Notices for the application of Plant master file (Including Application Form & Check list)

Plant Master File (PMF) Application

A. Introduction

International PIC/S GMP standards have already been adopted in our country, and the Food and Drug Administration of the MOHW became the 43rd member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) on January 1, 2013. In light of these facts, the TFDA, based on principles of risk management and with reference to international management systems, started thereafter to divide foreign pharmaceutical manufacturers into three classes of measures: those in non-PIC/S-member states, those in PIC/S member states, and those who fall within the scope of an agreement (MRA or MOU) signed off with our country on the mutual acceptance of inspection results in accordance with where they are located. Pharmaceutical manufacturers in PIC/S member states that may apply for written PMF review are further divided into three categories — namely non-sterile products, sterile products, and biological products and their raw materials — in accordance with the categories of the product they apply for; On January 30, 2013, the revised Information for Preparing the Plant Master File for Foreign Pharmaceutical manufacturers was announced, and these three categories and three classes of measures were enforced, in order to integrate international resources and enhance management efficacy. In order to reduce repetition in the technical data submitted and enhance time efficiency, for foreign pharmaceutical manufacturers that have just received the PMF Approval letter from the Ministry of Health and Welfare, the Food and Drug Administration of the MOHW agreed to referencing to the previous submission or approval letter through TFDA Risk No. 1051102938 on June 3, 2016, and announced the principles of application.

As pharmaceutical technology and equipment continue to upgrade, the PIC/S GMP standards are updating. It becomes urgent to revise the **Notices for the application of Plant master file** for Foreign Pharmaceutical manufacturers to accommodate the updates of PIC/S GMP standards; hence, the review standard, requirements, document preparation, and precautions were reorganized, and the original Forms 1 - 4 were changed to Forms A, B, and C1-5 in order to facilitate the applicants' preparation and to enhance submission quality and time efficiency of review.

B. Review Requirements

(I) Legal Basis:

- Article 57 of the Pharmaceutical Affairs Act,
- Pharmaceutical Good Manufacturing Practice Regulations,
- Regulations of Medicament Manufacturer Inspection,
- Standards for Medicament Factory Establishments.
  PIC/S: Guide to Good Manufacturing Practice for Medicinal Products including full texts and annexes

(II) Management System:

1. All pharmaceutical plants in non-PIC/S member countries undergo foreign on-site plant inspections.
2. Pharmaceutical manufacturers falling within the scope of an agreement (MRA or MOU) signed off with our country on the mutual acceptance of inspection results: The original copy of the GMP Certificate issued by the competent health authority in said country may be enclosed (the GMP Certificate shall be within its effective period, and the contents shall include both the dosage form being applied for and the scope of operation) in order to apply for simplified review (In other words, in which case Form A, the aforementioned GMP certificate and the latest version of the SMF all need to be enclosed).
3. Pharmaceutical manufacturers in PIC/S members states, which are further divided into the following categories in accordance with the content of the application:

(1) Non-sterile products: Simplified review/full review/Quote review may be applied for.

(2) Sterile products:
Simplified review or full review or Quote review may be applied for. For simplified or full review, the validation dossiers may be waived with alternative dossiers.

(3) Biological medicinal products/biological active drug substances/blood products derived from human blood or human plasma: Simplified review or full review/Quote review may be applied for. For simplified or full review, the validation dossiers may be waived with alternative dossiers (Please reference to (III), 2).

(III) Application Method:

1. Applications for simplified review: applicants may submit a "List of all GMP inspections conducted by the local competent health authority or foreign health authority in the last five years", and "The latest GMP site inspection report from local competent health authority and the GMP certificate (or other GMP approval dossiers which are issued by the local competent health authority) to waive the full set requirement.
   (1) The list of inspections should at least include but not limited to the inspection dates, inspection topics and scopes.
   (2) Inspection report and the GMP certificate (or other GMP approval dossiers which are issued by the local competent health authority):
      (i) The inspection scope shall cover the the dosage forms or the operations in the PMF application.
      (ii) Full Chinese or English translations of the GMP inspection report, along with the full original report.
      (iii) List of major changes to the applied dosage forms/operations (including premises, facilities, equipment, and manufacturing process) after said inspection to the date of submission.
2. Applications with alternative dossiers to substitute the Validation and Qualification documents: applicants may submit an "Original copy/hard copy of a certificate of pharmaceutical products (CPP) issued by A-10 countries or EMA", "Validation and Qualification Summary" and "Original letter of explanation" for substitution of validation and qualification documents.
   (1) A-10 countries include Germany, US, UK, France, Japan, Switzerland, Canada, Australia, Belgium, and Sweden .Original copy of the Certificate of pharmaceutical products (CPP) or hard copy: It is effective for two years from

the issuance date; If electronic CPP (e-CPP) is submitted, the paper version of CPP is not required.

(2) Validation and qualification summary: These shall be original copies with the responsible person's hand-written signature or electronical documents shall be signed electronically. The summary shall include information such as the overview for validation and qualification manufacturing process at the manufacturing site (including for the support systems (HVAC, water, and in-manufacturing process gases), equipment and facilities, computerized systems, cleaning validation, etc.).

(3) Original letter of explanation shall be the original copy/or electronical documents with electronic signature, with contents to include but not be limited to the following.

The manufacturer is aware that Taiwan FDA has the complete rights to conduct on-site inspections according to international practice if need.

3. For applicants to apply PMF for Quote review depending on different situations, the dossiers are required as following:

(1) An original holder of a GMP approval letter who intends to cite a previous submission (Including approval letters of overseas on-site inspection, PMF review, or follow-up inspection)when applying for a PMF review for additional dosage forms/products/ manufacturing processes at the same plant within the effective period of said approval letter, shall submit the following documents:

(i) Original copy of the Letter of Explanation with responsible person's hand-written signature or electronical documents shall be signed electronically , which shall specify:

a. Agreement to proceed pursuant to the previous submission.

b. Approval number of previous GMP approval letter issued by Taiwan FDA.

c. A description of changes occurring since the last PMF application

(ii) Photocopy of the previous GMP approval letter issued by Taiwan FDA

(iii) The latest SMF (including paper and electronic file)

(iv) PMF Inspection Forms A, B, C and relevant materials.

(v) Taiwan FDA reserves the right to request further submissions in cases where the documentation is incomplete or when otherwise necessary.

(2) A non-original holder of a GMP approval letter intending to cite an original approval letter (Including approval letters of overseas on-site inspection, PMF review, or follow-up inspection) when applying for a PMF review for additional dosage forms/products/manufacturing processes, shall submit the documentation listed below within the effective period of the approval letter. An approval letter with the same expiry date shall be issued if said documentation is found to be in compliance, and the conditions of the authorization will be added to the notations in said approval letter.

(i) Original copy of the Letter of Explanation with responsible person's hand-written signature or electronical documents shall be signed electronically, which shall specify:

a. Agreement to proceed pursuant to the previous submission.

b. Approval number of previous GMP approval letter issued by Taiwan FDA.

(ii) Authorization letter from the original holder of the GMP approval letter with responsible person's hand-written signature or electronical documents

shall be signed electronically, which shall specify the official document number of the GMP approval letter and the case number of the previous submission dossiers, and shall bear the company seal and the responsible person's seal.

(iii) Photocopy of the previous GMP approval letter issued by Taiwan FDA.

(iv) The most latest SMF(including electronic and paper file)

(3) A non-original holder of a GMP approval letter intending to cite a previous submission (Including approval letters of overseas on-site inspection, PMF review, or follow-up inspection) when applying for a PMF review for additional dosage forms/products/operations at the same plant within within the effective period of said approval letter, shall submit the following documents:

(i) Original copy of the Letter of Explanation with responsible person's hand-written signature or electronical documents shall be signed electronically, which shall specify:

a. Agreement to proceed pursuant to the previous submission.

b. Approval number of previous GMP approval letter issued by Taiwan FDA.

c. Brief presentation of changes being effected since the last PMF application

(ii) Authorization letter from the original holder of the GMP approval letter with responsible person's hand-written signature or electronical documents shall be signed electronically, which shall specify the official document number of the GMP approval letter and the case number of the previous submission dossiers, and shall bear the company seal and the responsible person's seal.

(iii) Photocopy of the previous GMP approval letter issued by Taiwan FDA.

(iv) The most latest SMF(including electronic and paper file)

(v) PMF Inspection Form A, B, C and relevant materials.

(vi) Taiwan FDA has the rights to request more relevant documents if considered necessary.

C. Administrative Information that Should Be Submitted with an Application for Review of a Foreign Manufacturer PMF and Precautions

I、 Requirements of Administrative Information:

1. Legalization requirements: Based on Article 5, Paragraph 2 of the Regulations of Medicament Manufacturer Inspection, the PMF application materials may meet any one of the following requirements for submission::

(1) Plant Master File (PMF) and Site Master File (SMF), which are to be certified by the highest competent health authority or the chamber of commerce in the country of origin or legalized by the embassy, representative office or agencies authorized by the Ministry of Foreign Affairs of R.O.C.

(2) Original copy or original certified photocopy of the Certificate of Compliance with local Good Manufacturing Practice, issued by the highest competent health authority in the country of origin or legalized by the embassy, representative office or agencies authorized by the Ministry of Foreign Affairs of R.O.C. (if the two original documents mentioned above were already submitted to the TFDA through other cases, a photocopy of the whole document may be enclosed, with indication of the case number where the original copies were submitted to the TFDA)

(3) Original copy or original certified photocopy of the Certificate of Pharmaceutical Product manufactured in compliance with the local Good Manufacturing Practice issued by the highest competent health authority in the country of origin or legalized by the embassy, representative office or agencies authorized by the Ministry of Foreign Affairs of R.O.C. (if the two original documents mentioned above were already submitted to the TFDA through other cases, a photocopy of the whole document may be enclosed, with indication of the case number where the original copies were submitted to the TFDA)

(4) If the paper based GMP certification is no longer available in the country of origin, or the drug product is contracted manufacturing, the license holder of an imported drug shall state why the GMP certification is not submitted. Therefore, the applicants may submit the original copy or photocopy with legalization of the Certificate of Pharmaceutical Product issued by any one of the A-10 countries, EMA, or by the highest competent health authority in the country where the contractor is located ,in accordance with the letter TFDA Risk No. 1051105400 dated October 17, 2016

(5) If the electronic GMP or CPP (e-GMP or e-CPP) are issued from the authority of country of origin, the web link is required for authenticity.

(6) For applicants applying for Quote review, legalization of the dossier is not required.

2. Authorization Letter:

(1) The original Letter of Authorization whereby the original manufacturer authorizes the Taiwan agents (pharmaceutical company) to submit PMF applications. The authorization letter shall be with responsible person's hand-written signature or electronical documents shall be signed electronically.

(2) When biological medicinal products/biological active substance/ blood products derived from human blood or human plasma are being applied for, the products/dosage forms and manufacturing process stage involved in the application shall be indicated in the Authorization Letter.

(3) To apply for Quote review, it is required to enclose the Authorization Letter from the manufacturer and the Authorization Letter from the Taiwan agents who holds the previous GMP approval letter.

3. Documents to be enclosed:

(1) The electronic dossiers could be delivered via compact disk (CD), flash drive, cloud drive and email, etc.

(2) The documents shall, in principle, be prepared on A4 (210 mm x 297 mm) paper and shall be legible and complete. Manufacturing Site Layout and illustrations are preferably in color. If the paper is larger than A4, please fold it to A4 size.

(3) Applicants are suggested to follow the principle of Good submission practice. In compiling and assembling of submission dossier, applicants need to ensure that every document has been prepared consistently and placed in the correct location of the dossier.

(4) Documents that are written in a foreign language other than English shall be translated into Chinese or English, and the accuracy of the contents of translated documents shall be confirmed.

(5) The documents are to be signed by quality assurance staff or respective responsible person at the manufacturing site.

(6) Forms A, B, and C of the PMF Inspection Form for Foreign Pharmaceutical manufacturers shall be completed and signed off by the Taiwan agents or the quality assurance staff or relevant responsible person at the manufacturing site, and the page numbers or appendixes of corresponding materials and documents submitted for review are to be specified in the form for each review item. The materials and documents asked for in the Inspection Form are to be enclosed as well.

(7) The dossier could be submitted via an electronic means, however, the certified or legalized document (ex, SMF, GMP, CPP) is still required when submission. If the electronic GMP or CPP are issued from the authority of country of origin, the web link is required for authenticity.

(8) The dossier , for example, the Letter of Explanation, Validation and qualification summary, authorization letter, list of major changes to the applied dosage forms/operations, Form C1~C5, shall be signed with responsible person's hand-written signature or electronical documents shall be signed electronically. Taiwan FDA has the rights to request original copy if considered necessary.

(9) In case a pharmaceutical dealer makes use of false information of evidentiary document(s) in applying for PMF, according to Article 214 of Criminal Code of the Republic of China, criminal responsibility should be involved, the case shall be referred to the competent judicial authority for investigation.

4. For the format and contents of the SMF, the Information for Preparing the Site Master File for Pharmaceutical manufacturers announced by the Ministry of Health and Welfare may be referred to; it shall be a Chinese or English version, and electronic files shall be enclosed. It is strongly suggested that the applicants compile and assemble the SMF according to 「EXPLANATORY NOTES FOR PHARMACEUTICAL MANUFACTURERS ON THE PREPARATION OF A SITE MASTER FILE」(PE008-4)in order to achieve successful manufacturing site registration.
5. Materials to be enclosed with applications for re-review:
   (1) Supplemental materials for re-review.
   (2) Previously-reviewed materials (for security reasons, do not open envelopes of returned materials; otherwise, re-review of the entire case will be necessary)
   (3) Where there are amendments/deletions of dosage forms or operational content, the Application Form for Plant Master File (PMF) Review for Foreign Pharmaceutical manufacturers Form A must be re-submitted.

II、 Precautions:

1. For each case, only one manufacturing site at a single address may be applied for.
2. For each case, up to 2 dosage forms/products/manufacturing processes may be applied for Manufacturing processes. The dosage forms /manufacturing processes shall be filled out based on Dosage form Classification Principles of Manufacturer's authorization and GMP certification announced by MOHW.
3. The applicant must hold business permit license; if necessary, it may be requested that such business permit license be enclosed.
4. The applicants shall fill out the following information in Form A: application method (Simplified review, full review or with alternative dossiers to substitute the documents of qualification and validation), orphan drug, or sterile products (aseptic preparation or terminal sterilization are specified; Large volume parenteral (LVP) or small volume parenteral (SVP) products). The applicant for expansion of

manufacturing site shall submit Form A, B and items with asterisk in Form C1 to C5, and the relevant documents shall be enclosed.

5. Review fees are to be paid in accordance with Standards of Review Fees for the Registration of Western Medicines and Medical Devices as most recently announced by the MOHW. If the case has already been reviewed, no review fees shall be refunded.
6. If the applicants do not submit PMF materials in accordance with **Notices for the application of Plant master file**, they will be notified through Taiwan FDA official letter to submit application materials again.
7. If the re-review PMF case is rejected, the PMF application materials will not be returned.

D. Forms to be Downloaded

- **Application Form for Plant Master File (PMF) Review for Foreign Pharmaceutical manufacturer**_Form A
- Checklist of Preparing submission dossiers of Plant Master File for Foreign Pharmaceutical manufacturers_Form B
- **Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer** _Form C -1 Documents in Common review
- **Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer**_Form C -2 Non-sterile medicinal products/ Biological medicinal product/ Biological active substances (including the substance claimed non sterile or low bioburden level) / Blood products derived from human blood or human plasma (simplified review)
- **Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer**_Form C -3 All products
- **Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer**_Form C -4 Biological active substances and medicinal products/ Blood products derived from human blood or human plasma
- **Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer**_Form C -5 Validation and Qualification