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Administrative Notice

To: Divisions of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

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

Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

Questions and Answers (Q&A) on MR Safety of Implantable Medical Devices, etc.

Regarding how the safety evaluation of implantable medical devices, etc. in MR testing should be conducted and how information on the safety evaluations should be provided in the package insert, we previously issued the Measures for MR Safety in Implantable Medical Devices, etc. (PSEHB/MDED Notification No. 0801-1, PSEHB/PSD Notification No. 0801-2 issued on August 1, 2019 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Welfare and Labour).

Recently, The Japan Federation of Medical Devices Association formulated questions and answers (Q&A) for the handling of the MR safety evaluation etc. submitted in the application for approval, instructions for package insert language, and transitional measures etc. as shown in the Appendix.

We request your cooperation in disseminating this information to marketing authorization holders (MAHs) under your jurisdiction.

Please note that an administrative notice to the same effect has been sent to other relevant organizations.

This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Appendix

Questions and Answers (Q&A) on MR Safety of Implantable Medical Devices, etc.

Formulated by:

Package-insert Statement TF regarding MR Conformity,
PMS Committee MR Conformity Arrangement WG,
Review-related Subcommittee, Legislation Committee
The Japan Federation of Medical Devices Association (JFMDA)

[Abbreviations used]
Two-director notification: PSEHB/MDED Notification No. 0801-1, PSEHB/PSD Notification No. 0801-2 Measures for MR Safety in Implantable Medical Devices, etc. issued on August 1, 2019 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, and Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau

PMDA notification: PMDA/OSI Notification No. 1226001, PMDA/OSII Notification No. 1226001 Points to Consider regarding the Notification and Publication of Package Insert Language issued on December 26, 2018 by the Director of Office of Safety I and Director of Office of Safety II of the Pharmaceuticals and Medical Devices Agency (PMDA)

[Note]
This Q&A represents the interpretation of the two-director notifications by JFMDA. Please consider consultations with the Division of Safety for Medical Devices, Office of Manufacturing Quality and Vigilance for Medical Devices, PMDA if you have any questions on preparing a package insert, regardless of whether the questions are addressed in the Q&A. When you have any questions on the handling at the time of approval review or certification review, please consider consultations with the organization to which the application for approval or certification was submitted.

1. Subjects of the evaluation of the safety in the MR Environment

Q1: Is it correct that the determination of the applicability of the two-director notification to an implantable medical device that contains metal etc. should be made by the market authorization holder (MAH) of the device taking into account the ingredients, usage, and other aspects of the device?

A1: Yes, this is correct. Of note, if the MAH determines the notification to be 'not applicable' to a device, the holder should be prepared to present the rationale.

Q2: The two-director notification 1. (1) states "implantable medical devices, etc. that contain metal." Can you be more specific regarding this description?

A2: They are medical devices made from resin that contain metal-derived ingredients: Devices containing metal used in an extremely small amount in a small portion of the device in a chip or the marker for X-ray imaging for example, and devices containing dyes or antibacterial agents, etc. that contain metal.

Q3: The two-director notification 1. (1) states "the medical devices that are temporarily inside a patient's body or placed outside the body and that are highly probable to enter the gantry of MR devices when subjected to MR examination in situ." Can you cite an example for the description?

A3: An example is a non-metal drain inside the body with metal embedded in the portion outside the body. Of note, the probability of the device entering the MR gantry must be properly determined by the MAH. (Basically, devices supposed to be removed from the body in the MR environment are not considered to be high probability.)

2. How to evaluate safety in the MR Environment

Q4: The two-director notification 1. (1) states "The MAH must evaluate the safety of implantable medical devices in the MR environment (evaluation for testing conditions) (Hereinafter referred to as "safety evaluation")." Can you cite specific standards that should be referred to for this evaluation? Moreover, isn't it acceptable to use other methods than specified in ASTM or ISO?

A4: Please refer to ISO/TS 10974 for active medical devices, and the following three standards for non-active medical devices:

- Magnetically Induced Displacement Force (ASTM F2052)
- Magnetically Induced Torque (ASTM F2213)
- Radio Frequency Induced Heating (ASTM F2182)

Of note, since the two-director notification requires the MAH to perform the evaluation as its own responsibility in order to provide information on MR safety to healthcare professionals, conducting a study based on the MAH's own standards or evaluation without conducting a study (i.e. an evaluation based on the relevant literature or use results) is assumed.

Q5: Is it essential to conduct a test to evaluate MR image artifacts?

A5: Although this item is not in the scope of the safety evaluation in the MR environment,

please bear in mind that the medical devices that are affected by the two-director notification 1. (2) must be evaluated for MR conformity, including artifacts in addition to MR safety.
Releasable information on artifacts should preferably be included if any in the package insert of medical devices that are not affected by the two-director notification 1. (2) in consideration of a strong demand from healthcare professionals.
As a point to remember for Q4 and Q5, please be sure to check Q14.

3. Evaluation of MR safety and matters related to application for approval

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Q6: For the medical devices that are referred to in the two-director notification 1. (2), results of MR safety evaluation should be attached if a partial change in the approval items is applied (excluding specific change + expedited applications) three years after the issuance of this notification or later. Is it correct that a partial-change application for approved items only for the review of the MR safety evaluation validity is not required?

A6: Yes, this is correct.

Q7: Is it correct that the following case is not subject to the requirement in the two-director notification 1. (2)?

(case)
The non-proprietary name of the applied product is absorbable ligament fixation anchor, and the product contains absorbable suture and an anchor made of titanium alloy as its components. In this case, the absorbable suture classified into a Class-IV medical device does not contain metal. The anchor made of titanium alloy, a component classified into Class III, is considered to be an implantable medical device that contains metal.

A7: Yes, this is correct. As shown in this case, regarding how to interpret the classification in determining the applicability of requirements by the two-director notification 1. (2), when an applied product contains components of different classes, the component that is subject to the requirements will be the one considered to be an implantable medical device, etc. that contains metal if that component satisfies the definition of a Class-IV medical device or Class-III active medical device, rather than the Class of the entire product (the highest Class of all constituent components). Note that the relevant review office of PMDA should be consulted if it is difficult to determine the class in cases like the above.

Q8: Is it correct that any products that are not affected by the two-director notification 1 (2), even implantable medical devices that contain metal, are not required to attach evaluation data of MR safety in their review?

A8: Yes, this is correct.

Q9: Is it correct that sealed therapeutic radiation sources are not affected by the two-director notification 1. (2)?

A9: Yes, this is correct. Of note, the package insert should provide necessary information, such as results of MR safety evaluation. Please refer to the following table for the generic names that are sub-classified into “sealed therapeutic radiation source.”

(Reference)

Generic name	JMDN code
Central circulatory permanent implant manual brachytherapy therapeutic radionuclide source	38303004
Central circulatory temporary placement manual brachytherapy therapeutic radionuclide source	38304004
Non-central circulatory permanent implant manual brachytherapy therapeutic radionuclide source	38303003
Non-central circulatory temporary placement manual brachytherapy therapeutic radionuclide source	38304003

4. Instructions for package insert language

Q10: Is it correct that it is not necessary to follow anew the sample statements from 2. (1) to (5) of the two-director notification for the package insert of an approved product if it has already provided the information on the MR environment?

A10: Yes, this is correct. When the package insert provides statements on the MR environment harmonized by product group, like those for pacemakers, it is acceptable to use the existing harmonized statements. It is also acceptable for newly marketed products to use the existing harmonized statements in their product group.

Q11: Is a statement accepted differently from the sample of the package insert provided in 2. (1) to (5), in that terms of “MR Safe,” “MR Unsafe,” and “MR Conditional” are replaced with different ones, for example, if representing the same idea?

A11: Yes, this is correct. In addition, information beyond the examples should also be provided as needed with demands in the clinical settings taken into account.

Q12: Is it acceptable to state “MR Safe” based on internal evaluations rather than conducting a study? If so, how should it be described?

A12: Yes, this is acceptable. In this case, the rationale for your judgment of “MR Safe” must be added.

Q13: Is it correct to state “MR Unsafe” based on internal evaluations for medical devices widely known to affect the MR environment without conducting a study based on ASTM or other standards?

A13: Yes, this is correct. For “MR Unsafe,” you may label it as “MR Unsafe” to contraindicate the MR environment without conducting a study when MR testing cannot be safely performed for reasons including “ferromagnetic materials are used,” “an electrically conductive metal is contained,” or “electronic circuits are installed.”

Q14: In what situation may “MR Conditional” be stated?

A14: “MR Conditional” may be stated only when a study was conducted in accordance with ASTM. Therefore, as stated in Q4 and Q5, please bear in mind that “MR Conditional” is not allowed if an artifact study (ASTM2119) was not included in the studies conducted for the purpose of MR safety evaluation. Even if an ASTM artifact study was not included, the package insert must provide necessary information in accordance with the two-director notification 2. (5).based on the studies conducted for MR safety evaluation.

Q15: Is it acceptable to state “MR Safe” in the package insert of medical devices made of plastic, glass or ceramics which are not subject to the two-director notification?

A15: You may state “MR Safe” for medical devices made of materials that meet all the conditions of being non-conductive, non-metallic, and non-magnetic.

5. Transitional measures, etc.

Q16: Does the two-director notification 3. (1) mean that it is also necessary to take measures in accordance with the two-director notification for Class-I or Class-II medical devices if they are considered implantable medical devices, etc. that contain metal? Does this mean that MAH should take measures for the package insert of Class-I products based on an internal review since Reviews are not required for Class-I medical devices?

A16: Yes, this is correct. Basically an equal level of handling is required for products subject to certification as those subject to approval.

Q17: For the two-director notification 3. (2), when an approved item has been evaluated for MR safety based on ASTM or ISO but not reviewed for this specific matter, should we also add “self-certified” unless a partial change in approved items is applied? Do we have to apply for a partial change in approved items in order to remove the note “self-certified”?

A17: Yes, this is correct. For MR safety, “self-certified” cannot be dispensed with unless the product has gone through the review regarding MR safety.

Q18: Regarding MR safety, is it acceptable to state “Study-based evaluation for MR safety was not performed for this product” in the package insert in accordance with the two-director notification 2.(1) and to continue marketing both during and after transitional measures?

A18: When MR safety was evaluated, not by conducting a study but based on literature or use results, you may market the product with the statement sample shown in the two-director notification 2. (1) added to the package insert, either before or after the transitional measures.
The requirements in the two-director notification are considered to be satisfied if MR safety was evaluated not by conducting a study but based on literature or use results, and the package insert is appropriately presented in accordance with any of the samples listed in the two-director notification 2. (1) to (5). It should be acknowledged that there will be “not-studied” products, but there will not be “not-evaluated” products after the period of transitional measures.

Q19: Is it necessary to consult with PMDA before a package insert is revised in accordance with the two-director notification?

A19: It is not necessary to consult with PMDA before a package insert is revised to satisfy the requirements in the two-director notification.
The MAH must consider the necessity of revision, etc. in the package insert based on this Q&A and the two-director notification.

Q20: What should the MAH consider when notifying the package insert?

A20: When notifying the package insert, the MAH needs to submit the before-and-after comparison table showing the revision details that respond to the two-director notification. For submission of notice for a revised package insert to respond to the two-director notification, the following consultation reference number should be noted:
Consultation reference number: 19-k-000174