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November 17, 2014

To: Directors-General
Department of Health
Prefectural Governments

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

Counsellor of Minister's Secretariat,
(for Medical Device and Regenerative Medicine Product Evaluation)
Ministry of Health, Labour and Welfare

(Official seal omitted)

Guideline on Utilization of Master File for Drug Substances, etc.

The “Act for Partial Amendment of the Pharmaceutical Affairs Act” (Act No. 84 of 2013, hereinafter referred to as the “Revised Act”), “Cabinet Order on Arrangement etc. of Relevant Cabinet Orders and Interim Measures Incidental to Enforcement of the Act for Partial Amendment of the Pharmaceutical Affairs Act” (Cabinet Order No. 269 of 2014) and “Ministerial Ordinance on Arrangement of Relevant Ministerial Ordinances Incidental to Enforcement of the Act for Partial Amendment of the Pharmaceutical Affairs Act and to Enforcement of Cabinet Order on Arrangement etc. of Relevant Cabinet Orders and Interim Measures Incidental to Enforcement of the Act for Partial Amendment of the Pharmaceutical Affairs Act” (MHLW Ordinance No.87 of 2014, hereinafter referred to as the “Revised Ministerial Ordinance”) have been promulgated, and regenerative medical products have been defined legally as a new category separately from pharmaceuticals and medical devices. Taking into account these situations, the following guideline on the utilization of the MF is published so that you could inform relevant businesses and organizations under your jurisdiction of the guideline for their sake of submitting applications for MF registration, etc.

This notification shall be applied from November 25, 2014, and the “Guideline on Utilization of Master File for Drug Substances, etc.” (PFSB/ELD Notification No. 0210004 dated February 10, 2005

by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau) will be abolished on the same day.

1 Master File System (MF)

Purpose of the MF is to share information necessary for approval reviews of pharmaceuticals, medical devices and regenerative medical products (ex. information on manufacturing methods, etc.) that the MF registrant possesses and also to protect the intellectual property of the MF registrant. MF is also aimed at streamlining the review process.

2 Scope of MF Utilization

- (1) Applications of MF registrations and changes to registered contents and notifications of minor changes to the registered contents shall be submitted to the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”), pursuant to the procedures and forms specified in the Ministerial Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (MHW Ministerial Ordinance No.1 of 1961, hereinafter referred to as the “Enforcement Regulations”).

(2) Items for registration

A. The following raw materials, etc. to be used for the manufacture of pharmaceuticals, medical devices and regenerative medical products (including those manufactured for export) can be registered in MF.

- 1) Drug substances, intermediates and pharmaceutical product materials (materials of pharmaceutical products with special dosage form, etc.)
- 2) New excipients and pre-mix excipients with a different composition ratio from existing ones
- 3) Materials for medical devices
- 4) Materials for regenerative medical products (cells, media, medium additives, materials for cell processing, etc.)
- 5) Containers/packaging materials

B. Drug substances, intermediates and pharmaceutical product materials (materials of pharmaceutical products with special dosage form, etc.) used for BTC drugs and OTC drugs (excluding OTC with new active ingredients or those with their active ingredients still in the reexamination period) (hereinafter referred to as “BTC/OTC drugs”) are not appropriate for registration in MF, as it is considered that their quality and safety are already established even in existing specification and test methods.

C. Items that can be registered consist of the manufacturing method, manufacturing process control, quality control tests, specifications and test methods, stability tests and non-clinical studies (mainly for new excipients), as well as the information described in the MF registration certificate, such as the name of manufacturing site, etc.

- D. New TSE data based on “TSE Data Number” (PFSB/ELD No. 0801001 dated August 1, 2003: PFSB/SD No. 0801001 Notification by the Director of the Evaluation and Licensing Division/Director of Safety Division, Pharmaceutical and Food Safety Bureau) implemented as part of BSE measures shall also be registered into MF.
- E. Items that can be registered into MF for materials for medical devices shall be information relating to the identification of raw materials.
- F. Registered raw materials shall be available regardless of the category of pharmaceuticals, medical devices and regenerative medical products.
- G. Items recommended for MF registration in the approval review process, etc. shall be registered in MF.

3 Form for Registration Information in MF

- (1) Registered information in MF shall be regarded as a part of information which should be described in the approval application form and attached document (for pharmaceuticals, the items described in “Data on Manufacturing Methods and Specifications/Test Methods,” “Data on Stability” and “Data on Pharmacological Action”). Also, it shall be regarded as a part of information which should be described in the attached documents of the clinical trial notification.
- (2) The registrant shall use the Form No. 120 specified in the Enforcement Regulations of Pharmaceutical Affairs Act for MF registration application form.
- (3) For data to be attached to the registration application form (hereinafter referred to as “registration data”), the following forms shall be used.
 - A. For pharmaceuticals (excluding generic drugs and BTC/OTC drugs), the form (hereinafter referred to as “CTD”) attached to the Notification by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, “Guideline on Preparing Data Attached to Application Form for Approval Application of Manufacture or Import of a New Pharmaceutical” (PFSB/ELD Notification No. 899, dated June 21, 2001) shall be used.
 - B. The form for generic drugs shall follow the Notification by the Director-General of the Pharmaceutical and Medical Safety Bureau, “Approval Application of Pharmaceuticals” (PMSB Notification No. 481, dated April 8, 1999).
 - C. BTC/OTC drugs and those among “2) New excipients and pre-mix excipients with a different composition ratio from the existing ones” and “5) Containers/packaging materials” specified in 2. (2) A. used only for BTC/OTC drugs, shall follow the pattern specified in the Notification by the Director-General of the Pharmaceutical and Food Safety Bureau, “Approval Application of BTC/OTC Drugs” (PFSB Notification No. 0612-6, dated June 12, 2014).
 - D. For regenerative medical products, refer to the “Guideline for Developing the Registration Application Form for Master File for Drug Substances, etc. and Documents to be Attached to the Application Regarding Materials Related to Manufacture of Cellular and Tissue-based Pharmaceutical Products, etc.” (Administrative Notice by Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated March 8, 2013).

- (4) Electronic forms for MF registration of drug substance, etc. shall follow the Notification by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, “Electronic Specifications on Common Technical Documents” (PFSB/ELD Notification No. 0604001 dated June 4, 2003).
- (5) For MF registration of drug substances, etc., submission of the data equivalent to Module 2 of CTD (summary of the attached data) is not required. However, as the contents registered in MF will be reviewed in the approval review process, the MF registrant shall submit the data equivalent to Module 2 of CTD to the reviewing authorities when the approval application is submitted.

4 Information that MF Registrant Should Disclose

- (1) MF registrant shall notify in advance the persons making clinical trial notifications of pharmaceutical products whose information in the attached documents is quoted by MF and the applicants of pharmaceutical products whose information in the approval application form is quoted by MF (hereinafter referred to as the “applicants, etc.”) of changes to the registered items. And also, if the items registered in MF are quoted in the approval review of already approved pharmaceutical products, the MF registrant shall also notify the approval holder of the changes as well.
- (2) Even in cases where a notification is submitted for minor changes in the registered contents, the MF registrant shall notify the relevant applicants, etc. or approval holders of the changes.
- (3) For the registered information, items that should be disclosed to the applicants, etc. or approval holders of pharmaceuticals products, etc. are shown in the attachment. When submitting an application for MF registration, information that should be disclosed shall also be written in the registration application form.
- (4) As for the information in (3), the applicants of pharmaceutical products, etc. who quote the corresponding information registered in MF can describe the information on the approval application form.
- (5) As to whether some changes to the registered items will affect the quality, etc. of pharmaceutical products, the MF registrant shall adequately consult with the applicants, etc. or approval holders who quote the registered information, by referring to the Notification by Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, “Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Act” (PFSB/ELD Notification No. 0210001, dated February 10, 2005) (hereinafter referred to as “Notification No. 0210001”).
- (6) Even the information such as TSE data shared with the applicants, etc. or approval holders of pharmaceutical products, that has a rationale and an advantage of using MF, can be registered into MF.

5 Procedures for Registration of MF

- (1) New registration

A. As for new registration, the application form with attached data shall be submitted to PMDA. Registration categories are defined as follows. The registration of materials related to manufacture of regenerative medical products and TSE data is included in Category iv).

i) Drug substances, etc. (that mean drug substances, intermediates and pharmaceutical product materials manufactured by a special manufacturing method) intended solely for use in the manufacture of pharmaceutical products (excluding those that are intended to be used exclusively for animals)

ii) Excipients that have not yet been used in the manufacturing of pharmaceutical products or excipients that have a different composition ratio as compared to existing ones (refers to new excipients and pre-mix excipients with a different composition ratio from existing ones respectively)

iii) Materials intended solely for use in the manufacture of medical devices (excluding those that are intended to be used exclusively for animals)

iv) Others (packaging materials, etc.)

B. Summary, etc. of the manufacturing methods to be registered shall be described on the application form for registration. Refer to Notification No. 0210001, etc. for filling out the form.

C. After MF registration, a registration certificate (refer to Form No. 120 of the Enforcement Regulations of Pharmaceutical Affairs Act) and a duplicate of the registration application form shall be issued. The registration certificate does not include any information that is not to be disclosed.

(2) When MF is utilized for a new approval application

A. If applicants are applying for approval of pharmaceutical products and regenerative medical products that quote MF for their application, the applicants shall indicate, on the approval application form, the name of the MF, its registration number, the issuance date of the registration certificate, and in cases where there is more than one manufacturing method, which manufacturing method is used. The applicant shall also attach a copy of the registration certificate and a copy of the contract with the MF registrant regarding the utilization of the MF. The following is an example of how to fill out the Manufacturing Method column on the approval application form.

Example) ●●● using the drug substance ▲▲▲▲▲ (MF Registration Number: ××××× ××××× (YYYY / MM / DD), Method ●)

B. In approval reviews, PMDA shall make inquiries regarding contents registered in MF directly to the MF registrant. If the MF registrant is a foreign manufacturer, inquiries shall be made to the in-country caretaker PMDA shall also inform the applicant who has submitted the relevant approval application of such inquiries.

C. Also, review of clinical trial notifications shall be in accordance with the same procedure as described above.

(3) Changes to registered items

- A. If changes have to be made to registered contents as a result of approval reviews, etc. of pharmaceutical products, the MF registrant shall submit an application for changing the registered items in MF. Thereafter, the registration certificate for that change shall be issued when the corresponding application of the pharmaceutical product is approved. If changes have to be made to registered contents during the approval review of the pharmaceutical product, promptly consult with the reviewing authorities.
- B. When changes are made to registered contents, an application for changing the registered contents with the attached data relating to such changes shall be submitted to PMDA. Changes only in the attached data cannot be filed. New registration, rather than an application for change, is required depending on the changes to registered items.
- C. In making changes to contents registered in MF, the MF registrant shall enter in the column for remarks, the commercial name, the approval number, the name and address of the marketing authorization holder (the name and location of the main business site if the licensed marketing approval holder is a corporate entity) for all pharmaceutical products that quote the relevant MF, as well as whether a partial change approval application or minor change notification is applied for each of the items.
- D. If MF under change is quoted in the already approved pharmaceutical products, it is necessary to submit a partial change approval application for all of these pharmaceutical products, together with an application for changing the contents registered in MF.
- E. When making changes to the items registered in the MF, but the existing items are still used for already approved pharmaceutical products, it shall be required to specify the items. For example, when adding a new manufacturing method, you shall be requested to number both the existing and added manufacturing methods so that it can be specified which manufacturing method is used for the pharmaceutical products approved by quoting the MF by those written numbers. In this case, applicants shall be required to submit a partial change approval application for the pharmaceutical products with added items and a minor change notification for pharmaceutical products with existing items, when they submit an application for changing the contents registered in MF.
- F. If changes to the items in MF will substantially alter the nature of drug substances, etc., a new MF registration form, not the change of registration must be submitted, and for pharmaceutical products that use the relevant MF, it is necessary to submit a partial change approval application so that these products can quote the newly registered items. In addition, in case changes to the items are significant and changed items are not regarded as being the same, the approval holder of pharmaceutical products should submit a new approval application rather than a partial change approval application. Therefore, for significant changes, consultation with the reviewing authorities is recommended.
- G. When making changes to the items registered in MF, the changes will be reviewed only after partial change approval applications for all the relevant pharmaceutical products are submitted. Meanwhile, such as in case E., when changes to the items in the MF are made but a minor

change notification is required for some of the products, such a notification shall be submitted immediately after issuance of the registration certificate for that change.

H. Changes in registered contents are handled according to the date that the modified registration certificate is issued, and the registration number remains the same even after the registered contents are changed.

(4) Minor changes to registered contents

A. The scope of minor changes to the items specified in MF registration form is the same as that in the minor change notification for the pharmaceutical products, in accordance with the PFSB/ELD Notification No. 0210001 dated February 10, 2005. It also applies to the attached data to the minor change notification.

B. For minor changes to the registered items in MF, it shall not be required for the approval holder of the pharmaceutical products that quote the relevant registered information to submit a minor change notification. The MF registrant shall submit a statement indicating that they have performed adequate validation and change control, along with the notification of minor changes to the registered contents in MF, to the reviewing authorities. If changes have to be made to registered contents during the approval review of the pharmaceutical product, promptly consult with the reviewing authorities.

(5) If the approval applicant needs to utilize the items registered in MF under the instructions of PMDA, the applicant shall revise the submitted application dossier to indicate the MF registration number, issuance date of the registration certificate, etc. on the approval application form, and additionally attach copies of the registration certificate and contract with the MF registrant regarding the utilization of MF.

(6) When transferring contents registered in MF to the third party, it shall be required to follow all the procedures specified in the Enforcement Regulations. In the transferring procedure, it is necessary to submit a copy of the contract between the transferor and transferee that specifies that the verification data for the registered contents and all the documents relating to the registration are transferred. Statement indicating that there are no changes in the manufacturing site and other manufacturing technology, etc. is also required.

(7) Items relating to MF registration, such as registration number, registration date, name of the registrant, name of the registered item, and registration category shall be made public by PMDA. However, as for the name of registered items, if disclosure causes competitive disadvantage for the registrant or applicant, for example, in cases where the registration is made during a clinical trial for the pharmaceutical product or before its approval, its concrete name that specifies the substance itself shall not be made public. Instead, generally recognizable names, such as the name of its chemical classification, shall be published.

6 Handling of Utilization of MF for Pharmaceutical Products Used in Common for Human and Animals

(1) For a pharmaceutical product that contains drug substances used both in humans and animals, if MF for the drug substance is quoted in the application of the approval review, the registration

application of MF shall, in principle, be applied to PMDA. However, if the drug substance is intended only for animals, the registration application of MF can be applied to the Ministry of Agriculture, Forestry and Fisheries.

- (2) Since the Ministry of Agriculture, Forestry and Fisheries administers approval review of pharmaceutical products for veterinary use, as for the case in (1), registered information in PMDA's MF shall be disclosed to the Ministry of Agriculture, Forestry and Fisheries in an appropriate manner upon their request.

In the review of the approval application of pharmaceutical products for veterinary use, the Ministry of Agriculture, Forestry and Fisheries shall make inquiries regarding contents registered in MF that have been disclosed to the Ministry by PMDA, directly to the MF registrant.

- (3) For a pharmaceutical product that contains drug substances used both for human and animals, when a change in the items registered in MF necessitates a partial change approval application for pharmaceutical product that has been approved by the Minister of Agriculture, Forestry and Fisheries, the approval holder of that product shall be responsible for submitting a partial change approval application to the Ministry of Agriculture, Forestry and Fisheries.