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Director of Evaluation and Licensing Division
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

To: Directors-General
Department of Health
Prefectural Governments

Guideline on Utilization of Master File for Drug Substances, etc.

Master file system for drug substances, etc. (hereinafter referred to as "MF") will be newly implemented in accordance with the Pharmaceutical Affairs Law (Law No.145, 1960, hereinafter referred to as "Revised Pharmaceutical Affairs Law") effective on April 1, 2005 as amended by Law on Revising Partially the Pharmaceutical Affairs Law and the Law on Blood Collection and Donation Services Control (Law No. 96, 2002). The following guideline on the utilization of the MF is published so that you could inform relevant businesses and organizations under your jurisdiction of the guideline for their sake of submitting applications for MF registration, etc.

1. Master File System (MF)

MF will be implemented based on the Revised Pharmaceutical Affairs Law to be enforced on April 1, 2005. Purpose of the MF is to share information necessary for approval reviews of pharmaceuticals and medical devices (ex. information on manufacturing methods, etc.) that MF registrant possesses and also to protect the intellectual property of the MF registrant. MF is also aimed at streamlining the review process.

As for MF for medical devices, which will also be effective on April 1, 2005, at first the target will only be materials for medical devices, but items registered in MF of medical devices would be considered for

[1] This English version of the Japanese Notification 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.

expansion. I would also consider utilization of MF in the certification process by the accredited bodies.

2. Scope of MF Utilization

(1) Applications of MF registrations and changes to registered contents and notifications of minor changes to the registered contents shall be submitted to the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"), pursuant to the procedures and forms specified in the Enforcement Regulations of the Pharmaceutical Affairs Law (MHW Ministerial Ordinance No.1, 1961).

(2) Items for registration

① The following raw materials to be used for the manufacture of pharmaceuticals and medical devices can be registered in MF.

1. Drug substances, intermediates and pharmaceutical product materials (materials of pharmaceutical products with special dosage form, etc.)
2. New excipients and pre-mix excipients with a different composition ratio from existing ones
3. Materials for medical devices
4. Containers / packaging materials

② Drug substances, intermediates and pharmaceutical product materials (materials of pharmaceutical products with special dosage form, etc.) used for OTC drugs (excluding OTC with new active ingredients or those with their active ingredients still in the reexamination period) are not appropriate for registration in MF, as it is considered that their quality and safety are already established even in existing specification and test methods.

③ Items that can be registered consist of the manufacturing method, manufacturing process control, quality control tests, specifications and test methods, stability tests and non-clinical studies (mainly for new excipients), as well as the information described in the MF registration certificate, such as the name of manufacturing site, etc.

④ New TSE data based on "TSE Data Number" (PFSB / ELD No. 0801001 dated August 1, 2003: PFSB/SD No. 0801001 Notification by the Director of the Evaluation and Licensing Division / Director of Safety Division, Pharmaceutical and Food Safety Bureau) implemented as part of BSE measures shall also be registered into MF.

⑤ Items that can be registered into MF for materials for medical devices shall be information relating to the identification of raw materials.

⑥ Items recommended for MF registration in the approval review process shall be registered in MF.

3. Form for Registration Information in MF

(1) Registered information in MF shall be regarded as a part of information which should be described in the approval application form and attached document (for pharmaceuticals, the items described in "Data on Manufacturing Methods and Specifications / Test Methods" "Data on Stability" and "Data on Pharmacological Action").

(2) Registrant shall use the Form No. 42 specified in the Enforcement Regulations of the Pharmaceutical Affairs Law for MF registration application.

(3) For data to be attached to the registration application form (hereinafter referred to as "registration data"), the following forms shall be used.

① For pharmaceuticals (excluding generic drugs and OTC), the form (hereinafter referred to as "CTD") attached to the Notification by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, "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.

② The form for generic drugs shall follow the Notification by the Director-General of the Pharmaceutical and Medical Safety Bureau, "Approval Application of Pharmaceuticals" (PMSB Notification No. 481, dated April 8, 1999).

③ OTC drugs and those among "2. New excipients and pre-mix excipients with a different composition ratio from the existing ones" and "4. Containers / packaging materials" specified in 2. (2) ① used only for OTC drug, shall follow the pattern specified in the Notification by the Director-General of the Pharmaceutical and Food Safety Bureau, "Application for Approval of Non-Prescription Pharmaceuticals" (PFSB Notification No. 0827003 dated August 27, 2003).

④ For medical devices, it shall be given in another notification.

(4) Electronic forms for MF registration of drug substance, etc shall follow the Notification by the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, "Electronic Specifications on Common Technical Documents" (PFSB/ELD Notification No. 0604001 dated June 4, 2003).

(5) For MF registration of drug substances, etc., submission of the data equivalent to Module2 of CTD (summary of the attached data) is not required. However, as the contents registered in MF will be reviewed in the approval review process, MF registrant shall submit the data equivalent to Module 2 of CTD to the reviewing authorities when the approval application is submitted.

4. Information that MF Registrant Should Disclose to Applicants and Approval Holders of Pharmaceutical Products in Advance

(1) MF registrant shall notify the applicants of pharmaceutical products whose information in the approval application form is quoted by MF of changes to the registered items. And also, if the items registered in MF are quoted in the approval review of already approved pharmaceutical products, the MF registrant shall also notify the approval holder of the changes as well.

(2) Even in cases where a notification is submitted for minor changes in the registered contents, MF registrant shall notify relevant applicants and the approval holders of the changes.

(3) For the registered information, items that should be disclosed to the applicant and the

approval holder of pharmaceuticals products are shown in the attachment. When submitting an application for MF registration, information that should be disclosed shall also be written in the registration application form.

(4) As for the information in (3), the applicants of pharmaceutical products who quotes the corresponding information registered in MF can describe the information on the approval application form.

(5) As to whether some changes to the registered items will affect the quality, etc. of pharmaceutical products, MF registrant shall adequately consult with the applicant and approval holder who quote the registered information, by referring to the Notification by Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, "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) (hereinafter referred to as "Notification No. 0210001").

(6) Even the information such as TSE data shared with the applicant or approval holder of pharmaceutical products, that has a rationale and an advantage of using MF, can be registered into MF.

5. Procedures for Registration of MF

(1) New registration

① As for new registration, the application form with attached data shall be submitted to PMDA. Registration categories are defined as follows. The registration of TSE data is included in Category iv).

i) Drug substances, etc. (that mean drug substances, intermediates and pharmaceutical product materials manufactured by special manufacturing method) intended solely for use in the manufacture of pharmaceutical products (excluding those that are intended to be used exclusively for animals)

ii) Excipients that have not yet been used in the manufacturing of pharmaceutical products or excipients that have a different composition ratio as compared to existing ones (refers to new excipients and pre-mix excipients with a different composition ratio from existing ones respectively)

iii) Materials intended solely for use in the manufacture of medical devices (excluding those that are intended to be used exclusively for animals)

iv) Others (packaging material, etc.)

② Summary, etc. of the manufacturing methods to be registered shall be described on the application form for registration. Refer to Notification No. 0210001, etc. for filling out the form.

③ After MF registration, a registration certificate (refer to Form No. 43 of Enforcement Regulations of Pharmaceutical Affairs Law) and a duplicate of the registration application shall be issued. The registration certificate does not include any information that is not to be disclosed.

(2) When MF is utilized for a new approval application

① If applicants applying for approval of pharmaceutical products that quote MF for their

application, the applicants shall indicate, on the approval application form, the name of the MF, its registration number, issuance date of the registration certificate, the number of times the registration certificate was revised, and in cases where there are more than one manufacturing method, which manufacturing method was used. The applicant shall also attach a copy of the registration certificate and a copy of the contract with the MF registrant regarding utilization of the MF. The following is an example of how to fill out the Manufacturing Method column on the approval application form.

Example) ・・・・using the drug substance ▲▲▲▲▲ (MF Registration Number: XXXXXXXXXX (YYYY/MM/DD, Version Number ■ of MF Registration), Method ●)

② Notifications regarding the procedure for using MF in approval applications for medical devices shall be given separately.

③ In approval reviews, PMDA shall make inquiries regarding contents registered in MF directly to the MF registrant. PMDA shall also inform the applicant who submitted the relevant approval application of such inquiries.

(3) Changes to registered items

① If changes have to be made to registered contents as a result of approval reviews of pharmaceutical products, MF registrant shall submit an application for changing the registered items in MF. Thereafter, the registration certificate for that change shall be issued when the corresponding application of pharmaceutical product is approved.

② When changes are made to registered contents, an application for changing the registered contents with the attached data relating to such changes shall be submitted to PMDA. Changes only in attached data can not be filed. New registration, rather than an application for change, is required depending on the changes to registered items.

③ In making changes to contents registered in MF, the MF registrant shall enter in the column for remarks, the commercial name, the approval number, the name and address of the marketing authorization holder (the name and location of the main business site if the licensed marketing approval holder is a corporate entity) 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 items.

④ If MF under change is quoted in the already approved pharmaceutical products, it is necessary to submit a partial change approval application for all of these pharmaceutical products, together with an application for changing the contents registered in MF.

⑤ When making changes to the items registered in the MF, but the existing items is still be used for the already approved pharmaceutical products, it shall be required to specify the items. For example, when you add new manufacturing method, you 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 the pharmaceutical products approved by quoting the MF by those written number. In this case, applicants shall be required to submit partial change approval application for the pharmaceutical products with added items and minor change notification for pharmaceutical products with existing items, when they submit application for

changing the contents registered in MF.

⑥ If changes to the items in MF will substantially alter the nature of drug substances, etc., new MF registration form, not the change of registration must be submitted, and for pharmaceutical products that use the relevant MF, it is necessary to submit a partial change approval application so that these products can quote the newly registered items. In addition, in case changes to the items is significant and changed items are not regarded as being the same, approval holder of pharmaceutical products should submit a new approval application rather than a partial change approval application. Therefore, for significant changes, consultation with the review authority is recommended.

⑦ When making changes to the items registered in MF, registration certificate for that change will be issued only after partial change approval applications for all the relevant pharmaceutical products are submitted and approved by scientific review. Meanwhile, such as in case ⑤, when making changes to the items in the MF, but minor change notification are required for some of the products, those notification shall be submitted immediately after issuance of the registration certificate for that change.

⑧ Changes in registered contents are handled according to the date that the modified registration certificate was issued, and the registration number remains the same even after the registered contents are changed.

(4) Minor changes to registered contents

① The scope of minor changes to the items specified in MF registration form is same as that in the minor change notification for the pharmaceutical products, in accordance with the PFSB / ELD Notification No.0210001 dated February 10, 2005. It also applies to the attached data to the minor change notification.

② For minor changes to the registered items in MF, it shall not be required for the approval holder of the pharmaceutical products that quote the relevant registered information to submit a minor change notification. MF registrant shall submit a statement indicating that they have performed adequate validation and change control, along with the notification of minor changes to the registered contents in MF, to the review authority.

(5) If the approval applicant needs to utilize the items registered in MF under the instructions of PMDA, the applicant shall revise the attached documents with the registration number and the issuance date of the registration certificate of the application form and attach copies of the registration certificate and contract with MF registrant regarding the utilization of MF.

(6) When transferring contents registered in MF to the third party, it shall be required to follow all the procedure specified in the Enforcement Regulations of the Pharmaceutical Affairs Law. 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 contents 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.

(7) Items relating to MF registration, such as registration number, registration date, name of the registrant, name of the registered item, and registration category shall be made public by PMDA.

However, as for name of registered items, if disclosure cause disadvantage for the registrant or applicant, for example, in cases where the registration is made during a clinical trial for the pharmaceutical product or before its approval, its concrete name that specify the substance itself shall not be made public. Instead, generally recognizable name, such as the name of its chemical classification, etc. shall be published.

6. Handling of Utilization of MF for Pharmaceutical products Used in Common for Human and Animals

(1) For pharmaceutical product that contains drug substances used both in human and animals, and if MF for the drug substance is quoted in the application of the approval review, the registration application of MF shall, in principle, be applied to PMDA. However, if the drug substance is intended only for animals, the registration application of MF can be applied to the Ministry of Agriculture, Forestry and Fisheries.

(2) Since the Ministry of Agriculture, Forestry and Fisheries administers approval review of pharmaceutical products for veterinary use, as for the case in (1), registered information in PMDA's MF shall be disclosed to the Ministry of Agriculture, Forestry and Fisheries in an appropriate manner upon their request.

(3) For pharmaceutical product that contains drug substances used both for human and animals, when a change in the items registered in MF necessitates a partial change approval application for pharmaceutical product that was approved by the Minister of Agriculture, Forestry and Fisheries, the approval holder of that product shall be responsible for submitting a partial change approval application to the Ministry of Agriculture, Forestry and Fisheries.

7. Handling of Drug Substances, etc. approved by March 31, 2005

As for MF registration in the following items, registration before the enforcement of Revised Pharmaceutical Affairs Law shall be accepted for smoother operation.

(1) Approved drug substances that are used for pharmaceutical products approved before March 31, 2005.

(2) Designated pharmaceuticals, etc. as not requiring for manufacturing or importing license by Minister of MHLW by March 31, 2005

(3) Regarding (1) and (2) above, by using the approval number and business license number, the submission of some of the items and attached data, that are normally required for MF registration, shall be submitted later. Furthermore, these numbers shall be considered to utilize these for notification of maintenance of descriptions on approval certificate, in accordance with the enforcement of the Revised Pharmaceutical Affairs Law. Details shall be notified separately.

8. Handling of Materials for Medical Devices Registered in MF for Medical Devices

Notifications regarding the handling of materials for medical devices that have been registered based on the Notification by the Director of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, "Database creation for materials of medical devices" (PMSB / ELD Notification No. 1286 dated December 6, 2000) will be given separately.

<Attachment 1>

Registration Items in Master File for Pharmaceuticals,

Disclosed and Non-Disclosed Information

Registration Items		Items of data that can be registered as documents	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.	3.2.S.1	General Information			
Name of Mfg. Site	3.2.S.1.1	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)		○	
	3.2.S.2	Manufacture			
Ingredients and their Quantity or Nature	3.2.S.2.1	Manufacturer(s)		○	
	3.2.S.2.2	Description of Mfg. Process & Process Controls (Production Flow and its explanations, Process Control, etc.)	○	○	(*)
Manufacturing Method	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		○	
	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		○	
Name & Address of Excipient Manufacturer, Mfg. Business License/Accreditation Category License/Accreditation No. (If any)	3.2.P.4	Control of Excipients			
	3.2.P.4.1	Specifications		○	
	3.2.P.4.2	Analytical Procedures		○	
Person in charge of communication	3.2.P.4.3	Validation of Analytical Procedures		○	
	3.2.P.4.4	Justification of Specifications	○	○	(*)
	3.2.P.4.5	Excipients of Human or Animal Origin	○	○	(*)
	3.2.P.4.6	Novel Excipients		○	
Name of Excipient					
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.

<Attachment 2 >

Registration Items in Master File for Medical Devices,
Disclosed and Non-disclosed Information

Registration Items (in accordance with Ministerial Ordinance)	Registration Data	Information disclosure	
		Restricted part	Disclosed part
Name and address of party manufacturing raw materials , etc.			
Person in charge of communication			
Name, components, composition and properties of material for medical devices, etc.	1. Non-proprietary name or common name (product name or trade name)		○
	2. Chemical name		○
	3. CAS Number, USAN, or Notification No. of Kashin-Ho* (if any).		○
	4. Chemical structure	○	
	5. Molecular weight, etc. (substitutable with melt index, viscosity, etc.)	○	
	6. Type and quantity of major excipient	○	
Manufacturing method and manufacturing process control	—		
QC tests, specifications & test	—		
Stability, storage method & expiry	—		

* Kashin-Ho: Law Concerning Examination and Regulation of Manufacture and Handling of Chemical Substances.