25 December 2020

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 [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 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/nonclinical safety assessment be identified and that such consultations be actively utilized to resolve such issues.

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 considerations 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, and outline of clinical study protocol, development roadmap, etc.), citations, etc., which are helpful for 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 PMDA.
- ☐ Include a table of contents and number 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.
- ☐ When explaining the outline of the study in animals, describe the species, group composition, number of animals, sex, age in weeks/ months, dose, route of administration, number of doses, duration of the study, observation/ test items, test results, etc.

Nonclinical safety assessments

Explain the following nonclinical safety evaluation items in the consultation materials in reference to "Ensuring the quality and safety of gene therapy products" (PSEHB/MDED Notification No. 0709-2, dated July 9, 2019) Chapter 4, Nonclinical Testing, 3. Nonclinical Safety Testing. 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) Gene integration assessment (assessment of the potential for integration of the vector into the chromosome and the risk of inadvertent germline integration)
(3) Evaluation of tumor formation and cancer potential (evaluation of carcinogenicity and tumorigenicity)
(4) Reproductive and developmental toxicity assessment (evaluation of fertility, embryo-fetal development, pre- and postnatal development)
(5) Immunotoxicity assessment (potential adverse effects on the immune system)
(6) Potential for the emergence of replication-competent viruses (when using replication incompetent viral vectors)

General toxicity assessment

☐ In evaluating the safety in humans, explain the reason for selection and relevance of the animal species to be used in the study from the following points of view: a) whether the transgene loaded on the expression vector expresses in the target cell; b) whether the nucleic acid or protein derived from the transgene exert the pharmacological action expected in humans; c) if using a viral vector, whether the infectivity and tropism to tissues/cells are similar to that in humans; and d) whether the same administration method proposed for the clinical use can be applied.

☐ Conducting studies using only one relevant species may be sufficient. In such cases, explain the rational reasons for evaluating a single animal species based on the biological characteristics of the vector and the target gene.

☐ 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.

☐ In order to adequately assess the hazards of the products in development, the highest dose for toxicity studies should be based on appropriate limits, such as the clinical dose, the dose at which the intended pharmacological effect is maximal, the maximum tolerated dose, and the maximum feasible dose. In addition, to confirm the dose dependency, multiple dose groups must be selected. Explain the appropriateness of dose selection based on the above.

☐ For products that expect long-term expression of a gene or protein for clinical purposes, it is necessary to consider using a study duration of up to 6 months in the nonclinical safety study, refer to "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH-S6)(R1)" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012). In this case, it is necessary to set the study duration for the toxicity study on the assumption that it is possible to evaluate the safety of the product in animals, considering the expression duration of the vector, immunogenicity of the product, etc. Explain the appropriateness of the study duration based on the above.

☐ In general, additional independent safety pharmacology studies will not be required if it is possible to evaluate the effects on major physiological systems (cardiovascular, respiratory, and central nervous systems) in general toxicity studies. In such cases, evaluate the effects on major physiological systems based on clinical observations in general toxicity studies, etc.

☐ Consider additional endpoints related to the pharmacological activity (e.g., immunological function tests, behavioral tests, neurological examination, and markers for cell proliferation activity) as appropriate.

☐ The microscopic examination should cover at least major organs including the brain, lung, heart, liver, kidney, spleen, the testes/ovaries, and the administration site, in addition to the organs/tissues in which

distribution is confirmed from biodistribution 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.

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. If any impurities derived from the manufacturing process that are not included in the test article used in the nonclinical safety studies are included in the investigational product, conduct a safety evaluation of the impurity based on published articles such as nonclinical studies and clinical administration experience.

☐ Consider using the following information, if available, for safety evaluation of the product in development.

- Information of the product which is similar to or using the same vectors as the developed product, regarding as follows; nonclinical safety studies, published papers about clinical safety, etc.
- Information on biological characteristics related to the transgene or protein expressed by the product.

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