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

(Q.1-1)
For MF registration in Japan, foreign pharmaceutical companies must rely on the decision and skill of an in-country caretaker (ICC). However, there may be differences between original documents and documents translated by the in-country caretaker and submitted to the authorities. Is it possible to register and respond to inquiries only in English and not through the ICC?
Is it possible to receive a consultation directly from foreign manufacturers?

(A.1-1)
The application form and documents to be attached to the application form (excluding CTD) are required to be written in Japanese by the laws and regulations. In addition, the ICC must be appointed when conducting registration and related clerical work for registration, etc. in Japan.

(A.1-2)
The role of the ICC is not limited to mere translation and mediation of inquiries and responses, and is expected also to provide information on law revisions and notifications in a timely manner and to explain their purposes, etc.

(A.1-3)
To facilitate communication between MF registrants and PMDA, a system of “Consultation for MF for generic drugs” was established in April 2021, in which the in-country caretaker and MF registrant (or a company which is to register) can consult directly with PMDA.

(A.1-4)
PMDA provides training to explain the latest examples, notifications, etc. to support the improvement of the capability of ICC.

(Q.2)
Is it possible to register a finished product with the MF?

(A.2)
The Japanese regulatory system does not permit MF registration of finished products to be released by the marketing authorization applicant/holders. The reason is based on the view that the quality of the finished product should be assured on the responsibility of the marketing authorization applicant/holder.

(Q.3)
In a case where the manufacture of a drug substance is entrusted to a contract manufacturing organization (CMO), we request that a company as contract giver be permitted to be a MF registrant.

(A.3)
Under the MF system in Japan, for a drug substance whose manufacture has been entrusted to a CMO by the contract giver, the company as contract giver cannot be the MF registrant. However, it is possible for the CMO itself as contractor to be a MF registrant.

(Q.4)
When a marketing authorization applicant/holder of a drug product requests an MF registrant to disclose confidential information at the time of submission of marketing approval application, how should a MF registrant respond?

(A.4-1)
The MF system was established to protect the intellectual property of the drug substance manufacturer, and the information related to the intellectual property can be closed to the marketing authorization applicant/holder of the drug product by the MF registrant. To the regulatory authorities, even confidential information must be disclosed upon request.

(A.4-2)
Examples of handling disclosed and closed information under the Japanese MF registration system are detailed in materials available on the PMDA website (https://www.pmda.go.jp/files/000227208.pdf). The MF registrant should discuss

with the marketing authorization applicant/holder and the ICC by reference to the materials.

(A.4-3)
If the marketing authorization applicant/holder of a drug product needs to use the closed information of the MF registrant in preparing responses to inquiries on the drug product, the MF registrant can submit the response/information directly to the Review Office in charge, not through the marketing authorization applicant/holder of the drug product.

(Q.5)
Where is the information on registered MFs available?

(A.5)
Following information is published on the PMDA website (Japanese version only);
https://www.pmda.go.jp/review-services/drug-reviews/master-files/0008.html
- Name of drug substance.
- Name and address of registrant.

(Q.6)
For a registered MF, if the MF registrant sells or renders the manufacturing site of registered substance to other companies, how should the MF be handled?

(A.6)
For the registered MF, if transfer etc. of the manufacturing site is performed, resulting in a situation where the manufacturing activities are not conducted by the registrant, and the registrant needs to be changed, it is necessary to take appropriate actions such as succession of the MF.

(Q.7)
What is to be done to use the stock of drug substance produced before abolition of the manufacturing site?

(A.7-1)
The inventory control of drug substances should be performed in a planned manner.

(A.7-2)
If transfer etc. of the manufacturing site is performed for a registered and reviewed drug substance, and the drug substance or manufacturing intermediate already released to the downstream manufacturing site is used, discuss the actions to be taken with the ICC by reference to Q11, etc. of the “Questions and Answers (Q & A) on Manufacturing License of Pharmaceuticals, etc. Accreditation of Foreign Manufacturers, etc.” (Administrative Notice dated March 29, 2016) (Japanese version only).

(Q.8)
Is an electronic signature acceptable for the signature of the MF registrant?

(A.8)
MHLW/PMDA revised the related regulation and a seal/signature is not required anymore. “Handling of Seals in PMDA” (PMDA Notification No. 1225054 dated December 25, 2020)
https://www.pmda.go.jp/about-pmda/news-release/0050.html (Japanese version only)

(Q.9)
How long is the review time of an application for partial change approval of the drug product using MF which is submitted in response to an application for MF change registration?

(A.9-1)
Refer to “Handling of Approval Applications for Improvement in Predictability of Approval of Generic Drugs and Concept of Total Review Time” (PSEHB/PED Notification No. 0223-1 dated February 23, 2018) (Japanese version only).

(A.9-2)
To improve the predictability in the review, consider using the above “Consultation for MF for generic drugs.”

(Q.10)
In foreign countries, changes are categorized into three levels of major, moderate and minor changes. In Japan, how should we handle a change corresponding to the moderate change?

(A.10-1)
In Japan, the law stipulates the change category of approved items as two categories of major and minor changes.

(A.10-2)
Items requiring change registration application and items requiring only a minor change notification are mainly notified by the following notification (Japanese version only).
- “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)
- “Results of Consideration to Clarify the Scope of Minor Change Notification” (Administrative Notice dated June 28, 2010)

(A.10-3)
As necessary, perform a consultation by utilizing the above “Consultation for MF for generic drugs,” etc.

(Q.11)
What should we do if we cannot respond within the response deadline of the inquiries presented by the reviewer during the review of application?

(A.11)
If the response within the deadline is difficult, contact the reviewer.

(Q.12)
We desire to set the specifications for drug substances, etc. to be registered with MF as EP or USP. Is it acceptable?

(A.12)
If the drug substances, etc. are registered with MF in Japan, it is possible to set the specifications as EP or USP. The EP and USP are not positioned as reference pharmacopoeias, and thus the appropriateness of the specifications for the drug substance described in the application form is judged for each individual product at the time of review.

(Q.13)
We desire to know how to obtain English translations of laws, regulations, notifications, etc.

(A.13-1)
For major laws and regulations, their English translations are posted on the PMDA website.
https://www.pmda.go.jp/english/review-services/regulatory-info/0002.html

(A.13-2)
Translating the laws and regulations, notifications, etc. that affect the registered MF into English and providing information in a timely manner are the roles expected for the ICC.

(Q.14)
We desire to know how to obtain the English translation of the Japanese Pharmacopoeia.

(A.14)
The English version of the Japanese Pharmacopoeia is published on the PMDA website.
https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0010.html

(Q.15)
We desire to know how to participate in the public comment.

(A.15-1)
For domestic laws and notifications, public comments are called for only in Japanese. As necessary, submit comments through the ICC.

(A.15-2)
For the Japanese Pharmacopoeia, public comments are called for in English on the PMDA website.
https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/pub-comments/0001.html

(Q.16)
We desire to know how to obtain English translations of the application for registration of MF (Form 120), application for MF change registration (Form 124) and minor change notification (Form 125).

(A.16)
They are published on the PMDA website.
Form No. 120:
https://www.pmda.go.jp/files/000234393.pdf
Form No. 124:
https://www.pmda.go.jp/files/000234394.pdf
Form No. 125
https://www.pmda.go.jp/files/000234395.pdf