

## **Notices for the Plant Master File (PMF) Application** **(Including Application Form & Check list)**

### **A. Introduction**

In consideration of the PIC/S GMP Guide have already been adopted by Taiwan (R.O.C), and the Taiwan Food & Drug Administration, Ministry of Health and Welfare (hereafter as TFDA) became the 43<sup>rd</sup> member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) on January 1, 2013, a risk-based approach has been applied to the assess GMP compliance. A foreign pharmaceutical manufacturer will be classified into those located in non-PIC/S-member states, those located in PIC/S member states, or those within the scope of an agreement (MRA or MOU) signed off with Taiwan on the mutual recognition of inspection. Pharmaceutical manufacturers located in PIC/S member states that may apply for PMF review are further divided into three categories — non-sterile products, sterile products, and **advanced therapy medicinal products (ATMPs)/biological medicinal substances and products** — 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 duplication in the technical data submitted and enhance efficiency, according to TFDA Risk No. 1051102938 on June 3, 2016, for foreign pharmaceutical manufacturers that have just received the GMP Approval letter from the Ministry of Health and Welfare, the TFDA agreed to referencing to the previous submission or approval letter when reviewing new PMF application. The principles of application were also announced accordingly.

As pharmaceutical technology and equipment continue to upgrade, the PIC/S GMP standards are updating. It becomes urgent to revise the **Notices for the Plant Master File (PMF) Application** 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 manufacturers located in non-PIC/S member states shall undergo oversea on-site inspections.
2. Pharmaceutical manufacturers within the scope of an agreement (MRA or MOU) signed

off with Taiwan on the mutual recognition of inspection: The original copy of the GMP Certificate issued by the hosting competent authority may be enclosed (the GMP Certificate shall be within its effective period, and the contents shall include the dosage form and manufacturing processes applied in the application) in order to apply for simplified review (i.e., Form A, GMP certificate and the latest version of the SMF shall be enclosed).

3. Pharmaceutical manufacturers located 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. For full review, the validation dossiers may be waived with alternative dossiers.
  - (2) Sterile products: Simplified review/full review/Quote review may be applied for. For simplified or full review, the validation dossiers may be waived with alternative dossiers.
  - (3) **ATMPs/biological medicinal substances and products**: Simplified review/full review/Quote review may be applied for. For simplified or full review, the validation dossiers may be waived with alternative dossiers.

### III. Application Modes:

1. Applicants may submit the following document to apply for simplified review:
  - (1) A list of all GMP inspections conducted by the hosting competent authority or other health authorities in the last five years. The list of inspections should at least include but not limited to the inspection dates, inspection topics and scopes.
  - (2) The latest GMP on-site inspection report from hosting competent authority and the GMP certificate (or other GMP approval dossiers which are issued by the hosting competent authority).
    - (i) The dosage forms or manufacturing processes in the PMF application shall be applicable for the inspection scope.
    - (ii) Full Chinese or English translations of the GMP inspection report, along with the full original report.
  - (3) List of major changes to the applied dosage forms/ manufacturing processes (including premises, facilities, equipment, and manufacturing process) after said inspection to the date of submission.
2. Applicants may submit the following alternative document to substitute the Validation and Qualification documents:
  - (1) Original or hard copy of the Certificate of pharmaceutical products (CPP) from EMA or A-10 countries (Germany, US, UK, France, Japan, Switzerland, Canada, Australia, Belgium, and Sweden.): It should be within two years from the issuance date.
  - (2) Validation and qualification summary: The original copies with signed with wet signature or electronically by the responsible person shall be submitted. The summary shall include information about the overview for validation and qualification in the manufacturing site [including utility (HVAC, water, and process-related gases), equipment and facilities, computerized systems, cleaning validation, etc.].
  - (3) Letter of explanation shall be original copies signed with wet signature or electronically. The contents shall 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, the dossiers required in different situations are 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 copies of letter of explanation signed with wet signature or electronically by responsible person, 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 description of changes related to the Dosage form/product/manufacturing process applied in the application effected since the last PMF application.
  - (ii) Photocopy of the previous GMP approval letter issued by Taiwan FDA
  - (iii) The latest SMF (electronic file)
  - (iv) PMF Inspection Forms A, B, C and relevant document.
  - (v) Taiwan FDA reserves the right to request further submissions in cases where the documentation is incomplete or when otherwise necessary.
- (2) Applicants intending to cite an GMP approval letter hold by others (Including approval letters of overseas on-site inspection, PMF review, or follow-up inspection) when applying for a PMF review for same 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 will be issued if said documentation is reviewed and found in compliance, and the conditions of the citation will be remarked in the approval letter.
  - (i) Original copy of the Letter of Explanation signed with wet signature or electronically by responsible person, 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 signed with wet signature or electronically by responsible person, 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 latest SMF (electronic file)
- (3) Applicants intending to cite an GMP approval letter hold by others (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 signed with wet signature or electronically by responsible person, 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 description of changes effected since the last PMF application.
  - (ii) Authorization letter from the original holder of the GMP approval letter signed with wet signature or electronically by responsible person, 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 latest SMF (electronic file)
  - (v) PMF Inspection Form A, B, C and relevant document.
  - (vi) Taiwan FDA has the rights to request more relevant documents if considered necessary.
4. For applicants to apply PMF for expansion of manufacturing site, the dossiers are required as following:
- (1) PMF Inspection Form A, B, C and relevant document. For Form-C, only the item which are marked with asterisk are required, and the relevant documents shall be enclosed.
  - (2) Photocopy of the previous GMP approval letter of the site intend to apply for expansion of manufacturing.
  - (3) Taiwan FDA has the rights to request more relevant documents if considered necessary.

## **C. Administrative Requirements that Should Be Followed when applying for PMF Review of Foreign Pharmaceutical Manufacturers**

- I、Legalization requirements: Based on Article 5, Paragraph 2 of the Regulations of Medicament Manufacturer Inspection, the PMF application dossier for submission shall meet one of the following requirements:
- 1. Plant Master File (PMF) and Site Master File (SMF), which are to be certified by the hosting competent 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 of documents from the hosting competent authority or certified photocopy of the said documents certified by the hosting competent authority or chamber of commerce in the country of origin proving that the manufacturer is in compliance with local pharmaceutical GMP standards. (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 and indication of the case number that the original copies were submitted.)
  - 3. Original copy of Certificate of Pharmaceutical Product (CPP) from the hosting competent authority or certified photocopy of the said documents certified by the

hosting competent authority or chamber of commerce in the country of origin clearly stating that said manufacturer is in compliance with local pharmaceutical GMP standards. (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 and indication of the case number that the original copies were submitted.)

4. If the paper based GMP certification is no longer available in the country of origin, or the drug product is contracted manufacturing, the statement of license holder of the imported drug shall be submitted explaining why the GMP certification and CPP is not available. Therefore, the applicants could submit the original copy or certified photocopy of the CPP issued by any one of the A-10 countries, EMA, or by the hosting competent 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 PMF for Quote review and for expansion of manufacturing site, legalization of the dossier is not required.

II 、 Authorization Letter:

1. The original Letter of Authorization whereby the foreign manufacturer authorizes the Taiwan agents (pharmaceutical company) to submit PMF applications. The authorization letter shall be signed with wet signature or electronically by the responsible person of the foreign manufacturer.
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, the Authorization Letter from the manufacturer and the Authorization Letter from the Taiwan agents who holds the previous GMP approval letter shall be enclosed.

III 、 The latest electronic copy of Site Master File (SMF): SMF shall be written in Chinese or English. The format and contents of the SMF shall complied with “EXPLANATORY NOTES FOR PHARMACEUTICAL MANUFACTURERS ON THE PREPARATION OF A SITE MASTER FILE」 (PE008-40)” announced by PIC/S; Otherwise, the applicants shall compile and assemble the SMF dossier accordingly in order to achieve successful manufacturing site registration.

**D. Dossier should be submitted when applying for an appeal:**

- I 、 Supplemental document for the deficiency listed on the rejection letter.
- II 、 If there is correction/deletions of dosage form or manufacturing process, the updated Application Form for Plant Master File (PMF) Review for Foreign Pharmaceutical manufacturers Form A shall be submitted.

## **E. Precautions to Documents to be submitted :**

- I. The electronic dossiers could be delivered via compact disk (CD), cloud drive and email, etc.
- II. 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.
- III. 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.
- IV. Documents that are written in language other than English shall be translated into Chinese or English, and the accuracy of the contents of translated documents shall be confirmed.
- V. The documents shall be signed by responsible personnel from quality assurance department or related department.
- VI. Forms A, B, and C of the PMF for Foreign Pharmaceutical manufacturers shall be completed and signed off by the Taiwan agents or the quality assurance personnel or relevant responsible person at the manufacturing site, and the page numbers or appendixes of corresponding documents submitted for review are to be specified in the form for each review item. The documents asked for in the Checklist are to be enclosed as well.
- VII. The dossier could be submitted via electronic means with an exception of certified document (ex, SMF, GMP, CPP). However, if the electronic GMP or CPP are issued from the authority of country of origin and could be authenticated through a web link, the hard copy document is not required for submission.
- VIII. The dossier, for example, the letter of Explanation, validation and qualification summary, authorization letter, list of major changes to the applied dosage forms/manufacturing process, Form C1~C5, shall be signed with wet signature or electronically by the responsible person of manufacturer.
- IX. In case a pharmaceutical company 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.

## **F. Precautions to PMF Application:**

- I. For each application, only one manufacturer site at a single address shall be applied for.
- II. For each application, up to 3 dosage forms/products/manufacturing processes shall be applied for. 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.
- III. The applicant must hold business permit license; if necessary, it may be requested that such business permit license be enclosed.
- IV. The applicants shall **completely and correctly** fill out the following information in Form A: **description of application [orphan drug, non-sterile products, sterile products (aseptic preparation or terminal sterilization; Large volume parenteral (LVP) or small volume parenteral (SVP) products) or biological medicinal products] and application mode**

(Simplified review, full review or with alternative dossiers to substitute the documents of qualification and validation, quote review).

- V. Review fees are charged in accordance with Standards of Review Fees for the Registration of Western Medicines as most recently announced by the MOHW. Once the case goes through the review process, no review fees shall be refunded.
- VI. If the applicants do not submit PMF document in accordance with **Notices for the Plant Master File (PMF) Application**, they will be notified through Taiwan FDA official letter to re-submit the application document.
- VII. **The PMF application dossier will not be returned to the applicants.**

## G. Appendix

- I. Application Form for Plant Master File (PMF) Review for Foreign Pharmaceutical manufacturer\_Form A
- II. Checklist of Preparing submission dossiers of Plant Master File for Foreign Pharmaceutical manufacturers\_Form B
- III. Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer\_Form C - 1 Documents in Common review
- IV. Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer\_Form C -2 Sterile medicinal products/ **ATMPs/biological active medicinal substances and products** (simplified review)
- V. Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer\_Form C -3 All products (Full review)
- VI. Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer\_Form C -4 **ATMPs/biological active medicinal substances and products**
- VII. Plant Master File (PMF) Checklist for Foreign Pharmaceutical manufacturer\_Form C -5 Validation and Qualification