Provisional Translation (as of April 2025)*

PMSB/ELD Notification No. 1023-2
October 23, 2024

To: Directors of Prefectural Health Department (Bureau)

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

Partial Revision of "Handling of Conditional Approval of Drugs"

The handling of conditional approval of drugs has been carried out in accordance with "Handling of Conditional Approval of Drugs" (PSEHB/PED Notification No. 0831-2 by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020; hereinafter referred to as "Director's Notification").

Handling of Conditional Approval of Drugs has been revised as shown in the attached new/old comparison table based on the review at the "Review Committee on Regulatory Affairs to Strengthen Drug Discovery and Development/Ensure Stable Supply," and it has been decided that the revision applies from today. We ask you to understand this revision and inform related parties under your jurisdiction of this matter.

The revised Director's Notification is attached for reference.

* 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.

Appendix

New/Old Comparison Table

(The underlined parts are revised.)

New	Old
1. Eligible products Drugs fulfilling all of the following criteria (1)-(4) shall be deemed to fall within the scope of this System. Please note, the application of this System to prophylactic drugs requires careful consideration. Furthermore, for products that have been approved in Europe, the United States, etc., under a system similar to the conditional approval system, and for which a confirmatory clinical trial (including a clinical trial in a different treatment line) is scheduled to be conducted after approval, the use of this System should be actively considered. (1) and (2) Omitted (3) Conducting confirmatory clinical trials 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. The applicability to this requirement is also considered for products requiring additional data in Japanese subjects. Furthermore, drugs for fatal diseases or diseases that rapidly and irreversibly progress, etc., for which there is uncertainty of their efficacy and safety in Japanese patients because the confirmatory evidence has not been obtained, also meet this requirement if conducting clinical trials that require a significant amount of time for approval, result in a significant disadvantage to patients. (4) Omitted	1. Eligible products Drugs fulfilling all of the following criteria (1)-(4) shall be deemed to fall within the scope of this System. Please note, the application of this System to prophylactic drugs requires careful consideration. (1) and (2) Omitted (3) Conducting confirmatory clinical trials 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) Omitted
4. Procedure for determining eligibility under the System 1) Omitted 2) The Ministry of Health, Labour and Welfare shall determine the applicability of this System using documents to support the fact that the submission of the results of confirmatory clinical trials is exempted and report the decision at the upcoming meeting of the relevant committee of the Pharmaceutical Affairs Council for approval. 3) The Ministry of Health, Labour and Welfare shall notify the applicant that the product has been determined to be eligible for this System. Furthermore, the Ministry shall make that fact and the outline of the conditions for exemption from submission	4. Procedure for determining eligibility under the System 1) Omitted 2) The Ministry of Health, Labour and Welfare shall determine the applicability of this System using documents to support the fact that the submission of the results of confirmatory clinical trials is exempted and report the decision at the upcoming meeting of the relevant committee of the Pharmaceutical Affairs and Food Sanitation Council for approval. 3) The Ministry of Health, Labour and Welfare shall notify the applicant that the product has been determined to be eligible for this System. Furthermore, the Ministry shall make that fact public after approval of the product.

public after approval of the product. 4) Even if the application mentioned in 1) is not made, the approval under the conditional approval system may be granted if it is judged as appropriate in the process of approval review. In such a case, the Ministry of Health, Labour and Welfare will also make the fact that the product was determined to be eligible for this System, as well as the outline of the conditions for exemption from submission, public after product approval.	
5. Conditions for exemption from submission Approval of applicable drugs should be granted under a condition requiring the applicant to conduct post-marketing surveillance or other studies that are necessary to re-confirm the efficacy and safety of the product. When conducting a confirmatory clinical trial to reconfirm the efficacy and safety of the drug after the conditional approval, the study population does not necessarily need to be completely consistent with the scope of the conditional approval. In addition, it may be acceptable to include patients in different treatment lines or at different stages of the disease, etc., taking into account the feasibility of conducting the clinical trial. Moreover, such the clinical trial does not necessarily need to include Japanese patients, and even confirmatory clinical trials being conducted or planned overseas may be accepted. Furthermore, clinical trials are not necessarily the sole option for reconfirming the efficacy and safety of the product after the conditional approval. As long as the scientific validity and feasibility of the clinical trial are considered, and if it is appropriate for the purpose of collecting information, post-marketing surveillance or studies using medical information databases, such as MID-NET, or patient registries, etc., can also be used as studies to fulfill the conditions for exemption from submission, 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 proper use of the product. (Omitted)	5. Conditions for exemption from submission Approval of applicable drugs should be granted under a condition requiring the applicant to conduct post-marketing surveillance or other studies that are necessary to re-confirm the efficacy and safety of the product. Studies using medical information databases, such as MID-NET, or patient registries, etc., can also be used as studies to fulfill the conditions for exemption from submission, 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 proper use of the product. (Omitted)
7. Evaluation of the results of surveillance, etc. conducted to fulfill the conditions for exemption from submission The marketing authorization holders of drugs approved under this System shall submit for evaluation (hereinafter referred to as "interim evaluation") the results of the surveillance, etc. conducted to fulfill the conditions for exemption	7. Evaluation of the results of surveillance, etc. conducted to fulfill the conditions for exemption from submission The marketing authorization holders of drugs approved under this System shall submit for evaluation (hereinafter referred to as "interim evaluation") the results of the surveillance, etc. conducted to fulfill the conditions for exemption

from submission within the period designated at the time of approval. For the interim evaluation, the marketing authorization holder shall submit necessary results to the PMDA with Form No. 22-2 as specified in the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961; hereinafter referred to as the "Regulation"), which was revised under the Ministerial Ordinance on the Development of Related Ministerial Ordinances in Accordance with Enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Ordinance No. 155 of 2020). The results of the interim evaluation of drugs approved under this system shall be made public regardless of their approval status.	from submission within the period designated at the time of approval. For the interim evaluation, the marketing authorization holder shall submit necessary results to the PMDA with Form No. 22-2 as specified in the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961; hereinafter referred to as the "Regulation"), which was revised under the Ministerial Ordinance on the Development of Related Ministerial Ordinances in Accordance with Enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Ordinance No. 155 of 2020).
8. Change in conditions for exemption from submission Based on the results of the interim evaluation, the Ministry of Health, Labour and Welfare shall make necessary changes in the conditions for exemption from submission, the content of approval, etc. after hearing opinions of the Pharmaceutical Affairs Council.	8. Change in conditions for exemption from submission Based on the results of the interim evaluation, the Ministry of Health, Labour and Welfare shall make necessary changes in the conditions for exemption from submission, the content of approval, etc. after hearing opinions of the Pharmaceutical Affairs and Food Sanitation Council.

Reference

PSEHB/PED Notification No. 0831-2
August 31, 2020
[Partially revised] October 23, 2024

To: Directors of Prefectural Health Department (Bureau)

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

Handling of Conditional Approval of Drugs

For drugs intended for the treatment of severe diseases with few effective treatment options and a small number of patients, and for which conducting clinical trials in Japan would be difficult, or for which clinical trials, even if possible, would require a considerable amount of time to conduct, we have granted approval based on the "Implementation of a Conditional Early Approval System for Pharmaceutical Products" (PSEHB/PED Notification No. 1020-1 issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated October 20, 2017; hereinafter referred to as the "Director's Notification") after evaluating individual circumstances without requiring the submission of the results of confirmatory clinical trials under the approval condition that the necessary post-marketing surveillance, etc. will be conducted.

To elucidate the legislation surrounding this conditional approval system (hereinafter referred to as "System") for drugs and its requirements and enhance information gathering activities, including post-marketing surveillance, and their evaluation, we have updated the handling of this System in accordance with the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, dated August 10, 1960; hereinafter referred to as the "Act"), which was revised under the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 63 of 2019), as described below.

This is to inform you of this change and to request you to inform the relevant organizations and institutions in your jurisdiction.

Please note, drugs for which an application for marketing approval or an application for partial change in marketing approval (hereinafter referred to as “approval application”) have been submitted in accordance with the Director's Notification will not be affected by this notification and continue to be handled as before.

Description

1. Eligible products

Drugs fulfilling all of the following criteria [1]-[4] shall be deemed to fall within the scope of this System.

Please note, the application of this System to prophylactic drugs requires careful consideration. Furthermore, for products that have been approved in Europe, the United States, etc., under a system similar to the conditional approval system, and for which a confirmatory clinical trial (including a clinical trial in a different treatment line) is scheduled to be conducted after approval, the use of this System shall be actively considered.

[1] The indication(s) has been classified as a serious condition based on a comprehensive assessment 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

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

[3] Conducting confirmatory clinical trials 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.

The applicability to this requirement is also considered for products requiring additional data in Japanese subjects. Furthermore, drugs for fatal diseases or diseases that rapidly and irreversibly progress, etc., for which there is uncertainty of their efficacy and safety in Japanese patients because the confirmatory evidence has not

been obtained, also meet this requirement if conducting clinical trials that require a significant amount of time for approval, result in a significant disadvantage to patients.

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

2. Consultation on the applicability of this System

1) Before approval application, 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, to have a discussion on appropriateness of the clinical data package required for approval application, and to receive an overview of the anticipated conditions under Article 14, Paragraph 10 of the Act (hereinafter referred to as "conditions for exemption from submission") for approval (hereinafter referred to as " System Eligibility").

2) To ensure that application materials are submitted promptly after the completion of the clinical trials required for approval application, PMDA consultations should take place immediately after the applicant learns that the results of clinical trials other than confirmatory clinical trials can assure certain level of efficacy and safety.

3) The PMDA shall judge the applicability of this System based on the results of clinical trials other than confirmatory clinical trials, etc. agree with the applicant on the outline of the conditions for exemption from submission, and prepare an evaluation report.

3. Role of PMDA consultation

As the System is intended to facilitate earlier access to drugs with particularly high medical needs, consultations with the 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 trials, this may not be appropriate.

4. Procedure for determining eligibility under the System

1) Applicants who wish to use this System shall, when applying for approval, enter "Exemption from submission of the results of confirmatory clinical trials" in the remarks column of the application form for the drug being applied for and attach documents to support the fact that the submission of the results of confirmatory clinical trials is exempted. These documents generally refer to the assessment reports

described in 2. 3).

2) The Ministry of Health, Labour and Welfare shall determine the applicability of this System using documents to support the fact that the submission of the results of confirmatory clinical trials is exempted and report the decision at the upcoming meeting of the relevant committee of the Pharmaceutical Affairs Council for approval.

3) The Ministry of Health, Labour and Welfare shall notify the applicant that the product has been determined to be eligible for this System. Furthermore, the Ministry shall make that fact and the outline of the conditions for exemption from submission public after approval of the product.

4) Even if the application mentioned in 1) is not made, the approval under the conditional approval system may be granted if it is judged as appropriate in the process of approval review. In such a case, the Ministry of Health, Labour and Welfare will also make, the fact that the product was determined to be eligible for this System as well as the outline of the conditions for exemption from submission public, after product approval.

5. Conditions for exemption from submission

Approval of applicable drugs should be granted under a condition requiring the applicant to conduct post-marketing surveillance or other studies that are necessary to re-confirm the efficacy and safety of the product. When conducting a confirmatory clinical trial to reconfirm the efficacy and safety of the drug after the conditional approval, the study population does not necessarily need to be completely consistent with the scope of the conditional approval. In addition, it may be acceptable to include patients in different treatment lines or at different stages of the disease, etc., taking into account the feasibility of conducting the clinical trial. Moreover, such the clinical trial does not necessarily need to include Japanese patients, and even confirmatory clinical trials being conducted or planned overseas may be accepted.

Furthermore, clinical trials are not necessarily the sole option for reconfirming the efficacy and safety of the product after the conditional approval. As long as the scientific validity and feasibility of the clinical trial are considered, and if it is appropriate for the purpose of collecting information, post-marketing surveillance or studies using medical information databases, such as MID-NET, or patient registries, etc., can also be used as studies to fulfill the conditions for exemption from submission, 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 proper use of the product.

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

6. Handling of priority reviews

Drugs to which this System has been applied are subject to priority review as they fulfill the requirements for application of priority review specified in the "Handling of priority reviews, etc." (PSEHB/ELD Notification No. 0831-1 and PSEHB/MDED Notification No. 0831-1 dated August 31, 2020).

7. Evaluation of the results of surveillance, etc. conducted to fulfill the conditions for exemption from submission

The marketing authorization holders of drugs approved under this System shall submit for evaluation (hereinafter referred to as "interim evaluation") the results of the surveillance, etc. conducted to fulfill the conditions for exemption from submission within the period designated at the time of approval. For the interim evaluation, the marketing authorization holder shall submit necessary results to the PMDA with Form No. 22-2 as specified in the Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961; hereinafter referred to as the "Regulation"), which was revised under the Ministerial Ordinance on the Development of Related Ministerial Ordinances in Accordance with Enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHLW Ordinance No. 155 of 2020).

The results of the interim evaluation of drugs approved under this System shall be made public regardless of their approval status.

8. Change in conditions for exemption from submission

Based on the results of the interim evaluation, the Ministry of Health, Labour and Welfare shall make necessary changes in the conditions for exemption from submission, the content of approval, etc. after hearing opinions of the Pharmaceutical Affairs Council.

9. Other

If it is determined that a confirmatory clinical trial is not necessary as the efficacy and safety of the drug claimed in the application can be confirmed without conducting such a

confirmatory clinical trial, this falls under the category of cases where there are reasonable grounds for not requiring the submission of the results of confirmatory clinical trials as specified in Article 40, Paragraph 2 of the Regulations; therefore, it is not necessary to attach the results of confirmatory clinical trials regardless of the applicability of this System.

10. Effective date

This notification became effective as of September 1, 2020.