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Provisional Translation (as of May 2025)

PSB/MDED Notification No. 1116-2
November 16, 2023

Attention to: Commissioner of Prefectural Health Supervising Department

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

Handling of the Two-step Approval Based on the Characteristics of Software as a Medical Device

Handling of cases where it is considered possible to file an approval application for medical devices including software as medical device (SaMD), regardless of whether new clinical trials are conducted before marketing, is explained in "Handling of Situations requiring submission of "Documents related to Clinical Study Results" for Medical Devices (Responses based on Measures across 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; hereinafter referred to as the "Notification of Rebalance

On this occasion, the ideal regulatory approval system, including the concept of two-step approval, was discussed from the viewpoint of efficient development and regulatory approval of SaMD in the "Project for the Improvement of Operation of the Regulatory Approval System with Consideration for the Characteristics of the Software as a Medical Device" (Principal Investigator: Shohei Nakano, Executive Director, Japan Association for the Advancement of Medical Equipment (JAAME)), and "Publication of the Guidance for the Appropriate and Prompt Approval and Development based on the Characteristics of the Software as a Medical Device" (Administrative Notice of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated May 29, 2023) was issued to clarify the handling and operation

related to two-step approval based on the characteristics of SaMD as described below. Please note that the concept of two-step approval is an option and regulatory approval can be obtained without the application of this approach.

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 notification 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.

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Section 1. Concept of two-step approval for SaMD for disease diagnosis

1. Basic concept

It is expected that development will take place for SaMD that calculates the physiological parameters, risk scores, or characteristic values for which the association between clinical symptoms or pathology and physiological conditions has not been widely recognized and the clinical significance and medical determination criteria have not been established sufficiently despite being considered for potential use as reference information for the diagnosis of diseases or prediction of prognosis, as well as SaMD that predicts the risk of exacerbation in patients through the analysis function of active monitoring medical devices, etc. for physiological indicators related to biological signals.

Since clinical significance may become clear by widespread use of these SaMDs for disease diagnosis, the following development strategy is expected: The applicant will consult with the Pharmaceuticals and Medical Devices Agency (PMDA) and explain the clinical significance of the calculated physiological parameters, etc., by using the summaries of clinical results, even at the step when the clinical significance as the final target has not yet been established. Following this, the applicant will obtain the first step approval by limiting the scope of intended use or effect that can be demonstrated by non-clinical studies or the results of studies, etc. on mechanical performance (measurement performance, detection performance, arithmetic performance). After the clinical evidence (including post-marketing clinical studies and real-world data) has been established in the post-marketing phase based on the experience of use in clinical practice, an application for partial changes or new application is filed for second step approval as

necessary.

2. Specific actions

When considering a development strategy based on the concept of two-step approval for SaMD to assist or support the diagnosis of a disease by calculation of physiological parameters, etc. that may be used as reference information for the diagnosis of the disease or prediction of prognosis, opinions should be exchanged with the reviewer side in advance using the pre-development consultation with PMDA. Protocol consultation for the second step approval, etc. should be conducted concurrently.

3. Eligible SaMDs

Examples of the eligible concepts of SaMD are shown below.

(1) SaMDs for the calculation of physiological parameters, etc. from active monitoring medical devices related to physiological indicators related to biological signals (e.g., devices for testing biological physical phenomena, devices for testing biological electrical phenomena, devices for monitoring biological phenomena, image diagnosis devices), the internal or external sensors of web camera etc. of general-purpose computers, including mobile information devices such as medical devices for non-invasive measurement and imaging, etc. and smartphones, and various test information.

(2) SaMDs provide one of several determination criteria separately as reference information for the diagnosis of diseases although the clinical significance as final target has not yet been established

(3) SaMDs that do not result in significant impact on human life or health if incorrect test results have been obtained

4. Ineligible SaMDs

It should be noted that the concept of two-step approval is not applied for the following cases as a principle since more detailed information is expected clinically. The concept of two-step approval may not apply depending on the scope of intended use or effect of the product to be developed; however, it may be judged that the product may be applicable to two-step approval depending on the characteristics, etc. of the product to be developed. For this reason, consultation must be held with PMDA.

(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

(2) Review categories where new information is provided on a daily basis, such as gene-

related tests

(3) The medical field for which the clinical significance and medical determination criteria have been established for the information provided by SaMD, such as pulmonary nodules and polyps (e.g., where similar approved products are available)

(4) Cases where second step approval has been obtained for medical devices or SaMD that has the same scope of intended use or effect as that of the product submitted for registration and are used in clinical practice

5. Planning of clinical evaluation, etc. for the obtaining of the second step approval

(1) Regarding the planning of clinical evaluation, etc. for the confirmation of clinical significance necessary for obtaining the second step approval, consultation should be held with PMDA at the time of consultation for the first step approval application and also concurrently after the submission of the first step approval application.

(2) Clinical evaluation data for the second step approval need to meet the data integrity standards for product application; however, 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. For this reason, consultations on the necessity of clinical studies and protocol consultations with PMDA, including the utilization of real-world data, should be conducted in advance to exchange opinions with the reviewers.

Section 2. Concept of two-step approval for SaMD for disease treatment

1. Basic concept

For SaMD with a performance or function that provides information to assist or support the treatment of a disease, but for which clinical evidence as a treatment has not been established, an evidence-based explanation on the clinical significance of the SaMD as a treatment method is required.

Meanwhile, for SaMD for treatment of diseases related to multifactorial diseases with combination of genetics, lifestyle, and other factors, as well as SaMD for the area of psychiatric disorders and treatment of diseases related to pain and functional syndromes where the subjective indicators of the patient is used as the primary endpoint for efficacy evaluation, there are cases where the feasibility of the clinical trial is low due to problems such as issues related to recruitment of subjects to Japanese clinical trials and prolonged period of evaluation.

While clinical evidence or clinical significance as a treatment method is lacking for these types of SaMD, some of these are expected to be useful for patients and medical practice based on the specific symptom relief or condition improvement demonstrated in exploratory clinical trial results or other means.

For the aforementioned SaMD, possible development strategy may be as follows: Consultation should be held with PMDA, and the applicant may obtain first-step approval for an intended use or effect, limited in scope, where a certain level of efficacy in specific symptom relief or improvement has been confirmed with feasibility based on the results of exploratory clinical studies and performance evaluation studies, even if the clinical significance as the final target has not yet been fully established. After the clinical evidence (including post-marketing clinical studies and real-world data) has been established in the post-marketing phase based on the experience of use in clinical practice, application for partial changes or new application is filed for second step approval as necessary.

2. Specific actions

When considering a development strategy based on the concept of two-step approval for programs to assist or support the treatment of disease, opinions should be exchanged with the reviewer side in advance using the pre-development consultation with PMDA. Protocol consultation for the second step approval, etc. should be conducted concurrently.

3. Eligible programs

Examples of the eligible concepts of SaMD are shown below.

(1) Programs that are able to confirm a certain level of efficacy with feasibility, such as specific symptom relief or improvement of the condition demonstrated by the results of exploratory clinical trials in addition to the results of studies for performance evaluation, although the clinical significance as a treatment method as the final target has not been established.

(2) Programs that are not expected to impact on the efficacy and safety of the existing treatment, etc. even when used to assist or support the treatment by a physician based on the information presented by SaMD.

4. Ineligible programs

It should be that the concept of two-step approval is not applied as a principle in cases where second step approval has been obtained for a medical device or SaMD that has the same scope of intended use or effect as that of the product submitted for registration and are used in clinical practice since more detailed information is expected clinically.

The concept of two-step approval may not apply depending on the scope of intended use or effect of the product to be developed; however, it may be judged that the product may be applicable to two-step approval depending on the characteristics, etc. of the product to be developed. For this reason, consultation must be held with PMDA.

5. Planning of clinical evaluation, etc. for the obtaining of the second step approval

(1) Regarding the planning of clinical evaluation, etc. for the confirmation of clinical significance necessary for obtaining the second step approval, consultation should be held with PMDA at the time of consultation for the first step approval application and also concurrently after the submission of the first step approval application.

(2) Clinical evaluation data for the second step approval need to meet the data integrity standards for product application; however, real-world 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. For this reason, consultations on the necessity of clinical studies and protocol consultations with PMDA, including the utilization of real-world data, should be conducted in advance to exchange opinions with the reviewers.

Section 3. Concept of two-step approval for SaMD for disease prevention

(Basic concept)

Programs that contribute to primary prevention such as health promotion do not meet the definition of SaMD and therefore do not fall under the category of medical devices.

Also, programs that contribute to the secondary prevention or tertiary prevention of diseases may fall under the category of SaMD for disease diagnosis or SaMD for disease treatment, and the development policies for these programs should be consulted with PMDA from the development step.

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