Administrative Notice
March 8, 2013

To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

About the Guidance for Preparation of Application Forms for Registration of Drug Master Files of Materials Relating to Manufacture of Cellular- and Tissue-Based Products and Data to be Attached

Guidelines on utilization of drug master files (hereinafter referred to as "MFs") were reviewed to reflect recent advancements of science and technology, and the "Partial Amendment to the 'Guidelines on Utilization of Master File for Drug Substances, etc.'"(PFSB/ELD Notification No. 1228-27, dated December 28, 2012, of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare [MHLW]. hereinafter referred to as "MF Amendment Notification") was issued. The amended guidelines additionally instruct handling of materials (e.g., cells, media, medium additives) relating to manufacture of human cellular- and tissue-based drugs and medical devices (hereinafter referred to as "cellular- and tissue-based products").

In view of the guidelines amended by the MF Amendment Notification, guidance for preparation of application forms for registration of drug master files of materials relating to manufacture of cellular- and tissue-based products (hereinafter referred to as "application forms") and data to be attached to the application forms has been developed as provided in the attachment. Please thoroughly inform the relevant business operators in your jurisdiction proceed with MF registration of human materials relating to manufacture of cellular and tissue-based products (e.g., cells, media, medium additives), taking into account not only the MF Amendment Notification but also the following guidance.

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1. For an application for MF registration of materials relating to manufacture of cellular- and tissue-based products, the application form provided as Form No. 42 in the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and

Welfare [MHW] Ordinance No. 1 of 1961, hereinafter referred to as “Regulation”) should be used pursuant to the provisions of Article 72, Paragraph 1 of the Regulation.

2. An application form for registration of drug master files and data to be attached to the concerned application form should be prepared by consulting the Guidance for Preparation in the attachment and, as appropriate, utilizing consultation service offered by the Pharmaceuticals and Medical Devices Agency (PMDA).
3. Depending on the types of materials relating to manufacture of cellular- and tissue-based products to be registered, data to be attached to an application form may be partially simplified.

(Attachment)

Guidance for Preparation of Application Forms for Registration of Drug Master Files of Materials Relating to Manufacture of Cellular- and Tissue-Based Products and Data to be Attached

Chapter 1 General matters

This Guidance for Preparation is developed for application for registration of drug master files for human cellular- and tissue-based drugs and medical devices (hereinafter referred to as "cellular- and tissue-based products") and covers items generally entered in application forms and points to note for preparation of data to be attached to application forms based on the "Guideline on Ensuring Quality and Safety of Products Derived from Processed Human Cells and Tissues (autologous cells)" (PFSB Notification No. 0208003, dated February 8, 2008, of the Pharmaceutical and Food Safety Bureau, MHLW) and "Guideline on Ensuring Quality and Safety of Products Derived from Processed Human Cells and Tissues (allogeneic cells)" (PFSB Notification No. 0912006, dated September 12, 2008, of the Pharmaceutical and Food Safety Bureau, MHLW, hereinafter referred to as the "Guideline"). It should be noted that depending on the types of materials relating to manufacture of cellular and tissue-based products to be registered (hereinafter referred to as "registration materials"), data to be attached to an application form may be partially simplified (see the appendix).

If there are any items needed to explain the quality and safety of a registration material other than those listed in this Guidance for Preparation, relevant data should be attached and explained irrespective of the Guidance for Preparation.

Chapter 2 Points to note for preparation of application form for MF registration

In an application form, each field should be given appropriate information with the following points noted, and data supporting the information filled in each field should be attached.

1 "Registration category" field

This field should be given appropriate information with reference to 5. (1) 1) in the "Partial Amendment to the 'Guidelines on Utilization of Master File for Drug Substances, etc.'" (PFSB/ELD Notification No. 1228-27, dated December 28, 2012, of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW).

2 "Name of drug substance, etc." field

The name of a material relating to manufacture of cellular- and tissue-based products to be registered (hereinafter referred to as "registration material") should be entered. The name should be entered in one of the following formats: "Cells XX (commercial name)" for cells; "Medium/medium additive XX (commercial name)" for media/medium additives; and "Raw material for cell processing XX (commercial name)" for the other materials relating to manufacture of cellular- and tissue-based products (e.g., enzymes used for cell processing, etc.) (hereinafter referred to as "Raw materials for cell processing, etc.").

3 “Name of manufacturing site” field

Name of the manufacturing site where the registration material is manufactured should be entered.

4 “Address of manufacturing site” field

Address of the manufacturing site where the registration material is manufactured should be entered.

5 “Ingredients and their quantities or nature” field

If the registration material is cells, description of the cells and ingredients and their quantities of the preservation medium should be entered. Information appropriate for this field should be ingredients and their quantities for media and ingredients and their quantities, nature, etc. for medium additives (e.g., serum, growth factors, cytokines) and raw materials for cell processing, etc.

For each of the ingredients of human or animal origin, the free-text field should be given appropriate information with reference to Attachment 2 of the “Administrative Handling in response to Partial Amendment of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices” (PFSB/ELD Notification No. 0520001, PFSB/SD Notification No. 0520001, PFSB/CND Notification No. 0520001, and PFSB/BBPD Notification No. 0520001, dated May 20, 2003, of the Evaluation and Licensing Division, Safety Division, Compliance and Narcotics Division, and Blood and Blood Products Division, Pharmaceutical and Food Safety Bureau, MHLW).

The appropriate information may include:

- Origin of the ingredients derived from humans or animals used as raw materials (e.g., animal species, country of origin, part of use)
- Details of donor screening (e.g., test items, testing methods)
- Methods to inactivate/remove bacteria, fungi, viruses, and other adventitious agents in the manufacturing process
- Steps in the manufacturing process deemed critical from the viewpoint of ensuring quality and safety

6 “Manufacturing method” field

(1) Raw materials and their acceptance

Where appropriate, raw materials of the registration material should be listed, and for each of them, specifications should be provided. If an acceptance test is performed, name of the test, method, and acceptance criteria should be provided.

For raw materials of the registration material that are of human or animal origin, specifications for the raw materials entered in this field should also include information required in 5. “Ingredients and their quantities or nature” field above. For the raw materials of the registration material that are of human or animal origin, explanation is required, but whether the raw material needs to be handled as one of human or animal origin should be determined with reference to the “Handling of Raw Materials Defined in the Standards for Biological Raw Materials” (Administrative Notice, dated March 27, 2009, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW).

(2) Manufacturing method in each step

If the manufacturing process has steps where bacteria, fungi, viruses, and other adventitious agents are inactivated/removed, names of such steps should be provided.

If the registration material is cells, the manufacturing method should be described for each step of the manufacturing process, including raw materials, process parameters, and process control, and the in-process control tests should be also described, including test items and acceptance criteria.

If the registration material has a cell bank system, a preparation method of the cell bank should be described, and frequency and methods of renewal as well as qualification criteria should be described where applicable.

7 "Specifications and testing methods" field

Where appropriate, the specifications and testing methods for the registration material should be described, including test items, testing methods, and pass/fail criteria.

8 "Information on stability" field

Where appropriate, this field should be filled based on stability testing results, etc.

9 "Storage method & expiry date" field

Storage method and expiry date of the registration material should be provided.

10 "Information on safety" field

Relevant information should be provided.

11 "Category of manufacturing business license or foreign manufacturer accreditation" field

Where appropriate, a code corresponding to the category of manufacturing business license or foreign manufacturer accreditation granted (or application for licensing or accreditation pending) should be entered.

12 "Manufacturing business license number or foreign manufacturer accreditation number and date" field

If manufacturing business license or foreign manufacturer accreditation is granted, this field should be filled. The "License number or accreditation number" field should be filled with the applicable manufacturing business license or foreign manufacturer accreditation number, and the "Date of licensing or accreditation" field should be filled with date of the license or accreditation (date when the shelf life starts). This field should be given a dummy number if neither license nor accreditation is required.

13 "In-country caretaker of drug substances" field

If the registration material is manufactured outside Japan, an in-country caretaker of drug substances should be appointed, and the name and address should be described.

Chapter 3 Data to be attached to application form for registration of drug master file and points to note for preparation of the summary

To an application form, documents such as reports and certificates supporting the information entered in this form should be attached, and a document summarizing them should be prepared. The document should be prepared with the following points noted.

1 Manufacturing method

(1) Raw materials of the registration material

A. Cells/tissues

1) Based on Chapter 2, Section 1.1 of the Guideline, necessary items should be explained. The explanation should include information on Items a to d below for each ingredient of the raw material (see Example of description 1 in the appendix).
   - a Origin of the cells/tissues, animal species, and country of origin (for an animal-derived material)
   - b Details and appropriateness of donor screening
   - c Manufacturer's specifications as well as acceptance specifications and testing methods to be performed
   - d Conformity with the Standards for Biological Raw Materials
2) If an established cell line used as feeder cells is a registration material or a raw material of the registration material, information on the origin (e.g., origin, history [background of acquisition]) should be collected wherever possible, and the conformity with the Standards for Biological Raw Materials should be explained on the basis of documented control activities starting with the receipt (e.g., raw material standards [manufacturer's specifications as well as acceptance specifications and testing methods to be performed], retention of the records).

B. Raw materials other than cells/tissues

Raw materials used in manufacture of the registration material should be tabulated with reference to Chapter 2, Section 1.2 of the Guideline (see Example of description 2 in the appendix). Then, each of the raw materials listed should be explained in detail where appropriate (see Example of description 3 in the appendix).

The explanation should be given in view of the following points.

1) For the raw materials falling under Chapter 2, Section 1.2 (1) to (3) of the Guideline, applicable items should be described where appropriate, and the intended use of each of the raw materials should be explained.
2) For raw materials of human or animal origin, Items a to c below should be explained for each of the raw materials, and, where appropriate, Items d and e should be also explained.
   - a Animal species, country of origin, part of use (for an animal-derived material)
   - b Tests for viruses in raw materials (test for presence or absence of viruses infectious or pathogenic to humans)
   - c Manufacturer's specifications as well as acceptance specifications and testing methods to be performed

d Conformity with the Standards for Biological Raw Materials (see Example of description 4 in the appendix).

e Steps in the manufacturing process where bacteria, fungi, viruses, and other adventitious agents are inactivated or removed

(note) Viral clearance studies should be tabulated (see Example of description 5 in the appendix).

If possible, the explanation should include justification of the viruses used, the method of viral clearance studies, justification of scaling down, the assay and its sensitivity for each virus, the list of virus titers at each sampling time, and virus reduction factors. In addition, the "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329, dated February 22, 2000, of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare) should be referred to. For the methods based on scientific knowledge in the public domain to inactivate or remove bacteria, fungi, viruses, and other adventitious agents adequately, examples in Attachment 1 of the "Handling of Virus Confirmation, etc. in Application for Partial Change Approval to Ensure the Quality and Safety of Drugs, Medical Devices, etc. Manufactured from Raw Materials of Human or Animal Origin" (PFSB/ELD Notification No. 1552, dated November 26, 2001, of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW) should be referred to.

(2) Manufacturing process

A. Manufacturing method in each step

If the registration material is cells, the manufacturing process should be outlined in a flow diagram with reference to Chapter 2, Section 2.2 of the Guideline, and the manufacturing method should be described in detail for each step of the manufacturing process (e.g., process parameters, in-process control tests) with supporting data (see Example of description 6 in the appendix). If the registration material has a cell bank system, a preparation method of the cell bank and its control method (tests periodically performed to check the stability during storage and acceptance limits, criteria for renewal of the cell bank) should be described with supporting data.

In addition, studies to validate the manufacturing method established at the time of registration and their results should be tabulated with reference to Chapter 2, Section 2.5 of the Guideline (see Example of description 7 in the appendix) and described in detail as well. If the manufacturing process of a registration material has steps that are intended to remove impurities, to inactivate/remove bacteria, fungi, viruses, and other adventitious agents, to differentiate cells, and/or to increase cell purity, and their process capabilities (e.g., capability of removing impurities, capability of delivering differentiated cells at consistent percentages or cells at consistent purity) have been evaluated, the overview should be provided in this section as well.

If the registration material is any of media, medium additives, and raw materials for cell processing, the manufacturing method should be outlined in a flow diagram and described where appropriate, and methods to inactivate or remove bacteria, fungi, viruses, and other adventitious agents should be described as well. If their capabilities of inactivating or removing bacteria, fungi, viruses, and other

adventitious agents have been evaluated, the details should be provided in this section as well.

B. In-process control tests

If the registration material is cells, details of the in-process control tests should be tabulated, including test items, acceptance criteria (or action limits), and steps where the test is performed, and the table should be provided in the application form (see Example of description 8 in the appendix). In addition, items and acceptance criteria (or action limits) of the in-process control tests should be justified for each step, and actions (e.g., disposition, reworking) taken in the event of a failure to conform to acceptance criteria (or action limits) in an in-process control test should be described. Where appropriate, the in-process control testing methods and their justification (including an overview of validation studies) should be described.

If the registration material is any of media, medium additives, and raw materials for cell processing, items and acceptance criteria or action limits of the in-process control tests should be described with justification where appropriate.

(3) Characterization

If the registration material is cells, the material and in-process products (intermediates) should be analyzed using appropriate indices with reference to Chapter 2, Section 2.3 of the Guideline, and the results should be tabulated (see Example of description 9 in the appendix). Their characteristics should be explained based on analysis results on each index. If impurities in the registration material have been characterized in addition to the material itself, the details should be provided as well (see Example of description 10 in the appendix).

If the registration material is any of media, medium additives, and raw materials for cell processing, the quality attributes should be described where appropriate.

2 Specifications and testing methods

(1) Specifications and testing methods

Quality control items should be appropriately specified, and a table should be prepared, including the test items, outlines of the testing methods, and acceptance limits (see Example of description 11 in the appendix). In addition, each testing method should be described in detail. If the registration material is cells, Chapter 2, Section 3.2 of the Guideline should be referred to.

(2) Justification of specifications and testing methods

If the registration material is cells, for each test item, a reason for the selection should be provided, and the specifications should be justified using data in (3) “Analysis results obtained from test specimens” below where appropriate, and thereby the established specifications and testing methods should be demonstrated to be capable of controlling the quality and safety of the registration material within a certain range. If the testing method is not a part of the scientific knowledge in the public domain, being outside of compendia such as the Japanese Pharmacopoeia, validation results for the testing method should be provided. For test items included in the characterization but not in the specifications, if any, justification for such exclusion should be provided.

If the registration material is any of media, medium additives, and raw materials for cell processing, for the specifications and testing methods, the reason for the selection should be provided where appropriate, and thereby the established specifications and testing methods should be demonstrated to be capable of controlling the quality and safety of the registration material within a certain range.

(3) Analysis results obtained from test specimens

For the registration material manufactured for quality-related tests, the results should be tabulated, including results from in-process control tests and specification tests by lot (or by manufacturing session for the registration material not manufactured on a batch basis) (see Example of description 12 in the appendix).

3 Information on stability

If the registration material is cells, stability studies conducted should be described, including study methods/conditions and their justification as well as study results with reference to Chapter 3 of the Guideline. The study methods/conditions should be justified by the following information: (a) their details; (b) the impacts of freezing and thawing operations if handling of the registration material involves such operations; and (c) containers and procedures for transportation of the registration material or in-process products (intermediates) if applicable and relevant data where appropriate.

If the registration material is any of media, medium additives, and raw materials for cell processing, stability studies conducted should be described where appropriate, including study methods/conditions and their justification as well as study results.

4 Storage method & expiry date

If the registration material is cells, the storage method and expiry date should be provided and justified with reference to Chapter 3 of the Guideline.

If the registration material is any of media, medium additives, and raw materials for cell processing, the storage method and expiry date should be provided where appropriate.

5 Information on safety

(1) Safety evaluation on toxicity

If the registration material (e.g., medium, medium additive, cell preservation medium) is potentially present in a final product (e.g., drugs), and safety information obtained from toxicity studies is available, a table should be provided, including names of the studies conducted, their objectives, study systems (e.g., type of cells, species of animals used), application methods, and results (see Example of description 13 in the appendix). The following information should be provided for each study: (a) details of the method; (b) rationale for selection of the method; (c) justification of the system; (d) results; and (e) discussion on the results.

(2) Safety evaluation on infections

If the registration material contains a raw material of human or animal origin, safety of the registration material concerning adventitious agents should be comprehensively explained in view of the manufacturing process's capability of removing/inactivating bacteria, fungi, viruses, and other adventitious agents

presented in 1 (1) and (2) above as well as results from tests for viruses and mycoplasma.

Chapter 4 Others

In addition to this Guidance for Preparation, the following guidelines should be referred to according to type and characteristics of the registration material.

- PMSB/ELD Notification No. 873, dated July 14, 2000, of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHW ”Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products”
- PMSB Notification No. 1314, dated December 26, 2000, of the Pharmaceutical and Medical Safety Bureau, MHW “Ensuring the Quality and Safety of Drugs, etc. Manufactured from Raw Materials of Human or Animal Origin”
- HPB/RDD Notification No. 0702001, dated July 2, 2004, of the Research and Development Division, Health Policy Bureau, MHLW “Guideline for Epithelial Regenerative Medical Products using 3T3J2 or 3T3NIH Cell Line as Feeder Cells Based on the “Guideline for Public Health Issues on Infections Associated with Xenotransplantation”
- PFSB/ELD Notification No. 0210001, dated February 10, 2005, of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW “Guideline for Information Entered in Application Forms for Marketing Approval of Drugs, etc. Based on the Amended Pharmaceutical Affairs Act”
- PFSB Notification No. 0907-2, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, MHLW ”Ensuring Quality and Safety of Products Derived from Human Processed Somatic Stem Cell (autologous cells)”
- PFSB Notification No. 0907-3, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, MHLW “Ensuring Quality and Safety of Products Derived from Human Processed Somatic Stem Cell (allogeneic cells)”
- PFSB Notification No. 0907-4, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, MHLW ”Ensuring Quality and Safety of Products Derived from Human Processed iPS(-like) Cell (autologous cells)“
- PFSB Notification No. 0907-5, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, MHLW “Ensuring Quality and Safety of Products Derived from Human Processed iPS(-like) Cell (allogeneic cells)”
- PFSB Notification No. 0907-6, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, MHLW “Ensuring Quality and Safety of Products Derived from Human Processed ES Cell”

(Appendix) List of attached data

Data required to be attached to an application form are provided in a table below (types of data required to be attached may differ depending on characteristics of the registration material). If there are any items needed to explain the quality and safety of a registration material other than ones provided in the table below, relevant data should be attached and explained irrespective of the Guidance for Preparation.

Data to be attached	Cells	Media/medium additives, other raw materials for cell processing
1 Manufacturing method		
(1) Raw materials of the registration material		
Origin and derivation, reason for selection	○	△
Properties and eligibility of cells/tissues	○	×
Inclusion criteria and eligibility for donors	○	△
Record on donors	○	△
Collection/storage/transport of cells/tissues	○	×
List of raw materials used in manufacture and manufacture-related substances	○	○
Specifications for raw materials used in manufacture and manufacture-related substances	○	○
(2) Manufacturing process		
Overview of the manufacturing process	○	△
Manufacturing method in each step	○	△
List of in-process control tests	○	△
Justification of in-process control tests	○	△
(3) Characterization		
Characterization	○	△
Consistency and justification of the manufacturing method	○	△
2 Specifications and testing methods		
(1) Specifications and testing methods	○	○
(2) Justification of specifications and testing methods	○	△
(3) Analysis results obtained from test specimens	○	△
3 Information on stability		
List of testing methods for stability and results	△	△
Justification of tests for stability and details	△	△
Impact of freezing and thawing operations on stability	△	×
Stability relating to transportation	△	×
4 Storage method & expiry date	○	○
5 Information on safety		
List of testing methods for safety and results	○	○
Justification of tests for safety and details	○	○

○ ... Data required for attachment
△ ... Data basically exempted from attachment but occasionally required for attachment
× ... Data exempted from attachment

Appendix

Example of description 1

Section 3.1 (1) A. Cells/tissues

Table Conformity with the Standards for Source Materials for Human Cell/Tissue-based Products

Provision in the Standard	Action to meet the provision
(1) Cells and tissues used as source materials or ancillary materials of human cell/tissue-based products (drugs or medical devices using source materials or ancillary materials of human origin [excluding blood and components manufactured from blood]. Hereinafter, the same definition applies) must be collected in facilities with personnel and equipment adequate for sanitation control required for the collection.	(1) The collection is performed in an operating room of a medical institution by surgeons. For the details, see XX.
. . .	. . .
. . .	. . .

Table Donor screening

Object to be tested	Specimen	Test method	Timing of test	Remarks
H○V	Serum	Detection of XX antigen by XX method	X and Y days before tissue collection	For detailed method, sensitivity, suitability for timing of the test, etc., see XX.
H○V	Serum	Detection of XX by NAT method	X days before tissue collection	For detailed method, sensitivity, suitability for timing of the test, etc., see XX.
. . .	. . .	. . .	. . .	. . .

* Test items, testing methods, etc. appropriate for characteristics of the raw material should be described.

Example of description 2

Section 3.1 (1) B. Table for raw materials other than cells/tissues

Table Composition of medium for culture of XX cells

Name of ingredient		Quantity	Approval number/specifications, etc.[*1]	Supplier
XX minimal essential medium			Product name XXX Manufacturer's specifications basically apply See Attached specifications X.	XX Co., Ltd.
Composition[*2]	Amino acid XX	○○ g/L		
	・・・	・・・		
XX serum		○○%	Manufacturer's specifications basically apply, and additionally in-house acceptance tests are performed. See Attached specifications X.	XX Co., Ltd.
○○ growth factor		○○ng/L	Manufacturer's specifications basically apply See Attached specifications X.	XX Co., Ltd.
XX (antimicrobial agent)		○○g/L	Approval number xxxxxxxx Product name XX See Attached specifications X.	XX Co., Ltd.
・・・		・・・	・・・	・・・

*1 For each ingredient, quality control, specifications, etc. should be explained by establishing the attached specifications where appropriate (see Example of description 3).

*2 Medium composition should be provided with reference to Chapter 2, Section 1.2 (1) 2) B. of the Guideline.

*3 Test items, testing methods, etc. appropriate for characteristics of the raw material should be described.

Example of description 3

Section 3.1 (1) B. Specifications for raw material (Part I)

Name of raw material: XX (product of animal origin)

Product name: XX
Manufacturer: XX
Animal species and part of use: XX of XX origin
Country of origin of the animal: XX
Source material: Example of description in Attachment 2 of the "Administrative Handling in response to Partial Amendment of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (PFSB/ELD Notification No. 0520001, PFSB/SD Notification No. 0520001, PFSB/CND Notification No. 0520001, and PFSB/BBPD Notification No. 0520001, dated May 20, 2003, of the Evaluation and Licensing Division, Safety Division, Compliance and Narcotics Division, and Blood and Blood Products Division, Pharmaceutical and Food Safety Bureau, MHLW) should be referred to.

Table Manufacturer's specifications

Test item		Test method	Acceptance criteria
Appearance		Visual	Free from abnormalities
Sterility		XX method	No microbial growth observed
Test for Mycoplasma		XX method	Negative
Virus	XX virus	XX test method	Negative
	XX virus	As per XX	Negative
	・・・	・・・	・・・
・・・		・・・	・・・

Table Acceptance specifications

Test item	Test method	Acceptance criteria
XX test	XX method	○○
・・・	・・・	・・・

Conformity with the Standards for Biological Raw Materials: XX (see Example of description 4)

*1 Acceptance specifications apply to tests performed at receipt of the raw material by a manufacturer of the product proposed for confirmation (acceptance tests) and corresponding acceptance criteria.
*2 Test items, testing methods, etc. appropriate for characteristics of the raw material should be described.

Section 3.1 (1) B. Specifications for raw material (Part II)

Name of raw material: XX (antimicrobial agent)

Product name: XX
Manufacturer: XX
Approval number: XX
If the raw material is manufactured using an ingredient of animal origin, the animal species, part of use, and country of origin should be provided.

Table Manufacturer's specifications

Test item	Specification
pH	○○
Osmolality	○○
・・・	・・・

Table Composition

Ingredient	Quantity	Specification	Remarks
XX salt	○○ g/L	XX Pharmacopoeia	Derived from XX (name of the microorganism)
・・・	・・・	・・・	・・・

* Test items, testing methods, etc. appropriate for characteristics of the raw material should be described.

Example of description 4

Section 3.1 (1) B. 2) Conformity with the Standards for Biological Raw Materials (Part I)

Conformity with the Standards for Biological Raw Materials relating to XX serum

Table Conformity with the Standards for Animal-Derived Raw Materials

Provision in the Standard	Action to meet the provision
・・・	・・・
(2) For the source material, country of origin of the animal and part of use as well as acquisition method of cells or tissues should be clearly described.	(2) Derived from XX of animals born in XX
・・・	・・・

(to use the material derived from a ruminant animal, the following information should be provided in addition to the above)

Table Conformity with the Standards for Ruminant-Derived Raw Materials

Provision in the Standard	Action to meet the provision
・・・	・・・
(3) If a raw material (except milk) derived from a ruminant is used in drugs, the concerned ruminant must have the origin in countries listed below. However, this may not apply to wool, lanolin, or skin-derived gelatin or collagen. If milk is used as a source material, the concerned ruminant must have the origin in countries other than the United Kingdom and Portugal. A. Argentina, B. India, C. Uruguay, D. El Salvador, E. Australia, F. Kenya, G. Costa Rica, H. Colombia, I. Singapore, J. Swaziland, K. Chile, L. Nigeria, M. Namibia, N. Nicaragua, O. New Caledonia...	(3) The country of origin is XX.
・・・	・・・

(For the material containing human plasma derivatives)

Table Conformity with the General Rules for Plasma Derivatives

Provision in the Standard	Action to meet the provision
・・・	・・・
(5) Blood to be used as a raw material of plasma derivatives must be subjected to serological tests for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV-1 and HIV-2) at least. If any of these tests indicates ineligibility, use of such blood must be avoided unless it is stipulated in an official monograph in the Minimum Requirements for Biological Products.	(6) The raw material is confirmed to test negative for HBV, HCV, HIV-1, and HIV-2.
・・・	・・・

* For raw materials other than the above, appropriate standards and guidelines should be selected accordingly, and necessary information should be provided as well.

Section 3.1 (1) B. 2) Conformity with the Standards for Biological Raw Materials (Part II)

Conformity with the Standards for Biological Raw Materials relating to animal cells and tissues

Animal species and part of use: XX of XX origin

Table Conformity with the Standards for Source Materials for Animal Cell/Tissue-based Products

Provision in the Standard	Action to meet the provision
(1) For collection of cells or tissues to be used as a raw material of animal cell/tissue-based products (drugs or medical devices using source materials or ancillary materials of non-human animal origin. Hereinafter, the same definition applies), necessary measures must be taken to prevent contamination with microbial pathogens and other pathogenic agents during the collection process.	(1) For the collection, measures of XX, XX, and XX are taken. For the details, see XX. (see Example 3)
(2) • • •	(2) • • •
(3) For use of living animal cells or tissues, a virus infection risk must be ruled out by tests.	(3) XX tested negative for XX, XX, and XX. For the details, see XX. (see Example 3)
• • •	• • •

(to use 3T3J2 or 3T3NIH cell line as feeder cells, the following information should be provided in addition to the above)

Table Conformity with HPB/RDD Notification No. 0702001, dated July 2, 2004

Provision in the Standard	Action to meet the provision
• • •	• • •
4.1 Quality control of master cells Each transplantation center should implement quality control on master cells as provided in Attachment 1 to rule out infection with pathogens.	4.1 Infection with pathogens is ruled out by the following action status.
Attachment 1 Section 3 (1) Indicator cells such as MRC-5 (human diploid lung cells) and Vero (African green monkey kidney cells) should be incubated with cell lysate followed by observation for cytopathic effect (CPE). Furthermore, chicken, guinea pig, rhesus monkey red blood cell (RBC) agglutination and hemadsorption tests should be performed.	Attachment 1 Section 3 (1) XX tested negative. For the details, see XX.
• • •	• • •

* Standards and guidelines appropriate for the raw material should be selected, and necessary information should be provided.

Example of description 5

Section 3.1 (1) B. 2) Viral clearance studies

Table Results of viral clearance studies for XX (name of ingredient) of human or animal origin

		"Model" viruses				Conditions in detail	
		XX virus	・・	・・	・・	Commercial process	Clearance study
Assay method		Infectivity assay $TCID_{50}$ assay	**	**	**		
Detection sensitivity		1 infectious particle	**	**	**		
Steps to inactivate/remove viruses	Heat treatment	>○	**	**	**	X ± Y°C, Y hours	X ± Y°C, X hours
	Nano-filtration	>○	**	**	**	X nm, ・・	X nm, ・・
Overall reduction factor		>○	**	**	**		

* Test items, testing methods, etc. appropriate for characteristics of the raw material should be described.

Example of description 6

Section 3.1 (2) A. Flow diagram of each step of the manufacturing process

Step for XX cell culture 1 (primary culture)

Objective: Primary culture
Culture method: Cells are incubated in X mL of a medium using a XX-mL culture flask.
Medium: Medium for primary culture
Operating condition: Cells are inoculated at $X \times Y^Z$ cells per flask and then incubated at X°C for X days with the cultured medium replaced with fresh one every X days

In-process control test 3:

1) Cell density
   Acceptance limit: Not less than $X \times Y^Z$ cells/mL
2) Cell viability
   Acceptance limit: Not less than Y%
3) ・・・

* Information appropriate for characteristics of the registration material should be provided.

Example of description 7

Section 3.1 (2) A. 1) List of data for consistency and justification of the manufacturing method of registration material using cells as a main ingredient

Table Consistency of manufacturing method

		Batch number, manufacturing number, etc.				
		Lot. a	Lot. b	Lot. c	・・	Lot. x
Manufacturing scale		X pieces	X pieces	X pieces	・・	X pieces
Date of manufacture		MM DD, YYYY	MM DD, YYYY	MM DD, YYYY	・・	MM DD, YYYY
In-process control tests	Cell count	○×△◇	○×△◇	○×△◇	・・	○×△◇
	・・				・・	
Specifications and testing methods	Cell count	○×△◇	○×△◇	○×△◇	・・	○×△◇
	Identification				・・	
	・・				・・	
Other characteristics	・・				・・	

* Test items appropriate for characteristics of the registration material should be provided.

Example of description 8

Section 3.1 (2) B. List of in-process control tests

Step	Test item	Test specimen	Testing method	Acceptance criteria	Remarks
In-process control test 1	XX test	XX fluid	XX test	Perform XX: the amount of XX is X.	For details, see XX.
	XX count assay	X mL from Step X.	XX method	Not less than XX	For details, see XX.
	XX test	・・・	XX test	Negative	For details, see XX.
	・・・	・・・	・・・	・・・	・・・
In-process control test X	Test for absence of XX	XX fluid	XX test method in the JP	Conforming	For details, see XX.
	XX rate assay	○○	XX method	Not less than X%	For details, see XX.
	・・・	・・・	・・・	・・・	・・・

* Test items, testing methods, etc. appropriate for characteristics of the registration material should be described.

Example of description 9

Section 3.1 (3) List of characterization results of processed cells

Step X

Characterization item	Specimen	Testing method	Results	Remarks
Cell count	Intermediate in Step X	Cells in a hemocytometer are counted under XX microscope.	Lot. a:○×△◇ Lot. b: Lot. c:	For details, see XX.
Cell viability	Intermediate in Step X	XX-stained cells in a hemocytometer are counted under XX microscope.	Lot. a:○% Lot. b:・ Lot. c:	For details, see XX.
Percent content of XX cells	Intermediate in Step X	XX-immunostained cells in a hemocytometer are counted under XX microscope.	Lot. a:○% Lot. b: Lot. c:	For details, see XX.
Cytomorphologic characteristics	Intermediate in Step X	Cells are observed under XX microscope.	Lot. a: Cytomorphology characteristic of Type X is observed. Lot. b: Lot. c:	For details, see XX.
Proliferation rate	Intermediate in Step X	The rate is calculated from cell counts at Steps X and Y.	Lot. a: X times Lot. b: Lot. c:	For details, see XX.
Production capability of XX	Cell culture supernatant at Step X	Specimens of cell culture supernatant are subjected to ELISA.	Lot. a:○ ng/mL Lot. b: Lot. c:	For details, see XX.
Barrier function	Final product	XX method	Lot. a:○○ Lot. b: Lot. c:	For details, see XX.

* Test items, testing methods, etc. appropriate for characteristics of the registration material should be described.

Example of description 10

Section 3.1 (3) Characterization results of processed cells (for impurities in the product)

Table Process-related impurities remaining in the product

Process-related impurity	Assay method	Residual amount/dose
XX serum albumin	X method	Lot. a: Y not more than X ng Lot. b: Lot. c:
XX (antimicrobial agent)	X method	Lot. a: Y not more than X μg Lot. b: Lot. c:
. . .	. . .	. . .
. . .	. . .	. . .

* Test items, testing methods, etc. appropriate for characteristics of the registration material should be described.

Example of description 11

Section 3.2 (1) List of specifications and testing methods

List of specifications and testing methods

Test item	Testing method	Test specimen	Acceptance limit/criteria
Cell purity	Flow cytometry	Cell suspension prepared from 1 product unit randomly withdrawn from 1 lot of the final product	CDX-positive, CDY-negative cells not less than X%
Secretion of X (humoral factor)	ELISA	Cell culture supernatant at the end of culture	≥○ ng/mL
・・・	・・・	・・・	・・・
・・・	・・・	・・・	・・・

* Time when the result becomes available should be provided where appropriate.
* Test items, testing methods, etc. appropriate for characteristics of the registration material should be described.

Example of description 12

Section 3.2 (3) List of analysis results of products subjected to tests

	Batch number, manufacturing number, etc.				
	Lot. a	Lot. b	Lot. c	・・	Lot. x
Manufacturing scale	X pieces	X pieces	X pieces	・・	X pieces
Date of manufacture	MM DD, YYYY	MM DD, YYYY	MM DD, YYYY	・・	MM DD, YYYY
Manufacturing site				・・	
Manufacturing method	Process X	Process X	Process X	・・	Process X
Cell count					
Identification					
・・					

* Test items, testing methods, etc. appropriate for characteristics of the registration material should be described.

Example of description 13

Section 3.5 List of information on safety

Test item	Specimen	Study system	Application method	Results	Remarks
Single-dose toxicity	Registration material X	XX animals	Cells at X/mL are intravenously administered at a rate of X mL/min.	Toxicological findings were obtained in X animals in the dose group on Day X.	For details, see XX.
. . .	. . .	. . .	. . .	. . .	. . .
. . .	. . .	. . .	. . .	. . .	. . .

* Test items, testing methods, etc. appropriate for characteristics of the registration material should be described.