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Guidance on Drug Master File System in Japan

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Notes

- In Japan, the Drug Master File (DMF) is called “Master File” or “MF”. So these phrase are represented a part of this presentation.

What is the Drug Master File System?

- The Drug Master File (DMF) System, allows the manufacturers of Active Pharmaceutical Ingredients (APIs) to submit the detailed information (manufacturing methods, data, etc.) of APIs to the Review Authority (PMDA).

- The registered information (manufacturing methods, data, etc.) is quoted as the necessary information for an approval review of the pharmaceutical products in which APIs is used.

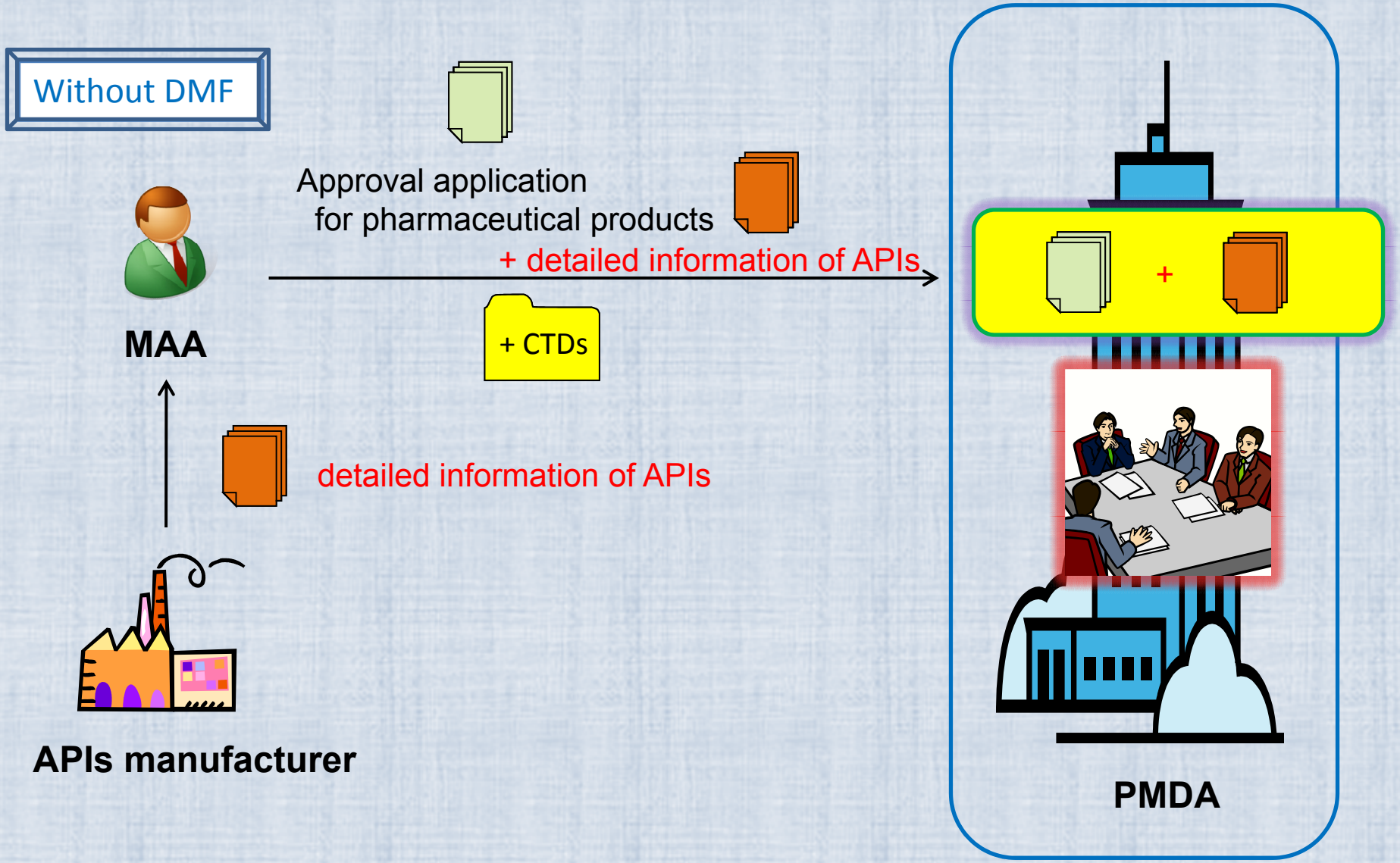
The Purpose of DMF

- To protect the “know-how” of API manufacturing methods against the marketing authorization applicant (MAA) / holder (MAH) of pharmaceutical products.

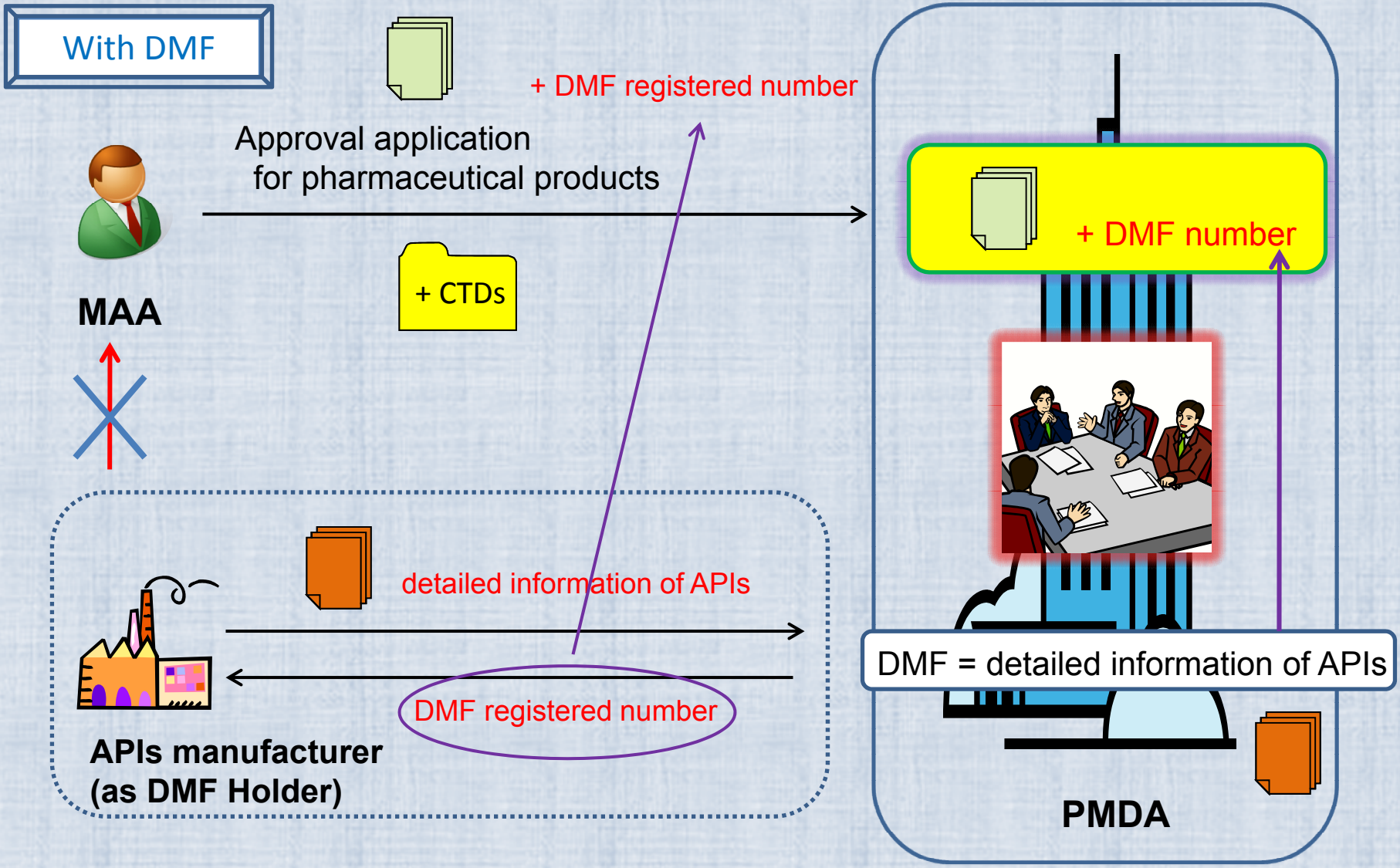
  * **DMF is not a patent.**

- To streamline the review process for approval application of pharmaceutical products.

Outline of Application Flow for Pharmaceutical Products



Outline of Application Flow for Pharmaceutical Products



Requirements for DMF Registration

- Who must register DMF?

  No, it is voluntary.

- How much is DMF registration fee?

  No fee shall be charged for DMF registration.

DMF Holder (a registrant)

The requirement as DMF Holder:

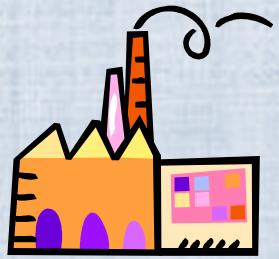
A company manufactures the APIs for DMF registrations practically.

[Attention]

Following conditions; No one will be a DMF Holder.

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

- the relationship between a client and a trustee
  (a client does not manufacture the APIs practically)



Items for DMF registration

- Drug substances, intermediates (for medical use)
- Pharmaceutical products materials (materials of pharmaceutical products with special dosage form, etc.)
- New excipients and pre-mix excipients with a different composition ratio from the existing ones
- Materials for medical devices (currently under consideration)
- Others

  (a) Containers/packaging materials

  (related to medical devices are currently under consideration)

  (b) TSE data

* DMF for Over-the-counter (OTC) products (except for new APIs, and TSE data) may not be utilized for now.

** TSE data: the aim is not to protect the “know-how”

DMF registered Items

Category	(%)
APIs (Drug substances, etc.) [a]	98.7
New excipients [b]	0.5
Materials for medical devices [c]	0.0
Others [d, e]	0.8

These are the figures for Sept. 30, 2010.

(a) Drug substances, etc. include the drug intermediates and the materials with special dosage form.
(b) New excipients include new-premix excipients with a different composition ratio from the existing ones.
(c) This category is currently under consideration.
(d) This category includes TES data.
(e) The related to medical devices are currently under consideration.

Attentions (1)

- In Japan, the application form, notification, and other related documents which are submitted to the Minister of Health, Labour and Welfare, the PMDA, etc. shall be written in Japanese (Article 283 of the Regulations).
- The DMF registration application form, notification, and other related documents shall be written in Japanese.
- It is necessary to prepare the registration application and notification forms in the application software (this site is Japanese only, http://web.fd-shinsei.go.jp/).

Attentions (2)

- To complete the approval application form for pharmaceutical products, the detailed description of the manufacturing method is needed in the manufacturing method column. (All of the processes, from the starting materials to the primary packaging process of the drug substances, shall be described according to the process sequence.)

- And the DMF registration application form shall be prepared according to the same manners. Because the DMF registered items shall be regarded as a part of information which should be described in an approval application form and attached documents for the pharmaceutical products.

Approval application of pharmaceutical products

DMF use	DMF not use
If the pharmaceutical products applicants quote DMF for their application, the applicant shall attach a copy of the registration certificate and a copy of the contract with the DMF Holder regarding utilization of the DMF.	If the pharmaceutical products applicants do not quote DMF for their application, the applicant shall describe the detailed manufacturing process for APIs (refer to the below examples) on the application form.
[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 approval application form (pharmaceutical products)] (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)』at『25℃ for 24 hours』. Add sodium borohydride 『(3.2 kg)』, and mix further at 『25℃ for 24 hours』. Filter the reaction mixture, and ble 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 equal.

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

The approval application of pharmaceutical products use DMF	**DMF registration application**
If the pharmaceutical products applicants quote DMF for their application, the applicant shall attach a copy of the registration certificate and a copy of the contract with the DMF Holder regarding utilization of the DMF.	The DMF registrant shall describe the detailed manufacturing process for APIs on the DMF registration application. If the DMF registrant is a foreign manufacturer, appointed in-country caretaker shall prepare the DMF 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 DMF 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)』 at『25℃ for 24 hours』. Add sodium borohydride 『(3.2 her at『25℃ for 24 hours』. Filter the reaction mixture, 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 equal.

Attentions (3)

- It is necessary for the MAH/MAA to understand the outline (summary) of the APIs manufacture methods if the APIs is DMF.

- The DMF Holder will discuss or notify the relevant MAH/MAA about the changes in the registered information (including the DMF registration application form).

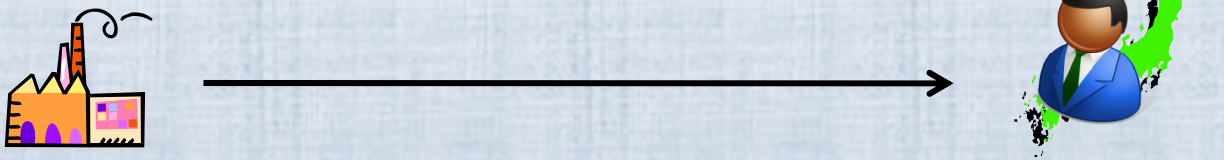
Foreign Manufacturers of APIs

The foreign manufacturers of APIs can apply for DMF registration.
But the foreign manufacturers cannot apply directly to PMDA.

[Essential matters]

- To appoint "in-country caretakers of DMF" in Japan.
- To obtain the foreign manufacturer accreditation.

Procedure of DMF registration application



Foreign manufacturers of APIs (DMF Holder)

In-country caretakers in Japan

the applications in Japanese + CTD M3

PMDA

In-country caretakers of DMF, who play important roles in the related administration procedures, etc. in Japan.

Duties of In-country Caretakers for DMF

- DMF 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 DMF play important roles in the related administration procedures.

- In the process of approval review for a drug (pharmaceutical product), if the inquiry regarding the quoted DMF registered contents is necessary, PMDA directly contacts the DMF Holder (if the DMF Holder 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 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 DMF Holder so as to decide on important items in advance.

DMF Holder for APIs from all parts of the world

Countries of DMF Holders	(%)
Japan	43.3
Asia (except Japan)	23.6
Europe	28.4
America	4.6
Other	0.07

These are the figures for Sept. 30, 2010.

Registration, and Changes in DMF

DMF Registration

- At the time of DMF registration, PMDA checks whether it is written in the correct format, e.g., minimum required items are included (application) and data is attached (CTD M3).
- DMF is reviewed at the time of the approval review for the pharmaceutical products quoting DMF.
- DMF registered items shall be regarded as a part of information which should be described in an approval application form and attached documents for the pharmaceutical products.

After DMF Registration

For the DMF Holder (or In-country caretaker)

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

At PMDA

- At a later date, DMF registration number, registration date, date of the change in registered item, name and address of the DMF Holder, the name of registered items, and the registration category will be published in the PMDA homepage.
(http://www.pmda.go.jp/operations/shonin/info/mf/mfkouji.html)
These published contents are Japanese only.

Changes in the registered contents

The DMF Holder will discuss or notify relevant MAH/MAA about the changes in the registered information (including the DMF registration application form).

- [Application for Change in Registered Master File for Drug Substances, etc.]; As a rule when changes the registered contents

- [Scope of minor change notification]; other than those describes 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

Changes in the registered contents (cont)

[Attention]

- If the changes in the items in DMF will substantially alter of APIs, please note that a new DMF registration form, not a change of registration must be submitted.

DMF Registration Application

◆ Application for Registration of Drug Substances, etc. (Form No.42)

- Application * (Original 1, Duplicate 1; Duplicate must not be a copy of Original)
- Data of Application for DMF Registration
- Attached document (including CTD Module3)
- Return Envelop for DMF Registration Certificate and Duplicate Application

* the cover page of application with a seal of the representative of API manufacturer as the DMF registrant (when the API manufacturer is foreign company, a handwritten signature of representative is accepted instead of seal) ; other document forms are the same manner (see next slide)

** the signature and seal of their in-country caretaker is not acceptable

Changes the registered contents (1)

◆ Application for Change in Registered Master File for Drug Substances, etc. (Form No.46)

- Application (Original 1, Duplicate 1; Duplicate must not be a copy of Original)
- Data of Application for DMF Registration
- Attached document (including CTD Module3); as necessary
- Original Registration Certificate
- Other (Old/New Comparison table, etc)
- Return Envelop for DMF Registration Certificate and Duplicate Application

Changes the registered contents (2)

◆ Minor Change Notification for Master File for Drug Substances, etc. (Form No.47)

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

* Do not forget to submit the statement. Remember that a seal (or a handwritten) of the DMF Holder (the API manufacturer) is need on "the cover page of Minor Change Notification" and "the statement".

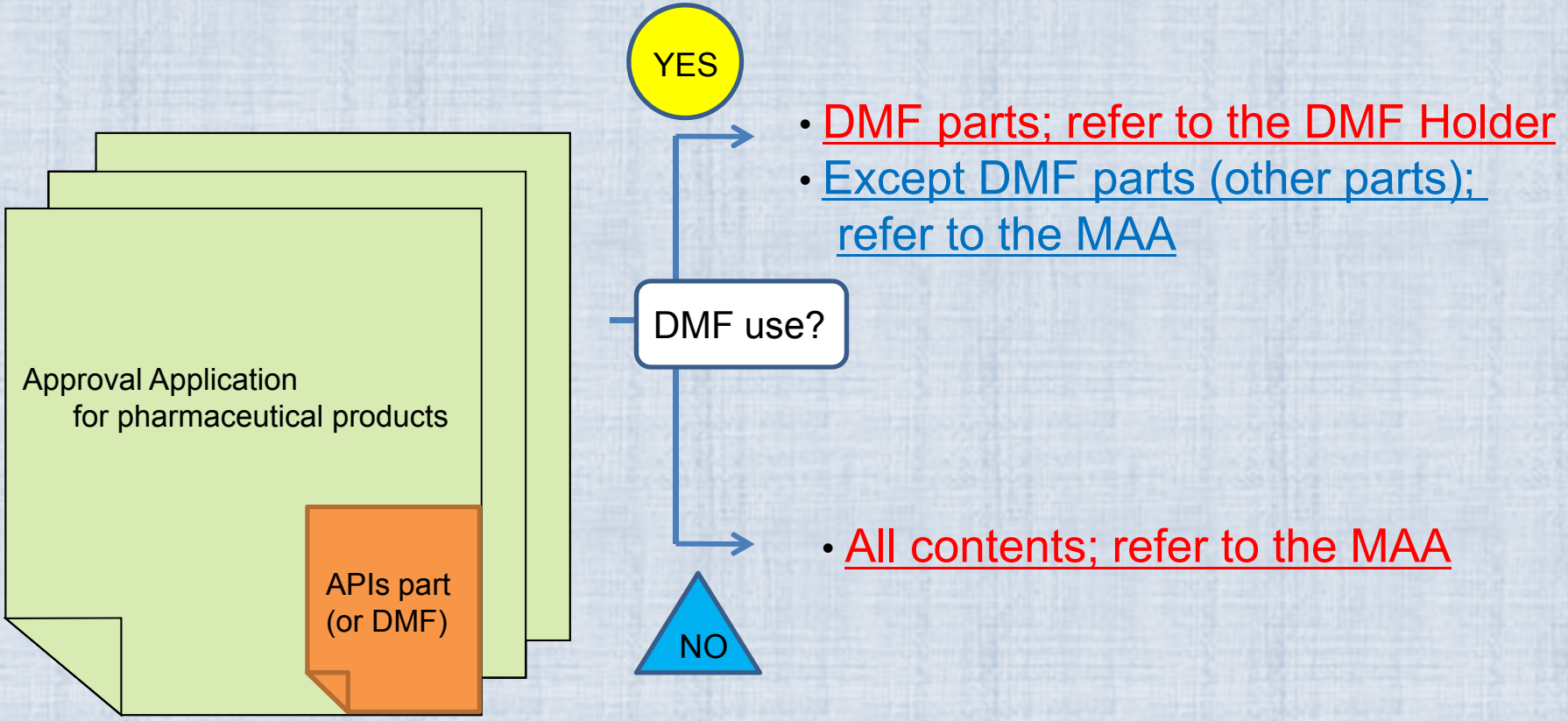
** The DMF Holder must submit the notification to PMDA within 30 days after the change made.

Relationship the registered date and the version number of registration after DMF registration

	Registered date	Version number of DMF registration
Application for Change in Registered Master File	Change	Change
Minor Change Notification for Master File	No change	No change
Application for MF certificate Rewriting *	No change	No change
Application for MF certificate Reissue *	No change	No change

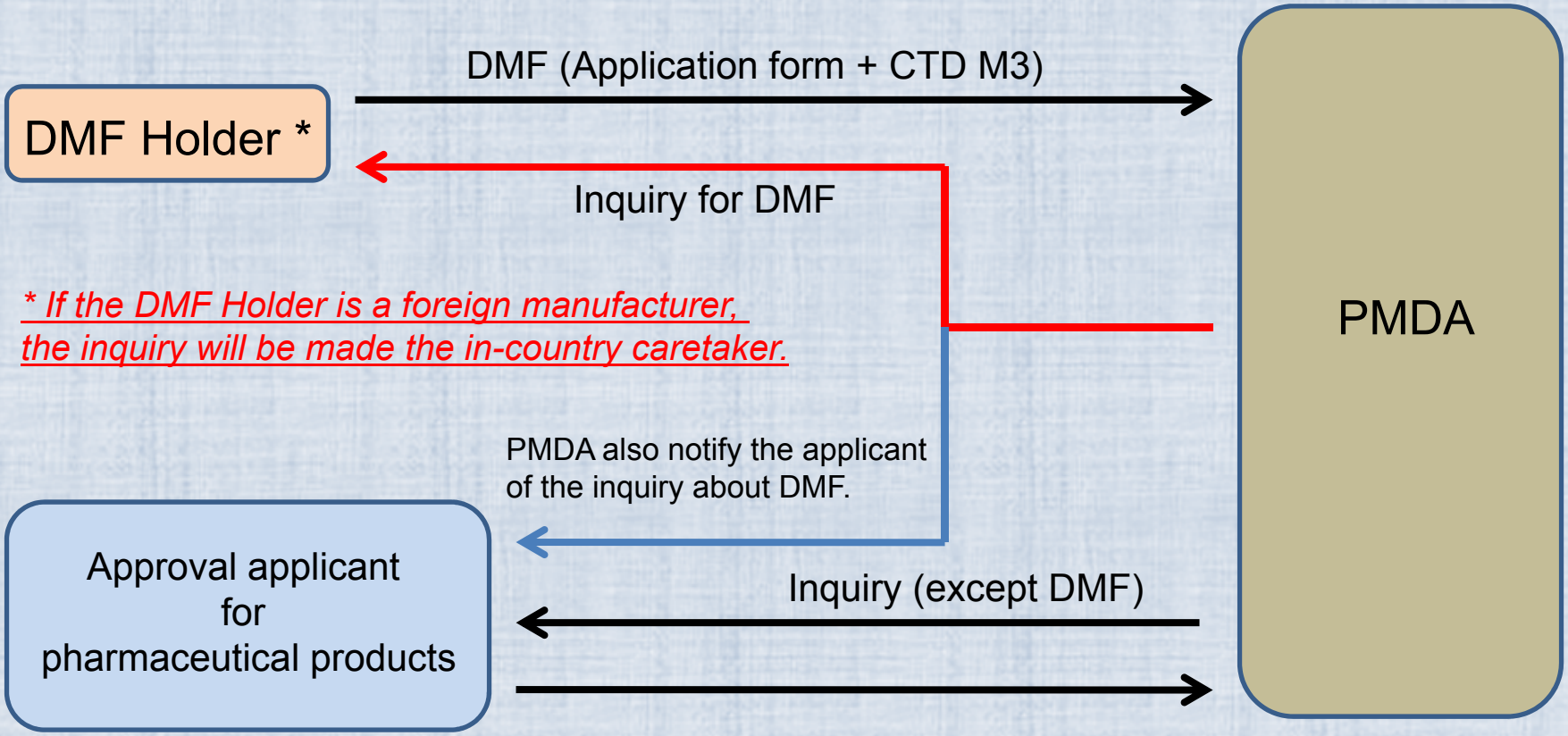
- DMF Registered Number is not be changed.
- DMF Registered Certificate will not be issued when DMF Holder submits the minor change notification
- * About DMF registration certificate

Handling with DMF



- The MAA is responsible for all contents (the approval application and DMF).

Inquiries (as questions) on Approval Reviews



- Approval application (with DMF registration number) and CTDs
- a copy of the contract with the DMF Holder regarding utilization of DMF
- a copy of DMF registration certificate

Cancellation of DMF

◆ Notification for MF Registration Cancellation

* Cancellation of registered DMF by DMF Holder.

** This notification does not prepare the application software. Therefore, the notification shall be submitted in writing.

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

Summary

- DMF is not a simple registration. And the DMF Holder should manage the registered contents appropriately.
- DMF registered contents will be regarded as a part of information which should be described in an approval application form and attached documents.
- It is important for the DMF Holder, the in-country caretaker and related persons to understand the Japanese regulation (Pharmaceutical Affairs Law) and the guidance.
- The MAA/MAH, the DMF Holder and the in-country caretaker need to communicate with each other.

Thank you for your attention

- PMDA Homepage (English)

  http://www.pmda.go.jp/english/index.html
- About DMF System (English)

  http://www.pmda.go.jp/english/service/master_file.html
- Registered DMF items for PMDA (Japanese only)

  http://www.pmda.go.jp/operations/shonin/info/mf/mfkouji.html