December 25, 2020

Points to consider (checkpoints) for efficient conduct of RS strategy consultation for quality and safety from the early stage of development of cellular and tissue-based products [Nonclinical safety]

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 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 nonclinical safety assessment of the product as well as the quality control of the raw materials and the product are important points for the initiation of clinical trials of cellular and tissue-based products.

From the earlier stages of development, it is recommended that key points be identified and that the consultations be actively used to resolve them.

As the following checkpoints have been prepared for the nonclinical safety assessment-related consideration 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.

General consideration for 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, nonclinical study protocols/study reports, outline of clinical study protocol, development roadmap, etc.), citations, etc., which are helpful for the consultation as needed.
- ☐ In the materials related to the contents of the consultation items, clearly and specifically describe the content that the consultant wants to obtain the advice from the PMDA.
- ☐ Include a table of contents and number pages in the consultation material.
- ☐ If abbreviations or special terms are used, attach a list of their definitions.
- ☐ Make active use of figures and tables.
- ☐ Include a list of nonclinical safety studies in the consultation material. To prepare the list, use the table shown in [Example of description] in the attached sheet.
- ☐ Clarify the origin of the test article if it is necessary to provide an overview of individual studies. In addition, when explaining the outline of the study in animals, describe the species, group composition, number of animals, sex, age in weeks (months), number of cells administered, route of administration, number of doses, duration of the study, observation items, test items, test results, etc.

Nonclinical safety assessment

☐ Explain the following nonclinical safety evaluation items in the consultation materials in reference to “Technical guidance for quality, nonclinical safety studies and clinical studies of regenerative medical products (human cell-processed products)” (PFSB/MDRMPE Administrative Notice, 2016.) Chapter 3, Nonclinical Safety and “Considerations in studies to detect undifferentiated pluripotent stem cells and transformed cells, tumorigenicity, and genetic instability of human cell-based products" (PSEHB/MDED Notification No .0627-1, 2019). In the case of consultation at a time when the results of nonclinical safety studies are not available, the plan of nonclinical safety study or strategies of nonclinical safety evaluation may be explained.

（1） General toxicity assessment (mainly safety assessment based on general toxicity studies)

（2） Tumorigenicity evaluation

（3） Safety evaluation of process-related impurities and excipients.

☐ If it is difficult to conduct a general toxicity study using a product to be used in a clinical trial (investigational product), a nonclinical safety study may be conducted using an animal-derived surrogate product that can be explained the similarity in quality to the investigational product.

General toxicity assessment

☐ Regarding the appropriateness of the study design, refer to "Partial Revision of the Guideline for Repeat-Dose Toxicity Studies" (PMSB/ELD Notification No. 655 dated April 5, 1999) based on the characteristics of the product. If you change or omit the study design from which described in the guideline, explain the reason.

☐ In order to adequately assess the hazards of the product, the highest dose for toxicity studies should be based on the maximum tolerated dose, the maximum feasible dose, etc. Explain the appropriateness of dose selection.

☐ Explain that the design of the toxicity study is appropriate in view of the protocol of the planned clinical trial.

☐ The effects on major physiological systems (cardiovascular, respiratory, and central nervous systems) should be evaluated based on clinical observations and respiratory rate measurements in general toxicity studies.

☐ If the organs/tissues to be subjected to histopathological examination are restricted, explain the reason for restriction and its effect on the safety evaluation of the product. Even if the product is administered locally and is unlikely to be distributed systemically, as a general rule, examinations should be performed on major organs and tissues (e.g., brain, lung, heart, liver, spleen, kidney), distributed organs and tissues, and gross lesions, besides the administration site.

Tumorigenicity evaluation

☐ Describe the outline of each study for evaluation of tumorigenicity.

☐ Explain why it is considered possible to evaluate the tumorigenicity of the product in development by the selected tests, taking into account the origin of cells and tissues, processing methods, etc.

☐ An *in vivo* tumorigenicity study is required for high-risk tumorigenicity products such as pluripotent stem-cell-derived products. The observation period of *in vivo* tumorigenicity study should be based on the time that the transplanted cells are no longer identified in the animals or the life span of the animal and the period during which spontaneous lesions do not affect the evaluation (for immunodeficient mice and rats, about a 12 months). Explain the appropriateness of the observation period on the basis of evidence.

Safety evaluation of process-related impurities and excipients

- ☐ With regard to process-related impurities which remain in the products, present the estimated exposure in humans based on the residual amount (estimated residual amount if there is no actual measurement) and the clinical dosage and administration.
- ☐ With regard to excipients, present the estimated exposure in humans based on the clinical dosage and administration.
- ☐ Explain the basis for determining that the safety of process-related impurities and excipients in humans can be ensured based on the results of toxicity studies of the product, published toxicity studies, and clinical experience as a drug or excipient.
- ☐ For chemicals, safety assessments can also be made using the acceptable intakes for exposure that are less than a lifetime (LTL) as described in "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (ICH-M7)(R1)" (JBIC Notification No. 627, dated June 27, 2018).
- ☐ Physiologically active substances can also be evaluated for safety using information on human serum levels, acceptable daily intake, and physiologically active concentrations.
- ☐ For process-related impurities, such as media composed of multiple components, strive to obtain information on the name and amount of each component. At the very least, confirm the presence or absence of poisonous and deleterious substances, physiologically active substances, and heavy metals, and explain their safety to humans.
- ☐ For topically administered products, explain the safety of topical administration as well as the systemic safety evaluation.

Others

Reflect the following information in the consultation material.

- ☐ If the manufacturing site or manufacturing process of the test article used in the nonclinical safety study differs from those of the product intended for use in the clinical trial (investigational product), clarify the differences in the manufacturing site, the manufacturing process and quality attributes and explain the effects of these differences on the safety assessment.
- ☐ Explain if there is information on the proliferative and differentiation potential of cells in the product and their kinetics in the body.

END

Attached Sheet

[Example of description]

List of nonclinical safety studies

Test item	Test substances	Assay	Administration regimen	Results	Status	Remarks
Single dose toxicity study	Surrogate products derived from animals (XX)	XX Animal	Intravenous Concentration: XX cells/mL Dose: YY cells/kg administration speed: ZZ mL/min	In the XX group, YY was found on day ZZ.	Completed	See XX for details
Repeat dose toxicity study	Human derived products	XX Animal	Intravenous VV days, WW times Concentration: XX cells/mL Dose: YY cells/kg administration speed: ZZ mL/min	Ongoing	Ongoing (Schedule to end: YYYYMM)	See XX for details
Karyotyping	Passage X	Karyotyping using XX		Lot.a: normal Lot.b: normal Lot. c: abnormal	Completed	See XX for details
	Passage Y			Lot.a: normal Lot.b: normal Lot. c: abnormal	Completed	See XX for details
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End