Guidance for Industry: Chemistry, Manufacturing, and Controls (CMC) Documentation for Initial Investigational New Drug Application of Therapeutic Recombinant Protein Drugs

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I. Introduction

In recent years, with the rapid development of biomedical industry, the number of Investigational New Drug (IND) applications of therapeutic recombinant protein drugs continues growing. In order to continuously deepen the reform of drug review and approval system, further improve the quality of CMC Dossiers for IND application of therapeutic biological products and better serve applicants, CDE has formulated the Guidelines according to ICH M4Q (R1) Guidelines and in combination with previous review practice experience.

The Guidelines are based on the overall framework of ICH M4Q (R1), with consistent format and style. Under its framework, in combination with the CMC study characteristics of therapeutic recombinant protein drugs, the writing requirements for the CMC Dossiers for IND application are refined, aiming to provide guiding suggestions for the writing of the CMC Dossiers for IND application of this class of drugs.

The application dossiers shall be provided according to the requirements of Requirements for Registration Classification and Application Dossiers of Biological Products and Guidelines for Registration Acceptance and Review of Biological Products and other relevant regulations and guidelines. This document is the writing guidelines for the application dossiers. For the technical requirements, please refer to the relevant regulations and technical guidelines that are continuously updated in China and internationally. With the update of ICH and other relevant guidelines, the relevant contents in the Guidelines will be continuously improved and updated.

II. Scope of application

The Guidelines are mainly applicable to the writing of CMC Dossiers for the initial IND application of therapeutic recombinant protein drugs. For other drugs containing recombinant protein components or other similar biological products, the writing of their CMC Dossiers may also refer to the Guidelines.

The format and style of the guidelines are consistent with ICH M4Q (R1). The detailed writing standards and suggestions of each section are provided for the applicants' reference. Applicants may assess the applicability of each item in combination with the characteristics and specific study situations of the applied products. If necessary, the contents and presentation forms may be adjusted. In addition, summary examples are provided in the guidelines for reference. It is suggested to summarize the corresponding contents at the end of each section of the dossiers by referring to the format of summary examples.

III. Main contents

3.1 Table of Contents of Module 3

Provide the list of application dossiers.

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 the generic name (if applicable), company or laboratory code, etc.

3.2.S.1.2 Structure

Provide amino acid sequence, specify glycosylation sites or other main 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: This product is an IgG1 λ monoclonal antibody, consisting of 2 identical heavy chains and 2 identical light chains through four inter-chain disulfide bonds, and the disulfide bond positions are: CXXX-CXXX, CXXX-CXXX, CXXX-CXXX and CXXX-CXXX, respectively. The heavy chains contain three amino acid mutations, which are mutation from XXX amino acid to XXX amino acid at XXX site, mutation from XXX amino acid to XXX amino acid at XXX site and mutation from XXX amino acid to XXX amino acid at XXX site, respectively, to minimize Fc effector's functions. Pyroglutamination occurs in 100% of the peptide chain at the N-terminal, lysine deletion occurs in more than 89.00% at the C-terminal, no deamidation site is found, and the oxidation site is methionine at position XXX. The glycosylation site is asparagine at position XXX, and the main glycoforms are G0F and G1F. Structure diagram is as follows.

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

3.2.S.2 Manufacturing

3.2.S.2.1 Manufacturer

List the names, addresses and responsibilities of the manufacturer and the testing facility. If it is contracted manufacturing/contracted testing, it shall be indicated.

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[1]It is usually called bulk in biological products, but in order to be consistent with ICH M4Q (R1), the expression of drug substance is used.

[Summary example - 3.2.S.2.1 Manufacturer]

Manufacturer:

Name	Address	Responsibility

3.2.S.2.2 Manufacturing Process and Process Control

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 Manufacturing process and process control]

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

3.2.S.2.3 Control of materials

1. Upstream development and cell bank

Provide the source, modification site and reason and other information of target gene, provide the target gene sequence and amino acid sequence information, and describe the screening process of target gene in detail.

Describe the development and screening process of expression vector in detail, and provide the functional element of expression vector, target gene sequence confirmation results and confirmation report (if any).

Specify the phenotype and genotype of host bacterium, and provide the source of host cell/host bacterium and its historical information, including subculture and modification process, cell bank generation and testing information (if any), etc.

Describe the generation and screening process of engineering cell/engineering bacterium in detail, including gene transduction/transfection method, screening conditions, monoclonal selection, optimal clone screening, etc.

Describe the generation process and testing results of the cell bank/strain bank in detail, including the name, batch number, passage number, medium components, cryoprotectant components, passage conditions, density of cryopreserved cell, storage conditions and other information of the cell bank/strain bank, and provide the testing report of the cell bank/strain bank in the form of attachment. Describe the cell bank/strain bank stability study process and results in detail (if any).

2. Other raw materials used for manufacturing

List the situations of the raw materials used for manufacturing, including the manufacturers of the culture medium, additive, reagent, chromatographic medium, filter membrane and other substances in the manufacturing process, whether they meet the pharmacopoeia specifications, use stages, etc., provide the internal control specifications for the main raw materials (if any), and provide the COA documents of the key raw materials in the form of attachments. Specify whether human-derived/animal-derived materials are used in the cell bank generation and manufacturing process, and if yes, specify the specific situations of use, including the use stages, use amounts, etc., and carry out safety risk assessment. Provide TSE/BSE statement or supporting document for control of adventitious agent of suppliers and other supporting documents.

If self-made raw materials are involved, specify whether human-derived/animal-derived materials are used, and provide upstream development, manufacturing process, quality study and control, stability study, etc. If the material is manufactured using CHO and other eukaryotic cells, the process shall include virus clearance/inactivation unit, virus clearanceclearance validation study protocol and results shall be provided, and the validation report shall be provided in the form of attachment.

[Summary example - 3.2.S.2.3 Material control]

Target gene: Variable region sequence is screened by phage display technology. The heavy chain constant region is derived from human IgG1 (XXX database number is XXX), and the light chain constant region is derived from human-derived κ chain constant region (XXX database number is XXX). Leucine at position 234 is mutated to alanine (L234A) by 4 amino acid modifications (L234A, XXX, XXX, XXX) in the heavy chain Fc region, to reduce antibody-mediated ADCC and CDC effects. XXX at position XXX is mutated to XXX (XXX), to enhance the binding ability of the antibody to FcRn receptor and improve the half-life of the antibody in vivo.

Expression vector: Plasmid is from XXX. The supporting document for the source of plasmid XXX is provided. The heavy chain gene and light chain gene are inserted into the expression vector by XXX/XXX and XXX/XXX double digestion, respectively, to obtain the expression vector XXX. The main functional elements include: GS gene, hCMV promoter, KanR, etc. The expression vector is subject to enzyme digestion validation and sequence determination. The enzyme digestion size and sequencing results are consistent with the theories. The sequencing report is provided.

Host cell/host bacterium: Host cell/host bacterium XXX (specify the phenotype and genotype

of host bacterium) is purchased from XXX. After purchase, serum-free adaptation is carried out. XXX cell bank is generated. XXX testing is carried out on the cell bank. The results meet the requirements of pharmacopoeia.

Engineering cell/engineering bacterium: The expression vector is linearized after XXX enzyme digestion. The expression vector is transferred into the host cell by electrotransfection. After the cell is optimized by selection under MSX pressure, the monoclonal antibody is screened by XXX method. After Fed-batch culture, the XXX cell strain is screened and obtained by growth characteristics, expression level and product quality for subsequent cell bank generation.

Cell bank: MCB and WCB are generated under GMP conditions (if any).

Name of cell bank	Batch number	Passage number	Medium	Cell density	Storage conditions

The cell bank is generated as follows:

PCB: XXX cell strain is recovered and transferred into the passage medium containing MSX (medium name/composition), and it is passaged and expanded every 2 - 3 days. After passage for XXX times, the cell viability is > 99%, and the total cell count reaches more than XXX. The passage is ended. The cell suspension is centrifuged to remove the supernatant, and the cell pellet is resuspended with the passage medium added with 10% (v/v) DMSO, and then dispensed into the cell cryovial. The cryovial is placed in a programmed cooling box, then transferred into a -80°C freezer for storage, and transferred into a liquid nitrogen tank 24 hours later. A total of XXX vials are cryopreserved, 1 ml/vial, cell density is XXX, viability during cryopreservation is XXX, PDL is XXX, name is XXX, batch number is XXX.

MCB: Same as PCB.

WCB (if any): Same as PCB.

EOPC (if any): Prepare EOPC using clinical batch XXX.

Testing of cell bank: XXX company is entrusted to carry out the testing. The testing method meets the requirements of ICH Guidelines/pharmacopoeia. The results are as follows. The original testing report is provided.

Item	Analytical procedure	Specification	Master cell bank	Working cell bank	EOPC
Cell identification	Carry out the testing according to the "Preparation and Quality Control of Animal Cell Substrates Used for Manufacturing of Biological Products" of Volume III of Pharmacopoeia of the People's Republic of China XXX				
Sterility test	Carry out the testing according to the "Preparation and Quality Control of Animal Cell Substrates Used for Manufacturing of Biological Products" and General Chapter XXX of Volume III of Pharmacopoeia of the People's Republic of China XXX				
Testing of mycobacterium	Carry out the testing according to the "Preparation and Quality Control of Animal Cell Substrates Used for Manufacturing of Biological Products" and General Chapter XXX of Volume III of Pharmacopoeia of the People's Republic of China XXX				
Testing of mycoplasma	Carry out the testing according to the General Chapter XXX of Volume III of Pharmacopoeia of the People's Republic of China XXX				
Testing of spiroplasma	Culture method/nucleic acid method				

Item		Analytical procedure	Specification	Master cell bank	Working cell bank	EOPC
Testing of endogenous and adventitious virus contamination	In vitro culture method	Inoculation culture method for different indicator cells in vitro (X cell, X cell and X cell, 28 days)				
	Inoculation in animal and embryonated chicken egg	Suckling mouse				
		Adult mouse				
		Embryonated chicken egg				
		...				
	Testing of retroviruses	Reverse transcriptase activity				
		Infectivity test				
		Transmission electron microscope examination method				
	Testing of species specific viruses	(Specify the virus type tested)				
		...				
	Testing of bovine viruses	(Specify the virus type tested)				
		...				
	Testing of porcine viruses	(Specify the virus type tested)				
		...				
	...					

Cell bank stability study (if any): Cell bank passage stability study and storage stability study are carried out.

Passage stability study (if any): 1 vial of the XXX cell strain is recovered and passaged to that PDL is XXX in XXX medium, under XXX pressure/without pressure. Cells are cryopreserved at PDLXXX, PDLXXX, PDLXXX and PDLXXX, respectively. Cryopreserved cells are recovered and subject to Fed-batch culture, respectively for growth status, cell viability, expression level, product quality (binding activity, SEC purity, nrCE-SDS purity, rCE-SDS purity, charge variant, glycosylation, peptide map, etc.), genetic stability (gene copy number, target gene sequence, etc.) and other testing. The target gene sequence of cell from each generation is consistent with the theoretical sequence, with no significant difference in each investigation item. It is preliminarily proposed that the passage limit of WCB is XXX, which may meet the manufacturing needs at the scale above XXXL.

Storage stability study (if any): May describe according to the actual storage stability study situations by referring to the description format of passage stability study.

Other raw materials used for manufacturing

Name	Manufacturer	Whether meet pharmacopoeia specifications	Use stage	COA	In-house specification (If any)
		Meet Chinese Pharmacopoeia specifications		Provided/not provided	Provided/not provided

Whether use human-derived/animal-derived materials: Yes ☐ No ☐

3.2.S.2.4 Control of Critical steps and Intermediates

If any, provide the process parameters or critical process parameters of the key step and the routine control item and specification limit of the intermediate or in the manufacturing process.

[Summary example - 3.2.S.2.4 Key step and control of intermediate]

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 attachment.

3.2.S.2.6 Manufacturing Process Development

Provide detailed process development dossiers and change situations of each process version. Specify the relevant information of drug substance batch manufactured in the development process, such as process version, batch number, manufacturing scale and use (such as stability, non-clinical trials/studies and reference substance), and specify the corresponding drug substance batch information or process version information of batch already used in clinical trials/studies (if any), batch intended for clinical trials/studies in China and toxicology batch.

Specify whether the corresponding drug substance manufacturing process of batch intended for clinical trials/studies in China and toxicology batch has been changed. If the manufacturing process has been changed, provide adequate comparability study dossiers. For products already used in clinical trials, provide a detailed description of the similarities and differences in the corresponding drug substance manufacturing process between batch intended for clinical

studies in China and batch already used in clinical trials, and provide adequate comparability study dossiers.

[Summary example - 3.2.S.2.6 Manufacturing process development]

Information of key batch:

Batch number	Manufacturing scale	Process version	Usage (such as pharmacological and toxicological studies, clinical trials, stability studies, reference substance batch, etc.)

The drug substance involves a total of X versions of the manufacturing process, which are Process A, Process B and Process C, respectively. The drug substance manufactured by Process B is used for toxicology trials/studies, and the drug substance manufactured by Process C is intended for clinical trials/studies in China.

The change situations between Process B and Process C are as follows; no other change occurs:

Change comparison		Process B	Process C
Cell bank			
Raw materials used for manufacturing			
Manufacturing	Manufacturer		
	Equipment		
	Scale		
	Process step and parameters		
	...		
Container closure system			
...			

Comparison of process performance (including control of intermediate) and quality comparability study are carried out between Process B and Process C.

Comparison of process performance: The comparison of process performance between batch XXX manufactured by Process B and batch XXX manufactured by Process C is provided, including intermediate quality, yield, etc., with no significant difference except for XXX. The differences are analyzed as follows: XXX.

Characterization comparability: Characterization comparability study is carried out for the batch XXX manufactured by Process B and the batch XXX manufactured by Process C. See the characterization identification section for details. The differences are analyzed as follows: XXX.

Batch analysis comparability: Batch analysis comparability studies were conducted for the XXX batches manufactured by Process B and the XXX batches manufactured by Process C. See the batch analysis section for details. The differences are analyzed as follows: XXX.

Stability comparability: Long-term, accelerated, stress and forced degradation comparability

studies were conducted for XXX batches manufactured by Process B and XXX batches manufactured by Process C. See the stability section for details. The differences are 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). The original study report is provided as an appendix.

3.2.S.3.2 Impurities

Provide studies on product-related impurities and process-related impurities, including impurity sources, test methods, and test results or safety assessment results of representative batches.

[Summary Example - 3.2.S.3 Characterisation]

Characterization identification	**Test item**			**Testing method**	**Test result**		
					Batch number	**Batch number**	**Batch number**
					Process version	**Same as left**	**Same as left**
Structure confirmation	Primary structure	Intact molecular mass					
		Deglycosylated molecular weight					
		Light chain molecular mass					
		Non-deglycosylated heavy chain molecular mass					
		Deglycosylated heavy chain molecular mass					
		Sequence coverage	Primary mass spectrometry				
			Secondary mass spectrometry				
		Post-translational modification	Modification 1				
			Modification 2				
			...				
		Characteristic peptide identification in CDR region					
		C/N-terminal amino acid sequence					
		Free sulfhydryl					
		Disulfide bond					

Characterization identification	Test item			Testing method	Test result		
					Batch number	Batch number	Batch number
					Process version	Same as left	Same as left
	Higher order structure	Circular dichroism	Far-UV				
			Near-UV				
		Fluorescence spectroscopy					
		Thermal stability					
		...					
	Glycosylation	N-glycosylation site					
		N-glycan type and proportion	G0F				
			G0				
			...				
		Sialic acid modification	NGNA				
			NANA				
Physical and chemical properties	Molar extinction coefficient						
	Isoelectric point						
	Purity and impurities	Size-exclusion chromatography	Aggregate				
			Principal peak				
			Fragment				
		Reducing CE-SDS electrophoresis	Light chain + heavy chain				
			Fragment				
		Non-reducing CE-SDS electrophoresis	Principal peak				
			Fragment				
		Charge variant	Acidic region				
			Principal peak				
			Basic region				
Biological function	Binding activity						
	Biological activity						
	Binding ability to FcγRI						
	Binding ability to FcγRIIa						
	Binding ability to FcγRIIb (KD, M)						
	Binding ability to FcγRIIIa (KD, M)						
	Binding ability to FcRn (KD, M)						
	Binding ability to C1q						
	ADCC						
	CDC						
	...						
Impurities	Product-relevant impurities	...					
	Process-relevant impurities	Residual Protein A					
		Residual adventitious DNA					
		Residual host cell protein					
		...					

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specifications

Provide a list of the specification of the drug substance, including test items, acceptance criteria and analytical procedures.

3.2.S.4.2 Analytical procedureProcedures

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

3.2.S.4.3 Validation of Analytical procedureProcedures

Provide methodology validation/verification information.

3.2.S.4.4 Batch Analyses

Provide batch information and batch analysis results of representative batches.

3.2.S.4.5 Justification of Specifications

Provide the justification for the specification.

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

Specification and batch analysis results:

Test item		**Testing method**	**Specification limit**	**Test results**		
				Batch 1	**Batch 2**	**Batch 3**
Identification test	Identification test item 1					
	Identification test item 2					
	...					
Glycosylation modification	N-glycan profile					
Physicochemical property	Appearance					
	pH					
	...					
Purity and impurities	Size-exclusion chromatography					
	Charge variant					
	Reducing CE-SDS electrophoresis					
	Non-reducing CE-SDS electrophoresis					
	Residual Protein A					
	Residual adventitious DNA					
	Residual host cell protein (HCP)					
	...					
Activity	Binding activity					
	Biological activity					
Content						
Bacterial endotoxin						
Bioburden						

Analytical procedures validation/verification:

Test item		Method	Contents of analytical procedures validation/verification							
			Specificity	Linearity	Precision	Accuracy	Limit of detection	Limit of quantification	Range	Robustness
Identification	Peptide mapping	HPLC	+	-	+	-	-	-	-	+
Purity and impurities										
Activity										
Content										
Safety										

Note: Fill in "+" if the preliminary method validation is completed, otherwise fill in "-".

3.2.S.5 Reference Standards or Materials

Provide information on reference standards or materials used for drug substance testing, including the preparation process and studies on reference standards or materials, such as characterisation, batch analysis, qualification of reference standards or materials (if applicable), and stability, etc.

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

Name	Reference standards or materials
Batch No.	
Batch No. of the drug substance	
Packaging container	
Content	
Formulation	
Storage conditions	
Useage	

Qualification of reference standards or materials (if applicable): The process and results of content qualification and biological activity qualification are provided.

Content qualification (if applicable): Content qualification was performed on X samples by X analysts, respectively. The overall RSD was XXX, and the mean value was XXX.

Biological activity qualification (if applicable): Biological activity qualification for XXX batch was performed using XXX batch as the reference. Biological activity qualification was performed on X samples by X analysts, respectively. The overall RSD was XXX, and the mean value was XXX.

Stability: Briefly describe the stability protocol (including study conditions and study items, etc.) and study results (if any).

3.2.S.6 Container Closure System

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

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

Item	Container closure system
Name of packaging materials	
Strength of packaging materials	
Composition of packaging materials	
Manufacturer of packaging materials	

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

Summarize the types of stability studies conducted, protocols used, and the results of the studies.

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

Provide the subsequent stability protocol.

3.2.S.7.3 Stability Data

Provide the results of stability studies in an appropriate format (e.g. tabular, graphic, narrative).

[Summary Example - 3.2.S.7 Stability]

Item		Storage conditions	Study time (completed)	Study item	Study batch (process version, use)
Study the container closure system		Whether it is consistent with the material of the applied container closure system: Yes☐ No ☐ If not, the representativeness of the container closure system should be assessed.			
Long-term					
Study results		Briefly describe the change trend and preliminary conclusion of the study items. For example, during the study period of XXX months, no significant change trend has been observed for each test item.			
Accelerated					
Study results		Briefly describe the change trend and preliminary conclusion of the study items. If there is significant change, it is necessary to analyze the degradation pathway and rate. For example, during the study period of XXX months, the main peak of molecular size variants 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 main peak of charge variants decreased (68.3% - 69.1% → 56.5% - 57.4%), and acidic variants increased (25.8% - 26.5% → 35.4% - 36.3%). The other test items showed no significant change trend. No new impurity peaks were observed in the impurity profile comparison.			
Stress testing	High temperature				
	Light				
	Freeze-thaw				
	...				

Item	Storage conditions	Study time (completed)	Study item	Study batch (process version, use)
Study results	Briefly describe the change trend and preliminary conclusion of the study items. If there is significant change, it is necessary to analyze the degradation pathway and rate. For example, during the study period of 30 days at high temperature, the biological activity exceeded the acceptance criteria (65%, criteria: 70% - 130%). The other test items met the proposed acceptance criteria. The main peak of molecular size variants decreased (99.7% → 95.6%), and high molecular weight (HMW) impurities increased (0.3% → 4.0%); the other test items showed no significant change trend. No new impurity peaks were observed in the impurity profile comparison.			
Transportation stability (if any)				
Study results				
Storage conditions and shelf life				

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 components, strength, and type of container closure system for the drug product. Provide the components per unit dose of the product, specifying the effects of each component and executive standards, etc.

For a drug product supplied with reconstitution diluent(s), provide the information on the diluent(s) in a separate part "P".

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

This product is a sterile injection made of a recombinant anti-XXX humanized monoclonal antibody expressed in CHO-K1 cells, supplemented with 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.

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

Component	Content	Supplier	Specification	Registration No.	Effect

Is there an overage: Yes ☐ No ☐

Is there overfill: Yes ☐ No ☐

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

The compatibility of excipients with the drug substance is preliminarily demonstrated. For combination products, the compatibility between each drug substance is preliminarily demonstrated.

3.2.P.2.2 Drug Product

Provide the detailed formula development process, such as screening of types and concentrations of excipients, buffer salts and stabilizers, pH screening, etc. Provide supporting data in case of overages.

3.2.P.2.3 Manufacturing Process Development

Provide detailed process development data and changes of each process version (including formula changes). Specify the relevant information for drug product batches manufactured during development, such as process version, batch number, production scale, and use (e.g., stability, non-clinical study, and reference substance). Specify the batch information or process version information for batches already used in clinical trials/studies (if any), batches intended for clinical trials/studies in China, and toxicology batches.

If the manufacturing process for batches intended for clinical trials/studies in China is different from that of toxicology batches, adequate comparability study data should be provided. For products already used in clinical trials, provide a detailed description of the similarities and differences in the drug product manufacturing process between batches intended for clinical studies in China and batches already used in clinical trials, and provide adequate comparability study data. For international multicenter clinical trial applications, specify the process or batch information intended for clinical trials in China.

3.2.P.2.4 Container Closure System

The suitability of the container closure system is preliminarily demonstrated. The compatibility of this product with the packaging materials may be assessed by combining the study data on packaging materials completed by the container closure system supplier and the stability study results of this product.

3.2.P.2.5 Microbiological Attributes

The sterility of this product is preliminarily demonstrated and the container-closure integrity is assessed.

3.2.P.2.6 Compatibility

Compatibility of the drug product with the reconstitution diluent and with the administration device will be addressed to support the proposed usage in the clinical protocol.

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

Key batch information:

Batch No. (batch No. of the drug substance)	**Manufacturing scale**	**Process version**	**Use**

The drug product involves a total of X versions of the manufacturing process, which are Process 1, Process 2, and Process 3. The drug product manufactured by Process 2 is used for toxicology trials/studies, and the drug product manufactured by Process 3 is intended for clinical trials/studies in China.

The changes between Process 2 and Process 3 are as follows; no other changes occurred:

Change comparison		**Process 2**	**Process 3**
Process version of the drug substance		**Process B**	**Process C**
Components of the drug product			
Strength			
Manufacturing	Manufacturer		
	Equipment		
	Scale		
	Process step and parameters		
	...		
Container closure system			
...			

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

Comparison of process performance: The comparison of process performance between XXX batches manufactured by Process 2 and XXX batches manufactured by Process 3 is provided, including intermediate quality, yield, etc., with no significant difference except for XXX. The differences are analyzed as follows: XXX.

Batch analysis comparability: Batch analysis comparability studies were conducted for the XXX batches manufactured by Process 2 and the XXX batches manufactured by Process 3. See the batch analysis section for details. The differences are analyzed as follows: XXX.

Stability comparability: Long-term, accelerated, stress and forced degradation comparability studies were conducted for XXX batches manufactured by Process 2 and XXX batches manufactured by Process 3. See the stability section for details. The differences are analyzed as follows: XXX.

Compatibility assessment: Based on the study data on packaging materials completed by the container closure system supplier and the stability study results of this product, the packaging materials is considered suitable for the intended use.

In-use stability study: Using XXX as the diluted solution, the drug product is diluted to XXX mg/ml in a syringe made of XXX material and studied for XXX hours under XXX conditions. Test items: XXX. Result: XXX. Conclusion: XXX.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Provide the names, addresses and responsibilities of the manufacturer and the testing facility. If it is entrusted manufacturing/entrusted testing, it shall be indicated.

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

Manufacturer:

Name	Address	Responsibility

3.2.P.3.2 Batch Formula

Provide the batch formula, specify all the components used in the drug product manufacturing process, describe the amount per batch and the executive specification for each component. Specify the overfill situation.

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

Provide manufacturing process information and specify the applied scale and batch size (if any). Provide the manufacturing process flow chart, describe each process step in detail, and clarify the process parameters of 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

If any, provide the process parameters or critical process parameters of the key step and the routine control item and specification limit of the intermediate or in the manufacturing process.

[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 attachment.

3.2.P.4 Control of Excipients

Provide the basic information of excipients, including name, manufacturer, specification and registration number (if any). Provide the test method (if applicable), methodology validation results and report (if applicable) of each excipient, and provide the justification of the specification of the excipient (if applicable).

Specify whether human-derived/animal-derived excipients and novel excipients are used.

If self-made excipients are involved, specify whether human-derived/animal-derived materials are used, and briefly describe upstream development, manufacturing process, quality studies and control, and stability studies, etc. If the excipient is manufactured by expression in eukaryotic cells such as CHO, the process includes a virus clearance/inactivation unit, the virus clearance validation study protocol and results shall be provided, and the validation report shall be provided as an attachment.

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

Name	Manufacturer	Specification	Registration No. (if any)
		Pharmacopoeial standards/enterprise standards	

Whether human-derived/animal-derived excipients 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)

Provide the specification of the drug product, including study items, acceptance criteria and analytical procedures.

3.2.P.5.2 Analytical Procedures

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

3.2.P.5.3 Validation of Analytical Procedures

Provide methodology validation/verification information. The validation content identical to that of the drug substance does not need to be provided repeatedly.

3.2.P.5.4 Batch Analyses

Provide batch information and batch analysis results of representative batches.

3.2.P.5.5 Characterisation of Impurities

Provide information on characterisation of impurities.

3.2.P.5.6 Justification of Specification(s)

Provide the justification for the specification.

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

Specification and batch analysis results:

Test item		**Testing method**	**Specification limit**	**Test results**		
				Batch No. 1	**Batch No. 2**	**Batch No. 3**
Batch No. of the drug substance				**Batch No. a**	**Batch No. b**	**Batch No. c**
Identification	Identification test item 1					
	Identification test item 2					
Physicochemical property	Colour					
	Clarity					
	Visible particles					
	Particulate matter					
	Fill volume					
	pH					
	Osmolality (mOsmol/kg)					
Purity and impurities	Size-exclusion chromatography					
	Charge variant					
	Reducing CE-SDS electrophoresis					
	Non-reducing CE-SDS electrophoresis					
Activity	Binding activity					
	Biological activity					
Content						
Sterility test						
Bacterial endotoxin						
Abnormal toxicity						
Excipient components to be controlled						
...						

Analytical procedures validation/verification:

Test item		**Method**	**Contents of analytical procedures validation/verification**							
			Specificity	**Linearity**	**Precision**	**Accuracy**	**Limit of detection**	**Limit of quantification**	**Range**	**Robustness**
Identification	Method 1	HPLC	+	-	+	-	-	-	-	+
Purity and impurities										
Activity										
Content										
Safety										

Note: Fill in "+" if the preliminary method validation is completed, otherwise fill in "-".

3.2.P.6 Reference Standards or Materials

Provide the information of the reference standard or material used for drug product testing. The requirements for document preparation are the same as those for the drug substance. The content identical to that of the drug substance does not need to be provided repeatedly. indicate "Same as reference standards or materials of the drug substance".

3.2.P.7 Container Closure System

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

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

Item	**Container closure system**		
Name of packaging materials			
Strength of packaging materials			
Composition of packaging materials			
Manufacturer of packaging materials			
DMF Registration No. of packaging materials (if available)			

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusions

Summarize the types of stability studies conducted, protocols used, and the results of the studies.

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

Provide the subsequent stability protocol.

3.2.P.8.3 Stability Data

Provide the results of stability studies in an appropriate format (e.g. tabular, graphic, narrative).

[Summary Example - 3.2.P.8 Stability]

Item		**Storage conditions**	**Study time (completed)**	**Study item**	**Study batch (process version, use)**
Study the container closure system		Whether it is consistent with the material of the applied container closure system: Yes☐ No ☐ If not, the representativeness of the container closure system should be assessed.			
Long-term					
Study results		Same as drug substance			
Accelerated					
Study results		Same as drug substance			
Stress testing	High temperature				
	Light				
	...				
Study results		Same as drug substance			
Transportation stability (if any)		Provide the results of drug product transportation stability study and assess whether they support the conduct of clinical trials.			
Study results					
Storage conditions and					

shelf life	

3.2.A Appendices

3.2.A.1 Facilities and Equipment

Briefly describe the flow chart of the manufacturing process, including the flow of materials, personnel, waste and intermediates inside and outside the manufacturing area.

Provide a summary description of the equipment in contact with the product and its use (dedicated or multi-use).

3.2.A.2 Adventitious Agents Safety Evaluation

Provide information on the risk assessment of potential contamination related to adventitious agents, including non-viral adventitious agents and viral adventitious agents.

Detail the control of viral adventitious agents in terms of cell lines, animal-derived and human-derived materials, unprocessed harvest, and viral clearance studies.

Provide the information of unprocessed harvest, including batch number, preparation process, testing facility (third-party or in-house), test items and test results (list can be attached). Provide the testing report of unprocessed harvest as an attachment.

Provide the viral clearance validation study process and results, and provide the validation report as an attachment (if applicable).

Virus clearance validation (if applicable)

Specify the validation institution, model viruses, samples for validation (batch number, process version), number of runs, representative analysis of scale-down model, validation results and virus safety assessment, etc. Assess the representativeness of the samples for validation. If samples of representative batches from the process for clinical application are not used for viral clearance validation and there are changes between the process used for the samples for validation and the process of clinical samples, provide quality comparisons of the load samples for each validation step, including but not limited to protein concentration and impurity level.

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

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

Unprocessed harvest: XXX company was contracted to test the clinical batch (batch No.) of UPB, and the original test report was provided.

Name	Item	Analytical procedure	Acceptance criteria	Batch number
Unprocessed harvest (UPB)	Mycoplasma	Chinese Pharmacopoeia XXX Edition Culture method		
		Chinese Pharmacopoeia XXX Edition Indicator cell method		
	Bioburden	Chinese Pharmacopoeia XXX Edition Membrane filtration method		
	Murine minute virus	qPCR		
	Endogenous and adventitious viruses Contamination testing	In vitro inoculation and culture method using various indicator cells in the Chinese Pharmacopoeia (XXX Edition)		
	...			

Virus clearance validation (if applicable)

Validation institution: XXX

Model virus: XXX

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

Number of runs: 2.

Comparison of study conditions:

Item	Parameter	Process parameter ranges for clinical samples	Process parameter ranges validated using a scale-down model	Worst-case process conditions after assessment
Low pH inactivation	Temperature			
	Protein concentration			
	Inactivation pH			
	Incubation time			
	...			
Virus retentive filtration	Filter model			
	Differential pressure across the membrane (specify the worst-case conditions validated by the supplier)			
	Volume loading			
...	...			

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 based on worst-case conditions such as the maximum clinical dose and the maximum number of retrovirus-like particles in UPB, there may be one potential retrovirus particle per XXX dose.

3.2.A.3 Excipients

3.2.R Regional Information

3.2.R.1 Process Validation

If any, provide the process validation protocol and report.

3.2.R.2 Batch Records

Provide batch manufacturing record and batch testing record representing the process of clinical trial samples.

Provide the certificate of analysis of the above batches.

3.2.R.3 Analytical Procedures Validation Report

Provide analytical procedures validation/verification report, including typical chromatograms (if any).

3.2.R.4 Chromatograms of Stability study

Provide typical chromatograms from stability studies.

3.2.R.5 Comparability Protocol (if applicable)

3.2.R.6 Others

IV. References

[1] National Pharmacopoeia Commission. Chinese Pharmacopoeia [2025 Edition]. Beijing: China Medical Science Press, 2025: 470–480.

[2] Center for Drug Evaluation (CDE), National Medical Products Administration (NMPA). Guideline on Platform Validation of Viral Clearance in Clinical Trial Applications of R ecombinant Proteins (Trial) [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 line

s of human or animal origin. 2023.

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