

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

(Q.1)

In “Guidance on Application for MF Registration before Implementation of the Revised Pharmaceutical Affairs Law” (hereinafter referred to as “Provisional MF registration”), PFSB / ELD Notification No. 0310002 dated March 10, 2005, manufacturers are supposed to submit “Application for change in registered master file” by March 31, 2010 to comply their registered items with the contents of the Revised Pharmaceutical Affairs Law. If the “Application for change in registered master file” is not submitted by that date, what is the appropriate procedure to take?

(A.1)

Please keep in mind that registration numbers could become invalid (sometimes provisional MF registrants could be ordered to return their registration certificates), unless they submit “Application for change in registered MF” by the settled date, which is March 31, 2010. However, it is preferable that provisional MF holders shall submit the application at their earliest convenience, for example, when they have chance to renew their business license or to submit “Partial change approval application” for the preparations approved by quoting MF number of the drug substances.

(Q.2)

What are the important points and procedures of “Application for change in registered MF” in order to make the items registered by “Provisional MF registration (application by flexible disk)” comply with the Revised Pharmaceutical Affairs Law?

(A.2-1)

When you submit “Application for change in registered MF”, please use “Application form for change in registered MF” (Form No.46). Please make sure it is not “New application of MF registration” or “Minor change notification.”

(A.2-2)

When you submit “Application for change in registered MF”, please describe all

¹This 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.

the items which are required. Abbreviated description should not be made. Also, supporting data such as Module 3, etc. of CTD should be attached to the application form.

(A.2-3)

When “Application for change in registered MF” is submitted, PMDA will issue a new MF registration certificate to you. Please return the previous certificate to PMDA. When you mail the previous certificate, please enclose it with “the Application form for change in registered MF. “

(Q.3)

What is the procedure to take and what are the important points if changes are made to the contents in the “Provisional MF Registration” (application by flexible disk) before applying for “Application for change in registered MF”, which needs to be submitted to comply with the Revised Pharmaceutical Affairs Law?

(A.3-1)

If significant changes are made to the items registered in the Provisional MF Registration (application by flexible disk), you need to submit “Application for change in registered MF”. In this case, the changed items should be described concretely in the remarks column of the application form, or a comparative list showing the new and old contents of the items should be attached. In addition, please make sure all the items described in the application form comply with the Revised Pharmaceutical Affairs Law. Other procedures are as shown in the answer to Q.2.

(A.3-2)

When the changes are minor, please submit “Notification form of the Minor Change” (Form No.47).

(A.3-3)

If you have any further questions, please contact Master File Management Group, Office of Review Management, Pharmaceuticals and Medical Devices Agency.

(Q.4)

Please explain in details about MF registration of only refining process or repackaging process, which is stated in the question No.4 in the Administrative Notice “Q&A on the Master File(MF) System, Part I” issued on July 28, 2005.

(A.4-1)

Basically, manufacturers have been required to submit their manufacturing process beginning with the starting materials. MF registration aims to help reviewers to smoothly track an entire manufacturing process from raw materials to final products by the same MF number. If multiple MF registration numbers exist at the different stages of a manufacturing process, it may cause confusion in the review process. Thus, it has not been allowed to register only refining process so far. However, when the following conditions are met, registration of only refining process shall be accepted hereafter.

[Conditions]

(1) Manufacturers in charge of the processes from starting materials before refining process (e.g. culture process, synthetic process) need to obtain MF registration numbers first. Then, manufacturers in charge of only refining process can apply for MF registration by quoting those obtained registration numbers.

(2) Basically the above mentioned procedure (1) is most recommended; however, if it is impossible to follow the procedure (1) due to unavoidable circumstances, following procedure could also be accepted:

- In principle, companies who take only refining process obtain all the information about the manufacturing methods from the manufacturers of other processes, and describe them in the application form for the refining process.

(3) In order to avoid any trouble, applicants need to communicate closely with the manufacturers who take the processes before refining. Close communication with the marketing authorization holders is also needed for the smooth information transition in case of any changes. Moreover, applicants need to

clarify where responsibility lies for troubles and other concerns caused by miscommunication.

However, MHLW and PMDA may add other conditions than the above after consultation, when necessary.

(A.4-2)

As in the past, application only for repackaging process is not accepted because it does not fit the purpose of MF system.

(A.4-3)

If you need more information, please contact Master File Management Group, Office of Review Management, PMDA.

(Q.5)

What are withdrawal of MF registration application and deletion of MF registration?

(A.5-1)

Withdrawal of MF registration application means that an applicant voluntarily withdraws its application before the issuance of registration certificate. You can download application withdrawal form in FD application software through PMDA's website. If you have difficulties in downloading the form, please fax your written questions to Helpdesk at +81-3-3506-9442.

(A.5-2)

As stated in Article 15 of the Pharmaceutical Affairs Law, if an applicant obtains MF certificate by unfair means, the registration shall be deleted. In this case, MHLW shall notify the applicant of the deletion, and the deletion shall be made public. The MF registrant must immediately return the MF certificate to the Minister of MHLW in accordance with Article 82-1 of the Enforcement Regulation of the Pharmaceutical Affairs Law.

(Q.6)

When a MF holder decides to discontinue manufacturing a registered drug substance, how will the registration be canceled?

(A.6-1)

“Notification of Cancellation of MF Registration” is supposed to be submitted when a MF registrant decides to voluntarily cancel the registration due to the discontinuance of a drug substance, etc.

(A.6-2)

Please submit “Notification of Cancellation of MF Registration” with the registration certificate to PMDA. When you cancel the registration, please make sure that there are no preparations which are approved by quoting the MF registration.

(Q.7)

Is it acceptable to use the documents attached to drug approval application under the previous Pharmaceutical Affairs Law, as supporting data for MF registration?

(A.7)

Yes, it is acceptable to use the documents attached to the marketing approval application under the previous Pharmaceutical Affairs Law. However, the applicant may need to submit additional documents if there is new knowledge or information after the authorization of marketing approval under the previous law, or when submission of additional documents other than the attached materials are requested by the reviewers.

(Q.8)

Are there any qualifications for an in-country caretaker of drug substances, etc in Japan? When it is hard for a foreign manufacturer to find an adequate caretaker for MF registration in Japan, is there any other way to take?

(A.8-1)

There is no official qualification to become an in-country caretaker in Japan. However, it is your responsibility to appoint an appropriate person or a company who is capable enough to take the important responsibility of MF registration, etc.

(A.8-2)

According to the article 72-2 of Enforcement Regulations of the Pharmaceutical

Affairs Law, it is mandatory for each foreign applicant of MF registration to appoint their own in-country caretaker in Japan.

(Q.9)

Can the same person be both an in-country caretaker and a contact person described on the application form?

Should a copy of the contract between a foreign manufacturer of a drug substance and its in-country caretaker be attached to the marketing approval application form?

(A.9-1)

If your in-country caretaker is capable enough for the responsibilities as stated in A8-1, the in-country caretaker can also be a contact person for MF registration application.

(A.9-2)

Copy of the contract between a foreign manufacturer of a drug substance and its in-country caretaker is not always needed to be attached to the marketing approval application. However, an applicant for marketing approval needs to attach a copy of the contract with the MF registrant, as stated in Paragraph 5 (2)-1 in "Guideline on Utilization of Master File for Drug Substance, etc." PF/SB / ELD Notification No. 0210004 dated February 10, 2005.

(Q.10)

When submitting marketing approval application by quoting the information registered in MF, should the information disclosed by the MF registrants be described in the application form?

(A.10-1)

As stated in the Paragraph 4-(3) "Information that MF Registrant Should Disclose to the Applicants and Approval Holders of Pharmaceutical Products in Advance" in "Guideline on Utilization of Master File for Drug Substance, etc." PF/SB / ELD Notification No. 0210004 dated February 10, 2005, the information on disclosed part (accessible information to applicants for marketing approval) shall be described in MF application form along with the information on restricted part (inaccessible information to applicants for marketing approval because it includes

manufacturing know-how).

(A.10-2)

Therefore, the disclosed information (including both disclosed and restricted information in Module 3 of CTD) does not need to be described in drug approval application form since reviewers can refer to the data registered in MF when a review is conducted.

.

(A.10-3)

However, a marketing approval applicant needs to prepare a summary document (Module 2 in CTD) based on the disclosed information. In the document, it is needed to describe the product development based on the qualitative characteristics of the drug substances, which affect efficacy, safety and quality of the pharmaceutical preparation. It is also needed to describe how the applicant guarantees efficacy, safety and quality.

(Q.11)

Is it possible that several caretakers obtain individual MF registration numbers for one drug substance manufactured by one foreign manufacturer?

(A.11-1)

Multiple MF registration numbers for one drug substance may cause confusion or delay in the marketing approval process. In such cases, the applicants shall take responsibility for all the inconvenience.

(A.11-2)

Due to the inconvenience mentioned above, multiple MF registration application for one drug substance is not preferable. If there are more than one registration numbers for one drug substance, please select one after reaching a consensus among the concerned caretakers.

(Q.12)

Is it allowed to register a pre-mixed active ingredient in MF?

(A.12)

Yes, it is allowed to register a pre-mixed active ingredient in MF. However, if the manufacturer purchases the drug substances from other companies, it needs to quote the MF registration numbers obtained by those companies or describe their manufacturing methods of drug substances in MF application form.

(Q.13)

PMDA asks manufacturers not to register the drug substances used for OTC drugs in MF, however, when TSE data is registered in MF, is it possible to quote the MF number for marketing approval application of OTC drugs?

(A.13)

Yes, if new TSE data is registered in MF, it is possible to quote the MF registration number for marketing approval application of OTC drugs.

(Q.14)

Is there any way for a priority MF registration?

Is there a time clock for issuing MF registration certificate?

(A.14)

There is no priority registration or time clock for issuing MF certificate. PMDA promptly registers applications in order of receipt.

(Q.15)

Is it possible to submit marketing approval application before the MF registration number and the certificate are issued?

(A.15-1)

Yes, it is possible. In this case, you shall submit marketing approval application with the receipt number of MF, and describe on the application form the fact that you have submitted MF registration application but not yet received the registration number.

(A.15-2)

However, once your MF registration number is issued, you should submit "Request form for number replacement" to replace the receipt number with the

registration number. In this case, please note that the approval review shall start only after the replacement procedure is completed.

(A.15-3)

When you make a minor change to the registered items and quote the MF registration number, you shall submit "Minor change notification" with the MF registration number. Please note that it is not allowed to submit "Minor change notification" by quoting receipt number of MF registration.