human or animal origin, unprocessed bulks, and viral clearance studies.

The information on unprocessed bulk shall be provided, including the batch number, preparation process, testing facilities (third-party or self-testing), test items and test results (a list may be attached). The test report of unprocessed bulk shall be provided in the form of an attachment.

The processes and results of the viral clearance validation study shall be provided, and the validation report shall be provided in the form of an attachment (if applicable).

Viral clearance validation (if applicable)

The validation institution, model virus, samples for validation (batch number, and process version), number of runs, representative analysis of

scale-down model, validation results and virus safety evaluation shall be specified. The representativeness of the samples for validation shall be evaluated. If no representative batches of samples made by the clinical application process are used for viral clearance validation and there is a process change between the samples for validation and the clinical samples, the quality comparison of the samples loaded for each validation step shall be provided, including but not limited to protein concentration, impurity level, etc.

If a platform process is involved, corresponding study basis may be provided by referring to *Technical Guidelines for Platform Validation of Viral Clearance Processes in Clinical Trial Applications for Therapeutic Recombinant Protein Products (Interim)*.

[Summary Example-3.2.A.2 Adventitious Agents Safety Evaluation]

Unprocessed bulk (UPB): XXX company was entrusted to test the clinical batch (batch number) of UPB, and the original test report was provided.

Name	Item	Analytical procedure	Acceptance criteria	Batch No.
Unprocessed bulk (UPB)	Mycoplasma	Culture method in the Chinese Pharmacopoeia (XXX Edition)		
		Indicator cell method in the Chinese Pharmacopoeia		

Name	Item	Analytical procedure	Acceptance criteria	Batch No.
		(XXX Edition)		
	Bioburden	Membrane filtration method in the Chinese Pharmacopoeia (XXX Edition)		
	Murine parvovirus	qPCR		
	Endogenous and adventitious viruses Contamination testing	*In vitro* inoculation and culture method using various indicator cells in the Chinese Pharmacopoeia (XXX Edition)		
	……			

Viral clearance validation (if applicable)

Validation institution: XXX

Model virus: XXX

Study sample (batch No.): XXX (process version, and purpose)

Number of runs: 2.

Comparison of study conditions:

Item	Parameter	Clinical sample process parameter range	Scale-down model validation process parameter range	Worst-case process conditions assessed

Item	Parameter	Clinical sample process parameter range	Scale-down model validation process parameter range	Worst-case process conditions assessed
Low pH inactivation	Temperature			
	Protein concentration			
	Inactivation pH			
	Incubation time			
	……			
Virus retentive filtration	Filter model			
	Trans-membrane differential pressure (specify worst-case conditions validated by the supplier)			
	Volume load			
……	……			

Summary of validation study results:

Process step	Model virus	Log_{10} reduction factor	
		Run 1	Run 2
Low pH inactivation			
Virus retentive filtration			
……			

Safety factor range: Calculated under worst-case conditions such as maximum clinical dose and maximum number of retrovirus-like

particles in UPB, one potential retrovirus particle per XXX dose may be present.

3.2.A.3 Excipients

3.2.R Regional Information

3.2.R.1 Process Validation

If any, the process validation protocol and report shall be provided.

3.2.R.2 Batch Record

The batch manufacturing record and batch test record representative of the process of the samples for clinical trials shall be provided.

The certificate of analysis of the above batches shall be provided.

3.2.R.3 Analytical Procedure Validation Report

The analytical procedure validation/verification report shall be provided, including typical maps (if any).

3.2.R.4 Stability Maps

Typical maps for stability studies shall be provided.

3.2.R.5 Comparability Protocol (if applicable)

3.2.R.6 Others

Provide the biosimilar similarity analysis report, including study samples, evaluation methods, characterization study similarity, batch analysis similarity, stability similarity and similarity analysis.

Study samples: Provide the information (e.g., source/process version, batch number, strength, date of manufacture, expiration date/tentative expiration date, and purpose) of the reference drug and candidate drug used in the similarity study. Specify the elapsed storage time of the candidate drug and the reference drug at the time of study. If the reference drug is pretreated/dispensed, describe the treatment process in detail, and evaluate the effect on the reference drug.

Evaluation method: Similarity study criteria, if set and graded, shall be provided.

Similarity of quality attributes: Provide the analysis results of the similarity in quality attributes between the candidate drug and the reference drug, including comparative study data on structure elucidation, biological activity, purity and impurities. Provide comparison results of batch analysis similarity between the candidate drug and the reference drug.

Stability similarity: Provide the study protocol and results of stability similarity evaluation, including the study batches, study items and study results.

Similarity analysis: It is recommended to visually display the quality attributes and stability of the candidate drug and the reference drug in combination with scatter plots and trend charts. Evaluate the differences, including the impact on biological activity and clinical safety and efficacy.

[Summary Example-3.2.R.6 Similarity Analysis]

Study samples:

Sample	**Source/Process version**	**Number of batches**	**Batch No.**	**Strength**	**Date of manufacture**	**Elapsed storage time at time of study**	**Expiration date/Tentative expiration date**	**Purpose**
Reference drug	China							
Candidate drug	Process version							

Similarity evaluation methods (which may be modified according to the study strategy):

Grade	**Quality attribute**	**Similarity evaluation method**

Grade	Quality attribute	Similarity evaluation method

Characterization study similarity:

Quality attributes and analytical procedures	Method category	Risk assessment	Similarity grade (if any)	Similarity evaluation criteria	Reference drug				Candidate drug				Similarity conclusion
					Batch	Batch	Batch	……	Batch	Batch	Batch	……	
	Qualitative												
	Quantitative												

Batch analysis similarity:

Test item		Test method	Acceptance criteria	Similarity evaluation criteria	Reference drug				Candidate drug				Similarity conclusion
					Batch	Batch	Batch	……	Batch	Batch	Batch	……	
Identification	Identification												

Test item		Test method	Acceptance criteria	Similarity evaluation criteria	Reference drug				Candidate drug				Similarity conclusion
					Batch	Batch	Batch	……	Batch	Batch	Batch	……	
	1												
	Identification 2												
Physicochemical properties	Color												
	Clarity												
	Visible particles												
	Particulate matter												
	Deliverable volume												
	pH												
	Osmolality (mOsmol/kg)												
Purity and impurities	Size exclusion chroma												

Test item		Test method	Acceptance criteria	Similarity evaluation criteria	Reference drug				Candidate drug				Similarity conclusion
					Batch	Batch	Batch	……	Batch	Batch	Batch	……	
	tography												
	Charge variant												
	Reduced CE-SDS												
	Non-reduced CE-SDS												
Activity	Binding activity												
	Biological activity												
Assay													
Sterility test													
Bacterial endotoxin													
Undue toxicity test													
Excipient requiring control													
……													

Stability similarity:

Study batches:

Sample	Source/Process version	Number of batches	Batch No.	Strength	Date of manufacture	Elapsed storage time at time of study	Expiration date/Tentative expiration date	Purpose
Reference drug	China							
Candidate drug	Process version							

Study items:

Item		Study conditions	Study item
Long-term			
Accelerated			
Influencing factor testing	High temperature		
	Light		
	Repeated freeze-thaw		
	Oscillation		
	Acid and alkali		
	Oxidation		
	……		
Forced degradation			

Item		Study conditions	Study item
……			

Study results: The description format is the same as that of study results in [Summary Example] of the stability study of the drug substance.

Similarity analysis: A quality attribute similarity study was conducted with 3 batches of the candidate drug and 6 batches of the reference drug. There were differences in post-translational modifications and charge variants between the candidate drug and the reference drug. The analysis evaluation is as follows: XXX. A stability similarity study was conducted with 3 batches of the candidate drug and 3 batches of the reference drug, and under the conditions of XXX, the rate of decrease in the principal peak of the charge variant of the candidate drug was slightly higher than that in the principal peak of the charge variant of the reference drug. The analysis evaluation is as follows: XXX.

IV. References

[1] Chinese Pharmacopoeia Commission. Pharmacopoeia of the People's Republic of China [S]. 2025 Edition. Beijing: China Medical Science Press, 2025: 470-480.

[2] Center for Drug Evaluation, NMPA. Technical Guidelines for Platform Validation of Viral Clearance Processes in Clinical Trial Applications for Therapeutic Recombinant Protein Products (Interim)

[EB/OL]. January 2024. https://www.cde.org.cn/main/news/viewInfoCommon/52daa6be5e529f9e3b1f5c89fc5607ce.

[3] ICH Q5A (R2). Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin. 2023.

[4] ICH M4Q (R1). The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality. 2002.