Guidance on Drug Master File System in Japan

Master File Management Group
Division of Pharmacopoeia and Standards for Drugs
Office of Review Management

Notes

In Japan, the Drug Master File (DMF) is called “Master File” or “MF”.

Topics

Part 1. How to register to MF in Japan

Part 2. Generic Drug Review System, MF System

Topics

Part 1. How to register to MF in Japan

Part 2. Generic Drug Review System, MF System

Contents

Part 1. How to register to MF in Japan

1. What is the Drug Master File(MF) System?
2. Registration, and Changes in MF “

Contents

What is the Drug Master File(MF) System?

“know-how” of API manufacturing methods

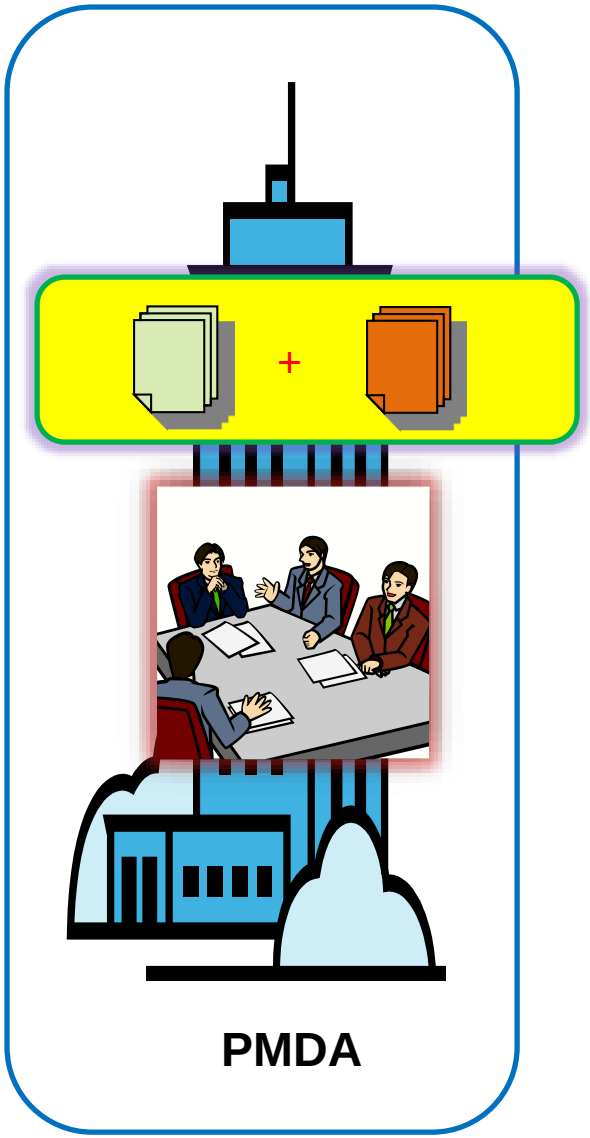
- To protect the “know-how” of API manufacturing methods from the marketing authorization applicant (MAA) / holder (MAH) of pharmaceutical products.(*** MF is not a patent.**)
- Registration in the MF is optional, not required by law. An MF registration certificate is not a marketing certificate.
- In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

Outline of Application Flow for Pharmaceutical Products

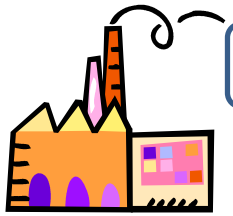
Without MF

marketing authorization applicant

Approval application
for pharmaceutical products



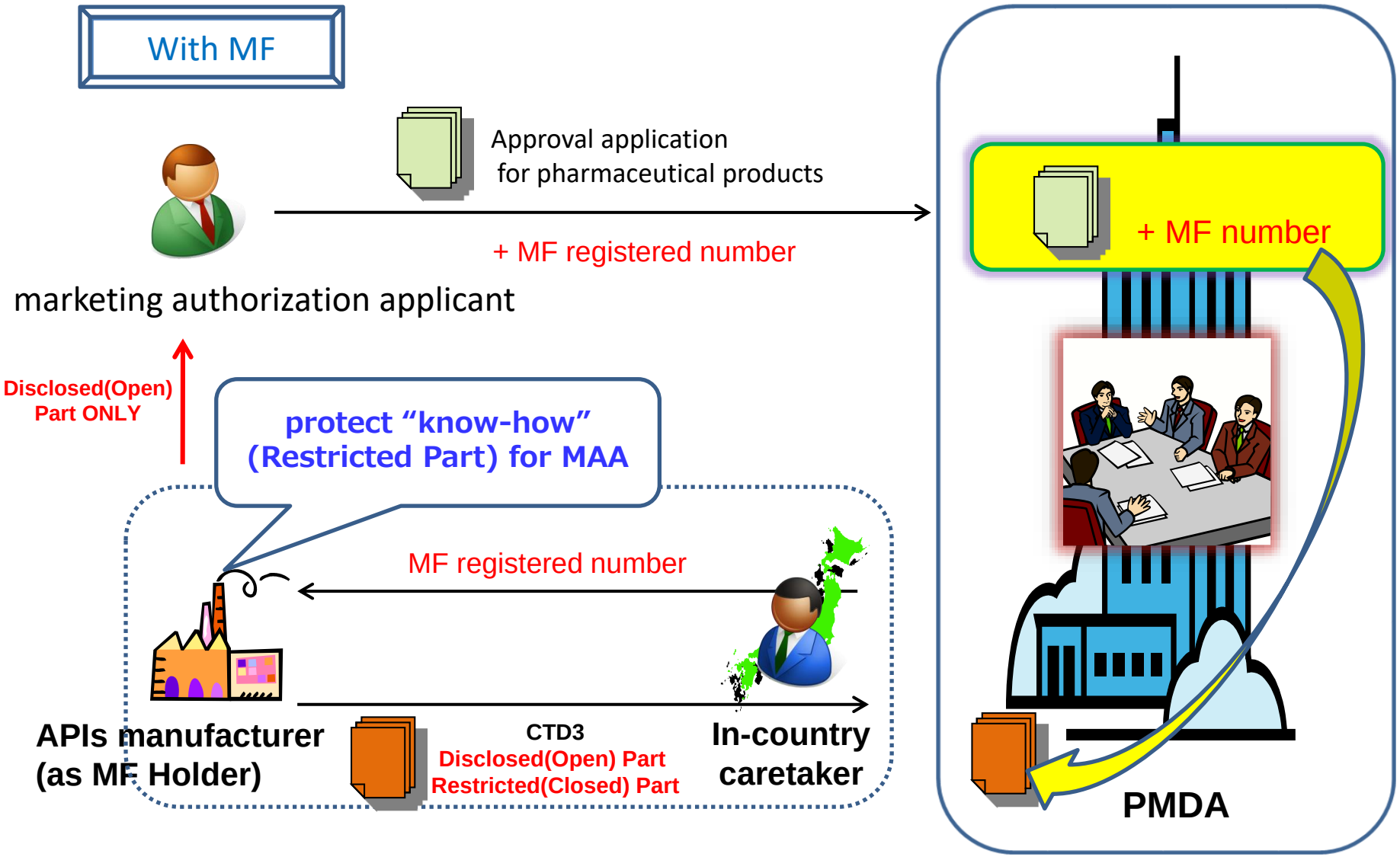
CTD-3
Disclosed(Open) Part
Restricted(Closed) Part



No need for protection

APIs manufacturer

Outline of Application Flow for Pharmaceutical Products

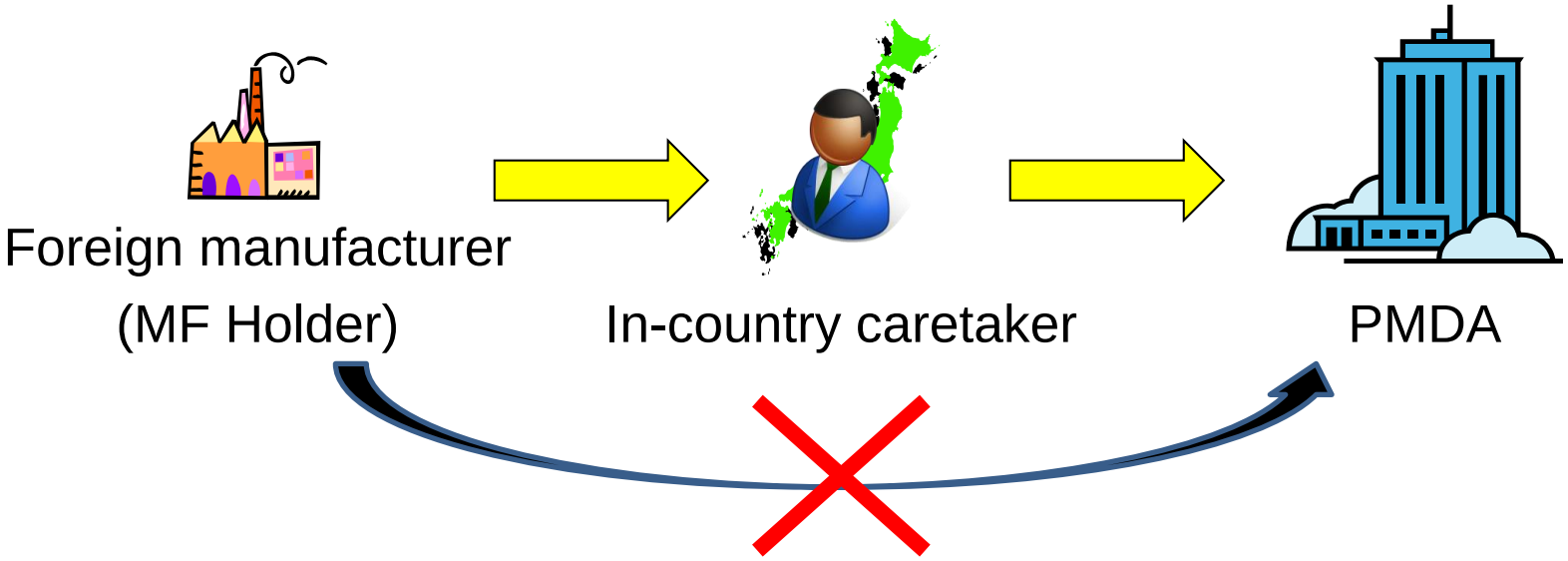


Foreign manufacturers applying for MF registration

the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics

[the Enforcement Regulations for PMD Act]

Select an in-country caretaker for drug substances (APIs) etc., who lives in Japan and will undertake clerical work for the relevant registration, etc.
Foreign manufacturer(MF Holder) cannot submit "CTD-3" of API manufacturing methods to PMDA directly.

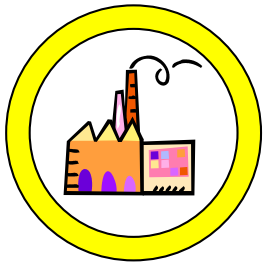


Items for MF registration

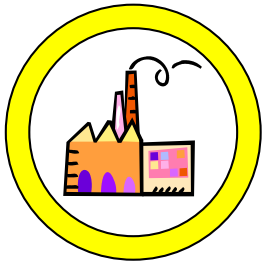
PFSB / ELD Notification No.11173 December 11, 2014

- Drug substances, intermediates (for medical use)
- New excipients and pre-mix excipients with different composition ratios from the existing ones
- Materials used for manufacturing Cellular and Tissue-based Products
  （Cell, Medium, Medium Excipient, etc.）
- Others

Qualification of MF Holder



manufacturer



Synthetic route development companies(manufacturer)

Synthetic route development companies(**not** manufacturer)

Qualification of MF Holder

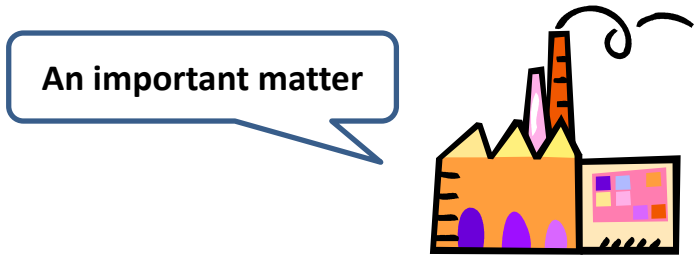
The requirement for MF Holder:

A company manufactures actually the APIs for MF registrations.

With Following conditions; no MF application is accepted.

- the processes of manufacturers are only following conditions;
  repackaging, packing, labeling, storage, examination
  (these processes are not fit the purpose of MF system)

- Customer and Contract Manufacturer combination status
  (A customer actually does not manufacture APIs)



the Drug Master File System Summary

- **It is important for the MAA/MAH, the MF Holder and the in-country caretaker to understand the Japanese regulation (PFSB / ELD Notification No. 0210001 February 10, 2005) and the guidance.**
- **[Disclosed(Open) part] The MAA/MAH, 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.**

Disclosed(Open) part／Restricted(Closed) part(2)

CTD module3	Disclosed(Open) part	Restricted(Closed) part
3.2.S.1 General Information (name, manufacturer)	○	
3.2.S.2 Manufacture (name, manufacturer)		
3.2.S.2.1 Manufacturer(s) (name, manufacturer)	○	
3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)	○	○
3.2.S.2.3 Control of Materials (name, manufacturer)		○
3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)		○
3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)		○
3.2.S.2.6 Manufacturing Process Development (name, manufacturer)		○
3.2.S.3 Characterisation (name, manufacturer)		
3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)	○	
3.2.S.3.2 Impurities (name, manufacturer)	○	
3.2.S.4 Control of Drug Substance (name, manufacturer)		
3.2.S.4.1 Specification (name, manufacturer)	○	
3.2.S.4.2 Analytical Procedures (name, manufacturer)	○	
3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)	○	
3.2.S.4.4 Batch Analyses (name, manufacturer)	○	○
3.2.S.4.5 Justification of Specification (name, manufacturer)	○	○
3.2.S.5 Reference Standards or Materials (name, manufacturer)	○	
3.2.S.6 Container Closure System (name, manufacturer)	○	
3.2.S.7 Stability (name, manufacturer)	○	

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.

Restricted(Closed) part

CTD module3	Disclosed (Open) part	Restricted (Closed) part
3.2.S.2.3 Control of Materials (name, manufacturer)		* ○
3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)		* ○
3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)		* ○
3.2.S.2.6 Manufacturing Process Development (name, manufacturer)		* ○

Note)
* Enter data related to the safety / pharmacological effects of related substances into the body of approval application dossier as necessary.

Disclosed(Open) part

CTD module3	Disclosed (Open) part	Restricted (Closed) part
3.2.S.1 General Information (name, manufacturer)	○	
3.2.S.2.1 Manufacturer(s) (name, manufacturer)	○	
3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)	○	
3.2.S.3.2 Impurities (name, manufacturer)	○	
3.2.S.4.1 Specification (name, manufacturer)	○	
3.2.S.4.2 Analytical Procedures (name, manufacturer)	○	
3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)	○	
3.2.S.5 Reference Standards or Materials (name, manufacturer)	○	
3.2.S.6 Container Closure System (name, manufacturer)	○	
3.2.S.7 Stability (name, manufacturer)	○	

The sections below are basically present in both the restricted and disclosed parts.

CTD module3	Disclosed (Open) part	Restricted (Closed) part
3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)	○	*○
3.2.S.4.4 Batch Analyses (name, manufacturer)	○	*○
3.2.S.4.5 Justification of Specification (name, manufacturer)	○	*○

Note)
*Items marked with in both the restricted and disclosed parts are basically disclosed. But, information related to intellectual properties of MF holder may not be disclosed.

Attentions

Disclosed(Open) part

- It is necessary for the MAH/MAA to understand the outline (summary) of the API's manufacturing methods part if the API is MF-registered.

protect "know-how" (Restricted Part) for MAA/MAH

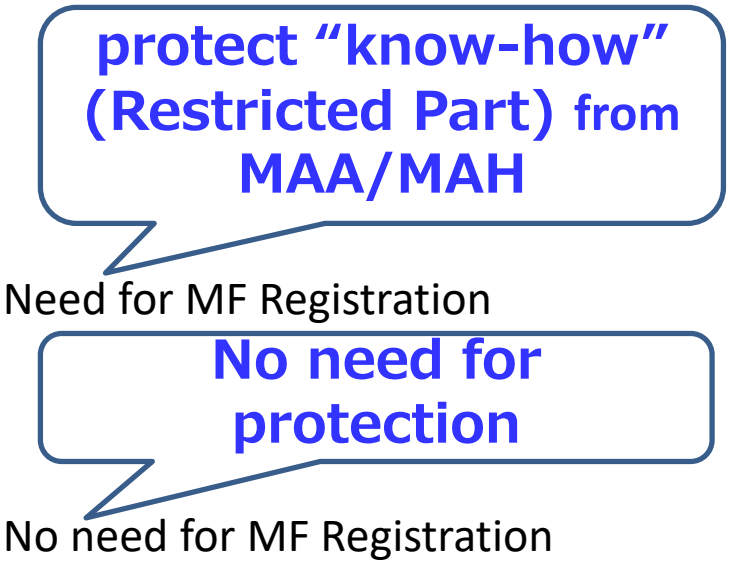
"Guidelines on Utilization of Master File for Drug Substances, etc 4(1)."

- The MF Holder must communicate with or notify the relevant MAH/MAA about the proposed data changes for items in the registered Disclosed(Open) part information (including the MF registration application form) in advance.

Requirements for MF Registration

- Must?

  No, it is not required by law(voluntary).

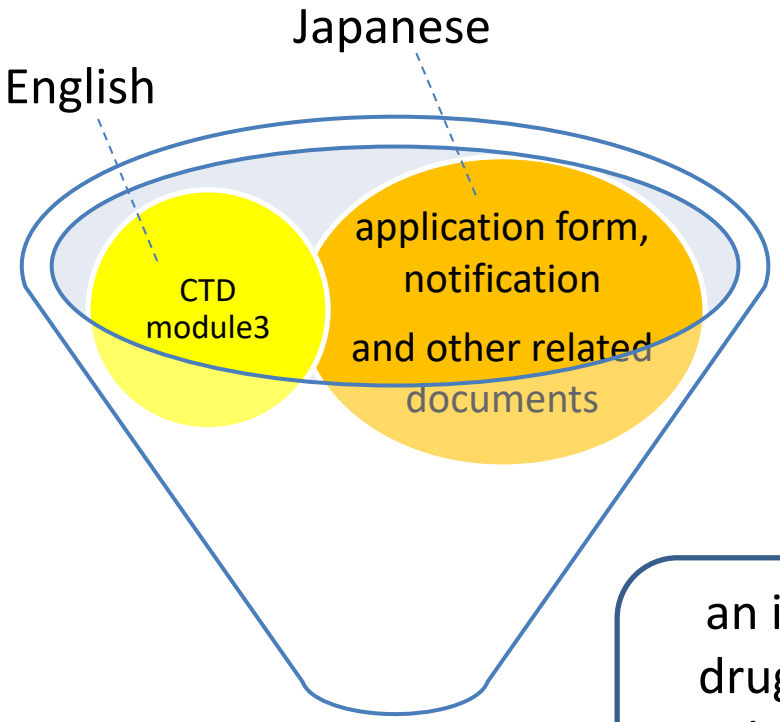


- How much is MF registration fee?

  No fee is charged for MF registration.

Registration, and Changes in MF

the application form, notification, and other related documents



- In Japan, the application form, notification, and other related documents for pharmaceutical products which are submitted to the PMDA, written in Japanese.
- The MF registration application form, notification, and other related documents shall be written in Japanese.

MF

an in-country caretaker for drug substances (APIs) etc., who lives in Japan and will undertake clerical work for the relevant registration.

In-country caretaker

Relationship between the approval application of pharmaceutical products and the MF registration application

The approval application of pharmaceutical products using MF	**MF registration application**
If the pharmaceutical product's applicant quotes MF for their application, the applicant shall attach a copy of the registration certificate and a copy of the contract with the MF Holder regarding utilization of the MF.	The MF Holder shall describe the detailed manufacturing process for API on the MF registration application. If the MF Holder is a foreign manufacturer, the appointed in-countrycaretaker shall prepare the MF registration application based on CTD M3, etc.
[Manufacturing Methods column on the approval application form (pharmaceutical products)] (Examples) ・・・・using the drug substance *A* (MF Registration Number: XXXXXXXXXX (YYYY/MM/DD, Version Number *X* of MF Registration), Method *B*)	[Manufacturing Methods column on the MF registration application] (Examples) Step 1 (Critical process) Mix 2-(1-triphenylmethyl-1*H*-tetrazole-5-yl)-4'-bromomethylbiphenyl [1]『(21.6 kg)』, 2-formyl-5-[(1E,3E)-1,3-pentadienyl]-1H-imidazole [2]『(6.9 kg)』, potassium carbonate『(11.8 kg)』, and dimethylformaldehyde『(60 L)』 urs』. Add sodium borohydride 『(3.2 her at『25℃ for 24 hours』. Filter the and remove the insoluble matter. Concentrate the filtrate under vacuum. Add water『(50 L)』to the residue, and extract it with ethyl acetate『(50 L)』. Wash the organic layer with water 『(50 L)』and"10%" saline solution『(30 L)』.

The information is equivalent.

“New MF Registration Application”

◆ Application for Registration of Drug Substances, etc.

- Application (Original 1, Duplicate 1; Duplicate must not be a Xerox copy of Original)
- Data of Application for MF Registration(including CTD Module3*)

*The CTD M3 submits only electronic data.

After New MF Registration

For the MF Holder (or In-country caretaker)

- After MF registration, an MF registration certificate and a duplicate of the registration application will be issued.

An MF registration certificate is not a marketing certificate.

At PMDA

- At a later date, MF registration number, registration date, date of the change in registered item, name and address of the MF Holder, the name of registered items, and the registration category will be published in the PMDA Japanese homepage. These published contents are Japanese only.

[excel,pdf] https://www.pmda.go.jp/review-services/drug-reviews/master-files/0008.html

“MF partial change approval application”

◆ **partial change approval application in PFSB / ELD Notification No. 0210001 February 10, 2005**

- Application (Original 1, Duplicate 1; Duplicate must not be a copy of Original)
- Data of Application for MF Registration(including CTD Module3*)
- Original Registration Certificate
- Other (Old/New Comparison table, etc)

*The CTD M3 submits only electronic data.

Scope of "MF partial change"

The MF Holder must communicate with or notify relevant MAH/MAA about the changes in the registered information (including the MF registration application form) .

▶ **[Scope of partial change approval application in PFSB / ELD Notification No. 0210001 February 10, 2005];**

(i) Changes in the manufacturing methods, etc. affecting the nature, characteristics, performance, and safety of the APIs.

(ii) Deletion of items listed in the specifications and test methods or changes in the specification.

(iii) Changes in the inactivation or removal methods for pathogenic factors.

(iv) The changes, other than those described in (i) to (iii), which may affect the quality, efficacy, or safety.

◆[Note] If the changes in the items in MF will substantially alter the API, please note that a new MF registration form, not a change of registration must be submitted.

“MF minor change notification”

◆ **minor change notification : PFSB / ELD Notification No. 0210001 February 10, 2005**

- Minor Change Notification (Original 1)
- Data of Application for MF Registration (including CTD Module3*); as necessary
- Statement (appropriate validation, change control, etc.)
- Other (Old/New Comparison table, etc)

*The CTD M3 submits only electronic data.

** Basicaly, the MF Holder must submit the notification to PMDA within 30 days after the change made.

Scope of “MF minor change”

The MF Holder must communicate with or notify relevant MAH/MAA about the changes in the registered information (including the MF registration application form) .

- **[Scope of minor change notification : PFSB / ELD Notification No. 0210001 February 10, 2005]; other than those described below.**

(i) Changes in the manufacturing methods, etc. affecting the nature, characteristics, performance, and safety of the APIs

(ii) Deletion of items listed in the specifications and test methods or changes in the specification

(iii) Changes in the inactivation or removal methods for pathogenic factors

(iv) The changes, other than those described in (i) to (iii), which may affect the quality, efficacy, or safety

◆[Note] “Minor change notification : PFSB / ELD Notification No. 0210001 February 10, 2005.” does not constitute any part of so called "annual report" which does not exist in Japan..

“Cancellation of MF”

◆ Notification for MF Registration Cancellation

- Notification (Original 1)
- Statement (confirming that there is no product using the MF number to be cancelled)
- Original MF Registered Certificate

Points to Consider

What is the Drug Master File System?

The Drug Master File (MF) system allows Japanese or foreign manufacturers of drug substances to register at the discretion of the holder the data on quality and manufacturing methods of their drug substances at the PMDA.

What is the Drug Master File System?

Q. What is the great merit of MF? (for manufacturers)

A. Protection of an intellectual properties and *know-how(Restricted-part)* etc,. including the registered-data from marketing authorization holders who are often competitors at the same time.

What is the Drug Master File System?

Q. Who should register the MF?

A. The registration of an MF is not required by law.

An MF is registered solely at the discretion of the MF holder (Actual manufacturers). That is to say, anybody (Actual manufacturers) can register.

What is the Drug Master File System?

Q. How much is the MF registration fee?

A. No fee is charged for MF registration.

What is the Drug Master File System?

Q. Is the MF registration the same thing as MF Approval?.

A. MF registration itself is Neither approved Nor disapproved. It is NOT a substitute for an marketing approval. The registered data are used as reference for an approval review of the drug (pharmaceutical products) in which the drug substance are applied.

Topics

Part 1. How to register to MF in Japan

Part 2. Generic Drug Review System, MF System

Generic Drug Review System, MF System

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Part 2. Generic Drug Review System, MF System

1. Approval review for drug products quoting MF
2. Considerations at MF reviews
3. Considerations at change of information registered in MF

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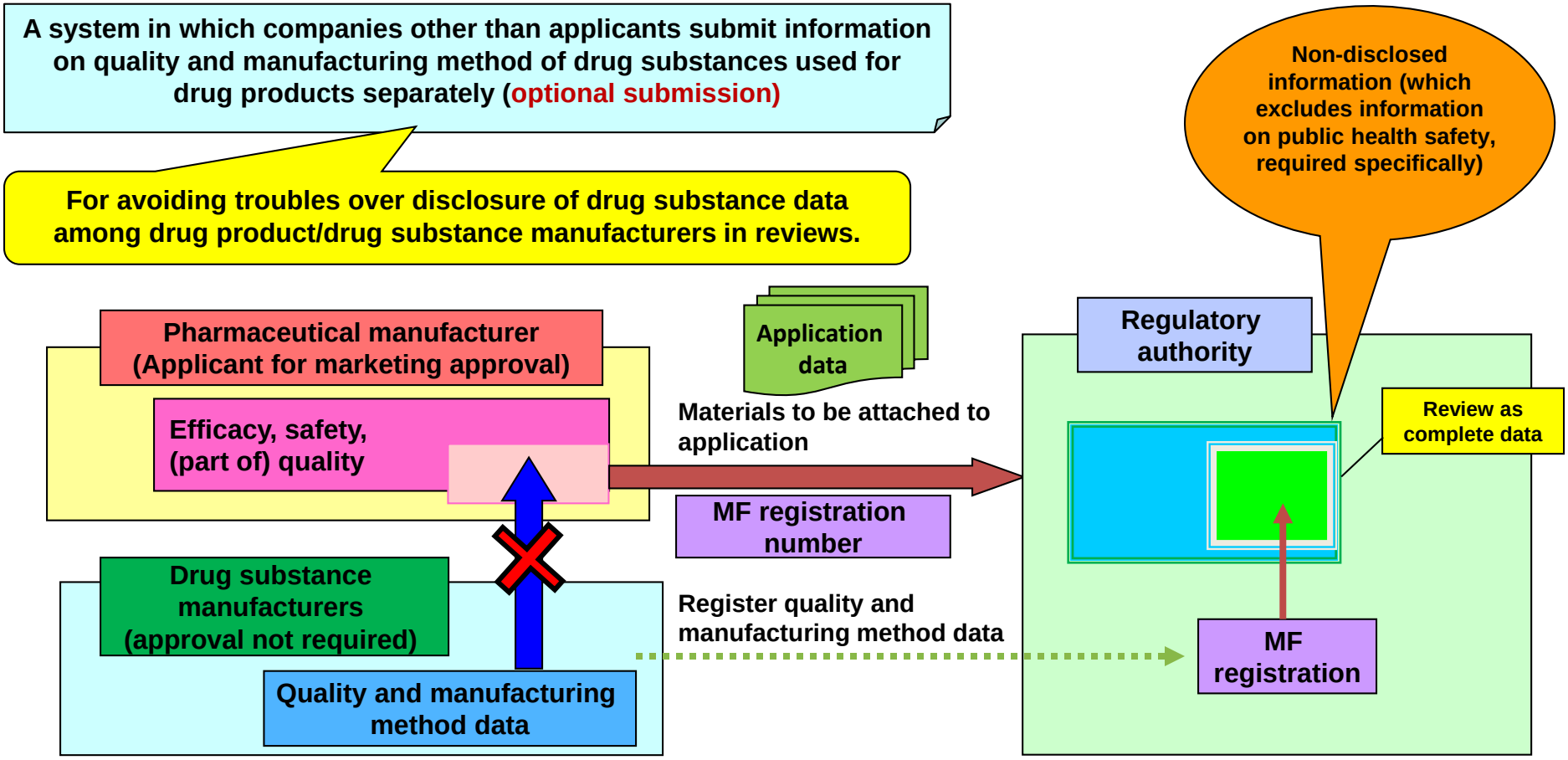
Part 2. Generic Drug Review System, MF System

1. Approval review for drug products quoting MF
2. Considerations at MF reviews
3. Considerations at change of information registered in MF

Approval reviews for drug products quoting MF (Simplified outline)



Issues in MF reviews

Warranty of consistency between use and non-use of MF

MF registration is optional system.

Ensure that the presence or absence of MF use makes no difference in information provided for reviews.

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

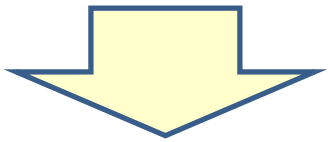
Does a change fall into "minor change" or "partial change application"?

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

<< >>

" "
' '

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



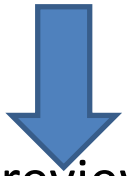
Sufficient cooperation between MF registrant (in-country caretaker) and marketing authorization holder is required for ensuring quality of drug product and smooth MF reviews.

Status of information registered in MF

Information registered in MF

Application form is filled in Japanese

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

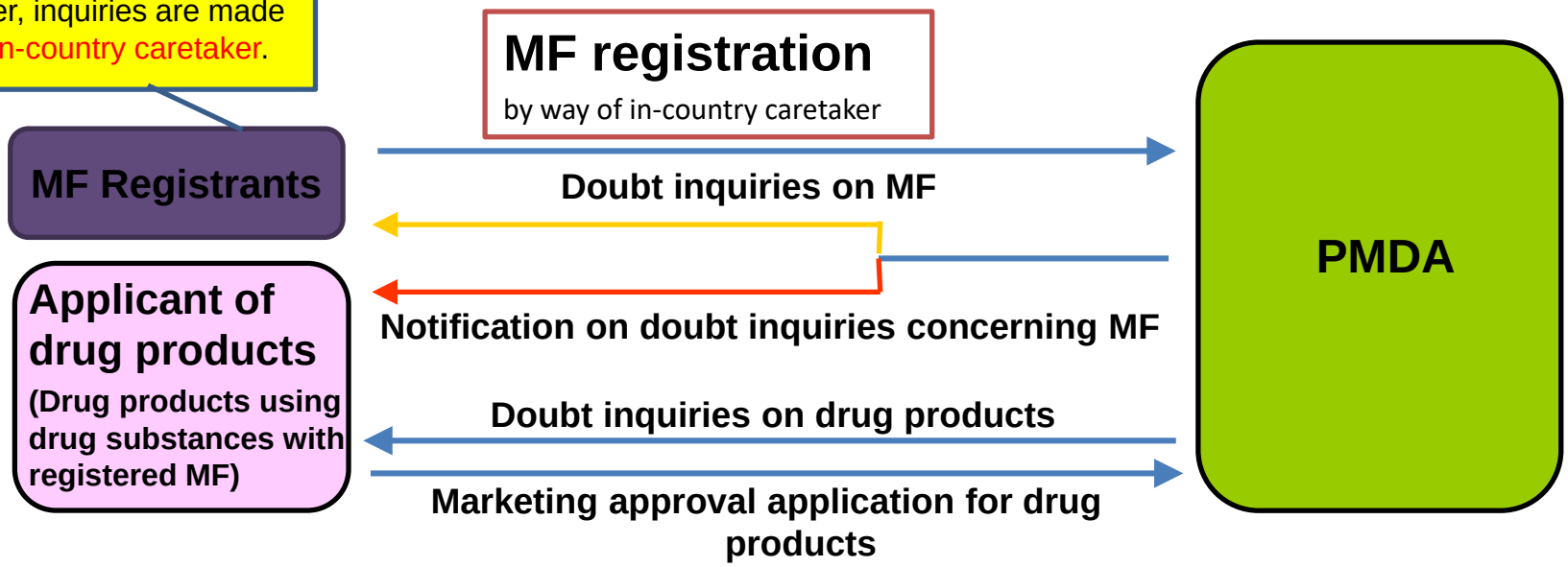


Original documents of Module 3 of CTD can be submitted only where it is written in English.
The summary written in Japanese or Module 2 of CTD is to be submitted where required by reviewers.

- The registered information is 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 a 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.

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

Contents

CONSIDERATIONS FOR PROCEDURE OF MF REGISTRATION APPLICATION

- "Guidance on handling of applications submitted on flexible disk etc." (PFSB/ELD Notification No. 0320005 dated March 20, 2006) should be referred to for considerations in preparing an application form.
- Before application procedure, check carefully that application data and attached documents are complete.
- Reflect the contents of past instruction related to inquiries to a new registration application.
- If anything is unclear in registration application procedure, use simple consultation for correct application and smooth reviews.
- Incorrect contact information causes wrong transmission of inquiries, etc.

Information on attached files

[Information on attached file] on an FD application form has [Appendix file name] and [File name of attached documents] . The difference is as follows:

[Appendix file name]

- ✓ Approved product information such as charts is required to be converted to PDF files and attached as well.

  e.g., structural formula, picture of a container
- ✓ List of drug products quoting the MF (not required to be attached where it is described in the remarks)
- ✓ Comparison table of before and after change (only for application for change registration and minor change notification)
- ✓ Statement (only for minor change notification)

[File name of attached documents]

- ✓ Reference data is required to be converted to PDF files and attached as well.
  Examples: "Flow diagram of manufacturing process," "Rationale for partial and minor changes," "Written reason for diverting foods and industrial products," and "particular account," etc.

Manufacturing method [1]

- Concept for description of manufacturing method

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

  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 established.
- 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 is required by reference to the Guideline for the Preparation of the Japanese Pharmacopoeia.

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

✓ Check carefully that the description is correct and complete.

Manufacturing site of drug substances

- Before application/notification, check carefully that information on manufacturing site is correct.
- Where the following dummy number is used for a manufacturing site of a drug substance, confirm the justification carefully and describe appropriate information.

<Reference>

⊙ For manufacturing sites of intermediates of drug substances (excluding case of diversion)

License (accreditation) No.: 99AZ666666

License (accreditation) date: April 1, 2005

⊙ In cases where foods or industrial products are necessarily diverted (only when the appropriateness is established)

License/accreditation No.: 99AZ777777/AG99977777

License (accreditation) date: April 1, 2005

CONSIDERATIONS FOR REPLACEMENT

For MF replacement, for all inquiries and response, the following materials should be submitted:

Both of

- A paper file of hard copies
- Electronic media (CD or DVD) with text

<Precaution for submitting electronic media>

- Convert it to a PDF file with text recognition available.
- Confirm electronic media is in accord with the paper media.
  (Attention should be paid to loss or overlap of pages, integrity of order)
- Electronic media of FD application, attached documents, and inquiry responses should be made separately.
- Generate a file name appropriately.
  (Too long names or symbol should not be used)
- Check for virus with the latest definition file before submission.

Other considerations

- For an in-country caretaker, prepare "in-country caretaker" column and describe it appropriately in the column, not in the remarks column.
- For MF registration application, data with logical explanation based on the results from sufficient evaluation and evidence should be prepared.
- Check carefully before application as incorrect or incomplete description may damage the confidence in the registrants.

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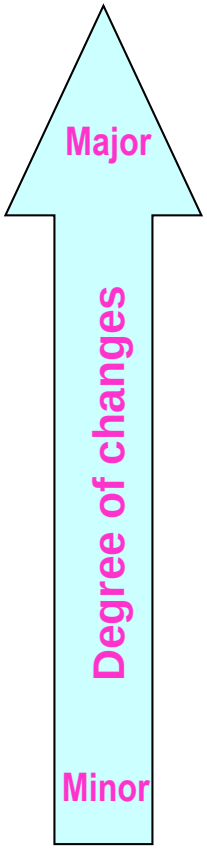
1. Application reviews of drug products quoting MF
2. Considerations at MF reviews
3. Considerations at change for information registered in MF
4. Case introduction

Procedure for changes in registered items



[1] Potential changes in the nature of drug substances due to changes in registered items

→ New application for registration

[2] Normal Changes (Changes not classified to [1] or [3])

→ Application for change registration

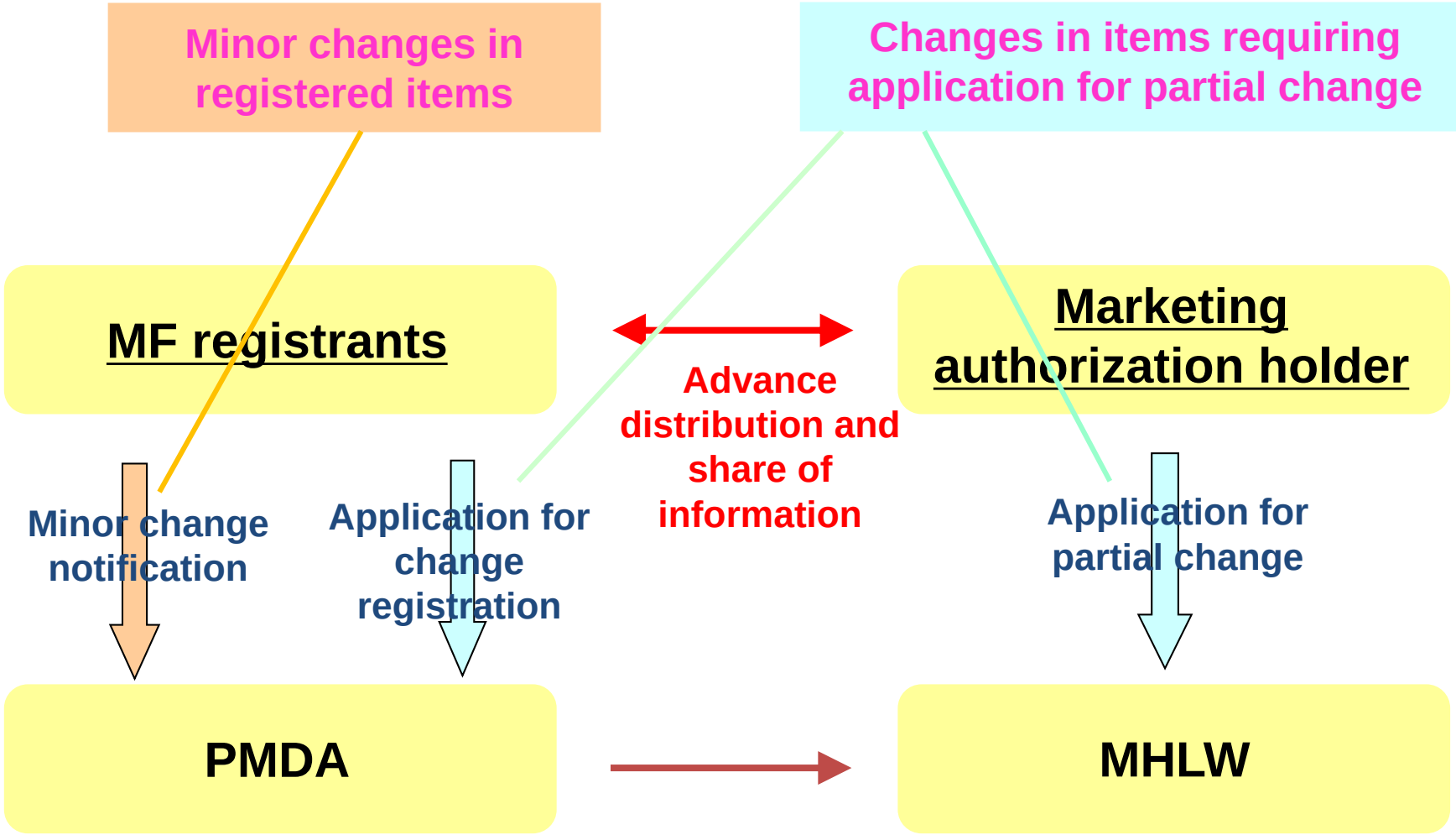
[3] Minor Change

Changes other than the following:

- Changes in the manufacturing method, etc. affecting the nature, characteristics, performance, and safety of drug substances.
- Deletion of the items listed in the specifications or changes in the specifications
- Changes in the inactivation or removal method for pathogenic factors
- Other changes which may affect the quality, efficacy, and safety.

→ Minor change notification

Changes in registered items in MF and partial changes of drug products



Changes in registered items [1]

- MF registrants should notify the applicants of changes in registered items in advance.

- Where a product has been already approved using the MF, the MF registrant also should notify the marketing authorization holder of the product of the change.
- In notification of minor changes in registered items, involving applicants and marketing authorization holders should be notified of the change.
- As this involves not only MF registrants but also the MA applicants or marketing authorization holders of drug products made with the substances, poor cooperation between them could led to troubles.

Changes in registered items [2]

- In the case of changing the items registered in MF

  MF registrants evaluate whether the change is classified as "minor change" or "not minor change" and is required to follow appropriate procedures for the change in registered items.

If the evaluation is difficult, they should sufficiently confer with MA applicant or marketing authorization holder of the drug product and confirm it.

Change registration	Not minor change (changes affecting the quality of drug substance)
Minor change notification	Minor change (changes unlikely to affect the quality of drug substance)

Changes in registered items as partial changes [1]

- Where registered items are changed partially, application for change registration of MF is basically required.

However,

- Even changes regarded as minor change may be required to be applied as MF change registration as well when the effect of the change on the drug product is assessed not minor.

- In these cases, marketing authorization holders of drug products evaluate whether the effect of the change is acceptable in view of contents of the marketing authorizations and should submit the applications for partial change of their drug products.

Changes in registered items as partial changes [2]

- In the cases that effect of a change is considered to be acceptable, in view of the contents of the relevant marketing authorizations.
  - MF registrants submit an application form for change registration of registered items to the regulatory authority.

    * Attached documents on changes in registered items

      Actual data

      Appropriate validation

      A statement for the fact that change control has been performed, etc.

  - Where contents of a change are considered to have an unacceptable effect, the marketing authorization holder may not accept the change.

Changes in registered items as minor changes [1]

- A minor change notification in MF registered items is submitted basically after confirming that the effect of the change is minor.

➢ In the cases that the change is confirmed to be minor

MF registrants submit notification of the minor change in the registered items to the regulatory authority.

* Attached documents

  Appropriate validation

  A statement for the fact that change control has been performed, etc.

* In this case, a marketing authorization holder of a drug product made with MF registered drug substance is not required to notify minor change in approved items.

Changes in registered items as minor changes [2]

- Justification for a change in MF registered items notified as a minor change is not reviewed at the time of the notification in principle.
  - An MF registrant (and an applicant of a drug product) takes *self-responsibility* for the notification.
  - Justification for minor change notification is assessed on review after an application for a partial change of a drug product or on GMP inspection after the notification.

Perform routinely the change control specified in revised GMP regulation.

Changes in registered items as minor changes [3]

- A minor change notification in MF registered items is submitted basically after confirming that effect of the change is minor.

However,

- In a case where effect of a change in MF registered items expected to be minor at registration has been assessed as not minor
  - * where results that can not deny effect on the quality have been indicated at change control procedure of a MF registrant, or
  - * where a change has been assessed as not minor as a result of discussion with the marketing authorization holder of the product.

The change is canceled, re-examined, notified as an application for a partial change or registered again as a new drug substance, etc.

Changes in registered items as minor changes [4]

- *Where GMP inspection has revealed that a change in manufacturing process, etc. which should not be treated as a minor change has been notified as a minor change*
  - The minor change notification becomes nullified.
  - It is likely to constitute a violation of the Pharmaceuticals and Medical Devices Law.
  - For products manufactured in the changed process, cancellation of shipments, recall, or other regulatory actions are to be taken according to risks due to the change.

Perform routinely the change control specified in revised GMP regulation.
Due communication should be made with marketing authorization holder.

Request

Where a MF registered item is changed, the procedure related to approval of the drug product is generated along with the procedure on MF registration. Sufficient information sharing and adequate regulatory measures between MF registrants and marketing authorization holder is critical.

Access on the PMDA website in Japanese

ホーム > 審査関連業務 > 承認審査業務（申請、審査等） > 原薬等登録原簿（MF）
https://www.pmda.go.jp/review-services/drug-reviews/master-files/0007.html