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PSB/MDED Notification No. 0311-1
March 11, 2025

To: Head of Prefectural Health Department (Bureau)

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

Complete Revision of "Revision of Basic Principles of Biological Safety Evaluation Required for Application for Market Approval of Medical Devices"

Of documents to be attached when making application for marketing approval, etc. of medical devices, documents concerning biological safety evaluation have been handled based on "Revision of Basic Principles of Biological Safety Evaluation Required for Application for Market Approval of Medical Devices" (PSEHB/MDED Notification No. 0106-1 issued by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated January 6, 2020; hereinafter referred to as "old PSEHB notification"). Recently, the old PSEHB notification was reviewed in terms of the basic principles for biological safety evaluation of medical devices and revised as follows so that marketing authorization holders of medical devices can refer to the methods, etc. of performing biological safety testing focusing on handling of marketing approval applications, etc. Therefore, please notify the related organizations, related operators, etc. under your jurisdiction of this revision. With the issuance of this notification, the old PSEHB notification will be abolished.

In addition, we would like to notify you that a copy of this notification will be sent to the Chief Executive of the Pharmaceuticals and Medical Devices Agency, the Chairman of the Japan Federation of Medical Devices Associations, the Chairperson of the American Medical Devices and Diagnostics Manufacturers' Association, the Chairperson of the Medical Equipment and IVD Committee of the European Business Council in Japan, and Chief Executive of Association of Registered Certification Body under PMD act.

Notice

1. Introduction

When applications for marketing approval, certification, and notifications for medical devices (including applications for partial changes in approval, applications for partial changes in certification, and notification of changes in notified items; hereinafter referred to as “application for approvals, etc.”) are filed, biological safety evaluation is required to be performed for medical devices (components) that directly or indirectly contact with human body. When performing biological safety evaluation, it shall be confirmed that the medical device to be evaluated has biocompatibility and that there is no unacceptable biological risk when used in clinical practice in accordance with international standard ISO 10993-1, Biological evaluation of medical devices—Part 1 (hereinafter referred to as "ISO 10993-1") or JIS T 0993-1 "Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process" (hereinafter referred to as JIS T 0993-1).

This notification is intended to provide points to consider for applicants to prepare materials related to biological safety evaluation of overall medical devices when preparing an application form for application for approval, etc. It should be noted that this notification does not assume a specific type of medical device.

The latest relevant official standards, etc. shall be referred to for how to judge whether biological safety evaluation tests are required or not and the outline of the tests.

2. Biological safety evaluation of medical devices

(1) Biological safety evaluation shall be performed on the final product. In the biological safety evaluation, information such as components of the medical device, intended clinical use, and sites of contact with the human body and duration of the contact should be clarified to identify the potential risks from the viewpoint of biocompatibility. For components, not only materials composing the medical device but also processing aids or additives that may remain, and residuals after sterilization shall be taken into consideration. If precedents of use of each components are used for evaluation of the final product, differences in the manufacturing method and sterilization method should also be taken into consideration.

In addition, as stated in ISO 10993-1 and JIS T 0993-1, biological safety evaluation of medical devices shall be conducted as a part of the risk management process specified in ISO 14971 Medical devices- Application of

risk management to medical devices (hereinafter referred to as "ISO 14971") or JIS T 14971 "Medical devices- Application of risk management to medical devices" (hereinafter referred to as “JIS T 14971”). Therefore, if a biological risk is found as a result of the biological safety evaluation, appropriate risk control should be performed after a comprehensive risk assessment including the results of the biological safety evaluation is performed in accordance with ISO 14971 and JIS T 14971 instead of immediately determining that the relevant medical device is ineligible.

(2) ISO 10993-1 and JIS T 0993-1 specify that risk assessment should be performed first when a biological risk assessment is performed, and then the risk should be evaluated based on the information obtained from the relevant risk assessment. The medical devices are classified based on the different categorization approaches; “categorization according to the exposure duration” and “categorization according to the contact site,” and divided into groups based on a combination of these categorizations, and the biological safety endpoints are set for each group. However, since these medical device categorizations are applied to the overall medical devices, applicants shall assume actual clinical use and keep it in mind that if any biological safety endpoints other than the endpoints specified based on the categorizations are found to be necessary, these endpoints should be added.

- In the “categorization according to the exposure duration,” the medical devices for which the cumulative total exposure duration is assumed to be within 24 hours are classified into “limited exposure” group; those for which the total exposure duration is assumed to be longer than 24 hours and within 30 days are classified into “prolonged exposure” group; and those for which the total exposure duration is assumed to be longer than 30 days are classified into “long-term exposure” group.
- In “categorization according to the contact site,” the medical devices are classified according to the contact sites such as tissues, mucosal membranes, and blood.
- As the endpoints necessary for biological safety evaluation, "cytotoxicity," "sensitization," "irritation," "systemic toxicity (acute, sub-acute, sub-chronic, chronic)," "implantation (local effects after tissue contact)," "genotoxicity," "carcinogenicity,” and "haemocompatibility" are specified. However, in light

of the actual clinical use conditions of medical devices, it is necessary to separately consider including "material-mediated pyrogenicity," "material degradation," and "reproductive and developmental toxicity" in the endpoints.

(3) When using animals for tests, animal welfare should be ensured in accordance with the Act on Welfare and Management of Animals (Act No. 105 of 1973), Standards relating to the Care and Keeping and Reducing Pain of Laboratory Animals (Notice No. 88 of the Ministry of the Environment in 2006), "Guidelines for Conduct of Animal Experiments in Institutions under the jurisdiction of the Ministry of Health, Labour and Welfare" (Notification No. 0220-1 issued by Director of Health Science Division, Minister's Secretariat, MHLW dated February 20, 2015), and ISO 10993-2, etc., and the following proper conduct of animal experiments shall be considered for animal welfare and alternatives to animal experiments; 3R's tenet comprised with 1) replacement (to replace animals to other methods), 2) reduction (to use fewer animals) and 3) refinement (to prevent, alleviate or minimize pain suffering, distress or lasting harm).

(4) Tests considered necessary for biological safety evaluation listed in (2) shall be performed in accordance with Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices (MHLW Ordinance No. 37 of 2005) (Good Laboratory Practice; hereinafter referred to as "GLP") based on "Handling, etc. of Data Related to Nonclinical Studies on the Safety of Drugs, Medical Devices, and Regenerative Medical Products to be Attached to the Application for Approval, etc. of Drugs, Medical Devices, and Regenerative Medical Products" (PFSB/ELD Notification No. 1121-9; PFSB/MDRMPE Notification No. 1121-13 dated November 21, 2014 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau/Counsellor of Minister's Secretariat (for Medical Device and Regenerative Medical Product Evaluation), MHLW). However, if the test is a test to evaluate the functionality/efficacy required for the product and safety evaluation is the secondary purpose, the provisions of Article 114, Paragraph 22 of the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Ordinance No. 1 of 1961) shall be complied with.

That is, tests to be performed for the purpose of biological safety evaluation should be performed in compliance with GLP. It should be noted that compliance with GLP is not always required for tests performed for other purposes, such as performance confirmation tests.

For designated controlled medical devices, GLP does not apply to biological safety testing.

3. Points to consider when describing biological safety evaluation results in attachments to the application form

Applicants shall evaluate the biological safety of the medical device subject to the application according to the following procedures and describe the results in the attached document (STED). For the tests performed, the certificate of analysis, etc. shall be attached as an attached document.

See the Pharmaceuticals and Medical Devices Agency website (https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/devices/0055.html) for the specific flow of evaluation methods and examples of descriptions in the attached document (STED). However, these examples of descriptions are just examples for the preparation, and it is acceptable if the descriptions are not the same as those examples if a sufficient explanation is provided according to relevant notifications including "Points to Consider during the Preparation of Attachments to Medical Device Marketing Approval Application Forms" (PFSB/MDRMPE Notification No. 0120-9 dated January 20, 2015 issued by the Counsellor of Minister's Secretariat (for Medical Device and Regenerative Medical Product Evaluation))" and "Points to Consider during the Preparation of Attachments to Medical Device Marketing Certification Application Forms" (PFSB/MDRMPE Notification No. 0210-1 dated February 10, 2015 issued by the Counsellor of Minister's Secretariat (for Medical Device and Regenerative Medical Product Evaluation), MHLW).

In addition, it is not always necessary to attach certificates of analysis, etc. when applying for certification to registered certification bodies.

Step 1. The biological risk assessment of the applicable product to the application should be performed.

(1) Presence or absence of the applicable product to biological safety evaluation

(2) Collection of clinical information and physical/chemical information related to the product to be evaluated

(3) Collection of information on bioequivalence with approved products/certified products/notified products

Step 2. The contact risk and biological effects of medical devices to be evaluated should be checked.

Step 3. The necessity of performing tests should be checked. Tests judged to be required should be performed.

Step 4. Comprehensive risk evaluation concerning biological safety (biological risk assessment) of the applicable product to the application should be performed.

4. List of official standards related to individual biological safety testing
   - ISO 10993-3: Biological evaluation of medical devices—Part 3 (Genotoxicity, carcinogenicity and reproductive and developmental toxicity)
   - ISO 10993-4: Biological evaluation of medical devices—Part 4 (Hemocompatibility)
   - ISO 10993-5: Biological evaluation of medical devices—Part 5 (Cytotoxicity)
   - ISO 10993-6: Biological evaluation of medical devices—Part 6 (Implantation: Local effects after tissue contact)
   - ISO 10993-10: Biological evaluation of medical devices—Part 10 (Sensitization)
   - ISO 10993-11: Biological evaluation of medical devices—Part 11 (Systemic toxicity)
   - ISO/TS 10993-20: Biological evaluation of medical devices—Part 20 (Immunotoxicology)
   - ISO 10993-23: Biological evaluation of medical devices—Part 23 (Irritation)
5. List of other official standards related to main biological safety evaluation
   - ISO 10993-1, Biological evaluation of medical devices—Part 1 (Basic Principles)
   - ISO 10993-2: Biological evaluation of medical devices—Part 2 (Animal welfare)
   - ISO 10993-7: Biological evaluation of medical devices—Part 7 (Ethylene oxide residuals)
   - ISO 10993-12: Biological evaluation of medical devices—Part 12 (Sample preparation)

- ISO 10993-17: Biological evaluation of medical devices—Part 17 (Toxicological risk assessment)
- ISO 10993-18: Biological evaluation of medical devices—Part 18 (Chemical characterization)

All ISO 10993 series including the above.

List of other main reference standards related to biological safety evaluation

- ISO/TS 21726: Biological evaluation of medical devices—Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents
- ISO 18562 series: Biocompatibility evaluation of breathing gas pathways in healthcare applications
- ISO 14971: Medical Devices—Application of risk management to medical devices
- ISO 9394: Ophthalmic optics—Contact lenses and contact lens care products—Determination of biocompatibility by ocular study with rabbit eyes

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