Provisional Translation (as of July 2026) *

Checklist for Quality-Related Documents for Biotechnology Products Derived from Cell Lines of Human or Animal Origin at the Time of Initial Clinical Trial Notification (Early Consideration)

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Pharmaceuticals and Medical Devices Agency
Office of Cellular and Tissue-based Products
Office of Vaccines and Blood Products

When an initial clinical trial notification (CTN) is submitted to the Pharmaceuticals and Medical Devices Agency (PMDA), the quality reviewer confirms issues related to ensuring the safety of clinical trial participants based on quality test data and other relevant information. This document provides a checklist for CTNs subject to the 30-day CTN review, particularly those involving biotechnology products derived from human or animal cell lines. This document is based on Q&A No.27 of the "Revision of Questions and Answers (Q&A) regarding the Notification of Clinical Trial Plans and Implementation of Clinical Trials for Drugs" (Administrative Notice dated August 31, 2022)[1)] and the "Checklist for 30-day Clinical Trial Notification Review Inquiries (Biopharmaceutical Quality Area)", and includes additional key points and illustrative examples reflecting inquiries frequently raised in recent years during the review of initial CTNs. In light of the increasing number of consultations and inquiries from overseas startups, venture companies, and other entities engaged in the development of innovative pharmaceuticals at PMDA's overseas offices, this document also provides specific examples of descriptions to be included in informed consent documents and related materials. Sponsors are expected to refer to this document when preparing documents to be attached to CTNs. For PMDA's approach to the quality review of biopharmaceuticals, please also refer to the publicly available e-learning video (YouTube: PMDA Channel: Review of CMC for Biotechnology-Derived Products)[2)].

Checklist for Quality-Related Documents for Biotechnology Products Derived from Cell Lines of Human or Animal Origin at the Time of Initial CTN

Item	Points to Consider / Examples of Description	✔
Initial CTN Form		
Is it stated in the manufacturing process section that the investigational product is manufactured using recombinant DNA technology?	These items should be described in accordance with the following notifications: • "Partial Revision of Handling of Notifications for Clinical Trial Plans Involving Drug Investigations by Sponsors" (PSB/PED Notification No. 0820-1, dated August 20, 2024)[3)] • "Partial Revision of Handling of Notifications, etc. of Clinical Trial Plans for Drugs by Persons Who Intend to Be Sponsor-investigators" (PSB/PED Notification No. 0820-2, dated August 20, 2024)[4)]	
Is the dosage form stated in the manufacturing process section?		
For a clinical trial using a drug expected to be designated as a biological product, is "Biological product (expected)" entered in the field for "Applicability of clinical trials using drugs expected to be designated as biological products"?		
For combination products, is "Applicable" entered in the field for the applicability of a clinical trial on a combination product?		
Clinical Trial Protocol		
Are exclusion criteria established for individuals with a history of hypersensitivity to components of the investigational product including drugs and excipients (or concomitant drugs)? Is this information clearly described in the informed consent document?	＜Clinical Trial Protocol＞ Subjects with a history of hypersensitivity to any component of the investigational product including drugs and excipients shall be excluded. ＜Informed Consent Document＞ Individuals with a history of hypersensitivity to any component of the investigational product including drugs and excipients are not eligible to participate.	

Investigator's Brochure		
Is it stated that the investigational product (or concomitant drugs) is a recombinant product manufactured using human- or animal-derived cell lines? Is this information also clearly described in the informed consent document?	This information may alternatively be described in the Clinical Trial Protocol. 【Example】 ＜Clinical Trial Protocol＞ The investigational product is manufactured using a recombinant Chinese hamster ovary (CHO) cell line. ＜Informed Consent Document＞ The investigational product used in this study is a recombinant product manufactured using Chinese hamster ovary cells.	
Is the composition of the investigational product described? If the composition is described in the quality documents, is it consistent with the description in those documents?	This information may alternatively be provided in the Clinical Trial Protocol.	
Quality Documents (Quality documents may also be submitted in English)		
Is a manufacturing flow diagram for the investigational product provided?	Manufacturing flow diagrams for both the drug substance and the drug product should be provided.	
Is it demonstrated that the cell banks (MCB and WCB) are free from contamination by infectious agents (e.g., bacteria, fungi, mycoplasma, and viruses, where the cell banks are of human or animal cell origin)?	The test items and results should be described with reference to the ICH Q5A(R2) Guideline [5]. 【Example】See Annex Table 1.	
Is it demonstrated that the culture fluids prior to purification (unprocessed bulk) are free from contamination with bacteria, fungi, mycoplasma, viruses, and other pathogens?	The test items and results should be described with reference to the ICH Q5A(R2) Guideline [5]. 【Example】See Annex Table 2.	
Is it stated whether human- or animal-derived raw materials are used and, if	The materials used during cell bank establishment (preparation), as	

used, whether compliance with the Standards for Biological Raw Materials[6-7] is demonstrated?	well as in the manufacturing processes of the drug substance and the drug product, should be described. If such materials are used, the process step in which each material is used should be identified, and their compliance with the Standards for Biological Raw Materials should be explained. If such materials are not used, it should be explicitly stated that they are not used. Particular attention should be paid to potential omissions in the description of human- or animal-derived raw materials used during cell bank establishment (preparation).	
Is the viral safety of the investigational product demonstrated?	The results of viral clearance studies for manufacturing steps associated with viral inactivation and/or removal should be presented with reference to the ICH Q5A(R2) Guideline[5], and the viral inactivation and/or removal capacity of the manufacturing process should be described. Multiple virus species should be selected to reflect differences in viral characteristics, including envelope status, size, and genome type. 【Example】See Annex Table 3.	
Are provisional specifications established for impurity control and safety-related tests included in the specifications for the drug substance and the drug product (e.g., tests for product-related impurities, process-related impurities, sterility, foreign insoluble matter, insoluble particulate matter,	• The specification limit for host cell-derived DNA should be established with reference to the WHO recommendations (Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products	

and endotoxins)?	and for the characterization of cell banks, Annex 3, TRS No. 978[8]), using 10 ng/dose or less as a guide. • If the specification limit for host cell-derived proteins exceeds 100 ng/mg, the actual measured value should be presented and the appropriateness of the specification limit should be justified. • The endotoxin specification limit should be established with reference to the Japanese Pharmacopoeia (JP)[9] (General Information), “Decision of Limit for Bacterial Endotoxins”. • The specification limit for insoluble particulate matter should be established with reference to the JP[9] General Tests, “Insoluble Particulate Matter Test for Injections <6.07>” or “Insoluble Particulate Matter Test for Therapeutic Protein Injections <6.17>”, using not more than 6,000 particles per container for particles ≥10 μm and not more than 600 particles per container for particles ≥25 μm as a guide.	

Table 1: Test Results for Adventitious Agents in the Master Cell Bank (Example)

Test	Result
Sterility test (JP)	No growth observed
Microbial limit test (JP)	Total aerobic microbial count (TAMC): < 10 CFU/mL Total yeast and mold count (TYMC): < 10 CFU/mL
Mycoplasma test (culture method：JP)	Not detected
In vitro adventitious virus assay (28-day cell culture using indicator cell lines [Vero, MRC-5, and CHO cells])	Not detected
In vivo adventitious virus assay (inoculation into adult mice, suckling mice, and embryonated eggs)	Not detected
In vitro porcine virus assay (9 CFR)	Not detected
In vitro bovine virus assay (9 CFR)	Not detected
Minute virus of mice (MVM) test (PCR)	Not detected
Mouse antibody production (MAP) test	Not detected
Hamster antibody production (HAP) test	Not detected
Transmission electron microscopy (TEM)	No particles other than endogenous retrovirus-like particles known to be present in the host cell line were detected
S^+L^- focus assay	Not detected
Reverse transcriptase activity assay (quantitative PCR)	Not detected

Table 2: Test Results for Unprocessed/Unpurified Bulk (Example)

Test	Result
Microbial limit test (JP)	Total aerobic microbial count (TAMC): < 10 CFU/mL Total yeast and mold count (TYMC): < 10 CFU/mL
Mycoplasma test (culture method: JP)	Not detected
In vitro adventitious virus assay (28-day cell culture using indicator cell lines [Vero, MRC-5, and CHO cells])	Not detected
Minute virus of mice (MVM) test (PCR)	Not detected
Transmission electron microscopy (TEM)	Not detected

Table 3. Results of Viral Clearance Studies (Example)

Manufacturing Step	Viral Clearance (log_{10} reduction factor)	
	Xenotropic murine leukemia virus (X-MuLV)	Minute virus of mice (MVM)
Protein A affinity chromatography	2.01	1.83
Low pH viral inactivation	5.53	Not performed
Anion exchange chromatography	≥5.88	≥6.30
Virus filtration	≥4.61	≥5.23
Overall viral clearance factor	≥18.03	≥13.36

References

1） Revision of Questions and Answers (Q&A) regarding the Notification of Clinical Trial Plans and Implementation of Clinical Trials for Drugs (Administrative Notice dated August 31, 2022)
https://www.pmda.go.jp/files/000248031.pdf

2） Learning Video (YouTube : Pmda Channel : Review of CMC for Biotechnology-Derived Products)
https://www.youtube.com/watch?v=nYVtkNMx2G8

3） Partial Revision of Handling of Notifications for Clinical Trial Plans Involving Drug Investigations by Sponsors (PSB/PED Notification No. 0820-1, dated August 20, 2024)
https://www.pmda.go.jp/files/000270151.pdf

4） Partial Revision of Handling of Notifications, etc. of Clinical Trial Plans for Drugs by Persons Who Intend to Be Sponsor-investigators (PSB/PED Notification No. 0820-2, dated August 20, 2024)
https://www.pmda.go.jp/files/000279231.pdf

5） ICH Q5A(R2) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
https://www.pmda.go.jp/files/000265997.pdf

6） Standards for Biological Raw Materials (Ministry of Health, Labour and Welfare. Notification No. 210, dated May 20, 2003)
https://www.pmda.go.jp/files/000280407.pdf

7） Standards for Biological Raw Materials, Operational Guideline (PFSB/ELD Notification No. 1002-1 PFSB/MDRMPE Notification No. 1002-5, dated October 2, 2014)
https://www.pmda.go.jp/files/000268475.pdf

8） Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks, Annex 3, TRS No 978 (Replacement of Annex 1 of WHO Technical Report Series, No. 878)
https://www.who.int/publications/m/item/animal-cell-culture-trs-no-978-annex3

9） Japanese Pharmacopoeia
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000066597.html