Criteria for biological ingredients

(May 20, 2003)
(MHLW Ministerial Announcement No. 210)

In accordance with provisions in Article 42, Paragraph 1 (including the cases where it is applied mutatis mutandis pursuant to Article 68-5) and Paragraph 2 of the Act of the Pharmaceutical Affairs Act (Act No. 145 of 1960), the Standards for biological ingredients shall be established as follows and applied from July 30, 2003 (provisions pertinent to records and storage of biological raw materials in the concerned standards shall be applied from October 30, 2003), and the standard for cell- and tissue-based drugs and medical devices (MHLW Announcement No. 101 of 2001) shall be repealed on July 29, 2003. To drugs, quasi-drugs, cosmetics, and medical devices actually approved on the said date under provisions in Article 14 (including the cases where it is applied mutatis mutandis pursuant to Article 23) or Article 19-2 of the Act, the provisions then in force shall remain applicable until October 29, 2003.

Standards for biological ingredients

1 General notices

1 The purpose of the concerned standards is to ensure the quality, efficacy, and safety of drugs, quasi-drugs, cosmetics, medical devices, and regenerative medical products (hereinafter referred to as "drugs, etc.") by establishing standards for actions on ingredients, etc. derived from human and other living organisms (except for plants) included in drugs, etc. (including materials used in a manufacturing process as additives and culture medium components) that should be taken when used in manufacture.

2 The concerned standards, however, shall not be applied to ingredients, etc. included in in-vitro diagnostics and other products not directly used in human bodies as well as microorganisms and viruses used in manufacture of vaccines, etc.

3 The term "raw materials" refers to sources of ingredients or materials used in manufacture of drugs, etc., and the term "ingredients, etc." refers to ingredients or materials, or their raw materials.

4 The term "raw plasma" refers to plasma separated from ingredients, etc. by an appropriate method where necessary and represents individual plasma fractions used in a group for manufacture of plasma fraction preparations or a mixture of all or a part of these fractions.

5 The term "donor" refers to a person who provide cells or tissues turning into ingredients, etc. of drugs, etc. (except for ones related to brain-dead human bodies stipulated in Article 6, Paragraph 2 of the Act on Organ Transplantation [Act No. 104 of 1997]).

6 The term "donor animals" refers to non-human animals which provide cells or tissues turning into ingredients, etc. of drugs, etc.

7 The term "donor screening" refers to qualification activities to judge whether the concerned donor or donor animal is adequately eligible to provide cells or tissues turning into ingredients, etc. of drugs, etc. by performing diagnosis through interview and examination, etc. for donors or testing/inspection and rearing management for donor animals.

8 The term “window period” refers to a period at an early stage of infection in which neither microorganisms such as bacteria, fungi and yeasts, and viruses nor their relevant substances such as antigens, antibodies, and genes are detected.

9 To drugs, etc. for which an approval document issued upon approval for marketing, etc. has the statement to the effect that the quality and safety have been confirmed to be adequate as required under the provisions in the concerned standards or more, the relevant provision in the concerned standards shall not be applied.

10 Drugs, etc. approved for marketing, if appropriately used as ingredients, etc. in the other drugs, etc., shall be deemed as ingredients, etc. conforming to the concerned standards.

2 General rules for blood products

1 General rules for blood products for transfusion

(1) Persons who provide blood to be included in blood products for transfusion (hereinafter referred to as “blood donors” in the General rules for blood products for transfusion) shall be free from suspected bloodborne infectious diseases as determined through interview, etc., and confirmed to be adequately eligible to provide blood turning into ingredients, etc. of blood products for transfusion. This, however, may not be applied to blood products for transfusion for which an approval document issued upon approval for marketing has the statement to the effect that the manufacturing process has been demonstrated to inactivate or remove bloodborne infectious bacteria, fungi and yeasts, viruses, etc.

(2) Blood collection must be performed by any of the following blood collection procedures.

A Whole blood collection Procedure using a blood set, which has been prepared by attachment of a blood collection needle immediately after injection of an appropriate anticoagulant solution for blood storage, and sealing and autoclaving.

B Blood component collection Only specified blood component such as plasma and platelet are collected, while the other components are returned to the donor by either of the following procedures.

(A) Procedure in which from the whole blood collected in accordance with A, a specified blood component is collected by an appropriate method, and the other blood components are returned to the donor

(B) Procedure in which a specified blood component is collected with a blood component collection device by circulating blood extracorporeally and adding an appropriate anticoagulant solution for blood storage

(3) Ingredients, etc. for blood products for transfusion shall be prepared from any of the following materials collected by blood collection procedures specified in (2) unless otherwise separately specified.

A Blood collected by the whole blood collection procedure

B Platelet rich plasma or platelet concentrate plasma collected by the blood component collection procedure

C Plasma collected by the blood component collection procedure

(4) Ingredients, etc. of blood products for transfusion must be stored at 1°C to 10°C. Such materials, however, may be stored at ordinary temperature for manufacture of platelet preparations or for separation of blood component where applicable.

(5) Of blood to be used as ingredients, etc. of blood products for transfusion, all the individual portions separated by donor must be subjected to serology tests for at least Treponema pallidum, hepatitis B virus(HBV), hepatitis C virus(HCV), human immunodeficiency virus (HIV-1 and HIV-2), and human T-cell leukemia virus-1 (HTLV-1). Any portion disqualified by the above tests must not be used as ingredients, etc. of blood products for transfusion except for cases stipulated under monographs in the Minimum Requirements for Biological Products (MHLW Ministerial Announcement No. 155 of 2004).

(6) Blood to be used as ingredients, etc. of blood products for transfusion must be subjected to nucleic acid amplification tests for at least hepatitis B virus DNA, hepatitis C virus RNA, and human immunodeficiency virus RNA. Any blood portion in which hepatitis B virus DNA, hepatitis C virus RNA or human immunodeficiency virus RNA is detected in these tests must not be used as ingredients, etc. of blood products for transfusion.

(7) Of blood to be used as ingredients, etc. of blood products for transfusion, all the individual portions separated by donor must be subjected to blood typing using antibodies for ABO blood typing and for Rh blood typing.

ABO blood typing must use known type A and type B erythrocytes on the serum or plasma to judge the blood type, and antibodies for A blood typing or dried ones and antibodies for B blood typing or dried ones to be used in the blood typing must conform to the Criteria for Blood-typing Antibodies (MHW Ministerial Announcement No. 204 of 1994).

Rh blood typing must use antibodies for anti-D blood typing or mixed antibodies for anti-D blood typing conforming to the Criteria for Blood-typing Antibodies, and be performed in accordance with the specified procedure to judge D (Rho) positive or negative. Any portion tested negative for D must be further tested using anti-human globulin antibody (multispecific antibody) conforming to the Criteria for Blood-typing Antibodies.

(8) With respect to blood to be used as ingredients, etc. of blood products for transfusion, the following items must be recorded and retained so that information necessary for ensuring the quality and safety can be identified.

A Name of blood collection site involved in blood collection

B Date of blood collection

C Records on medical examinations of blood donors such as medical records

D Results from serology tests and nucleic acid amplification tests

E Course of operations of the concerned blood collection

F Number identifying the blood donor of the concerned blood

G Information necessary for ensuring the quality and safety of blood products for transfusion other than ones listed in A to F

2 General rules for plasma fraction preparations

(1) Persons who provide blood to be included in plasma fraction preparations (hereinafter referred to as "blood providers" in the General rules for plasma fraction preparations) shall be free from suspected bloodborne infectious diseases as determined through interview, etc., and confirmed to be adequately eligible to provide blood turning into ingredients, etc. of plasma fraction preparations. This provision, however, may not be applied to plasma fraction preparations for which an approval document issued upon approval for marketing has the statement to the effect that the manufacturing process has been demonstrated to inactivate or remove bloodborne infectious bacteria, fungi and yeasts, viruses, etc.

(2) Blood collection must be performed by any of the blood collection procedures specified in (2) under 1 General rules for blood products for transfusion.

(3) Ingredients, etc. for plasma fraction preparations shall be prepared from any of the following materials collected by blood collection procedures specified in (2) unless otherwise separately specified.

A Blood collected by the whole blood collection procedure

B Platelet rich plasma or platelet concentrate plasma collected by the blood component collection procedure

C Plasma collected by the blood component collection procedure

(4) Ingredients, etc. of plasma fraction preparations must be stored at 10°C or lower but not in a frozen condition for ingredients, etc. classified under (3) A or at 10°C or lower for ones under (3) B or C.

(5) Blood to be used as ingredients, etc. of plasma fraction preparations must be subjected to serology tests for at least hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV-1 and HIV-2). Any portion disqualified by the above tests must not be used as ingredients, etc. except for cases stipulated under monographs in the Minimum Requirements for Biological Products.

(6) Raw plasma of plasma fraction preparations must be subjected to nucleic acid amplification tests for at least hepatitis B virus DNA, hepatitis C virus RNA, and human immunodeficiency virus RNA. This provision, however, may not be applied if none of hepatitis B virus DNA, hepatitis C virus RNA, and human immunodeficiency virus RNA have been detected from blood which is the ingredients, etc. of the raw plasma by nucleic acid amplification tests. Any plasma portion in which hepatitis B virus DNA, hepatitis C virus RNA, or human immunodeficiency virus RNA is detected in these tests must not be used as raw plasma.

(7) Raw plasma must be stored at 6°C or lower.

(8) With respect to blood and raw plasma to be used as ingredients, etc. of plasma fraction preparations, the following items must be recorded and retained so that information necessary for ensuring the quality and safety can be identified.

A Name of blood collection site involved in collection of ingredients, etc.

B Date of collection of ingredients, etc.

C Records on medical examinations of blood providers of blood deriving raw plasma such as medical records

D Records of serology test and nucleic acid amplification tests

E Course of operations of collecting ingredients, etc. and those of manufacturing raw plasma
F Manufacturing numbers of ingredients, etc. and raw plasma
G Number identifying blood provider of blood deriving raw plasma
H Information necessary for ensuring the quality and safety of plasma fraction preparations other than ones listed in A to G

3 General rules for human-derived ingredients

1 Standards for human cell- and tissue-based ingredients

(1) Human-derived cells or tissues to be used as ingredients, etc. (hereinafter referred to as "human cell- and tissue-based ingredients, etc."), comprising drugs, etc. (except for blood products), must be collected in a facility with personnel and equipment enough to implement appropriate hygiene management.

(2) For collection of human cell- and tissue-based ingredients, etc., the following actions must be taken.

A On a process of collecting human cell- and tissue-based ingredients, etc., actions appropriate for prevention against contamination with microbial pathogen and other pathogenic agents shall be taken.

B The collected human cell- and tissue-based ingredients, etc. shall be appropriately examined in light of the latest knowledge about infections as necessary, and shall be confirmed to be free from contamination with microbial pathogen and other pathogenic agents.

(3) A donor must meet all of the following items and be adequately eligible to provide human cell- and tissue-based ingredients, etc. In the case where the donor is also the recipient of the drugs, etc., donor screening may not be always required.

A Before collection of human cell- and tissue-based ingredients, etc., interview, medical examination, and tests shall rule out infection with bacteria, fungi and yeasts, or viruses depending on the intended use.

B Test items and test methods in A shall be appropriate in light of the latest knowledge about infections.

C The tests or management shall be performed in consideration of the window period; for instance, re-tests are performed in appropriate timing for test items and test methods in A.

D The donor must be judged to be eligible as a donor not only through interview, medical examination, and tests about relevant diseases in addition to Items A to C but also in consideration of his or her past history of transfusion or transplantation therapy.

(4) The person engaged in collecting human cell- and tissue-based ingredients, etc. must confirm that the concerned human cell- and tissue-based ingredients, etc. meet the following requirements, and thus are appropriate for being used in drugs, etc.

A In the case where human cell- and tissue-based ingredients, etc. are collected from a deceased person, the person in charge of the collection shall appropriately explain to the bereaved family about intended use of the human cell- and tissue-based ingredients, etc. and other necessary information on the collection with documents

using as plain language as possible, while keeping appreciation in mind, and then obtain informed consent in writing.

B Before human cell- and tissue-based ingredients, etc. are received, the person in charge of the collection shall appropriately explain to the donor about the following matters with documents using as plain language as possible, and then obtain informed consent in writing.

(A) Intended use of human cell- and tissue-based ingredients, etc.

(B) Expected hazards and disadvantage associated with provision of human cell- and tissue-based ingredients, etc.

(C) Voluntary decision to become a donor

(D) Matter about consent withdrawal

(E) No disadvantages given to the person who does not provide human cell- and tissue-based ingredients, etc. or who withdraws the consent to providing human cell- and tissue-based ingredients, etc.

(F) Matter about expenses related to provision of human cell- and tissue-based ingredients, etc.

(G) Matter about compensation for injury related to provision of human cell- and tissue-based ingredients, etc.

(H) Matter about protection of the donor's personal information

(I) Matters about patents, copyrights, and other property rights or belonging of economic earnings related to drugs, etc. using human cell- and tissue-based ingredients, etc.

(J) Other matter necessary for attributes of drugs, etc. using human cell- and tissue-based ingredients, etc.

C Before human cell- and tissue-based ingredients, etc. are received under consent of the legally acceptable representative of the donor, the person in charge of the collection shall appropriately explain to the legally acceptable representative about the following matters with documents using as plain language as possible, and then obtain informed consent in writing.

(A) Intended use of human cell- and tissue-based ingredients, etc.

(B) Expected hazards and disadvantage associated with provision of human cell- and tissue-based ingredients, etc.

(C) Voluntary decision to become a legally acceptable representative

(D) Matter about legally acceptable representative's consent withdrawal

(E) No disadvantages given to the legally acceptable representative who does not consent or who withdraws his or her consent

(F) Matter about expenses related to provision of human cell- and tissue-based ingredients, etc.

(G) Matter about compensation for injury related to provision of human cell- and tissue-based ingredients, etc.

(H) Matter about protection of the donor's and legally acceptable representative's personal information

(I) Matters about patents, copyrights, and other property rights or belonging of economic earnings related to drugs, etc. using human cell- and tissue-based ingredients, etc.

(J) Other matter necessary for attributes of drugs, etc. using human cell- and tissue-based ingredients, etc.

D In the case where human cell- and tissue-based ingredients, etc. are provided under consent of the legally acceptable representative, records shall be prepared to document the legally acceptable representative's consent and a relationship between the legally acceptable representative and the person providing human cell- and tissue-based ingredients, etc.

E Any donor shall have a chance to withdraw the consent to use of his or her human cell- and tissue-based ingredients, etc. in drugs, etc. before the concerned ingredients, etc. are used for culture or other processing.

F Human fertilized embryos, when received, shall be stored at the medical institution and not be subjected to operation for establishment of human embryonic stem cells until at least 30 days have passed since consent to provision of the human cell- and tissue-based ingredients, etc. so that the donor can have a chance to withdraw the consent.

G Human fertilized embryos, if received, shall meet the following requirements.

(A) Fertilized embryos prepared to be used for assisted reproductive technology which are not planned to be used for the concerned purpose in the near term and for which loss is confirmed to be accepted by the donor

(B) Fertilized embryos cryopreserved

(C) Fertilized embryos within 14 days after fertilization except for the cryopreservation period

(D) Fertilized embryos from which proper establishment of human embryonic stem cells has been formalized through necessary procedures

H Unpaid provision of human cell- and tissue-based ingredients, etc. This, however, may not be applied to transportation fees and other actual expenses that are incurred in association with provision of human cell- and tissue-based ingredients, etc.

I Collection of human cell- and tissue-based ingredients, etc., if operated, shall be given the first priority so that the collected ingredient is not a material incidentally obtained through medical procedure, surgery, or change of the other treatment strategy.

(5) With respect to human cell- and tissue-based ingredients, etc., the following items must be recorded and retained so that information necessary for ensuring the quality and safety can be identified.

A Facility involved in collection of human cell- and tissue-based ingredients, etc.

B Date of collection of human cell- and tissue-based ingredients, etc.

C Results of diagnosis through interview, medical examinations and tests for donor screening and status

D Course of operations of collecting human cell- and tissue-based ingredients, etc.

E Review result of ethics committee

F Explanatory document and informed consent form

G Identification number of the donor

H Information necessary for ensuring the quality and safety of drugs, etc. other than ones listed in A to G

2 Standards for human urine-derived ingredients

(1) To human urine or urine pool (mixture of urine portions collected from one provider or multiple providers, hereinafter the same) (hereinafter referred to as "human urine") to be used as ingredients, etc. of drugs, etc., the provision in (4) H of the Standards for human cell- and tissue-based ingredients shall be applied mutatis mutandis.

(2) Human urine must be confirmed to be free from contamination with microbial pathogen, etc. by appropriate tests for infections at an appropriate stage. This, however, may not be applied to human urine for the product for which an approval document issued upon approval for marketing, etc. has the statement to the effect that the manufacturing process has been demonstrated to inactivate or remove microbial pathogen and other pathogenic agents.

(3) Urine pool must be subjected to nucleic acid amplification tests for at least hepatitis B virus DNA, hepatitis C virus RNA, and human immunodeficiency virus RNA at an appropriate stage. This, however, may not be applied if none of hepatitis B virus DNA, hepatitis C virus RNA, and human immunodeficiency virus RNA have been detected from the urine to be used as ingredients, etc. by nucleic acid amplification tests.

(4) Human urine must be confirmed to have bacteria, fungi and yeasts, and viruses inactivated or removed in the manufacturing process. This, however, may not be applied to human urine for the product for which an approval document issued upon approval for marketing, etc. has the statement to the effect that omission of such processing is justified.

(5) With respect to human urine, the following items must be recorded and retained so that information necessary for ensuring the quality and safety can be identified.

A Name of institution involved in preparation of human urine

B Date of preparation of human urine

C Results from tests of human urine

D Process for preparation of human urine

E Lot number of human urine

F Information necessary for ensuring the quality and safety of the concerned drugs, etc. other than ones listed in A to E

3 Standards for human-derived ingredients

(1) Human cells or tissues (including cell lines and cells at the end of culture for the products produced in cell culture using the cell bank as the starting substrate) deriving human materials (except for human cell- and tissue-based ingredients, etc., human urine, and materials scientifically known to have no infection risk with bacteria or virus, hereinafter referred to as "human-derived ingredients, etc.") to be used as ingredients, etc. of drugs, etc. (except for blood products) must be subjected to virus tests at an appropriate stage. The human-derived ingredients, etc. in which adventitious viruses are detected in the above tests, if any, must not be used in manufacture of drugs, etc. in principle. This, however, may not be applied to the ingredients, etc. which are prepared from a human-derived cell bank already

constructed as of the application timing of the concerned standards and for which the relevant approval document issued upon approval for marketing, etc. has the statement to the effect that use of the ingredients, etc. is justified to an extent as done by the above tests or more from a viewpoint of ensuring the quality and safety.

(2) Persons who provide human blood-derived ingredients, etc. shall be free from suspected bloodborne infectious diseases as determined through interview, etc., and confirmed to be adequately eligible to provide blood turning into human-derived ingredients, etc.

(3) For human-derived ingredients, etc., the manufacturing process must include treatments to inactivate or remove bacteria, fungi and yeasts, and viruses. This, however, may not be applied to human-derived ingredients, etc. for the product for which an approval document issued upon approval for marketing, etc. has the statement to the effect that omission of such processing is justified.

(4) With respect to human-derived ingredients, etc., the following items must be recorded and retained so that information necessary for ensuring the quality and safety can be identified.

A Name of institution involved in preparation of human-derived ingredients, etc.
B Date of preparation of human-derived ingredients, etc.
C Results from tests of human-derived ingredients, etc.
D Lot number of human-derived ingredients, etc.
E Information necessary for ensuring the quality and safety of the concerned product other than ones listed in A to D

4 General rules for animal-derived ingredients

1 Standards for ruminant-derived ingredients

(1) For ruminant materials to be used as ingredients, etc. of drugs, etc. (except for ingredients, etc. manufactured through high temperature or alkaline treatment, or other appropriate treatment, hereinafter referred to as “ruminant-derived ingredients, etc.”), the parts listed below must not be used.

A Pituitary
B Thymus
C Dura mater
D Trigeminal ganglion
E Pineal gland
F Spinal cord
G Spinal column
H Placenta (except for bovine tissue)
I Cranial bone
J Intestine
K Brain
L Cerebrospinal fluid
M Dorsal root ganglion
N Spleen (except for bovine tissue)
O Adrenal gland

P Tonsils
Q Eye
R Lymph node

(2) The country of origin of ruminant-derived ingredients, etc. must be one of the countries which is recognized by the Office International des Epizooties to be a country with a negligible risk of transmission of bovine spongiform encephalopathy or a country listed below. This, however, shall not be applied to the following products: Gelatin (including collagen) derived from wool, milk, bone, and skin (hereinafter referred to as "low-risk ingredients, etc."); injections manufactured through cell culture using ruminant-derived ingredients, etc. produced in Canada (hereinafter referred to as "Canadian ingredients") (limited to the injections manufactured through the process in which Canadian ingredients are used only for the cell bank) and other equivalents; vaccines manufactured using Canadian ingredients (limited to oral vaccines); injections (limited to the injections manufactured through the process in which Canadian ingredients are used only for seed culture) or oral products manufactured through microbial culture using Canadian ingredients and other equivalents; and products for external use manufactured using Canadian ingredients.

A El Salvador
B Kenya
C Costa Rica
D Swaziland
E Nigeria
F Namibia
G Nicaragua
H New Caledonia
I Pakistan
J Vanuatu
K Botswana
L Mauritius

(3) With respect to ruminant-derived ingredients, etc. (except for low-risk ingredients, etc.), the following items must be recorded and retained so that information necessary for ensuring the quality and safety can be identified.

A Country of origin
B Date of preparation of ruminant-derived ingredients, etc.
C Breeding and sacrifice conditions of ruminant deriving ruminant-derived ingredients, etc.
D Course of treatment and operation on ruminant-derived ingredients, etc. to prevent transmissible spongiform encephalopathy
E Lot number of ruminant-derived ingredients, etc.

(4) For drugs, quasi-drugs, medical devices, and regenerative medical products for which the therapeutic benefit outweighs the risk of using ruminant-derived ingredients, etc. inevitably even not conforming to (1) or (2), the approval document issued upon approval for marketing shall justify such use.

(5) For cosmetics, if ruminant-derived ingredients, etc. not conforming to (2) are used inevitably, only the ingredients, etc. meeting requirements specified by the Director-general of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare shall be acceptable.

2 Standards for animal cell- and tissue-based ingredients, etc.

(1) Animal-derived cells and tissues to be used as ingredients, etc. (hereinafter referred to as "animal cell- and tissue-based ingredients, etc."), comprising drugs, etc., must be collected in a facility with personnel and equipment enough to implement appropriate hygiene management.

(2) On collection of animal cell- and tissue-based ingredients, etc., actions appropriate for prevention against contamination with microbial pathogen and other pathogenic agents in the collection process shall be taken.

(3) A donor animal of animal cell- and tissue-based ingredients, etc. must be confirmed to be adequately eligible to provide animal cell- and tissue-based ingredients, etc. This, however, may not be applied to products that are obtained from cell culture initiated from a characterized cell bank, derive materials of drugs, etc., and have been actually used in manufacture of drugs, etc.

(4) Animal cell- and tissue-based ingredients, etc. must be confirmed to have been verified for virus infection risk and subjected to other appropriate procedures before use.

(5) With respect to animal cell- and tissue-based ingredients, etc., the following items must be recorded and retained so that information necessary for ensuring the quality and safety can be identified. This, however, may not be applied to products that are obtained from cell culture initiated from a characterized cell bank, derive materials of drugs, etc., and have been actually used in manufacture of drugs, etc.

A Facility involved in collection of animal cell- and tissue-based ingredients, etc.

B Date of collection of animal cell- and tissue-based ingredients, etc.

C Status of acceptance of donor animals as well as testing/inspection and rearing management

D Course of operations of collecting animal cell- and tissue-based ingredients, etc.

E Lot number of animal cell- and tissue-based ingredients, etc.

F Information necessary for ensuring the quality and safety of the concerned product other than ones listed in A to E

3 Standards for animal-derived ingredients

(1) Animal-derived materials to be used as ingredients, etc. of drugs, etc. (except for animal cell- and tissue-based ingredients, etc. and materials scientifically known to have no infection risk with bacteria, fungi and yeasts, and virus, hereinafter referred to as "animal-derived ingredients, etc.") must be collected from healthy animals or confirmed to have been subjected to demonstration of sterility, verification of virus infection risk and other appropriate procedures.

(2) Products obtained from cell culture initiated from a characterized animal-derived cell bank must be subjected to virus tests at an appropriate stage. The animal-derived ingredients, etc. in which adventitious viruses are detected in the above tests, if any, must not be used in manufacture of drugs, etc. in principle. This, however, may not be

applied to the ingredients, etc. which are prepared from a cell bank already constructed as of the application timing of the concerned standards and for which the relevant approval document issued upon approval for marketing, etc. has the statement to the effect that use of the ingredients, etc. is justified to an extent as done by the above tests or more from a viewpoint of ensuring the quality and safety.

(3) To products initialed from entire living animals, provisions in (2) of the concerned standards and (3) of the Standards for animal cell- and tissue-based ingredients, etc. shall be applied mutatis mutandis.

(4) For animal-derived ingredients, etc. the manufacturing process must include treatments to inactivate or remove bacteria, fungi and yeasts, and viruses. This, however, may not be applied to animal-derived ingredients, etc. for the product for which an approval document issued upon approval for marketing, etc. has the statement to the effect that omission of such processing is justified.

(5) With respect to animal-derived ingredients, etc., the following items must be recorded and retained so that information necessary for ensuring the quality and safety can be identified. This, however, may not be applied to products that are obtained from cell culture initiated from a characterized cell bank, derive materials of drugs, etc., and have been actually used in manufacture of drugs, etc.

A Name of institution involved in preparation of animal-derived ingredients, etc.

B Date of preparation of animal-derived ingredients, etc.

C Results from tests of animal-derived ingredients, etc.

D Lot number of animal-derived ingredients, etc.

(6) To drugs, quasi-drugs, cosmetics, and medical devices other than products designated as biological products, provisions in (2) to (4) shall not be applied.

Revised text (Excerpt) (MHLW Ministerial Announcement No. 157 of March 30, 2004)

It shall be applied from the date of promulgation. To drugs, quasi-drugs, cosmetics, and medical devices actually approved as of the application timing of the concerned ministerial announcement under provisions in Article 14 (including the cases where it is applied mutatis mutandis pursuant to Article 23) or Article 19-2 of the Act and manufactured or imported by September 30, 2004, the provisions then in force shall remain applicable.

Revised text (Excerpt) (MHLW Ministerial Announcement No. 262 of July 5, 2004)

It shall be applied from the date of promulgation. To the following products, however, the provisions then in force shall remain applicable: (a) Drugs, quasi-drugs, cosmetics, or medical devices (hereinafter referred to as “drugs, etc.”) manufactured using gelatin or collagen manufactured from the trigeminal ganglion, spinal column, cranial bone, or dorsal root ganglion of ruminants (hereinafter referred to as “bone-derived gelatin, etc.”) originating in India, Kenya, Costa Rica, Colombia, Nigeria, Pakistan, or Mauritius that are manufactured or imported by September 30, 2005; (b) drugs, etc. manufactured using bone-derived gelatin, etc. originating in Argentine, Uruguay, El Salvador, Australia, Singapore, Swaziland, Chile, Namibia, Nicaragua, New Caledonia, New Zealand, Panama, Vanuatu, Paraguay, Brazil, or Botswana as well as drugs, etc. manufactured using ruminant-derived ingredients originating in the United States of America that were collected in 1986 and before (hereinafter referred to as “American ingredients”); (c) injections manufactured through cell culture using American ingredients

(except for injections manufactured through the process in which American ingredients are used only for the cell bank) and other equivalents, injections manufactured through a purification process using American ingredients and other equivalents, injections manufactured using American ingredients as the active ingredient or excipient (except for injections manufactured using bone-derived gelatin, etc. originating in the United States of America or cholic acid, etc. manufactured from ruminant-derived raw materials originating in the United States of America [hereinafter referred to as "American cholic acid, etc."]) and other equivalents, implantable medical devices manufactured using American ingredients that are manufactured or imported by September 30, 2004 (the above drugs, etc. may be manufactured or imported until manufacture and others of ruminant-derived ingredient-free drugs, etc., which is defined below, if approval applications for these drugs, etc. are filed by the said date in accordance with the provisions in Article 14, Paragraph 1 of the Pharmaceutical Affairs Act that prohibits use of ruminant-derived ingredients (including the case where it is applied mutatis mutandis under Article 23 of the Act) or Article 19-2, Paragraph 1, or Article 14, Paragraph 7 of the Act (including the case where it is applied mutatis mutandis under Article 19-2, Paragraph 4 or Article 23 of the Act) (hereinafter referred to as "ruminant-derived ingredient-free application"); and manufacture or import is to be implemented immediately after the application is approved (hereinafter referred to as "manufacture and others of ruminant-derived ingredient-free drugs, etc."); and (d) oral products or injections manufactured using bone-derived gelatin, etc. originating in the United States of America and other equivalents, oral products manufactured using American ingredients as the active ingredient or excipient (except for oral products manufactured using American cholic acid, etc. and ones manufactured through microbial culture using American ingredients) and other equivalents, injections manufactured using American cholic acid, etc. and other equivalents, vaccines manufactured using American ingredients (except for oral vaccines), injections manufactured through microbial culture using American ingredient (except for ones manufactured through the process in which American ingredients are used only for seed culture) and the other equivalents that are manufactured or imported by March 31, 2005 (for vaccines [except for oral vaccines], application for the test under Article 43, Paragraph 1 of the Act [except for ones at the interim stage] shall be filed by the said date. These drugs, etc. may be manufactured or imported until manufacture and others of ruminant-derived ingredient-free drugs, etc., if a ruminant-derived ingredient-free application is filed by September 30, 2004, and manufacture and others of ruminant-derived ingredient-free drugs, etc. is implemented immediately after the application is approved.).

(partially revised by MHLW Announcement No. 343 of 2009)

Revised text (Excerpt) (MHLW Ministerial Announcement No. 177 of March 31, 2005)

It shall be applied from April 1, 2005.

Revised text (Excerpt) (MHLW Ministerial Announcement No. 343 of July 1, 2009)

It shall be applied from the date of promulgation.

Revised text (Excerpt) (MHLW Ministerial Announcement No. 375 of September 26, 2014)

It shall be applied from November 25, 2014. To drugs, quasi-drugs, cosmetics, and medical devices approved before application of this announcement under provisions in Article 14, Paragraph 1 or Article 19-2, Paragraph 1 of the Act, the provisions then in force shall remain applicable.