Provisional Translation (as of February 2025)*

Administrative Notice
June 27, 2016

To: Division of Pharmaceutical Affairs, Prefectural Health Department (Bureau)

Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Technical Guidance for Quality, Nonclinical Safety Studies and Clinical Studies of Regenerative Medical Products (Human Cell-Processed Products)

Recently, the Pharmaceuticals and Medical Devices Agency has submitted a report on the title, as shown in the attached sheet. Please inform the relevant contractors under your jurisdiction to use the report as a reference for future operations.

*This English translation of the Japanese Administrative Notice is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Annex
Notification No. 0614043 of PMDA
June 14, 2016

Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare
Review and Management of Medical Devices and Regenerative Medicine

Chief Executive of Pharmaceuticals and Medical Devices Agency

Technical Guidance for Quality, Nonclinical Safety Studies and Clinical Studies of Regenerative Medical Products (Human Cell-Processed Products)

Handling of regenerative medical products is indicated in "Points to Consider in Marketing Application for Regenerative Medical Products" (Notification No. 0812-5 by the Counsellor of Minister's Secretariat (for Medical Device and Regenerative Medicine Product Evaluation), MHLW, dated August 12, 2014). The Pharmaceuticals and Medical Devices Agency has compiled technical guidance on the points to consider when developing regenerative medical products such as human cell-processed products, as an attachment, and hereby reports.

This guidance is a compilation of basic concepts based on current scientific knowledge, and the content will be reviewed periodically. It does not necessarily require adherence to the methods described in this guidance.

Attachment
June 14, 2016
Pharmaceuticals and Medical Devices Agency

Technical Guidance for Quality, Nonclinical Safety Studies and Clinical Studies of Regenerative Medical Products (Human Cell-Processed Products)

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1. Introduction

Regenerative medical products are attracting attention as they represent a promising therapy option, especially after several innovations including the development of induced pluripotent stem (iPS) cells. However, they have safety concerns due to lack of related experience and knowledge so far. In order to guarantee safety of the products carefully, regenerative medical products are being developed for clinical use, based on the relevant guidelines on ensuring the quality and safety.

As with pharmaceuticals/medical devices, there are several requirements prior to the clinical trials of regenerative medical products: quality of an investigational product must be ensured, obvious safety concern when administered to humans must be relieved, and a study design that can demonstrate efficacy and safety appropriately must be formulated. For pharmaceuticals/medical devices, the evaluation methodology has been established for quality control such as the specifications, characterization, and for nonclinical safety studies. However, as for regenerative medical products, sufficient development experience has not been obtained. Their evaluation using animals is difficult because they are made from human cells/tissues, and they are manufactured by a variety of processes from materials of different origins (embryonic stem (ES) cells, iPS cells, somatic stem cells, somatic cells, etc.). Therefore, the quality and nonclinical safety evaluation of regenerative medical products have to be flexible and rational on a case-by-case basis according to the characteristics of the products.

The design of clinical trials of pharmaceuticals/medical devices may be used as a reference for regenerative medical products. However, there are considerations specific to regenerative medical products because of the differences mentioned above. In addition, as a conditional and time-limited approval scheme is in place, the design and objectives of clinical studies at each development phase of regenerative medical products may differ from those of pharmaceuticals /medical devices. Furthermore, there are various kind of regenerative medical products which differ in characteristics such as human cell-processed products [autologous, allogeneic] and gene therapy products. The design and purpose of clinical trials should be considered according to the characteristics of each product.

This guidance outlines principles for quality control and presents matters to be considered in connection with a nonclinical safety evaluation and clinical studies of human cell-processed products. The principles/matters for consideration are summarized from experience of the Pharmaceuticals and Medical Devices Agency (PMDA) in consultation and review, issues often discussed in consultations and the details of PMDA's advice for human cell-processed products. Note that this guidance does not cover matters specific to gene therapy products. Also, this guidance will not limit the effect of a guideline expected to be established in the future. The recommendations in this guidance are subject to continuing revision as scientific advances in this field are made over time. Thus, the guidance should be revised on regular basis.

In summary, matters to be considered in quality control, nonclinical safety evaluation and clinical trials of human cell-processed products are different from those for pharmaceuticals /medical devices: human cell-processed products must be evaluated and tested flexibly according to their unique characteristics on a case-by-case basis. The applicant is advised to make use of PMDA's Regulatory Science Strategy consultation, to facilitate development of human cell-processed products with better efficacy and safety.

2. Quality

Since human cell-processed products contain living cells and are expected to provide clinical effects due to the diverse characteristics of the cells, it is not easy to strictly identify the quality attributes that are highly correlated with their efficacy and safety (critical quality attributes). In addition, it is difficult to constantly ensure the quality of a product only from tests on the final product because of some reasons as follows: high heterogeneity in product quality caused by raw materials and manufacturing processes, a lack of appropriate

standard reference and large variation in biological activity tests and restriction of the quantity of sample used for testing when the production quantity of a product is limited.

Therefore, it is important to establish a quality control strategy including control during manufacturing (such as control of raw materials and ancillary materials, process parameters, in-process control, control of intermediate products, specification of final products, etc.), in addition to testing a final product. Especially, in a quality control strategy, it is necessary to deal with appropriately to the following problems: stringent control is difficult because the raw materials are human-derived cells or tissues, process parameters cannot fully be optimized due to difficulty in obtaining enough amount of raw materials, and adventitious infectious substances such as microorganisms and viruses cannot be completely inactivated/removed during manufacture such as pharmaceuticals. Manufacturers must solve these problems based on quality risk management as suggested in "Quality Risk Management (ICH-Q9)" (PFSB/ELD Notification No. 0901004, PFSB/CND Notification No. 0901005, dated September 1, 2006). Matters for consideration during the establishment of a quality control strategy are summarized as follows.

2.1 Qualification of raw materials, ancillary materials and source materials

2.1.1 Principles

In principle, control items for raw materials and ancillary materials should be set to ensure the quality required for the final products. The quality (sterility, impurities, etc.) of raw materials and ancillary materials should be considered so that safety concerns do not arise to the final product even when the raw materials and ancillary materials are used. It is important to set necessary items for raw materials and ancillary materials (and their source materials on demand) based on the quality characteristics of the raw materials and ancillary materials, the complexity and management status of the manufacturing processes of the raw materials and ancillary materials. Particularly, when raw materials and ancillary materials are made of human or animal-derived ingredients, and when materials of human/animal origin are used for manufacturing of the raw materials or the ancillary materials, it is necessary to obtain necessary information based on the "Standards for Biological Raw Materials" (MHLW Notification No. 210, 2003) regarding the risk of contamination with adventitious agents such as viruses, and to establish management items so that such risks can be managed.

2.1.2 Scope of raw materials, etc. subject to the Standards for Biological Raw Materials

The scope of raw materials, etc. subject to the Standards for Biological Raw Materials (MHLW Notification No. 210, 2003) is defined in "1. 1. General notices" in " Standard for Biological Raw Materials, Operational Guideline " (PFSB/ELD Notification No. 1002-1 and PFSB/ MDRMPE Notification No. 1002-5, dated October 2, 2014). It is necessary to confirm whether human or animal-derived ingredients are contained not only in the raw materials and ancillary materials themselves, but also in the materials used in the manufacturing process of the raw materials or ancillary materials. For example, the culture medium which contains recombinant protein used for manufacture of human cell-processed products, the recombinant protein itself is not a human or animal-derived material, but if a human or animal-derived component is used in the manufacturing process of the recombinant protein, the human or animal-derived component is subject to the Standards for Biological Raw Materials.

2.1.3 Viral safety of cells/tissues used for raw materials

Regarding to the cells and tissues that serve as raw materials for human (allogeneic)-derived product, it is necessary to confirm that the donor is sufficiently eligible according to the Standard for Biological Raw Materials or reference 3), 5), 7) and 8) listed in "5. References". Usually, PMDA asks for an explanation regarding the donor eligibility of raw materials when the developer submits the initial clinical trial notification. Particularly, according to the Standard for Biological Raw Materials " III. General Rules for

Human-Derived Raw Materials, 1. Standards for Human Cell/Tissue-based Raw Materials (3) A, B and C", careful selection of the virus species to be tested is required. A re-test taking the window period is a test, which denies the possibility that it could not be detected because it was infected with the virus at the time of the initial examination but was less than the detection sensitivity, and is a test with higher accuracy in the judgment of the eligibility evaluation of the donor. Thus, the appropriate re-test is necessary in principle.

For human (autologous)-derived product, the virus species to be tested should be selected in view of the specific use of the products.

In order to mitigate the risk of virus contamination as far as feasible in the final product, viral safety must be ensured by qualification of donors of the cells/tissues used as the material. In addition, when a cell bank system is established, the intermediate or the final product must be controlled in accordance with the Japanese Pharmacopoeia, General Information "Basic Requirements for Viral Safety of Biotechnological/Biological Products listed in Japanese Pharmacopoeia" and "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (ICH-Q5A)" (PMSB/ELD Notification No. 329 dated February 22, 2000)

Among controls to ensure viral safety, especially for the virus-free tests, it is necessary to examine the appropriateness of the samples used in the test, test items and the test methods. In order to ensure viral safety, samples that show the highest sensitivity for detection of virus contamination should be subjected to testing. Also, in order to avoid overlooking virus contamination, it is important to consider setting both specific and non-specific virus test items for ensuring a wide detection of viruses based on a risk assessment according to the virus species that might be contaminated with the cells/tissues for raw materials or ancillary materials, infectivity to humans, and seriousness of the infection, etc.. Because the incidence of viral contamination has not been fully elucidated in the early stage of development, it is more desirable to establish a control strategy for ensuring viral safety by considering the implementation of non-specific virus tests to detect a wide range of virus species.

The test method must be evaluated by validation of analytical procedures with reference to "Validation of Analytical Procedures" (PAB/PCD Notification No. 755 dated July 20, 1995 and PMSB/ELD Notification 338 dated October 28, 1997) (ICH-Q2) to assure test performance that is consistent with the intended purpose. At the same time, the conditions of the test must be defined to ensure the precision and reliability of each test.

2.1.4 Viral safety of human or animal derived ancillary materials

When any material of human or animal origin (bovine serum, feeder cells, etc.) is used in a manufacturing process, it is necessary to obtain as much information as possible on the viruses that could potentially contaminate the material, and to conduct necessary virus testing. Based on the results, appropriate control items should be established to control the risk of virus contamination in the products. In addition, based on the intended use of these materials, it is important to carry out viral inactivation/removal procedures in principle, if feasible. In particular, it is required to carry out the viral inactivation/removal treatment for the ingredients that are obtained by isolation and purification in principle because it is considered possible during the manufacturing process of the component. It is important to carry out the viral inactivation/removal treatment that the viral clearance ability reflecting the manufacturing condition has been evaluated in advance, with reference to the Japanese Pharmacopoeia, General Information "Basic Requirements for Viral Safety of Biotechnological/Biological Products listed in Japanese Pharmacopoeia".

2.1.5 Information on raw materials, etc. that must be obtained by marketing authorization holders

From the viewpoint of appropriate quality control and safety measure, information on quality and safety of the raw materials, etc. that marketing authorization holders must obtain includes compliance with the Standards for Biological Raw Materials, and process-related impurities that may remain in the final products.

For compliance with the Standards for Biological Raw Materials, it is necessary to obtain and understand the rationale information on the content of the qualification evaluation of donors and the storage status of records, etc. for cells and tissues that are human-derived raw materials or ancillary materials. In addition, it is necessary to obtain and understand information on the conditions and supporting data for viral clearance of animal-derived materials that are derived from healthy animals or that can be inactivated/removed by the manufacturing process, such as proteins and other components derived from human or animal animals or cells. When the records specified in the Standards for Biological Raw Materials are stored in an external organization, it is necessary to establish a system in which the necessary information is managed and can be obtained as soon as possible.

Usually, PMDA asks the developer for a specific explanation on the risk of exogenous infectious substance contamination by viruses and so forth when the initial clinical trial notification is submitted. It is generally important to note that in the initial clinical trial notification the developer should be able to explain the risk of contamination with adventitious agents such as viruses.

In addition, it should be noted that, at the time of the initial clinical trial notification, an explanation based on the results of safety assessment based on human exposure is usually required regarding the safety of process-related impurities that may remain in the final product, including media components used in the manufacturing process. (See 3. Nonclinical Safety Studies.)

2.2 Specification and in-process control test

Human cell-processed products contain cells as an active substance and they are manufactured from cells/tissues derived from humans (autologous, allogeneic) via a process such as cell culture using various substances of human or animal origin. Therefore, human cell-processed product shows very heterogenous characteristics that are affected by variations in the raw material or manufacturing processes. The quality of human cell-processed products includes various fluctuations and variations that are caused by complicated influences from raw materials, manufacturing processes, and equipment performance during manufacturing. It is important that their quality must be ensured not only by specification of the final product, but also by control/monitoring of such variations through the control of raw materials and ancillary materials, in-process control, test for intermediates, and so on.

2.2.1 Quality control strategy

Quality control items for human cell-processed products are not merely an array of quality attributes obtained through previous research and development, but should cover the quality attributes necessary for human cell-processed product, based on the administration route in the clinical, distribution of the administered cells, and the critical quality attributes based on the expected efficacy or performance. Therefore, it is important to examine the quality control items carefully according to the required product quality, extensive characterization, results of tests that evaluate effects/performance and findings in the latest publications.

Major test items, test method and points to consider regarding specifications for quality testing of human cell-processed products are shown in Table 1. It is important to identify the test method for potency and efficacy tests from extensive characterization, such as confirming the potential characteristics of cells expected prior to administration if various biological activities are expected or if efficacy/performance is expected by matured/differentiated cells *in vivo* after administration.

Table 1 Examples of specifications

Evaluation items	Test items	Point to consider regarding specification
Identity	Appearance, cell phenotype, differentiation, cell type, etc.	In principle, the specification must be defined for the final product. Highly specific test items must be selected in order to verify the essential characteristics of the product.
Purity	Cell phenotype, abnormal growth, etc.	In principle, the specification must be defined for the final product. The specification must be defined to control the heterogeneity of the cells contained and an acceptable level of contamination with non-targeted cells when the drug is administered to humans.
Process-related impurities	Process-related impurities (serum albumin, antibiotics, etc.)	In principle, the specification must be defined for the final product. When it is verified that the impurities can be sufficiently eliminated during manufacturing processes based on the results of evaluation on the capability of elimination, verified impurity testing is not mandatory. However, it is often the case that only limited information is obtained during development. The amount of impurities must be measured in the investigational product as far as feasible, and impurities to be controlled and their limits must be defined in the specification for commercial products.
Impurities with undesirable physiological activities	Physiologically active substance, etc.	When there is a risk that a substance with unintended physiological activities is produced from cell, the necessity of its control in the final product must be carefully evaluated.
Safety	Chromosomal aberrations, soft agar colony formation, virus, mycoplasma, endotoxin, sterility, etc.	Mycoplasma, endotoxin, sterility testing must be defined for the final product in principle (see section 2.4)
Potency test, efficacy test, mechanical compatibility	Protein expression, secretion of physiologically active substances, differentiation, cell phenotype, cell proliferation, durability, etc.	In principle, the specification must be defined for the final product. A variety of specifications may be possible according to the characteristics of the product. An in-process control test and test of intermediates may be used in place of the final product test, if it's appropriate.
Content	Cell count, cell viability	In principle, the specification must be defined for the final product.

2.2.2 In-process control test

In-process control, test items and considerations for the testing of human cell-processed products are shown in Table 2. In principle, in-process control items should be set to control quality risks for each manufacturing process based on the identification of critical quality attributes required for the product along with possible variations in these attributes during the manufacturing process. For effective control of quality risks, it is important to establish test methods, test samples and the sample quantities to ensure high detectability for quality risks. For investigational products, in-process control items must be selected considering the issues listed in Table 2 as a minimum requirement. For marketing approval applications, it is desirable that a quality control strategy is established that allows for the quality assurance of the final product more consistently and robustly, including the identification of critical process parameters and critical in-process control items that are factors that affect the critical quality attributes considering the historical manufacturing data of the investigational product.

Table 2　Examples of in-process control items and test method

Examples of in-process control	Test item	Consideration
In-process control to guarantee sterility	Sterility test, bioburden test, mycoplasma test, etc.	The sensitivity of the test of the final product cannot fully guarantee sterility. Strategies to guarantee sterility include technically feasible reduction of microbial contamination such as sterilization or bioburden control of raw materials, and a microbial control test as part of in-process control (see section 2.4)
In-process control to guarantee viral safety	Virus test (see ICH-Q5A)	The virus contamination risk must be controlled in samples in a way that allows detection of viruses at high sensitivity (raw materials, intermediates, etc.). Use a test method with high specificity (NAT test, etc.). If feasible, a non-specific virus test (*in vitro*, *in vivo* and electron microscopy) should be used concomitantly. Virus species to be tested should be selected based on the risk assessment of virus species that may be present, seriousness of infection, and acceptability of virus risk.
In-process control as quality control strategy to ensure expected quality attributes	Identification, purity, appearance, potency, efficacy, etc.	Based on the purpose of the process, a test method that can detect with high sensitivity any unexpected defect in a product during manufacturing must be selected. Desirably, critical quality attributes should be evaluated in the test. Surrogate parameters can be selected that are related to the critical quality attributes, while taking the characteristics of the process and feasibility of the test into consideration.

2.2.3 Critical quality attributes and specification

For a product approved for marketing, the efficacy and safety of the product confirmed in the clinical trial must be consistently ensured. Therefore, it is a principle to specify the quality so that they can be ensured, and to confirm that quality control and manufacturing control including specification tests have been achieved before release. For quality, it is required to establish a control method as a quality control strategy, including the establishment of specifications, so that critical quality attributes and process parameters that can control important quality attributes (critical process parameters) can be identified and controlled to the extent possible.

The establishment of a quality control strategy is one of the most critical issues in research and development for commercialization, but such knowledge is not sufficiently obtained especially in the initial stage of the development. Therefore, in principle, quality is ensured by verification as a quality control strategy on the investigational products at the start of clinical trials. The specification and test methods should be set based on the findings on possible critical quality attributes and their process parameters obtained at that point, by characterization and information on the efficacy and safety of the product. It is important that the specification is reviewed as appropriate with reference to the knowledge obtained as the development stage progresses. For ensuring rapid subsequent development, it is important to collect a wide range of quality information as much as possible by monitoring the quality characteristics that are considered to be highly relevant to efficacy, in consideration of the establishment of a quality control strategy for the investigational product used for the clinical trials in the following phases. In the late stage of development, it is necessary to identify critical quality attributes based on the quality characterization of the products manufactured by the manufacturing process that have been updated based on the process understanding and the more information on the efficacy and safety obtained from clinical trials, and to establish a quality control strategy that can appropriately control them. For the marketing approval application, a quality control strategy should have been established that ensures consistent quality through entire development stage, and the validity of the strategy should have been confirmed by process validation or verification.

Since human (autologous)-derived products have the following characteristics, careful quality development plans are required because of their unique characteristics. In addition, it is assumed that the verification master plan based on the valid quality control strategy may be required for human (autologous)-

derived products. It is more efficient to use quality consultation after the start of clinical trials and proceed with caution.

- Due to the difficulty in obtaining samples from patients before the start of the clinical trial, there are cases where characterization is performed using samples from healthy donors. In these cases, the results of characterization of the test product from healthy donors may not be comparable to the results of characterization of the clinical trial product from patients.
- For human (autologous)-derived products, which need to be manufactured for each patient, variable factors of the process are complicated and difficult to identify because of variation in the cell characteristics among patients. Also, as clinical trials are often conducted in a small number of subjects because of manufacturing limitation, compared to human (allogeneic)-derived products, the information on the efficacy and safety obtained in clinical trials is often limited.
- There is a limitation in the amount of manufactured product, and it is considered that sufficient amount of sample cannot be obtained in performing the characterization.

2.3 Stability test

Generally, human cell-processed products are markedly unstable because they contain viable cells/tissues. When sufficient stability of the investigational product is not obtained at the start of the clinical trial, time limitation may occur to conduct quality control. So it is important to ensure the necessary stability with consideration of prescription setting. In addition, the stability should be evaluated considering the clinical use of the product. Refer to "Quality of Biotechnological Products: Stability Testing of Biotechnological/biological Products (ICH-Q5C)" (PMSB/ELD Notification No. 6 dated January 6, 1998) for consideration of stability evaluation.

2.3.1 Long-term stability study

The stability profile of a product should be evaluated under the proposed storage conditions. Stability studies should be conducted to evaluate changes over time during storage in the actual conditions, and the appropriate storage condition and shelf life should be established based on the results. When an intermediate is to be stored, its stability should also be evaluated.

2.3.2 Transport Stability study

The impact of transportation conditions from product shipment to medical institutions, etc. (temperature, time, route and container, etc.) on the quality of the product should be evaluated. It is important to record the temperature in the shipping container using a temperature logger to evaluate whether temperature control was properly carried out during transportation.

2.3.3 Stability after freezing and thawing (In-use stability study)

When a product is manufactured as a frozen product, and thawed at the time of use in a medical site after product shipment, it is necessary to evaluate the impact of the freezing and thawing process on its quality, and to define the time lag acceptable between thawing and administration to a patient.

2.4 Sterility test and mycoplasma test

2.4.1 Principle

As the sterility test and mycoplasma test are conducted to determine the safety of the product, these tests should be conducted using final products in principle. For test methods, those specified in the Japanese Pharmacopoeia are preferable, but they may be not practicable for human cell-processed products due to the

limitation of sample quantity and limitations from the aspect of the time allowable for the tests. In such cases, an alternative test method which scientifically justified can be employed instead of a test specified in the Japanese Pharmacopoeia. The better test method should be selected according to the stability of the final product, the limitation on the amount of samples manufactured, and the amount of samples used for other specification test. When selecting a test method, it is important to carefully evaluate the risks that may affect the test results based on the principles of the test method and the characteristics of the measurement, and to perform the necessary validation of the analytical procedure. In addition, it is necessary to appropriately set the system suitability criteria and test controls to ensure the reliability of specification tests.

Since the sterility test and the mycoplasma test generally take time to obtain the results, it is desirable to ensure the storage stability of the final product and to ensure the time required for testing for release. If possible, the test result should be obtained before the product is administered to a patient in consideration of therapeutic suitability and condition of the patient. If the results of the study are obtained after administration to the patient due to technical difficulty, the situation must be explained to the patient using an informed consent form/explanatory document and the patient's consent should be obtained in advance. In this case, it is important to set measures for patient protection when any contamination is revealed.

When the dosing solution is prepared at each medical institution after the final product has been shipped, it is important to prepare the procedure manual for the dosing solution preparation and provide training to the staff who prepares the dosing solution before beginning the clinical trial. In addition, it is desirable to confirm the sterility of the dosing solution by conducting sterility and mycoplasma tests using a washing solution after preparation as a test sample. The sterility test of the dosing solution should also be included in the above-mentioned explanation to the patient and patient protection measures. At the time of marketing approval application, the applicant must explain the validity of the method used to prepare dosing solution based on the manuals for the preparation and the results of sterility tests.

2.4.2 Sterility test

If there is a limit to the sample volume of the sterility test for human (autologous)-derived products, it is necessary to perform validation on the limit of detection of the sterility test with a limited amount of sample before the start of the clinical trial. In that validation, it is necessary to confirm to what extent performance is reduced compared to the test specified in the Japanese Pharmacopoeia. If there are any concerns about sensitivity, it is important to control the sterility as strictly as practicable over the entire manufacturing process including the In-process control items. To assure that there is no contamination of the final product, using the intermediate such as culture medium waste, wash buffer waste as s sample should be consider. When time is limited because of the stability of the product, it is desirable to consider the use of a rapid microbiological methods (RMM) to obtain results before administration to the patient. To ensure the appropriateness of the RMM, the microbial count should be monitored continuously after results of the RMM are obtained, if possible.

When an intermediate is used for the test instead of final product, the possibility of microbial contamination that may occur in the subsequent processes should be denied. Appropriate explanations should be provided regarding the suitability of manufacturing control, container closure integrity for the primary package of the final product, microbial contamination control of packaging materials, etc.

2.4.3 Mycoplasma test

Even when a commercially available kit is used to test for the absence of mycoplasma, it is necessary to confirm the detection sensitivity and specificity of the mycoplasma test at its own facilities using equipment and samples used for the test. For the test method, refer to "Mycoplasma Testing for Cell Substrates used for the Production of Biotechnological/ Biological Products" in General Information of the Japanese

Pharmacopoeia. Since a false-positive result may be led when the sample is tested with "B. indicator cell culture method (method B)", it is desirable to combine the test using another appropriate method. After appropriate validation, "C. nucleic acid amplification test (NAT) method (method C)" may be used as an alternative to "A. culture method (method A)" and/or method B.

When method C is employed, the detection sensitivity of 7 different mycoplasma species must be 10 CFU/mL, according to the provisions contained in General Information of the Japanese Pharmacopoeia. If a primer specified in the General Information of the 16th Japanese Pharmacopoeia is employed, it should be noted that *A. laidlawii* cannot be detected with the primer and that the sensitivity of detecting *M. pneumoniae* is inadequate (reference 1). Therefore, it should be noted that additional testing for these two types of mycoplasma species may be required.

2.5 Verification

Process validation or verification is crucial to assure the quality of investigational products and commercial products. For commercial products, process validation is mandatory for manufacturing control and quality control, in principle. However, for regenerative medical products, especially for human (autologous)-derived products, only a limited number of samples are available due to ethical considerations. Since the product has to be developed based on limited manufacturing experience or process validation is not feasible due to technological limitations, quality assurance by verification is also specified.

Process validation is designed to verify the control strategy before starting the production of commercial products by monitoring the parameters identified and conducting in-process control tests. Quality risks and variable factors such as critical process parameters affecting the operability of manufacturing and product quality should be identified before the process validation. The aim is to assure that high quality final products are consistently manufactured. In principle, it is mandatory to guarantee that products with the targeted quality can be stably obtained from the manufacturing process by conducting the process validation.

However, when such process validation is not feasible due to circumstantial or technical limitations, verification is used instead to define the quality control strategy based on risk management, in order to confirm the quality of each lot of manufactured products. In other words, the purpose of verification is not only to confirm the results of quality tests, but also to assure that the expected results can also be obtained by manufacturing control and quality control. In the verification, a comprehensive evaluation of the quality of raw materials, process parameters and in-process control tests should also be implemented. Even when quality is confirmed by verification, quality should be continuously verified in accordance with a verification plan after release of the product. Unlike process validation, verification is a continuous process throughout the development to the post-marketing phase. Refer to "Questions and Answers Regarding Good Gene, Cellular and Tissue-based Products Manufacturing Practice (Q&A), No. 2" (PFSB/CND Notification No. 0728-4 dated July 28, 2015).

Although the principle of verification is substantially the same for investigational products and commercial products for quality assurance, it should be considered that investigational products are manufactured during the development phase when their manufacturing process or test methods have not been fully established. So the quality control strategy should be formulated and verification should be carried out based on the characteristics of the quality and manufacturing process clarified up until that time and on risk management.

3. Nonclinical safety study

Principles for nonclinical safety of human cell-processed products are described in 7 notifications (references 2 to 8) including " Guidelines on Ensuring the Quality and Safety of Products Derived from the Processing of Autologous Human Cells/Tissues ". The notifications specify that animal experiments are required when technically feasible and scientifically justified, and that the quality and safety of non-cellular

components and process-related impurities should be evaluated using physicochemical analytical methods as much as possible. Therefore, when evaluating nonclinical safety of a human cell-processed products, it is appropriate to classify them into 3 components, “cellular components” such as target cells/tissues, “non-cellular components” which mean other than target cells/tissues (e.g., cryoprotectant agents, scaffolds, etc.) and “process-related impurities” (media component remaining in the final products, etc.) so that their safety can be evaluated.

For pharmaceuticals/medical devices, nonclinical safety is evaluated in several steps for risk assessment of clinical adverse effect. Hazards are identified as an *in vivo* safety concern at first, and nonclinical safety is comprehensively evaluated taking into account pharmacokinetic data (absorption, distribution, metabolism and excretion). However, for human cell-processed products, information which can be obtained from nonclinical safety studies is considered to be limited for several reasons; Administration of human-derived substances may induce heterologous immune responses in animals, exposure assessment conducted with low-molecular-weight pharmaceuticals may not be appropriate, therefore quantitative risk assessment is difficult. Therefore, as for human cell processed products, it is critical to design nonclinical safety studies and extrapolate its results, in view of these limitations.

3.1 General toxicity study

General toxicity studies of a human cell processed product can be planned with reference to an Appendix "Guidelines for Toxicity Testing of Pharmaceuticals" of "Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals" (PFSB/ELD Notification No. 0219-4 dated February 19, 2010) for the moment. However, this guideline describes general principles applicable to pharmaceuticals. Therefore, following points should be especially noted when designing studies of human cell-processed products.

3.1.1 Selection of animal species

Considerations in selecting animal species for nonclinical safety studies of human cell-processed products are as follows.

3.1.1.1 Avoidance of heterologous immune responses

In order to avoid heterologous immune responses that may be occurred in animals, the use of immunodeficient animals (nude, SCID, NOD/SCID/γCnull, etc.) can be considered. In case that the administration route proposed for humans is not suitable for immunodeficient animals (rats or mice), animals receiving an immunosuppressant may be used instead. In this case, it is important to understand historical background data of the animal used, and the possible effects of the immunosuppressant on the results of the study in advance.

The use of an equivalent product of animal origin in place of the product of human origin can be considered as an approach to avoid heterologous immune responses. In this case, the extrapolability of the results obtained from animals to humans should be explained based on difference in raw materials, manufacturing process, efficacy or performance.

3.1.1.2 In the case of safety evaluation in an *in vivo* efficacy studies

When *in vivo* studies using animal models of disease are conducted as a proof of concept (POC) studies and they are used for safety evaluation, the effect of insufficient background data on the animal models and that of background values artificially selected to prepare the model cannot be ruled out. Whether the general toxicity can be appropriately evaluated by these studies, and whether the data integrity of the results of these studies are ensured should be carefully examined.

3.1.2 The number of animal species used for studies

For pharmaceuticals, general toxicity studies are usually required to use two animal species. However, for a human cell-processed products, they are likely to have no differences in metabolism among animal species, and heterologous immune responses may occur in any animal species. Therefore, studies using single animal species is possible in general.

3.1.3 Dosage and administration

3.1.3.1 Dosage

For studies of a human cell-processed product in animals, heterologous immune responses will inevitably occur and the bioactivity of physiologically active substances (such as cytokines) produced from human derived products may be different from human. Quantitative risk assessment is difficult, therefore, dose group should be at least two study groups; a treatment group and a control group so that hazard can be assessed. In addition, it is essential to set the maximum dose as many cells as practicable, taking into account the maximum tolerated dose (MTD), maximum feasible dose (MFD) and animal welfare.

3.1.3.2 Frequency of administration

It is recommended that the frequency of administration in animal studies be as similar as possible to the intended clinical dosing regimen. However, repeated administration is not necessarily required when accumulation or cells or worsening of toxicity after repeated administration of human cell-processed products is not likely to occur in animals.

3.1.3.3 Route of administration

It is recommended that the route of administration in animal studies be the same as the intended clinical route because the biological effect of a human cell-processed product may depend on the microenvironment of the administration or transplantation site.

3.1.4 Observation period

Due to the limitation of the safety evaluation of human cell-processed products in animals, which comes from species difference, setting observation period as approximately 14 days can be acceptable, which is the minimum duration that the systemic toxicity can be evaluated. However, if a safety-related risk is evident based on the mechanism of action of the product and such a risk can be evaluated in animals, observation period can be determined with reference to POC studies.

3.1.5 Sex, the number of animals, observations and parameters

Human cell-processed products remain in the body for a certain period even after single dose. Sex, the number of animals, observations and parameters, etc. should be selected with reference to the guideline for repeated dose toxicity studies rather than that for single dose toxicity studies in "Guidelines for Toxicity testing of Pharmaceuticals" because the purpose of a single dose study is to evaluate acute toxicity.

For pharmaceuticals, safety pharmacology studies are conducted to investigate the potential undesirable pharmacodynamic effects of a substance on physiological function. However, the guideline "Safety Pharmacology Studies for Human Pharmaceuticals (ICH-S7A)" (PMSB/ELD Notification No. 902 dated June 21, 2001) is intended for pharmaceuticals. In addition, extrapolation of results obtained from animal studies to humans and quantitative risk assessment is difficult for human cell-processed products. Therefore, the test (evaluation) items listed in the guideline are not directly applicable to these products. It should be noted, however, that prior to the start of the clinical trial, it should be ensured that no particular concerns regarding major physiological systems (e.g., central nervous system, cardiovascular system and respiratory

system) based on the characteristics of human cell-processed products and the results obtained in general toxicity studies.

3.2 Tumorigenicity study

Tumorigenicity is a concern associated with human cell-processed products because of their potential of forming ectopic tissues or tumors due to the effect of manufacturing processes including the isolation of cells, artificial proliferation, treatment with agents, and genetic engineering modification, etc. Tumorigenicity studies should be conducted to evaluate the potential risk. Tumorigenic concerns of human cell-processed products depend on the differentiation stage of the cells, processing method, duration of culture, experience with similar products, etc. In general, the risk of malignant transformation (unintended proliferation or transformation, etc.) of the final product is high in the order of ES/iPS cells, somatic stem cells, and somatic cells. The risk of teratoma formation should also be evaluated when the product is manufactured from ES/iPS cells because residual pluripotent stem cells may induce teratoma (Figure 1, reference 9). On the other hand, *in vivo* tumorigenicity studies are not always required for products manufactured from bone marrow-derived mesenchymal stem cells or somatic cells because they have a lower tumorigenicity risk.

In vitro studies (karyotyping, soft agar colony formation assay, etc.) and *in vivo* studies (transplantation to immunodeficient animals, etc.) are known as tumorigenicity studies for human cell-processed products. It should be noted that studies suitable for the developed product should be selected on a case-by-case basis, according to the level of tumorigenicity risk. Considerations in planning *in vivo* tumorigenicity studies are described below.

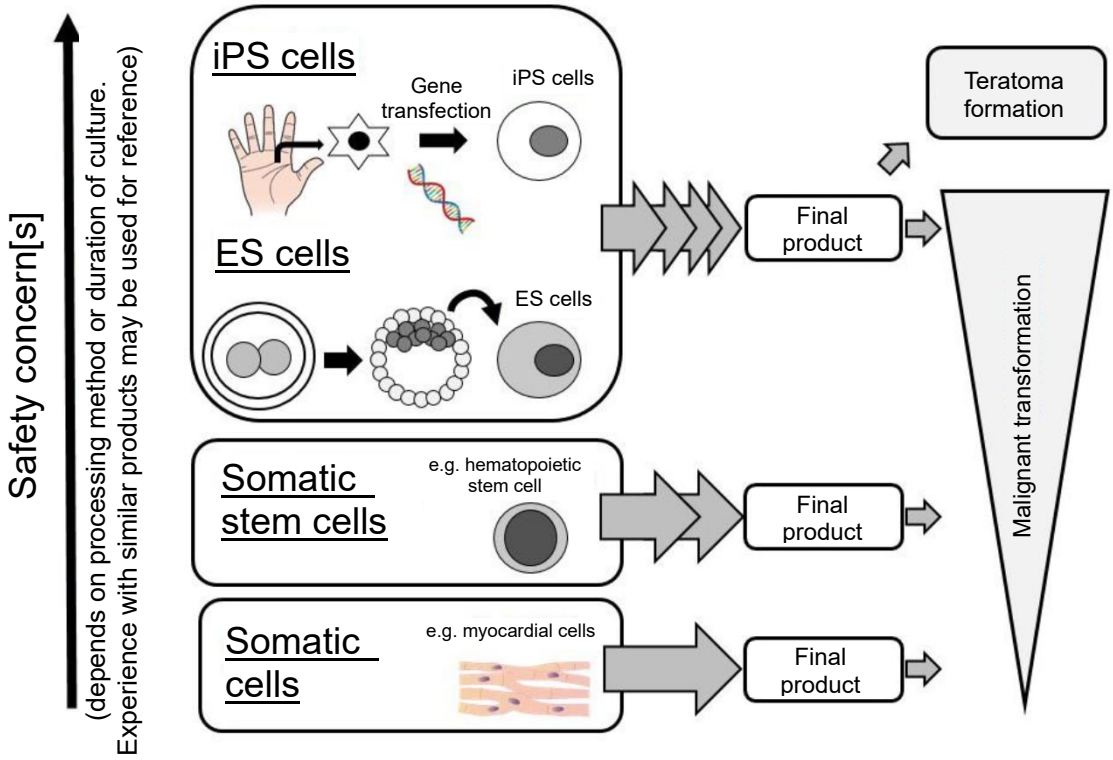

Figure 1 Tumorigenicity risk of human cell-processed products

3.2.1 Selection of animal species

When selecting animal species for a tumorigenicity study, the most important thing is to avoid heterologous immune response. Immunodeficient mice (nude, SCID, NOD/SCID/γCnull, etc.) are generally selected, due

to their clear historical control data regarding tumor outcome and the results obtained so far from the candidate animals. When immunodeficient mice cannot be used via a clinical administration route, immunodeficient rats can be used instead. Similar to general toxicity studies, single animal species suffices to evaluate tumorigenicity.

3.2.2 The number of animals

As for the number of animals to be used in a tumorigenicity study, it is currently considered difficult to establish statistically like carcinogenicity study of pharmaceuticals. The sample size usually used for general toxicity studies can also be used for tumorigenicity studies (10 animals per group at the final evaluation stage).

3.2.3 Dosage and administration

3.2.3.1 Dosage

In a tumorigenicity study of human cell-processed products, it is essential to set the dose as many cells as practicable, taking into account the maximum tolerated dose (MTD), maximum feasible dose (MFD) and animal welfare, in order to confirm the residue of pluripotent stem cells or malignant transformed cells. The potential of tumorigenicity can be evaluated in at least two groups; a control (negative) group and a treatment group. Because of differences in tumorigenicity among products, setting a positive control group (HeLa cells) is not scientifically relevant, unless there is a technical concern such as one related to the administration procedure.

3.2.3.2 Frequency of administration

In order to form tumors in immunodeficient animals, a certain number of cancer cells must be present in the transplantation site. When the number of transplanted cells with tumorigenicity is insufficient to the threshold for tumorigenic potential at the transplantation site, a false-negative result may be obtained and the tumorigenicity potential cannot be accurately evaluated. As many cells as practicable should be transplanted in single dose regimen, regardless of clinical dosage and administration.

3.2.3.3 Administration route

Administration route should be selected depending on the cells to be tested for tumorigenicity, with consideration of following points;

- Risk of residual pluripotent stem cells

  For ES/iPS cell-derived products, subcutaneous dorsal transplantation into the immunodeficient mice is desirable. This is an administration route that has been widely used for studies used to detect residual pluripotent stem cells, which have the potential to form teratoma. When other administration routes are used to evaluate teratoma formation potential, their non-inferiority in terms of detection sensitivity must be confirmed.

- Risk of malignant transformed cells

  Since formation of malignant transformed cells that may occur during the differentiation (manufacturing) process of the final product may be affected by the microenvironment of the transplantation site, the risk of malignant transformed cell formation should be evaluated in a study using the clinical administration route. If the clinical administration route is technically difficult to use, other administration routes such as subcutaneous dorsal transplantation can be used instead. In this case, the validity of using the route should be scientifically justified.

3.2.4 Study period

The study period should be defined according to the degree of tumorigenic concern. For example, for ES/iPS cell-derived products which have a high concern of tumorigenicity, study period should be selected

from two options so that the risk of malignant transformed cells can be assessed appropriately; the period that the transplanted cells are no longer identified in the animals transplanted, or the maximum period during which spontaneous lesions or mortality in the test species do not confound the test results. To evaluate the risk of teratoma formation caused by residual pluripotent stem cells, study period established with evidence in published paper can be selected as another approach. For somatic cell-derived products which have less concern of tumorigenicity, the study period (4 to 16 weeks) recommended in WHO guideline TRS978 (Reference 10) can be used as a reference, and a supplementary histopathological evaluation can be used to rule out the presence of atypical cells or aberrant proliferation of cells.

3.3 Safety evaluation of non-cellular components

Human cell-processed products may intentionally contain non-cellular components such as chemicals (DMSO, etc.), biotechnology-derived pharmaceuticals (biopharmaceuticals) or scaffolds. The safety of these non-cellular components should be evaluated according to their characteristics and content amount, and making full use of information obtained from published data and general toxicity studies of the human cell-processed products. Physicochemical methods should be used whenever possible. When nonclinical safety studies focused on these components are considered necessary, the study should be designed with reference to the guidelines of "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH-M3)(R2)" (PFSB/ELD Notification No. 0219-4 dated February 19, 2010) for chemicals, "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH-S6)(R1)" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012) for biopharmaceuticals, and "Basic Principles of Biological Safety Evaluation Required for Application for approval to Market Medical Devices" (PFSB/ELD/OMDE Notification No. 0301-20 dated March 1, 2012) for materials such as scaffolds. When the product is indicated for any serious disease such as advanced cancer, the nonclinical safety study can be omitted or abbreviated, according to ICH-M3(R2) or "Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH-S9)" (PFSB/ELD Notification No. 0604-1 dated June 4, 2010).

3.4 Safety evaluation of process-related impurities

For process-related impurities, it is important to eliminate them from final product as much as possible first, using a strategy formulated according to factors known to be involved in the manufacturing process (e.g., raw materials, substances used in manufacturing, manufacturing process, quality control of final products). In addition, their residual risk should be identified and assessed by physicochemical procedures whenever possible, with reference to the published data or information obtained from nonclinical safety studies of the final product. Examples of published data include toxicity profile of chemical and biological products (e.g., no observed adverse effect level, minimum anticipated biological effect level), information on human endogenous substances (e.g., normal level of the substance in blood), experience of administration in humans (e.g., experience as a pharmaceutical or an excipient, acceptable intake), ICH guidelines regarding impurities such as "Impurities: Guideline for Residual Solvents (ICH-Q3C)" (PMSB/ELD Notification No. 307 dated March 30, 1998), "Guideline for Elemental Impurities (ICH-Q3D)" (PFSB/ELD Notification No. 0930-4 dated September 30, 2015), "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (ICH-M7)" (PSEHB/ELD Notification No. 1110-3 dated November 10, 2015) and toxicological concepts (e.g., threshold of toxicological concern). When safety in humans cannot be evaluated by any of the approaches mentioned above, the impurities should be evaluated through a nonclinical safety study as well as non-cellular components.

4. Clinical studies

4.1 Principles

Human cell-processed products are different from pharmaceuticals/medical devices because of their unique characteristics: uniform quality cannot be expected and unknown risks cannot be ruled out. The characteristics of each product must be taken into account when clinical studies are designed. For some products, cells/tissues need to be collected from patients, for some other products, time is needed for manufacturing during the clinical studies, and other products may remain in the body for a long period. For these products, approaches different from those used for pharmaceuticals may be required when designing the clinical studies and safety monitoring of the subjects.

On the other hand, there are some characteristics which are common to both some regenerative medical products and pharmaceuticals/medical devices. For such regenerative medical products, the basic principles for clinical studies of pharmaceuticals/medical devices can be applied. Design, administration and evaluation of the efficacy and safety of such regenerative medical products can be defined according to their characteristics and with reference to similar pharmaceuticals/medical devices.

The basic principles of benefit/risk assessment are not significantly different between human cell-processed products and pharmaceuticals/medical devices. In consideration of entire phase of development, the benefits/risk of a human cell-processed product should be assessed based on its specific characteristics, with reference to those of existing pharmaceuticals/medical devices for the same indication.

4.2 Study population and study design

During development of a human cell-processed product, reference should be made to "General Considerations for Clinical Trials (ICH-E8)" (PMSB/ELD Notification No. 380 dated April 21, 1998) for basic principles of development phase, "Statistical Principles for Clinical Trials (ICH-E9)" (PMSB/ELD Notification No. 1047 dated November 30, 1998) for basic principles of study design, and "Choice of Control Group and Related Issues in Clinical Trials (ICH-E10)" (PMSB/ELD Notification No. 136 dated February 27, 2001) for principles of control groups. Points to consider on first-in-human study specified in "Guidance for Establishing Safety in First-in-Human Studies during Drug Development" (PFSB/ELD Notification No. 0402-1 dated April 2, 2012) are also generally applicable to human cell-processed products.

4.2.1 Early phase clinical trials including first-in-human studies

A first-in-human (FIH) study in healthy volunteers is difficult for human cell-processed products because tissues have to be collected from subjects and unknown risks cannot be ruled out. Such a study might be excessively invasive and pose unacceptable risks to subjects. Therefore, a FIH study of human cell-processed product often conducted in patients with the indicated medical condition. Information not only on safety but also on efficacy may be collected in the FIH study. Due to this difference, clinical trials conducted during an early development phase should be deliberately designed according to the specific characteristics of each product. Especially, when the number of subjects that can be included in clinical trials in the overall development is limited from the viewpoint of feasibility, it is important to make the information obtained from a limited number of subjects to be fully utilized. Factors that may have an influence on efficacy and safety (e.g., effect of standard treatment or placebo effect that may induce bias, effect of surgical procedure) should be taken into consideration for planning a clinical trial in the early development phase. When clinical trials can be conducted from the early development phase in a number of subjects sufficient for statistical evaluation, it is preferrable to design the study with reference to pharmaceuticals.

4.2.2 Blinding and randomization

The feasibility of a blinded study varies markedly depending on the individual human cell-processed products: some products may need cells/tissues to be collected from subjects, and a variety of procedures may be used for administration unlike pharmaceuticals. A placebo can be used for blinding when collection of tissue is not necessary and administration procedure is not highly invasive such as intravenous administration. On the other hand, when an invasive procedure is necessary for administration, surgery for example, a blinded study must be carefully designed, while taking into account invasiveness and ethical aspects of a sham operation. When a sham operation for blinding is not feasible, other measures for blinding, a rater-blinded design for example, should be considered. Not only the necessity of blinding but the necessity of randomization, including setting a control group should be examined.

Reference: "Current Status and Perspectives of Placebo-Controlled studies (Subcommittee on Placebo-controlled Studies)" Report of Science Board dated March 9, 2016)

4.2.3 Definition of eligibility and analysis set

The eligibility of subjects and populations must be carefully defined when the product is manufactured between the enrollment of subjects and administration of the product. The condition of the subjects may change during the period when the human (autologous)-derived product is manufactured. The eligibility of a patient has to be evaluated at enrollment and at collection of cells/tissues, and sometimes at administration of the product to verify that the subject is a suitable candidate for evaluating efficacy and safety.

4.2.4 Control setting

Regardless of the study design, whether a blinded study or a non-blinded study, use of an internal control group must be considered to improve the scientific level of the information on efficacy and safety during clinical trial. If use of an internal control group is not feasible due to the product's characteristics, an external control group may be employed instead. Note that an external control group has the limitation that it cannot control bias as described in ICH-E10, and the results obtained are not fully persuasive. Therefore, as for products for which collection of tissues from subjects is not necessary and can be administered by a route that is not highly invasive (i.v. for example), use of the external control design should be restricted to products that the effect of treatment is dramatic and the usual course of the disease highly predictable.

When setting a control group is not feasible due to variable limitations, the validity of the study must be enhanced as far as practicable by setting a threshold value for efficacy in advance based on the clinical data, for example.

Sample size to evaluate efficacy and safety may be limited throughout the development phase for some human cell-processed products. For these products, the specific methodology used for evaluation of orphan drugs may be more relevant than that used for non-orphan pharmaceuticals.

In these cases, a certain evidence level must be qualified. Designing the study as a rater-blinded study instead of double-blinded study, randomization using a control group with least bias, and setting the objective efficacy endpoints that can show the clinical significance, may be some tactics to improve the evidence level.

4.2.5 Other considerations regarding study design

Because quality is not uniform for regenerative medical products, factors related to quality or manufacturing may influence the design of a clinical trial. For example, the product may have to be administered before obtaining results regarding infection; the amount or quality of the product is different due to the characteristics of the subject, especially for human (autologous)-derived products; or a product cannot be administered to the patient because it is out of specification or could not be manufactured. These

problems have to be addressed on a case-by-case basis because characteristics of the indication and the product itself vary markedly among the products.

Since regenerative medical products may have multiple mechanisms of action, information that provides any insight into the specificity and interpretation of the results is helpful. The study design should allow evaluation of reproducibility, and consistency/inconsistency with the latest findings obtained from other studies.

4.3 Dosage and administration

For human cell-processed products, the significance of examining the dose-response relationships in evaluating efficacy and safety has not been ascertained. At the very least, the administration route and optimal dosage that can exert clinical efficacy have to be explored. Information has to be collected throughout development to support the dosage and administration proposed in a marketing application. Risks specific to the product, for example, possible dose-dependent increase in risks or immune response after repeated doses, must be assessed. When a special procedure is used for administration, the risks associated with such procedure also have to be assessed.

4.4 Efficacy evaluation

The procedure for the efficacy evaluation must be defined according to the study design used for the product tested and product-specific limitations in the evaluations performed in clinical trials must be understood.

The sample size of clinical trials may be limited because of the characteristics of the indication or the product. In this case, effort should be made to maximize the information obtained from clinical trials for the efficacy evaluation. Information obtained in clinical trials conducted outside of Japan should be used as well. Employing both true endpoints and surrogate endpoints that sensitively detect change and can provide supplemental information is one tactic to maximize the amount of information. When the purpose of the product is to repair tissue or organs, imaging and biomarkers may be of help to demonstrate performance and the effect of the product to support efficacy.

When efficacy is evaluated by a non-blinded and non-controlled study, endpoints that are as objective as possible should be selected. For some products, only subjective evaluation can be used as true endpoints. In this case, secondary endpoints that can demonstrate objective efficacy may support the results obtained by administration of the investigational product.

Even when efforts such as the above are made to improve the evidence level of the study, efficacy and safety may have to be evaluated in only limited number of subjects. Comprehensive information collected from the subjects may be of help to improve clinical significance. Particularly, when efficacy is to be evaluated by comparison with the natural course of the disease for which only limited number of treatments are currently available, medical information relating to the true endpoint is essential for evaluation.

Human cell-processed products may have multiple mechanisms of action. Information that provides any insight into the specificity and interpretation of the results concerning the change on the efficacy or safety in the subjects is helpful. The study design should allow evaluation of reproducibility, and consistency/inconsistency with the latest findings obtained from other studies.

4.5 Safety evaluation

Unlike pharmaceuticals/medical devices, for human cell-processed products, safety information that supports clinical application may depend on the characteristics of the product because some human cell-processed products require collection of cells/tissues and their manufacturing schedule differs from pharmaceuticals.

As specified in "Ministerial Ordinance on Good Clinical Practice for Regenerative Medical Products" (Ordinance No. 89 of Ministry of Health, Labour and Welfare dated July 30, 2014), an adverse event is any disease or its clinical signs occurring in a subject who has been administered an investigational product used in the clinical trial or a product used in the post-marketing clinical trial. In addition, as specified in "Enforcement of Ministerial Ordinance on Good Clinical Practice for Regenerative Medical Products" (PFSB Notification No. 0812-16 dated August 12, 2014), adverse events include any untoward condition/sign in a subject occurring during collection of cells/tissues for manufacturing of the investigational product used in the clinical trial or the product used in the post-marketing clinical trial. This type of adverse event must also be collected as safety information. In addition, these adverse events include an event caused by failure of devices for combination products.

One of the risks specific to human cell-processed products is the risk of failure of the engraftment of administered cells. The period of safety monitoring and the procedure for collection of information must be defined according to the characteristics of each product. When it is not known how long it takes for the product to be eliminated from the body, safety information must be collected for at least for a year. The necessity of follow-up for a period exceeding a year has to be examined based on the characteristics of each product.

For human (autologous)-derived products, adverse events that occur after collection of cells/tissues and before administration of the investigational product are obviously not related to the investigational product itself. However, in clinical application, the collection of cells/tissues is a part of treatment. Events occurring during collection of cells/tissues are clinically significant information and have to be considered as part of the risk/benefit assessment. Especially, when cells/tissues are collected but the investigational product cannot be administered due to some problem in the subject or in the investigational product, such safety information is important data that reflects the characteristics of a cell-processed product. The protocol should define the procedure for properly collecting information on any untoward occurrence throughout the entire duration of the study.

4.6 Other considerations

4.6.1 Clinical data obtained in Japanese patients

For human-cell processed products, ethnic factors have to be considered when the results of overseas clinical trials are used as reference or development involves international clinical trials. The applicant has to explain efficacy and safety of the product in Japanese patients under the circumstances in Japan. Intrinsic and extrinsic ethnic factors described in "Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH-E5)" (PMSB Notification No. 739 dated August 11, 1998) should be taken into account.

4.6.2 Conditional and time-limited approval scheme and development lifecycle

Since regenerative medical products are eligible for conditional and time-limited approval, it is important to define the target benefit of the product in clinical development lifecycle so that following information can be collected; on a certain level of efficacy demonstrated in exploratory clinical trials during the early development phase and a protocol to demonstrate efficacy and safety during post-marketing phase. In other words, it is appropriate to consider the launch of a product under conditional and time-limited approval as being in the process of the clinical development lifecycle followed by subsequent regular approval review and reexamination. When a product is developed for conditional and time-limited approval scheme, a feasible post-marketing clinical study to assess efficacy and safety should be designed before submitting the marketing authorization application. When a product is approved conditionally with a limited time, a patient may want to be treated with the product rather than the standard of care. In this case, collection of information on the natural course of the disease without using the product may be difficult compared to collection before

or during development. Methods for collecting and evaluating information on the efficacy and safety of the product in this course of the product's lifecycle in clinical development need further discussion.

When it is impossible to collect a control group data during post-marketing, i.e., a group not receiving product in order to obtain information prospectively on the natural course of the disease, efficacy evaluation is limited because of the limited number of endpoints. If a post-marketing clinical study cannot adequately demonstrate clinical efficacy, the benefits of the product remain unclear. Under these circumstances, regular approval review and marketing approval would be difficult.

5. References

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