Provisional Translation (as of July 2018) *

PSEHB Notification No. 0731-1
July 31, 2017

To: Prefectural Governors

Director-General of the Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

(Official seal omitted)

Conditional Early Approval System for Innovative Medical Device Products (Fast-Break Scheme)

Although a growing number of innovative medical devices are being developed by start-up companies, these R&D programs often face a dilemma between the gathering of sufficient clinical evidence, which can prolong the development period and ensuring early patient access. As the consequences of a prolonged development period can be especially significant for patients with life-threatening diseases for which no effective therapies currently exist, there is a need for measures to expedite the access to medical devices with the potential to treat such diseases whenever possible while still ensuring their safety and efficacy.

This same view was presented at the "Meeting for the Promotion of Start-up Companies Involved in Medical Innovation". The meeting resulted in the proposal of the establishment of a new review framework designed to accelerate the approval of innovative medical devices by minimizing burdens related to pre-marketing clinical studies while enhancing the post-marketing surveillance activities corresponding to such products. In response, MHLW established a new conditional early approval system allowing applications for approval in early stages granted as appropriate in consideration of particular features and the envisaged lifecycle management of eligible medical device products. The Ministry devised this system by drawing on past experiences in case-by-case decision-making based on limited clinical data during its evaluations of the safety and efficacy of medical devices indicated for rare diseases and requiring expanded institutional control of post-marketing risks.

The following paragraphs offer a description of the new "Conditional Early Approval System for Innovative Medical Device Products" (hereinafter, the "System"). Medical devices eligible for the System include those anticipated to fulfill an area of great and unmet medical need but for which limited or only specific types of clinical data are available at the time of initial application submission. This System will allow for applications for approval to be submitted with limited clinical data on the assumption that applicants will implement suitable post-marketing risk management activities, such as the collection of post-marketing usage or adverse event data, or establish usage requirements. We request your cooperation in circulating the information contained in this Notification to marketing authorization holders (MAHs) of medical devices, etc. under your supervision.

Recipients of this Notification are also requested to inform their associates and subordinates of each of the following: the "Implementation of the 'Ministerial Ordinance for Partial

∗ This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Amendment of the Enforcement Regulations of the Act on Securing the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics,' 'Ministerial Ordinance for Partial Amendment of the Ministerial Ordinance concerning Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices,' and the 'Ministerial Ordinance concerning the Partial Amendment of the Ministerial Ordinance on Good Post-Marketing Surveillance Practices for Medical Devices'" (PSEHB Notification No. 0731-4, by the Director-General of the Pharmaceutical Safety and Environmental Health Bureau (PSEHB), Ministry of Health, Labour and Welfare (MHLW), dated July 31, 2017), the "Development of Post-marketing Risk Management Plans for Medical Devices" (PSEHB/MDED Notification No. 0731-3 and PSEHB/PSD Notification No. 0731-3, by the Director of the Medical Device Evaluation Division (MDED), PSEHB, MHLW and the Director of the Pharmaceutical Safety Division (PSD), PSEHB, MHLW, dated July 31, 2017 (hereinafter, the "Procedural Notification"), and the "Policy for Post-marketing Risk Management Plans for Medical Devices" (PSEHB/MDED Notification No. 0731-1 and PSEHB/PSD Notification No. 0731-1, by the MDED Director, PSEHB, MHLW and the PSD Director, PSEHB, MHLW, dated July 31, 2017 (hereinafter, the "Policy Notification".)

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1. System rationale

The efficacy and safety data obtained from clinical studies is highly important, especially in the evaluation of innovative medical devices with designs, intended modes of use, and therapeutic effects that substantially differ from existing medical devices, and regulatory approval of such products is in principle founded upon this body of data.

However, the accumulation of the clinical data necessary for a typical manufacturing/marketing approval application can occasionally encounter various daunting obstacles, such as prolonged clinical development periods due to difficulties enrolling the desired number of patients in clinical studies. The consequences of a prolonged development period can be especially significant for patients with life-threatening diseases for which no effective therapies currently exist.

We decided to launch the System in consideration of this backdrop. The System aims to accelerate patient access to innovative medical devices intended to treat life-threatening diseases for which no therapies whose benefits outweigh the risks currently exist. The System was designed to target cases where the clinical development of a promising and innovative medical device product encounters critical impasses. The System aims to lend support in such situations by offering an expedited pathway to approval in exchange for the applicant's commitment to devising a plan for a comprehensive post-marketing risk management including the designation of product use requirements, the monitoring and accumulation of post-marketing data at the development stage of the product lifecycle, and mandating stringent measures to counter risks identified after the product's market debut that were not apparent from the limited clinical data available prior to conditional approval.

More specifically, this program requires applicants to submit a "Post-marketing Risk Management Plan for Medical Devices" (RMP) as an attachment to the main application for approval. The RMP must include standards for proper use of the medical device product in question (for both medical facilities and eligible patients) as well as a plan for the implementation of post-marketing risk management activities such as data collection and measured based on the collected safety information. This RMP should also be prepared in close cooperation with relevant academic societies or similar entities. During approval

review, the efficacy and safety of the candidate medical device product will be investigated based on the body of clinical data available prior to marketing on the assumption that the risk management activities described in the corresponding RMP will be sufficiently implemented. After the medical device is approved, the satisfactory implementation of the content of the RMP will be designated as a condition precedent for product manufacturing/marketing approval under Article 79 of the Act on Securing the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960, hereinafter referred to as the "PMD Act"). In consideration of the limited body of pre-approval clinical data, the applicant is required to ensure that its medical device product is used carefully and appropriately until a sufficient amount of clinical use data can be accumulated.

2. Product types eligible for the System

(1) Applicable product items are those that meet all of the following criteria and are considered to be new medical devices.

a.	Medical devices for life-threatening diseases or irreversible progressive diseases with profound adverse effects on patient activities of daily living (ADL)
b.	Medical devices for diseases for which no effective therapies, prophylaxes, or diagnostic methods are available, or for which the efficacy and/or safety is anticipated to be substantially more favorable compared with existing therapies
c.	Medical devices for which suitable clinical data is available for specific types of evaluation
d.	Medical devices with appropriate use standards decided in close collaboration with relevant academic societies or similar entities, and for which a concrete plan to guide the monitoring and collection of post-marketing data and its subsequent evaluation has been proposed
e.	Medical devices for which acceptable justification for an assertion of difficulty or inability to conduct additional/new clinical trial(s) has been presented

(2) If a party intends to submit an application for approval under the System, such party shall prepare a "Summary of Eligibility for the Conditional Early Approval System with Conditions for Innovative Medical Devices" (hereinafter referred to as a "Summary of Eligibility"), as an appendix to the primary application, and shall submit these materials together to the Pharmaceuticals and Medical Devices Agency (PMDA) in advance of arranging a medical device pre-development consultation. During this consultation, the applicant, MHLW, and PMDA will discuss whether the candidate product is eligible for the System.

(3) Following the consultation described in the previous paragraph, MHLW and PMDA will consider internally whether the candidate product is eligible for the System in consideration of the five criteria a-e described in paragraph (1) above. Applicants may be requested to submit additional materials or data to aid MHLW and PMDA's review. In addition, where necessary, MHLW may request that the candidate product's circumstances in terms of the seriousness of the proposed indication(s) and the availability of treatment alternatives be considered further by the "Working Group for

the Expedited Introduction of Medical Devices Fulfilling Areas of Highly Unmet Medical Need". In such cases, MHLW and PMDA will proceed with their considerations based on the results of the Working Group's assessment.

If the candidate product is judged to be eligible for the System, this result shall be memorialized in the Medical device pre-development consultation record. If a judgment concerning the System eligibility is not reached before the preparation of the consultation record (within 30 working days after the face-to-face consultation session), MHLW and PMDA shall notify the applicant to such effect.

(4) If the candidate product is judged to be a medical device indicated for a rare disease or that fulfills an area of high unmet medical need, determination of System eligibility may be reached without the medical device pre-development consultation described in paragraph (2) above, and in such cases applicants shall prepare a Summary of Eligibility and then consult with MDED at MHLW prior to applying for a Medical device pre-development consultation.

(5) The following are points to consider in describing the Summary of Eligibility:

[1] Requirement A

The applicant shall provide a summary of the available data concerning the product candidate, including descriptions of the disease(s) targeted, target patient characteristics, and the size of the target patient population, in addition to any supporting data and all information sources cited.

[2] Requirement B

Regarding any existing therapies for the proposed indication for the candidate product, to the extent such therapies exist, applicants shall describe the relevant procedures, medical device(s) used, clinical performance data, and other issues as needed, and then proceed to explain in detail the aspects in which the candidate product exhibits superior performance. Applicants shall also provide a list of the references cited in support of these assertions, Japanese and overseas clinical practice guidelines, and medical reference texts, and attach a copy of each as supplementary materials.

If similar product(s) are currently under development in Japan, applicants shall provide descriptions of such to the extent possible.

[3] Requirement C

The applicant shall describe the currently available body of clinical study data and explain that the product has demonstrated a novel or superior degree of clinical efficacy while presenting an acceptable level of risk. Although results from exploratory trials and clinical studies are expected, performance data and literature concerning advanced medical treatments and clinical studies may also be cited. In principle, applicants should also make individual case data available for review. Applicant shall prepare a list of the above types of supporting materials and attach a copy of each to the extent possible.

Applicants shall explain the protocols and ethical considerations applicable to each clinical study conducted and references in support of the application, as well as planned measures to ensure data reliability, where applicable.

Applicants shall also provide a summary of any clinical studies currently in progress.

[4] Requirement D

The applicant shall ensure that it works closely with relevant academic societies or similar entities to prepare use standards for the candidate product. Applicants shall complete a Summary of Eligibility containing, in principle, brief descriptions of the following: content of the draft use standards, the current status of progress on the formulation of these use standards, and the draft plan for the gathering and assessment of post-marketing use data.

The draft use standards shall specify requirements for physicians and facilities that may use the medical device to be proposed, and may include actions on patients requiring special consideration (for reasons such as the presence of complications, etc.), plans for instructional seminars, training programming, and/or proctoring; and concepts for facility expansion or similar. Relevant academic societies or similar entities are expected to be members of the Japanese Association of Medical Sciences or Japanese Association for Dental Science (hereinafter, "Member Societies".) In essence, academic societies or similar entities involved in preparing such use standards should have a significant connection to the use of candidate product and to the treatment of complications that may occur during its use. If an entity other than a Member Society has significant involvement, applicants shall explain involvement of the Member Societies, and the Member Societies will subsequently cooperate with such entity in the preparation of draft use standards as necessary. Applicants shall also provide the contact details of each Member Society or other involved entity.

Draft plans for the collection and assessment of post-marketing use data shall include descriptions of the target(s) and method(s) of data collection, evaluation methodology, and the timing of the evaluation. Such draft plans shall also include descriptions of the mode of investigation for expansion of facilities in accordance with the draft use standards, as well as methods for the provision of the latest information about use performance and malfunctions to healthcare professionals using the medical device in question.

In addition, where possible, applicants shall attach a draft post-marketing medical device RMP (including draft use standards and a use-results surveillance plan.) Further information concerning post-marketing medical device RMPs is provided separately.

[5] Requirement E

Applicants shall also provide a detailed description of the current status of product development and specific reasons for why conducting additional clinical studies would be impracticable at the time of application to the System. Comments from related academic societies should also be provided as attachments to the extent available. Applicants shall also explain the anticipated term needed to conduct a new clinical study or complete a clinical study currently in progress, where applicable.

[6] Other

If the candidate product under development is judged to be a medical device indicated for a rare disease or that fulfills an area of high unmet medical need, this designation shall be included in the Notes field.

3. Procedure for pre-application consultation and application for approval

(1) Consultation on the necessity of medical device clinical trials

If a party submits an application for approval of a candidate product eligible for the System without conducting additional clinical studies, such party shall make arrangements with PMDA for a "Consultation on the necessity of medical device clinical trials" to clarify details concerning the evaluation of the available clinical data and the appropriateness of the draft post-marketing RMP for the product in question. Specifically, this consultation will be held in the presence of medical experts as necessary, and will aim to provide advice and guidance concerning whether an appropriate level of risk-benefit assessment will be feasible based on the existing body of clinical data and draft use standards for the candidate medical device product in consideration of the seriousness of the target disease(s) as well as specifics of the proposed post-marketing RMP with respect to ensuring proper use and data collection.

In addition, applicants shall mention in the Notes field in the consultation application form that the candidate product is believed to be eligible for the System, and also attach the consultation record described in 2 (3) above (MHLW will contact applicants individually with respect to applications not involving the medical device pre-development consultation described in 2 (4).)

(2) Application for approval and review process

[1] When submitting an application for product approval, applicants shall attach the draft post-marketing medical device RMP as a part of the application materials related to clinical study results. Applicants shall also mention in the Notes field in the consultation application form that the candidate product is believed to be eligible for the System, and also add include date (code) for the consultation session attended as described in 2 (3) and 3 (1) above. Applicants shall proceed while taking steps as appropriate to ensure that an application for QMS conformity audit can be submitted immediately after submission of the product approval application.

[2] Applicants are advised to refer to the Procedures Notification and the Policy Notification for more detailed information concerning post-marketing medical device RMPs.

[3] During application review, the sufficiency of the post-marketing RMP will be evaluated, and efficacy and safety are subsequently evaluated on the premise that the RMP will be implemented wholly and appropriately. In principle, products eligible for the System shall be subjected to use-results assessment, and following approval, the content of the RMP will be designated as a condition for approval as provided under Article 79 of the PMD Act.

4. Post-approval procedures

(1) In principle, the applicant shall submit the post-marketing risk management plan for the candidate medical device to PMDA at least 1 month prior to the desired launch date. The above plan will facilitate collection of post-marketing information, communications with healthcare professionals and patients, and the implementation of suitable countermeasures, thereby ensuring the appropriate use of the medical device and preventing undue hazards or risks to the public health.

(2) If use-results surveillance data is obtained from case registries maintained by relevant academic societies or similar entities, applicants shall ensure that appropriate data is accessible upon the request of the Ministry of Health, Labour and Welfare or PMDA, and also designate in advance persons to be responsible for the management and use of this data.

(3) During use-results surveillance period, applicants should submit annual reports on the surveillance data gathered in accordance with Article 23-2-9, Paragraph 6 of the PMD Act (periodic reporting). The applicants must make efforts to share the latest periodic reporting information with physicians using medical devices. For more details concerning use-results surveillance, please refer to related Ministerial Notifications, such as "Handling of Use-results Evaluation related to Manufacturing/Marketing Approval of Medical Device and *In Vitro* Diagnostic Products" (PFSB/MDRMPE Notification No. 1121-44, by the Director of the Medical Device and Regenerative Medicine Product Evaluation (MDRMPE), PFSB, MHLW, dated November 21, 2014).

(4) If an applicant intends to change the content of the post-marketing RMP (including device use standards), and expand facilities based on the use-results assessment data, post-marketing malfunction/error trends, and accumulation of post-marketing use data, applicant should arrange for consultation with PMDA about such intention in advance.

(5) Applicants are strongly advised to take advantage of the various consultation services offered by PMDA when devising plans for the collection and use of post-marketing data, so that post-marketing data collected through use-results surveillance, post-marketing clinical studies, and registries for medical devices eligible for this System support not only the review of post-marketing risk management-related concerns, but also the future improvement of the medical device itself.

5. Points to consider

(1) If the provisions set forth in "Treatment of Off-label Use of Medical Devices by Physicians" (HPB/RDD Notification No. 0522001 and PFSB/ELD Notification No. 0522001, by the Director of the Research and Development Division (RDD), Health Policy Bureau (HPB), MHLW and the ELD Director, PFSB, MHLW, dated May 22, 2006" apply, submission of an application for approval without using the System may be appropriate. In such cases, applicants should arrange for individual consultation with the Evaluation and Licensing Division of the Pharmaceutical and Food Safety Bureau at the Ministry of Health, Labour and Welfare.

(2) Applicants are advised to consider utilizing the face-to-face consultation services offered by PMDA if the provisions set forth in "Clarification of the Treatment of Clinical Study Data concerning Medical Devices for Rare Diseases" (PFSB/ELD/OMDE Notification No. 0329-1, by the Director of Office of Medical Devices Evaluation (OMDE), ELD, PFSB, MHLW, dated March 29, 2013) apply and evaluation of the clinical efficacy and safety of the product under development based on nonclinical study data from laboratory performance and animal model studies alone has been determined to be feasible. After the above, applicants may consider taking advantage of the System as needed.

(Appendix)

Summary of the Criteria for Eligibility for the Conditional Early Approval System for Innovative Medical Devices" (Summary of Eligibility)

<table>
<tr><td colspan="2">Name of prospective applicant</td><td></td></tr>
<tr><td rowspan="2">Name</td><td>Generic name</td><td>(Note, if none of the existing generic names are applicable, enter "new")</td></tr>
<tr><td>Branded name</td><td></td></tr>
<tr><td colspan="2">Proposed use(s) or indication(s)</td><td></td></tr>
<tr><td rowspan="2">Requirement A</td><td>Severity of the target disease</td><td>☐ Life-threatening diseases
☐ Irreversible progressive diseases with profound adverse effects on patient ADL</td></tr>
<tr><td colspan="2">(Summary of target disease)</td></tr>
<tr><td rowspan="2">Requirement B</td><td>Existing therapies</td><td>☐ Currently no therapy available
☐ Efficacy and/or safety is expected to be significantly more favorable than the existing treatment(s)</td></tr>
<tr><td colspan="2">(Differences from existing treatment(s))</td></tr>
<tr><td rowspan="2">Requirement C</td><td>Existing clinical data</td><td>☐ Clinical trial ☐ Clinical research ☐ Publications ☐ Other</td></tr>
<tr><td colspan="2">(Summary of study results indicative of efficacy)</td></tr>
<tr><td rowspan="2">Requirement D</td><td>Post-marketing risk management</td><td></td></tr>
<tr><td colspan="2">(Progress of discussions with related academic societies or similar entities concerning standards for the appropriate use of medical device products)</td></tr>
<tr><td rowspan="2">Requirement E</td><td>Issues related to clinical trial execution</td><td></td></tr>
<tr><td colspan="2">(Current status of development and reason(s) for inability to conduct clinical studies)</td></tr>
<tr><td>Remarks</td><td colspan="2">(Note: If the product candidate has been designated as a medical device for rare diseases or that fulfills a high unmet medical need, describe such in detail.)</td></tr>
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