

# Master File System for Drug Substances, etc.

## 1. Master File (MF) System

Master file (hereinafter referred to as “MF”) system for drug substances, etc. allows Japanese or foreign manufacturers of drug substances etc. to voluntarily register the data concerning the quality/manufacturing methods of their drug substances, etc. used for manufacture of drugs (pharmaceutical products) to the review authority.

The registered data is quoted as the necessary information for an approval review of the drug (pharmaceutical product) in which the drug substance is used.

Japanese or foreign drug manufacturers can register in MF by submitting the specified forms (application form for MF registration, application for change in registered items, minor change notification, etc.) to Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) in accordance with the procedures described in the Enforcement Regulations for the Pharmaceutical Affairs Law (hereinafter referred to as “Regulations”). (See Article 72, 79, and 81 of the Regulations (\*1); “Documents to be Submitted”).

Foreign manufacturers of drug substances, etc. can also apply for MF registration. In order to apply for MF registration, it is necessary for a foreign manufacturer to obtain a foreign manufacturer accreditation (\*2) because the accreditation category, the accreditation number, and the date of accreditation of the foreign manufacturing site must be entered in the MF registration application form.

In addition, when a foreign manufacturer applies for the accreditation and MF registration, the manufacturer codes for the foreign manufacturer and for the manufacturing site are required. Thus the both codes must be registered in advance.

When a foreign manufacturer applies for MF registration, a person to undertake the duties concerning the relevant MF registration with an address within Japan (in-country caretaker of drug substances) shall be appointed (Article 72 of the Regulations).

MF registration application form, notification, and other related documents shall be written in Japanese (Article 283 of the Regulations).

(\*1) The basic items related to MF registration are explained in “Guideline on Utilization of Master File for Drug Substances, etc.” (PFSB/ELD Notification No. 0210004, dated February 10, 2005) as well as in the related Articles of the Regulations.

(\*2) A manufacturer (foreign manufacturer) plans to manufacture drugs, medical devices, or quasi-drugs to be exported to Japan in the foreign country accredited under the Foreign Manufacturer Accreditation (Article 13-3 of the Pharmaceutical Affairs Law) can be accredited by the Minister of Health, Labour and Welfare. The accreditation is given to each manufacturing site according to the category.

## 2. Items for MF Registration

- 1) Drug substances, intermediates, and pharmaceutical product materials (materials of pharmaceutical products with special dosage form, etc.)  
However, the drug substances, intermediates and pharmaceutical product materials used in OTC drugs (excluding OTC drugs with new active ingredients) are not appropriate for registration in MF, as it is considered that their quality and safety are already established even in the existing specifications and test methods.
- 2) New excipients and new pre-mix excipients with a different composition ratio from the existing ones
- 3) Materials for medical devices
- 4) Containers/packaging materials

Other than the above 1) to 4), country of origin and data on inspection/certification (including the new TSE data based on TSE Data Number) of bovine-derived raw-materials, and the items considered appropriate to quote their MF registration numbers under approval reviews can also be registered. MF registrations of the items in 3) "Materials for medical devices" and the items related to medical devices among 4) "Containers/packaging materials" are currently under consideration.

## 3. MF Registration

- 1) Items that can be registered in MF
  - a) Name of drug substances, etc.
  - b) Name of manufacturing site and other information
  - c) Information about ingredients and their quantity or nature of drug substances, etc.
  - d) Manufacturing method, manufacturing process control, and quality control test
  - e) Specifications and test methods
  - f) Stability tests, storage method, and expiry date
  - g) Non-clinical study (mainly for new excipients)
  - h) Information on safety
  - i) Category of license for manufacturing operation or accreditation of foreign manufacturer
  - j) Number of license for manufacturing operation or number and date of accreditation of foreign manufacturer
  - k) Name and address of in-country caretaker if the applicant for the MF registration is manufacturing drug substances, etc, outside Japan
- 2) Forms for MF registration information

At the time of MF registration, PMDA checks whether it is written in the correct format, e.g., minimum required items are included or data (Module 3: in English

or Japanese) is attached.

MF registered items shall be regarded as a part of information which should be described in an approval application form and attached documents (“Data on Manufacturing Methods and Specifications/Test Methods”, “Data on Stability”, and “Data on Pharmacological Action”) for a drug (pharmaceutical product) and therefore, the MF registered items are also reviewed at the time of the approval review for the drug (pharmaceutical product) quoting the MF.

### 3) Fee and submission of the application for MF registration

No fee shall be charged for MF registration. When registering for MF, the registration application form and attached documents shall be submitted to Administration Division 1, Office of Review Administration, PMDA (see “Documents to be Submitted”).

When a foreign drug manufacturer registers for MF, the cover page (seal) of application form can be completed with its name and address written in their own language and a handwritten signature of the representative is accepted instead of seal.

Application form must be submitted with the handwritten signature of the representative of the foreign drug manufacturer. Application form with the signature and seal of their in-country caretaker is not acceptable. Documents such as “Application for change in registered items” and “Minor change notification” described in the following section shall also be handled in the same manner. In addition, “Replacement order” and the statement required for “Minor change notification” cannot be accepted with the signature and seal of the in-country caretaker.

#### a) Application Form for MF Registration

For a new registration, application form for MF registration (addressed to the Chief Executive of PMDA) prepared in duplicate (photocopy of the original sheet is not acceptable) using the Form No. 42 of the Regulations ([Attachment 1 \(PDF\)](#)), flexible disk (hereinafter referred to as “FD”), and attached documents to verify the registration items described under b) shall be submitted.

In addition, please note the followings when submitting the application form.

- In the name of drug substance, etc. section, both of generic name and commercial name shall be stated.
- Information that should be disclosed to the applicants or approval holders of drugs (pharmaceutical products) shall also be written in the registration application form.
- The data attached to the approval application of a drug substance

under the previous Pharmaceutical Affairs Law can be reused for the MF registration application as the supporting data. However, please submit new information obtained after the approval of the drug substance under the previous law, or documents requested by the review authority other than those already attached.

- It is necessary to prepare the registration application form in FD. Please prepare the descriptions according to “Guidance on Handling of Applications Submitted on Flexible Disk etc.” (PFSB/ELD Notification No. 0331023, dated March 31, 2005).
- For the summary, etc. of the drug substance manufacturing methods; please refer to “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).
- For questions regarding the operation of the application software, please send your specific questions by fax or e-mail to Helpdesk (FAX: 03-3507-0114, E-mail: fd\_iyaku@pmda.go.jp).
- If license for manufacturing operation or accreditation for the manufacturing site of the drug substance, etc. is in progress, MF registration (issuance of the number) cannot be processed until the certification/accreditation is obtained. Please allow enough time for application.

b) Attached document (registration data)

Data to be attached to the registration application form (registration data) shall be prepared by using the following forms.

- I) For pharmaceuticals excluding generic drugs and OTC drugs, Common Technical Document (hereinafter referred to as “CTD”) attached to “Guideline on Preparing Data Attached to Application Form for Approval Application of Manufacture or Import of a New Pharmaceutical” (PFSB/ELD Notification No. 899, dated June 21, 2001) shall be used.

Submission of the data equivalent to Module 2 of CTD (Summary of the Attached Data) is not required at the time of MF registration. The timing of submission shall be instructed by PMDA reviewers in charge of the approval review for the drug (pharmaceutical product). Electronic forms for MF registration shall comply with “Electronic Specifications on Common Technical Documents” (PFSB/ELD Notification No. 0604001, dated June 4, 2003 issued by Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau).

- II) For drug substances used in generic drugs, “Approval Application of

Pharmaceuticals” (PFSB Notification No. 0331015, dated March 31, 2005) shall be followed.

- III) OTC drugs and those among “New excipients and pre-mix excipients with a different composition ratio from the existing ones” and “Containers/packaging materials”, the drug substance used only for OTC shall follow the pattern specified in “Application for Approval of Non-Prescription Pharmaceuticals” (PFSB Notification No. 0827003, dated August 27, 2003).

#### **4. Issuance and Publication of MF Registration Certificate**

After the registration, a MF registration certificate in the Form No. 43 of the Regulations and a duplicate of the registration application form shall be issued to the MF registrant. The registration certificate does not include any confidential information.

At a later date, the MF registration number, registration date, date of the change in registered items, name and address of the registrant, the name of registered item, and the registration category will be posted in the PMDA homepage.

#### **5. Information to be Disclosed to Applicants and Approval Holders of Drugs (Pharmaceutical Products)**

[Attachment 4 \(PDF\)](#) describes the examples of the MF registered information to be disclosed to the applicants or approval holders of drugs (pharmaceutical products).

The information that should be disclosed shall also be written in the registration application form. Applicants of drugs (pharmaceutical products) who quote the information registered in MF can include it in the approval application form for the marketing authorization.

#### **6. Changes in MF Registered Items**

- 1) If changes have to be made to registered items, an application for change in the registered items or minor change notification shall be submitted. When changing the registered items, it is necessary for the MF registrant to discuss in advance with the approval holders of drugs (pharmaceutical products) who utilize the MF.

Changes only in the attached documents cannot be filed.

If the changes in the items in MF will substantially alter the nature of drug substances, etc., please note that a new MF registration form, not a change of registration must be submitted. In this case, for pharmaceutical products that use the relevant MF, it is necessary to submit a partial change approval application so that the newly registered MF can be quoted for these products.

However, in case changes in the items are significant and the changed items are not regarded as being the same, the approval holders of pharmaceutical products should submit new approval application. Therefore, for significant changes, please consult with PMDA in advance.

2) Application for changes in MF registration

a) Documents to be submitted

When applying for changes in MF registration, submit an original sheet (for the attention of Chief Executive of PMDA) and a duplicate sheet (photocopy of the original sheet is not acceptable) of the application for change in the registered items in the Format No. 46 of the Regulations ([Attachment 2 \(PDF\)](#)), FD, table to compare the new and old items, original registration certificate, data concerning the content of the changes in registered items, and the return envelope for the MF registration certificate. When making changes to items registered in MF, MF registrant shall enter in the column for remarks of application form for change in the registered items in MF, the commercial name, the approval number, the name and address of the marketing authorization holders (the name and location of the main business sites if the licensed marketing approval holders are corporate entities) for all pharmaceutical products that quote the relevant MF, as well as whether a partial change approval application or minor change notification was applied for each of the drugs (pharmaceutical products). They can be listed in a separate sheet (see "Documents to be Submitted").

b) In-advance Notification to Approval Applicants of Drugs (Pharmaceutical Products)

When making changes to the registered items, MF registrant shall notify in advance the applicants or approval holders of the drugs (pharmaceutical products) who quote the MF. The approval holders of the drug (pharmaceutical product) are required to submit partial change approval application or minor change notification depending on the content of the change.

c) Partial Change Approval Application for Drug (Pharmaceutical Product)

If MF under change is quoted in the already approved drugs (pharmaceutical products), the approval holders of all these drugs (pharmaceutical products) are required to submit partial change approval applications in accordance with the application for change in the registered items.

Review for a change to the registered items commence only after all the partial change applications for the necessary relevant drugs have been submitted. When these partial changes are approved, the MF registration certificate for the change with revised registration date, etc. will be issued by PMDA.

When making changes to the items in the MF, but the existing items are still used for the already approved drugs, it shall be required to specify the items. For example, when adding a manufacturing method, the MF registrant shall be requested to number both of the existing and added manufacturing methods so that it can be specified that which manufacturing method is used for pharmaceutical products approved by quoting the MF. In this case, marketing authorization holders of drugs (pharmaceutical products) shall be required to submit partial change approval applications for the products with added items, and minor change notifications for pharmaceutical products with existing items.

### 3) Minor change notification

#### a) Scope of minor change notification

If there is a minor change in the MF registered items, a minor change notification in Form No. 47 of the Regulations ([Attachment 3 \(PDF\)](#)) shall be submitted. The scope of the minor changes is other than those described below (Article 80 of the Regulations).

- I) Changes in the manufacturing methods, etc. affecting the nature, characteristics, performance, and safety of the drug substance, etc.
- II) Deletion of the items listed in the specifications and test methods or changes in the specification
- III) Changes in the inactivation or removal method for pathogenic factors
- IV) The changes, other than those described in I) to III), which may affect the quality, efficacy, or safety

The registrants shall judge personally whether or not the changes in the registered items affect the quality, etc. of the products referring to “Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law” (PFSA/ELD Notification No. 0210001, dated February 10, 2005).

For minor changes in the registered items, the MF registrant shall submit a minor change notification (1 original sheet), table to compare the new and old items, and statement indicating that the adequate validation and change control have been performed to PMDA within 30 days after the changes are made (after shipping the drug substance, etc. manufactured with the changes) (see “Documents to be Submitted”).

When submitting the minor change notification, the MF registrant shall notify and provide necessary information to the applicants and approval holders of the drugs (pharmaceutical products) that utilize the MF.

#### b) Handling of drugs (pharmaceutical products) related to minor changes in

## MF registered items

Basically, approval holders are not required to file partial change approval applications for the drugs (pharmaceutical products) related to minor changes in the MF registered items. However, the approval holders are advised to obtain the relevant information from the MF registrant according to the contract between them, etc.

### 4) Simple consultation for MF registration application

PMDA provides "Simple consultation" for the matters related to the MF registration application described in PSFB/ELD Notification No. 0210004, dated February 10, 2005 and PMDA Notification No. 1101014, dated November 1, 2005.

If the drug (pharmaceutical product) for which "consulted MF" is a new drug, the consultation classification is "writing applications for new drugs". For a generic drug, the classification is "generic drugs".

Examples of the consultation are as follows:

- Whether or not the change is regarded as a partial change to manufacturing methods, etc. in the approval application or MF registration application:
  - a) Validity of the evaluation protocol performed for the change
  - b) Appropriateness of the judgment that the change imposes no obvious impact on the quality based on the result of the test conducted according to the protocol
  - c) Other items that require consultation when changing the section of manufacturing methods
- Whether a significant change in the MF registered items is subject to a partial change approval application or a new application.

### 5) Handling of drug substances, etc. registered using "abbreviated descriptions"

PSFB/ELD Notification No. 0310002 dated March 10, 2005 states that the description of the drug substance for which the MF registration application filed by using "abbreviated descriptions" by March 31, 2005, shall be revised to the description suitable under the Revised Pharmaceutical Affairs Law (so-called "detailed descriptions", without omission) by March 31, 2010. This change shall be made as "Application for change in registered items". In this case, the data described in 3. 3) b) which verifies the items of the detailed description shall also be submitted.

If the change in the "abbreviated descriptions" is not minor, the registered items shall be changed by submitting application for change in registered items. In this case, please describe concretely the change in the remarks section of the application form or attach a table to compare the new and old contents.

In both cases, the application shall be prepared to ensure the registered items comply with the Revised Pharmaceutical Affairs Law.

## **7. Approval Application and Approval Review for Drugs (Pharmaceutical Products) that quote MF**

- 1) Approval application for drugs (pharmaceutical products) that quote MF
  - a) When the MF registration is completed

In the manufacturing methods section of approval application form, enter the name of the drug substance, etc., its MF registration number, latest issue date of the registration certificate, and the number of times the registration certificate was revised. Enter “1” for the first registration, and add 1 each time the registration is revised. However, the number does not change for the minor change notification. If more than one manufacturing method is registered in one MF, also specify which method is used.

Example: “... using the drug substance A (MF Registration Number: XXXXXXXXXXX (YYYY/MM/DD, Version Number X of MF Registration), Method B) ...”

When applying for the approval of a drug (pharmaceutical product), a copy of the MF registration certificate and a copy of the contract with the MF registrant for utilization of the MF shall be regarded as a part of documents to be attached to the approval application form, such as “Data on Manufacturing Methods and Specifications/Test Methods” and “Data on Stability”.

- b) When the MF registration is not yet completed

Even if the MF registration is not yet completed, if the MF registration application has been submitted, approval application for a drug (pharmaceutical product) can be submitted, using the system receipt number assigned at the time of application, and indicating that “MF registration is in progress” in the application form.

When the MF registration is complete (registration number is issued), contact the Office of Review Administration immediately and request to replace the approval application. The approval review for the drug (pharmaceutical product) will actually commence only after the approval application concerning the MF number is replaced.

- 2) Approval review for drugs (pharmaceutical products) that quote MF

In the approval review process for a drug (pharmaceutical product), if an inquiry regarding the quoted MF registered items is necessary, PMDA directly contacts the MF registrant (if the MF registrant is a foreign manufacturer, the inquiry will be made through the in-country caretaker).

As a result of the review, if there are any changes to the registered items, the MF registrant is required to immediately submit application for change in the registered items or minor change notification. In the case of change in the registered items, PMDA issues the registration certificate related to the change at the time the related drug is approved. However, application for change in the registered items cannot be filed for changes only in the already submitted attached document.

Depending on the registered item to be changed and its content (for example, when the change may affect the nature of the drug substance, etc.), a new MF registration application, not an application for change in the registered items, may have to be submitted.

## **8. Duties of In-Country Caretakers for Drug Substances, etc.**

MF registration application forms, notifications, and other related documents have to be written in Japanese (Article 283 of the Regulations), and thus, in-country caretakers for drug substances, etc. play important roles in the related administration procedures.

In the process of approval review for a drug (pharmaceutical product), PMDA may inquire about the MF registered items. If the MF registrant is a foreign manufacturer, PMDA will make the inquiry through its in-country caretaker without directly contacting the manufacturer. Thus the in-country caretaker shall act as the contact for the inquiries and be engaged in the related administrative procedures and control after the registration.

In order to ensure the smooth operation of these duties, the in-country caretaker should fully discuss with the MF registrant so as to decide on important items in advance.

It is possible to change in-country caretakers. Please submit a minor change notification if there is a change in the in-country caretaker.

## **9. Transfer of Registration**

When transferring MF registration to a third party, the procedure specified in Article 83 of the Regulations shall be taken. In the transferring procedure, it is necessary to submit a copy of the contract between the transferor and transferee that specifies that the verification data for the registered items and all the documents relating to the registration. Statement indicating that there are no changes in the manufacturing site and other manufacturing technology, etc. is also required.

### **Notifications etc. Related to MF System**

- “Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law” (PF/SB/ELD Notification No.

0210001, issued by Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated February 10, 2005)

- “Guideline on Utilization of Master File for Drug Substances, etc.” (PFSB/ELD Notification No. 0210004, issued by Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated February 10, 2005)
- “Q&A on the Master File (MF) System, Part 1” (Administrative Notice issued by Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated July 28, 2005)
- “Q&A on the Master File (MF) System, Part 2” (Administrative Notice issued by Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 20, 2005)

## **Documents to be Submitted**

### **1) Application for Registration of MF for Drug Substance, etc. (Registration Application) ...Article 72 of the Enforcement Regulations of the Pharmaceutical Affairs Law**

- Application Form for Registration of Master File for Drug Substances, etc. (total of 2 sheets consisting of original and duplicate sheets: photocopy of the original sheet is not acceptable for the duplicate) (Attachment 1 (PDF))
- FD or CD-R (containing the data prepared according to the FD application system, the same hereinafter).
- Attached documents
  - Drugs (excluding generic drugs and OTC drugs): see PFSB Notification No. 899 dated June 21, 2001
  - Generic drugs: see PFSB Notification No. 0331015 dated March 31, 2005
- Return envelope for the registration certificate and the duplicate sheet of the application form

### **2) Application for Changes in the Registered MF for Drug Substance, etc. (Application for changes in the registered items) ...Article 79 of the Enforcement Regulations of the Pharmaceutical Affairs Law**

- Application Form for Change in Registered Master File for Drug Substance, etc. (total of 2 sheets consisting of original and duplicate sheets: photocopy of the original sheet is not acceptable for the duplicate) (Attachment 2 (PDF))
- FD or CD-R

- Attached documents (also required when changing from “abbreviated descriptions” to “detailed descriptions”)
  - Drugs (excluding generic drugs and OTC): see PFSB Notification No. 899, dated June 21, 2001
  - Generic drugs: see PFSB Notification No. 0331015, dated March 31, 2005
- Return envelope for the registration certificate and the duplicate sheet of the registration application form
- Original registration certificate
- Others (comparison table for the old and new items, etc.)
  - \* Registration number of a MF registration certificate does not change as a result of the changes in the registered items. However, a new registration certificate will be issued due to the registration date change. Thus the registration certificate before the change (original) should be submitted.
  - \*\* Application for change in the registered items cannot be filed for the changes only in the already submitted attached document.

**3) Minor Change Notification for MF for Drug Substances, etc. (Minor changes in the registered items) ...Article 81 of the Enforcement Regulations of the Pharmaceutical Affairs Law**

- Minor Change Notification for Master File for Drug Substances, etc. (1 original sheet) (Attachment 3 (PDF))
- FD or CD-R
- Attached document (if necessary)
- Statement (to indicate adequate validation and change control have been performed)
- Others (comparison table for the new and old items, etc.)
  - \* When a minor change notification is filed, the registration number of the MF registration certificate and the issuance date remain the same (a new registration certificate will not be issued).
  - \*\* Notification cannot be filed for the minor changes only in the already submitted attached document. Notification cannot be filed for matters other than those required under the instruction of PMDA while registration application or application for changes is in process.

**宣誓書**  
**Statement**

このたび提出いたしました軽微変更届出に記載した変更は、適切なバリデーション、変更管理を実施したことを宣誓します。

This is to declare that adequate validation and change control have been performed for the change described in the Minor Change Notification.

平成 年 月 日  
YYYY/MM/DD

住所

Address

氏名 (届出者の氏名) (印)

Name (Name of the person notified the change) (Seal)

独立行政法人医薬品医療機器総合機構理事長 殿

To: Chief Executive of Pharmaceuticals and Medical Devices Agency

都道府県知事 殿

To: Prefectural Governors

**(Attachment 1)**

様式第四十二（第七十二条関係）

Form No. 42 (in relation to Article 72)

原薬等登録原簿登録申請書  
Application for Registration of Master File for Drug Substances, etc.

登録区分 (原薬等の種類) Classification of Registration (Type of Drug Substances, etc.)		
原薬等の名称 Name of Drug Substances, etc.		
製造所の名称 Name of Manufacturing Site		
製造所の所在地 Address of Manufacturing Site		
成分及び分量又は本質 Ingredients and their Quantity or Nature		
製造方法 Manufacturing Method		
規格及び試験方法 Specifications and Test Methods		
安定性に関する情報 Information on Stability		
貯蔵方法及び有効期間 Storage Method and Expiry Date		
安全性に関する情報 Information on Safety		
製造業の許可区分又は 外国製造業者の認定区分 Classification of License for Manufacturing Operation or Accreditation of Foreign Manufacturer		
製造業の許可番号又は 外国製造業者の認定番号及び年月日 Number of License for Manufacturing Operation or Number and Date of Accreditation of Foreign Manufacturer		
原薬等国内管理人 In-Country Caretaker	氏名 Name	
	氏名 Address	
備考 Remarks		

上記により、原薬等登録原簿の登録を申請します。  
I hereby apply for the registration of Master File for drug substances, etc.

年 月 日  
Year Month Day

住所 Address (法人にあつては、主たる事務所の所在地  
Address of head office if undersigned is a corporate body )

氏名  
Name

法人にあつては、名称及び代表者の氏名  
Name of corporation and its representative if undersigned  
is a corporate body

㊞ Seal

独立行政法人医薬品医療機器総合機構理事長 殿  
To: Chief Executive of Pharmaceuticals and Medical Devices Agency

(注意)

(Instruction for filling out the form)

- 1 用紙の大きさは、日本工業規格 A4 とすること。  
1 Print the form on A4 (Japanese Industrial Standards-JIS) paper.
- 2 この申請書は、正副 2 通提出すること。  
2 Submit both the original and a copy of the completed form.
- 3 字は、墨、インク等を用い、楷書<sup>かい</sup>ではっきりと書くこと。  
3 Use 'sumi' ink or ordinary ink for writing, and write Japanese letters clearly in standard (square) style.
- 4 登録区分欄には、第 44 条各号のいずれに該当するかを記載すること。  
4 Specify in the section "Classification of Registration" which paragraph of Article 44 applies.
- 5 製造業の許可区分又は外国製造業者の認定区分欄及び製造業の許可番号又は外国製造業者の認定番号欄には、当該製造業者が法第 13 条の許可又は法第 13 条の 3 の認定を受けている場合に記載すること。  
5 Fill out the section "Classification of License for Manufacturing Operation or Accreditation of Foreign Manufacturer" and "Number of License for Manufacturing Operation or Number and Date of Accreditation of Foreign Manufacturer" only when the applicant has been granted a license under Article 13 or a accreditation under Article 13(3).
- 6 製造方法欄、規格及び試験方法欄、安定性に関する情報欄、貯蔵方法及び有効期限欄及び安全性に関する情報欄に当該記載事項のすべてを記載することができないときは、同欄に「別紙のとおり」と記載し、別紙を添付すること。  
6 If all particulars do not fit in any of "Manufacturing Method," "Specifications and Testing Methods," "Information on Stability," "Storage Method and Expiry Date," or "Information on Safety," write "As per annex" in the section and attach a separate sheet.
- 7 原薬等国内管理人欄は、第 72 条第 2 項の規定により原薬等国内管理人が選任されている場合に記載すること。  
7 Fill out the section "In-Country Caretaker" only when an in-country caretaker for drug substances, etc., has been appointed in pursuant to Article 72, Paragraph 2.
- 8 原薬等を外国において製造する者にあつては、外国語により申請者の住所及び氏名を並記すること。また、署名をもって押印に代えることができるものとする。  
8 For foreign manufacturers who produce drug substances, etc., outside of Japan, include the name and address of the applicant in the language used in the applicant's country as well. A signature may be substituted for a seal.

**(Attachment 2)**

様式第四十六（第七十九条関係）  
Form No. 46（in relation to Article 79）

原薬等登録原簿変更登録申請書  
Application for Change in Registered Master File for Drug Substances, etc.

登録区分 (原薬等の種類) Classification of Registration (Types of Drug Substances, etc.)			
原薬等の名称 Name of Drug Substances, etc.			
登録番号及び登録年月日 Registration Number and Date			
製造所の名称 Name of Manufacturing Site			
製造所の所在地 Address of Manufacturing Site			
許可又は認定の区分 Classification of License or Accreditation			
許可又は認定番号及び年月日 Number and Date of License/Accreditation			
変更予定年月日 Scheduled Date of Change			
変更内容 Content of Change	事項 Information to be Changed	変更前 Before Change	変更後 After Change
備考 Remarks			

上記により、原薬等登録原簿の変更の登録を申請します。

I hereby apply for the registration of change in registered Master File for drug substances, etc.

年 月 日  
Year Month Day

住所  
Address

〔法人にあつては、主たる事務所の所在地  
Address of head office if undersigned is a corporate body〕

氏名  
Name

〔法人にあつては、名称及び代表者の氏名  
Name of corporation and its representative if undersigned is a corporate body〕

⑥ Seal

独立行政法人医薬品医療機器総合機構理事長 殿  
To: Chief Executive of Pharmaceuticals and Medical Devices Agency

(注意)

(Instruction for filling out the form)

- 1 用紙の大きさは、日本工業規格 A4 とすること。
- 1 Print the form on A4 (Japanese Industrial Standards-JIS) paper.
- 2 字は、墨、インク等を用い、楷書ではっきりと書くこと。
- 2 Use 'sumi' ink or ordinary ink for writing, and write Japanese letters clearly in standard (square) style.
- 3 登録区分欄には、第 44 条各号のいずれに該当するかを記載すること。
- 3 Specify in the section of "Classification of Registration" which paragraph of Article 44 is applicable.
- 4 許可又は認定の区分欄は、当該製造業者が法第 13 条の許可又は法第 13 条の 3 の認定を受けている場合に記載すること。
- 4 Fill out the section "Classification of License or Accreditation" only when the manufacture concerned has been granted a license under Article 13 of the Law or a accreditation under Article 13 (3) of the Law.
- 5 変更内容欄に変更事項のすべてを記載することができないときは、同欄に「別紙のとおり」と記載し、別紙を添付すること。
- 5 If all the particulars to be amended do not fit in the section "Content of Change" write "As per annex" in the section and attach a separate sheet.
- 6 原薬等国内管理人が選任されている場合には、備考欄に原薬等国内管理人の氏名（法人にあつては、名称及び代表者の氏名）及び住所（法人にあつては、主たる事務所の所在地）を記載すること。
- 6 Specify in the section of "Remarks" the name of the in-country caretaker (in the case of corporate body, the name of the body and the name of the representative) and the address of the caretaker (the address of the head office, in the case of corporate body).
- 7 原薬等を外国において製造する者にあつては、外国語により申請者の住所及び氏名を並記すること。また、署名をもって押印に代えることができるものとする。
- 7 As for foreign manufacturers who produce drug substances, etc., outside of Japan, include the name and address of the applicant in the language used in the applicant's country as well. The signature can substitute for the seal.

**(Attachment 3)**

様式第四十七（第八十一条関係）  
Form No. 47 (in relation to Article 81)

原薬等登録原簿軽微変更届書  
Minor Change Notification for Master File for Drug Substances, etc.

登録区分 (原薬等の種類) Classification of Registration (Types of Drug Substances, etc.)			
原薬等の名称 Name of Drug Substances, etc.			
登録番号及び登録年月日 Registration Number and Date			
製造所の名称 Name of Manufacturing Site			
製造所の所在地 Address of Manufacturing Site			
許可又は認定の区分 Classification of License or Accreditation			
許可又は認定番号及び年月日 Number and Date of License/Accreditation			
変更内容 Content of Change	事項 Information to be Changed	変更前 Before Change	変更後 After Change
変更年月日 Date of Change			
備考 Remarks			

上記により、原薬等登録原簿の軽微変更の届出をします。  
I hereby notify a minor change in Master File for drug substances, etc.

年 月 日  
Year Month Day

住所  
Address

（法人にあつては、主たる事務所の所在地  
Address of head office if undersigned is a corporate body）

氏名  
Name

（法人にあつては、名称及び代表者の氏名  
Name of corporation and its representative if undersigned  
is a corporate body）

Ⓢ Seal

独立行政法人医薬品医療機器総合機構理事長 殿  
To: Chief Executive of Pharmaceuticals and Medical Devices Agency

(注意)

(Instruction for filling out the form)

- 1 用紙の大きさは、日本工業規格 A4 とすること。
- 1 Print the form on A4 (Japanese Industrial Standards-JIS) paper.
- 2 字は、墨、インク等を用い、楷書ではっきりと書くこと。
- 2 Use 'sumi' ink or ordinary ink for writing, and write Japanese letters clearly in standard (square) style.
- 3 登録区分欄には、第 44 条各号のいずれに該当するか記載すること。
- 3 Specify in the section of "Classification of Registration" which paragraph of Article 44 is applicable.
- 4 許可又は認定の区分欄は、当該製造業者が法第 13 条の許可又は法第 13 条の 3 の認定を受けている場合に記載すること。
- 4 Fill out the section "Classification of License or Accreditation" only when the manufacture concerned has been granted a license under Article 13 of the Law, or a accreditation under Article 13 (3) of the Law.
- 5 変更内容欄に変更事項のすべてを記載することができないときは、同欄に「別紙のとおり」と記載し、別紙を添付すること。
- 5 If all the particulars to be amended do not be fit in the section of "Content of Change" write "As per annex" in the section and attach a separate sheet.
- 6 原薬等国内管理人が選任されている場合には、備考欄に原薬等国内管理人の氏名（法人にあつては、名称及び代表者の氏名）及び住所（法人にあつては、主たる事務所の所在地）を記載すること。
- 6 Specify in the section of "Remarks" the name of the in-country caretaker (in the case of corporate body, the name of the body and the name of the representative) and the address of the caretaker (the address of the head office, in the case of corporate body).
- 7 原薬等を外国において製造する者にあつては、外国語により申請者の住所及び氏名を並記すること。また、署名をもって押印に代えることができるものとする。
- 7 As for foreign manufacturers who produce drug substances, etc., outside of Japan, include the name and address of the applicant in the language used in the applicant's country as well. The signature can substitute for the seal.

**Registration Items in Master File for Pharmaceuticals,  
Disclosed and Non-Disclosed Information**

Registration Items		Items of data that can be registered as document:	Restricted part	Disclosed part
The items to be registered on Drug Master Files specified in Law Article 14-11, Paragraph 1 are as follows		Statement on Reporting Any Changes in Manufacture and Control of Drug Substances, etc.  Data Items based on CTD		
Name of Drug Substances, etc.				
Name of Mfg. Site	3.2.S.1 3.2.S.1.1	General Information Nomenclature (INN, Chemical Name, Development Code, etc)		○
Address of Mfg Site	3.2.S.1.2	Structure (Structural and molecular formulas, molecular Weight)		○
Mfg. Business License, Accreditation Category, License/Accreditation No. (If any)	3.2.S.1.3	General Properties (Properties and Physicochemical Properties such as Solubility)		○
Ingredients and their Quantity or Nature	3.2.S.2	Manufacture		
	3.2.S.2.1	Manufacturer(s)		○
Manufacturing Method	3.2.S.2.2	Description of Mfg. Process & Process Controls (Production Flow and its explanations, Process Control, etc.)	○	○ (*)
	3.2.S.2.3	Control of Materials	○	
	3.2.S.2.4	Control of Critical Steps and Intermediates	○	
Specifications and Test Methods	3.2.S.2.5	Process Validation and /or Evaluation	○	
	3.2.S.2.6	Mfg. Process Development	○	
Information on Stability	3.2.S.3	Characterization		
	3.2.S.3.1	Elucidation of Structure and Other Characteristics (Elementary analysis, NMR, etc. for determining the Structure)		○
Storage Method & Expiry Date	3.2.S.3.2	Impurities (Related substances, Decomposition pathway, Residual Solvents, etc.) †		○
Information on Safety	3.2.S.4	Control of Drug Substance		
	3.2.S.4.1	Specification		○
	3.2.S.4.2	Analytical Procedures		○
	3.2.S.4.3	Validation of Analytical Procedures		○
	3.2.S.4.4	Batch analyses	○	○ (*)
	3.2.S.4.5	Justification of Specification (Evidence and Data)	○	○ (*)
	3.2.S.5	Reference Standards or Materials		○
Name & Address of Excipient Manufacturer, Mfg. Business License/Accreditation Category License/Accreditation No. (If any)	3.2.S.6	Container Closure System		
	3.2.S.7	Stability		
	3.2.S.7.1	Stability Summary & Conclusions		○
	3.2.S.7.2	Post-Approval Stability Protocol and Stability Commitment		○
	3.2.S.7.3	Stability Data		○
	3.2.P.4	Control of Excipients		
	3.2.P.4.1	Specifications		○
Person in charge of communication	3.2.P.4.2	Analytical Procedures		○
	3.2.P.4.3	Validation of Analytical Procedures		○
	3.2.P.4.4	Justification of Specifications	○	○ (*)
Name of Excipient	3.2.P.4.5	Excipients of Human or Animal Origin	○	○ (*)
	3.2.P.4.6	Novel Excipients		○
Property of Excipient		Properties, etc.	○	○ (*)
Mfg. Method & Mfg. Process Control		Manufacturing Method and Process Control	○	○ (*)
Quality Control Tests, Specifications				

Note)

\* shown in both of the restricted and disclosed part are basically disclosed. But, information related to intellectual properties of MF holder may not be disclosed.

† Enter data related to the safety / pharmacological effects of related substances into the body of approval application as necessary