Provisional Translation (as of May 2024)*

PFSB/ELD Notification No. 1002-1
PFSB/MDRMPE Notification No. 1002-5
October 2, 2014

To: Directors of Prefectural Health Departments (Bureaus)

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

Counsellor of Minister's Secretariat, Ministry of Health, Labour and Welfare
(Person in charge of review control of medical devices, regenerative medical products, etc.)
(Official seal omitted)

Standards for Biological Raw Materials, Operational Guideline

The Standards for Biological Raw Materials (Ministry of Health, Labour and Welfare Notification No. 210, 2003) were revised in accordance with "Partial Amendments of the Standards for Biological Raw Materials " (Ministry of Health, Labour and Welfare Notification No. 375, 2014), taking into account that a system to ensure the safety of regenerative medical products and to accelerate their practical application was established in the Act for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 84, 2013) and reviewing how to satisfy the standards for raw materials derived from humans or animals used for drugs, medical devices, regenerative medical products, etc. in light of the latest scientific knowledge.

This time, the operation of the revised Standards for Biological Raw Materials has been specified as shown in the Attachment. Please understand the content and notify related companies under your jurisdiction of it.

This notification shall apply from November 25, 2014; "Handling of Applications for Partial Change Approval for Ensuring the Quality and Safety of Drugs Manufactured from Raw Materials of Human or Animal Origin" (PMSB/ELD Notification No. 1046 dated July 10, 2001), "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" (PMSB/ELD Notification No. 1552 dated November 26, 2001), "Administrative Procedures, etc. after
Partial Revision of the Enforcement Regulations of the Pharmaceutical Affairs Law" (PMSB/ELD Notification No. 0520001, PMSB/SD Notification No. 0520001, PMSB/CND Notification No. 0520001, PMSB/BBPD Notification No. 0520001 dated May 20, 2003), "Handling of Raw Materials Specified in the Standards for Biological Raw Materials" (Administrative Notice of the Evaluation and Licensing Division dated March 27, 2009), "Self-inspection of Pharmaceuticals and Medical Devices, etc. Manufactured using Materials Derived from Bovine Specimens, etc. Originating from Brazil" (PFSB Notification No. 1211-8 dated December 11, 2012) and "Q&A about Self-inspection of Pharmaceuticals and Medical Devices, etc. Manufactured using Materials Derived from Bovine Specimens, etc. Originating from Brazil" (Administrative Notice of the Evaluation & Licensing Division dated December 27, 2012) shall be withdrawn as of that date.

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 is a source of raw materials and ancillary materials, the following examples or equivalent materials cannot be said to be appropriate for handling similarly to 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 (genetical 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 (genetical 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 "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.

(4) 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 is used as raw materials, etc. for other drugs, etc., in consideration of the risks and benefits of the product, 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 "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.

(4) 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.

(5) 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 brain disorders

(6) With regard to the consent of donors in the Standards for Human Cell/Tissue-based Raw Materials (4)-B, it is also applicable to the case 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.

(7) 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 himself/herself has difficulty in receiving the explanation and giving consent or lacks the ability to give complete consent on his/her own.

b. There is a reasonable reason 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.

(8) 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.

(9) 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.

(10) 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 covered by 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 the case 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 for the evaluation of the treatment 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. Fatty acids, glycerin, fatty acid ester, amino acids, synthetic oligopeptides, etc. listed in Attachment 2 (however, excluding beef tallow, beef tallow hardened oil, succinylated gelatin, gelatin, hydrolyzed gelatin, hard fat, yolk lecithin, fatty acids (derived from beef tallow), hydrogenated egg-yolk lecithin, purified egg-yolk lecithin, and egg-yolk lecithin).

b. Bone charcoal

c. 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.

d. Materials treated by the following methods or equivalent methods

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

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

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

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

- Immerse in 1 mol/L sodium hydroxide solution and autoclave at 121℃ for 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 1 hour; autoclave at 121℃ for 1 hour; clean and subject to routine sterilization.
- Immerse in sodium hydroxide solution or sodium hypochlorite solution for 1 hour; wash with water; autoclave at 121℃ (in a case of weight pressurized and degassing autoclave) or 134℃ (in a case of vacuum degassing autoclave) for 1 hour; clean and subject to routine sterilization.
- Immerse in sodium hydroxide solution and boil for 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 1 hour at room temperature; clean; wash with

water and subject to routine sterilization.

- Autoclave at 134℃ for 18 minutes (note that, for brain tissue bake-dried onto surfaces, infectivity will be largely but not completely removed.)

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

- Pour 2 mol/L sodium hydroxide or sodium hypochlorite stock solution, allow it to stand for 1 hour, and wash with water.

[5] 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 121℃ or higher for 1 hour in a vacuum degassing autoclave (for small dry material that can withstand exposure to sodium hydroxide or sodium hypochlorite).

- Autoclave at 134℃ for 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).

* The [1] and [2] were cited from "Guidance for minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (issued by European Medicines Agency in May 2001), and the [3] to [5] 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 following countries which are currently applicable to the "countries which the World Organization of Animal Health recognizes as having a negligible transmission risk of bovine spongiform encephalopathy" in the Standards for Ruminant-Derived Raw Materials (2).

Date of release of accreditation	Country
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, USA
May 30, 2014	Bulgaria, Croatia, Estonia, Hungary, Latvia, Luxembourg, Malta, Portugal, Romania, Slovakia, South Korea, China (excluding Hong Kong and Macao)

The countries listed here 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/#ui-id-2[1]), etc.

(5) If the World Organization of 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 meeting of the World Organization of Animal Health in which the recognition is discussed. It shall be noted that the ruminant-derived raw materials, etc. in the relevant country can be used after the above date including the countries listed in the above 5 (4).

(6) The "wool" and "milk" in the Standards for Ruminant-Derived Raw Materials (2) include wool 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.

[1] Updated for April 2024. It is different from the original Japanese version.

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. are taken appropriately.

d. Standard operating procedures describing the methods and procedures for breeding control of donor animals have been prepared.

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

f. Donor animals are handled based on the spirit 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 raw material or the main cell component of the pharmaceutical product.

(4) The "past uses" described in the provisory clause in the Standards for Animal Cell/Tissue-based Raw Materials (3) include 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, a demonstration of sterility 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 "Public Health Guidelines on Infectious Disease Issues in Xenotransplantation" (HPB/RDD Notification No. 0709001, July 9, 2002) and the "Guidance on Epithelial Regenerative Medicine Using 3T3J2 Strain or 3T3NIH Strain as the Feeder Cells Following the Public Health Guidelines on

Infectious Disease Issues in Xenotransplantation" (HPB/RDD Notification No. 0702001, July 2, 2004).

(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 severer conditions depending on the properties of intended raw materials at an appropriate time point during the manufacturing process, the risk assessment 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, the possibility that the risk of transmission of prions will not be eliminated by chemical processing, etc. alone cannot be ruled out. The Standards for Ruminant-Derived Raw Materials shall apply to animal-derived raw materials, etc. that are described in Attachment 2 and not covered by the Standards for Animal-Derived Raw Materials but are ruminant-derived raw materials, etc. not listed in the above 5 (2).

(2) The "healthy" in the Standards for Animal-Derived Raw Materials (1) are 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 16th edition, and meeting the "food standard" shall mean meeting 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 should not be captured in an area where they are not allowed to be captured.

(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 assource 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 the case where a test to detect viruses can be performed more accurately by promoting a very partial process of the manufacturing 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 elimination 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, a demonstration of sterility 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 approval, 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 approval 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. However, in such a case, the manufacturer, etc. shall be controlled so that necessary information can be obtained promptly for the records stored by the relevant raw materials, etc. vendor.

(5) Refer to Attachment 3 for the description of the approval letter issued at the marketing approval.

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.

DL-Serine	Succinylated gelatin	Polyethylene glycol fatty acid ester
L-aspartic acid or its salts	Prednisolone succinate	Polyoxyethylene oleyl ether
L-Alanine	Cholecalciferol	Polyoxyethylene cholestanol
L-Arginine	Cholesterol	Polyoxyethylene cetyl ether
L-isoleucine	Cholesterol lanolin fatty acid ester	Polyoxyethylene sorbitan monooleate
L-Carbocisteine	Cyanocobalamin	Polyoxyethylene sorbitan fatty acid ester
	Glyceryl Monostearate, Self-emulsifying Type	Polyoxyethylene lanolin
L-Cystine	Distearate	Polyethylene glycol 6000 polysorbate
	Betamethasone dipropionate	Macrogol 400
L-Cysteine	Sucrose fatty acid ester	Polyethylene glycol monooleate
	Sucrose fatty acid ester-S	Sorbitan monooleate
L-Cysteine monohydrochloride	Stearyl alcohol	Polyoxyethylene sorbitan monooleate
L-Serine	Stearic acid and its salts	Polyglyceryl monooleate
L-Tyrosine	Polyoxyl stearate	Glycerin monostearate
L-Tyrodine	Sorbitan sesquioleate	Sorbitan monostearate
L-Tryptophan	Cetanol	Propylene glycol monostearate
L-Threonine	Gelatin	Polyethylene glycol monostearate
L-Valine	Hydrolyzed Gelatin	Polyoxyethylene sorbitan monostearate
L-Hydroxyproline	Sorbitan fatty acid ester	Sorbitan monolaurate
L-Phenylalanine	Albumin tannate	Coconut oil fatty acid hydrolyzed collagen triethanolamine
L-Proline	Sodium deoxycholate	Yolk lecithin
L-Leucine	Dexamethasone sodium metasulfobenzoate	Lauryl alcohol
L-Cysteine hydrochloride	Dexamethasone	Sodium lauryl sulfate
N-Acetyl-L-cysteine	Sodium desoxycholate	Lactulose
	Dehydrocholic acid or its salts	Lactobionic acid

Sodium N-stearoyl-L-glutamate	Triacetin	Erythromycin lactobionate
N-coconut oil fatty acid/hardened beef tallow fatty acid sodium acyl-L-glutamate	Triamcinolone acetonide	Lanolin
Di(Cholesteryl/2-Octyldodecyl) N-Lauroyl-L-Glutamate	Sorbitan trioleate	Lanolin alcohol
α-Monoisostearyl glyceryl ether	Sorbitan tristearate	Lanolin fatty acid cholesterol ester
Acetylated sucrose denatured alcohol 95 vol%	Glyceryl Tritallowate	Cysteine malate
Amerchol CAB	Lactose	
Alfacalcidol	Hydroxyapatite	Hydrocortisone sodium phosphate
Isostearic acid	Hard fat	Betamethasone phosphate or its salts
Ursodeoxycholic acid	PANACET 810	Riboflavin sodium phosphate
Ursodesoxycholic acid	Isopropyl palmitate	Lecithin
Ethanol/anhydrous ethanol	Cetyl palmitate	Ethyl L-cysteine hydrochloride
Epidihydrocholesterin	Methyl hyodeoxycholate	L-Methylcysteine hydrochloride
Oleyl alcohol	Vitamin A + D2 powder	Reduced lanolin
Oleic acid	Vitamin B12	Betamethasone valerate
Decyl oleate	Vitamin D	Prednisolone valerate acetate
Caprylic acid, capric acid	Vitamin D2	Fatty acid (derived from beef tallow)
Galactose	Vitamin D3	Glyceryl Monostearate, Self-emulsifying Type
Calcitriol	Cholesteryl hydroxystearate	Glyceryl Monostearate, Lipophilic
Beef tallow	Hydrocortisone	Gonadorelin acetate
Beef tallow hardened oil	Prednisolone farnesylate	Dexamethasone acetate
Glyceryl triacetin	Phenylethyl alcohol denatured alcohol 95 vol%	Paramethasone acetate
Glycerin	Mometasone furoate	Hydrocortisone acetate
Glycerin oleate	Fluocinonide	Buserelin acetate
Glycerin fatty acid ester	Fluocinolone acetonide	Prednisolone acetate
Chenodeoxycholic acid	Prednisolone	Hydrogenated yolk lecithin
	Protirelin	Purified yolk lecithin

Geraniol denatured alcohol 95 vol%	Betamethasone	Medium-chain fatty acid triglyceride
Cholic acid	Decaglyceryl pentaoleate	Calcium lactate
Succinylated gelatin	Decaglyceryl pentastearate	Yolk lecithin

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 approval letter issued at the marketing approval

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.)