October 1, 2021

Points to consider (checkpoints) for efficient conduct of RS strategy consultation for quality and safety from the early stage of development of gene therapy products [Quality]

In the "Consultation on the quality and safety of regenerative medical products" of the Regulatory Science (RS) strategy consultation, we provide the advice from the aspect of safety perspectives prior to the initial clinical trial notification for the gene therapy products.

In the initiation of clinical trials for gene therapy products, it is important to ensure the quality and safety of the products in accordance with Ensuring the Quality and safety of Gene Therapy Products (PSEHB/MDED Notification No. 0709-2 dated July 9, 2019). From an earlier stage of development, it is recommended that issues related to quality/non-clinical safety assessment be identified and that consultations be actively utilized to resolve such issues.

As the following checkpoints have been prepared for the quality control-related considerations that are often requested to respond to the extent possible in this consultation, please utilize them in preparing the documents for consultation (consultation materials). Thus, refer to the guidelines related to the product depending on the characteristics of the product and the contents of the consultation, etc. The following checkpoints are only examples and do not require that all items be fulfilled in a uniform manner.

Preparation of documents

- ☐ The general structure of the consultation materials is 1) an outline of the consultation (a brief description of the consultation items and their backgrounds), 2) basic information on the product (product outline and information on the indication to be developed), and 3) documents related to the contents of the consultation items (detailed contents of the consultation matter, the views of the developer on the consultation matter and its basis). Attach reference data (current draft of investigator's brochure, study reports, and draft of protocol including the information of target patients and dosage and administration (Even the outline will be accepted.), development roadmap, etc.), citations, etc., which are helpful in the consultation as needed. (Example of consultation items: Compliance with the Standards for Biological Raw Materials; In-process control testing and specifications; Stability, etc.)
- ☐ In the documents related to the contents of the consultation items, describe the clear and specific explanation about what the developer wants to obtain the advice from PMDA.
- ☐ In the product summary, describe the information on Expression Construct (viral vectors, etc.), such as origin, characteristics, structure, function, vector genome sequences, and plasmids for construction of the viral vectors.
- ☐ Include a table of contents and number the pages in the consultation document.
- ☐ If abbreviations, special terms, etc. are used, attach a list of their definitions.
- ☐ Make active use of figures and tables.
- ☐ Describe the status and the schedule of an application for Cartagena Act Type-1 or Type-2 approval.

Raw materials

- ☐ Prepare a list of all raw materials used in the manufacturing process of the product and explain where each raw material is used in the manufacturing process.

☐ The following points should be considered when explaining that the biological raw materials comply with the Standards for Biological Raw Materials (MHLW Notification No. 210 of 2003). Please also refer to Standards for Biological Raw Materials, Operational Guideline (PFSB/ELD Notification No. 1002-1, PFSB/MDRMPE Notification No. 1002-5 dated October 2, 2014, hereafter, "Operational Notification").

- Prepare a list of all biological ingredients (including viral vector-producing cells, fetal bovine serum used to construct viral vector-producing cell lines, enzymes used in the manufacturing process of viral vectors, etc.). Secondary raw materials (e.g. Biological ingredients used in the manufacture of enzymes used in the manufacturing process of viral vectors) should also be included in the list.
- Regarding the biological ingredients subject to the application of the Standards for Biological Raw Materials, explain the status of compliance with each requirement of Standards for Biological Raw Materials. Please also refer to the Standards for Biological Raw Materials and the Operational Notification. Use the corresponding table shown in [Example 1].
- Biological ingredients derived from ruminants (cattle, goats, sheep, etc.) should be compliant with the Standards for Animal-Derived Raw Materials and the Standards for Ruminant-Derived Raw Materials.
- When the manufacturing process for biological raw materials involves inactivation or removal of viruses, explain the inactivation ability or removal ability of viruses, etc. based on the results of the viral clearance study. In explaining the inactivation ability of the process, it is also possible to use the "Heating conditions validated for virus inactivation (Operational Notification Attachment 1)" and "Components that are considered to have gone through a severe purification process from the viewpoint of inactivation of bacteria, fungi, viruses, etc. (Operational Notification Attachment 2)" as a basis. Use the table shown in [Example 2] to explain the information.

Quality of products

☐ The following points should be considered when explaining quality control:

- Explain the manufacturing process, in-process control and specifications for the product. Use the flow chart for [Example 3] and the table for [Example 4] and [Example 5].
- Regarding specifications, in-process control tests and characterization tests for the product (drug substance and final product), explain the outline of the test (test purpose, test principle, test method, etc.) if it is non-compendial test.
- In-process control test item, specification test items and acceptance criteria for the product (drug substance and final product), as well as the basis for setting them, should be explained based on the historical manufacturing data of the product. Use the table shown in [Example 6] to explain the historical manufacturing data of the products. As for the test items and acceptance criteria related to the biological activity or potency of the product, explain the rationale based on the in vitro or in vivo non-clinical studies to support efficacy or performance.
- If there are any quality control items that have been evaluated during the development stage but are not included in the in-process control test and specification for the investigational product, explain the reason why they are not included.
- In the case of using cell bank system or virus bank system, explain the quality management strategy including the test items of identity and purity, analytical methods and acceptance criteria of these test items, storage condition, shelf life, and renewal plan for the bank. Use the table shown in [Example 7] to explain. Also explain the testing items for cells at the limit of in vitro cell age (CAL).

- Since product-related impurities (abnormal plasmids contained in plasmid products, empty or partial capsid of vectors contained in viral vector products, etc.) may cause adverse effects by directly and/or indirectly enhancing immunogenicity, explain whether these impurities are sufficiently removed in the manufacturing process based on the test results.
- As for process-related impurities and excipients, safety assessment should be conducted based on the non-clinical toxicology studies or literature information using the test substance which has equivalent impurity and secondary ingredients profile of the product used in the clinical trial.

□ The following points should be considered when explaining safety of the final product against endotoxins and infectious agents (bacteria, fungi, adventitious viruses, etc.).

- Explain the test methods, test samples, test sample amounts, and acceptance criteria.
- Explain the measures taken for the risk control of adventitious virus contamination (e.g., acceptance inspection of raw materials, virus testing in the manufacturing process, and the evaluation of viral clearance process) of the product.

□ If the manufacturing process of the product for the clinical trial differs from that of the product used for the nonclinical safety study, the differences in the manufacturing process and quality attributes should be clarified and the comparability among each manufacturing process should be explained based on the historical manufacturing data.

Stability of products

□ The following points should be considered when explaining the stability of the product.

- Explain the actual transport and storage condition of the product (drug substance, final product, etc.) (expected shelf life, storage temperature, container closure system, etc. at the time of clinical trial notification). If necessary, explain in-use stability including the expected shelf life, storage temperature, melting and preparation methods at the time of clinical trial notification. Use the table shown in [Example 8] when explaining the container closure system.
- Explain the test items, test methods, manufacturing process, number of batches, time point of measurement, test results, etc. of the stability study (long-term stability, transport validation, in-use stability, etc.). Use the table shown in [Example 8] to explain. In principle, the specification items should be set for stability study items. If there are any items that are set in the specification but not in the stability study, explain why they were not set. If the manufacturing process of the samples used in the stability study differs from these of the investigational product, clarify the differences in the manufacturing process and quality characteristics and explain the effects of these differences on the stability evaluation.
- As for the stability, it would be possible to discuss the stability study design (if results have not yet been obtained) or the results of the stability study.

END

Please prepare the consultation document in Japanese.

[Example 1]

[Status of compliance with the Standards for Biological Raw Materials]

- Compliance with the Standards for Biological Raw Materials for human-derived XXX cells using XXX cell banks produced by XXX vectors

Table X Compliance with Standards for Human-Derived Raw Materials

Content of the standard	Response status
When raw materials or ancillary materials derived from humans (excluding human cell/tissue-based raw materials, etc., human urine, and those considered to be known publicly in the scientific field to have no risk of bacterial or viral infection; hereinafter, "human derived raw materials, etc.") are used as raw materials, etc. of drugs, etc. (excluding blood preparation), the cells or tissues that are origins of the human-derived raw materials, etc. (including cell strains and cells after the termination of their culture, if the products are manufactured through cell culture using a cell bank as the starting material) must be subjected to a virus test at an appropriate stage. If in this test, an adventitious virus is detected, the human-derived raw materials, etc. must not be used to manufacture drugs, etc., in principle. Provided, that this shall not apply to cases where the raw materials, etc. consist of cell banks derived from humans, and really assembled when these standards are applied, and also it is confirmed, in terms of guarantee of quality and safety, that the use as raw materials, etc. has the validity equivalent or superior to that confirmed in this test and written in the approval letter issued at the marketing approval.	(Explain how you are dealing with it.)
The person who donates human-derived raw materials, etc. derived from human blood must be considered sufficiently eligible to donate blood serving as the human-derived raw materials, etc., and must be free from suspected bloodborne infectious diseases determined through interview, etc.	(Explain how you are dealing with it.)
……	……

- Compliance with the Standards for Biological Raw Materials for XXX (ruminant)-derived serum

Table X Compliance with Standards for Animal-Derived Raw Material

Content of the standard	Response status
When raw materials, etc. derived from animals (excluding animal cell/tissue-based raw materials, etc. and those considered to be known publicly in the scientific field to have no risk of infection with any pathogens including bacteria, fungi, viruses, etc.; hereinafter, "animal-derived raw materials, etc.") are used as raw materials, etc. of drugs, etc., it must be confirmed, unless derived from a healthy animal, that the animal-derived raw materials, etc. are aseptic, and have been subjected to test for viral infection risk and other tests required.	(Explain how you are dealing with it.)
If a characterized animal-derived cell bank is used as the starting material to manufacture products through cell culture, a virus test must be conducted at an appropriate stage. If in this test, an adventitious virus is detected, the cell bank must not be used to manufacture drugs, etc., in principle. Provided that this shall not apply to cases where the raw materials, etc. consist of cell banks, and really assembled when these standards are applied, and also it is confirmed, in terms of guarantee of quality and safety, that the use as raw materials, etc. has the validity equivalent or superior to that confirmed in this test and written in the	(Explain how you are dealing with it.)

approval letter issued at the marketing approval.	
……	……

Table X Compliance with Standards for Ruminant-Derived Raw Material

Content of the standard	Response status
When raw materials, etc. derived from ruminant animals (excluding raw materials, etc. produced by heating and alkali treatment, etc. produced by other appropriate treatments; hereinafter, "ruminant-derived raw materials, etc.") are used as raw materials, etc. of drugs, etc., the following parts of the ruminant animals must not be used: A. Pituitary gland B. Thymus C. Dura mater D. Trigeminal ganglion E. Pineal body F. Spinal cord G. Backbone H. Placenta (excluding bovine origin) I. Skull J. Intestine K. Brain L. Cerebrospinal fluid M. Dorsal root ganglion N. Spleen (excluding bovine origin) O. Adrenal gland P. Tonsil Q. Eye R. Lymph node	(Explain how you are dealing with it.)
The ruminant-derived raw materials, etc. must be native to the countries in which the risk of BSE pathogen propagation is considered negligible by the World Organisation for Animal Health, and those listed below. Provided, however, that this shall not apply to cases where gelatin (including collagen) derived from wool, milk, bone, and skin (hereinafter, "low-risk raw materials, etc.") and ruminant-derived raw materials, etc. native to Canada (hereinafter, "Canadian raw materials") are used to manufacture injection through cell culture (Canadian raw materials are used in cell banks only), and other equivalent; cases where Canadian raw materials are used to manufacture vaccine (oral vaccine only); cases where Canadian raw materials are used to manufacture injection by microbial culture (Canadian raw materials are only used in the seed culture) or oral preparation, and other equivalent; or cases where Canadian raw materials are used to manufacture external preparation. A. El Salvador B. Kenya C. Costa Rica D. Swaziland E. Nigeria F. Namibia G. Nicaragua H. New Caledonia I. Pakistan J. Vanuatu K. Botswana L. Mauritius	(Explain how you are dealing with it.)
……	……

[Example 2]

[Viral Clearance Studies]

Table X Result of virus clearance test on (human or animal species)-derived (component name)

		Spiked virus and Log_{10} reduction value			
		Virus A	Virus B	Virus C	Virus D
Inactivation or removal process	Treatment 1	≧○	≧○	≧○	≧○
	Treatment 2	≧□	≧□	≧□	≧□
Total LRV		≧○□	≧○□	≧○□	≧○□
Method		Infectivity using indicator cells	Same as left	Same as left	Same as left

[Example 3]

[Outline of Manufacturing Process]

Cell line XX

| XX cell culture process

| MCB production process

XX cell line MCB

| XX cell culture process

| WCB production process

XX cell line WCB

| WCB thawing, XX cell culture

| Plasmid transfection into XX cells

| ----------In-process control test 1

Viral vector harvest

| Viral vector purification step 1

| ----------In-process control test 2

Intermediate product

| Viral vector purification step 2

| ----------In-process control test 3

Intermediate product or drug substance (API)----------Specification testing of the drug substance

| Dilution, filling, and packaging processes

Final product----------Specification test

[Example 4]

[List of in-process control tests]

Table X In-process control

Process	Test item	Test specimen	Test method	Acceptance Criteria	Remarks
In-process control test 1	○○test	○○solution	○×test	△（confirm, detected, monitoring, etc）（when the ○○ solution is ○× tested）	See ○○ for details
	Quantification of ○○	○○solution	○○method	△△ or more	See ×× for details
In-process control test 2	○□-free test	○○solution	Japanese Pharmacopeia ○○method	confirm	See ○× for details
	○○ potential test	○○solution	○○method	□IU or more	See ○□ for details
……	……	……	……	……	……

* Test items, test methods, etc. should be established according to the characteristics of the product.

[Example 5]

[List of specifications]

Table X Specifications of Drug Substance/Drug Product

Test Item	Test method	Acceptance criteria
Appearance	○○test	Slightly whitish turbid liquid
Identification (vector genome)	○○test	Be identical to the theoretical sequence
Protein A quantitation	○○test	○～× ng/mL
Potency	○○test	○～× IU/mL
Capsid ratio	○○test	Empty capsid: less than X%
Osmolality	○○test	○～△ mOsm/kg
pH	○○test	○～×
Subvisible particles	○○test	>10 um; ○ >25 um; ○
Visible Particles		Free from visible particles
Extractable volume	○○test	Conformity
Replication-competent virus	○○test	Not detected
Sterility	○○test	No growth
Endotoxin	○○test	＜○EU/mL
Residual benzonase	○○test	○ ng/mL
Residual host-cell protein	○○test	○ ng/mL
……	……	……

*Set test items, test methods, etc. according to the characteristics of the product.

[Example 6]

[List of the quality test results of viral vectors during development]

Table X List of the quality test results of viral vectors during development

Characterization item	Sample	Test method	Test result	Remarks
Production ability	Final product	Infect □□ cells with △ IU/mL to check ○ ○ production	Lot a: ≦○μg/cell Lot b: ≦×μg/cell Lot c: ≦×μg/cell	See × × for detail
Function	Final product	Infect □□ cells with △ IU/mL to check × × reduction of □ □ cells.	Lot a: ○% Lot b: ×% Lot c: ×%	See ○ × for detail
……	……	……	……	……

*Set test items, test methods, etc. according to the characteristics of the product.

[Example 7]

[Quality testing of cell bank of production cells]

Table X

Test item	Test method	Acceptance criteria	Result
Identification	PCR	XX cells and bands pattern match	Matched
Endogenous retrovirus test	Electron microscopy	Negative	Negative
	Infectivity	Negative	Negative
	Reverse transcriptase	Negative	Negative
Adventitious virus test	In vitro test (cells)	Negative	Negative
Bovine/Porcine virus test	9CFR	Negative	Negative
Mycoplasma test	JP Supplement (XX method)	Negative	Negative
Sterility	JP (Direct method)	Negative	Negative
Cell viability	Cell count	Result reporting	○%
……	……	……	……

[Quality testing of virus bank]

Table X

Test item	Test method	Acceptance criteria	Result
Identification	PCR	Match	Matched
Replicant-competent virus	Infectivity using ○○ cells	Negative	Negative
Mycoplasma	JP Supplement (●● method)	Negative	Negative
Sterility	JP (Direct method)	Negative	Negative
Potency	Infectivity	Result reporting	IU/mL
……	……	……	……

[Example 8]

[Container/closure system]

Table X Container/closure system

	Container 1	Container 2
Vial	○mL borosilicate glass vial	○mL borosilicate glass vial
Plug	Silicone rubber	Silicone rubber
Seal	Aluminum ring	Aluminum ring
Filling amount	○mL	○mL

[List of Stability evaluation]

Table X List of Stability Test Items (Drug Substances and Final Products)

Test Item	Test method	Acceptance criteria
Appearance	○○test	Slightly whitish turbid liquid
Identification (vector genome)	○○test	Be identical to the theoretical sequence
Protein A quantitation	○○test	○～× ng/mL
Potency	○○test	○～× IU/mL
Capsid ratio	○○test	Empty capsid: less than X%
Osmolality	○○test	○～△ mOsm/kg
pH	○○test	○～×
Subvisible particles	○○test	>10 um; ○ >25 um; ○
Visible Particles	○○test	Free from visible particles
Sterility	○○test	No growth
Endotoxin	○○test	＜○EU/mL
Container integrity	○○test	No leakage
……	……	……

[Table for stability test]

Table X Long-term stability study (-X±Y°C)

		Time point				
Test items	Specification/acceptance criteria	0 M	3 M	6 M	9 M	12 M
Appearance test	Slightly whitish turbid liquid	■	■	■	■	■
Identification test (vector) Genomic studies	Be identical to the theoretical sequence	■	■	■	■	■
×× protein assay Quantity Test	○～×ng/mL	■	■	■	■	■
○○Titer test	○～×IU/mL	■	■	■	■	■
Capsid ratio	Empty capsid less than 0%	■	■	■	■	■
Osmolality	○～△mOsm/kg	■	■	■	■	■
pH	○～×	■	■	■	■	■
Subvisible particulate	>10 um; ○, >25 um; ○	■	■	■	■	■
Visible Particles	Free from visible particles	■	■	■	■	■
Sterility test	Negative	■	■	■	■	■
Endotoxin	<○EU/mL	■	■	■	■	■
Container integrity	No leakage	■	■	■	■	■
……	……	……	……	……	……	……

*Set test items, test methods, etc. according to the characteristics of the product.