How to register to MF in Japan
Points to Consider

Master File Management Group
Division of Pharmacopoeia and Standards for Drugs
Office of Standards and Guidelines Development
KENTARO HASHIMOTO

Notes

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

Today's Topics

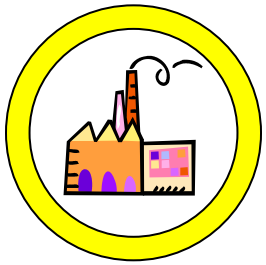
1. What is the Drug Master File(MF) System?
2. in-country caretaker
3. Disclosed(Open) part／Restricted(Closed) part for MAH/MAA
4. Case introduction
5. addition item in new MF registration

What is the Master File System?

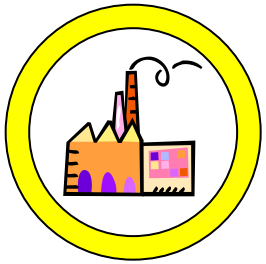
What is the Master File System?

- To protect the “know-how” of API manufacturing methods against the marketing authorization applicant (MAA) / holder (MAH) of pharmaceutical products.(* MF is not a patent.)

MF Holder



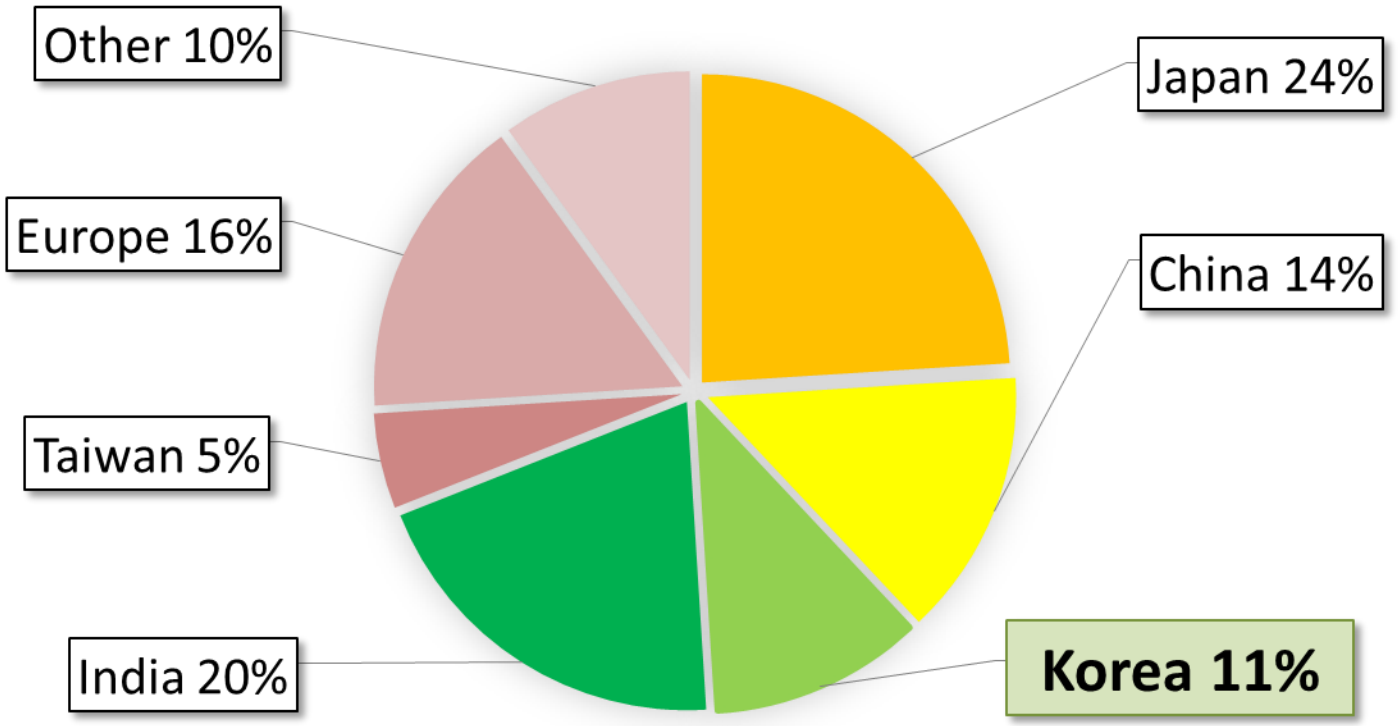
manufacturer



Synthetic route development companies(manufacturer)

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

Tendency of latest four years in new MF registration



What is the Master File System?

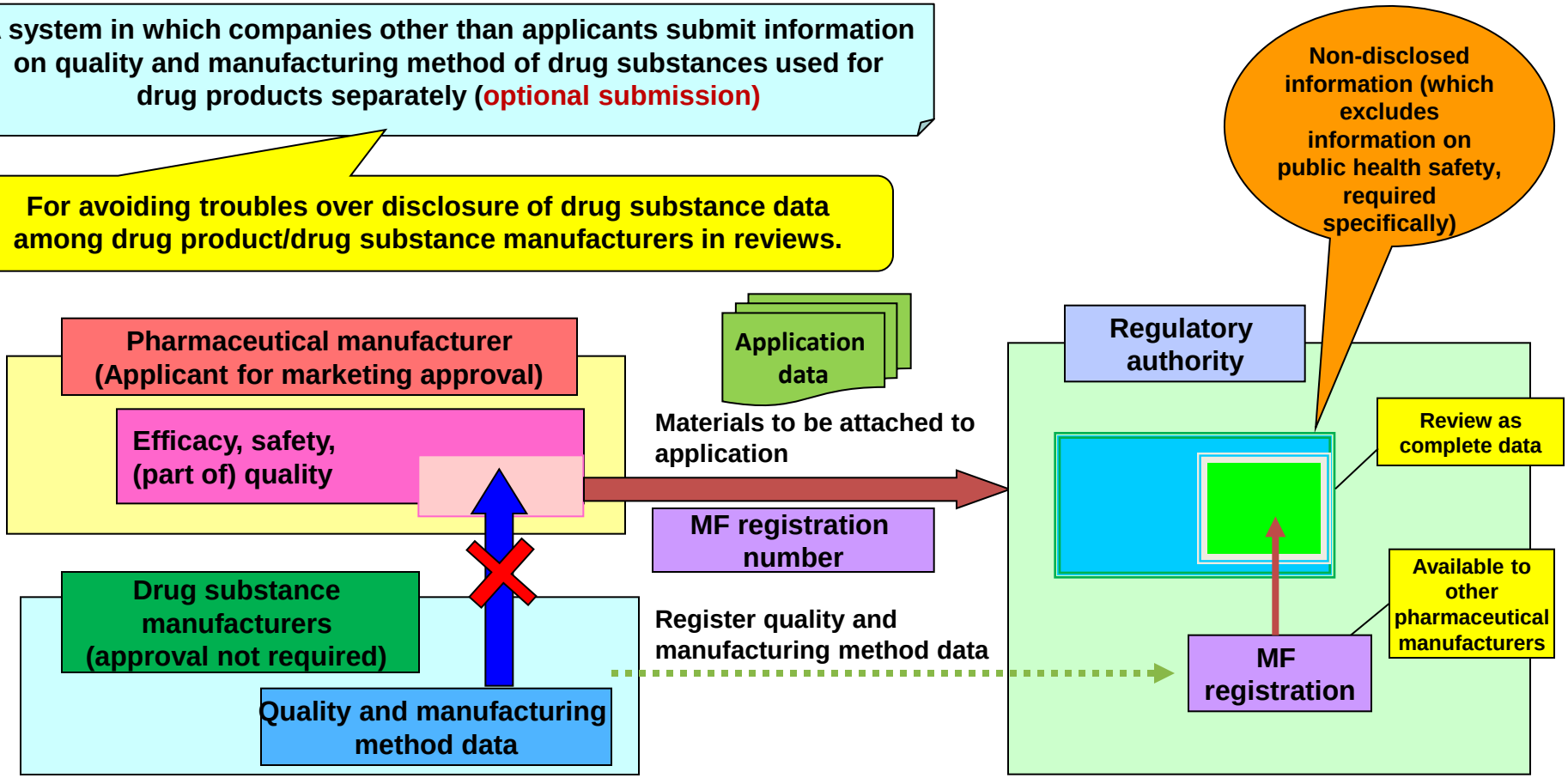
- Registration in the MF is optional. An MF registration certificate is not a marketing certificate.
- In a regulatory review, items registered in the MF are quoted as information necessary for the review. Some of these items will be approved items.

Approval reviews for drug products quoting MF

Master file is used both in US and EU

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.



in-country caretaker

in-country caretaker

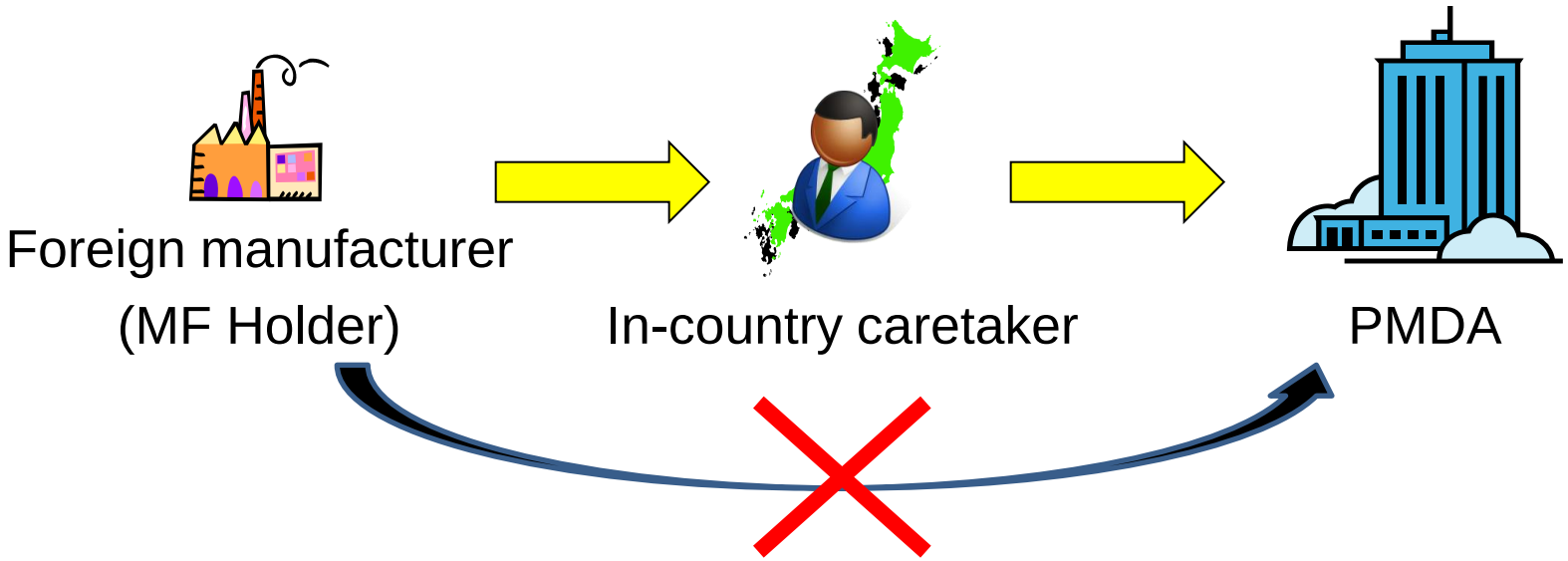
- Foreign manufacturers applying for MF registration must select an in-country caretaker for drug substances (APIs), etc.

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 is living in Japan and will undertake clerical work for the relevant registration, etc. Foreign manufacturer(MF Holder) cannot submit "know-how" of API manufacturing methods to PMDA directly.



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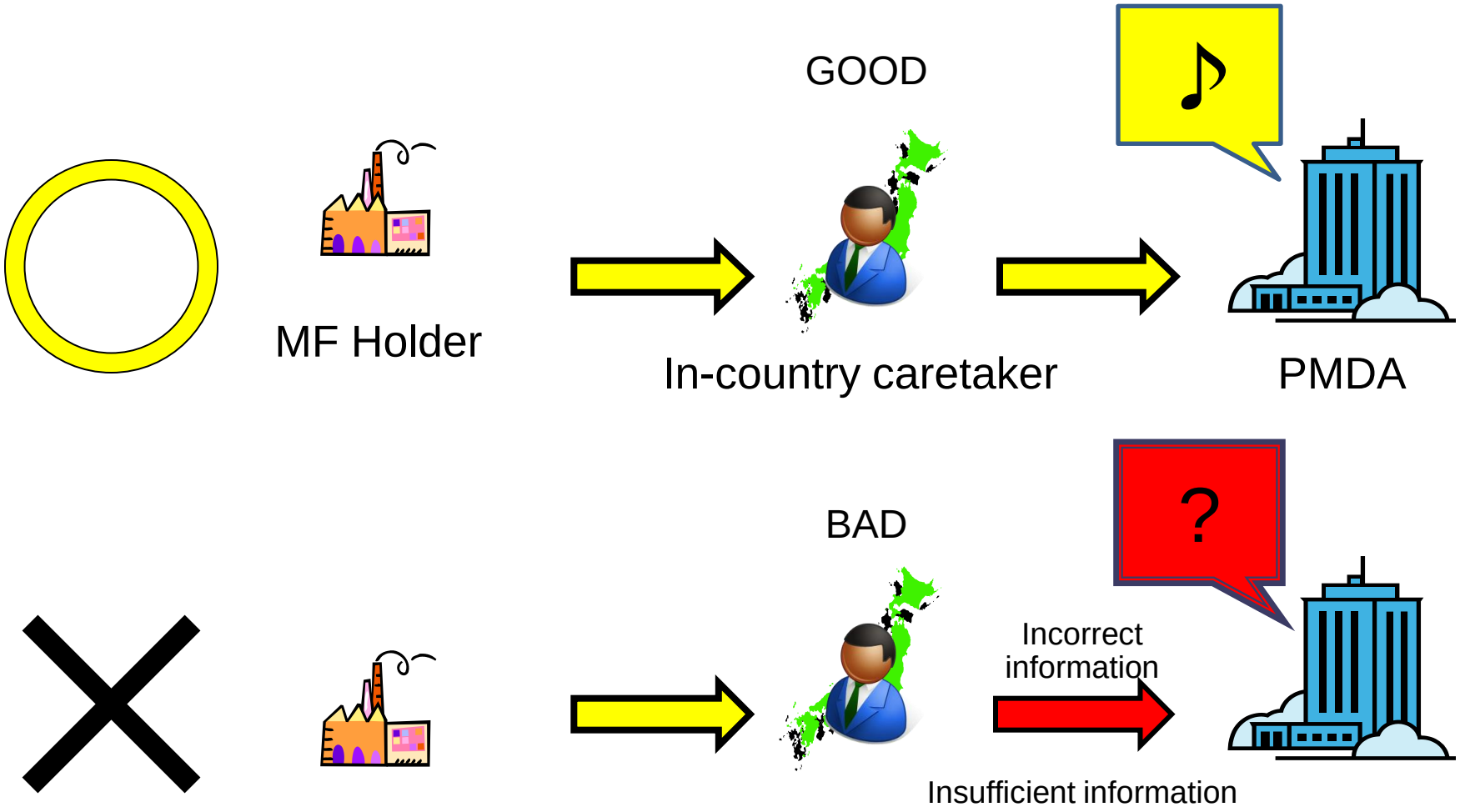


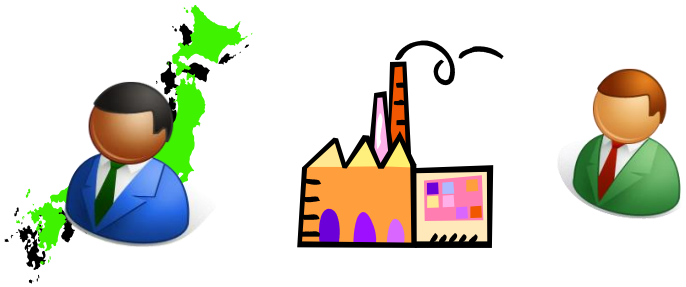
Mutual understanding and mutual cooperation are necessary

Registration

GMP

Review

Others



Checklist for Application Form for MF Registration

(http://www.pmda.go.jp/review-services/drug-reviews/master-files/0005.html)

This checklist does not cover all of the requirements for preparing the approval application form. For the descriptions on manufacturing methods, please refer to Attachment 1 “Guideline for Descriptions on Approval Application Forms for the Manufacturing Method of Chemical Drug Substances,” PFSB/ELD Notification No. 0210001 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated February 10, 2005.

Disclosed(Open) part／ Restricted(Closed) part

Disclosed(Open) part／ Restricted(Closed) part(1)

- **It is important for the MAA/MAH, the MF Holder and the in-country caretaker to understand the Japanese regulation (PMD Act, PFSB / ELD Notification No. 0210001 February 10, 2005 and PFSB / ELD Notification No.11173 December 11, 2014).**

- **[Disclosed(Open) part] The MAA/MAH, the MF Holder and the in-country caretaker must to communicate with each other, in advance.**

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

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.2.4 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.2.4 Manufacturing Process Development (name, manufacturer)		* ○

Note)

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

Disclosed(Open) part

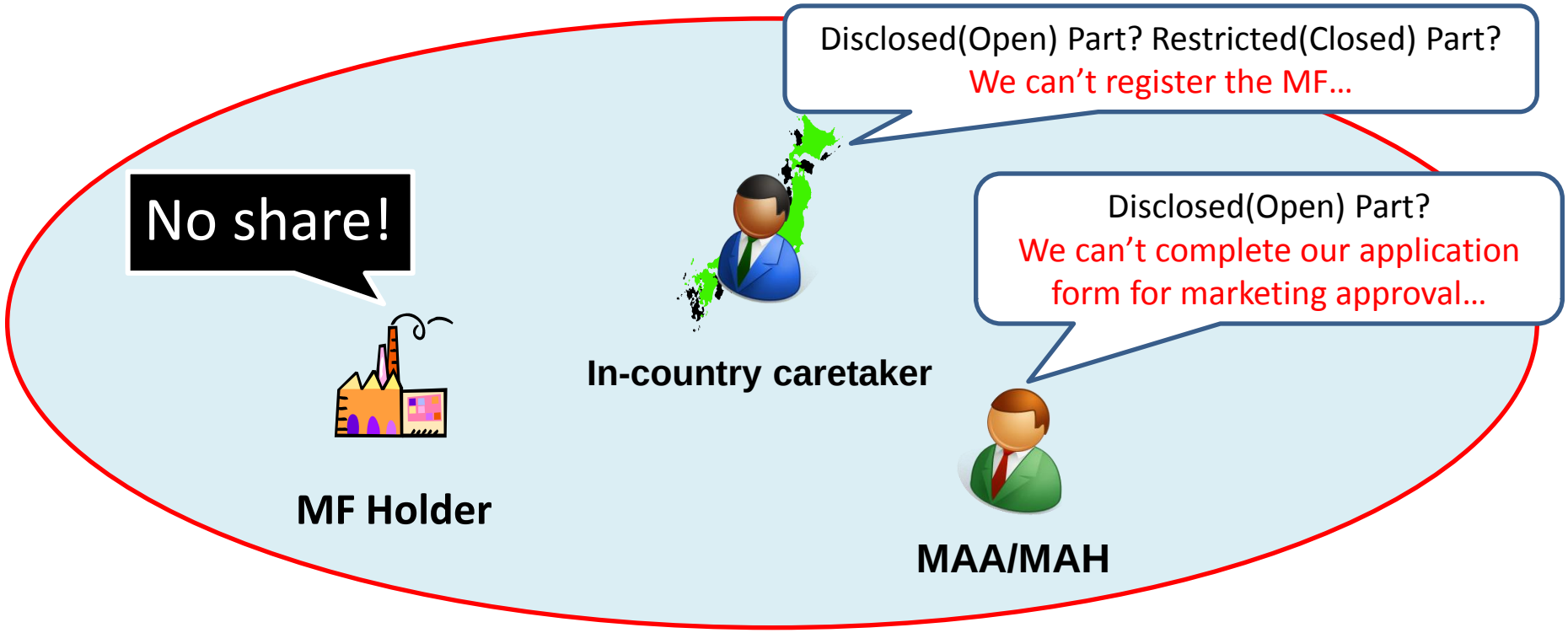
CTD module3	Disclosed (Open) part	Restricted (Closed) part
3.2.S.1 General Information (name, manufacturer)	○	
3.2.S.2.1 Manufacturer(s) (name, manufacturer)	○	
3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)	○	
3.2.S.3.2 Impurities (name, manufacturer)	○	
3.2.S.4.1 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)	○	

both of the restricted and disclosed part are basically disclosed

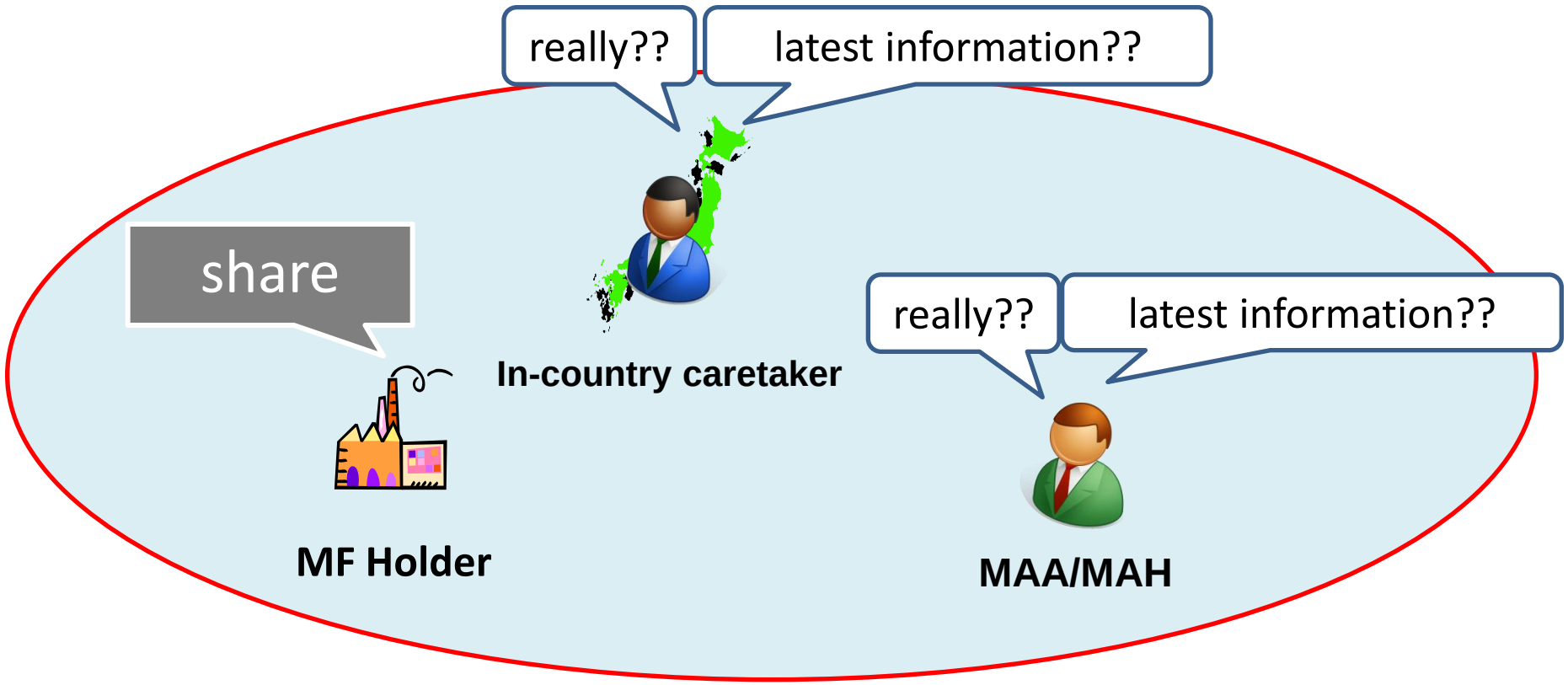
CTD module3	Disclosed (Open) part	Restricted (Closed) part
3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)	○	*○
3.2.S.4.4 Batch Analyses (name, manufacturer)	○	*○
3.2.S.4.5 Justification of Specification (name, manufacturer)	○	*○

Note)
* 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.

It is necessary to hold information sharing beforehand

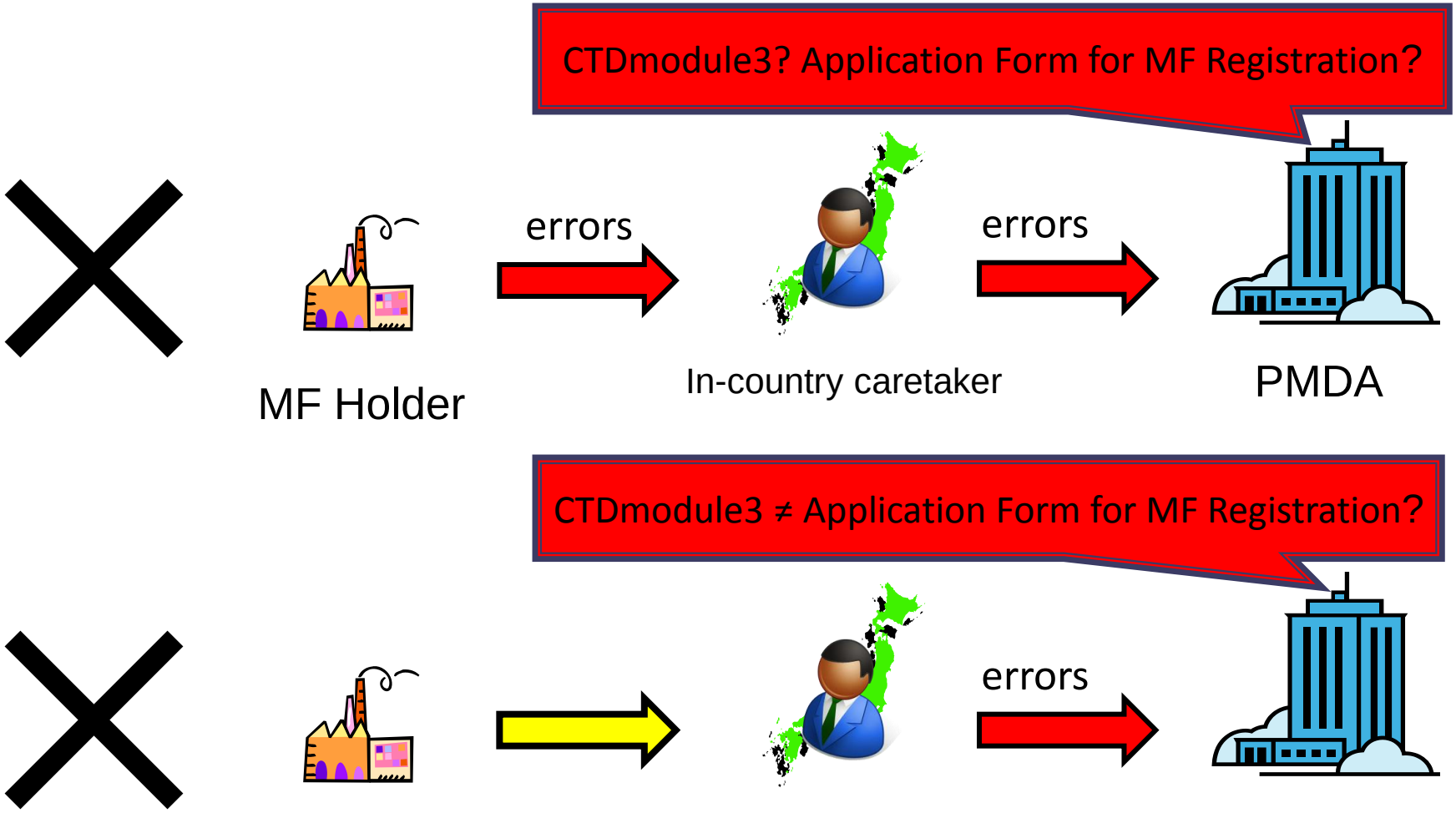


It is necessary to hold information sharing in an appropriate timing

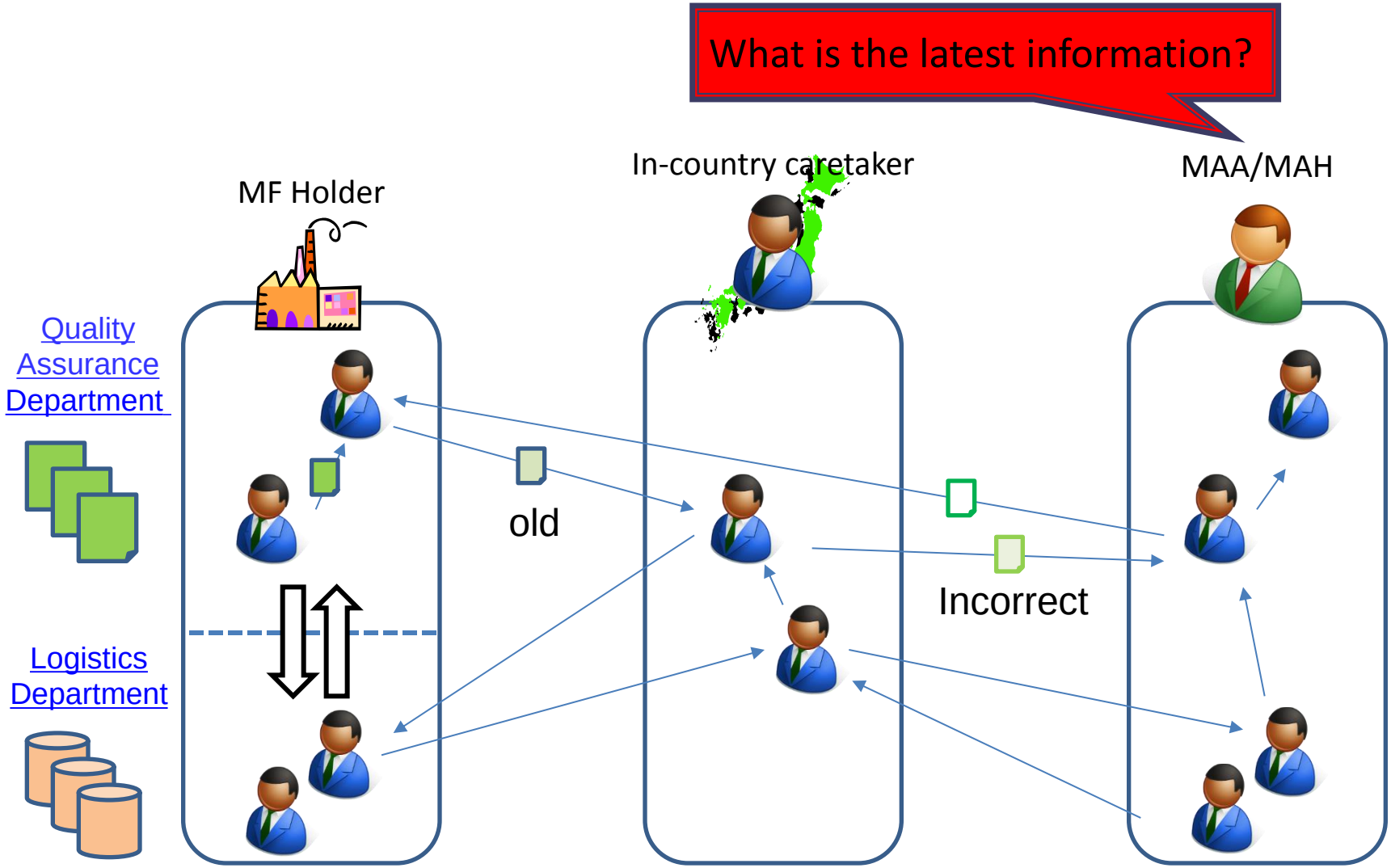


Case introduction

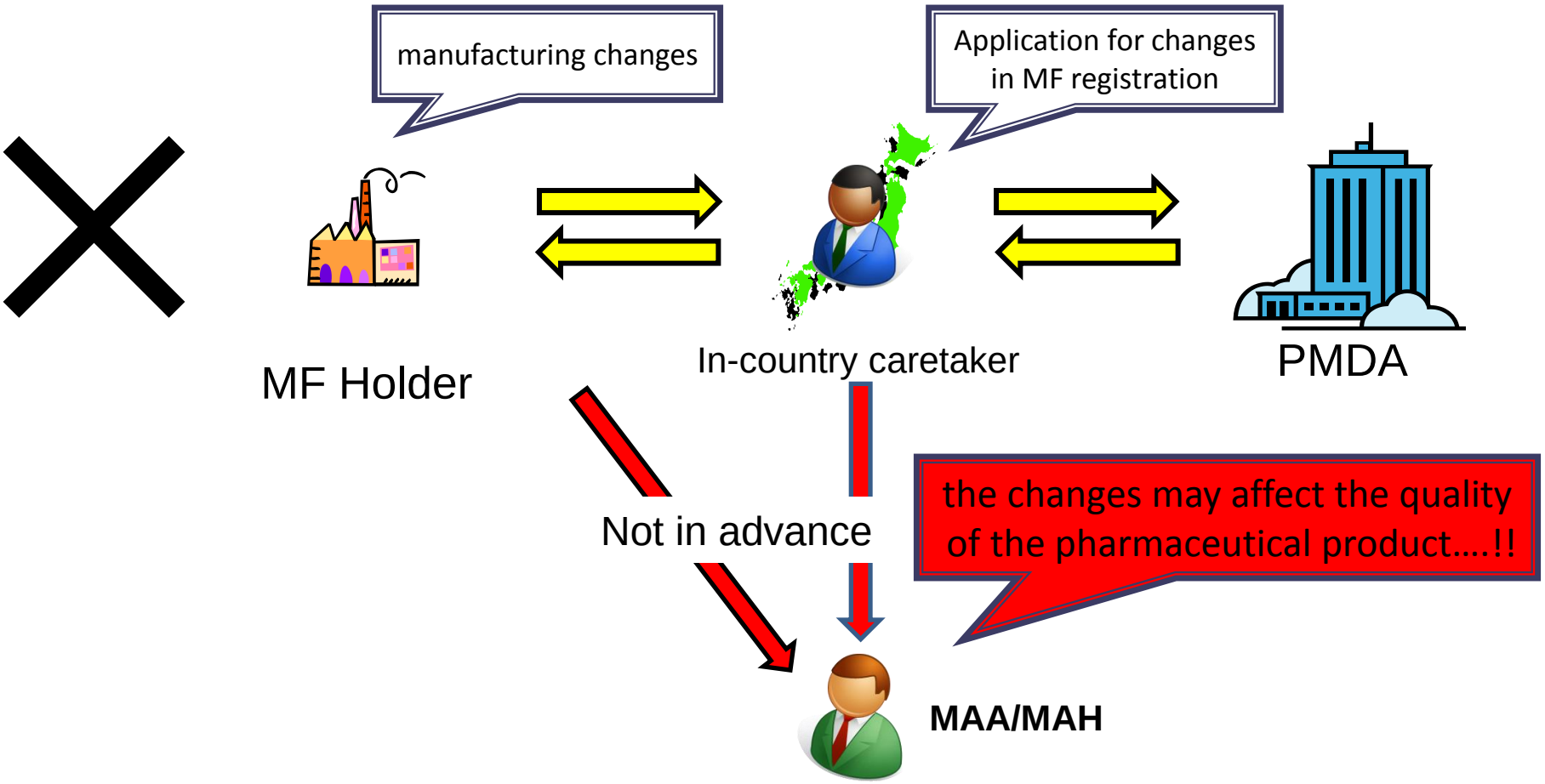
Case 1 : There are some (sometimes serious) errors in CTDmodule3, Application Form for MF Registration .



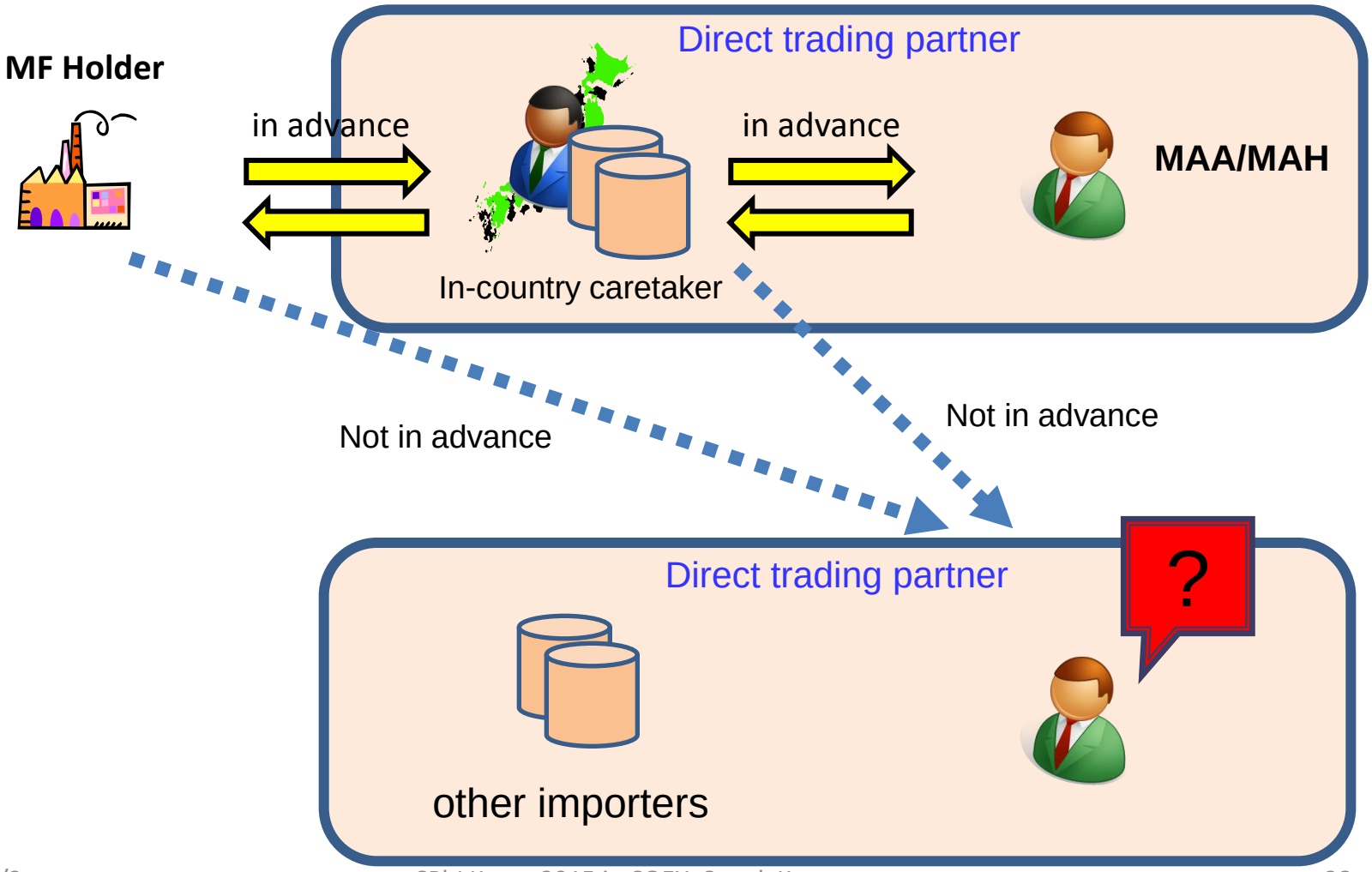
Case 2 : It does not work information transmission between an In-country caretaker, a MF Holder, a MAA/MAH



Case 3 :It is lacking in concreteness to hold information sharing beforehand



Case 4 :It has not been made abundantly clear to hold information sharing beforehand



Addition item in MF registration

PFSB / ELD Notification No.11173 December 11, 2014

<Items for MF registration: at this time>

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

Note) 31 MF (Medium, Medium Excipient, etc) were registered at 2015/06/30.

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 at an appropriate time between MF Holders and marketing authorization holder is critical.

Pharmaceuticals and Medical Devices Agency

Thank you for your kind attention.