Provisional Translation (as of May 2025)

Administrative Notice
June 12, 2024

To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

Medical Device Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare

Q&A about “Handling of the Two-step Approval Based on the Characteristics of Software as a Medical Device”

The concept of the two-step approval for software as a medical device (SaMD) is as described in the “Handling of the Two-step Approval Based on the Characteristics of Software as a Medical Device” (PSB/MDED Notification No. 1116-2 issued by the Director of Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated November 16, 2023).

On this occasion, we have compiled a list of questions and answers related to this notification as shown in the attachment. We ask for your understanding of this notification and ask to inform the relevant business operators and relevant organizations in your jurisdiction regarding this notification.

Please be advised that copies of this administrative notice have been sent to the Japan Federation of Medical Devices Associations, the American Medical Devices and Diagnostics Manufacturers’ Association, the European Business Council Medical Devices and IVD Committee, the Japan Digital Health Alliance, the Japan Medical Venture Association, Council for AI Medical Devices, the Japan Pharmaceutical Manufacturers Association (JPMA), and the Pharmaceuticals and Medical Devices Agency.

Attachment

Q&A about
"Handling of the Two-step Approval Based on the Characteristics of Software as a Medical Device"

Abbreviations used	Term
Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145, 1960)
Ministerial Ordinance for Enforcement	Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHW Ordinance No. 1, 1961)
GCP Ordinance	Ministerial Ordinance on Good Clinical Practice for Medical Devices (MHLW Ordinance No. 36, 2005)
Notification of Rebalance	"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)" (PSEHB/MDED Notification No. 1117-1 and PSEHB/PSD Notification No. 1117-1 issued jointly by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated November 17, 2017)
Notification of Rebalance for SaMD	"Handling of the Two-step Approval Based on the Characteristics of Software as a Medical Device" (PSB/MDED Notification No. 1116-2 issued by the Director of Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated November 16, 2023)

Improvement Design within Approval for Timely Evaluation and Notice (IDATEN)	"Handling of the Confirmation Application for Medical Device Change Plan" (PSEHB/MDED Notification No. 0831- 14 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020)

[Considerations]

If there is any question after referring to the above notification, etc., consider consulting the Pharmaceuticals and Medical Devices Agency (PMDA).

Q&A about
"Handling of the Two-step Approval Based on the Characteristics of Software as a Medical Device"

Question 1	What is the difference between the first step approval in the concept of two-step approval for SaMD and the standard marketing approval?

(Answer) Standard marketing approval may be obtained for SaMD if it is possible to show the clinical significance or medical judgment criteria for information, etc. presented by the product based on the results of clinical studies, etc. conducted, or if it is possible to show clinical evidence or clinical significance as a treatment method for a disease.

Meanwhile, according to the concept of two-step approval of SaMD, marketing approval may be obtained for the program as first step approval with the scope limited to the confirmed intended use or effect in cases where clinical significance or medical determination criteria for the information, etc. presented by the program have not been established or clinical evidence or clinical significance as a therapy for a disease is not sufficient, but a certain level of efficacy can be confirmed with feasibility for specific symptom relief in the target disease or improvement of the condition based on the results of exploratory clinical trials, etc. and the benefit can be expected.

PMDA should be consulted as necessary for documents required for the approval application, since these differ depending on the individual product and the development policy.

Question 2	What is the difference between a Notification of Rebalance for SaMD and the Notification of Rebalance?

(Answer) The concept described in "Section 1. Concept of two-step approval for SaMD for disease diagnosis" of the Notification of Rebalance for SaMD is the same as that in "Section 3. Consultation on a diagnostic device for the measurement of physiological parameters which may be used as reference information for diagnosis" in the Notification of Rebalance.

Meanwhile, the concept described in "Section 2. Concept of two-step approval for SaMD for disease treatment" of the Notification of Rebalance for SaMD does not exist in the Notification of Rebalance and has been established with consideration for the characteristics of SaMD.

Programs included in medical devices approved as tangible are not subject

to Notification of Rebalance for SaMD and are subject to the Notification of Rebalance.

Question 3	What is different between the concept of two-step approval for SaMD and the Improvement Design within Approval for Timely Evaluation and Notice (IDATEN)?

(Answer) According to the two-step approval of SaMD, the first step approval can be obtained by limiting the scope of intended use or effect that can be demonstrated by the marketing approval application documents even if the clinical significance, etc. as a diagnostic method or treatment method of disease as the final target has not been established. For products with first step approval, application for partial changes (hereinafter referred to as "partial change applications") or new marketing authorization application (hereinafter referred to as "new application" will be submitted as necessary after the clinical evidence has been established based on the experience of clinical use or other means, which leads to the obtaining of the second step approval according to this development strategy.

In contrast, Improvement Design within Approval for Timely Evaluation and Notice (IDATEN) is a system which allows changes to be made through submission of a notification even if partial change application is normally required for the change plan related to the intended use or effect, shape, structure, principle, raw materials, specifications related to performance and safety, use method, storage method, shelf life, manufacturing method, etc. of a medical device approved based on Article 23-2-5, Paragraph 1 of the Act in cases where change or study is implemented in accordance with the confirmed change plan and the criteria are met by receiving the necessary confirmation from the PMDA.

Question 4	Is it acceptable to consider that the first step approval based on the two-step approval is the same as the approval based on Article 23-2-5, Paragraph 1 of the PMD Act?

(Answer) Yes.

Question 5	Has a change been made to the standard review period for the first step approval from the published standard review period for each marketing approval application classification?

(Answer) No.

Question 6 Is it possible to flexibly change the development policy based on the test results obtained during the development of SaMD? For example, is it possible to change from the usual clinical trial plan to the development plan using the two-step approval or vice versa?

(Answer) Yes, this is possible. Change in development policy should be thoroughly discussed with PMDA.

Question 7 Notification of Rebalance for SaMD states that the concept of two-step approval does not apply as a principle for "cases where second step approval has been obtained for medical devices or SaMDs that have the same scope of intended use or effect as that of the product submitted for registration and are used in clinical practice." Is it possible to file a marketing application for the first-step approval of other similar products before the second step approval is obtained for the product with the first step approval?

(Answer) Yes, this is possible.

Question 8 If a particular marketing authorization holder obtained a second step approval after a similar first-step approval has been obtained by multiple marketing authorization holders, is it possible for the remaining marketing authorization holders to also apply for a second step approval?

(Answer) It is possible to obtain the second step approval of other similar products even if a particular marketing authorization holder has obtained the second step approval. The handling of the partial change application in such cases should be consulted with PMDA.

Question 9 Is it possible to add new functions in the period between the obtaining of the first step approval and the second step approval?

(Answer) Functions may be added by performing the necessary regulatory procedures such as partial change application.

Since the scope of the claims in the first step approval may be exceeded depending on the details of the change, the details of the functions to be added, the purpose of addition, and other matters should be clarified in advance and individual consultation should be held with PMDA.

Question 10 If the marketed programs for disease treatment will have added functions for the calculation of physiological parameters where clinical significance or medical determination criteria are not considered to be sufficiently established but may be used as reference information for diagnosis, is it possible to handle the addition of such a function as the first step approval?

(Answer) Yes, this is possible.

Question 11 For SaMD with artificial intelligence (AI), it is possible that partial change application (not second step approval) will be filed by additional learning of data after the first step approval has been obtained. In such cases, the performance, etc. of the relevant product may be changed from the time of the first step approval at the time of the second step approval application. Will the concept of the two-step approval for SaMD be applicable?

(Answer) It is possible that performance, etc. required for SaMD with artificial intelligence (AI) may be enhanced in the period between the obtaining of the first step approval and the second step approval. However, if the extent of change in performance, etc. exceeds the scope of a single product as a result of additional learning after marketing, this may be outside the scope of the second step approval application. For this reason, individual consultation should be held with PMDA on whether the concept of two-step approval for SaMD will be applicable.

Question 12 Notification of Rebalance for SaMD states that “protocol consultation for the second step approval, etc. should be conducted concurrently.” Is it mandatory to present the plans, etc. to obtain second step approval to the PMDA at the time of submission for the first step approval application? Also, with regards to specification as “protocol consultation,” is it essential to conduct a post-marketing clinical study for the obtaining of the second step approval?

(Answer) Presentation of the plan for obtaining the second-step approval to the PMDA is not mandatory at the time of the first step approval application; however, it is desirable to concurrently conduct a protocol consultation, etc. for the second step approval for development in anticipation of the second step approval. However, with regards to the types of evaluation required for obtaining the second-step approval, the evaluation methods for some products may be examined in cooperation with related academic societies, etc. after obtaining of the first step approval and use in clinical practice, therefore the

timing of protocol consultations, etc. for the obtaining of the second-step approval should be considered for the individual products. Also, in addition to post-marketing clinical studies, utilization of real-world data, etc. may be used as a method of clinical evaluation necessary for the obtaining of the second step approval.

Question 13 Notification of Rebalance for SaMD states that "clinical evaluation data at the second step of approval need to meet the data integrity standards for product application." While compliance with the GCP Ordinance is required for the conduct of post-marketing clinical study, is compliance with the GCP Ordinance also necessary for the utilization of real-world data?

(Answer) In the second step approval, clinical evaluation data utilizing real-world data, etc. do not need to comply with the GCP ordinance. However, if the real-world data, etc. that do not comply with the GCP Ordinance are used, these must be compliant with each item of Article 114, Paragraph 22 of the Enforcement Ordinance that stipulates the data integrity standards for product application. For this reason, consultation must be held with PMDA as necessary. In addition, when utilizing registry data as real-world data, "Considerations for Ensuring the Reliability of Registry Data in Approval Applications" (PSEHB/PED Notification No. 0323-2 and PSEHB/MDED Notification No. 0323-2 by the Director of Pharmaceutical Evaluation Division and Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour, and Welfare, dated March 23, 2021) should be referred to.

Question 14 In "Section 5. Planning of clinical evaluation, etc. for the obtaining of the second step approval" of the Notification of Rebalance for SaMD, it is stated that "real-world data and other data, including registries, may be used as the method of clinical evaluation necessary to obtain the second step approval in addition to the post-marketing clinical study results". Is it possible to use the clinical evaluation report for this purpose?

(Answer) Yes, this is possible. However, the acceptability based on the clinical evaluation report shall be considered with reference to the administrative notice dated November 17, 2017 "Release of Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices," as well as "Guidance for the preparation of clinical evaluation

reports and documents for clinical evaluation consultation Part 1: Procedures for preparation" and "Guidance for the preparation of clinical evaluation reports and documents for clinical evaluation consultation Part 2: Basic concepts for the acceptance of clinical evaluation reports" issued by the Japan Federation of Medical Devices Associations, and consultation with the PMDA shall be held as necessary.

Question 15 In "Section 1. Concept of two-step approval for SaMD for disease diagnosis" of the Notification of Rebalance for SaMD, "3. Eligible programs" includes the description "(3) Programs that do not result in significant impact on human life or health if incorrect test results have been obtained." Do the programs covered by Notification of Rebalance for SaMD only include controlled medical devices, with exclusion of specially controlled medical devices?

(Answer) The Notification of Rebalance for SaMD covers both the controlled and specially controlled medical devices.

Question 16 In "Section 1. Concept of two-step approval for SaMD for disease diagnosis" of the Notification of Rebalance for SaMD, "4. Ineligible programs" includes "(1) Programs where the results of the test/diagnosis significantly impact the medical decisions, for example the treatment policies for cancer and initial treatment policies in emergency medical care." Is two-step approval applicable in cases such as SaMD related to treatment policies for cancer and initial treatment policies in emergency medical care with a clinical positioning that is not expected to impact the medical decisions?

(Answer) Consultation should be held with PMDA for individual cases.

Question 17 For "Section 2. Concept of two-step approval for SaMD for disease treatment" of the Notification of Rebalance for SaMD, is it acceptable to provide the intended use or effect as the final target in the first step approval in anticipation of the second step approval?

(Answer) It is not acceptable to claim the intended use or effect as the target for the second step approval from the time of first step approval.

Consultation with the PMDA on individual products is necessary for the claims to be made in the first step approval, and it is expected that notification of the considerations for use and other measures will be taken.

Question 18 "Section 2. Concept of two-step approval for SaMD for disease treatment" of the Notification of Rebalance for SaMD includes the description "obtain first step approval for an intended use or effect, limited in scope, where a certain level of efficacy has been confirmed with feasibility" What is the definition of "feasibility" and what are the examples of "a certain level of efficacy has been confirmed with probability"?

(Answer) It is difficult to provide a uniform definition of "feasibility" in "concept of two-step approval for SaMD for disease treatment." Meanwhile, it is assumed that "a certain level of efficacy has been confirmed with feasibility" means that specific symptom relief or improvement in condition, etc. in the results of exploratory clinical trials, etc. can be confirmed with statistical difference in principle. Since the details to be presented differ depending on individual products and development policy (e.g., various cases are possible, including comparison with control group or open-label study), consultation should be arranged with the PMDA with reference also to the list of possible examples to be prepared and published by related industrial groups.

Question 19 What studies are intended to be included as "exploratory trials" in the Notification of Rebalance for SaMD? Also, is it possible to submit the marketing approval application for the first step approval using a specified clinical research as the supporting material other than exploratory trials?

(Answer) In "Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices," summarized in the "Research on the Appropriate Conduct of Clinical Trial Guidance Required to Facilitate the Speedy and Accurate Approval and Development of Medical Devices" (2016, the Japan Agency for Medical Research and Development (AMED), Research on Regulatory Harmonization and Evaluation of Pharmaceuticals and Medical Devices; Representative Researcher: Shohei Nakano, Executive Director of Executive Director, Japan Association for the Advancement of Medical Equipment (JAAME)), exploratory trials are described as follows: "While exploratory trials may not be necessarily required for medical devices, exploratory clinical trials may be conducted in the development of medical devices not only to improve the design of medical devices themselves but also to concurrently examine the indicated cases and related procedures, which may allow to stabilize the procedures, narrow appropriate subjects, and set appropriate primary endpoints." Therefore, "exploratory trials" in the

Notification of Rebalance for SaMD intends to refer to studies equivalent to Phase II studies in “General Considerations for Clinical Evaluation of New Drugs” (Notification No. 43 of the New Drug Division, PAB dated June 29, 1992) that are studies other than confirmatory studies with the intention of precisely and objectively clarifying the efficacy and safety of the investigational device for the target disease, etc. and to evaluate and obtain positioning of clinical benefit for the target disease of the investigational device. These studies also refer to the examination of the efficacy and safety in the investigational device in a limited number of patients in an appropriate disease state with the purpose of collecting the information for proceeding to confirmatory studies, for example the justification of indicated disease or method of use.

While specified clinical researches are not included in the exploratory trials, it is acceptable to use specified clinical researches as supporting documents in the first step approval. However, for the utilization of the specified clinical research as the supporting documents, this should be investigated with reference to the administrative notice dated June 5, 2024 “Examples of Considerations and Concepts for Utilization of Study Results Obtained in Specified Clinical Researches for the Approval Application of Medical Devices and Cellular and Tissue-based Products” and in consultation with PMDA as necessary.