

Administrative Notice
March 31, 2016

To: Pharmaceutical Administration Divisions, Health Departments (Bureaus), Prefectural Governments

Office of Medical Devices and Regenerative Medicine Products,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Notice concerning the Publication of Guidance Materials concerning Application for
Marketing Approval of Medical Device Software

In the report “Research on Desirable Regulatory Affairs Practices for Discrete Software for Medical Devices” (Grants by the Japan Agency for Medical Research and Development (AMED) during FY2015 for Research on Regulatory Science related to Pharmaceuticals and Medical Devices), discussion was conducted on common issues among approval reviews of Software and storage media with the software recorded (hereinafter, “medical device software, etc.”) that require prior approval to be marketed as medical devices. Guidance concerning applications for approval of medical device software, etc. has been prepared as provided in the Appendix. The Ministry of Health, Labour and Welfare (MHLW) requests your cooperation in notifying all relevant business entities under your jurisdiction that this guidance and the attached reference materials should be consulted in conjunction with the preparation of applications for marketing approval of software intended to be used for the diagnosis and/or treatment of disease.

This guidance was prepared in response to the following strategy mapped out during the second Public-Private Dialogue towards Investment for the Future under the Headquarters for Japan’s Economic Revitalization (November 5, 2015): “Within three years, we will enable use in clinical practice related to medical diagnostic support systems utilizing artificial intelligence technologies. To this end, by spring next year, we will publish a new guidance to be used for review of medical diagnostic support-related software.”

Please note that copies of this Administrative Notice will be sent to the Japan Federation of Medical Devices Associations, the Japan Association of Clinical Reagents Industries, the Medical Devices and Diagnostics Subcommittee of the American Medical Devices and Diagnostics Manufacturers’ Association, the European Business Council in Japan, the IVDs

* 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.

Committee of the European Business Council in Japan, the Pharmaceuticals and Medical Devices Agency (PMDA), and the Association of Registered Certification Bodies under J-PMD Act.

Guidance for Application for Marketing Approval of Medical Device Software

Common potential issues arising in conjunction with reviews of medical device software, including evaluations required for the review, are organized as follows. These issues were identified based on experiences with the past approval reviews of medical device software (software classified as medical devices according to definition of medical devices) used for disease diagnosis support or treatment plan. Broad dissemination of these issues among public and private organizations is expected to facilitate development of medical devices with medical device software or equivalent software integrated as well as to contribute to preparation of high-quality application data. In the application for approval of medical device software, etc., it is desirable to attach the relevant data (attached data) to the application form, prepared in consideration of necessary evaluation provided as the issues below.

If the medical device software is suspected to be one that will require authorization through an application procedure, it is strongly recommended that relevant business entities proceed with product development by utilizing various consultation services offered by the Pharmaceuticals and Medical Devices Agency (PMDA) where necessary to resolve problems related to the application for approval.

1. Determination of whether a software is to be classified as a medical device

Clarify the intended use, function, use situation (extent of the impact of the result), and users of the software, and then determine whether the software in question should be classified as a medical device based on the following items.

Medical device software are installed in general-purpose personal computers, personal digital assistants (smartphones, tablets, etc.) when made available in a tangible form. Such software are intended to be used for the diagnosis, treatment, or prevention of diseases in humans, or to have an impact on the physical structure or functions of the human body in the same manner as tangible medical devices according to definition of medical devices specified in Article 2, Paragraph 4 of the “Act on Securing the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics” (Act No. 145 of 1960; hereinafter, the “PMD Act”).

To determine whether the software in question must be classified as a medical device software, the impact on human life and health or functions in light of its intangible properties must be considered in addition to the following two points:

- (1) The extent to which the medical device software in question contributes to the treatment or diagnosis of the disease in light of importance of the result provided by the software; and,
- (2) The probability of a comprehensive risk including a potential impact of malfunction of

the medical device software (risk associated with malfunction) and the extent of the potential impact on human life or health.

Because software for which any malfunction is believed to be unlikely to have any significant impact on human life or health are excluded from the scope of medical device software, and whether the software in question is to be classified as a medical device software should be determined in consideration of this aspect.

For more specific examples, refer to “Basic Rationale for Applicability of Software as Medical Devices” (PFSB/CND Notification No. 1114-5, by the Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 14, 2014).

2. Classification and generic name

(1) Classification

In addition, classification of the generic name shall be determined in accordance with the classification rules provided in the Ministerial Notification for Classification (“Implementation of Specially Controlled Medical Devices, Controlled Medical Devices and General Medical Devices Specified by the Minister of Health, Labour and Welfare according to the Provisions of Article 2, Paragraphs 5 to 7 of the Pharmaceutical Affairs Law [Ministerial Notification] and Specially Designated Maintenance and Management Required Medical Devices Specified by the Minister of Health, Labour and Welfare according to the Provisions of Article 2, Paragraph 8 of the Pharmaceutical Affairs Law [Ministerial Notification]” [PFSB Notification No. 0720022, by the Director-General of the Pharmaceutical and Food Safety Bureau, MHLW, dated July 20, 2004]).

In principle, classification rules (9 to 11) for active devices shall apply to medical device software, etc.

Because software of which any adverse drug reaction or functional disorder is unlikely to have any impact on human life or health and storage media with such software recorded are excluded from the scope of medical devices under Appendix Table 1 of the Order for Enforcement, software classified as Class I (general medical devices) will not be recognized as medical devices.

(2) Generic name

According to the Ministerial Notification for Classification (“Specially Controlled Medical Devices, Controlled Medical Devices and General Medical Devices Specified by the Minister of Health, Labour and Welfare according to the Provisions of Article 2, Paragraphs 5 to 7 of the Pharmaceutical Affairs Law” [Ministerial Notification No. 298 of 2004]), software for disease diagnosis and ones for disease treatment are given 154 (all for Class II) and 11 (5 for Class II, 6 for Class III) generic names, respectively (as of March 2016),

applicants must determine, in consideration of the classification of the medical device software under development, whether an appropriate generic name is present among the existing names. If no appropriate generic name can be found among the existing names, the applicant must determine whether a new generic name must be created.

Current generic names and definitions can be found on the “Information about Standards for Medical Devices” website managed by PMDA (available at: <http://www.std.pmda.go.jp/stdDB/index.html>).

* If results of the determination conducted with respect to items (1) and (2) above indicate that a generic name appropriate for the medical device software in question exists among those for which (a) certification standards have been established and (b) the intended use and functions of the medical device software in question conform to the applicable certification standards identified in (a), the software in question shall be considered to be subject to the marketing certification requirements specified in Article 23-2-23 of the Act, but not subject to the marketing approval requirements specified in Article 23-2-5 of the Act. In such cases, refer to the published Ministerial Notifications related to applications for marketing certification. (Further details concerning the handling of marketing certification applications is outside the scope of this guidance)

3. Approval application form

Complete each field of the application form for approval of medical device software by referring to relevant regulatory notifications such as “8. Handling of application for marketing approval” in the “Handling of Medical Device Software” (Joint PFSB/MDRMPE Notification No. 1121-33, PFSB/SD Notification No. 1121-1, and PFSB/CND Notification No. 1121-29, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, Director of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, and Director of Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 21, 2014; hereinafter, the “Fundamental Notification on Software”) and “Examples of Marketing Authorization (Certification) Application Forms of Medical Device Software and Attached Data” (FSB/MDRMPE Administrative Notice, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated on February 10, 2015; hereinafter, the “Administrative Notice on Form Examples”).

4. Review-related issues

The following are noteworthy issues arising during reviews related to the evaluation of the

safety and efficacy of medical device software intended for supporting disease diagnosis and treatment plans based on scientific evidence. When inputting information relevant to these issues in a marketing approval application or in attached data, applicants should describe all information objectively and logically in a clear and concise manner while referring to the examples provided in the Administrative Notice on Form Examples. These issues shall apply not only to new applications for approval, but also to application for approval of partial changes (submitted after approval and are required for changes that affect the efficacy or safety of medical device software, such as the addition of new functionality and/or changes to algorithms.)

These issues should be considered with respect to medical device software being developed using the most current technologies. These issues are subject to amendment or revision in the future in response ongoing accumulation of knowledge.

(1) Matters for concept of medical device software and entity of the function

[1] Clinical significance

Applicants are required to clarify the clinical significance of using the medical device software based on the concept of the device in question.

[2] Understanding and identification of functionality

Applicants are required to understand the details of the design specifications for the medical device software, and to identify the functions of the medical device software in question. Applicants are also required to identify the types of input data and corresponding output data.

[3] Clarification of computational algorithms

Regarding medical device software by which input data are processed through specified computations to produce output data, applicants are required to clarify the input conditions that ensure normal operations, flow of computations of the medical device software in question, and algorithms (including details of the processing, criteria, and cut-off values).

[4] Requirements for platform and use environment

A medical device software is designed to be installed in a platform for use. The applicant is required to clarify requirements for a platform to fulfill design requirements. Although the fundamental safety of the platform is assumed to be ensured by a manufacturing business operator of the concerned product, the applicant is required to clarify that the safety of the patients and users (for instance, electrical safety and electromagnetic compatibility) is ensured when the platform with the medical device software in question installed is used in a clinical practice environment, as a developer of the medical device software.

In addition, the applicant is required to investigate an impact of the other software that

potentially coexists in the same platform.

- [5] Identification of conditions involving medical devices and drugs expected to be used concurrently

If the medical device software is expected to require input from or output to the other medical device to achieve the specified function, or to be used concurrently with drugs, the applicant is required to identify conditions involving medical devices or drugs expected to be used concurrently. In addition, applicants are required to investigate necessity of co-development of the medical device anticipated to be used concurrently and applicable regulatory procedures.

(2) Matters for evaluation of medical device software

- [1] Evaluation of computational algorithms based on validity and clinical significance

Applicants are required to clarify, based on appropriate supporting evidence, that the clinical significance and computational algorithm of the medical device software clarified in 4(1) have already been established, or have been verified or validated clinically. If these aspects have already been established, the clinical efficacy and safety of the medical device software may not require additional evaluation. If the verification and validation results are found to be insufficient, additional clinical evaluation may be necessary.

- [2] Version control of test specimen

Applicants are in principle required to evaluate the performance of the medical device software using the version of the software specified in the application for approval as a test specimen. If evaluating the performance of the medical device software using a version of the software different from that of the application for approval is unavoidable, applicants are required to explain the difference(s) between the versions and to justify the evaluation of performance of the medical device software using the other version.

- [3] Validity of comparators

If a comparator is necessary for evaluation of the medical device software, the applicant is required to include an appropriate comparator in the evaluation in light of the intended use and use method of the medical device software (e.g., measurement and diagnosis results obtained using the existing standard and physician's diagnosis against computer-aided diagnosis [CAD]).

- [4] Validity of input and output data

Applicants are required to implement necessary verification on input data to the medical device software, comprehensively covering the expected range of input data in consideration of the use situation of the medical device software in question. Applicants are required to clarify points to be considered for standardization of input

data (designation of the imaging conditions if applicable. In addition, applicants are required to justify the output data from the medical device software in consideration of clinical significance of the medical device software in question.

[5] Evaluation of precision

For medical device software in which precision has to be specified for output values, appropriate endpoints should be evaluated to ensure that the precision is clinically acceptable. (e.g., treatment plan software used to calculate distance, angle, and dose distribution)

[6] Evaluation for correlations between analysis results from a medical device software with the real test and evaluation for precision of simulation in comparison with the real test

A method to validate output results from a medical device software may differ depending on the type of the software, but the degree of correlation of analysis results from the medical device software with the real test or precision of simulation in comparison with the real test may require evaluation. For medical device software intended to support diagnoses by providing appropriate information to physicians, it is important to calculate the incidence of Type I and Type II errors by comparing the output results with ones from clinical diagnoses made separately without the use of the software in question.

(3) Matters related to post-approval changes on medical device software

If the medical device software under development is approved for marketing in the future, and approved matters are subsequently intended to be amended in response to accumulation of the post-marketing data (matters described in the “Intended Use or Effect column,” “Shape, Structure and Principle column,” and “Performance and Safety Specifications column” in the approval certificate of the concerned product items), and the proposed amendments affect the efficacy or safety of the software, an application for approval of partial changes may be required. Therefore, if post-approval changes are expected such as addition of functions and changes to algorithm in the future, applicants are required to investigate matters and functions that should be included in the initial application for approval in consideration of the above.

In addition, medical device software developed in the future are anticipated to include mechanisms by which the algorithm or performance is adjusted in response to the use environment (e.g. data accumulation in reference databases that influences the criteria or diagnosis performance of the medical device software in question). For such medical device software, one of two options are available to applicants: either an application for partial changes as described previously, or evaluation data regarding the change in algorithm or performance compiled in advance by the applicant for the initial application for approval. The latter option can be anticipated to necessitate highly complex evaluation of the efficacy and safety of the medical device software in addition to the applicant’s

proposed methods for ensuring the efficacy and safety of the software. It is desirable for applicants to consult with PMDA regarding the following matters by utilizing PMDA's consultation offerings as appropriate: (a) any modifiable functions integrated in the software that could complicate evaluation of its efficacy and/or safety; and (b) what data or verification methods will be necessary during evaluation of the software.

5. Others

(1) Lifecycle process

Although provisions in Article 12, Paragraph 2 of the Standards for Essential Requirements for Medical Devices (deference to medical devices using software) will not apply until November 24, 2017, establishing lifecycle processes for development based on JIS T 2304 (medical devices - software-software lifecycle process) or IEC 62304 (Medical device software - Software lifecycle processes) is recommended.

(2) Risk management

In accordance with Article 2 of the Standards for Essential Requirements for Medical Devices (risk management), risk management is required for all the medical devices including medical device software. The applicable standard is JIS T 14971 (medical devices - application of risk management to medical devices). For applications for approval, attached data shall include the implementation status of risk management measures and residual risk. Applicants are also required to consider the above actions.

(3) Cybersecurity

In accordance with the Standards for Essential Requirements for Medical Devices, the applicant is also required to identify a risk related to cybersecurity as known or foreseeable harm, to evaluate the hazard attributable to the intended use method and foreseeable misuse, and to eliminate it wherever reasonably practicable. Regarding medical device software that are considered to have a cybersecurity risk and can be connected with the other medical devices, medical device component, the Internet and other similar networks, or portable storage media such as USB memory sticks (including cases where a platform of the medical device software can be connected with them), the applicant is required to take appropriate actions based on "Ensuring Cybersecurity of Medical Devices" (Joint PFSB/MDRMPE Notification No. 0428-1 and PFSB/SD Notification No. 0428-1, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW and the Director of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated April 28, 2015). (a supplemental guidance concerning the aforementioned Ministerial Notification is planned to be published in the future.)

(4) Other relevant guidelines

The following guidelines are available: “Evaluation Indices for Computer-aided Diagnosis Units” (Appendix 3 of the “Release of Evaluation Indices for the Next-Generation Medical Devices” [PFBS/ELD/OMDE Notification No. 1207-1, by the Director of the Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated December 7, 2011]) is for medical device software that support physicians’ diagnostic activities, such as software that aid in the tumor detection by providing locational information of potential lesions with markers based on medical images obtained from medical imaging devices used in the clinic; and “Evaluation Indices for Custom-Made Orthopedic Implants by Three-Dimensional Printing Technology using Patient Imaging Data” (Appendix 3 of the “Release of Evaluation Indices for the Next-Generation Medical Devices and Regenerative Medicine Products” [PFBS/ELD/OMDE Notification No. 0925-1, by the Director of the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 25, 2015]) is for software facilitating the assembly of three-dimensional data from clinical imaging data (e.g., CT data). These evaluation indices should be consulted during the preparation of applications for marketing approval.

(5) License and registration of marketing business and manufacturing business

For marketing of medical device software, appropriate license of manufacturing business, registration of manufacturing business, and QMS inspection, etc. is required in addition to marketing authorization. Although this guideline does not cover these procedures in detail, applicants are required to proceed with development by taking appropriate steps based on the relevant notifications such as Fundamental Notification on Software.

(End of Document)

(References) Major relevant notifications

- **“Basic Rationale for Applicability of Software to Medical Devices”** (PFSB/CND Notification No. 1114-5, by the Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 14, 2014).
- **“Handling of Medical Device Software”** (Joint PFSB/MDRMPE Notification No. 1121-33, PFSB/SD Notification No. 1121-1, and PFSB/CND Notification No. 1121-29, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, the Director of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, and the Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 21, 2014).
- **“Questions & Answers about Handling of Medical Device Software”** (Joint PFSB/MDRMPE, PFSB/SD, and PFSB/CND Administrative Notice, by the Director of the Medical Device and Regenerative Medicine Product Evaluation, Pharmaceutical and Food Safety Bureau, MHLW, the Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, and the Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 25, 2014)
- **“Questions & Answers about the Handling of Medical Device Software (Part 2)”** (Joint PFSB/MDRMPE and PFSB/CND Administrative Notice, by the Director of the Medical Device and Regenerative Medicine Product Evaluation, Pharmaceutical and Food Safety Bureau, MHLW and the Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 30, 2015)
- **”Applications for Medical Device Marketing Approval”** (PFSB Notification No. 1120-5, by the Director-General of the Pharmaceutical and Food Safety Bureau, MHLW, dated November 20, 2014)
- **“Points to Consider for Preparation of Application Form for Medical Device Marketing Approval”** (PFSB/MDRMPE Notification No. 1120-1, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 20, 2014)
- **“Points to Consider during the Preparation of Attachments to Medical Device Marketing Approval Application Forms”** (PFSB/MDRMPE Notification No. 0120-9, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated January 20, 2015)
- **“Examples of Marketing Authorization (Certification) Application Forms of Medical Device Software and Attached Data”** (FSB/MDRMPE Administrative Notice by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division,

Pharmaceutical and Food Safety Bureau, MHLW, dated February 10, 2015)

- **“Handling of the Standards for Medical Devices and In Vitro Diagnostics Specified by the Minister of Health, Labour and Welfare according to the Provisions of Article 41, Paragraph 3 of the Act on Securing the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics”** (PFSB/MDRMPE Notification No. 1105-5, by the Director of the Medical Device and Regenerative Medicine Product Evaluation, Pharmaceutical and Food Safety Bureau, MHLW, dated November 5, 2014)
- **“Ensuring Cybersecurity of Medical Devices”** (Joint PFSB/MDRMPE Notification No. 0428-1 and PFSB/SD Notification No. 0428-1, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW and Director of Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated April 28, 2015).
- **“Specially Controlled Medical Devices, Controlled Medical Devices and General Medical Devices as Specified by the Minister of Health, Labour and Welfare according to the Provisions of Article 2, Paragraphs 5 to 7 of the Act on Securing the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics”** (Ministerial Notification No. 298 of 2004, by MHLW)
- **“Enforcement of Specially Controlled Medical Devices, Controlled Medical Devices and General Medical Devices Specified by the Minister of Health, Labour and Welfare according to the Provisions of Article 2, Paragraphs 5 to 7 of the Act on Securing the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Ministerial Notification) and Specially Designated Maintenance and Management Required Medical Devices Specified by the Minister of Health, Labour and Welfare according to the Provisions of Article 2, Paragraph 8 of the Act on Securing the Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Ministerial Notification)”** (PFSB Notification No. 0720022, by the Director-General of the Pharmaceutical and Food Safety Bureau, MHLW, dated July 20, 2004)
- **“Handling of Generic Names of Medical Devices and In Vitro Diagnostics without Appropriate Generic Names Available”** (PFSB/MDRMPE Notification No. 1125-26, by the Director of the Medical Device and Regenerative Medicine Product Evaluation Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 25, 2014)
- **“Release of Evaluation Indices for Next-Generation Medical Devices”**

(PFSB/ELD/OMDE Notification No. 1207-1, by the Director of Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated December 7, 2011) Appendix 3: “Evaluation Indices for Computer-aided Diagnosis Units”

- **“Release of Evaluation Indices for the Next-Generation Medical Devices and Regenerative Medicine Products”** (PFSB/ELD/OMDE Notification No. 0925-1, by the Director of the Office of Medical Devices Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 25, 2015) Appendix 3: Evaluation Indices for Custom-Made Orthopedic Implants by Three-Dimensional Printing Technology using Patient Imaging Data

* Relevant notifications, etc. can be found on the following websites:

- MHLW Law and Regulation Database

<http://www.hourei.mhlw.go.jp/hourei/>

- PMDA Website (relevant notifications)

<https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/devices/0039.html>

<https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/devices/0040.html>

- Japan Association for the Advancement of Medical Equipment (Handling of medical device software in pharmaceutical and medical device products)

<http://www.jaame.or.jp/mdsi/program.html>