Provisional Translation (as of October 2020)

PSEHB/MDED Notification No. 1117-1
PSEHB/SD Notification No. 1117-1
November 17, 2017

To: Directors of Health Departments (Bureaus) Prefectural Governments

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

Director of the Pharmaceutical Safety Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(official seal omitted)

Handling on the Scope of Situations where "Documents related to Clinical Study Results" is Necessary on Medical Devices (Operations based on Measures through Pre- and Post-Marketing Phases)

The scope of situations where submission of documents related to clinical study results is necessary to complete an application for marketing approval of a medical device is specified in "Scope where Clinical Study Data are Necessary on Medical Devices" (PFSB/ELD/OMDE Notification No. 0804001, by the Director of the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), dated August 4, 2008) and "Determination regarding the Handling of Clinical Study Data for Medical Devices Indicated for Rare Diseases" (PFSB/ELD/OMDE Notification No. 0329-1, by the Director of the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 29, 2013).

Because medical devices are frequently upgraded or improved in various respects, guidance for the implementation of clinical trials was discussed from the viewpoint of facilitating efficient development of medical devices in the "Research on Desirable Guidance for Clinical Trials Required for Speedy and Accurate Approval and Development of Medical Devices" (Research Representative: Shohei Nakano, Executive Director of the Japan Association for the Advancement of Medical Equipment. Grant by the Japan Agency for Medical Research and Development (AMED) in FY 2016 for Research on Regulatory Science of Pharmaceuticals and

Medical Devices). Based on the above discussion, MHLW has structured its operations related to cases where applications for approval may be filed by taking pre- and post-marketing measures to ensure adequate and consistent clinical safety and efficacy, irrespective of conduct of additional pre-marketing clinical trials as described below. MHLW thereby aims through this Ministerial Ordinance to clarify its operations related to the handling of product approval applications. The Ministry of Health, Labour and Welfare (MHLW) requests your cooperation in notifying all relevant business entities under your jurisdiction of this Ministerial Notification and in urging complete understanding of its contents.

Please note that copies of this Ministerial Notification will be sent to the Japan Federation of Medical Devices Associations, the Medical Devices and Diagnostics Subcommittee of the American Medical Devices and Diagnostics Manufacturers' Association in Japan, the Medical Devices and IVDs Committee of the European Business Council in Japan, the Pharmaceuticals and Medical Devices Agency (PMDA), and the Japan Certification Council for Drugs and Medical Devices.

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1. Handling of clinical trials performed to evaluate compatibility with the Japanese medical environment

(1) Summary

If pivotal clinical study results obtained in foreign countries are available, the product's clinical efficacy and safety in Japan will be evaluated in consideration of ethnic differences between Japanese and other groups (ethnic factors) as well as differences in environmental factors and actual clinical settings. Regarding medical devices that have been developed outside of Japan and have uses that require completely new procedures, development in Japan could give rise to various issues, mainly related to extrinsic factors such as the prevalence of these procedures in Japan (including procedures regarding complications). In such cases, whether the clinical efficacy and safety are observed in the Japanese medical environment as found in an overseas pivotal study is evaluated in an additional pre-marketing clinical trial.

Some of these medical devices, however, may be used in a safe and appropriate manner without evaluation based on data from pre-marketing clinical trials if the relevant medical device is used carefully in the specified facilities after marketing, and clinical data collection and safety measures are appropriately in place under inference of risk and precaution points related to differences in the medical environment.

In cases such as this, applicants are advised to prepare an appropriate development plan through considerable discussions about need of clinical trials and post-marketing measures for proper use with the PMDA even at the early stages of development.

(2) Details of actions

[1] Discussion about direction of the development at a pre-development consultation for medical devices

PMDA's pre-development consultation for medical devices may be utilized in cases

where pivotal clinical study results obtained in foreign countries are available and the only pertinent concerns involve differences between Japan and other countries with respect to conditions in medical environments, such as the prevalence of related procedures. This consultation may determine the overall direction of the development program: for example, rather than conducting a Japanese clinical trial including a limited number of subjects, the clinical safety and efficacy of the product in question may be ensured through the establishment and adherence to standards for proper use and in addition to post-marketing safety data collection and subsequent implementation of appropriate measures.

For the consultation, applicants shall present a summary of the characteristics of the medical device in question, issues concerning its use risks and benefits that may potentially be affected by differences in the medical environment, as well as the applicant's draft actions based on foreign clinical study data, non-clinical study data, and the relevant published literature. In addition, applicants shall be prepared to explain the status of any partnerships with related academic societies that are intended to be users of the relevant medical device in clinical settings, as these partnerships will play an important role in establishment of the standards for proper use and implementation of training programs.

[2] Use of consultation for regarding the need of clinical studies for medical devices

In light of results from the pre-development consultation for medical devices, applicants shall perform detailed analyses on the risk and points to consider based on the existing information and investigate specific potential actions such as compliance with the standards for proper use and post-marketing clinical data collection. Applicants shall then consult with PMDA regarding the aforementioned items by availing themselves of PMDA's consultation regarding the need of clinical studies for medical devices service. For more specific potential actions, refer to the policy for post-marketing risk management plan for medical devices (Appendix to the "Policy for Post-marketing Risk Management Plan for Medical Devices" (Joint PSEHB/MDED Notification No. 0731-1 and PSEHB/PSD Notification No. 0731-1, by the Director of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, and by the Director of the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated July 31, 2017).

If facility criteria are established in the standards for proper use, applicants shall investigate availability of facilities that meet the relevant criteria and consider what requirements should be set to add facilities by changing the facility criteria.

In addition, applicants shall determine the planned time of reporting to PMDA through consultation with PMDA in advance (if reporting is necessary in addition to specified reporting such as periodic reporting of use-results survey). This reporting shall cover compliance status with the standards for proper use, results from post-marketing clinical data collection, and actions taken based on the clinical data collection. The applicant shall report these results to PMDA as soon as these clinical data are summarized after marketing.

2. Handling of clinical trials of improved medical devices in which additional clinical value is relatively small and thus unlikely to raise serious risks

(1) Summary

In development of medical devices that belong to the Improved Devices requiring Clinical Data category, upgrade-related differences from currently marketed versions of the device are presumed to be unlikely to give rise to serious risks, and non-clinical study results or accumulated clinical evidence can explain comparability of the clinical efficacy and safety to currently marketed devices. In some cases, however, clinical trials may be conducted with a limited number of subjects, and clinical safety and efficacy are verified based on clinical use data.

For a product which is one upgraded from a medical device with substantial clinical use results, of which the clinical safety and efficacy are evaluated by comparison from the existing ones, and of which differences from the existing one are presumed to be fairly unlikely to raise a serious risk; if the device is approved without pre-market human use data, safety concerns compromising the risk-benefit balance are presumed to be unlikely to occur after marketing. For a medical device in which various problems are likely to occur at the initial stage of introduction, and of which use in humans is substantially inadequate, by contrast, it should be noted that prompt identification of issues specific to the medical device and acting swiftly to implement countermeasures are critical.

For such products, the following actions may ensure safe and appropriate use of the relevant medical devices without evaluation through pre-marketing clinical trials including a limited number of subjects: Exhaustive risk analysis on results from non-clinical studies, literature information, and use experience with similar medical devices is performed to evaluate clinical safety and efficacy; and a certain number of patients are carefully monitored at the early post-marketing stage to collect information.

In this case, applicants are advised to draw an appropriate development plan and determine the application category (with or without clinical data required) through considerable discussions about contents of the risk analysis, need of clinical trials, and early post-marketing collection of clinical safety information with PMDA even at the early stage of development.

(2) Details of actions

[1] Discussion about direction of the development at a pre-development consultation

If the proposed product is a medical device that belongs to Category of Improved Medical Devices requiring Clinical Data; the clinical safety and efficacy are explained at high probability based on the non-clinical study data, literature information, principle of the relevant medical device, technique, and experience with similar medical devices; and no serious risk is presumed compared with the existing products: The applicant shall utilize re-development consultation for medical devices to consult about issues in the review attributable to the fact that clinical data from its use experience in clinical settings are lacking.

[2] Use of consultation about necessity of clinical studies

(a) Applicants shall conduct additional non-clinical studies and perform additional

risk analysis on information and literature about the similar products to estimate potential risk in clinical settings based the results of the pre-development consultation. Subsequently, applicants shall evaluate any residual risks and their overall tolerability and then develop a data gathering plan for early post-marketing phase vigilance (EPPV) as a method for ensuring consistent pre- and post-marketing clinical safety and efficacy data. The plan shall include the following activities referred to as EPPV safety information collection: Medical representatives (MRs) involved with medical devices frequently visit medical institutions to follow detailed status of each patient and collect safety information; where necessary, such MRs shall take action in response to the obtained information immediately as well as organize this data for reporting.

This plan, which serves means for gathering data used monitor conditions in actual clinical settings, shall specify noteworthy events occurring after marketing; period of and medical institutions subject to intensive information collection; method of information collection; planned date of reporting results from information collection and planned actions based on the collected information to PMDA, (e.g. reflecting the collected information in the package insert and facilitating the dissemination of this information). (proper reference format is provided in Appendix 1)

It should be noted that the above EPPV safety information collection is mainly intended to collect relatively short-term data on an improved medical device in which clinical additional value is quite small and thus unlikely to raise a serious risk and thereby confirm its use status at the early post-marketing stage; and it is different from the use-results survey that serve to collect mid-to-long-term post-market data in Japanese clinical setting, mainly for a new medical device.

(b) Then, applicants shall utilize consultation for need of clinical studies of medical devices to discuss contents of the EPPV safety information collection plan in consideration of the performed risk analysis. If the relevant consultation indicates that the appropriate application category is “Improved Devices requiring No Clinical Data” on the assumption of appropriate implementation of the post-marketing early safety information collection, applicants shall submit two copies of the post-marketing early safety information collection plan in the application for approval of the relevant product. (for details concerning the overall flow, refer to Appendix 2.)

(c) After marketing, applicants shall actively collect safety information about the events to which special attention should be paid in accordance with the post-marketing early safety information collection plan. For this purpose, they shall ask medical institutions at the time of launch to provide such information. In addition, applicants shall summarize results from the post-marketing early safety information collection and actions taken in response to the above information to ensure the safety, and submit the summary to PMDA.

3. Consultations concerning diagnostic devices that measure physiological parameters

to obtain potential reference information for diagnosis

(1) Summary

Of the various physiological parameters or numerical values obtained by processing these parameter values, some are considered to be potential reference information for diagnosis, but their relationships to clinical symptoms and pathological conditions have not been widely recognized, and thus these parameters or values are unlikely to be used in medical practices at the present. In essence, their clinical significance or medical utility have not been firmly established.

In cases where a device that measures and displays data concerning such these physiological parameters is to be developed as a medical device, applicants is potentially able to file the application for approval of the device with the limited intended use or indications which have been demonstrated by the previous clinical results and test results on mechanical performance (measuring performance), even if the clinical significance of its final target has not been established. In addition, the following approach may be taken as a development strategy: an application for approval of partial changes may be filed where necessary when clinical evidence is established based on use experience under clinical settings after the approval. In such cases, discussion with the reviewing agency through PMDA's pre-development consultation in advance may be useful.

(2) Details of actions

Applicants who intend to develop a medical device designed to offer diagnostic support that measures physiological functions in the body (excluding devices whose primary use concerns specimen examinations) and meet the following characteristics shall discuss acceptance of the above actions with the reviewing agency through PMDA's pre-development consultation in advance.

(applicable devices)

1) Non-invasive medical device that actively monitors physiological indicators related to biological signals (devices for examining biophysical phenomena, devices for examining bioelectrical phenomena, devices for examining biological phenomena, etc.) and offers new indicators by processing the information obtained from the existing sensors of which the measurement principle is well characterized.
2) Medical devices that provide information serving as one of several discrete types of reference information used for diagnostic purposes, although the clinical significance of the final target has not been established.
3) Medical devices that would have no significant impact on human life or health even if it presents wrong examination results.

Appendix 1: Format example

Data gathering plan for Early Post-marketing phase vigilance for medical devices

MM/DD/YYYY

To: Chief Executive of the Pharmaceuticals and Medical Devices Agency

Address: (address of the primary place of business or representative office of a company)

Name: (company name and name of the primary representative) (Seal/signature)

I hereby submit this document concerning the above matter.

Summary of Product			
Date of approval		Approval number	
Generic name			
Brand name			
Intended use or indications			
Summary of information collection plan			
Events with special attention and the basis for specifying them			
Planned sample size for information collection and basis for specifying it			
Information collection method			
Information collection period and planned reporting time			
Medical institutions (planned)			
Methods to reflect the evaluation results and to provide the information (planned)			
Remarks			

Instructions for entries

○ The form must be JIS A4 in size.

○ If a blank column is small for matters to be entered, an appendix may be attached with a note, “Refer to Appendix X”, entered in the column.

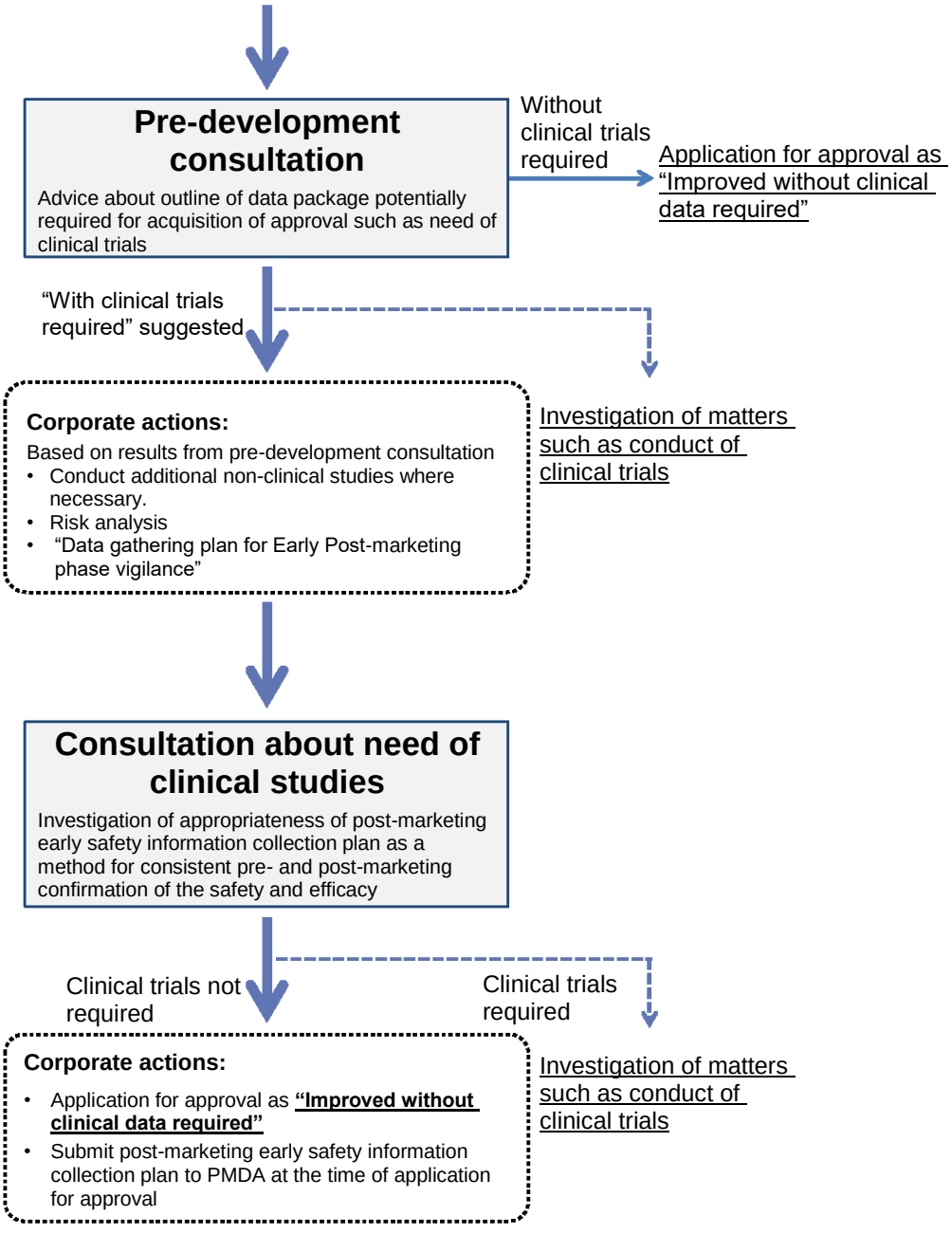
○ If there are no applicable items to be entered in the column, a note to this effect may be entered.

○ The following matters shall be entered in the “Remarks” column.

- Name, department, and contact information such as telephone number of the person in charge
- If the applicant is a designated foreign holder of special approval, a signature of the approval holder shall be put under the Name column, and information about the in-country designated marketing authorization holder (“in-country caretaker”) shall be entered in the Remarks column.

Appendix 2

Flow chart for confirmation of the development provisions and application categories under Note 2. “Handling of clinical trials of improved medical devices in which clinical additional value is relatively small and are therefore unlikely to raise serious risks”



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