Version of March 26, 2025

Guideline for Preparation of Attached Data and Overviews for Applications for Approval of Regenerative Medical Products

Module 2.3 Quality Overall Summary

The Quality Overall Summary (hereinafter referred to as "QOS") summarizes the data in Module 3 "Quality" according to its scope and structure. The QOS should not contain matters, data or discussion that are not included elsewhere in Module 3 or the attached data.

The QOS should include sufficient content for each section to give the quality reviewer an overall picture of Module 3. The QOS should clarify important matters of the proposed regenerative medical products and justify the data and documents prepared, without reference to the existing guidelines. The QOS should include discussion on key issues that integrates information from sections in the Quality Module (Module 3) and supporting information from other Modules (Modules 4 and 5) (e.g. characterization of primary efficacy or performance, tumorigenicity, etc. described in the nonclinical sections), including cross-referencing to volume and page number in other Modules.

The underlined figures, numerical values, etc. in the QOS text may be directly cited from those in Module 3.

The guideline for preparation of data on cell processed products is provided as follows. For regenerative medical products, all the sections may not be necessarily applicable depending on the manufacturing method or shape of the final product. In such cases, the non-applicability should be determined on a case-by-case basis and explained. For gene therapy products, the data should be prepared as instructed in Appendix 3 "Guideline for Preparation of the Data in Modules 2.3 and 3 to be Attached to the Approval Application Forms" (hereinafter referred to as "Guideline for Preparation of CTD-Quality Data") of the "Guideline on Preparing Data Attached to Application Form for Approval Application of Manufacture or Import of a New Pharmaceutical" (PMSB/ELD Notification No. 899, dated June 13, 2001, by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHLW). However, the following contents should be prepared with reference to this guideline for preparation: the description on starting materials (plasmids and cell banks) in Section 3.2.S.2.3 [Viral vector(s)], description on conformity status with the Standards for Biological Raw Materials in Section 3.2.A.2, description on sub-ingredients in Section 3.2.A.3, and data on sub-components.

[Section Configuration]

For preparation of application data for cell processed products, the "Points to Consider for Applications for Marketing Approval of Regenerative Medical Products" (PFSB/ELD/OMDE/CMS Notification No. 0812-5, dated August 12, 2014) should always be referred to. The relevant notification indicates what content should be included in the application data, and the application data that include all the contents as indicated in the notification, if applicable, would be acceptable. An example of the section configuration of the data in CTD format is provided below but it may not always need to be followed, because the notification does not specify a particular format.

[1] Section Configuration of Modules S and P

In the manufacturing process of cell processed products, the final product is manufactured in a series of steps starting with cell collection. There are some cases where the manufacturing process of a cell processed product cannot be clearly divided into the process for the drug substance and one for the product, unlike the manufacturing process of general drugs. In CTD format, Modules S and P have sections of the

overlapping contents. In such cases, either of the overlapping sections should include the content, and the other should be provided with reference to the above section. For example, the specifications may be described in Section 2.3.P.5 (3.2.P.5) [Product], and Section 2.3.S.4 (3.2.S.4) [Constitutive Cells or Tissues] may be provided with reference to Section 2.3.P.5 (3.2.P.5) [Product].

Alternatively, if one of the overlapping sections includes the data, the rest may be simply omitted. However, the section numbers subject to omission should be just left missing to keep all the section numbers unchanged, because the content in a section should preferably correspond to the section number generally used in CTD format.

An example of combinations of sections that may be omitted and their referenced sections is shown in Table 1. For example, Sections S.4, S.6, and S.7 may be omitted by referring to P.5, P.7, and P.8, respectively, in the prepared data. Some cell processed products may not have the reference materials. In such cases, Sections S.5 and P.6 may have a statement such as "No reference materials have been established."

Of note, data in the sections may be divided into Modules S and P if such section structures improve organization of the data and are convenient for the persons who are preparing the data for development.

Table 1 Combinations of sections that may be omitted and their referenced sections

Section that may be omitted	Referenced sections
S.4 Control of Constitutive Cells or Tissues	P.5 Control of Product
S.5 Reference Standards or Materials	-
S.6 Container Closure System	P.7 Container Closure System
S.7 Stability	P.8 Stability
P.2.2.3 Physicochemical and biological properties	S.1.2 History and Characterisation of Cells Used as the Origin of Constitutive Cells S.1.3 General Properties of Constitutive Cells S.3.1 Characteristics of Constitutive Cells
P.2.3 Manufacturing Process Development	S.2.6 Manufacturing Process Development
P.3.1 Manufacturer(s)	S.2.1 Manufacturer(s)
P.3.3 Description of Manufacturing Process and Process Controls	S.2.2 Description of Manufacturing Process and Process Controls
P.3.4 Controls of Critical Steps and Intermediates	S.2.4 Controls of Critical Steps and Intermediates
P.3.5 Process Validation and/or Evaluation	S.2.5 Process Validation and/or Evaluation
P.5.5 Characterisation of Impurities	S.3.2 Unintended Cellular and Process-related Impurities
P.6 Reference Standards or Materials	-

[2] Section Configuration for *ex vivo* Gene Therapy Products

Some *ex vivo* gene therapy products are designed to genetically modify constitutive cells using recombinant viral vector(s). Because viral vector(s) used for genetic modification are critical intermediates in the quality control of the final product, they require control equivalent to that for drug substances of biopharmaceuticals, and the manufacturing method, specifications as well as stability are all subject to review. The quality control of viral vector(s) should be detailed in a separate Module S. Quality control of constituent cells should be described as instructed in [1].

That is, the section configuration for *ex vivo* gene therapy products is assumed to be as shown in Table 2 below.

Of note, Section 2.3.A may include information on both viral vector(s) and cells.

Table 2 Example of section configuration for *ex vivo* gene therapy products

Module	2.3 (3.2).S VIRAL VECTOR(S)
	2.3 (3.2).S CONSTITUTIVE CELLS OR TISSUES
	2.3 (3.2).P PRODUCT
	2.3 (3.2).A APPENDICES

[3] Section configuration for products using multiple main components

Of cell processed products, which vary in composition, some may have multiple ingredients corresponding to the main components. One example is a CAR-T cell product comprised of a CD4-positive cell product and a CD8-positive cell product, which are packaged together as the main components and are both administered to patients. CTD for such products may possibly have Sections 2.3 (3.2).S [Constitutive Cells or Tissues] and 2.3 (3.2).P [Product] for each main component (Table 3) or Sections 2.3 (3.2).S [Constitutive Cells or Tissues] and 2.3 (3.2).P [Product] each including information on both main components (Table 4), but any section configuration may be used according to the convenience for the persons who are preparing the data for development.

If multiple components share information on many aspects, the section configuration should be designed to enable comparisons between the components such as using the same section numbers and including the shared information in one of the overlapping sections and omitting the rest (re-numbering sections should be avoided).

Table 3 Example 1 of Section Configuration with Multiple Main Components

Module	2.3 (3.2).S VIRAL VECTOR(S)
	2.3 (3.2).S CONSTITUTIVE CELLS OR TISSUES (CD4)
	2.3 (3.2).P PRODUCT (CD4)
	2.3 (3.2).S CONSTITUTIVE CELLS OR TISSUES (CD8)
	2.3 (3.2).P PRODUCT (CD8)
	2.3 (3.2).A APPENDICES

Table 4 Example 2 of Section Configuration with Multiple Main Components

Module	2.3 (3.2).S VIRAL VECTOR(S)
	2.3 (3.2).S CONSTITUTIVE CELLS OR TISSUES (CD4 and CD8)
	2.3 (3.2).PRODUCT (CD4 and CD8)
	2.3 (3.2).A APPENDICES

[4] Sections on sub-components

Of cell processed products, which vary in composition, some may include diluents for administration and/or special delivery devices as sub-components. Examples of possibly applicable section configurations for each type of the sub-components are shown below.

i) Preservative fluid used for transporting collected cells or tissues to the manufacturing site and diluents used for administration

For these subcomponents, the same data configuration as that for drugs can cover necessary information, and thus a possible action may be to provide a separate Module P (3.2.P Sub-component). If the manufacturing process is divided into parts for the drug substance and product, and specifications have been separately established for both drug substance and product, the data should be divided into Module S and Module P (i.e., divided into 2 sections of [3.2.S Sub-component] and [3.2.P Sub-component].

ii) Delivery devices

For syringes, autoinjectors, and other devices that also function as containers, information may be included in Section P.7 of the main component, as done in the CTD for drugs. On the other hand, for delivery devices and other devices that are expected to be used as medical devices if distributed alone, a separate Module R should be provided to include the data corresponding to the Summary Technical Document (hereinafter “STED”) specified in the “Points to Consider in Preparing Applications for Medical Devices” (PFSB/ELD/OMDE/CMS Notification No. 0120-9, dated January 20, 2015).

[5] Products with critical intermediates controlled by the specifications as with the drug substance

For some cell processed products, a portion of the in-process material is frozen for long-term cryopreservation as a critical intermediate or is used to establish the specifications to control critical quality attributes. Quality control of such critical intermediates can be described in Section 2.3.S.2.4 (3.2.S.2.4) [Constitutive Cells or Tissues]. Of note, the specifications, container closure system, and stability of the critical intermediate may be included in Sections 2.3.S.4 (3.2.S.4) [Constitutive Cells or Tissues], 2.3.S.6 (3.2.S.6) [Constitutive Cells or Tissues], and 2.3.S.7 (3.2.S.7) [Constitutive Cells or Tissues] if such disposition is convenient for the persons who are preparing the data for development. In this case, however, which section includes which information should be clarified.

[6] Matters closely related to nonclinical safety evaluation

Some quality control matters of cell processed products are required to be explained from the viewpoint of nonclinical safety evaluation. For example, the following matters may be included in the relevant Quality sections (Modules 2 and 3) or in the Nonclinical safety data (Section 2.6.6).

- Safety evaluation of process-related impurities (2.3.S.2 (3.2.S.2) [Constitutive Cells or Tissues])
- Safety evaluation of sub-ingredients (2.3.A.3 (3.2.A.3))
- Gene insertion site analysis of viral vector(s) in *ex vivo* gene therapy products (2.3.S.3 (3.2.S.3) [Constitutive Cells or Tissues])

[7] Matters related to preparation at medical institutions

Many cell processed products are delivered to medical institutions in a frozen state, thawed at the time of administration, and administered using infusion sets or the like. Depending on the product, preparation operations such as washing may be performed at a medical institution. An outline of the operations and temperature control performed at medical institutions should be included in Section 2.3.P.2.6 (3.2.P.2.6) [Product]. In addition, the following matters to justify these operations should be included in Section 2.3.P.2.6 (3.2.P.2.6) [Product] as well. Information on in-use stability testing may be included in Section 2.3.P.8 (3.2.P.8) [Product]. If a separate Module R has been established for the delivery device, an appropriate place in the Module R should have a statement to the effect that results from compatibility studies with the device (infusion set, delivery device, etc.) are included in Section 2.3.P.2.6 (3.2.P.2.6) [Product].

- Results from compatibility studies of devices for administration of the product (infusion set, delivery device, etc.) conducted under conditions simulating use of the product in post-marketing settings
- Outline of in-use stability testing and the results

In view of the basic concept concerning section configuration above, information to be explained in each section is described below. The following instructs preparation of the CTD data for an assumed *ex vivo* gene therapy product with sub-components, which requires the largest number of sections, but the section configuration may be established as appropriate for the intended product (for a product without sub-components, sections for sub-components may be unnecessary, for a product without gene transfer via viral vector(s), Module S for viral vector(s) may be unnecessary, etc.).

2.1 Table of Contents

The Table of Contents section details the tables of contents in Modules 2 to 5. Attachments may be omitted.

2.2 Introduction

The introduction should include the brand name, non-proprietary name of the constitutive cells, company name, final form(s), content(s), route of administration, and proposed indication(s).

2.3 Quality Overall Summary

2.3.S Viral vector(s) (name, manufacturer)

2.3.S.1 General Information (name, manufacturer)

Information from Section 3.2.S.1 [Viral vector(s)] should be included.

2.3.S.2 Manufacture (name, manufacturer)

Information from Section 3.2.S.2 [Viral vector(s)] should be included with the following matters taken into account.

- Information on the manufacturer;
- A brief description of the manufacturing process (including descriptions on starting materials, critical steps, and reprocessing) and the controls that are intended to result in the consistent production of viral vector(s) of appropriate quality;
- A flow diagram, as provided in Section 3.2.S.2.2 [Viral vector(s)];
- A description of the starting materials and raw materials of biological origin used in the manufacture of the viral vector(s), as described in Section 3.2.S.2.3 [Viral vector(s)];
- A discussion of the selection and justification of critical steps, process controls, and acceptance criteria. Especially, critical intermediates should be included, as described in Section 3.2.S.2.4 [Viral vector(s)];
- A description of process validation and/or evaluation, as described in Section 3.2.S.2.5 [Viral vector(s)]; and
- A brief summary of major changes made to the manufacturing method throughout development and conclusions from the assessment used to evaluate product comparability, as described in Section 3.2.S.2.6 [Viral vector(s)] The QOS should also cross-refer to the nonclinical and clinical studies that used post-change batches, as provided in the modules and sections for non-clinical study reports and clinical study reports in the application data.

2.3.S.3 Characterisation of Viral Vector(s) (name, manufacturer)

A description of the intended product and product-related substances and a summary of general properties, characteristic features, and characterization data (tests on viral vector(s) and characterization of the product constitutive cells genetically modified via viral vector(s)) as described in Section 3.2.S.3.1 [Viral vector(s)], should be included. The QOS should compare the impurity levels in batches used in the nonclinical and clinical studies with those in typical batches manufactured by the proposed commercial process and discuss the results. The specified acceptance limits for process-related impurities should be justified.

A tabulated summary of the data provided in Section 3.2.S.3.2 should be included. Graphical representation, where appropriate, should be included.

2.3.S.4 Control of Viral Vector(s) (name, manufacturer)

A brief summary of the justification of the specifications, analytical procedures, and validation of the analytical procedures should be included.

Specifications from Section 3.2.S.4.1 [Viral vector(s)] should be provided.

A tabulated summary of the batch analyses from Section 3.2.S.4.4 [Viral vector(s)] should be included. Graphical representation, where appropriate, should be included.

2.3.S.5 Reference Standards or Materials (name, manufacturer)

Information from Section 3.2.S.5 [Viral vector(s)] (tabulated presentation, where appropriate) should be included. If no reference standards or materials are established, a statement to this effect should be included.

2.3.S.6 Container Closure System (name, manufacturer)

A brief description and discussion of the information from Section 3.2.S.6 [Viral vector(s)] should be included.

2.3.S.7 Stability (name, manufacturer)

A summary of the studies conducted (conditions, batches, test methods) and a brief discussion of the results and conclusions, the storage conditions, and shelf life, where relevant, as described in Section 3.2.S.7.1 [Viral vector(s)], should be included.

The post-approval stability protocol, as described in Section 3.2.S.7.2 [Viral vector(s)], should be included.

A tabulated summary of the stability results from Section 3.2.S.7.3 [Viral vector(s)] should be provided. Graphical representation, where appropriate, should be included.

2.3.S Constitutive Cells or Tissues (name, manufacturer)

2.3.S.1 General Information (name, manufacturer)

Information from Section 3.2.S.1 [Constitutive Cells or Tissues] should be included.

2.3.S.2 Manufacture (name, manufacturer)

Information from Section 3.2.S.2 [Constitutive Cells or Tissues] should be included with the following matters taken into account.

- Information on the manufacturer;
- A brief description of the manufacturing process (including descriptions on starting cells or tissues, critical steps, and reprocessing) and the controls that are intended to result in the consistent production of cells or tissues of appropriate quality;
- A flow diagram, as provided in Section 3.2.S.2.2 [Constitutive Cells or Tissues];
- A description of the starting cells or tissues and raw materials of biological origin used in the manufacture of the constitutive cells or tissues, as described in Section 3.2.S.2.3 [Constitutive Cells or Tissues];
- A discussion of the selection and justification of critical steps, process controls, and acceptance criteria. Especially, critical intermediates should be included, as described in Section 3.2.S.2.4 [Constitutive Cells or Tissues];
- A description of process validation (verification) and/or evaluation, as described in Section 3.2.S.2.5 [Constitutive Cells or Tissues]; and
- A brief summary of major changes made to the manufacturing method throughout development and conclusions from the assessment used to evaluate product comparability, as described in Section 3.2.S.2.6 [Constitutive Cells or Tissues]. The QOS should also cross-refer to the nonclinical and clinical studies that used post-change batches, as provided in the modules and sections for non-clinical study reports and clinical study reports in the application data.
- A description of safety evaluation of process-related impurities

2.3.S.3 Characterisation of Constitutive Cells or Tissues (name, manufacturer)

A description of the intended cells and a summary of general properties, characteristic features, and characterization data (cell population and biological activity), as described in Section 3.2.S.3.1 [Constitutive Cells or Tissues], should be included. The QOS should summarize the data on unintended cells and the basis for setting the acceptance criteria for percent contents of individual unintended cells. The QOS should compare the unintended cell populations in batches used in the nonclinical and clinical studies with those in typical production batches manufactured by the proposed commercial process and discuss the results, if the manufacturing scales differ. The specified acceptance limits for intended cells/unintended cells should be justified. The specified acceptance limits for process-related impurities should be justified.

A tabulated summary of the data provided in 3.2.S.3.2 [Constitutive Cells or Tissues] should be included. Graphical representation, where appropriate, should be included.

2.3.S.4 Control of Constitutive Cells or Tissues (name, manufacturer)

A brief summary of the justification of the specifications, analytical procedures, and validation of the analytical procedures should be included. This section may be omitted if the equivalent description is provided in Section 2.3.P.5 [Product].

Specifications from Section 3.2.S.4.1 [Constitutive Cells or Tissues] should be provided.

A tabulated summary of the batch analyses from Section 3.2.S.4.4 [Constitutive Cells or Tissues] should be included. Graphical representation, where appropriate, should be included. For a product that has been used in less than 10 subjects in clinical trials, all the manufacturing results of the investigational product should be included in this section.

2.3.S.5 Reference Standards or Materials (name, manufacturer)

Information from Section 3.2.S.5 [Constitutive Cells or Tissues] (tabulated presentation, where appropriate) should be included. If no reference standards or materials are established, a statement to this effect should be included.

2.3.S.6 Container Closure System (name, manufacturer)

A brief description and discussion of the information from Section 3.2.S.6 [Constitutive Cells or Tissues] should be included. This section may be omitted if the equivalent description is provided in Section 2.3.P.7 [Product].

2.3.S.7 Stability (name, manufacturer)

A summary of the studies conducted (conditions, batches, test methods) and a brief discussion of the results and conclusions, the storage conditions, and shelf life, where relevant, as described in Section 3.2.S.7.1 [Constitutive Cells or Tissues], should be included.

The post-approval stability protocol, as described in Section 3.2.S.7.2 [Constitutive Cells or Tissues], should be included.

A tabulated summary of the stability results from Section 3.2.S.7.3 [Constitutive Cells or Tissues] should be provided. Graphical representation, where appropriate, should be included.

Both sections above may be omitted if the equivalent description is provided in Section 2.3.P.8 [Product].

2.3.P PRODUCT (NAME, DOSAGE FORM or FINAL FORM)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form or final form)

Information from Section 3.2.P.1 [Product] should be provided.

Composition from Section 3.2.P.1 [Product] should be provided.

2.3.P.2 Product Development (name, dosage form or final form)

A discussion of the information and data from Section 3.2.P.2 should be presented. A tabulated summary of the compositions of formulations used in clinical studies should be provided, as necessary. Of note, Sections 2.3.P.2.2.3 [Product] as well as 2.3.P.2.3 [Product] may be omitted if the equivalent descriptions are provided in Sections 2.3.S.1.2 [Constitutive Cells or Tissues], 2.3.S.1.3 [Constitutive Cells or Tissues], and 2.3.S.3.1 [Constitutive Cells or Tissues] as well as 2.3.S.2.6 [Constitutive Cells or Tissues], respectively.

2.3.P.3 Manufacture (name, dosage form or final form)

Information on the following matters from Section 3.2.P.3 [Product] should be included. The content other than that in Section 2.3.P.3.2 [Product] may be omitted if it is included in Section 2.3.S.2 [Constitutive Cells or Tissues].

- Information on the manufacturer;
- Batch formula;
- A brief description of the manufacturing process and the controls that are intended to result in the consistent production of product of appropriate quality;
- A flow diagram, as provided in Section 3.2.P.3.3 [Product];
- Control of critical intermediates; and
- A description of process validation (verification) and/or evaluation, as described in Section 3.2.P.3.5 [Product].

2.3.P.4 Control of Sub-ingredients (name, dosage form)

A brief summary on the quality of sub-ingredients, as described in Section 3.2.P.4 [Product], should be included.

2.3.P.5 Control of Product (name, dosage form or final form)

A brief summary of the justification of the specifications as well as a summary of analytical procedures, validation of the analytical procedures, and characterization of impurities (for example, residual raw materials such as antibiotics) should be provided.

Specifications from Section 3.2.P.5.1 [Product] should be provided.

A tabulated summary of the batch analyses from Section 3.2.P.5.4 [Product] should be included. Graphical representation, where appropriate, should be included. For a product that has been used in less

than 10 subjects in clinical trials, all the manufacturing results of the investigational product should be included in this section.

2.3.P.6 Reference Standards or Materials (name, dosage form or final form)

Information from Section 3.2.P.6 [Product] (tabulated presentation, where appropriate) should be included. If no reference standards or materials are established, a statement to this effect should be included.

2.3.P.7 Container closure system (name, dosage form or final form)

A brief description and discussion of the information from Section 3.2.P.7 [Product] should be included.

2.3.P.8 Stability (name, dosage form or final form)

A summary of the studies conducted (conditions, batches, test methods) as well as a brief discussion and conclusions about the results from the studies and data analyses should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf life should be given.

A tabulated summary of the stability results from Section 3.2.P.8.3 [Product] should be included. Graphical representation, where appropriate, should be included.

The post-approval stability protocol, as described in Section 3.2.P.8.2 [Product], should be included.

2.3.P Sub-components (name, dosage form or final form)

In this section, quality control of sub-components such as preservative fluid used for transporting collected cells or tissues to the manufacturing site and diluents used for administration should be described. On the other hand, for delivery devices and other devices that are expected to be used as medical devices if distributed alone, the data should be included in Module R shown below.

2.3.P.1 Description and Composition of Sub-components (name, dosage form or final form)

Information from Section 3.2.P.1 [Sub-component(s)] should be provided.

Composition from Section 3.2.P.1 [Sub-component(s)] should be provided.

2.3.P.2 Sub-component Development (name, dosage form or final form)

A discussion of the information and data from Section 3.2.P.2 [Sub-component(s)] should be presented.

A tabulated summary of the compositions of formulations used in clinical studies should be provided, as necessary.

2.3.P.3 Manufacture (name, dosage form or final form)

Information on the following matters from Section 3.2.P.3 [Sub-component(s)] should be included.

- Information on the manufacturer;
- A brief description of the manufacturing process and the controls that are intended to result in the consistent production of sub-components of appropriate quality;
- A flow diagram, as provided in Section 3.2.P.3.3 [Sub-component(s)]; and
- A description of process validation and/or evaluation, as described in Section 3.2.P.3.5 [Sub-component(s)].

2.3.P.4 Control of Sub-ingredients of Sub-components (name, dosage form)

A brief summary on the quality of sub-ingredients, as described in Section 3.2.P.4 [Sub-component(s)], should be included.

2.3.P.5 Control of Sub-components (name, dosage form or final form)

A brief summary of the justification of the specifications as well as a summary of analytical procedures, validation of the analytical procedures, and characterization of impurities should be provided.

Specifications from Section 3.2.P.5.1 [Sub-component(s)] should be provided.

A tabulated summary of the batch analyses from Section 3.2.P.5.4 [Sub-component(s)] should be included. Graphical representation, where appropriate, should be included.

2.3.P.6 Reference Standards or Materials (name, dosage form or final form)

Information from Section 3.2.P.6 [Sub-component(s)] (tabulated presentation, where appropriate) should be included. If no reference standards or materials are established, a statement to this effect should be included.

2.3.P.7 Container closure system (name, dosage form or final form)

A brief description and discussion of the information from Section 3.2.P.7 [Sub-component(s)] should be included.

2.3.P.8 Stability (name, dosage form or final form)

A summary of the studies conducted (conditions, batches, test methods) as well as a brief discussion and conclusions about the results from the studies and data analyses should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf life should be given.

A tabulated summary of the stability results from Section 3.2.P.8.3 [Sub-component(s)] should be included. Graphical representation, where appropriate, should be included.

The post-approval stability protocol, as described in Section 3.2.P.8.2 [Sub-component(s)], should be included.

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (name, manufacturer)

A summary of facility information described in Section 3.2.A.1 should be included.

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

A discussion on measures implemented to control endogenous and adventitious agents in raw materials of the cell processed product and materials used in the manufacture of the product should be included.

Conformity status with the Standards for Biological Raw Materials, as provided in Section 3.2.A.2, should be included.

2.3.A.3 Sub-ingredients

A summary of information described in Section 3.2.A.3 should be included. An outline of safety evaluation of sub-ingredients should be included in this section.

2.3.R REGIONAL INFORMATION

A brief description of the requirements specific to the region, as provided in Section “3.2.R,” should be included, where appropriate.

If a delivery device is used as a sub-component, an independent Module R should be established and provided with the data corresponding to STED. Of note, if results from compatibility studies with the delivery device are included in Section 2.3.P.2.6 (3.2.P.2.6) [Product], an appropriate place in the Module R should have a statement to this effect.

Module 3
Quality
Scope

This guideline is intended to provide guidance on the format of the application data (items and orders) for constitutive cells and the product as well as sub-components as defined in the scope of regenerative medical products. The format specified in this guideline may also be appropriate for other regenerative medical products than the above. The applicants who intend to submit applications for these regenerative medical products should consult with the Pharmaceuticals and Medical Devices Agency (PMDA) to determine the applicability of this guideline.

The text following each section title is intended to be explanatory and illustrative only. The content in each section is prepared based on notifications listed below, but it should be noted that the existing guidelines is not available all the contents. Items listed in the "Body of Data" in this guideline merely indicates where the information should be located. This guideline does not specify the type or extent of required specific data, which should be determined on a case-by-case basis depending on the product.

- Ensuring the Quality and Safety of Drugs, etc. Manufactured from Raw Materials of Human or Animal Origin (PMSB Notification No. 1314, dated December 26, 2000) (hereinafter, "No. 1314")
- Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (autologous cells) (PFSB Notification No. 0208003, dated February 8, 2008) (hereinafter, "Guideline (autologous) of 2008")
- Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (allogeneic cells) (PFSB Notification No. 0912006, dated September 12, 2008) (hereinafter, "Guideline (allogeneic) of 2008")
- Ensuring Quality and Safety of Products Derived from Human Processed Somatic Stem Cell (autologous cells) (PFSB Notification No. 0907-2, dated September 7, 2012) (hereinafter, "Guideline (autologous somatic stem) of 2012")
- Ensuring Quality and Safety of Products Derived from Human Processed Somatic Stem Cell (allogeneic cells) (PFSB Notification No. 0907-3, dated September 7, 2012) (hereinafter, "Guideline (allogeneic somatic stem) of 2012")
- Ensuring Quality and Safety of Products Derived from Human Processed iPS(-like) Cell (autologous cells) (PFSB Notification No. 0907-4, dated September 7, 2012) (hereinafter, "Guideline (autologous iPS) of 2012")
- Ensuring Quality and Safety of Products Derived from Human Processed iPS(-like) Cell (allogeneic cells) (PFSB Notification No. 0907-5, dated September 7, 2012) (hereinafter, "Guideline (allogeneic iPS) of 2012")
- Ensuring Quality and Safety of Products Derived from Human Processed ES Cell (allogeneic cells) (PFSB Notification No. 0907-6, dated September 7, 2012) (hereinafter, "Guideline (ES) of 2012")

3.1 TABLE OF CONTENTS OF MODULE 3

A list of attached data should be prepared.

3.2 BODY OF DATA

3.2.S Viral vector(s) (name, manufacturer)

3.2.S.1 General Information of viral vector(s) (name, manufacturer)

3.2.S.1.1 Nomenclature of viral vector(s) (name, manufacturer)

Information on the nomenclature of the viral vector(s) such as company or laboratory code, if any, should be provided.

3.2.S.1.2 Structure of viral vector(s) (name, manufacturer)

The structure of the viral vector including its capsid, sequence information of the vector genome, and a schematic diagram should be provided, where appropriate.

3.2.S.1.3 General Properties of viral vector(s) (name, manufacturer)

General properties of viral vector(s) should be provided. For replication-incompetent virus vectors, the development of the viral vector design should be described, including explanation about principles of the method for depriving the virus vector of the replication competence.

3.2.S.2 Manufacture of viral vector(s) (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production sites or facilities involved in manufacturing and testing of viral vector(s) (CPC, quality control areas, etc.) should be provided. In addition, a description of the external laboratories that perform virus tests and mycoplasma tests for harvests in the viral vector manufacturing process as well as tests for renewal of cell banks should be included.

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

The applicant should explain the manufacturing method of the viral vector(s).

To adequately describe the manufacturing process and process controls, the following should be included, for example:

<u>Batch(es) and scale</u>

An explanation of the batch numbering system, including information regarding any pooling of unprocessed/unpurified bulks or intermediates and batch size or scale, should be provided.

<u>Cell culture and harvest</u>

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g. cells that are contained in one or more vials of the working cell bank and then used for seeding) up to the last harvesting operation. The diagram should include all steps (i.e., all the unit operations) and critical intermediates, including relevant information in each step (e.g., cell concentration, volume, pH, incubation time, hold time, temperature). Critical steps and critical intermediates for which specifications have been established (e.g., cryopreserved intermediates) (See Section 3.2.S.2.4 [Viral vector(s)]) should be identified.

A description of each step in the flow diagram should be provided, including the scale, media, and other additives (see Section 3.2.S.2.3 [Viral vector(s)]) and process controls (in-process control tests, operational control items, equipment, critical intermediates and their acceptance criteria (See Section 3.2.S.2.4 [Viral vector(s)]), etc.).

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s) up to the step preceding filling of the viral vector(s).

The diagram should include all steps and critical intermediates as well as relevant information in each step (e.g., volume, pH, processing time for critical operations/steps, hold time, temperature, dissolution profile, selection of fractions, storage of intermediates, as applicable). Critical steps and critical intermediates for which specifications have been established (See Section 3.2.S.2.4 [Viral vector(s)]) should be identified.

A description of each step in the flow diagram should be provided, including the scale, buffer, and other reagents (see Section 3.2.S.2.3 [Viral vector(s)]) as well as materials. For materials such as membranes and chromatography resins, information about conditions of use and reuse should also be provided (for validation studies for the reuse and regeneration of columns and membranes, relevant information should be provided in Section 3.2.S.2.5 [Viral vector(s)]). The description should also cover process controls (including in-process tests and operational control items) with acceptance criteria, steps, equipment, and critical intermediates (the relevant information should be provided in Section 3.2.S.2.4 [Viral vector(s)]).

Steps involving reprocessing with criteria for reprocessing of all applicable intermediates or vector(s) should be described (the relevant information should be provided in Section 3.2.S.2.5 [Viral vector(s)]).

Filling, freezing, storage and transportation (shipping)

A description of the filling method of the viral vector(s), process controls (including in-process tests and operational control items), and acceptance criteria should be provided (the relevant information should be provided in Section 3.2.S.2.4 [Viral vector(s)]). The container closure system(s) used for storage of the viral vector(s) (the details should be provided in Section 3.2.S.6 [Viral vector(s)]) as well as storage and transportation (shipping) conditions of the viral vector(s) should be described. If viral vector(s) are transported between manufacturing sites, the outline and results of the transport validation should be provided.

3.2.S.2.3 Control of Raw Materials (name, manufacturer)

Raw materials used in the manufacture of the viral vector(s) (e.g., cell banks, media, medium additives) should be listed, identifying in which step each raw material is used. Information on the quality and control of these raw materials should be provided. Data supporting that the raw materials meet standards appropriate for their intended use (including the clearance or control of bacteria, fungi, viruses, and other adventitious agents) should be provided, as necessary.

Media used in the manufacturing process

For media used in the culture process and preservative fluid used to suspend manufactured viral vector(s), any changes in their composition would need to be reviewed for the impact. The compositions should therefore be either provided in this section and approval application form or registered in the MF, which is then referred to in this section (the MF registration name and registration number should be provided in this section).

Raw materials of human and animal origin

For raw materials of human or animal origin, data on their origin, manufacture, and properties should be included (details on conformity status with the Standards for Biological Raw Materials are provided in Section 3.2.A.2).

Starting materials

Unlike conventional biopharmaceuticals, most viral vector(s) are manufactured starting with transfection of plasmids, expression constructs, into a cell line such as HEK293 cells for each batch. In this case, the starting materials are the cell line and plasmids. For each of the materials, the following information should be included in this section:

[1] Cell line

- History of development of cell banks, i.e., information on procedures and raw materials used in the development process;
- Characterization, specifications/acceptance criteria performed to ensure the quality of the cell bank system (indicator cells and inoculated animals should be provided for *in vitro* [human, bovine, and porcine] virus tests and *in vivo* virus tests, respectively, performed as a part of purity tests, and for virus tests by NAT method, the target viruses to be detected should be provided);
- Stability of the cell banks; and
- Renewal criteria and methods in the cell bank system.

[2] Plasmids

- History of plasmid construction, i.e., information on the constitutive genes of the plasmid and the construction procedure
- Outline of plasmid preparation methods
- Map, elements, and nucleotide sequence of each plasmid
- Outline of test items, test methods, and control standards for plasmids and *E. coli* cell banks

For plasmids, an independent Module S may not need to be established.

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

For critical steps identified in Section 3.2.S.2.2 [Viral vector(s)], characterization and test methods/acceptance criteria (with justification, including experimental data) performed to ensure the process control at the critical steps in the manufacturing process should be provided. Information on the quality and control methods of the critical intermediates should be provided. Stability data supporting storage conditions of the critical intermediates should be provided.

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

Process validation and/or evaluation should be described.

The data should be provided from evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose, to substantiate selection of critical process controls (in-process control tests), and to justify the acceptance criteria in the critical steps (e.g., cell culture, harvesting, purification).

The study plan as well as results, discussion, and conclusions of the study should be described. The test methods (analytical procedures) and corresponding validations should be cross-referenced (e.g., Sections 3.2.S.2.4 [Viral vector(s)] and 3.2.S.4.3 [Viral vector(s)]) or provided as a part of the data justifying the selection of critical process controls and specifications/acceptance criteria.

Process evaluation of aseptic and sterilization processes should be described.

For steps intended to remove or inactivate viral contaminants, if any, the data for viral clearance studies should be provided in Section 3.2.A.2.

Of note, if manufacturing process parameters are classified based on their criticality by QbD approaches, grounds leading to that parameter classification (e.g., outline and results of FMEA analysis as well as rationales for classifying the parameters as a CPP, pCPP, KPP, or other parameter in view of the relevant analysis) should be explained.

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

The developmental history of the manufacturing process, as described in Section 3.2.S.2.2 [Viral vector(s)], should be provided. The description of change(s) made to the manufacture of the viral vector batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. In addition, the relevant information on the constitutive cell batches involved in the changes and manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability testing, nonclinical studies, reference material), should be provided.

The significance of the change should be assessed based on its potential to impact the quality of the viral vector(s) (and/or critical intermediates, if appropriate). For changes that are considered significant, data from comparative analytical testing between the pre- and post-change viral vector batches should be provided to determine the impact on quality of the viral vector. A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the quality of the viral vector(s) and the corresponding product can also include nonclinical and clinical studies (see ““Guideline for Comparability of Human Cell-Processed Products Subject to Changes in Their Manufacturing Process” and Questions and Answers (Qs&As)” (PSB/MDED Notification No. 0329-1, dated March 29, 2024). In such cases, cross-reference to the location of these studies in other modules of the submission should be provided.

3.2.S.3 Characterisation of Viral Vector(s) (name, manufacturer)

3.2.S.3.1 Elucidation of Structural and Other Characteristics (name, manufacturer)

The intended product and product-related substances of the viral vector(s) should be characterized for, where appropriate, the structure, physicochemical properties, biological properties, purity, and impurities. The characterization data (from tests on viral vector(s) and characterization analyses on the product constitutive cells genetically modified via the viral vector(s)) should be detailed.

CQAs of viral vector(s) identified based on results from the characterization analyses and through the development process should be listed.

3.2.S.3.2 Impurities (name, manufacturer)

Information on process-related impurities should be provided For product-related impurities, if any, the analysis results should be provided. For both process-related and product-related impurities, adequate removal through the commercial manufacturing process should be demonstrated (the details may be provided in Section 3.2.S.2.5 [Viral vector(s)]. The explanation about the removal performance should include the outline of test methods for quantifying the impurities, the limit of detection/limit of quantitation, and the antigen coverage of the antibody used to detect HCP). A description of potential development of replication-competent viruses should also be included.

3.2.S.4 Control of Viral Vector(s) (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

Specifications for viral vector(s) should be provided.

3.2.S.4.2 Analytical Procedures (name, manufacturer)

Details of test methods (including methods for checking system suitability) in the specifications for viral vector(s) should be provided. For the test methods that are compliant with those listed in the official compendia outside Japan (USP, EP, etc.), unless harmonized, details should be provided.

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

A description of the analytical validations of test methods (analytical procedures) for viral vector(s), including study results, should be provided.

3.2.S.4.4 Batch Analyses (name, manufacturer)

A description of batches and results of batch analyses should be provided.

3.2.S.4.5 Justification of Specification (name, manufacturer)

Justification for the selected specifications should be provided.

3.2.S.5 Reference Standards or Materials (name, manufacturer)

Information on the reference standards or materials used for specification tests and in-process control tests for viral vector(s) should be provided.

3.2.S.6 Container Closure System (name, manufacturer)

A description of the container closure system(s) should be provided, including the identity of each material that constitutes the primary package. In addition, the specifications of the container closure system(s) should be provided. The specifications should include appearance, description, and identification (and critical dimensions with drawings, where appropriate). Where appropriate, non-compendial test methods should be included with their validation.

For functional secondary packaging components, the additional functions should be described.

The suitability of the container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials with the viral vector(s), including sorption to the container, leaching, and safety of the materials.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

The types of studies conducted, protocols, and results from the studies should be summarized with reference to ICH Q5C (differences between materials and capacity of the sample container and volume of the drug solution subjected to the studies and those specified in Section 3.2.S.6 [Viral vector(s)] should be clarified). Results, for example, from stress studies and accelerated studies should be included. Conclusions on storage conditions and, where appropriate, shelf life should be summarized.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

The post-approval stability protocol and stability commitment should be provided with reference to ICH Q5C.

3.2.S.7.3 Stability Data (name, manufacturer)

Results from the stability testing (e.g., stress studies and accelerated studies) should be presented in an appropriate format, such as a tabular, graphical, or narrative format, with reference to ICH Q5C. The analytical procedures and their validation should also be described.

3.2.S Constitutive Cells or Tissues (name, manufacturer)

3.2.S.1 General Information on Constitutive Cells (name, manufacturer)

3.2.S.1.1 Nomenclature of Constitutive Cells (name, manufacturer)

Information on the nomenclature of constitutive cells should be provided.

The information should include the Recommended International Nonproprietary Name (r-INN), compendial name (if relevant), chemical name(s), company or laboratory code, and other non-proprietary name(s) (national name(s) such as BAN, USAN, and JAN). For regenerative medicine products, the non-proprietary names are determined during the review process, but for ones with the INN, proposing as a tentative name its translated words in katakana according to the translation table in the "Administrative Procedures for Handling Non-proprietary Names of Drugs" (PFSB/ELD Notification No. 0331001, dated March 31, 2006) is recommended.

3.2.S.1.2 History and Characterisation of Cells Used as the Origin of Constitutive Cells (name, manufacturer)

Where appropriate, the origin and characteristics of the cells used as the origin of constitutive cells should be described. For *ex vivo* gene therapy products, the information such as the proviral sequence of the gene to be transferred, the structural diagram of the expressed protein, the amino acid sequence, and the individual constituent domains should be included.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 1 1(1)
Guideline (allogeneic) of 2008 Chapter 2 Section 1 1(1) and (2)[1]
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 1 1(1)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 1 1(1) and (2)[1]
Guideline (autologous iPS) of 2012 Chapter 2 Section 1 1(1)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 1 1(1) and (2)[1]
Guideline (ES) of 2012 Chapter 2 Section 1 1(1) and (2)[1]

3.2.S.1.3 General Properties of Constitutive Cells (name, manufacturer)

General properties of constitutive cells should be provided.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 3
Guideline (allogeneic) of 2008 Chapter 2 Section 2 3
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 3
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 3
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 3
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 3
Guideline (ES) of 2012 Chapter 2 Section 2 3

3.2.S.2 Processing into Constitutive Cells (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production sites or facilities involved in manufacturing and testing of cell processed products (CPC, quality control areas, etc.) should be provided. In addition, a description of the external laboratories that perform tests for renewal of cell banks should be included.

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

The applicant should explain the manufacturing method of the constitutive cells.

To adequately describe the manufacturing process and process controls (usually, information on the process from cell/tissue isolation or thawing of cell banks, etc., through processing such as culture, filling, freezing, and storage up to release conditions), the following should be included, for example:

Batch(es) and scale

An explanation of the batch numbering system, including information regarding any pooling of unprocessed/unpurified bulks or intermediates and batch size or scale, should be provided.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 1
Guideline (allogeneic) of 2008 Chapter 2 Section 2 1
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 1
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 1
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 1
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 1
Guideline (ES) of 2012 Chapter 2 Section 2 1

Processing of cells or tissues

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g., cells or tissues that are morcellated and isolated and then used for inoculation) up to the last harvesting operation. The diagram should include all steps (i.e., all the unit operations) and critical intermediates, including relevant information in each step (e.g., enzyme treatment conditions, cell density, culture environment such as temperature, culture time). Critical steps and critical intermediates for which specifications have been established (e.g., cell banks of constitutive cells, cryopreserved intermediates) (See Section 3.2.S.2.4 [Constitutive Cells or Tissues]) should be identified.

A description of each step in the flow diagram should be provided, including the scale, media, and other additives (see Section 3.2.S.2.3 [Constitutive Cells or Tissues]) and process controls (in-process control tests, operational control items, equipment, critical intermediates and their acceptance criteria (See Section 3.2.S.2.4 [Constitutive Cells or Tissues]), etc.).

Although the starting point of the manufacturing process differs depending on the product, the general concept is as follows. However, the following is only a general concept. If it is difficult to determine the starting point of manufacture, consultation with PMDA is recommended.

[1] Products without established cell banks (autologous somatic cell processed products, etc.)

[2] For products with established cell banks that are expected to be renewed (autologous somatic stem cell processed products, etc.), the starting point of the manufacturing process is when the raw material cells are received at the manufacturing site.

[3] For products with established cell banks that do not require renewal semi-permanently (cell line-derived products, etc.), the starting point of the manufacturing process is when an aliquot of the established cell bank is thawed (if a two-stage cell bank system is used, when an aliquot of the working cell bank is thawed). However, even in this case, a history of development of cell banks, i.e., the information on procedures and raw materials used in the development process, should be provided in Section 2.3.S.2.3 (3.2.S.2.3) [Constitutive Cells or Tissues].

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 2 (3) to (5)
Guideline (allogeneic) of 2008 Chapter 2 Section 2 2 (3) to (6)
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 2 (3) to (5)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 2 (3) to (6)
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 2 (3) to (7)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 2 (3) to (7)
Guideline (ES) of 2012 Chapter 2 Section 2 2 (3) to (6)

Filling, freezing, storage and transportation (shipping)

A description of the filling method of the intermediates or product, process controls (including in-process tests and operational control items), and acceptance criteria should be provided (the relevant information should be provided in Section 3.2.S.2.4 [Constitutive Cells or Tissues]). If an ingredient equivalent to the drug substance is stored, the container closure system(s) used for the storage (the details should be provided in Section 3.2.S.6 [Constitutive Cells or Tissues]) as well as storage and transportation (shipping) conditions should be described.

Reference Guidelines: Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 4 and 5 as well as Chapter 3
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 4 and 5 as well as Chapter 3
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 4 and 5 as well as Chapter 3
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 4 and 5 as well as Chapter 3
Guideline (ES) of 2012 Chapter 2 Section 2 4 and 5 as well as Chapter 3

Batch control and batch release at manufacturers in Japan

If the applicant intends to be exempted from testing and inspection at a manufacturer in Japan based on the "Question and Answer on Testing and Inspection of Regenerative Medical Products" (Administrative Notice, dated May 30, 2024), an explanation should be provided in this section that 4 requirements listed in the relevant administrative notice are met.

In addition, the manufacturing method should be described, including the following contents.

- For the specification tests performed at manufacturing sites outside Japan, a statement to the effect that "the test is performed" should be provided to the applicable places.
- For manufacturing sites in Japan responsible for release judgment, a statement to the effect that the following actions are taken should be provided to the applicable places.
  - ✓ Visually confirm that there are no problems with appearance or shape.
  - ✓ Confirm with the certificate of analysis of the product that the specifications defined in the approval application form are met.

- ✓ Review the records of tests and inspections on the product with the relevant control number performed at the manufacturing site outside Japan and thereby confirm that they have no problems (in addition, for abnormalities and deviations, if any, review the handling and decisions and thereby confirm that they have no problems or doubts). Documentation of this review can be substituted for conduct of the testing and inspections.
- ✓ Because identification tests are not performed at the manufacturing site in Japan, checking the identification number of the product only with labels is not adequate, and thus a control system should be established to trace the manufacturing process starting with collection of tissues or cells and thereby to ensure the traceability.

3.2.S.2.3 Control of Raw Materials (name, manufacturer)

Raw materials used in the manufacture of the constitutive cells (e.g., cells or tissues (including feeder cells), media, medium additives, cell stripping agents, non-cellular ingredients such as scaffolds) should be listed, identifying in which step each raw material is used. Information on the quality and control of these raw materials should be provided. Data supporting that the raw materials meet standards appropriate for their intended use (including the clearance or control of bacteria, fungi, viruses, and other adventitious agents) should be provided, as necessary.

Media used in the manufacturing process

For media used in the culture process and preservative fluid used to suspend the cells, any changes in their composition would need to be reviewed for the impact. The compositions should therefore be either provided in this section and approval application form or registered in the MF, which is then referred to in this section (the MF registration name and registration number should be provided in this section).

Raw materials of human and animal origin

For raw materials of human or animal origin, data on their origin, manufacture, and properties should be included (details on conformity status of each raw material with the Standards for Biological Raw Materials are provided in Section 3.2.A.2).

Origin, history, preparation method, and characteristics of the cell line from which the constitutive cells are derived and the feeder cells used in manufacture

The origin, history, preparation method, and characteristics of the cell line from which the constitutive cells are derived should be described (including the following specific items). The raw materials of human or animal origin used to establish the cell line should be provided. If feeder cells are used in manufacture, equivalent information should be provided.

- Details of interviews and tests for infectious diseases performed during cell donor screening
- Information on cell collection procedures and preservative fluid and containers for the collected cells
- Information on transport of the collected cells to the manufacturing site (transport procedures (air transport, etc.), temperature conditions during transport, maximum transport time, etc.) and the outline and results of the transport validation
- Acceptance tests and acceptance criteria for cells received at the manufacturing site (which may be provided in Section 3.2.S.2.2 [Constitutive Cells or Tissues] or 3.2.S.2.4 [Constitutive Cells or Tissues] as the information on in-process tests)
- For products with established cell banks, the following information about the cell banks:
  - ➢ History of development of cell banks, i.e., information on procedures and raw materials used in the development process;
  - ➢ Characterization, specifications/acceptance criteria performed to ensure the quality of the cell bank system
  - ➢ Stability of the cell banks; and

➢ Renewal criteria and methods in the cell bank system.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 1 2 (1)[7] Section 2 2 (5) and 3
Guideline (allogeneic) of 2008 Chapter 2 Section 1 2 (1)[7] Section 2 2 (5) (6) and 3
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 1 2 (1)[4] Section 2 2 (5) and 3
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 1 2 (1)[4] Section 2 2 (6) and 3
Guideline (autologous iPS) of 2012 Chapter 2 Section 1 2 (1)[4][8] 3 to 5 Section 2 2 (4) (5) (7) and 3
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 1 2 (1)[4][8] 3 to 5 Section 2 2 (4) (5) (7) and 3
Guideline (ES) of 2012 Chapter 2 Section 1 2 (1)[4] 3 to 5 Section 2 2 (2) to (4) (6) and 3

Quality control of apheresis product for autologous CAR-T cell product

The quality of apheresis product use as raw material cells for an autologous CAR-T cell product depends on the performance of the apheresis device used. A list of the apheresis device and other apparatuses (apheresis device, tubes, and accessories) should be provided, including use results during clinical trials and ones to be used in post-marketing settings. In addition, for the apheresis device to be used in post-marketing settings, evaluation results should be presented, demonstrating that it is capable of manufacturing the product of appropriate quality from the sample collected from a patient.

Modification of cell properties using genetic engineering techniques

A description of the expression constructs (plasmids, etc.) should be provided with reference to the following guidelines. If viral vector(s) are used to perform genetic modification, a statement "For the details, see Section 3.2.S [Viral vector(s)]" may be presented.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 1 2 (3)
Guideline (allogeneic) of 2008 Chapter 2 Section 1 2 (3)
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 1 2 (3)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 1 2 (3)
Guideline (autologous iPS) of 2012 Chapter 2 Section 1 2 (3) to (7)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 1 2 (3) to (7)
Guideline (ES) of 2012 Chapter 2 Section 1 2 (3)

Combination with non-cellular ingredients

A description of the quality and safety of non-cellular ingredients and the interactions with constitutive cells should be provided with reference to the following guidelines.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 1 2 (2)
Guideline (allogeneic) of 2008 Chapter 2 Section 1 2 (2)
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 1 2 (2)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 1 2 (2)
Guideline (autologous iPS) of 2012 Chapter 2 Section 1 2 (2)

Guideline (allogeneic iPS) of 2012 Chapter 2 Section 1 2 (2)
Guideline (ES) of 2012 Chapter 2 Section 1 2 (2)

Single-use products/materials such as culture bags and filters used in the manufacturing process

For extractables and leachables from single-use products/materials, the type and amount of each compound should be presented, and results from the evaluation performed as done for process-related impurities should be provided. The results provided may be from evaluation on extractables and leachables performed only with a set of the materials assessed as high risk ones in view of the extent and duration of contact with the drug solution, but it should be noted that whether the materials subjected to the evaluation are adequate or not will be determined in the review.

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

For critical steps identified in Section 3.2.S.2.2 [Constitutive Cells or Tissues], characterization and test methods/acceptance criteria (with justification, including experimental data) performed to ensure the process control at these steps in the manufacturing process should be provided. Quality and control methods for critical intermediates (intermediates isolated during the manufacturing process. For example, samples that are cryopreserved during manufacture) should be described. Stability data supporting storage conditions of the critical intermediates should be provided.

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

Process validation and/or evaluation should be described.

The data should be provided from evaluation studies to demonstrate that the manufacturing process (including passage number, culture duration, and removal capacity of impurities) is suitable for its intended purpose, to substantiate selection of critical process controls (in-process control tests), and to justify the criteria for release of the critical intermediates and constitutive cells.

The study plan as well as results, discussion, and conclusions of the study should be described. The test methods (analytical procedures) and corresponding validations should be cross-referenced (e.g., Sections 3.2.S.2.4 [Constitutive Cells or Tissues] and 3.2.S.4.3 [Constitutive Cells or Tissues]) or provided as a part of the data justifying the selection of critical process controls and specifications/acceptance criteria.

Evaluation on aseptic processes should be described.

For steps intended to remove or inactivate viral contaminants, if any, the data for viral clearance studies should be provided in Section 3.2.A.2.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 3, 5 and Section 3 2 (5) to (8)
Guideline (allogeneic) of 2008 Chapter 2 Section 2 3, 5 and Section 3 2 (5) to (8)
Guideline (autologous somatic stem) of 2012 Chapter 2 3, 6 and Section 3 2 (5) to (8)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 3, 6 and Section 3 2 (5) to (8)
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 3, 6 and Section 3 2 (5) to (8)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 3, 6 and Section 3 2 (5) to (8)
Guideline (ES) of 2012 Chapter 2 Section 2 3, 6 and Section 3 2 (5) to (8)

Of note, if manufacturing process parameters are classified based on their criticality by QbD approaches, grounds leading to that parameter classification (e.g., outline and results of FMEA analysis as well as rationales for classifying the parameters as a CPP, pCPP, KPP, or other parameter in view of the relevant analysis) should be explained.

Some cell processed products need to be continuously controlled by verification in post-marketing settings, because the validated status of the manufacturing process cannot be confirmed. For such products, the verification control plan should be provided in this section. The verification control plan should be described, including the verification control items and rationales for their establishment.

Verification control requires preparation of a master plan, which may not need to be included in the CTD (to be checked during the GCTP compliance inspection).

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

The developmental history of the manufacturing process, as described in Section 3.2.S.2.2, should be provided. The description of change(s) made to the manufacture of the constitutive cells batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. In addition, the relevant information on the constitutive cell batches involved in the changes and manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability testing, nonclinical studies, reference material), should be provided.

The significance of the change should be assessed based on its potential to impact the quality of the constitutive cells (and/or critical intermediates, if appropriate). For changes that are considered significant, data from comparative analytical testing between the pre- and post-change constitutive cell batches should be provided to determine the impact on quality of the constitutive cells. A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the quality of the constitutive cells and the corresponding product can also include nonclinical and clinical studies (see ""Guideline for Comparability of Human Cell-Processed Products Subject to Changes in Their Manufacturing Process" and Questions and Answers (Qs&As)" (PSB/MDED Notification No. 0329-1, dated March 29, 2024). In such cases, cross-reference to the location of these studies in other modules of the submission should be provided.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 3 and 6
Guideline (allogeneic) of 2008 Chapter 2 Section 2 3 and 6
Guideline (autologous somatic stem) of 2012 Chapter 2 3 and 7
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 3 and 7
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 3 and 7
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 3 and 7
Guideline (ES) of 2012 Chapter 2 Section 2 3 and 7

3.2.S.3 Characterisation of Constitutive Cells or Tissues (name, manufacturer)

3.2.S.3.1 Characterisation of Constitutive Cells (name, manufacturer)

For the constitutive cells contained in products applied to patients including clinical ones, methods and results of the analyses performed should be described covering, for example, cell purity to check for unintended cell contamination, cell viability, morphological features, growth properties, biochemical indicators, immunological indicators, characteristic produced substances, karyotypes, and other appropriate indicators of genotype or phenotype. Where appropriate, methods and results of functional analyses performed should be described.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 3
Guideline (allogeneic) of 2008 Chapter 2 Section 2 3
Guideline (autologous somatic stem) of 2012 Chapter 2 3
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 3
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 3
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 3
Guideline (ES) of 2012 Chapter 2 Section 2 3

CQAs of constitutive cells identified based on results from the characterization analyses and through the development process should be listed.

3.2.S.3.2 Unintended Cellular and Process-related Impurities (name, manufacturer)

For unintended cells evaluated for contamination based on cell purity in the characterization analyses in Section 3.2.S.3.1 [Constitutive Cells or Tissues], analysis items such as population changes over time should be selected where appropriate, and the analysis results should be provided. For process-related impurities, adequate removal through the commercial manufacturing process should be demonstrated (the details may be provided in Section 3.2.S.2.5 [Constitutive Cells or Tissues]. The explanation about the removal performance should include the outline of test methods for quantifying the impurities and the limit of detection/limit of quantitation). For *ex vivo* gene therapy products designed to modify constitutive cells genetically using viral vector(s), explanation about removal performance of residual viral vector(s) and control of replication-competent viruses should be included.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 3 and Section 3 2(4)(5)
Guideline (allogeneic) of 2008 Chapter 2 Section 2 3 and Section 3 2(4)(5)
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 3 and Section 3 2(4) (5)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 3 and Section 3 2(4) (5)
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 3 and Section 3 2(4)(5)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 3 and Section 3 2(4)(5)
Guideline (ES) of 2012 Chapter 2 Section 2 3 and Section 3 2(4)(5)

In the review of regenerative medical products, safety evaluation results of process-related impurities are checked as a part of the review activities for nonclinical safety. For all the process-related impurities, compound names should be listed in this section. Details of the safety evaluation performed based on the residual amount of each process-related impurity in the final product should be provided. The details of the safety evaluation should include:

[1] Residual amount of each process-related impurity in the final product and human exposure (measured or estimated value); and
[2] An explanation qualifying the residual amount of each process-related impurity calculated in [1] above and human exposure (explanation based on ICH Q3D and M7 guidelines).

3.2.S.4 Control of Constitutive Cells or Tissues (name, manufacturer)

Matters that should be included in Sections 3.2.S.4.1 to 3.2.S.4.5 [Constitutive Cells or Tissues] are provided below, but any of them may be omitted if it is included in Section 3.2.P.5 [Product].

3.2.S.4.1 Specification (name, manufacturer)

Specifications for constitutive cells should be provided.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 3 1 and 2(1) to (4)
Guideline (allogeneic) of 2008 Chapter 2 Section 3 1 and 2(1) to (4)
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 3 1 and 2(1) to (4)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 3 1 and 2(1) to (4)
Guideline (autologous iPS) of 2012 Chapter 2 Section 3 1 and 2(1) to (4)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 3 1 and 2(1) to (4)
Guideline (ES) of 2012 Chapter 2 Section 3 1 and 2(1) to (4)

3.2.S.4.2 Analytical Procedures (name, manufacturer)

Details of test methods (including methods for checking system suitability) in the specifications for constitutive cells should be provided. For the test methods that are compliant with those listed in the official compendia outside Japan (USP, EP, etc.), unless harmonized, details should be provided.

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

A description of the analytical validations of test methods (analytical procedures) for constitutive cells, including study results, should be provided.

3.2.S.4.4 Batch Analyses (name, manufacturer)

A description of batches and results of batch analyses should be provided. If the product is not manufactured on a batch basis, analysis results on the constitutive cells of the clinical product should be provided.

3.2.S.4.5 Justification of Specification (name, manufacturer)

Justification for the selected specifications should be provided.

3.2.S.5 Reference Standards or Materials (name, manufacturer)

Information on the reference standards or materials used for specification tests and in-process control tests for constitutive cells should be provided.

3.2.S.6 Container Closure System (name, manufacturer)

Matters that should be included in this section are provided below, but any of them may be omitted if it is included in Section 3.2.P.7 [Product].

Where appropriate, a description of the container closure system(s) used for storage and transportation of constitutive cells should be provided, including the identity of each material that constitutes the primary package. In addition, the specifications of the container closure system(s) should be provided. The specifications should include appearance, description, and identification (and critical dimensions with drawings, where appropriate). Where appropriate, non-compendial test methods should be included with their validation.

For functional secondary packaging components, the additional functions should be described.

The suitability of the container closure system should be discussed with respect to compatibility of the materials with the constitutive cells, including safety of the materials.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 3
Guideline (allogeneic) of 2008 Chapter 3
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 4 and Chapter 3
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 4 and Chapter 3
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 4 and Chapter 3
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 4 and Chapter 3
Guideline (ES) of 2012 Chapter 2 Section 2 4 and Chapter 3

3.2.S.7 Stability (name, manufacturer)

Matters that should be included in Sections 3.2.S.7.1 to 3.2.S.7.3 [Constitutive Cells or Tissues] are provided below, but any of them may be omitted if it is included in Section 3.2.P.8 [Product].

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

The types of studies conducted, protocols, and results from the studies should be summarized with reference to ICH Q5C (differences between materials and capacity of the sample container and volume of the drug solution subjected to the studies and those specified in Section 3.2.S.6 [Constitutive Cells or Tissues] should be clarified). Results, for example, from stress studies and accelerated studies, if any, should be included. Conclusions on storage conditions and, where appropriate, shelf life should be summarized.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 3
Guideline (allogeneic) of 2008 Chapter 3
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (ES) of 2012 Chapter 2 Section 2 5 and Chapter 3

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

The post-approval stability protocol and stability commitment should be provided with reference to ICH Q5C.

3.2.S.7.3 Stability Data (name, manufacturer)

Results from the stability testing (e.g., stress studies and accelerated studies) should be presented in an appropriate format, such as a tabular, graphical, or narrative format, with reference to ICH Q5C. The analytical procedures and their validation should also be described.

3.2.P PRODUCT (NAME)

3.2.P.1 Composition of the Product (name)

A description of the product and its composition should be provided with reference to ICH Q6B. The information provided should include, for example:

- Dosage form (bag capacity, liquid volume in each bag);

- Quantities of constitutive cells (main ingredient) and sub-ingredients including non-cellular ingredients such as the agent used to suspend constitutive cells and scaffold, that is, a list of all ingredients in the dosage form, their amounts per unit (including overages, if any), functions, and reference quality standards (e.g., compendial monographs or manufacturer's specifications) should be provided; and
- The type of the container closure system used for the product should be provided, where appropriate.

If a sub-ingredient used is a premix product such as a composite electrolyte solution of which composition is not disclosed by the supplier, the MF of the relevant composite electrolyte solution in which the composition is provided should be referred to (the registration name and number of the MF should be provided in this section).

3.2.P.2 Product Development (name)

The Product Development section should include studies conducted during the development to demonstrate that the dosage form, product design and formulation, manufacturing process, container closure system, microbiological attributes, and method of use are appropriate for the intended use. The studies described in this section should be distinguished from routine tests for quality control performed in accordance with the specifications. Additionally, this section should identify and describe the attributes (critical parameters) of the product design, formulation, and commercialization process that can influence batch reproducibility, product performance, and product quality. Supportive data and results from specific studies or published literature can be included within or attached to this section. Additional data (on the product performance) can be referenced to the relevant nonclinical or clinical sections in the application data.

3.2.P.2.1 Components of the Product (name)

3.2.P.2.1.1 Description and Interactions of Constitutive Cells (name)

Key physicochemical characteristics (e.g., description of the tissue, cell size distribution) of the constitutive cells that can influence the product performance should be described and discussed.

Interactions of constitutive cells with non-cellular ingredients listed in Section 3.2.P.1 [Product] should be discussed. For products composed of more than one type of constitutive cells, interactions between different types of the constitutive cells should be discussed.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 1 2 (2) and Section 2 4
Guideline (allogeneic) of 2008 Chapter 2 Section 1 2 (2) and Section 2 4
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 1 2 (2)[1][2] and Section 2 4
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 1 2 (2)[1][2] and Section 2 4
Guideline (autologous iPS) of 2012 Chapter 2 Section 1 2 (2)[1][2] and Section 2 4
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 1 2 (2)[1][2] and Section 2 4
Guideline (ES) of 2012 Chapter 2 Section 1 2 (2)[1][2] and Section 2 4

3.2.P.2.1.2 Characteristics of Sub-ingredients in the Product (name)

For sub-ingredients in the product listed in Section 3.2.P.1 [Product], reasons for their selection, quantities used, and characteristics that can influence the product performance should be discussed relative to their respective functions.

3.2.P.2.2 PRODUCT (NAME)

3.2.P.2.2.1 Formulation Development (name)

A brief summary describing the product development should be provided with the proposed route of administration and regimen taken into account. The differences between clinical formulations/dosage form and the product formulation described in Section 3.2.P.1 [Product] should be discussed, where appropriate. Results from *in vitro* or *in vivo* comparability studies (e.g., characterization) should be discussed where appropriate.

Number of cells filled in autologous cell processed products

In autologous cell processed products, the number of cells manufactured may vary from patient to patient, and the filling strategy may be changed flexibly depending on the number of cells manufactured. In such cases, the filling strategy should be defined, such as how to determine the number of cells per container (e.g., cell bag) according to the number of cells manufactured. For *ex vivo* gene therapy products such as CAR-T cell products, which cell population count (e.g., total cell count including dead cells, total viable cell count, T cell count including dead cells, viable T cell count, total CAR expressing T cell count including dead cells, viable CAR expressing T cell count) will be used to determine the filling quantity should be defined.

3.2.P.2.2.2 Overages of constitutive cells (name)

If overage is inevitable from the viewpoint of cell viability in the product, and the overage of the product formulation is described in Section 3.2.P.1 [Product], the justification should be provided.

3.2.P.2.2.3 Physicochemical and Biological Properties (name)

Matters relating to the product attributes should be described. Of note, data on the constitutive cells may be included. In such cases, cross-reference to the characterization analysis results in Sections 3.2.S.1.2 [Constitutive Cells or Tissues], 3.2.S.1.3 [Constitutive Cells or Tissues], and 3.2.S.3.1 [Constitutive Cells or Tissues] should be provided. Or this section may be omitted if all the data are provided in Sections 3.2.S.1.2 [Constitutive Cells or Tissues], 3.2.S.1.3 [Constitutive Cells or Tissues], 3.2.S.3.1 [Constitutive Cells or Tissues], and elsewhere.

For kit products, the data should be provided for each component.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 3
Guideline (allogeneic) of 2008 Chapter 2 Section 2 3
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 3
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 3
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 3
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 3
Guideline (ES) of 2012 Chapter 2 Section 2 3

3.2.P.2.3 Manufacturing Process Development (name)

The selection and optimization of the manufacturing process described in Section 3.2.P.3.3 [Product], in particular its critical aspects, should be explained. Where appropriate, the method of sterilisation should be explained and justified.

Differences (e.g., formulation changes) between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Section 3.2.P.3.3 [Product] (or 3.2.S.2.2 [Constitutive Cells or Tissues]) that can influence the product attributes should be discussed.

The contents in this section may be omitted if they are provided in Section 3.2.S.2.6 [Constitutive Cells or Tissues].

3.2.P.2.4 Container Closure System (name)

The suitability of the container closure system (see Section 3.2.P.7 [Product]) used for storage, transportation (shipping), and use of the product should be discussed. This discussion should cover, for example, choice of materials, protection from moisture and light, compatibility of the constitutive materials with the product (including sorption to the container and leaching), safety of the constitutive materials, and performance (such as reproducibility of the delivery volume from the container when proposed as a part of the product).

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 4
Guideline (allogeneic) of 2008 Chapter 2 Section 2 4
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 4
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 4
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 4
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 4
Guideline (ES) of 2012 Chapter 2 Section 2 4

Evaluation of Extractables and Leachables from Container and Closure Systems of Product

Because the primary containers are required to be evaluated for extractables and leachables, results from the safety evaluation performed using the same approach as that for process-related impurities, as described in Section 2.3.S.2.3 [Constitutive Cells or Tissues], should be provided.

Transport validation of the product and storage conditions at medical institutions

The storage container and temperature conditions of the product during transport to and after arrival at the medical institution as well as maximum transport time and storage period at the medical institution should be provided. In addition, results from the transport validation and stability studies that support the transport conditions and storage at medical institutions should be presented.

3.2.P.2.5 Microbiological Attributes (name)

Where appropriate, the microbiological attributes of the product should be discussed (e.g., for products containing antimicrobial preservatives, the rationale for the selection and the effectiveness). Because cell processed products are expected to be sterile, the integrity of the container closure system to prevent microbial contamination should be addressed.

3.2.P.2.6 Compatibility (name)

Compatibility of the product with reconstitution diluents or dosage devices (e.g., infusion sets, delivery devices) (e.g., aggregation of constitutive cells in the vehicle, sorption on injection vessels, sterility) as well as outline and results of in-use stability testing should be provided to ensure that appropriate and necessary information is included in the package insert, etc. The presented results of in-use compatibility studies with the devices should include the following contents.

- Whether the studies cover the off-the-shelf devices in Japan mainly in terms of materials or not; and
- Results on specification test items, demonstrating that the drug solution (cell suspension) maintained the quality attributes after administration under conditions simulating use of the product in post-marketing settings (e.g., loss of the cells due to sorption, decrease in potency).

3.2.P.3 Manufacture (name)

3.2.P.3.1 Manufacturer(s) (name)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production sites or facilities involved in manufacturing and testing of cell processed products (CPC, quality control areas, etc.) should be provided. The contents in this section may be omitted if they are provided in Section 3.2.S.2.1 [Constitutive Cells or Tissues].

3.2.P.3.2 Batch Formula (name)

A list of all ingredients used in the manufacturing process of the product and their amounts per batch (including overage, if any) as well as reference quality standards should be provided.

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name)

Matters on the general commercialization process that should be included in this section are provided below, but they may be omitted if they are included in Section 3.2.S.2.2 [Constitutive Cells or Tissues].

A flow diagram should be presented, providing steps in the manufacturing process and showing which step each material enters. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified.

For the manufacturing process including the packaging step, the sequence of the steps and manufacturing scale should be described. In particular, novel processes or technologies and packaging operations that directly affect product quality should be described in detail.

For each step in the manufacturing process, appropriate process parameters such as time and temperature should be identified. Numeric values for the parameters can be presented as an expected target range. The expected target numerical ranges for the critical process parameters should be justified in Section 3.2.P.3.4 [Product].

Proposals for reprocessing of the product should be justified, if any. The data to support this justification should be either included or referenced in this section.

Where appropriate, Section 3.2.A.1 (Facilities and Equipment) should be referred to.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 3 1
Guideline (allogeneic) of 2008 Chapter 2 Section 3 1
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 3 1
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 3 1
Guideline (autologous iPS) of 2012 Chapter 2 Section 3 1
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 3 1
Guideline (ES) of 2012 Chapter 2 Section 3 1

Batch control and batch release at manufacturers in Japan

The same matters as those in Section 3.2.S.2.2 [Constitutive Cells or Tissues] should be described.

3.2.P.3.4 Controls of Critical Steps and Intermediates (name)

For critical steps identified in Section 3.2.P.3.3 [Product], test methods/acceptance criteria (with justification, including experimental data) performed to ensure the process control at these steps in the manufacturing process should be provided. Information on the quality and control methods of the critical intermediates should be provided. Stability data supporting storage conditions of the critical intermediates should be provided.

This section may be omitted if the equivalent description is provided in Section 3.2.S.2.4 [Constitutive Cells or Tissues].

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 3 1
Guideline (allogeneic) of 2008 Chapter 2 Section 3 1
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 3 1
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 3 1
Guideline (autologous iPS) of 2012 Chapter 2 Section 3 1
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 3 1
Guideline (ES) of 2012 Chapter 2 Section 3 1

3.2.P.3.5 Process Validation and/or Evaluation (name)

Description, documentation, and results of the process validation and/or evaluation should be provided for critical steps or critical tests in the manufacturing process (e.g., validation of the filling process).

This section may be omitted if the equivalent description is provided in Section 3.2.S.2.5 [Constitutive Cells or Tissues].

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 3, 5 and Section 3 2 (5) to (8)
Guideline (allogeneic) of 2008 Chapter 2 Section 2 3, 5 and Section 3 2 (5) to (8)
Guideline (autologous somatic stem) of 2012 Chapter 2 3, 6 and Section 3 2 (5) to (8)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 3, 6 and Section 3 2 (5) to (8)
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 3, 6 and Section 3 2 (5) to (8)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 3, 6 and Section 3 2 (5) to (8)
Guideline (ES) of 2012 Chapter 2 Section 2 3, 6 and Section 3 2 (5) to (8)

3.2.P.4 Control of Sub-ingredients (name)

3.2.P.4.1 Specifications (name)

Specifications should be provided for all product sub-ingredients. If they are compliant with specifications in the Japanese official compendia (the Japanese Pharmacopoeia, Minimum Requirements for Biological Products, or Japanese Pharmaceutical Excipients), a statement to that effect should be included.

If a sub-ingredient used is a premix product such as a composite electrolyte solution of which composition is not disclosed by the supplier, the specifications for the composite electrolyte solution should be provided, and appropriateness of the relevant control method should be explained (whether this control method is acceptable or not will be determined in the review). It should be noted that, if the composition is not disclosed by the supplier, the MF in which the composition is provided should be referred to, as described in Section 3.2.P.1 [Product].

3.2.P.4.2 Analytical Procedures (name)

The test methods in the specifications should be provided in detail for all product sub-ingredients unless they are compliant with specifications in the Japanese official compendia (the Japanese Pharmacopoeia, Minimum Requirements for Biological Products, or Japanese Pharmaceutical Excipients). Of note, for the test methods that are compliant with those listed in the official compendia outside Japan (USP, EP, etc.), unless harmonized, details should be provided.

3.2.P.4.3 Validation of Analytical Procedures (name)

A description of the analytical validations of test methods (analytical procedures) for product sub-ingredients, including study results, should be provided.

3.2.P.4.4 Justification of Specification (name)

Justification for the specifications proposed for the product sub-ingredients should be provided, where appropriate.

3.2.P.4.5 Product Sub-ingredients of Human or Animal Origin (name)

For product sub-ingredients of human or animal origin, information on adventitious agents (e.g., origin, specifications, description of the tests performed, viral safety data) should be provided (the details are provided in Section 3.2.A.2).

3.2.P.4.6 Novel Sub-ingredients (name)

Details of the safety evaluation performed based on the content of each sub-ingredient in the final product should be provided. It should be noted that the product sub-ingredients (corresponding to pharmaceutical excipients) to be qualified are, not limited to those outside of the scope of precedent use as pharmaceutical excipients, all the sub-ingredients in the final product.

Even if a sub-ingredient used is a premix product registered in the MF that includes the composition, any ingredient should be subjected to safety evaluation. This section should include the information on names of ingredients contained in the relevant premix product and their contents required for the safety evaluation (assumed maximum amounts, etc.) as well as results from the safety evaluation.

If the above information is all provided in Section 3.2.A.3, it may be omitted.

3.2.P.5 Control of Product (name)

3.2.P.5.1 Specifications (name)

Specifications for the product should be provided.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 3 1 and 2
Guideline (allogeneic) of 2008 Chapter 2 Section 3 1 and 2
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 3 1 and 2
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 3 1 and 2
Guideline (autologous iPS) of 2012 Chapter 2 Section 3 1 and 2
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 3 1 and 2
Guideline (ES) of 2012 Chapter 2 Section 3 1 and 2

3.2.P.5.2 Analytical Procedures (name)

Details of test methods (including methods for checking system suitability) in the specifications for the

product should be provided. For the test methods that are compliant with those listed in the official compendia outside Japan (USP, EP, etc.), unless harmonized, details should be provided.

3.2.P.5.3 Validation of Analytical Procedures (name)

A description of the analytical validations of test methods (analytical procedures) for the product, including study results, should be provided.

3.2.P.5.4 Batch Analyses (name)

A description of batches and results of batch analyses should be provided. If the product is not manufactured on a batch basis, analysis results on the constitutive cells of the clinical product should be provided.

Information on OOS in autologous cell processed products

Autologous cell processed products are manufactured from raw material cells derived from patients on an individual-patient basis. Thus, because of the condition of the raw material cells, a certain percentage of the final products are found out of specification (OOS). If the manufacturing experience up to application have any OOS case associated with product manufacture failure, specific explanation should be provided with the data, including a test item with the result deviating from the acceptance limit, the batch with the OOS, frequency, and trending on the test item with non-conformance to the acceptance limit. Results from cause investigation of the deviation and development status of the solutions should also be explained.

3.2.P.5.5 Characterisation of Impurities (name)

Information on characteristics of the impurities not included in Section 3.2.S.3.2 [Constitutive Cells or Tissues] should be provided. If the information for all the impurities is provided in Section 3.2.S.3.2 [Constitutive Cells or Tissues], this section may be omitted.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 3 2(5)
Guideline (allogeneic) of 2008 Chapter 2 Section 3 2(5)
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 3 2(5)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 3 2(5)
Guideline (autologous iPS) of 2012 Chapter 2 Section 3 2(5)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 3 2(5)
Guideline (ES) of 2012 Chapter 2 Section 3 2(5)

3.2.P.5.6 Justification of Specification (name)

Justification for the specifications for the product should be provided.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 3 1
Guideline (allogeneic) of 2008 Chapter 2 Section 3 1
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 3 1
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 3 1
Guideline (autologous iPS) of 2012 Chapter 2 Section 3 1
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 3 1

Guideline (ES) of 2012 Chapter 2 Section 3 1

3.2.P.6 Reference Standards or Materials (name)

If there are reference standards or materials that are used in product specification tests or in-process tests and not described in Section 3.2.S.5 [Constitutive Cells or Tissues], the information on the relevant reference standards or materials should be provided.

3.2.P.7 Container Closure System (name)

A description of the container closure system(s) used for storage and shipping of the product should be provided, including constitutive materials of the primary package and the shapes and dimensions. In addition, the specifications of the container closure system(s) should be provided (if it is compliant with the official specifications in or outside Japan, the relevant specifications should be provided). The specifications should include appearance, description, and identification. Where appropriate, non-compendial test methods should be included with their validation. The principle of sterilization, sterilization conditions (e.g., maximum dose for radiation sterilization), sterility assurance levels, reference sterilization validation criteria, and post-sterilization residue requirements for ethylene oxide sterilization should also be provided.

For functional secondary and subsequent packaging components such as containers used for product transportation, the additional functions should be described.

Suitability information on the container closure system(s) should be located in Section 3.2.P.2 [Product].

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 4
Guideline (allogeneic) of 2008 Chapter 2 Section 2 4
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 4
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 4
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 4
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 4
Guideline (ES) of 2012 Chapter 2 Section 2 4

3.2.P.8 Stability (name)

3.2.P.8.1 Stability Summary and Conclusions (name)

The types of studies conducted, protocols, and results from the studies should be summarized with reference to ICH Q5C (differences between materials and capacity of the sample container and volume of the drug solution subjected to the studies and those specified in Section 3.2.P.7 [Product] should be clarified). The summary should include, for example, storage conditions and shelf life. Where appropriate, conclusions with respect to in-use storage conditions and shelf life should be summarized.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 5 and Chapter 3
Guideline (allogeneic) of 2008 Chapter 2 Section 2 5 and Chapter 3
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (ES) of 2012 Chapter 2 Section 2 5 and Chapter 3

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name)

The post-approval stability protocol and stability commitment should be provided with reference to ICH Q5C.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 3
Guideline (allogeneic) of 2008 Chapter 3
Guideline (autologous somatic stem) of 2012 Chapter 3
Guideline (allogeneic somatic stem) of 2012 Chapter 3
Guideline (autologous iPS) of 2012 Chapter 3
Guideline (allogeneic iPS) of 2012 Chapter 3
Guideline (ES) of 2012 Chapter 3

3.2.P.8.3 Stability Data (name)

Results from the stability testing relating to storage or transportation should be presented in an appropriate format, such as a tabular, graphical, or narrative format, with reference to ICH Q5C. The test methods (analytical procedures) and their validation should also be described.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 5 and Chapter 3
Guideline (allogeneic) of 2008 Chapter 2 Section 2 5 and Chapter 3
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 5 and Chapter 3
Guideline (ES) of 2012 Chapter 2 Section 2 5 and Chapter 3

3.2.P Sub-components (name)

3.2.P.1 Composition of the Sub-components (name)

A description of the sub-components (preservative fluid for collected cells or tissues, diluents used for administration, etc.) and their compositions should be provided with reference to ICH Q6B. The information provided should include, for example:

- Dosage form
- Quantities of constitutive ingredients in the sub-components, that is, a list of all ingredients in the dosage form, their amounts per unit (including overages, if any), functions, and reference quality standards (e.g., compendial monographs or manufacturer's specifications) should be provided; and
- The type of the container closure system used for the sub-components should be provided, where appropriate.

3.2.P.2 Sub-component Development (name)

The Sub-component Development section should include studies conducted during the development to demonstrate that the dosage form, product design and formulation, manufacturing process, container closure system, microbiological attributes, and method of use are appropriate for the intended use. The studies described in this section should be distinguished from routine tests for quality control performed in accordance with the specifications. Additionally, this section should identify and describe the attributes (critical parameters) of the product design, formulation, and commercialization process that can influence batch reproducibility, product performance, and product quality. Supportive data and results from specific

studies or published literature can be included within or attached to this section. Additional data (on the product performance) can be referenced to the relevant nonclinical or clinical sections in the application data.

3.2.P.2.1 Ingredients in the Sub-components (name)

3.2.P.2.1.1 Description and Interactions of ingredients in the Sub-components (name)

Key physicochemical characteristics of the ingredients that can influence the product performance should be described and discussed.

Interactions with constitutive ingredients in the sub-components described in Section 3.2.P.1 [Sub-component(s)], if expected, should be discussed.

This section may be omitted if the applicable sub-component is a diluent, etc. used for administration and does not contain ingredients directly related to the efficacy of the main component of the product.

3.2.P.2.1.2 Characterisation of Constitutive Ingredients in the Sub-Components (name)

For sub-ingredients in the sub-components listed in Section 3.2.P.1 [Sub-component(s)], reasons for their selection, quantities used, and characteristics that can influence the product performance should be discussed relative to functions of the constitutive ingredients in each sub-component (for example, for antibiotics in the preservative fluid, reasons for their selection and effectiveness should be included).

3.2.P.2.2 Sub-components (name)

3.2.P.2.2.1 Design of Sub-components (name)

A brief summary describing the product development should be provided with the proposed route of administration and regimen taken into account. The differences between clinical formulations and the formulation described in Section 3.2.P.1 [Sub-component(s)] should be discussed, where appropriate.

3.2.P.2.2.2 Overages (name)

If the overage of the formulation is described in Section 3.2.P.1, the justification should be provided.

3.2.P.2.2.3 Physicochemical and Biological Properties (name)

Matters relating to the product attributes of sub-components should be described.

3.2.P.2.3 Manufacturing Process Development (name)

The selection and optimization of the manufacturing process described in Section 3.2.P.3.3, in particular its critical aspects, should be explained. Where appropriate, the method of sterilisation should be explained and justified.

Differences (e.g., formulation changes) between the manufacturing process(es) used to produce pivotal clinical batches and the process described in Section 3.2.P.3.3 [Sub-component(s)] that can influence the product attributes should be discussed.

3.2.P.2.4 Container Closure System (name)

The suitability of the container closure system (see Section 3.2.P.7 [Sub-component(s)]) used for storage, transportation (shipping), and use of the sub-components should be discussed. This discussion should cover, for example, choice of materials, protection from moisture and light, compatibility of the constitutive materials with the product (including sorption to the container and leaching), safety of the constitutive

materials, and performance (such as reproducibility of the delivery volume from the container when proposed as a part of the product).

3.2.P.2.5 Microbiological Attributes (name)

Where appropriate, the microbiological attributes of the sub-components should be discussed (e.g., for nonsterile products, the rationale for not performing microbial limit tests; for products containing antimicrobial preservatives, the rationale for the selection and the effectiveness). Because for regenerative medical products, the sub-components are also expected to be sterile, the integrity of the container closure system to prevent microbial contamination should be addressed.

3.2.P.2.6 Compatibility (name)

Compatibility of the applicable sub-components with dosage devices (e.g., infusion sets, delivery devices) (e.g., precipitation of constitutive ingredients in the vehicle, sorption on injection vessels, sterility, stability) should be provided to ensure that appropriate and necessary information is included in the package insert, etc. This section may be omitted if the equivalent description is provided in Section 3.2.P.2.6 [Product].

3.2.P.3 Manufacture (name)

3.2.P.3.1 Manufacturer(s) (name)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production sites or facilities involved in manufacturing and testing of regenerative medical products should be provided.

3.2.P.3.2 Batch Formula (name)

A list of all ingredients used in the manufacturing process of the sub-components and their amounts per batch (including overage, if any) as well as reference quality standards should be provided.

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name)

A flow diagram should be presented, providing steps in the manufacturing process and showing which step each material enters. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified.

For the manufacturing process including the packaging step, the sequence of the steps and manufacturing scale should be described. In particular, novel processes or technologies and packaging operations that directly affect product quality should be described in detail.

For each step in the manufacturing process, appropriate process parameters such as time, temperature, pH should be identified. Numeric values for the parameters can be presented as an expected target range. The expected target numerical ranges for the critical process parameters should be justified in Section 3.2.P.3.4 [Sub-component(s)].

Proposals for reprocessing of the product should be justified, if any. The data to support this justification should be either included or referenced in this section.

Where appropriate, Section 3.2.A.1 (Facilities and Equipment) should be referred to.

3.2.P.3.4 Controls of Critical Steps and Intermediates (name)

For critical steps identified in Section 3.2.P.3.3 [Sub-component(s)], test methods/acceptance criteria (with justification, including experimental data) performed to ensure the process control at these steps in

the manufacturing process should be provided. Information on the quality and control methods of the critical intermediates should be provided. Stability data supporting storage conditions of the critical intermediates should be provided.

3.2.P.3.5 Process Validation and/or Evaluation (name)

Description, documentation, and results of the process validation and/or evaluation should be provided for critical steps or critical tests in the manufacturing process (e.g., validation of the sterilization, aseptic, or filling process).

Where appropriate, a description of viral safety evaluation should be provided in Section 3.2.A.2.

3.2.P.4 Control of Constitutive Ingredients in the Sub-components (name)

3.2.P.4.1 Specifications (name)

Specifications should be provided for all constitutive ingredients in the sub-components. If they are compliant with specifications in the Japanese official compendia (the Japanese Pharmacopoeia, Minimum Requirements for Biological Products, or Japanese Pharmaceutical Excipients), a statement to that effect should be included.

3.2.P.4.2 Analytical Procedures (name)

The test methods in the specifications should be provided in detail for all constitutive ingredients unless they are compliant with specifications in the Japanese official compendia (the Japanese Pharmacopoeia, Minimum Requirements for Biological Products, or Japanese Pharmaceutical Excipients). Of note, for the test methods that are compliant with those listed in the official compendia outside Japan (USP, EP, etc.), unless harmonized, details should be provided.

3.2.P.4.3 Validation of Analytical Procedures (name)

A description of the analytical validations of test methods (analytical procedures) for constitutive ingredients in the sub-components, including study results, should be provided.

3.2.P.4.4 Justification of Specification (name)

Justification for the specifications proposed for constitutive ingredients in the sub-components should be provided, where appropriate.

3.2.P.4.5 Constitutive ingredients of Human or Animal Origin in the Sub-components (name)

For constitutive ingredients of human or animal origin in the sub-components, information on adventitious agents (e.g., origin, specifications, description of the tests performed, viral safety data) should be provided (the details are provided in Section 3.2.A.2).

3.2.P.4.6 Novel constitutive ingredients in the sub-components (name)

Details of the safety evaluation performed based on the content of each constitutive ingredient in the final formulation should be provided. It should be noted that the constitutive ingredients (corresponding to pharmaceutical excipients) to be qualified are, not limited to those outside of the scope of precedent use as pharmaceutical excipients, all the constitutive ingredients in the final formulation.

Even if a sub-ingredient used is a premix product registered in the MF that includes the composition, any ingredient should be subjected to safety evaluation. This section should include the information on names of ingredients contained in the relevant premix product and their contents required for the safety evaluation (assumed maximum amounts, etc.) as well as results from the safety evaluation.

If the above information is all provided in Section 3.2.A.3, it may be omitted.

3.2.P.5 Control of Sub-components (name)

3.2.P.5.1 Specifications (name)

Specifications for sub-components should be provided.

3.2.P.5.2 Analytical Procedures (name)

Details of test methods (including methods for checking system suitability) in the specifications for the sub-components should be provided. For the test methods that are compliant with those listed in the official compendia outside Japan (USP, EP, etc.), unless harmonized, details should be provided.

3.2.P.5.3 Validation of Analytical Procedures (name)

A description of the analytical validations of test methods (analytical procedures) for the sub-components, including study results, should be provided.

3.2.P.5.4 Batch Analyses (name)

A description of batches and results of batch analyses should be provided.

3.2.P.5.5 Characterisation of Impurities (name)

Information on characteristics of the impurities in the sub-components should be provided, where appropriate.

3.2.P.5.6 Justification of Specification (name)

Justification for the specifications for the sub-components should be provided.

3.2.P.6 Reference Standards or Materials (name)

Information on the reference standards or materials used for specification tests and in-process control tests for the sub-components should be provided.

3.2.P.7 Container Closure System (name)

A description of the container closure system(s) used for storage and shipping of the sub-components should be provided, including constitutive materials of the primary package and the shapes and dimensions. In addition, the specifications of the container closure system(s) should be provided (if it is compliant with the official specifications in or outside Japan, the relevant specifications should be provided). The specifications should include appearance, description, and identification. Where appropriate, non-compendial test methods should be included with their validation. The principle of sterilization and sterility assurance levels should also be provided.

For functional secondary packaging components, the additional functions should be described.

Suitability information on the container closure system(s) should be located in Section 3.2.P.2 [Sub-component(s)].

3.2.P.8 Stability (name)

3.2.P.8.1 Stability Summary and Conclusions (name)

The types of studies conducted, protocols, and results from the studies should be summarized (differences between materials and capacity of the sample container and volume of the drug solution subjected to the

studies and those specified in Section 3.2.P.7 [Sub-component(s)] should be clarified). The summary should include, for example, storage conditions and shelf life. Where appropriate, conclusions with respect to in-use storage conditions and shelf life should be summarized.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name)

The post-approval stability protocol and stability commitment should be provided.

3.2.P.8.3 Stability Data (name)

Results from the stability testing relating to storage or transportation should be presented in an appropriate format, such as a tabular, graphical, or narrative format. The test methods (analytical procedures) and their validation should also be described.

3.2.A. APPENDICES

3.2.A.1 Facilities and Equipment (name, manufacturer)

A flow diagram should be provided illustrating the movements of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be a factor in ensuring the quality of regenerative medical products (corresponding to constitutive cells and the product, hereinafter the same).

Information on all developmental or approved regenerative medical products manufactured or handled in the same areas as those for the proposed product should be included.

A summary description of equipment that comes in contact with regenerative medical products and their use (dedicated or multiuse) should be provided. Information on preparation, cleaning, sterilization, and storage of the equipment and materials should be included, where appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the areas and facilities (e.g., area classifications) to prevent contamination or cross-contamination in the places where preparation of cell banks or manufacture of regenerative medical products are performed.

Reference Guidelines: Guideline (autologous) of 2008 Chapter 2 Section 2 2(6)
Guideline (allogeneic) of 2008 Chapter 2 Section 2 2(7)
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 2 2(6)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 2 2(7)
Guideline (autologous iPS) of 2012 Chapter 2 Section 2 2(8)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 2 2(8)
Guideline (ES) of 2012 Chapter 2 Section 2 2(7) (8)

3.2.A.2 Adventitious Agents Safety Evaluation on Exogenous Raw Materials (name, manufacturer)

Information assessing the risk with respect to potential contamination with adventitious agents should be provided. Of the explanations on the matters listed below, one on conformity status with each requirement in the Standards for Biological Raw Materials should be provided with the supportive attached data such as COAs and COOs.

<u>Cells Used as the Origin of Constitutive Cells</u>

Explanations on the applicable items should be provided. In particular, the following a to d should be explained for each ingredient of the raw material.

a Origin of the cells or tissue, animal species, country of origin (if animal), country of collection (if human)

b Details and appropriateness of donor screening

c Manufacturer's specifications as well as acceptance specifications to be performed

d Conformity with the Standards for Biological Raw Materials

Reference Guidelines: No. 1314 Attachment 1
Guideline (autologous) of 2008 Chapter 2 Section 1 1 (2) to (3)
Guideline (allogeneic) of 2008 Chapter 2 Section 1 1 (2)[2], (3) and (4)
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 1 1(2) to (4)
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 1 1(2)[2], (3) and (4)
Guideline (autologous iPS) of 2012 Chapter 2 Section 1 1 (2) to (4)
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 1 1 (2)[2], (3) and (4)
Guideline (ES) of 2012 Chapter 2 Section 1 1 (2)[3], (3) and (4)

Feeder cells

Information on the origin of feeder cells (origin, history (background of acquisition), etc.) 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 (raw material standards (manufacturer's specifications as well as acceptance specifications and test methods to be performed) and retention of the records, etc.).

Reference Guidelines: No. 1314 Attachment 1
Guideline (autologous) of 2008 Chapter 2 Section 1 2 (1)[7]
Guideline (allogeneic) of 2008 Chapter 2 Section 1 2 (1)[7]
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 1 2 (1)[4]
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 1 2 (1)[4]
Guideline (autologous iPS) of 2012 Chapter 2 Section 1 2 (1)[4]
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 1 2 (1)[4]
Guideline (ES) of 2012 Chapter 2 Section 1 2 (1)[4]

Raw materials other than cells or tissues

The raw materials of human and animal origin used in manufacture should be listed and identified. Then, for each listed ingredient, details should be given as appropriate.

For each of the raw materials of human or animal origin, the following a to e should be explained.

a Animal species, part of use, country of origin (if animal), country of collection (if human)

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 test methods to be performed

d Conformity with the Standards for Biological Raw Materials

e Steps in the manufacturing process of a raw material where bacteria, fungi, viruses, etc. are inactivated or removed

(note) Viral clearance studies to assess the inactivation or removal steps should be tabulated. Of note, 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) should be referred to. For the methods scientifically known to inactivate or remove bacteria, fungi, and viruses 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 Notification No. 1552, dated November 26, 2001).

Reference Guidelines: No. 1314 Attachment 1
Guideline (autologous) of 2008 Chapter 2 Section 1 2
Guideline (allogeneic) of 2008 Chapter 2 Section 1 2
Guideline (autologous somatic stem) of 2012 Chapter 2 Section 1 2
Guideline (allogeneic somatic stem) of 2012 Chapter 2 Section 1 2
Guideline (autologous iPS) of 2012 Chapter 2 Section 1 2
Guideline (allogeneic iPS) of 2012 Chapter 2 Section 1 2
Guideline (ES) of 2012 Chapter 2 Section 1 2

Testing at appropriate stages of production

The selection of virus tests that are performed during the manufacturing process (e.g., cell substrate or cell banks, viral vector(s), or unprocessed/unpurified bulk of the product) should be justified. The type, sensitivity, specificity, and frequency of the tests should be described. Results from the test, performed at an appropriate stage in the manufacturing process, confirming that the product is free from viral contamination should be provided (for related information, see Sections 3.2.S.2.2 and 3.2.S.2.4).

3.2.A.3 Sub-ingredients of the Product

All the sub-ingredients (corresponding to pharmaceutical excipients) in the final product, not limited to those outside of the scope of precedent use as pharmaceutical excipients, should be listed with their ingredient names and contents. Details of the safety evaluation performed based on the content of each sub-ingredient should be provided. The details of the safety evaluation should include:

[1] Content of each sub-ingredient in the product at the clinical dose
[2] Explanation that the amount of each sub-ingredient at the clinical dose calculated in [1] above falls within the known qualified information based on the following information
- Nonclinical toxicity studies
- Clinical experience
- Literature information
- Physiological concentration

Even if a sub-ingredient used is a premix product registered in the MF that includes the composition, any ingredient should be subjected to safety evaluation. This section should include the information on names of ingredients contained in the relevant premix product and their contents required for the safety evaluation (assumed maximum amounts, etc.) as well as results from the safety evaluation.

3.2.R REGIONAL INFORMATION

Where appropriate, data addressing requirements specific to each region should be provided. If a delivery device is used as a sub-component, an independent Module R should be established and provided with appropriate data such as study reports.

3.3 LITERATURE REFERENCES

Where appropriate, literature referenced should be provided.