Provisional Translation (as of February 2018) *

PSEHB/PED Notification No. 1020-1
October 20, 2017

To: Directors of Prefectural Health Department (Bureau)

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

Implementation of a Conditional Early Approval System for Pharmaceutical Products

The execution of clinical studies of pharmaceutical products for severe diseases affecting small patient populations and that lack effective treatment options is often impeded by various difficulties, and in Japan such studies can require substantially longer implementation periods if the study is practicable at all. In the past, such products were reviewed individually, and many have been granted approval subject to certain conditions (e.g., requiring post-marketing safety and efficacy assessments rather than requiring results of confirmatory clinical studies).

In such cases, entities applying for regulatory approval (hereinafter referred to as "applicants") filed an application including certain materials, such as study results of a certain level of comprehensiveness (agreed to beforehand by the reviewing authority), as required documents. Post-marketing activities were subsequently discussed during review procedures. The applicant's acceptance and commitment to such post-marketing activities was designated as a condition for product approval.

As the above protocol involved largely case-by-case decision-making, this process flow will henceforth be reformed and clarified under a new "Conditional Early Approval System" (hereinafter, the "System") to improve the consistency and predictability of regulator interactions with industry in order to facilitate swifter patient access to new pharmaceutical products.

Specific details regarding the System are explained below. Please familiarize yourself with the information provided herein and circulate amongst relevant applicants or other stakeholders.

Please note that this System is not intended to change how the materials required for applications for regulatory approval are handled.

1. Eligible products

Pharmaceutical products fulfilling each of the following criteria [1] - [4] shall be deemed to fall within the scope of the System.

[1] The product's indication has been classified as a serious condition based on a comprehensive review of the following:
   1) The condition presents a substantial risk to patient survival (life-threatening)
   2) The condition is irreversible and presents a significant hindrance on daily activities
   3) Other factors as deemed appropriate

[2] The clinical utility of the product for its planned indication(s) has been determined to be high based on a comprehensive review of the following:
   1) No treatments, prophylactic measures, or diagnostics currently exist
   2) The product offers superior clinical utility over existing treatments, prophylactic measures, or diagnostics in terms of efficacy, safety, and physical/psychological burden on patients

[3] Conducting confirmatory clinical studies is believed to be impracticable, or, if deemed feasible, execution is anticipated to require considerable time due to some difficulties such as a small subject population.

[4] Results of clinical studies other than confirmatory clinical studies suggest a certain level of efficacy and safety.

2. Protocol for determining eligibility under the System

1) Applicants should avail themselves of the consultation services provided by the Pharmaceutical and Medical Devices Agency (PMDA) to become familiar with the eligibility requirements for the System, the types of materials required for regulatory submissions, and to receive an overview of the anticipated conditions for approval (hereinafter referred to as "System Eligibility").
2) To ensure that application materials are submitted promptly after the completion of the clinical studies required for marketing approval, PMDA consultations should take place immediately after the applicant learns that the results of nonconfirmatory clinical studies can assure certain level of efficacy and safety.
3) PMDA will prepare an assessment report regarding System Eligibility based on the result of nonconfirmatory clinical studies even if the expected application data package includes the results of ongoing or future studies. Both PMDA and the applicant should agree on the content of the assessment report.
4) Upon submitting their applications, applicants should indicate "Consultation on the eligibility for the conditional early approval system already held" in the remarks field of the application form for the applicable new product and attach the corresponding assessment report.
5) The Ministry of Health, Labour and Welfare (MHLW) will report the results of its

consideration concerning System Eligibility to the immediate relevant committee of the Pharmaceutical Affairs and Food Sanitation Council in reference to the assessment report, and obtain the Council's endorsement.

6) MHLW will notify applicants about its decision concerning System Eligibility. MHLW will also announce it when the relevant new product is approved.

3. Role of PMDA consultations

As the System is intended to facilitate swifter access to medical products indicated for severe diseases and that offer high clinical utility, consultations with PMDA regarding System Eligibility should be prioritized. However, if a product has been determined to fall outside the scope of the System in view of the nature of its target disease or the results of clinical studies, this may not be appropriate.

4. Conditions for approval

Approval of applicable pharmaceutical products should be granted under a condition requiring the applicant to conduct post-marketing surveys or other studies that are necessary to re-confirm the efficacy and safety of the product. Such surveys may utilize medical information databases such as MID-NET (Medical Information Database-Network [currently in testing]) and patient registry data as necessary. In addition, such product approval conditions may include requirements for applicants to act to ensure the implementation of policies directing medical facilities and other organizations to ensure the optimal use of the product.

The anticipated approval conditions agreed between the applicant and PMDA may be modified during the review process based on the content of materials submitted with the regulatory approval application.

5. Handling of priority review products

Since pharmaceutical product to which this system is applied fulfill the requirements for priority review stipulated in "Outlook on priority review" (PSEHB/PED notification No. 0122-12, PSEHB/MDED notification No. 0122-2, dated January 22, 2016), such products will be the subject to priority review.

6. Modification to approval conditions

Whether an applicant associated with a pharmaceutical product determined to have System Eligibility has satisfactorily fulfilled the product approval conditions will in principle be confirmed at the time of product re-examination. However, applicants may consult with PMDA regarding changes to such conditions in cases where revision of approval conditions is deemed proper due to completion of post-marketing surveys or required clinical studies.

Please refer to the "Q&A for use-result surveys and early post-marketing phase vigilance of prescription drugs by all-case surveillance" (Administrative Notice issued by the Evaluation and Licensing Division/Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 7, 2009) for detailed information regarding removal of the product approval conditions. In the event of any condition left unspecified by this administrative notice, applicants should consult with MHLW for information concerning procedures and deadlines for submission of a change request.

7. Effective date

This notification became effective as of October 20, 2017.