March 8, 2013

Points to consider (checkpoints) for efficient conduct of pharmaceutical affairs consultation on R & D strategy for quality and safety from the early stage of development of cellular and tissue-based 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 prior to the initial clinical trial notification for the cellular and tissue-based products.

As shown in "Examples of important points of investigation (30-day investigation) in initial notification for cell/tissue products", the quality control of the raw materials and the product as well as the nonclinical safety assessment of the product are important points for the initiation of clinical trials of cell and tissue processing products. From the earlier stages of development, it is recommended that key points be identified and that the consultation be actively used to resolve them.

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 when 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.
- ☐ 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 the PMDA.
- ☐ Include a table of contents and number the pages in the consultation document.
- ☐ If abbreviations or special terms are used, attach a list of their definitions.
- ☐ Make active use of figures and tables.

Raw materials

- ☐ In explaining the compliance of biological ingredients used in the manufacture of products with the Standards for Biological Raw Materials (MHLW Notification No. 210 of 2003), points to be considered are as follows.
  - Prepare a list of all biological ingredients including fetal bovine serum used to cell culture, enzymes used for cell preparation. Biological ingredients used for manufacture of enzymes, etc. used in the cell processing should also be included in the list (see "Handling of raw materials specified in the Standards for Biological Materials" (Administrative Notice dated March 27, 2009).

- Explain the status of compliance with each requirement of Standards for Biological Raw Materials in accordance with 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 informed of the compliance with the Standards for Animal-Derived Raw Materials and the compliance with 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 test. Use the table shown in [Example 2] for the explanation.

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].
- If there are any characterization data, explain the outline of the test (study purpose, test method, etc.). If there are any tests that are planned to be conducted but have not yet been conducted, also explain the outline of the test. Use the table shown in [Example 6] to explain.
- The residual level of the substances such as non-cell/tissue ingredients and impurities that can remain in the final products should be determined, and should be explained that there are no safety concerns on humans at the residual levels when the product is administrated into humans in the clinical trial based on the published literature and/or the results of toxicological studies, etc. Use the table shown in [Example 7]. If the manufacturing process includes a process to remove impurities, explain this.

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

- Explain the test methods, test samples, test sample amounts, and acceptance criteria and the timing when the results can be obtained (at the time of release, ○days after release, etc.).
- Explain the measures taken for the viral safety (e.g., acceptance inspection of raw materials and virus testing in the manufacturing process) of the product.

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

- Explain the actual transport and storage condition of the product (shelf life, storage temperature, transport and storage solution, form, etc.).
- Explain the results of the evaluation of the changes in quality over time in the above transport and storage conditions (outline of the stability study (test items, test methods, test periods, test results, etc.)). If there are any tests that are planned to be conducted but have not yet been conducted, also explain the outline of the test.

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 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 approval letter issued at the marketing approval.	(Explain how you are dealing with it.)
……	……

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-	(Explain how you are dealing with it.)

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	
……	……

[Example 2]

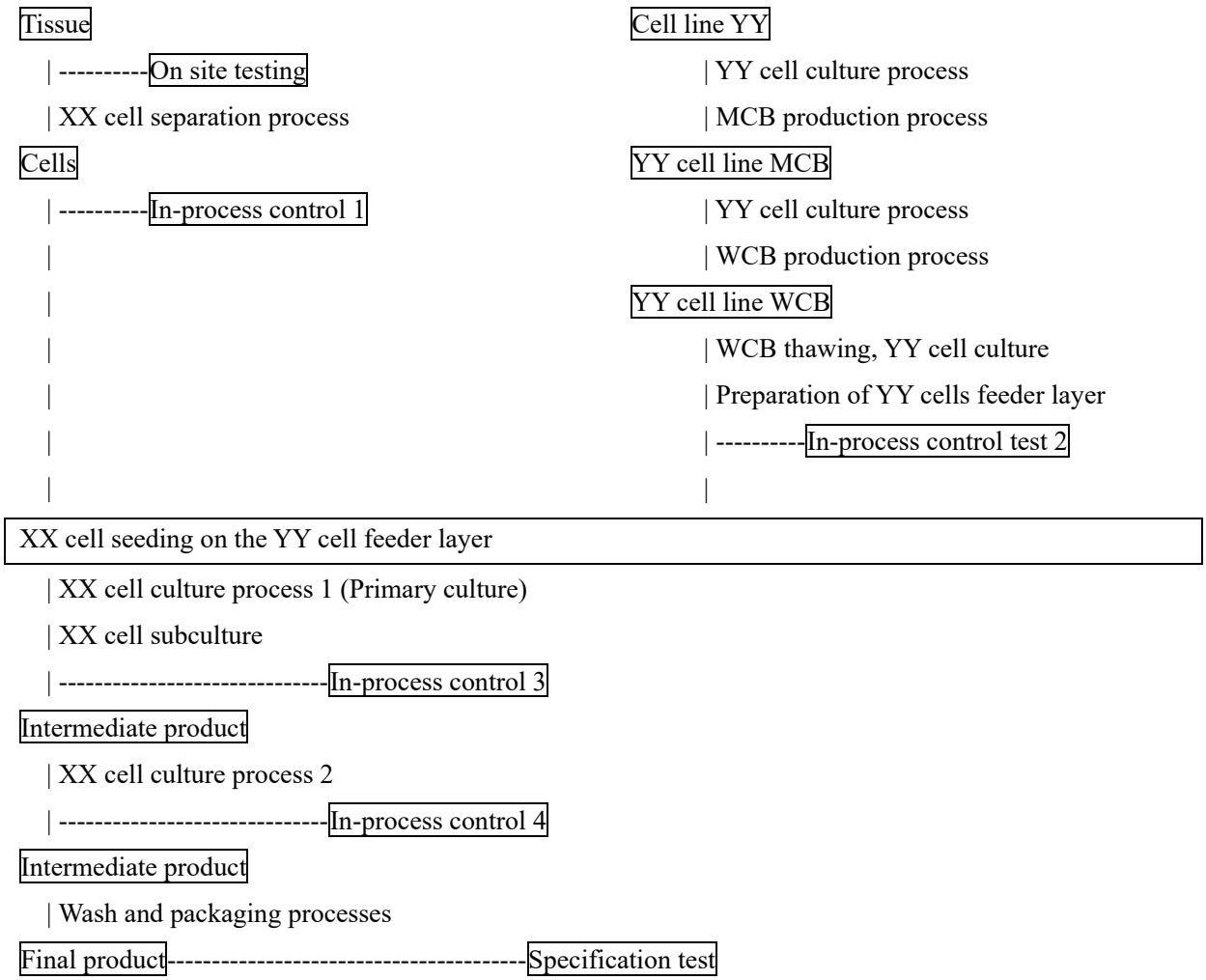
[Viral Clearance Studies]

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]



[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	≧△△	See ×× for details
In-process control test 2	○□-free test	○○solution	Japanese Pharmacopeia ○○method	Confirm	See ○× for details
	○○ potential test	○○solution	○○method	≧□IU	See ○□ for details
……	……	……	……	……	……

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

[Example 5]

[List of specifications]

Test Item	Test method	Test sample	Acceptance criteria
Cell Purity	Flow Cytometry	Cell suspension prepared by one product randomly selected from one lot of final products	Slightly whitish turbid liquid
Secretion amount of ○ (Cytokines, etc.)	ELISA	Cellular supernatant at the end of culture	≧○ ng/mL
……	……	……	……

*If necessary, state the timing when the results can be obtained.

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

[Example 6]

[List of the characteristics of processed cells]

Characterization item	Sample	Test method	Test results	Remarks
Number of cells	Intermediate product in process○	Count and calculate under a microscope using a blood cell counting plate	Lot a: ○×10□ Lot b: ○×10□ Lot c: ○×10□	See ○○ for detail
Cell viability	Intermediate product in process○	Stain, count and calculate under a microscope using a blood cell counting plate	Lot a: ○% Lot b: △% Lot c: □%	See ×× for detail
Content of ○cell	Intermediate product in process○	Measurement of CDX-positive cells using FCM	Lot a: ○% Lot b: □% Lot c: ○%	See ○× for detail
Cellular morphological characteristics	Cells at passage in process△	Observation under microscope (spindle-shaped)	Lot a: accepted Lot b: accepted Lot c: accepted	See ○□ for detail
○○productivity	Final product	Supernatant is collected and assayed by ELISA	Lot a: ○ng/mL Lot b: □ng/mL Lot c: △ng/mL	See ×× for detail
○○function	Final product	○○method	Lot a: accepted Lot b: accepted Lot c: accepted	See ○× for detail
……	……	……	……	……

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

[Example 7]

[Safety assessment of impurities remaining in the final product]

Table X Impurities remaining in the final product

Impurities	Method	Residual amount per use	Safety evaluation
FBS-derived protein	○○method	Lot a: ≦○ng Lot b: ≦×ng Lot c: ≦×ng	See ×× for details
○○ (Antibiotic)	○○method	Lot a: ≦△ng Lot b: ≦○ng Lot c: ≦○ng	See ○× for details
……	……	……	……

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