PSEHB/MDED Notification No. 1117 (1)
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November 17, 2017

To: Directors of Prefectural Health Departments (Bureaus)

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

Handling of Situations requiring submission of "Documents related to Clinical Study Results" for Medical Devices (Responses based on Measures across Pre- and Post-Marketing Phases)

The scope for the submission of documents on clinical study results needed for marketing approval applications for medical devices have been shown in the "Scope of Required Clinical Study Data on Medical Devices" (PFSB/ELD/OMDE Notification No. 0804001, dated August 4, 2008 issued by the Director of Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) and the "Clarification of Handling of Clinical Trial Data on Medical Devices, etc. for Rare Diseases" (PFSB/ELD/OMDE Notification No. 0329-1 dated March 29, 2013 issued by the Director of Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).

Because medical devices have characteristics such as frequent and diverse improvement, guidance related to clinical studies was examined in the "Research on the ideal form of clinical trial guidance necessary for the rapid and accurate approval and development of medical devices" (representative: Shohei Nakano, Senior Director of Medical Devices Center, Japan) conducted in 2016, as part of the Research on Regulatory Harmonization and Evaluation of Pharmaceuticals (Research Expenses Outsourced to the

Japan Agency for Medical Research and Development), this research aimed to facilitate the more efficient development of medical devices while utilizing these characteristics. Based on the review conducted, we have organized the handling of cases in which approval applications may be considered regardless of whether new clinical trials are conducted before marketing by implementing safety and efficacy assurance measures consistently from the pre-marketing to the post-marketing phase. We have also clarified how these measures are implemented. We would appreciate it if you would take note of this and disseminate the information to relevant businesses and organizations under your jurisdiction.

Please note that a copy of this notice will be sent to the Chairman of the Japan Federation of Medical Devices Associations, the Chairman of the Advanced Medical Technology Association (AMDD), the Chairman of the Medical Technology and IVD Committee of the European Business Council, and the President of the Pharmaceuticals and Medical Devices Agency (PMDA).

Notice

1. Handling Clinical Studies to Assess Compliance with the National Medical Environment

(1) Overview

If the results of a foreign pivotal clinical study are available, the efficacy and safety in Japan should be evaluated while considering racial differences between Japanese and non-Japanese, environmental factors, and actual medical practice (ethnic factors) in Japan compared to foreign countries. For medical devices developed in foreign countries with very high novelty of the procedure, if the main points at issue are external factors, such as the degree of widespread use of the procedure (including measures against complications) in Japan, additional pre-marketing clinical trials are conducted to evaluate, for example, whether efficacy and safety outcomes similar to those reported in foreign pivotal studies can be demonstrated in the Japanese medical environment.

In such cases, it is possible that the safety and appropriate use of the medical device can be ensured regardless of evaluation through pre-marketing clinical trials by estimating the risks and considerations caused by differences in medical environments, carefully using the medical device at limited facilities after marketing, and appropriately collecting data and implementing safety measures.

In this case, from the early stage of development, it is desirable to draw up an appropriate development plan after sufficient consultation with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the “PMDA”) regarding the necessity of clinical trials and post-marketing measures for proper use.

(2) Specific responses

i. Examination of the direction of development during predevelopment consultation for medical devices

If the results of a foreign pivotal clinical study are available and the only difference in the medical environment between Japan and overseas is an issue, such as the extent of the spread of related procedures, the direction of development, such as securing safety and efficacy through the preparation of and compliance with the proper use standards, collection of post-marketing data, and implementation of necessary measures based on the data, etc., may be considered instead of conducting a domestic clinical study with a small number of patients by utilizing the PMDA's predevelopment consultation for medical devices.

At the time of consultation, a summary of the medical device in question should be presented, along with points to consider that may influence the risks and benefits brought by differences in the medical environment and proposed countermeasures, taking into account foreign clinical study data, non-clinical study data, literature information, etc. In addition, it is important to cooperate with academic societies related to the actual use of the relevant medical devices in preparing standards for proper use and providing training. The status of cooperation with related academic societies should also be explained.

ii. Utilization of consultation on clinical necessity of medical devices

Based on the results of the predevelopment consultation for medical devices, conduct a detailed analysis of risks and considerations again using existing information, and consider specific countermeasures such as compliance with proper use standards and post-marketing data collection. Additionally, consult with the PMDA regarding these contents by utilizing the consultation on the necessity of clinical studies for medical devices. When considering a specific response plan, refer to the Guidelines for Post-marketing Risk Management for Medical Devices (Attachment to "Guidelines for Post-marketing Risk Management for Medical Devices" (PSEHB/MDED Notification No. 0731-1 and PSEHB/PSD Notification No. 0731-1 dated July 31, 2017) issued jointly by the Director of Medical Device Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare).

When setting facility standards in the proper use standards, consider how many facilities meet the standards and the requirements that must be met when expanding the facilities due to changes in the facility standards.

Furthermore, the scheduled timing for reporting the status of compliance with the proper use standards, results of post-marketing data collection, and measures taken based on data collection to the PMDA in advance should be determined in consultation with the PMDA (when it is necessary to report separately from the specified report such as periodic report of drug use results survey). The results should be reported to the PMDA as soon as they are available.

2. Handling Clinical Studies of Improved Medical Devices for which the Additional Clinical Value is Relatively Small and Significant Risks are Not Assumed

(1) Overview

In the development of medical devices corresponding to the improved medical device (with clinical data) category, it is assumed that differences from existing devices due to the improvement will not cause any significant risk. Additionally, non-clinical studies or accumulated clinical evidence should demonstrate that the efficacy and safety are almost equivalent to those of existing medical devices. However, in some cases, safety and efficacy will be confirmed by conducting a clinical study with a small number of patients and presenting the results of actual clinical use.

An improved product of a type of medical device with sufficient clinical use results, where safety and efficacy can be evaluated by comparison with the existing product and the difference from the existing product is assumed to have a high probability of not posing a serious risk, is unlikely to cause a safety problem that compromises the risk-benefit balance, even if there is no human use experience at all. However, it is important to note that medical devices may cause various problems at an early stage of introduction. Particularly if there is no experience of use in humans, product-specific issues should be identified early, and appropriate measures should be taken.

For this reason, it is considered that the safety and appropriate use of these medical devices can, in some cases, be ensured by conducting a thorough risk analysis to evaluate clinical safety and efficacy based on non-clinical studies, literature information, and experience with similar medical devices, without evaluating them through a small number of clinical studies before marketing. Additionally, this can also be achieved by grasping and collecting detailed information on each case for a certain number of cases in the early post-marketing phase.

In such cases, it is desirable to thoroughly deliberate the contents of the risk analysis, the necessity/unnecessity of clinical trials, and the collection of safety information in the early post-marketing phase with the PMDA from the early stage of development to draw up an appropriate development plan and finalize the application classification (with or without clinical studies).

(2) Specific responses

i. Examination of the direction of development at the predevelopment consultation

If the product is a medical device corresponding to an improved medical device (with clinical data), and it is possible to explain a high probability for its clinical safety and efficacy based on data from non-clinical studies, literature information, principle of the medical device in question, surgical procedure, and experience with similar medical devices, and no significant risk is expected compared to the existing product, a consultation should be held regarding issues in terms of review due to lack of data in terms of clinical use experiences by utilizing a predevelopment consultation for medical devices.

ii. Consultation on the clinical necessity for medical devices

(a) On the basis of the results of the predevelopment consultation for medical devices, the company should conduct additional non-clinical studies, perform further analysis of information on similar products and literature, and reassess risk analysis, including the estimation of clinically possible risks. As a method to evaluate residual risks and overall acceptance of risks, ensuring safety and efficacy consistently from pre-marketing to post-marketing activities, medical device information representatives should visit medical institutions frequently during the early post-marketing phase for a certain number of patients to carefully grasp and collect information on each patient's status, take actions promptly based on the obtained information as necessary, and draw up a reporting plan for the results (hereinafter referred to as "early post-marketing safety information collection").

The plan shall specify, as a survey of the actual status of clinical practice, the events that need to be intensively checked after marketing, the period and target medical institutions for intensive information collection, the method of information collection, the scheduled timing for reporting the results of information collection to the PMDA, and the scheduled action based on the evaluation results of the collected information (e.g., reflection in the package insert, provision of information on the results of information collection, etc.), etc. (The reference form is shown in Attachment 1.)

Note that the above early post-marketing safety information collection mainly focuses on collecting relatively short-term data and confirming the early post-marketing use of improved medical devices with relatively small additional clinical value and no assumed significant risks, which aim to collect mid- to long-term use data for new medical devices.

(b) Then, based on the risk analysis conducted by utilizing consultation on the necessity of clinical studies for medical devices, the contents of the plan for the collection of early safety information should be consulted. If the appropriate application category for the consultation is "Improved Medical Devices (without clinical data)" on the premise that early post-marketing safety information is appropriately collected, two copies of the early post-marketing safety information collection plan shall be submitted to the PMDA at the time of application for product approval. (For the overall flow, see Attachment 2.)

(c) After marketing, based on the plan for collecting early post-marketing safety information, medical institutions are requested to provide information on events that require particularly focused confirmation at the start of marketing, and actively collect information. In addition, the results of early post-marketing safety information collection and the safety assurance measures taken based on the collected information should be summarized and reported to the PMDA in accordance with the plan.

3. Consultation with Diagnostic Devices to Measure Physiological Parameters that may be Reference Information for Diagnosis

(1) Overview

Because some physiological parameters or numerical values obtained through arithmetic processing are considered potential reference information for diagnosis, their relationship with clinical symptoms or pathological conditions is not yet widely recognized, nor are they expected to be widely used in medical practice at present. Additionally, their clinical significance and medical judgment criteria have not been sufficiently established.

When developing a device that measures and presents such physiological parameters as a medical device, an application for approval may be filed only for the intended use or the range of effects that can be shown based on past clinical results or study results on mechanical performance (measurement performance), even if its clinical significance as the final target is not yet established. In addition, a development strategy may involve filing an application for partial changes after clinical evidence is established through experience gained from clinical practice after approval. In this case, utilizing the PMDA predevelopment consultation for medical devices in advance can facilitate the exchange of opinions with the reviewer.

(2) Specific responses

If devices that measure physiological functions of the living body (excluding those related to sample testing) and fall under any of the following categories are to be developed as medical devices to support diagnosis, the PMDA's predevelopment consultation for medical devices should be used in advance to exchange opinions with reviewers on the appropriateness of the above responses.

(Target equipment)

1) An active monitoring medical device for noninvasive measurement of physiological indicators indicated as biological signals (so-called devices for testing biological physical phenomena, devices for testing biological electrical phenomena, devices for monitoring biological phenomena, etc.) that provides a new indicator through computing information obtained from existing sensors, with clear measurement principles.
2) Although the final target of clinical significance has not yet been established, it is positioned as a medical device that provides one of several judgment criteria independently as reference information for diagnosis.
3) Erroneous test results are unlikely to have a significant impact on human life or health.

Attachment 1: Example of the form

Early post-marketing safety information collection plan for medical devices

MM DD, YYYY

To: President, Pharmaceuticals and Medical Devices Agency

Address: (address of the main office in the case of a corporation)

Name: (name of the corporation and its representative in the case of a corporation) Seal

I hereby submit the document mentioned in the title as follows.

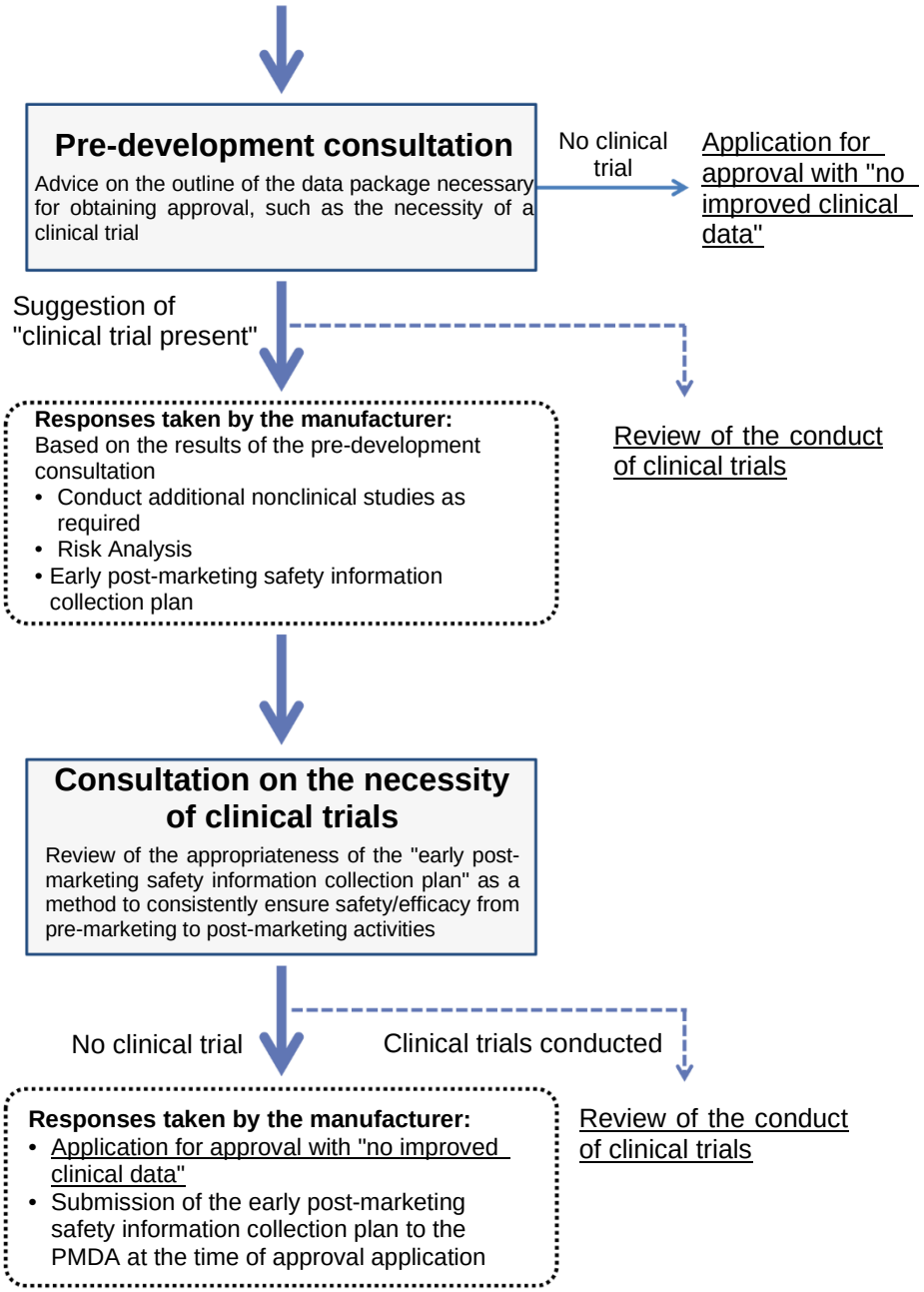
General Information			
Date of approval		Approval No.	
Nonproprietary name			
Proprietary name			
Intended use or effects			
General information about the information collection plan			
Major events to be verified and reasons for setting			
Planned number of patients from whom information will be collected and the rationale for the setting			
Information collection method			
Information collection period and reporting timetable			
Target medical institution (planned)			
Method for reflection of evaluation results and provision of information (planned)			
Remarks			

Description guideline

- ○ Use a Japanese Industrial Standards A4-sized paper.
- ○ If all required information cannot be entered in the specified column, enter “as per Attachment ○” in the column and prepare the attachment.
- ○ If there is no applicable matter for each item, it is acceptable to describe it as such.
- ○ “Remarks” should include the following information:
  - Name, affiliation, contact number, etc. of the person in charge
  - In the case of exceptional foreign approval, enter the signature of the approval holder under the name column and describe the domestically appointed commercial manufacturer in the remarks column.

Appendix 2

Flow chart for verification of the development policy and application category for the "Handling clinical trials for improved medical devices with relatively small additional clinical value and no significant risk" (2)



Note: The consultation process may differ depending on the amount of information, content, etc., available from non-clinical studies and risk analysis.