Tentative translation (as of November 14, 2008)[1]

Q&A on the Master File (MF) System, Part I

(Q.1)
To whom should application form for MF registration be submitted?
Is it possible to send it by mail?
How much is the application fee?

(A.1)
Application form for MF registration shall be submitted to Master File Management Group, Office of Review Management, Pharmaceuticals and Medical Devices Agency (PMDA).

(A.1-2)
We also accept your application sent by mail. For more detailed information, please visit PMDA website in Japanese and refer to 「PMDA の業務」→「承認審査業務」→「承認審査業務情報」→「原薬等登録原簿について」→「１．MF 制度について」(“Services of PMDA” → “Reviews and Related Services” → “Master File System” → ”Guidance on Master File System (PDF)”)

(A.1-3)
No registration fee is required for the application of MF registration.

(Q.2)
Is it mandatory to register all the drug substances in MF?
With which division or office of PMDA can an applicant consult about MF registration?

(A.2-1)
To register drug substances in MF is optional. It is not mandatory for a manufacturer to register all the drug substances in MF.

(A.2-2)
Please consult with Master File Management Group, Office of Review Management, Pharmaceuticals and Medical Devices Agency, about procedure on MF registration application.

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

(A.2-3)
Regarding the contents of MF registration application, please utilize “MF simple consultation service” provided by PMDA.

(Q.3)
When a foreign manufacturer applies for MF registration, which part of the application form should be written in Japanese?

(A.3-1)
As for the cover page of application form, a foreign manufacturer can write their company address and name in their own language. Application forms need to be made in duplicate.

(A.3-2)
All the contents of Flexible Disks (FD) application must be written in Japanese.

(A.3-3)
If you have any questions regarding supporting data for application, please refer to “Guideline on Utilization of Master File for Drug Substances, etc” Notification No. 0210004 issued by Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, Minister of Health, Labour and Welfare (hereinafter called PFSB / ELD Notification No. 0210004) dated February 10, 2005.

(Q.4)
Is it allowed for a drug substance manufacturer who operates only refining process or repackaging process to register their substances in MF?

(A.4-1)
It is not allowed for a manufacturer who only operates refining process or repackaging process to register MF. Basically, Revised Pharmaceutical Affairs Law (PAL) requires manufacturers to describe the entire manufacturing process beginning with the starting materials in “Manufacturing Methods” section in MF application form. The purpose of MF registration is to protect manufacturers’

confidential information such as know-how of manufacturing process of drug substances, etc. Since describing only refining process or repackaging process does not suit that purpose, such a manufacturer is not eligible for MF registration.

(A.4-2)
However, depending on the contents of refining process, some cases could be considered as an exception. So please consult us about your case with specific examples.

(Q.5)
As for drug substances, etc. listed in foreign pharmacopoeias, is it still required to submit the validation data of testing methods?
As for drug substances listed in EP and USP, is it possible to quote the description in the pharmacopeias for the application of MF?

(A.5-1)
Article 2, Paragraph 1-(4) of “Specifications and Test Methods of New Pharmaceuticals” PFSB / ELD Notification No. 568 dated May 1, 2001, states that “Testing methods described in pharmacopoeias such as Japanese Pharmacopoeia (JP) or agreed in global harmonization are considered to be validated.” In principle, the testing methods that are agreed in global harmonization promoted among JP, EP, and USP are considered to be validated. However, the submission of validation data could be requested during review process, whenever it is considered to be necessary. As for the test methods described in foreign pharmacopoeias other than EP or USP, submission of the validation data is basically needed.

(A.5-2)
Even for the drug substances, etc. listed in EP or USP, drug manufacturers need to register their own manufacturing process, method of quality control, specifications and test methods, etc. which they actually apply for MF.

(Q.6)
Is it allowed for an applicant to register drug substances which were already approved as preparations and sold as pharmaceutical product

materials?
What is the definition of pharmaceutical product materials?

(A.6-1)
According to PFSB / ELD Notification No.0210004, pharmaceutical product materials (materials of pharmaceutical products with special dosage form, etc.) are listed as items for MF registration. But for the moment, if they were already approved as preparations, please refrain from MF registration. However, if they are mainly used as pharmaceutical product materials, in some cases, they could be registered in MF. As needed, please consult us about your case with specific examples.

(A.6-2)
“Pharmaceutical product materials (materials of pharmaceutical products with special dosage form, etc.)” are, for example, “pharmaceuticals that are mainly provided for the manufacturing of preparations and have a special dosage form with an additional pharmaceutical function such as extended release.” As an illustration, some capsules which are manufactured by methods with certain technical know-how and mostly used as materials of preparations can be registered in MF.

(Q.7)
Is it possible to register drug substances that are used both for ethical and OTC drugs in MF?

(A.7-1)
Yes, it is possible to register those kinds of drug substances in MF, if applicants wish to.

(A.7-2)
However, as stated in PFSB / ELD Notification No. 0210004, MF registration numbers can be quoted only in approval applications for ethical drugs and OTC drugs containing new active ingredients. Please refrain from quoting MF numbers for other types of products application.

(Q.8)

According to "Guidance on Application for MF Registration before Implementation of the Revised Pharmaceutical Affairs Law" PFSB / ELD Notification No. 0310002 dated March 10, 2005, the items registered provisionally before the revision of the Pharmaceutical Affairs Law (hereinafter called "Provisional MF registration") are required to be replaced in order to comply with the Revised Pharmaceutical Affairs Law by submitting "Application for changes in MF" by March 31, 2010. When is the best timing to submit that form?

(A.8)

When you apply for the official MF registration after "Provisional MF registration" is completed, you need to submit an "Application for changes in MF" with required documents in order to comply with the Revised Pharmaceutical Affairs Law. In principle, you are expected to complete this procedure by March 31, 2010. However, to avoid congestion right before the deadline, most recommended timing shall be when you have chance to renew your business license or to submit "Partial change approval application" for preparations approved by quoting MF number.

(Q.9)

When you apply for marketing approval application of pharmaceuticals manufactured from drug substances registered in MF, "Data equivalent to module 2 of CTD" is required to submit. Does it mean Quality Overall Summary?

When should the document be submitted?

(A.9-1)

When marketing approval application is made, the applicants who have MF registration certificate need to submit quality overall summary data which proves how the quality of the drug substance is guaranteed (including consideration on its efficacy and safety as needed). This document is called "Data equivalent to module 2 of CTD."

(A.9-2)

Although submission of "Data equivalent to module 2 in CTD" is not required at

the time of MF registration application, when PMDA conducts scientific review for marketing approval of preparations, the items registered in MF are reviewed as well. Therefore, it is advisable to submit the data at the same timing of applying for marketing approval. Regarding the timing of submission, please follow the PMDA reviewer's instruction.

(Q.10)
If the manufacturing methods and specifications of a drug substance are different by company to which the drug substance is sold, is it necessary to register each of them in MF separately?

(A.10-1)
Basically, it is needed to register all the different manufacturing methods or specifications, etc. of a drug substance separately. This means drug substances that have different manufacturing principles (for example, each manufacturing method has various basic chemical reactions.) need to be registered in MF separately.

(A.10-2)
However, since the handling may differ on each case, please consult PMDA about your specific cases as necessary.

(Q.11)
Is it allowed to add or delete the listed preparations which are manufactured from the drug substance to or from the contents of the "Provisional MF registration"? What is the procedure in this case?

(A.11)
As for the Appendix 3 of PFSB / ELD Notification No. 0310002 dated March 10, 2005, if you have an addition or deletion in the description, please submit the revised version of the "Provisional MF registration" on FD form with a written statement of change.

(Q.12)
Is it allowed to apply for "Provisional MF registration" when registering a drug substance approved in and after April 2005, under the previous

Pharmaceutical Affairs Law?
Does “data equivalent to Module 3 in CTD” need to be submitted as supporting data for MF registration?

(A.12-1)
No, “Provisional MF registration” for the drug substances approved on and after April 1, 2005 is not acceptable. Target of “Provisional MF registration” is only the drug substances used for the preparations approved by March 31, 2005 and application form for “Provisional MF registration” should be submitted by that date to the Division director of Evaluation and Licensing Division of Pharmaceutical and Food Safety Bureau, MHLW. Regarding drug substances used for the preparations approved on and after April 1, 2005, “New application of MF registration” needs to be submitted.

(A.12-2)
When you file “New application of MF registration”, please make sure the registration items comply with the Revised Pharmaceutical Affairs Law. Also please attach the supporting data (Module 3 in CTD, etc.) to the application form without fail.

(Q.13)
Do manufacturers of drug substances need to register all the items on the application form? Is it allowed for them to choose the registration items?

(A.13)
The applicants do not necessarily need to fill in all the items on MF application form, but the items needed for more efficient marketing approval review should be registered. For example, information on manufacturing methods, specifications and test methods should basically be registered, since they are indispensable to guarantee the quality of preparations.

(Q.14)
Who can I inquire about the usage of Flexible Disk application software for MF registration?
How can I put the information of “Deemed Accredited Foreign Manufacturers*” on the Flexible Disk application form?

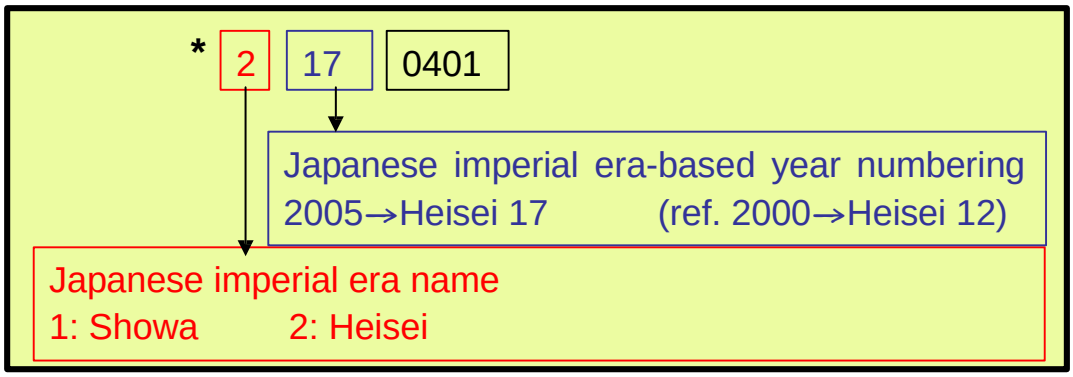
**A foreign manufacturer of the drug or medical device, etc. whose marketing approval holder has an effective importing license granted under the previous Pharmaceutical Affairs Law as of April 1, 2005, is deemed to be temporarily accredited under the Revised Pharmaceutical Law by the end of its laws effective period. The manufacturer satisfying the above condition is referred to as a "Deemed Accredited Foreign Manufacturer".*

(A.14-1)
For inquiries about the usage of Flexible Disk application software for MF registration, please fax us at +81-3-3506-9442. We only accept your written questions with your specific cases sent by fax.

(A.14-2)
Regarding information on "Deemed Accredited Foreign Manufacturers", please enter the following tentative information. For further information, please refer to "Q&A on Electronic Application Software for Drug Approval (Issued by MHLW)".

In the case of Deemed Accredited Foreign Manufacturers importing/ exporting drugs to Japan:

[License No. or Deemed Accreditation No.] :AG99999999
[License Date or Deemed Accreditation Date]:***2170401 (April 1, 2005)**



(Q.15)
Is it allowed for a marketing authorization holder to register a drug substance in MF, if they obtain the detailed manufacturing information of a drug substance from its manufacturer?

(A.15-1)
Purpose of MF system is to provide detailed manufacturing information on drug substances to be used in the review process, while protecting manufacturers' intellectual property. Therefore, MF registration shall be made by manufacturers who wish to keep their manufacturing know-how confidential.

(A.15-2)
If a marketing authorization holder has already obtained detailed manufacturing information on a drug substance, they can supply that information when they apply for marketing approval and there is no need to register it in MF.

(Q.16)
As for "TSE data" based on "TSE data number", if manufacturers change the raw materials from bovine-derived materials to non-bovine-derived (such as plant-derived or herbs) materials, what procedure should they take for MF registration and approval certificate?

(A.16-1)
In this case, the manufacturers need to apply "New MF registration."

(A.16-2)
As for marketing authorization used by these raw materials, if manufacturers only change country of origin of bovine they need to submit "Application of minor change notification". However, if they change the raw materials from bovine-derived to plant-derived, submission of "Partial change approval application" is basically required.

(Q.17)
Is it allowed that a foreign manufacturer of a drug substance directly applies for MF registration without appointing any in-country caretaker in Japan?

(A.17)
No, it is not allowed. When a foreign manufacturer applies for MF registration in Japan, it is essential to appoint an in-country caretaker in Japan. In any case, a

foreign manufacturer needs to appoint an in-country caretaker first, then proceed to register the drug substance in MF.

(Q.18)
When a manufacturer applies for MF registration of a drug substance which is already listed in pharmacopoeia, is it still required to submit the detailed information of the manufacturing method?

(A.18)
As specified in “Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law” PFSB/ELD Notification No. 0210001 dated February 10, 2005, even when your drug substance is listed in pharmacopoeia, it is still required to submit the information of the manufacturing method when you apply for “New MF registration.”

(Q.19)
When submitting “Application for change in registered master file”, does the applicant also need to apply “Partial change approval application” for approved pharmaceuticals manufactured from the drug substance registered in MF?

(A.19-1)
When the change to the registered item in MF is not minor, “Application for change in registered master file” is required. At the same time, submission of “Partial change approval application form” to the approved preparations which are manufactured from the drug substance registered in MF is also needed. Therefore, the MF registrant needs to discuss or contact carefully with the marketing authorization holders in advance if any change is made to the drug substance. In addition, the information on “Partial change approval application” to the preparations approved by quoting the MF number should be noted in the remarks column of the “Application for change in registered master file” form.

(A.19-2)
In Article 5, Paragraph 3, Item 7 of PFSB / ELD Notification No.0210004, it is noted that “Application for change in registered master file” shall be reviewed

only after the submission of “Partial change approval application” for all the preparations approved with the MF number is completed. Therefore, it is desirable to submit “Application for change in registered master file” and “Partial change approval application“ at the same timing, right after the change is made to the drug substance.

(Q.20)
Can we assume that the completion of MF registration means that the drug substance acquired some sort of approval?

(A.20)
No, purpose of MF registration is to protect manufacturers’ intellectual property, etc. Therefore we only check if the application form and the supporting materials are sufficiently prepared to meet the requirements or not. It shall not be assumed that the validity and assurance of the drug substance’s quality and adequacy are officially approved by MF registration.
When marketing approval application of pharmaceuticals is submitted, the contents registered in MF shall be reviewed through checking the usage, dosage form, and the characteristics of the pharmaceutical products made from the drug substance. If inadequate contents in MF are detected, it is required to be corrected. At that point, you can eventually consider the contents of MF registration as a part of the drug approval.