Provisional Translation (as of April 2024)*

PSB/PED Notification No. 0116-3
January 16, 2024

To: Prefectural Health Departments (Bureaus)

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

Partial Revision of "Handling of Re-Examination Period"

Re-examination periods of prescription drugs have been shown in "Re-Examination Period of Prescription Drugs" (PSEHB Notification No. 0831-11 dated August 31, 2020 by Director-General of Pharmaceutical Safety and Environmental Health Bureau, Labour and Welfare), and "Handling of Re-Examination Period" (PSEHB/PED Notification No. 0831-16 dated August 31, 2020 by Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, hereinafter referred to as "the Notification by Director").

In association with the issue of "Partial Revision of 'Designation of Orphan Drugs'" (Joint PSB/PED Notification No. 0116-1 issued by Director of Pharmaceutical Evaluation Division, and PSB/MDED Notification No. 0116-1 issued by Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated January 16, 2024) based on the review at "Review Committee on Regulatory Affairs to Strengthen Drug Discovery/Ensure Stable Supply," handling of the re-examination period of orphan drugs etc. has been revised as shown in the attached old-and-new comparison table. The revision applies from today. We ask you to understand and inform related parties under your administration.

The revised Notification by Director 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

Old-and-new comparison table

(The underlined parts are the revised.)

After amendment	Before amendment
1 Matters related re-examination period 1 The investigation period specified in Article 14-4 (1) of the revised Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as "the Act") by the Amendment Act is as shown below in principle. Re-examination must be conducted within 3 months after this investigation period. (1) Orphan drug (A) Those to which the following apply 10 years 1) The first approval of the designated indication (If the drug has the same active ingredients as a drug already approved for marketing, this shall be limited to the approval of an indication that is clearly different from that of the approved drug.) 2) Addition of clearly different doses such as pediatric doses etc. (B) (omitted)	1 Matters related re-examination period 1 The investigation period specified in Article 14-4 (1) of the revised Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as "the Act") by the Amendment Act is as shown below in principle. Re-examination must be conducted within 3 months after this investigation period. (1) Orphan drug (A) First approval of the designated indication 10 years (B) (omitted)

Reference

PSEHB/PED Notification No. 0831-16
August 31, 2020
[Partially revised] January 16, 2024

To: Prefectural Health Departments (Bureaus)

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

Handling of Re-Examination Period

The handling of the re-examination period of prescription drugs has been shown in "the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Act and the Act on the Fund for Adverse Drug Reaction Relief and R&D Promotion" (PAB Notification No. 725 dated August 25, 1993 by Director-General of Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, hereinafter referred to as "1993 Notification by Director"), "the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Act and the Act on the Fund for Adverse Drug Reaction Relief and R&D Promotion" Joint PAB/NDD Notification No. 92, dated October 1, 1993 by Director of New Drug Division, Director of Medical Device Development Division, Safety Division, Pharmaceutical Affairs Bureau,, Ministry of Health and Welfare, hereinafter referred to as "Joint Notification by Directors"), "Enforcement of Ministerial Ordinance of Partial Revision of the Ministerial Ordinance on Good Post-Marketing Surveillance Practice and Revision of Post-Marketing Surveillance in Relation to Re-Examination of Drugs" (PMSB Notification No. 1324 dated December 27, 2000 by Director of Medicinal Safety Bureau, Ministry of Health and Welfare, hereinafter referred to as "2000 Notification by Director"), "Re-Examination Period of Drug" (PMSB/ELD Notification No. 1813 dated December 27, 2000 by Director, Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, hereinafter referred to as "the Notification by Director") and "Re-Examination Period for Drug with a New Active Ingredient" (PFSB Notification No. 0401001 dated April 1, 2007 by Director-General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare).

In association with the stipulation of the designation system for drugs for specific use by the "Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, and Other Acts" (Act No. 63 of 2019; hereinafter referred to as the "Amendment Act"), a notification "Re-Examination Period of Prescription Drugs" (PSEHB Notification No. 0831-11 dated August 31, 2020 by Director-General of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) was issued. The details of handling of the re-

Reference

examination period have been specified as shown below. We ask you to instruct related parties under your administration.

This notification shall come into effect as from September 1, 2020.

Note

1 Matters related re-examination period

1 The investigation period specified in Article 14-4 (1) of the revised Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as "the Act") by the Amendment Act is as shown below in principle. Re-examination must be conducted within 3 months after this investigation period.

(1) Orphan drugs

(A) Those to which the following apply 10 years

1) The first approval of the designated indication (If the drug has the same active ingredients as a drug already approved for marketing, this shall be limited to the approval of an indication that is clearly different from that of the approved drug.)

2) Addition of clearly different doses such as pediatric doses etc.

(B) Those to which the following apply Period of >6 years and ≤8 years designated by the Minister of Health, Labour and Welfare

1) Same as drugs already approved for marketing in terms of the active ingredients and indications but different in terms of the route of administration

2) New combination drug of orphan drugs already approved for marketing

(2) New drugs for which assessment on post-marketing surveillance is clearly required on the overall efficacy in patients in a pharmacoepidemiological manner based on life prolongation by its long-term use, QOL improvement, and complication prevention etc. 10 years

(3) Drugs that are clearly different from marketing-approved drugs in terms of active ingredients (except drugs listed in the above (1) and (2)) 8 years

(4) Drugs for specific use Period of ≥4 years and <6 years designated by the Minister of Health, Labour and Welfare

(5) New drugs that are clearly different from marketing-approved drugs only in terms of indications (except drugs listed in the above (1))

(A) Innovative drugs (designated under the SAKIGAKE system) Period of >6 years and ≤8 years designated by the Minister of Health, Labour and Welfare

(B) Drugs already approved for marketing with only the indication designated for the orphan drugs (except the drugs listed in the above (A)) 5 years 10 months

(C) Other cases than the above (A) and (B) 4 years

(6) New drugs that are clearly different from approved drugs in terms of the dosage (except the route of administration) or doses but are the same in terms of the active ingredients and route of administration, and new drugs that are regarded

as having minor differences from other drugs already approved for marketing (except drugs listed in the above (1), (4) and (5)) 4 years

(7) New drugs other than those listed in the above (1) to (6) 6 years

2 Drugs that are regarded as equivalent to a new drug in terms of their active ingredients, contents, administration, dosage, indications, efficacy, etc., and that are approved during the investigation period of the new drug must be re-examined within a period designated by the Minister of Health, Labour and Welfare to coincide with the period to apply for re-examination of the new drug.

3 If a drug already approved for marketing is found to require assessment on the overall efficacy in patients in a pharmacoepidemiological manner based on life prolongation by its long-term use, QOL improvement, and complication prevention etc. during post-marketing surveillance after approval, the investigation period may be extended to 10 years in accordance with the regulation in Article 14-4 (3) of the Act. The necessity of the investigation period extension should be examined based on the risk management plan etc. submitted by those who have received approval.

4 With regard to drugs that are considered, at the time of approval, to clearly require a dose-finding study in pediatrics, if the development plan for finding dosage in pediatrics is submitted by the end of review on marketing approval and if the planned clinical study is started without delay, the investigation period may be extended to a period not exceeding 10 years in accordance with Article 14-4 (3) in the Act.

2 Handling of drugs for which post-marketing surveillance is conducted in a pharmacoepidemiological manner (the above 1-1 (2) and 3)

1 Generally, drugs used for chronic diseases with significantly highly innovative structures or pharmaceutical effects compared to those existing drugs fall under drugs requiring post-marketing surveillance in a pharmacoepidemiological manner.

2 The necessity of the investigation period extension for re-examination should be considered individually after approval, and then the investigation period should be extended.

3 Interim measures

1 New drugs which are approved by the end of March 2021 after the enforcement of this notification and for which the development plan for finding dosage in pediatrics is not submitted by the end of review for the marketing approval may be deemed to fall under the above 1-4 if the development plan for finding a dosage in pediatrics is summarized with the use of a consultation system provided by the Pharmaceuticals and Medical Devices Agency and the planned clinical study is

started without delay after the approval. Such cases should be consulted individually with Pharmaceutical Evaluation Division.

2 For new drugs that are approved by August 31, 2020 and that meet the following (1), the provisions then in force shall remain applicable. If a post-marketing clinical study or clinical trial is found to be necessary to verify a pediatric dosage, it is desirable to promptly consider conducting the clinical study or clinical trial.

(1) If the results of post-marketing surveillance or post-marketing clinical study of a drug already approved for marketing reveal that it is necessary to conduct a post-marketing clinical study or clinical trial to verify the dosage and administration in pediatrics, the investigation period may be extended to a period not exceeding 10 years from the date of approval in accordance with Article 14-4 (2) of the Act. The necessity of the investigation period extension should be examined based on the protocol of the post-marketing clinical study or clinical trial etc. submitted by those who have received approval.

4 Revision of notification

"1-2 (4) of the Notification by Director-General" in the Note 3 of the Notification by Director will be revised to "Note 3-2 (1) of 'Handling of Re-Examination Period' (PSEHB/PED Notification No. 0831-16 dated August 31, 2020 by Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare), and "post-marketing surveillance basic protocol (additional notification)" will be revised to "protocol of post-marketing clinical study or clinical trial."