Provisional Translation (as of May 2025)*

Administrative Notice

June 30, 2015

To: Division of Pharmaceutical Affairs, Prefectural Health Department (Bureau)

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

Counsellor Office of medical devices, regenerative medical products,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Questions and Answers (Q&A) on the Operation of the Standards for Biological Raw Materials

The operation of the Standards for Biological Raw Materials (MHLW Notification No. 210, 2003) has been shown in "The Standards for Biological Raw Materials, Operational Guideline" (PFSB/ELD Notification No. 1002-1, PFSB/MDRMPE Notification No. 1002-5, 2014).

Q&A on the operation of the Standards for Biological Raw Materials have been compiled as attached. Please notify relevant stakeholders under your jurisdiction.

* 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.

Attachment

Q&A on the operation of the Standards for Biological Raw Materials

Q1 For low-risk raw materials, etc.[1)] , is it permissible to omit to describe a country of origin in an approval application form or registration form of a master file (MF) for drug substances, etc. as indicated in Attachment 3 of the Standards for Biological Raw Materials, Operational Guideline (PFSB/ELD Notification No. 1002-1, PFSB/MDRMPE Notification No. 1002-5, October 2, 2014) (hereinafter referred to as the "Operational Guideline")?
In such cases, is it permissible to delete the description regarding a country of origin of low-risk raw materials, etc. from an approval letter or MF by submitting a minor change notification?

A1 Yes, to both questions. Refer to an example for the description of an approval application form for "low-risk raw materials, etc." in Attachment 3 of the Operational Guideline. In this case, it is acceptable to leave a country of origin field for bovine-derived source materials, etc. blank in sections of composition or manufacturing method in an approval application form or MF registration application form. It is not necessary to submit a minor change notification solely for this change. It is acceptable to make this minor change notification along with other minor change notification or partial change application.

Q2 For low-risk raw materials, etc., is it permissible to delete TSE information (data number) from an approval letter by submitting a minor change notification?

A2 Yes, it is.

Q3 As shown in Section II-5 (3) of the Partial Revision of the Standards for Biological Raw Materials (PFSB Notification No. 1002-27, October 2, 2014), low-risk raw materials, etc. are considered highly likely to have risk-causative agents inactivated or removed during the manufacturing process. Therefore, is it permissible to assume that the exemption, etc. indicated in the proviso of (2), and (3) of the Standards for Ruminant-Derived Raw Materials are applied even if the materials were manufactured before the date on which the countries were accredited as having "a negligible BSE risk" by the World Organization for Animal Health (WOAH, founded as OIE)?

A3 Yes, it is.

Q4 For ruminant-derived raw materials, is it still prohibited to use hazardous parts (e.g., ischial bone) as the source of bone gelatin for the use of capsules, etc. in Japan?

A4 As before, the use of hazardous parts from ruminant animals is prohibited. Therefore, be aware of the differences from food regulations, and information about the parts, etc. of the ruminant animals should be checked when obtaining raw materials for gelatin and its source material.

1) For definition, refer to the Standards for Biological Raw Materials (MHLW Notification No. 210, 2003).

Q5 In cases where any country of origin of low-risk raw materials, etc. is already described in an approval letter or MF, is a partial change application or a minor change notification required to add the new country of origin to those documents?

A5 No, it's not required. Since the restriction on a country of origin has been abolished for low-risk raw materials, etc., neither partial change application or minor change notification is required to add a country of origin.

Q6 For ruminant-derived raw materials listed in the Operational Guideline 5 (2) a and b, is it permissible not to include the description indicated in Attachment 3 of the Operational Guideline in an approval application form or a MF registration application form? In this case, is it permissible to delete such information from the approval letter or MF by submitting a minor change notification?

A6 Yes, to both questions. It is not necessary to submit a minor change notification solely for this change. It is acceptable to make this minor change notification along with other minor change notification or partial change application. However, regarding ruminant-derived raw materials applicable to the Operational Guideline 5 (2) c and d, a partial change application is required to delete the description, as it is necessary to identify and review the raw materials and the methods of virus inactivation or removal, etc..

Q7 For ruminant-derived raw materials, etc., is it permissible to submit a minor change notification to add a country of origin newly accredited as having "a negligible BSE risk" by OIE (WOAH) to an approval letter or MF?

A7 Yes, it is. However, this is limited to cases where the source of the raw materials, etc. were collected after the date on which the country was accredited and publicly recognized as having "a negligible BSE risk" by OIE (WOAH). For drugs, etc.[2)] that are manufactured using ruminant-derived raw materials, etc. from countries that were previously prohibited as countries of origin but are now accredited as such, and that have been approved under the condition that the ruminant-derived raw materials, etc. are required to be switched at the time of approval, the collection date of the source materials should be stated in the approval letter to ensure clarity in handling (Refer to Q8).

Q8 Regarding the drugs, etc. that were approved under the condition that the country of origin of ruminant-derived raw material is required to be switched from the United States (U.S.) to countries conforming to the Standards for Biological Raw Materials, there is no need to switch the U.S.-origin ruminant-derived raw materials on the basis of safety, since U.S. has become an accredited country. Is it not obligatory to comply with the requirement to switch the raw materials at the time of approval? Additionally, how should deleted the description regarding the timing of switch in the approval letter or the relevant information in the package insert or the MHLW website?

A8 The U.S. was recognized as the country with negligible BSE risk on May 29, 2013, by OIE. Consequently, bovine-derived raw materials manufactured from source materials collected in the U.S. before the

2) For definition, refer to the Standards for Biological Raw Materials (MHLW Notification No. 210, 2003).

accreditation date must still be switched. However, bovine-derived raw materials manufactured from source materials collected in the U.S. after the accreditation date do not have to be switched as these materials conform to the Standards for Biological Raw Materials.

Since the situation differs for each product, please consult with the Pharmaceuticals and Medical Devices Agency individually regarding the method of deleting the relevant description (e.g., timing of switch) from the approval letter, etc..

Q9 Do insect-derived cell banks fall under "a characterized animal-derived cell bank" in the Standards for Animal-Derived Raw Materials (2)?

A9 Yes, they do, although insect itself is not included in the definition of animals in the Standards for Biological Raw Materials. While insect-derived cell banks have been used in the manufacturing processes of some products, it is not known whether viruses that persist and proliferate during the culture of insect-derived cell banks are the same as viruses that persist and proliferate in the original insect hosts. Therefore, as before, insect-derived cell banks are treated as being included in "a characterized animal-derived cell bank" in the Standards for Animal-Derived Raw Materials (2).

Q10 Are the conditions listed in Attachment 1 of the Operational Guideline applicable to "the treatment steps to inactivate or remove any pathogens including viruses, etc." in the Standards for Animal-Derived Raw Materials (4)?

A10 Yes, it is. Refer to ICH-Q5A for evaluation when processing is not performed under the conditions listed in Attachment 1 or under more stringent conditions.

Q11 For animals-derived raw materials, etc., when it is confirmed in a review that donor animals are healthy, is it permissible to omit to describe a country of origin or a part of use in an approval application form or MF registration application form as described in Attachment 3 of the Operational Guideline?

A11 Yes, it is. However, this is not applicable to raw materials, etc. subject to the Standards for Ruminant-Derived Raw Materials. This does not apply either when it is deemed necessary during a review, for example, when treatment conditions are specified depending on a part of use.

Q12 For the animal-derived raw materials, etc., when the materials are processed under the conditions listed in Attachment 1 of the Operational Guideline or under more stringent conditions, is it permissible to omit to describe a country of origin or a part of use in an approval application form or a MF registration application form as indicated in Attachment 3 of the Operational Guideline, notwithstanding the Operational Guideline 7 (4)? In this case, is it permissible to delete such information from the approval letter or MF by submitting a minor change notice?

A12 Yes, to both questions. However, this is not applicable to raw materials, etc. subject to the Standards for Ruminant-Derived Raw Materials. It is not necessary to submit a minor change notification solely for this

change. It is acceptable to make this minor change notification along with other minor change notification or partial change application.

Q13 It is stated that the name of ingredients derived from human or other living organisms, as well as the name of the origin of these ingredients and their part of use, etc. should be described in package insert according to the description in the approval letter in Section III-1 (3) ① and III-2 (2) ①, Attachment 1 of Instructions for Package Inserts of Biological Products (PFSB/SD Notification No. 0520004, May 20, 2003). In cases where it is deemed not necessary to describe the country of origin or the part of use in an approval application form according to the Standards for Biological Raw Materials, is it permissible to omit to describe the country of origin or the part in the package insert?

A13 Yes, it is. However, from the perspective of providing appropriate information in the package insert, there may be cases where description of the part of use, etc. is required in the review to clarify the ingredients used.