Provisional Translation (as of July 2026)*

PSB/PED Notification No. 0331-1
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March 31, 2026

To: Directors of Prefectural Health Departments (Bureaus)

Director of Pharmaceutical Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Director of Medical Device Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Partial Revision of "Standards for Biological Raw Materials, Operational Guideline"

The operation of the Standards for Biological Raw Materials (MHLW Notification No. 210 of 2003) has been set out in the "Standards for Biological Raw Materials, Operational Guideline" (Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare , Counsellor of Minister's Secretariat, Ministry of Health, Labour and Welfare (Person in charge of review control of medical devices, regenerative medical products, etc.).

Following the enforcement of the "Partial Revision of the Standards for Biological Raw Materials" (MHLW Notification No. 155 of 2026), this notification has been revised as attached based on international trends and the latest scientific knowledge. Please take note of this revision and ensure that the relevant business operators under your jurisdiction are duly informed.

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

Standards for Biological Raw Materials, Operational Guideline

1. I. General Notices

(1) The term “source materials” specified in the Standards for Biological Raw Materials refers specifically to the tissues or body fluids collected from humans or animals, extracts of tissues, etc., or their pooled materials, which are made into raw materials or ancillary materials used as starting materials in the manufacture of drugs, medical devices, regenerative medical products (hereinafter, “drugs, etc.”).

(2) Among the source materials, which are sources of raw materials and ancillary materials, the following examples or equivalent materials cannot be regarded as appropriate for handling in the same manner as raw materials, etc. of drugs, etc., and therefore do not fall under the source materials specified in the relevant Standards.

Example 1: Source materials used only for construction of a cell bank of the cells (*Escherichia coli*, etc.) that produce human insulin (genetic recombination) used as a component of culture media in the cell culture process

Example 2: Source materials used for manufacture of a bacterium-derived ingredient (peptidase) used for partial decomposition in the manufacturing process of human insulin (genetic recombination) used as a medium ingredient in the cell culture process

Example 3: Human immunoglobulin G used for purification of (bacterium-derived) protein A that composes the carrier of protein A affinity chromatography, which is used in a purification process for antibody drugs, etc.

Example 4: Source materials used for selection media for seed cells in the process of establishing a master cell bank for recombinant drugs

Example 5: Source materials that are the master cell bank or master seed used for manufacture of drugs, etc. for which sufficient characteristic analysis of pathogens and denial of contamination with pathogens have been done, and that have been used in the process of establishing them. However, it is limited to those for which the applicability to source materials specified in the relevant standards has been confirmed in the approval review for drug, etc.

(3) The term “drugs, etc. approved for marketing in Japan” in General Notices10 shall, in principle, refer to drugs, etc. that have obtained marketing authorization in Japan, and shall not refer to drugs, etc. that have obtained marketing authorization overseas but not in Japan.
However, in cases where drugs, etc. that have obtained marketing authorization overseas but not in Japan are used as raw materials, etc. for other drugs, etc., and, due to unavoidable circumstances, it is difficult to obtain the information necessary to confirm compliance with

the standards, such drugs, etc. may be regarded as "raw materials, etc. conforming to the standards" in certain cases, taking into account the following items listed in (a) through (d):

(a) The severity of the indication of the drug, etc. to be marketed, and the extent of deterioration in quality of life (QOL) caused by the disease.

(b) The availability in Japan of other existing useful therapeutic options for the indication of the drug, etc. to be marketed.

(c) The number of patients in Japan with the indication of the drug, etc. to be marketed.

(d) The approval status, in countries specified by Cabinet Order pursuant to Article 14-3, Paragraph 1, item (ii) of the Pharmaceuticals and Medical Devices Act (Article 28-2 of the Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices) (i.e., the United States, the United Kingdom, Canada, Germany, or France), or in countries with regulatory systems equivalent to those of any of these countries (i.e., EU member countries other than Germany and France), of drugs, etc. that have not obtained marketing authorization in Japan and that are used as raw materials, etc. for the drug, etc. to be marketed; as well as the contents of the review reports (or approval documents), and available information on clinical use experience and safety.

(4) The term "appropriately used" in General Notice 10 refers to, for example, not using a dosage far exceeding the approved dosage and administration as a dose when used as raw materials, etc. of a drug, etc.

(5) In applying the General Notice 10, if a drug, etc. that is allowed to be used as raw materials, etc. not conforming to the Standards for Biological Raw Materials in consideration of the risks and benefits of the product, is used as raw materials, etc. for other drugs, etc., it shall be necessary to newly evaluate the risks and benefits for the product to be used and judge the propriety of use as raw materials, etc.

2. II. General Rules for Blood Products

(1) When the human blood components are used as excipients, media, etc. in the manufacturing processes of drugs, etc. (excluding blood products), the Standards for Human-Derived Raw Materials shall be applied.

3. III. General Rules for Human-Derived Raw Materials, 1. Standards for Human Cell/Tissue-based Raw Materials

(1) "Human cell/tissue-based raw materials, etc." are defined as the human-derived cell or tissue serving as raw materials, etc. constituting drugs, etc. Human cell/tissue-based raw materials, etc. shall include the cells and tissues before undergoing the relevant processing, such as iPS (-like) cell-derived cells, if the relevant cells and tissues have undergone the processing such as differentiation and genetic manipulation.

(2) The meaning of "if it necessary" in the Standards for Human Cell/Tissue-based Raw Materials (2)-B is that autologous human cell/tissue-based raw materials, etc. are not required in principle. However, even if they are autologous human cell/tissue-based raw

materials, etc., if there is a concern about viral proliferation, etc. in the culture process of the product, it is necessary to confirm viral infection at an appropriate timing such as the collection stage in order to secure the safety of the product.

(3) With regard to "by interview, medical examinations, tests, etc." described in the Standards for Human Cell/Tissue-based Raw Materials, (3)-A, if the donor's age is one month or less at the time of procurement of human cell/tissue-based raw materials, etc., the donor infection testing may be substituted by infection testing, etc. of the donor's biological mother at the time of procurement, in order to avoid imposing a medically unnecessary burden on the neonate, unless exposure events other than mother-to-child vertical transmission (including cases where the mother is an HIV-infected individual who has been treated) are suspected. Conversely, if the donor's age is more than one month at the time of procurement of human cell/tissue-based raw materials, etc., specimens for infection testing should be collected from the donor. However, it should be noted that, in humans, the immune system is still developing up to 18 months of age, and protective antibodies against infection may not yet have been produced; therefore, serological testing in children at or below that age may not necessarily yield sufficient results.

(4) With regard to "infection of the donor with any pathogens including bacteria, fungi, viruses, etc. is denied by interview, examinations, tests, etc." described in the Standards for Human Cell/Tissue-based Raw Materials (3)-A, products for which bacteria, fungi, viruses, etc. cannot be inactivated or removed in the manufacturing process shall be confirmed that they have been subjected to test for sterility, verification of viral infection risk, and other tests required in the manufacturing process, in addition to determine the eligibility of donors.

(5) With regard to the "re-tests" in the Standards for Human Cell/Tissue-based Raw Materials (3)-C, re-test is not always necessary if umbilical cord blood is provided as human cell/tissue-based raw materials, etc. and the method of supplying such umbilical cord blood conforms to the standards established by the MHLW Ministerial Ordinance under the provisions of Article 32 of the Act for Appropriate Provision of Hematopoietic Stem Cells to be Used in Transplantation (Act No. 90 of 2012), and if cells other than umbilical cord blood have been controlled similarly to these standards.

(6) With regard to "re-tests" in (3)-C of the Standards for Human Cell/Tissue-based Raw Materials, if it has been confirmed that hepatitis B virus, hepatitis C virus, and human immunodeficiency virus are not detected by means of nucleic acid amplification testing on each individual donor, in addition to serological testing for these viruses conducted on specimens collected for infection testing at or around the time of procurement of the human cell/tissue-based raw materials, etc. (i.e., on the date of procurement or within 7 days thereafter; provided, however, that where such timing is not appropriate, within 7 days prior to the date of procurement), and if it has also been confirmed that these viruses are not detected in viral testing conducted at an appropriate stage of the manufacturing process, re-tests are not necessarily required. In cases where re-tests are not conducted, it is required that the qualifications of facilities and personnel for infection testing, and the reliability of test data are sufficiently ensured.

(7) With regard to "re-tests" in (3)-C of the Standards for Human Cell/Tissue-based Raw Materials, if it has been confirmed that hepatitis B virus, hepatitis C virus, and human immunodeficiency virus are not detected by means of nucleic acid amplification testing on each individual donor, in addition to serological testing for these viruses conducted on specimens collected for infection testing at or around the time of procurement of the human cell/tissue-based raw materials, etc. (i.e., on the date of procurement or within 7 days thereafter; provided, however, that where such timing is not appropriate, within 7 days prior to the date of procurement), and if the processes for inactivation or removal of the viruses subject to the testing are implemented in the manufacturing process, re-tests are not necessarily required. In cases where re-tests are not conducted, it is required that the qualifications of facilities and personnel for infection testing, and the reliability of test data are sufficiently ensured. In addition, in evaluating the process for the inactivation or removal of viruses, ICH Q5A(R2): "Partial Revision of Guideline of Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PSB/PED Notification No. 0109-3, dated January 9, 2025) should be referred to.

(8) The "important diseases" in the Standards for Human Cell/Tissue-based Raw Materials (3)-D include the following:

a. Bacterial infections, such as syphilis (Treponema pallidum), chlamydia, gonorrhea, and tubercle bacillus

b. Sepsis or suspected sepsis

c. A malignant neoplasm

d. Serious metabolic and endocrine diseases

e. Collagen and blood diseases

f. Hepatic diseases

g. Confirmed or suspected transmissible spongiform encephalopathy (TSE) or other dementia

(9) With regard to the consent of donors in the Standards for Human Cell/Tissue-based Raw Materials (4)-B, it is also applicable to cases where the human cell/tissue-based raw materials, etc. that have already been provided is explained again and consent is obtained when the marketing authorization holder, etc. receives them as raw materials, etc. of drugs, etc. separately from the explanation given at the time of collection. However, for human embryonic stem cells, the guidelines provided separately shall be followed.

(10) When the consent of proxy for the person donating specified in the Standards for Human Cell/Tissue-based Raw Materials (4)-C is obtained, it is desirable to meet the following requirements:

a. The donor has difficulty in receiving the explanation and giving consent or lacks the ability to give complete consent independently.

b. There is a reasonable basis that the collection of human cell/tissue-based raw

materials, etc. from the relevant donor is considered necessary from the viewpoint of securing the quality, efficacy, and safety of drugs, etc.

c. The proxy for the person donating is a person who is judged to be able to best represent the intentions and benefits of the donor.

d. A person collecting human cell/tissue-based raw materials, etc. shall give an explanation to the donor in accordance with his/her understanding as much as possible and make efforts to obtain consent from the donor.

e. The ethics committee, etc. of the collection facility has reviewed and approved the scientific and ethical validity of the collection of human cell/tissue-based raw materials, etc. from the relevant donor.

(11) The method of anonymization, etc. of the donor's personal information shall be handled in accordance with the separately established guidelines, etc., but it is desirable to be linkable.

(12) The "Working records during collection of the human cell/tissue-based raw materials, etc." in the Standards for Human Cell/Tissue-based Raw Materials (5)-D refers to the measures, etc. taken to prevent contamination with pathogenic microorganisms shown in the Standards for Human Cell/Tissue-based Raw Materials (2)-A or other causes of diseases.

(13) The "Results of discussion by the ethics committee, etc." described in the Standards for Human Cell/Tissue-based Raw Materials (5)-E are applicable when deliberation is conducted at the ethics committee, etc.

4. III. General Rules for Human-Derived Raw Materials, 3. Standards for Human-Derived Raw Materials

(1) Human-derived raw materials, etc. shall include cell-derived extracts such as proteins, hormones, nucleic acids, etc. Moreover, the "cells or tissues that are origins of the human-derived raw materials, etc." in the Standards for Human-Derived Raw Materials (1) shall include human blood, etc. which are the origin of the human blood components falling under the above 2-(1). Furthermore, amino acids made from human hair are not subject to the Standards for Human-Derived Raw Materials because they are considered to have gone through a severe purification process from the viewpoint of inactivation of bacteria, fungi, viruses, etc.

(2) The "appropriate stage" in the Standards for Human-Derived Raw Materials (1) includes the unprocessed or unpurified bulk stage (such as the time of blood collection for human blood) or the cell bank stage when a cell bank is established. However, this shall not apply to cases where the test to detect viruses can be performed more accurately by carrying forward a very small part of the manufacturing process of raw materials, etc. or product.

(3) When performing the virus test in the Standards for Human-Derived Raw Materials (1), at least the nucleic acid amplification test for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus must be performed. When a human blood-derived raw material is used, a serological test and nucleic acid amplification test must be performed at least for

hepatitis B virus, hepatitis C virus, and human immunodeficiency virus with reference to the General Rules for Blood Products.

(4) For the Standards for Human-Derived Raw Materials (3), the human-derived raw materials, etc. are not cells/tissues as a rule, but the processes related to inactivation or removal of pathogens are considered feasible. Therefore, the processes shall be implemented in principle. However, with regard to "when there is a rational reason for not performing the relevant treatment," it is not always necessary to perform the inactivation or removal process for human autologous serum, etc. used in the culture process for autologous human cell/tissue-based raw materials, etc. Even in this case, pathogens shall be inactivated or removed at any stage of the manufacturing process of the product, or the risks related to infection with pathogens or proliferation, etc. in the culture process shall be appropriately controlled.

(5) Refer to ICH-Q5A(R2) "Partial Revision of Guideline of Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PSB/PED Notification No. 0109-3, dated January 9, 2025) for the evaluation of the steps to inactivate or remove substances specified in the Standards for Human-Derived Raw Materials (3).

(6) "Results of test, etc. of the human-derived raw materials, etc." described in the Standards for Human-Derived Raw Materials (4)-C refer to the tests, etc. shown in the Standards for Human-Derived Raw Materials (1) and (2).

5. IV. General Rules for Animal-Derived Raw Materials, 1. Standards for Ruminant-Derived Raw Materials

(1) The term "ruminant animals" in the Standards for Ruminant-Derived Raw Materials (1) refers to cattle, sheep, goats, buffalos, deer, antelopes, etc.

(2) The "raw materials, etc. produced by heating and alkali treatment, etc. produced by other appropriate treatments" described in the Standards for Ruminant-Derived Raw Materials (1) include the following:

a. Listed in Attachment 2 (however, excluding succinylated gelatin or gelatin succinate, gelatin, hydrolyzed gelatin, heart extract, hard fat, animal tallow and animal tallow derivatives, beef tallow hardened oil, and fatty acids (derived from beef tallow)).

b. Raw materials, etc. for which it can be evaluated that the safety of the product is ensured based on the clearance values of prions that may contaminate raw materials, etc. calculated based on the simulation of the dilution rate in the manufacturing process of raw materials, etc. or the reduction rate of prions in the purification process.

c. Animal tallow, animal tallow derivatives, beef tallow hardened oil, and fatty acids (derived from beef tallow) treated by the following methods or equivalent methods

[1] Transesterification reaction or hydrolysis at not less than 200℃ for not less than 20 minutes under pressure

[2] The following processes using 12 mol/L sodium hydroxide:

- Batch process at not less than 95°C for not less than 3 hours
- Continuous process at not less than 140°C under pressure for not less than 8 minutes, or equivalent process

[3] Distillation at not less than 200°C

* Items [1] to [3] were cited from "Guidance for minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01 rev.3 issued by European Medicines Agency in March 2011).

d. Materials that have been processed by any of the following methods, or by methods equivalent thereto (excluding succinylated gelatin or gelatin succinate, gelatin, hydrolyzed gelatin, animal tallow and animal tallow derivatives, beef tallow hardened oil, and fatty acids (derived from beef tallow)).

[1] Either of the following as the autoclaving/chemical method (heat resistant materials)

- Immerse in 1 mol/L sodium hydroxide solution and autoclave at not less than 121°C for not less than 30 minutes; clean; wash with water and subject to routine sterilization.
- Immerse in sodium hydroxide solution or sodium hypochlorite solution (effective chlorine concentration of 2%) for not less than 1 hour; autoclave at not less than 121°C for not less than 1 hour; clean and subject to routine sterilization.
- Immerse in sodium hydroxide solution or sodium hypochlorite solution for not less than 1 hour; wash with water; autoclave at not less than 121°C (in a case of weight pressurized and degassing autoclave) or not less than 134°C (in a case of vacuum degassing autoclave) for not less than 1 hour; clean and subject to routine sterilization.
- Immerse in sodium hydroxide solution and boil for not less than 10 minutes at atmospheric pressure; clean, wash with water and subject to routine sterilization.
- Immerse in sodium hypochlorite solution (preferred) or sodium hydroxide solution for not less than 1 hour at room temperature; clean; wash with water and subject to routine sterilization.
- Autoclave at not less than 134°C for not less than 18 minutes (note that, for brain tissue bake-dried onto surfaces, infectivity will be largely but not completely removed.)

[2] The following chemical method (heat-labile materials)

- Pour 2 mol/L sodium hydroxide or sodium hypochlorite stock solution, allow it to stand for not less than 1 hour, and wash with water.

[3] Either of the following methods is used for autoclave sterilization and the chemical method of dry material.

- Immerse in sodium hydroxide solution or sodium hypochlorite solution; and autoclave at not less than 121℃for not less than 1 hour in a vacuum degassing autoclave (for small dry material that can withstand exposure to sodium hydroxide or sodium hypochlorite).
- Autoclave at not less than 134℃ for not less than 1 hour in a vacuum degassing autoclave (for bulky materials and dry materials of any size that cannot withstand exposure to sodium hydroxide or sodium hypochlorite).

* Items [1] to [3] were cited from "WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies, Report of a WHO Consultation (2000.3) Annex III."

(3) It is desirable to pay attention to the following restrictions on the age of cattle from which ruminant-derived raw materials are derived for each country of origin.

[1] Harvesting of materials from cattle originating from Japan: The Enforcement Ordinance of the MHLW-related Implementation Rules for the Law on Special Measures against Bovine Spongiform Encephalopathy (Ministry of Health, Welfare and Labour Ordinance No. 89 of 2002) and the Enforcement Ordinance of the Slaughterhouse Act (Ministry of Health and Welfare Ordinance No. 44 of 1953).

[2] Harvesting of materials from cattle originating from the US: the "Handling of Beef, etc., Imported from the US" (PFSB/ISD/FSD Notification No. 0201-3 from the Director of the Inspection and Safety Division, Food Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated February 1, 2013).

[3] Harvesting of materials from cattle originating from the Netherlands: the "Handling of Beef, etc., Imported from the Netherlands" (PFSB/ISD/FSD Notification No. 0201-6 from the Director of the Inspection and Safety Division, Food Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated February 1, 2013).

(4) The countries which are currently applicable to the "countries which the World Organization for Animal Health recognizes as having a negligible transmission risk of bovine spongiform encephalopathy" in the Standards for Ruminant-Derived Raw Materials (2) are those listed in Attachment 4. The countries listed in Attachment 4 shall be updated in a timely manner via the website of World Organization for Animal Health (https://www.woah.org/en/disease/bovine-spongiform-encephalopathy/;

https://www.woah.org/en/who-we-are/structure/framework/resolutions-and-recommendations/resolutions-adopted-by-the-world-assembly-of-delegates/), etc.

(5) If the World Organization for Animal Health recognizes a new country to have “a negligible BSE risk,” regardless of whether this notification is amended or not, the time point for the country to be regarded as the country of origin of usable materials under the Standard is the day of publication of the result of the general session of the World Organization for Animal Health in which the recognition is discussed. It shall be noted that the ruminant-derived raw materials, etc. from such countries, obtained on or after May 25, 2007, the date on which the World Organization for Animal Health first designated countries as having “a negligible BSE risk” can be used after the above designated date including the countries listed in Attachment 4. The use of ruminant-derived raw materials, etc. collected in Australia, Argentina, New Zealand, Singapore, or Uruguay prior to May 25, 2007, shall not be precluded. In cases where a designation of “a negligible BSE risk” has been withdrawn (i.e., where the BSE risk is no longer considered negligible), the relevant ruminant-derived raw materials shall be deemed not to comply with the Standards for Ruminant-Derived Raw Materials. However, this shall not apply to materials derived from cells or tissues collected prior to the date of such withdrawal or after re-designation, namely during the period in which the country was designated as having "a negligible BSE risk".

(6) The “animal hair” and “milk” in the Standards for Ruminant-Derived Raw Materials (2) include animal hair- derived raw materials and milk-derived raw materials, respectively.

(7) With regard to the “breeding or slaughter conditions of the ruminant animals” and the “working records of treatment and other measures to prevent the spread of transmissible spongiform encephalopathy” in the Standards for Ruminant-Derived Raw Materials (3)-C and D, it is possible to replace the record with a citation of the applicable part of the law, etc., and a declaration of compliance, so long as these matters are regulated by the law, etc., of the country of origin.

(8) The “because they are necessary” described in the Standards for Ruminant-Derived Raw Materials (4) include the cases where suppliers of raw materials, etc. are limited.

6. IV. General Rules for Animal-Derived Raw Materials, 2. Standards for Animal Cell/Tissue-based Raw Materials

(1) Animal cell/tissue-based raw materials, etc. shall contain cells or tissues derived from animals used for biological valves and pericardial patches.

(2) The “sufficiently eligible” in the Standards for Animal Cell/Tissue-based Raw Materials (3) refers to all of the following:

a. When donor animals are selected, microbiological characteristics of each animal species shall be taken into consideration.

b. Testing/inspections at and after acceptance of donor animals shall be performed after setting the items of the relevant tests and inspections and the criteria for

evaluating the results of the relevant tests and inspections in advance. Particularly, for the testing/inspections on infections, etc., it shall be noted that the items to be tested differ among animal species.

c. At acceptance of donor animals, the measures to prevent transmission of infections, etc. shall be taken appropriately.

d. Standard operating procedures describing the methods and procedures for breeding control of donor animals shall be established.

e. To prevent transmission of infection, etc., donor animals shall be kept and managed in facilities equipped with containment and other appropriate facilities.

f. Donor animals shall be handled in accordance with the principles of animal welfare.

(3) The term "ancillary material" used in the provisory clause in the Standards for Animal Cell/ Tissue-based Raw Materials (3) refers to a material that is used only in the manufacturing stage and remains in the finished product only as a residual process-related impurity, such as feeder cells, but not to the active ingredients or the main cell components of the pharmaceutical product.

(4) The term "past uses" described in the provisory clause in the Standards for Animal Cell/Tissue-based Raw Materials (3) includes the uses for drugs, etc. that have pharmaceutical approval and past uses for regenerative medicine, etc. under the "Act on Securing Safety of Regenerative Medicine" (Act No. 85 of 2013).

(5) With regard to the Standards for Animal Cell/Tissue-based Raw Materials (4), when live animal cells or tissues are used, the risk of viral infection must be verified. In other cases, sterility assurance and verification of viral infection risk must be performed.

(6) With regard to the "verify for viral infection risk" in the Standards for Animal Cell/Tissue-based Raw Materials (4), if live animal cells or tissues are used, refer to the "Guidelines on the Risk Management of Xenogeneic Infection Associated with the Implementation of Xenotransplantation" (Attachment) set forth in the notification entitled "Implementation of Xenotransplantation Conducted under the Act on Securing Safety of Regenerative Medicine" (HPB/RDD Notification No. 0117-1 and Infectious Disease Control Notification No. 0117-7, dated January 17, 2025, issued by the Director of the Research and Development Policy Division, Health Policy Bureau, and the Director of the Infectious Disease Control Division, Health and Sanitation Bureau, Ministry of Health, Labour and Welfare)..

(7) With regard to the "verify for viral infection risk" in the Standards for Animal Cell/Tissue-based Raw Materials (4), refer to the examples shown in Attachment 1. If the heating process for virus inactivation is under the illustrated conditions or more stringent conditions depending on the properties of intended raw materials at an appropriate time point during the manufacturing process, such verification is not required.

(8) The record of "status of acceptance" of donor animals in the Standards for Animal Cell/Tissue-based Raw Materials (5)-C refers to the description of the measures in the above

(2)-C that are specified at the time of acceptance in the rearing facility and the slaughtering facility, and the implementation record.

7. IV. General Rules for Animal-Derived Raw Materials, 3. Standards for Animal-Derived Raw Materials

(1) "Those considered to be known publicly in the scientific field" described in the Standards for Animal-Derived Raw Materials (1) are semisynthetic and highly-purified animal-derived raw materials, etc. and animal-derived raw materials, etc. shown in Attachment 2 that are considered to have gone through a severe purification process from the viewpoint of inactivation of bacteria, fungi, viruses, etc., as well as animal-derived raw materials, etc. made from raw materials originated from animals other than mammals, birds, reptiles, and amphibians. However, it cannot be ruled out that the risk of prion transmission may not be eliminated by chemical processing, etc. alone. Therefore, the Standards for Ruminant-Derived Raw Materials shall apply to animal-derived raw materials, etc. that are described in Attachment 2 and not subject to the Standards for Animal-Derived Raw Materials but are ruminant-derived raw materials, etc. not listed in 5 (2) above.

(2) The term "healthy" in the Standards for Animal-Derived Raw Materials (1) refers to those specified in 4.1 of 4, Basic Requirements for Viral Safety of Biological Products in the Japanese Pharmacopoeia, 18 of General Information of Japanese Pharmacopoeia 18th edition, (following revision of the Japanese Pharmacopoeia, the requirements as revised) and meeting the "food standard" in the basic requirements means satisfying any of the following or an equivalent level:

[1] Materials that underwent the inspection specified in Article 14 of the "Slaughterhouse Act" (Act No. 114, 1953).

[2] Materials that underwent the inspection specified in Article 15 of the "Poultry Slaughtering Business Control and Poultry Inspection Law" (Law No. 70, 1990).

[3] Materials conforming to the standard specified in Article 3 of the "Ministerial Ordinance on Milk and Milk products Concerning Compositional Standards, etc." (Ministry of Health and Welfare Ordinance No. 52 of 1951)

[4] Materials that have been certified for use in food in foreign countries

(3) In addition to (2), wild animals that cannot be confirmed as "healthy animals" shall meet the following requirements specified in the "Recommended International Code of Hygienic Practice for Game CAC/RCP 29 -1983. Rev. 1 (1993)" issued by the Codex (Joint FAO/WHO Food Standards Programme). For raw materials, etc. derived from wild animals, it is desirable to inspect samples of heat-resistant bacteria with reference to the "Specifications and Standards for Food and Food Additives etc. " (VSD/EHB Notification No. 54 by the Director of Veterinary Sanitation Division, Environmental Health Bureau, Ministry of Health and Welfare, dated March 17, 1993, etc.).

[1] Animals shall be slaughtered, and the parts of raw materials shall be sampled in an

appropriate manner to avoid contamination of the parts.

[2] When slaughtering animals, a method that ensures immediate death shall be selected.

[3] Animals shall not be captured in areas where their capture is prohibited.

(4) The term "aseptic, and have been subjected to test for viral infection risk and other tests required" in the Standards for Animal-Derived Raw Materials (1) refers to an appropriate stage of the process (including the process of raw materials, etc. or products) to ensure the sterility and verify the viral infection risk if the relevant animal-derived material, etc. does not use a well-characterized cell bank as the starting material. It refers to the fact that the site of origin and part of use of animals have been confirmed and, if cells or tissues are used as source materials, how to obtain them has been confirmed.

(5) The "appropriate stage" in the Standards for Animal-Derived Raw Materials (2) includes the cell bank or seed lot stage when a cell bank or seed lot is established, the stage of unprocessed or unpurified bulk, and cases where a test to detect viruses can be performed more accurately by carrying forward a very small part of the manufacturing process of raw materials, etc. or products.

(6) The "cases where there is a reasonable reason this treatment is not conducted" in the Standards for Animal-Derived Raw Materials (4) include, for example, the cases where the intended characteristics of the raw materials, etc. are lost by the inactivation or removal treatment based on the current knowledge and it is not possible to change it to other raw materials, etc. In such cases, after confirming that the source animals are healthy, sterility assurance and verification of viral infection risk shall be implemented at an appropriate time point in the process, and the place of origin and part of use of animals shall be confirmed, and if cells or tissues are used as source materials, how to obtain them shall be confirmed.

8. Others

(1) "General Rules for Blood Products in the Minimum Requirements for Biological Products" described in the approval letter issued at the marketing authorization, etc. shall be regarded as corresponding descriptions in the General Rules for Blood Products in the Minimum Requirements for Biological Raw Materials.

(2) With regard to the quality and safety assurance of ruminant-derived raw materials, the descriptions of "PMSB Notification No. 1226, issued by the Director-General of Pharmaceutical and Medical Safety Bureau, dated December 12, 2000" and "PMSB Notification No. 1069, issued by the Director-General of Pharmaceutical and Medical Safety Bureau, dated October 2, 2001" in the approval letter issued at the marketing authorization shall be regarded as corresponding descriptions in the Standards for Ruminant-Derived Raw Materials.

(3) With regard to the storage of records, it is acceptable to store duplicates of documents (e.g., certificates) with which necessary information can be checked, instead of standard written records, as long as the traceability as the original purpose can be confirmed.

(4) The records specified in the Standards for Biological Raw Materials shall be retained by the manufacturer, etc. in principle, but the filing can be assigned to the person who manufactures the raw materials, etc. (hereinafter referred to as the "raw materials, etc. vendor") based on the contract with the relevant raw materials, etc. vendor. However, in such a case, the manufacturer, etc. shall be controlled so that necessary information can be obtained promptly for the records retained by the relevant raw materials, etc. vendor.

(5) Refer to Attachment 3 for the description of the application form for marketing authorization.

Attachment 1. Heating conditions validated for virus inactivation

Heating conditions	Examples of relevant components
71℃ for 3 hours, 121℃ for 15 seconds, and 101℃ for 30 seconds	Tryptone
71℃ for at least 3 hours and 101℃ for at least 30 seconds	Lactalbumin
92℃ for 1 hour and 125℃ ± 2℃ for 3 to 4 seconds	Chondroitin sulfate sodium
100℃ for 30 minutes	Chicken extract
Intermittent sterilization at 100℃ for 30 minutes	Skimmed milk
120℃ for at least 15 minutes	Tryptone, polypeptone, Casamino acid
122℃ for 30 minutes	Trypticase Soy Broth
122℃ for 55 minutes	Peptone
Boil for 30 minutes, dry in oven (180℃ to 190℃) for 16 to 48 hours, and 121℃ for 60 minutes	Peptone
123℃ for 20 minutes	Bovine liver, bovine heart, bovine muscle
200℃, 40 bar, 20 minutes	Beef tallow
Autoclaving	Lactalbumin hydrate, Casamino acid, Casitone, Heart extract, Bacto tryptone, Liver extracts, Bovine liver
Spray drying (150℃)	Yolk lecithin

Attachment 2. Components that are considered to have gone through a severe purification process from the viewpoint of inactivation of bacteria, fungi, viruses, etc.

Asparagine	Sorbitan fatty acid esters	α-Monoisostearyl glyceryl ether
Aspartic acid and its salts	Albumin tannate	Sorbitan monooleate
N-Acetyl-L-cysteine	Tyrosine	Polyethylene glycol monooleate
Acetylated sucrose denatured alcohol (95 vol%)	Sodium deoxycholate or sodium desoxycholate	Polyoxyethylene sorbitan monooleate
Amacol CAB	Dexamethasone sodium metasulfobenzoate	Polyglyceryl monooleate
Alanine	Dexamethasone	Glyceryl monostearate
Arginine	Dehydrocholic acid and its salts	Sorbitan monostearate
Alfacalcidol	Triacetin	Propylene glycol monostearate
Isostearic acid	Triamcinolone acetonide	Polyethylene glycol monostearate
Isoleucine	Sorbitan trioleate	Polyoxyethylene sorbitan monostearate
Ursodeoxycholic acid or ursodesoxycholic acid	Sorbitan tristearate	Sorbitan monolaurate
Ethanol; anhydrous ethanol	Tryptophan	Sodium N-acyl-L-glutamate (coconut fatty acid/hydrogenated tallow fatty acid)
Epidihydrocholesterol	Glyceryl tri (tallow fatty acid)	Coconut fatty acid hydrolyzed collagen triethanolamine
Oleyl alcohol	Threonine	Egg yolk lecithin
Oleic acid	Trehalose	Lauryl alcohol
Decyl oleate	Heart extract	Sodium lauryl sulfate
Casamino acids	Hard fat	N-lauroyl-L-glutamic acid di (cholesteryl/octyldodecyl)
Caprylic acid and capric acid	Hydroxyapatite	Lactulose
Galactose	Panacete 810	Lactobionic acid
Calcitriol	Valine	Erythromycin lactobionate
Carbocisteine	Isopropyl palmitate	Lanolin
Carmine	Cetyl palmitate	Lanolin alcohol
Glycine	Methyl hyodeoxycholate	Lanolin fatty acid cholesterol ester
Glyceryl triacetate	Histidine	Lysine
Glycerin	Vitamin A + D2 powder	Cysteine malate
Glycerol oleate	Vitamin B12	Hydrocortisone sodium phosphate
Glycerol fatty acid esters	Vitamin D	Betamethasone phosphate and its salts

Glutamine	Vitamin D2	Riboflavin sodium phosphate
Glutamic acid and its salts	Vitamin D3	Lecithin
Chenodeoxycholic acid	Cholesteryl hydroxystearate	Leucine
Chenocholic acid	Hydroxyproline	L-Ethylcysteine hydrochloride
Geraniol-denatured alcohol (95 vol%)	Hydrocortisone	L-Methylcysteine hydrochloride
Cholic acid	Prednisolone farnesylate	Reduced lanolin
Succinylated gelatin or gelatin succinate	Phenylalanine	Betamethasone valerate
Prednisolone succinate	Phenethyl alcohol denatured alcohol (95 vol%)	Prednisolone valerate acetate
Cholecalciferol	Mometasone furoate	Beef tallow
Cholesterol	Fluocinonide	beef tallow hardened oil
Cholesterol lanolin fatty acid ester	Fluocinolone acetonide	Bone charcoal
Cyanocobalamin	Prednisolone	Fatty acids (derived from tallow)
Cystine	Protirelin	Self-emulsifying glyceryl monostearate
Distearic acid	Proline	Tallow and tallow derivatives
Cysteine	Betamethasone	Lipophilic glyceryl monostearate
Cysteine hydrochloride	Peptone	Gonadorelin acetate
Betamethasone dipropionate	Decaglyceryl pentaoleate	Dexamethasone acetate
Sucrose fatty acid esters or sucrose fatty acid esters-S	Decaglyceryl pentastearate	Paramethasone acetate
Stearyl alcohol	Polyethylene glycol 6000 polysorbate	Hydrocortisone acetate
Polyoxyl stearates	Polyethylene glycol fatty acid esters	Buserelin acetate
Stearic acid and its salts	Polyoxyethylene oleyl ether	Prednisolone acetate
Sodium N-stearoyl-L-glutamate	Polyoxyethylene cholestanol	Hydrogenated egg yolk lecithin
Sorbitan sesquioleate	Polyoxyethylene cetyl ether	Purified egg yolk lecithin
Cetanol	Polyoxyethylene sorbitan monooleate	Medium-chain triglycerides
Gelatin	Polyoxyethylene sorbitan fatty acid esters	Calcium lactate
Gelatin hydrolysates	Polyoxyethylene lanolin	Lactose
Shellac	Macrogol 400	Egg yolk lecithin
Serine	Methionine	

Note) Components equivalent to those included in the above list (e.g. esters with different alkyl groups, fatty acids with only different side chain lengths, surfactants, fatty acid esters with different polymerization degrees, etc.) may be objectively regarded as equivalent to those included in the above list.

Attachment 3. Examples of the description in application form for marketing authorization

1. Raw materials, etc. derived from cattle, etc.
   (Component name ○○○) is derived from (a body part of use △△△) of (animal name such as cattle) (country of origin). The manufacturing method complies with the attached specifications ○○ (or specifications in the official compendium). It is manufactured using raw materials derived from healthy animals. It uses the collected △△△ so that raw materials derived from BSE-infected animals and any body parts prohibited to be used by the Standards for Ruminant-Derived Raw Materials in the Standards for Biological Raw Materials will not be mixed in the manufacturing process. (These raw materials meet the conditions described in Note 2-(1)-[2] of PMSB Notification No. 1069, issued by the Director-General of Pharmaceutical and Medical Safety Bureau, dated October 2, 2001, based on the provision of Paragraph 4 of the relevant standards.)

   (Component name ○○○) is derived from (a body part of use △△△) of (name of animal such as cattle) and falls under the category of low-risk raw materials, etc. controlled so as not to be contaminated during the manufacturing process with raw materials derived from BSE-infected animals and parts prohibited by the Standards for Ruminant-Derived Raw Materials in the Standards for Biological Raw Materials.

2. Raw materials, etc. derived from humans, animals, etc.
   (Component name ○○○) is derived from the (a body part of use) of humans (animal name in the case of animals). The relevant raw material was obtained from humans (animal name in the case of animals) after confirming their acceptability through donor screening (describe the test items and test methods performed). The materials obtained were subjected to inactivation/elimination of pathogens by the method in ○○○○.

   (Component name ○○○) is derived from the (a body part of use) of humans (animal name in the case of animals). The relevant raw material derived from healthy humans (or animal), tests on ○○○ (describe the classification of raw material or process) (describe the test items and test methods performed) were performed, and pathogens were inactivated/eliminated by the method in ○○○○.

3. Blood products, etc.
   (Blood component name ○○○) is derived from blood collected in (country of blood collection). Blood collected in the countries and blood collection sites listed below meets the definition of blood donation specified in PMSB Notification No. 0515020 issued by the Director-General of Pharmaceutical and Medical Safety Bureau dated May 15, 2003. (List possible countries and name of blood collection sites.)

Attachment 4. Countries in which the risk of BSE pathogen propagation is considered negligible by the World Organization for Animal Health (as of May 30, 2024)

Date of release of accreditation	Countries
May 25, 2007	Australia, Argentina, New Zealand, Singapore, Uruguay
May 30, 2008	Finland, Iceland, Norway, Sweden, Paraguay
May 29, 2009	Chile
May 26, 2010	India, Peru
May 27, 2011	Denmark, Panama
May 25, 2012	Austria, Belgium, Brazil, Colombia
May 29, 2013	Israel, Italy, Japan, Netherlands, Slovenia, United States
May 30, 2014	Bulgaria, Croatia, Estonia, Hungary, Latvia, Luxembourg, Malta, Portugal, Romania (designation withdrawn in 2015), Slovakia, South Korea, China (excluding Hong Kong and Macao)
May 29, 2015	Cyprus, Czech Republic, France (designation withdrawn in 2016), Ireland (designation withdrawn in 2016), Liechtenstein, Switzerland
May 27, 2016	Costa Rica, Germany, Lithuania, Mexico, Namibia, Romania (re-designated), Spain
May 23, 2017	United Kingdom (limited to Northern Ireland and Scotland; Scotland designation withdrawn in 2019), Poland
May 25, 2018	Nicaragua
May 31, 2019	Serbia
May 30, 2020	Bolivia, United Kingdom (limited to Jersey)
May 28, 2021	Ireland (re-designated)
May 26, 2022	Canada, France (re-designated)