4th Joint Conference of Taiwan and Japan on Medical Products Regulation

Description of the demanded document of API for the application of registration of generic medicine in Japan

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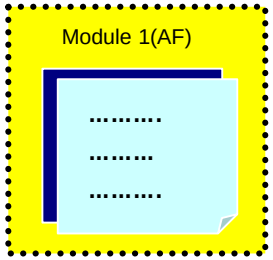
Today's Contents

1. Introduction
2. Approval review for drug products quoting MF
3. Considerations for MF reviews
4. Recent activity

What is the Drug Master File(MF) System?

- To protect the “know-how” of API manufacturing methods against the marketing authorization applicant of pharmaceutical products.(*** MF is not a patent.**)
- Registration in the MF is optional. An MF registration certificate is not a marketing certificate.
- In a regulatory review, items registered in the MF are quoted as information necessary for the review. Some of these items will be approved items.
- Foreign manufacturers applying for MF registration must select an in-country caretaker for drug substances, etc.



Approval Matters (JAPAN)
(Contents of AF)

- General name
- Brand name
- Composition
- Manufacturing process, including control of materials
- Specifications and analytical procedures
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Manufacturing sites information

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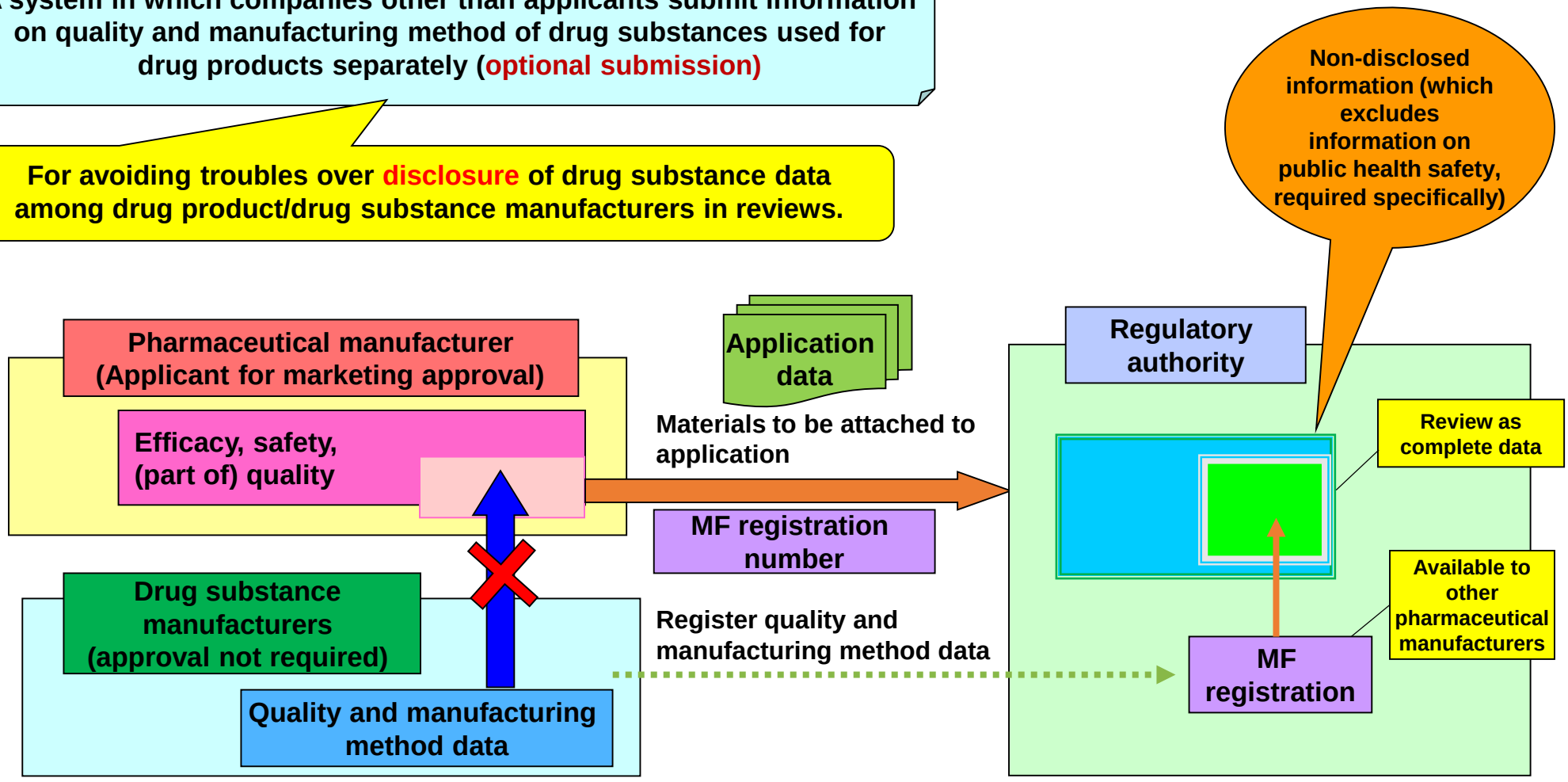
Approval reviews for drug products quoting MF

A system in which companies other than applicants submit information on quality and manufacturing method of drug substances used for drug products separately (optional submission)

For avoiding troubles over disclosure of drug substance data among drug product/drug substance manufacturers in reviews.



Issues in MF reviews

Consistency between use and non-use of MF

MF registration is optional system.

There are no difference in information provided for reviews in the case of MF usage or not.

PFSB/ELD Notification No. 0210001
dated February 10, 2005

Does a change fall into "minor change" or "partial change application"?

In registration application, a change is classified into minor change notification or application for partial change based on the expected effect on product quality.

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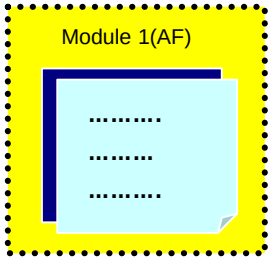
" " ' '

If registrant is an overseas manufacturers, a MF registrant shall appoint a in-country caretaker who has an address in Japan and delegate MF registration application to the representative.

Sufficient cooperation between MF registrants (in-country caretaker) and marketing authorization holder is required for ensuring quality of drug product and smooth MF reviews.



Matters to be described in manufacturing field of AF

All processes from starting material(s) to packaging process

- A flow diagram of manufacturing process including:
  - ・Starting materials ・Charge-in amount ・Yield
  - ・Solvent ・Intermediate materials
  - ・Process parameter (e.g. Target Value/Set Value)
- A narrative description of manufacturing process
  - Acceptance criteria of starting material(s) and intermediate materials
  - In process control, Design Space and RTRT etc.
- Enter items other than target/set values in
  - Nothing: Partial Change Matter
  - “ ” : Minor Change Matter
- Enter target/set values of process parameters and standard charge-in amounts in
  - 《 》: Partial Change Matter
  - 『 』: Minor Change Matter

→**AF system in Japan provides clear description of post approval change controls**.

Status of information registered in MF

Information registered in MF

- ✓ Partial documents for marketing approval application for a drug products

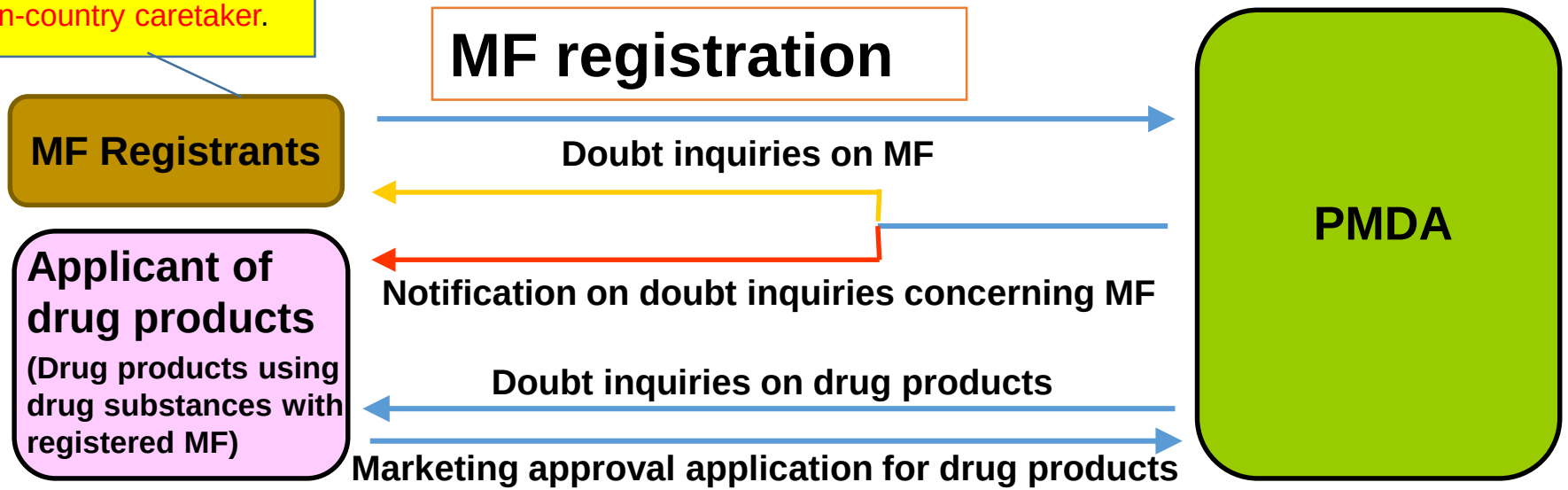
Application form is filled in Japanese

Original documents of Module 3 of CTD can be submitted only where it is written in English.
The summary written in Japanese or Module 2 of CTD is to be submitted where required by reviewers.

- The registered information are reviewed in the approval application for the drug product using the relevant MF.
- In the review of the product, submission of data equivalent to Module 2 (Summary of Attached Data) is recommended as well as Module 3 of CTD.

Overview of approval review for drug products quoting MF

If registrant is an overseas manufacturer, inquiries are made by way of in-country caretaker.



Management of impurities and residual solvent is reviewed based on required measured data and, in some cases, results of validation of analytical procedure.

Data specified in the Enforcement Ordinance of the Pharmaceutical Affairs Law, Article 40-1-1.	Scope of the left column (PFSB Notification No. 0331015 dated on March 31, 2005)
A. Origin or history of discovery and usage conditions in foreign countries etc.	1 Origin or history of discovery 2 Usage conditions in foreign countries 3 Characteristics and Comparison with other drugs
B. Manufacturing methods and specifications	1 Identification and physicochemical properties 2 Manufacturing process 3 Specifications
C. Stability	1 Long-term testing 2 Stress testing 3 Accelerated testing

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Manufacturing method [1]

Administrative Notice from ELD, PMSB, MHLW, dated May 20, 2008

- Concept for description of manufacturing method

  Refer to "Question-and -Answer (Q&A) on Description of Manufacturing Method in Application Forms for Drugs"

- Concept for eligibility for minor change notification/application for partial changes
  - Each company should evaluate eligibility based on the following notifications. Simple consultation is available for a case in a gray zone.

PFSB/ELD Notification No. 0210001 dated February 10, 2005

- "Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law"
- Other relevant notification and administrative notice (Q&A)
  - Administrative Notice from ELD, PFSB, MHLW, dated Nov 16, 2006
  - Administrative Notice from ELD, PFSB, MHLW, dated Dec 14, 2006
  - PFSB/ELD Notification No. 0112001 dated Jan 12, 2007
  - Administrative Notice from ELD, PFSB, MHLW, dated Jun 28, 2010
  - Administrative Notice from ELD, PFSB, MHLW, dated Jul 26, 2010
  - PFSB/ELD Notification No. 0530-8 dated May 30, 2014
  - PFSB/ELD Notification No. 0710-9 dated Jul 10, 2014

Manufacturing method [2]

PFSB/ELD Notification No. 0210001 dated February 10, 2005

- Manufacturing method of chemical drug substance
  - According to Appendix 1 of the notification, describe more than one reaction process in principle, starting with an appropriate starting material.

    Reaction process: process including formation or cutting of a covalent bond, excluding base exchange or purification process.
  - Note that only sufficiency of number of reaction processes is evaluated, not appropriateness of manufacturing method.

    →Justification for selection of a starting material

    →Evaluation on control strategy
  - Control standards for starting materials, raw materials, critical intermediates, and final intermediates are appropriately developed.
  - Control standards for raw materials after final intermediates are developed in principle.

Manufacturing method [3]

PFSB/ELD Notification No. 0210001 dated February 10, 2005

- Critical processes are established based on data collected appropriately.

  Critical process: A process impacting the quality and including process conditions, tests, and other relevant parameters in which operation within predetermined action limits to ensure conformity of drug substances to specifications is required.

  Where inquiry on rationale for critical process is made during review, the applicants should provide scientific explanation based on data, etc.

- Abbreviated description of Manufacturing method of specific drug substances listed in Appendix 1 of PFSB/ELD Notification No. 0304018 dated March 4, 2009 can be acceptable.

- Manufacturing site information, range of manufacturing process and flow diagram of manufacturing method (flow diagram is attached as appendix [PDF file]) are to be described to indicate summary of manufacturing process.

Specifications [1]

- ## Residual solvent in drug substance

  In view of manufacturing process and classification of solvents (Guideline for Residual Solvents), it should be considered whether including in the manufacturing method or establishing the specifications is necessary.

  If not necessary, explanation based on scientific evidence such as actual data is given.

→ Actual data and the results of validation of analytical procedure are to be submitted at registration to explain the necessity of listing as specifications or process controls and the justification for acceptance criteria.

- ## Impurities in drug substances

  List all expected impurities and related substances, which are included as applicable in controls of starting materials or intermediates and specifications of final drug substances.

→List of structures of expected impurities, actual data, and the results of validation of analytical procedure are to be submitted at registration to explain the necessity of the final specifications or establishing the control values of starting materials or intermediates, and justification for acceptance criteria.

  * It should be kept in mind that insufficient confirmation on expected impurities may lead to delay of reviews.

Specifications [2]

- In cases where manufacturer's specifications are established,

✓ Full description of the specifications are required by reference to the Guideline for the Preparation of the Japanese Pharmacopoeia.

✓ Where non-pharmacopoeial reagents/test solutions are used, develop a column for reagents/test solutions in which the quality and preparation procedure are described.

✓ Check carefully that the description is correct and complete.

The important points

- It is important for the applicant, the MF Holder and the in country caretaker to understand the Japanese regulation (PMDAct, PFSB / ELD Notification No.0210001 February 10, 2005) and the guidance

- [Disclosed (Open) part] The applicant, the MF Holder and the in-country caretaker must communicate with each other.

- [Restricted (Closed) part] The MF Holder and the in-country caretaker must communicate with each other.

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Recent activity

- ✓ Completely change to CTD format from the application after March 2017

- ✓ Mock up of CTD 1, 2, and 5 are available in JGA HP
  Particularly, in mock up of CTD 2, the detailed contents are written (In Japanese only)
  http://www.jga.gr.jp/ctd/

- ✓ Checklist have been published on 11th March 2016 by MHLW to ensure the appropriate application documents are received for review (In Japanese only)
  186 items regarding to CTD 1 and CTD 2

J Pharm Pharm Sci (www.cspsCanada.org) 19(2) 290 - 300, 2016

Similarities and Differences of International Practices and Procedures for the Regulation for Active Substance Master Files/Drug Master Files of Human Use: Moving Toward Regulatory Convergence

Maki Matsuhama, Tomoko Takishita, Ryosuke Kuribayashi, Kazunori Takagi, Rika Wakao, and Kenichi Mikami

Office of Generic Drugs, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan

Open Access

✓ Project of ASMF/DMF working group of IGDRP

✓ Participants : 12 international organizations

Anvisa, EU, HC, HSA, MCC, MFDS, PMDA, Swissmedic, TFDA, TGA, EDQM, and WHO

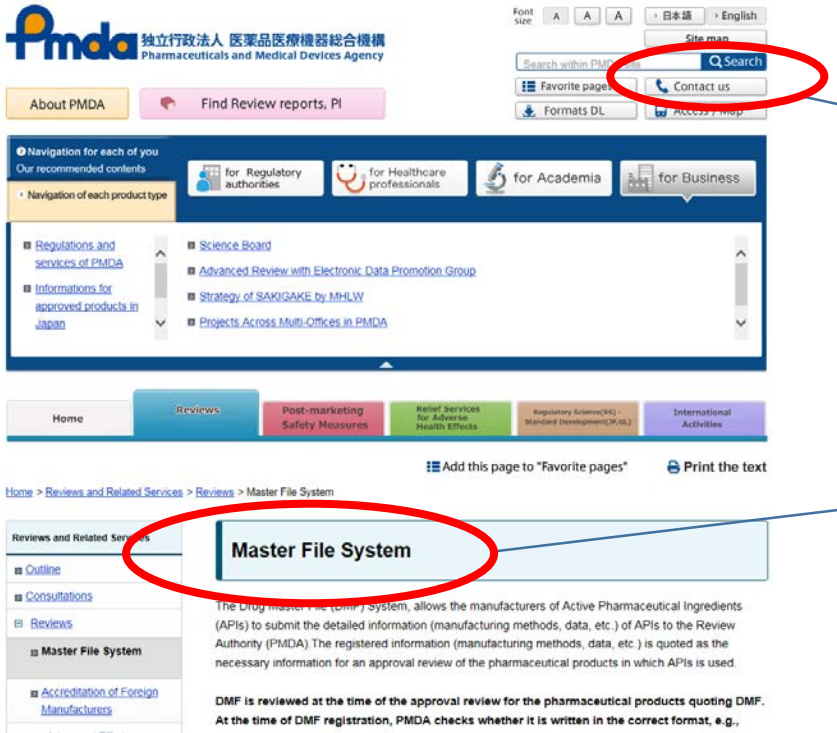
✓ 84 Questionnaires

1. An outline of ASMF/DMF systems
2. Submission requirements for ASMFs/DMFs
3. The assessment process for ASMFs/DMFs
4. The technical requirements for APIs
5. The generation of assessment reports for ASMFs/DMFs
6. Procedures for changing ASMF/DMF details
7. Good Manufacturing Practice (GMP) inspection/certification

PMDA website

PMDA website started to provide information about MF System in English.
http://www.pmda.go.jp/english/review-services/reviews/mf/0001.html

If you have any question, feel free to “Contact us.”



Contact us by email from here.

Guidance on DMF, Q&A on DMF etc. are provided in English PDF.

Pharmaceuticals and Medical Devices Agency

Thank you for your kind attention.

太谢谢你了