Pharmaceutical Regulations in Japan

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* A Japanese translation is the official edition.

Today's contents

- Drug manufacturing/marketing
- Accreditation of foreign manufacturer and GMP compliance review
  - Accreditation of foreign manufacturer
  - GMP compliance review in Regulatory review
- Drug Substance Master File (MF)

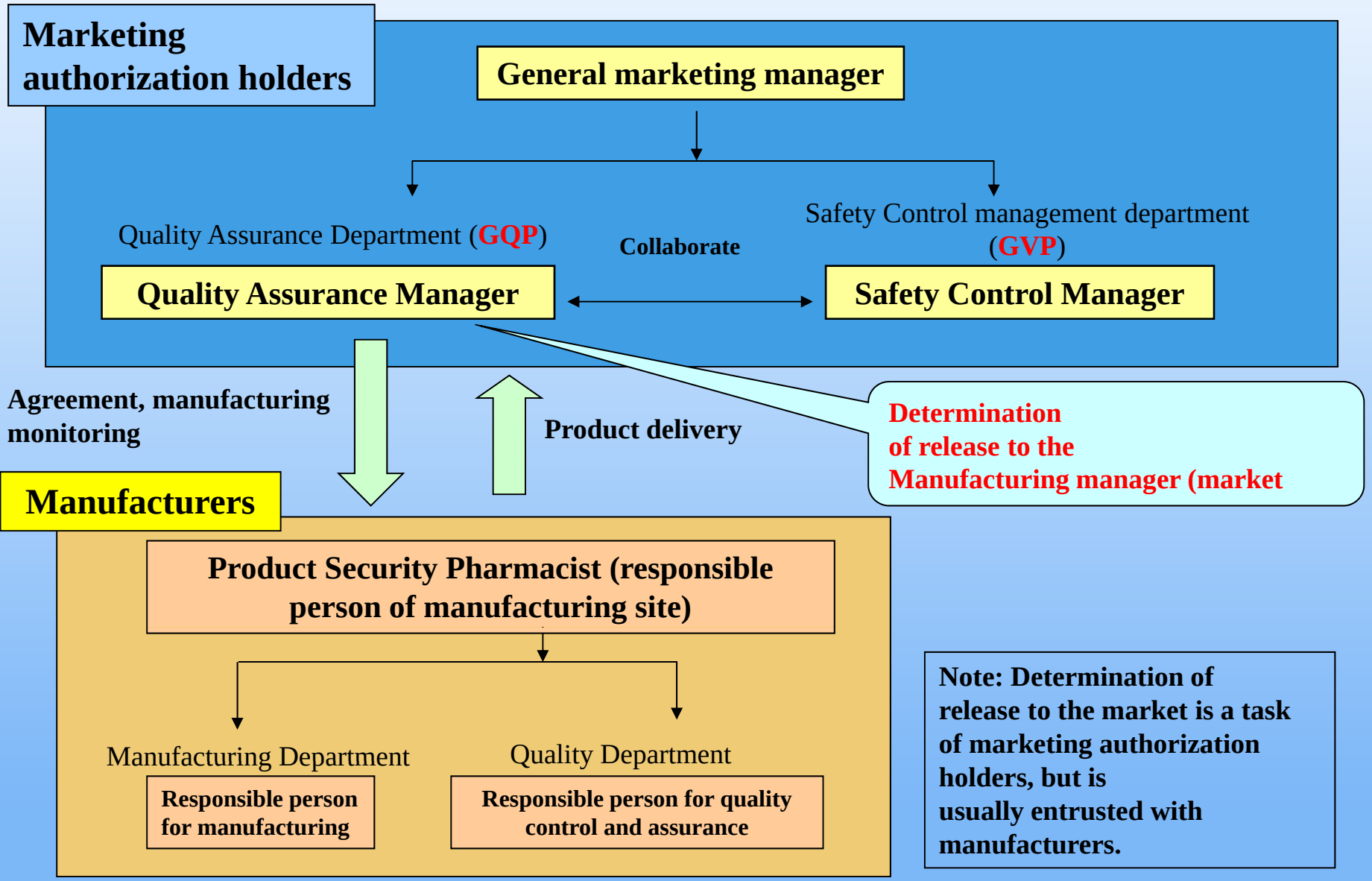
DRUG MANUFACTURING/MARKETING

Regulations Related to Drug Manufacturing/Marketing

- Manufacturing/marketing refers to selling or delivering the manufactured (including commissioned manufacturing) or imported drugs (excluding drug substance).

- There are various provisions in the Pharmaceutical Affairs Law so that the drug manufacturer/market authorization holder takes all responsibilities from manufacturing to post-marketing affairs.

Collaboration between Marketing Approval Holders and Manufacturers



For the marketing of pharmaceutical products

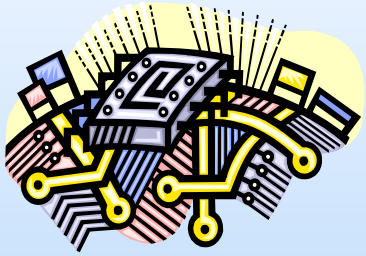
- License of manufacturer/market authorization holder is necessary.
- Obtain license by demonstrating that the business entity is capable of responsible manufacturing, quality control and post-marketing safety control of pharmaceutical products.
- License (accreditation) of manufacturer is necessary.
  - License (accreditation) of manufacturer is obtained by showing that the party concerned has capacity to manufacture drugs.
- Manufacturing/marketing approval is necessary.
  - It is necessary to collect the data related to drug quality, efficacy and safety and have those reviewed and approved by the Minister of Health, Labour and Welfare.

Marketing approval requirements for pharmaceutical products (Section 2, Article 14 of the Law)

- License of manufacturer/market authorization holder
- License (accreditation) of manufacturer at the manufacturing site
- Absence of problems in drug quality, efficacy and safety
  - Compliance with Good Manufacturing Practice (GMP) at the manufacturing site

ACCREDITATION OF FOREIGN MANUFACTURER AND GMP COMPLIANCE REVIEW

Manufacturing/marketing approval and requisites for it



Requisites for approval

○ Quality, efficacy and safety: Regulatory review

○ License of manufacturer/marketing authorization holder and license (accreditation) of manufacturer: Review of requisites for license (accreditation)

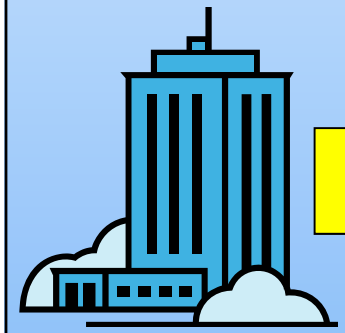
○GMP compliance: GMP review of the plant

Application for manufacturing/ marketing approval

Review / Inspection

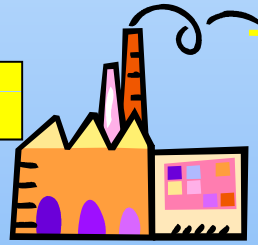
Manufacturing/ marketing approval

Release



Manufacturer/MAH

Manufacturer



License
Human resource requisites, GQP/GVP compliance

License (accreditation)
Human resource requisites, buildings/facilities

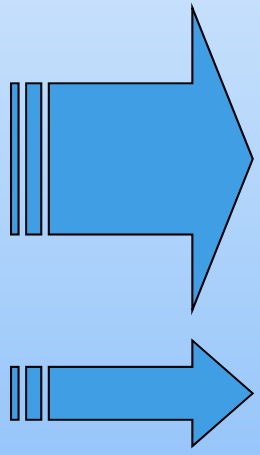
GMP compliance

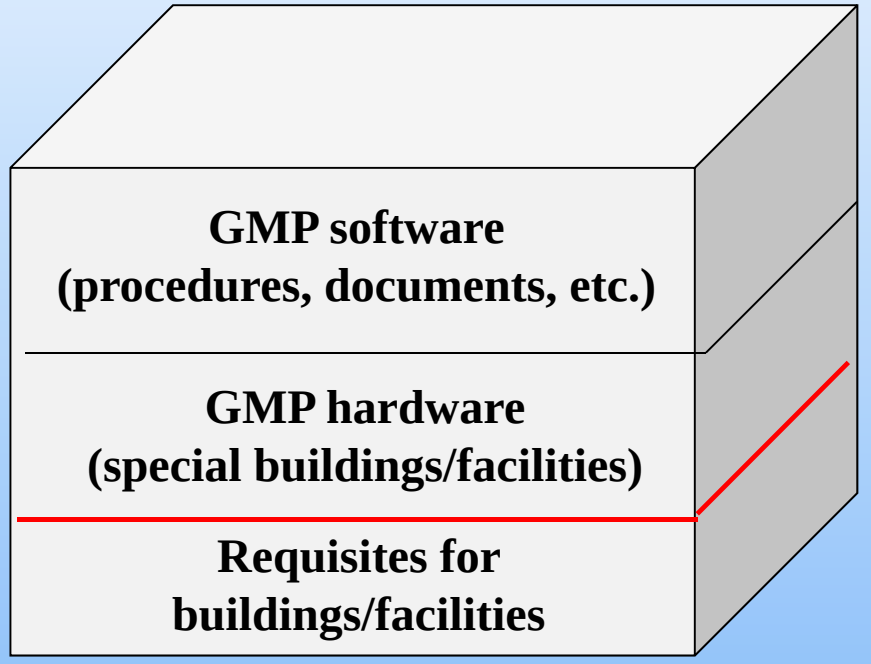
Renewal is necessary every 5 years

GMP compliance review / review of requisites for license (accreditation)

GMP compliance review

Review of requisites for license (accreditation)





Manufacturing site

Ministry Ordinances related to GMP and license (accreditation)

- GMP Ministry Ordinance
  - “Ministry Ordinance of Good Manufacturing Practice for Drugs and Quasi Drugs” Drug / Quasi Drug GMP Ministry Ordinance (MHLW Ordinance No. 179 in 2004)
- Ministry Ordinance on License (Accreditation) of Manufacturer
  - “Regulations for Buildings and Facilities for Pharmacies and Others” (MHW Ordinance No. 2 in 1961
- For both the GMP compliance review and the license (accreditation), renewal is necessary every 5 years.

ACCREDITATION OF FOREIGN MANUFACTURER

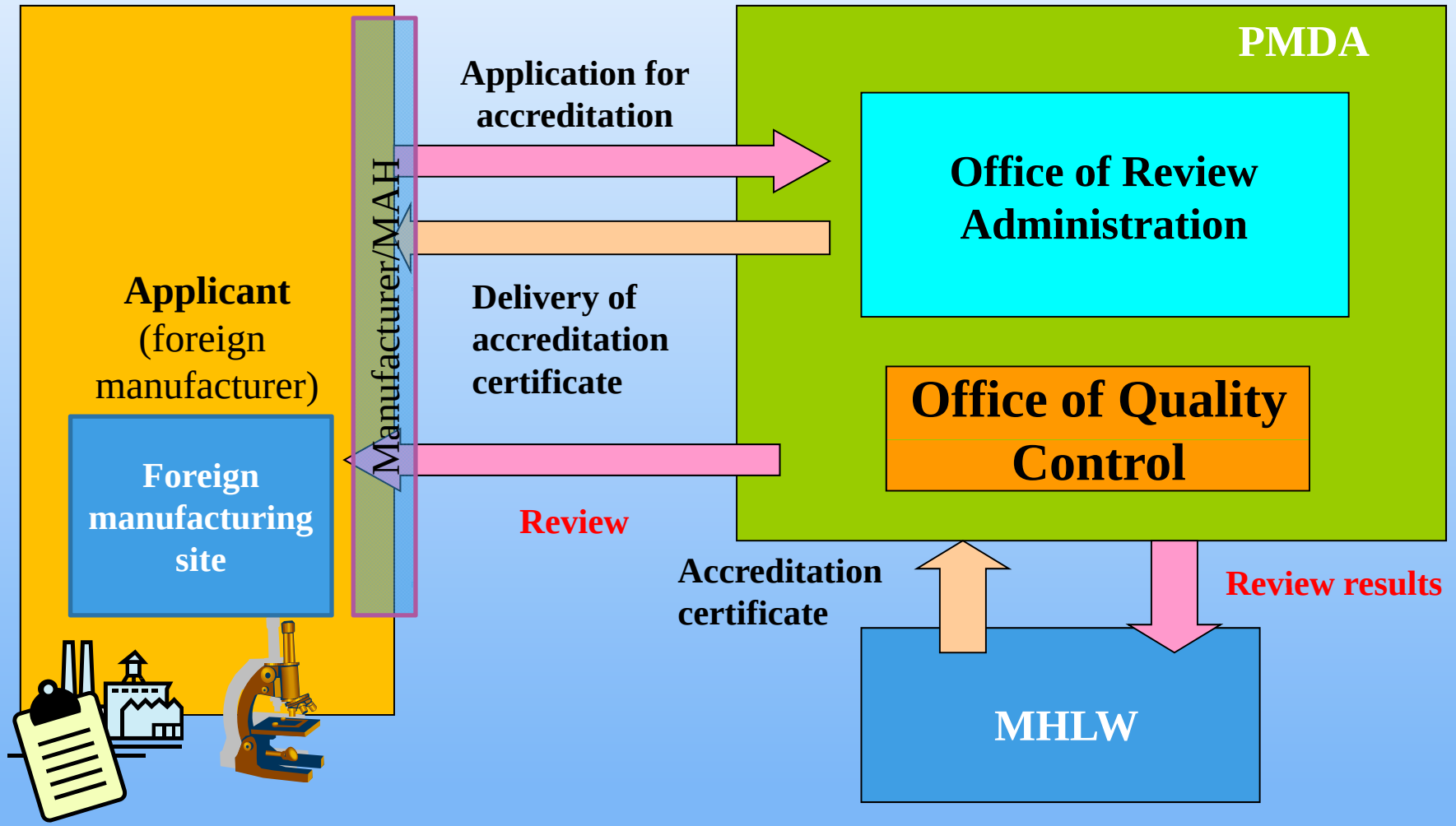
Foreign manufacturer

- Foreign manufacturer
  - The party going to manufacture outside Japan the drugs, quasi drugs or medical devices to be imported to Japan
  - Like the license of domestic manufacturer, the accreditation of foreign manufacturer is the requisite for the manufacturing/marketing approval of the drug concerned (also a foreign manufacturer manufacturing only the drug substance to be imported to Japan needs the accreditation).

Accreditation of foreign manufacturer

- Accreditation of foreign manufacturer is given by the Minister of Health, Labour and Welfare.
- Accreditation is given to each manufacturing site according to the classification.
- The valid term is 5 years.
- For obtaining the accreditation, the predefined application procedures and fee are necessary.
- The PMDA reviews whether the standards specified in the MHLW Ordinance (Regulations for Buildings and Facilities for Pharmacies and Others) are met.

Flow to accreditation of foreign manufacturer



Accreditation classes of foreign manufacturer

1. **Biological preparations, etc.** (Enforcement Regulations for Pharmaceutical Affairs Law: Article 36 Section 1 Item 1)
   The party performing all or part of the manufacturing process for biological preparations, drugs with national test certificate, genetic recombination technology-applied drugs, cell culture technology-applied drugs , cell tissue drugs and specific biological preparations

2. **Radioactive drugs** (Enforcement Regulations for Pharmaceutical Affairs Law: Article 36 Section 1 Item 2)
   The party performing all or part of the manufacturing process for radioactive drugs

3. **Sterile drugs** (Enforcement Regulations for Pharmaceutical Affairs Law: Article 36 Section 1 Item 3)
   The party performing all or part of the manufacturing process for sterile drugs

4. **General** (Enforcement Regulations for Pharmaceutical Affairs Law: Article 36 Section 1 Item 4)
   The party performing all or part of the manufacturing process for drugs other than drugs shown in the previous three items

5. **Packaging/Labeling/Storage** (Enforcement Regulations for Pharmaceutical Affairs Law: Article 36 Section 1 Item 5)
   The party performing only packaging, labeling or storage

GMP COMPLIANCE REVIEW

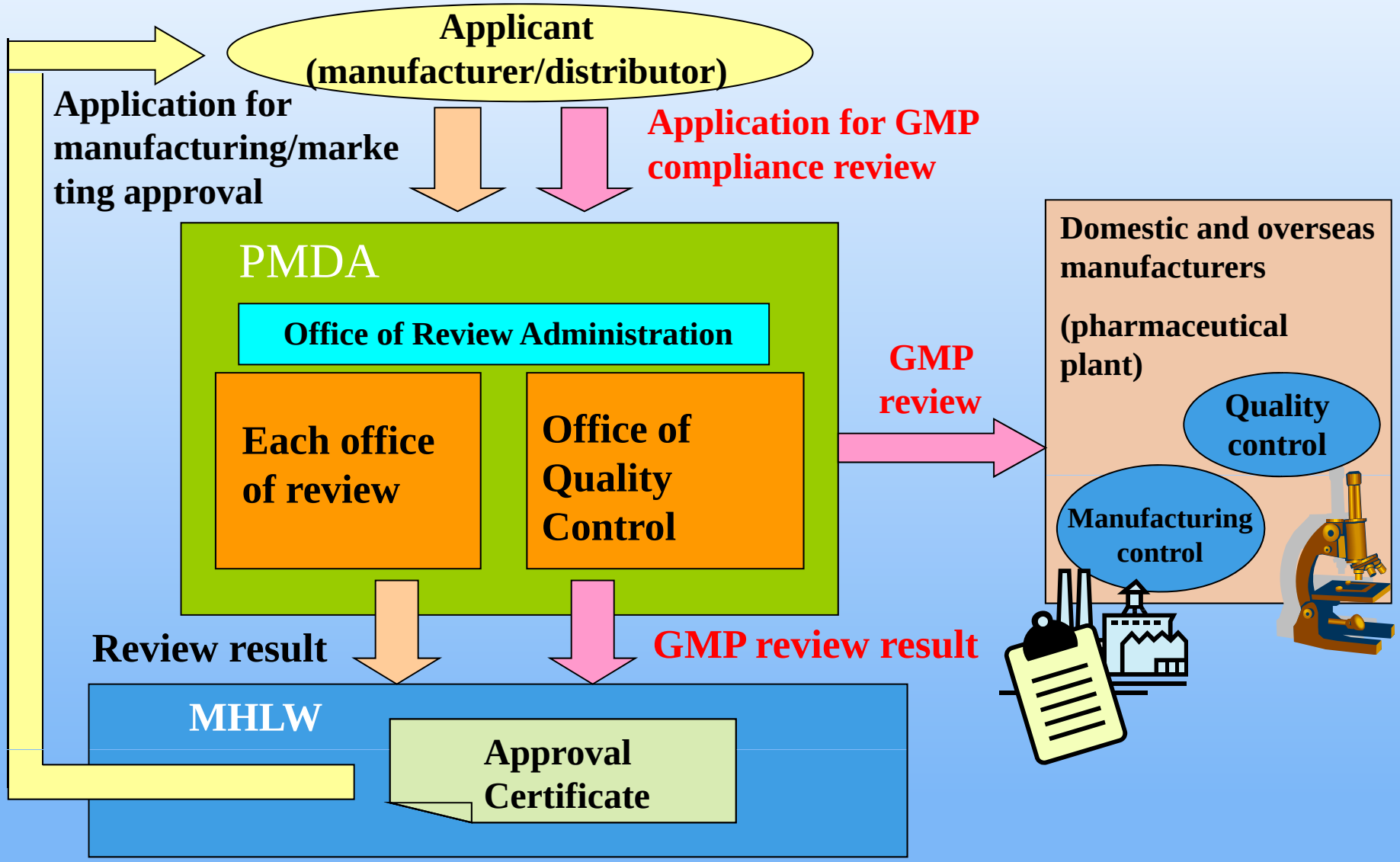
GMP compliance review (drug) performed by PMDA

- (1) Domestic facilities manufacturing the following products
  - Domestic manufacturing sites manufacturing new drugs (drugs before reexamination results are obtained), biological preparations, drugs with national test certificate, radioactive drugs, genetic recombination technology technology-applied drugs, cell culture technology-applied drugs, cell tissue drugs, special biological preparations

- (2) Foreign manufacturing sites for drugs and quasi drugs

* Other manufacturing sites are reviewed by each prefectural government.

Flow of drug GMP on-site inspection



Items to be kept in mind for on-site inspection of foreign manufacturing site

- To conduct the same level of inspection as domestic manufacturing site, in principle
- To provide the manufacturer with the necessary information such as Japanese GMP Ordinance, etc. in advance
- To prepare the documents corresponding to the master production document, manufacturing standard code and standard operating procedures required by the Japanese GMP Ministry Ordinance
- To prepare the document enabling confirmation of the agreement between the manufacturer/distributor and the manufacturer based on the Japanese GQP Ministry Ordinance
- To secure the staff-in-charge capable of making responses depending on the review items (the system enabling completion of the review at the manufacturing site concerned)
- To secure appropriate interpreters
- To translate the materials as necessary
- To prepare an efficient review schedule

Instruction items seen frequently at foreign manufacturing sites

- Inconsistencies with the approval application dossier (e.g., specifications in the column of component/content, manufacturing conditions, etc.)
- Defects related to GQP agreement (agreement on technical conditions, change control, etc.)
- Defects in compliance with Japanese GMP Ministry Ordinance and Japanese Standards (especially compliance with the Minimum Requirements for Biological Raw Materials, record-keeping period, etc.)

MF SYSTEM

What is approval application dossier?

- CTD Module 1 (administrative documents in each region)
  - Including the documents specific to each region such as manufacturing/marketing approval application dossier, package insert (draft), etc.
- Manufacturing/marketing approval application dossier
  - The brand name, components and contents, manufacturing method, indication, storage, effective term, specifications / testing methods, etc. are included, and these will become the approved items after approval.
  - When the contents are changed after approval, it is necessary to submit the application for partial change of approved items or the minor change notification.

Specific example descriptions in the manufacturing method column

Scope of minor change notification

- **Step 1 (key process)**
- Mix and stir 2-(1-triphenylmethyl-1H-tetrazol-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 dimethylformamide (60 L) [at 25 ºC for 24 hours]. Add sodium borohydride (3.2 kg) and stir further [at 25 ºC for 24 hours]. Remove the insoluble matters by filtration of the reaction mixture, and concentrate the filtrate under reduced pressure. Add water (50 L) to the residue and extract with ethyl acetate (50 L). Wash the organic layer with water (50 L) and then with a "10 %" sodium chloride solution (30 L). Concentrate the organic layer under reduced pressure to about half volume. Stir the remaining solution [at 5 ºC for 3 hours]. Centrifuge the precipitated crystals and wash with ethyl acetate (10 L). Dry the crystals at <<40 ºC>> for 8-10 hours under reduced pressure to obtain 1-[2'-(1- triphenylmethyl-1H-tetrazol-5-yl)-4-biphenyl-methyl]-5-(1E,3E)-1,3-pentadienyl]-2-hydroxylmethylimidazole [3].

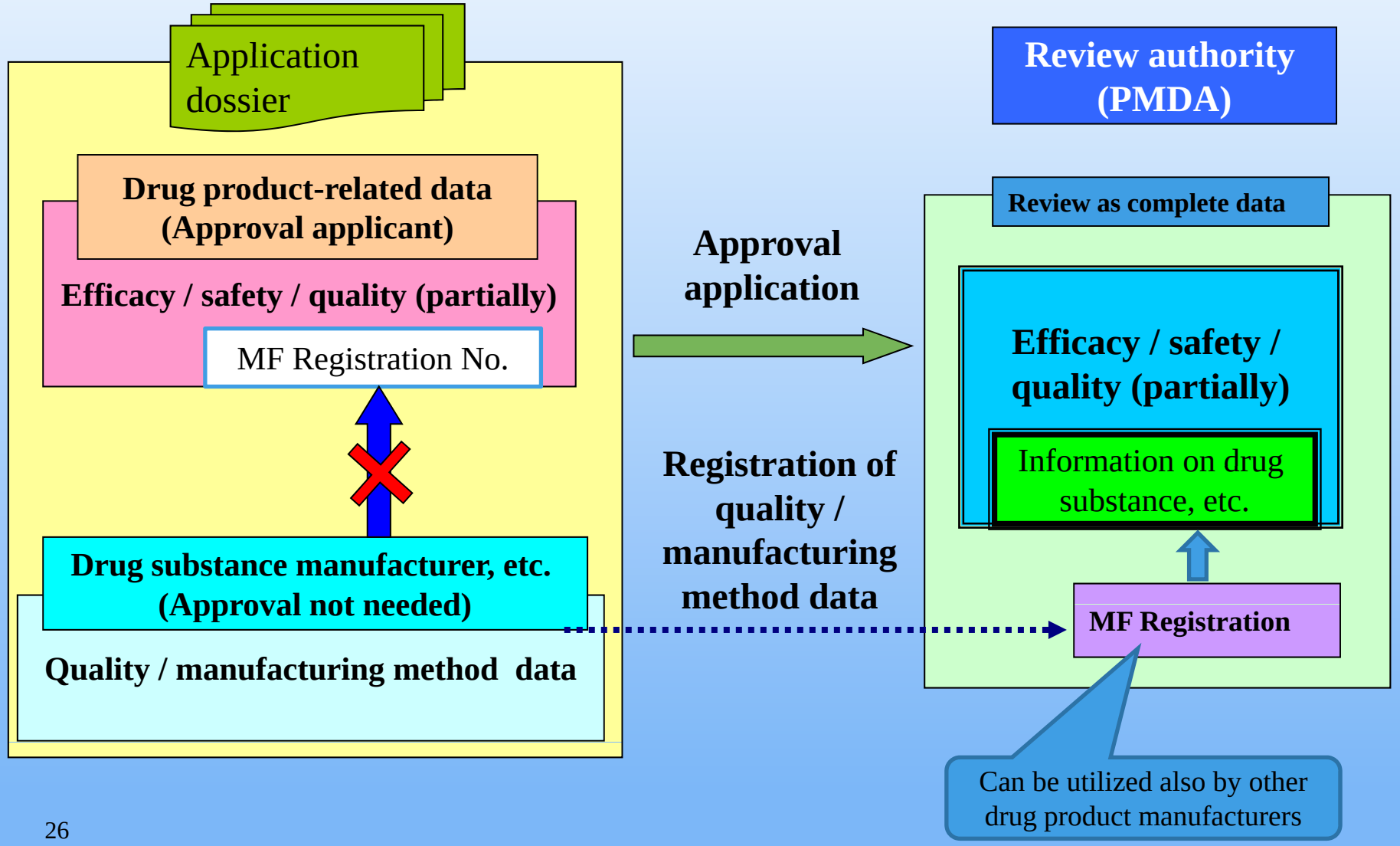
Scope of partial change approval application

- **Step 2**
- Mix and stir the intermediate [3] (about 22 kg) obtained in Step 1, "10 %" hydrochloric acid (200 L) and tetrahydrofuran (400 L) [at 25 ºC for 4 hours]. Add a "10 %" sodium hydroxide aqueous solution (200 L) to the reaction mixture. Concentrate the mixture under reduced pressure. Add water (100 L) to the residue, and remove the insoluble matters by filtration. Adjust the pH of the filtrate to 3 ± 0.5 with "35 %" hydrochloric acid. Separate the precipitated crystals by centrifugation and wash with water. Dry the crystals at <<40 ºC>> under reduced pressure to obtain crude crystals of 1-[2'-(1H- tetrazol-5-yl)biphenyl-4-ylmethyl]-5-(1E,3E)-1,3-pentadienyl]-2-hydroxymethyl-1H-imidazole [4].

Drug Substance Master File (MF) System

- The system in which a drug substance manufacturer not wishing to disclose the know-how related to the manufacturing method, etc. to a party applying for drug product approval can register the information including the know-how as MF
- The system in which the information on the quality and manufacturing method of the drug substance, etc. contained in the drug product can be submitted by a manufacturer other than the approval applicant
- Whether to register in MF is up to the manufacturer of the drug substance, etc. and is not legally required (voluntary registration)

Approval application utilizing MF



Eligibility of MF registration

- Manufacturers of drug substances (APIs) etc. in Japan and overseas

- Foreign businesses who apply for MF registration shall assign an in-country caretaker for drug substances (APIs) etc., who undertake clerical affairs for the relevant registration etc. in Japan. Ensure to assign an in-country caretaker for drug substances (APIs) etc. before applying for MF registration.

(Reference) Section 2, Article 72, Enforcement Regulations for thePharmaceutical Affairs Law

Items targeted for Master File (MF) Registration

- **(Ethical) drug substances (APIs), intermediates and pharmaceutical product materials (materials of pharmaceutical products with special dosage form, etc.)**
- **Excipients (new excipients, new pre-mix excipients)**
- **Materials for medical devices - *Currently under consideration***
- **Containers, packaging materials - *Currently under consideration for medical devices***

* The use of MF shall be refrained for the time being for drug substances (APIs), intermediates and pharmaceutical product materials for OTC drugs (excluding those containing new active ingredients). (This excludes TSE materials)

Drug Substance Master File (MF) Registration Items

- Name of the drug substance (API) etc.
- Name of the manufacturing site etc.
- Information concerning the ingredients, contents and/or inherit properties
- Manufacturing method, manufacturing process control and quality control test
- Specifications and test methods
- Stability test, preservation method and shelf life
- Nonclinical test (mainly for new excipients)
- Category of manufacturer license or foreign manufacturer accreditation
- Manufacturer license number or foreign manufacturer accreditation
- In-country caretaker for the drug substance (API) etc.

Issuance and publication of Master File (MF) registration certificate

After **MF registration -**

To MF registrants

Master File registration certificate and copy of registration application are issued

To the publics

- **Publication based on provisions under Section 3, Article 14-11 of the Pharmaceutical Affairs Law**

  => Published on the website of PMDA (http://www.pmda.go.jp/)

- **Published information:**
  MF registration number, date of registration (of change), name and address of registrant, name of registered item, category of registration

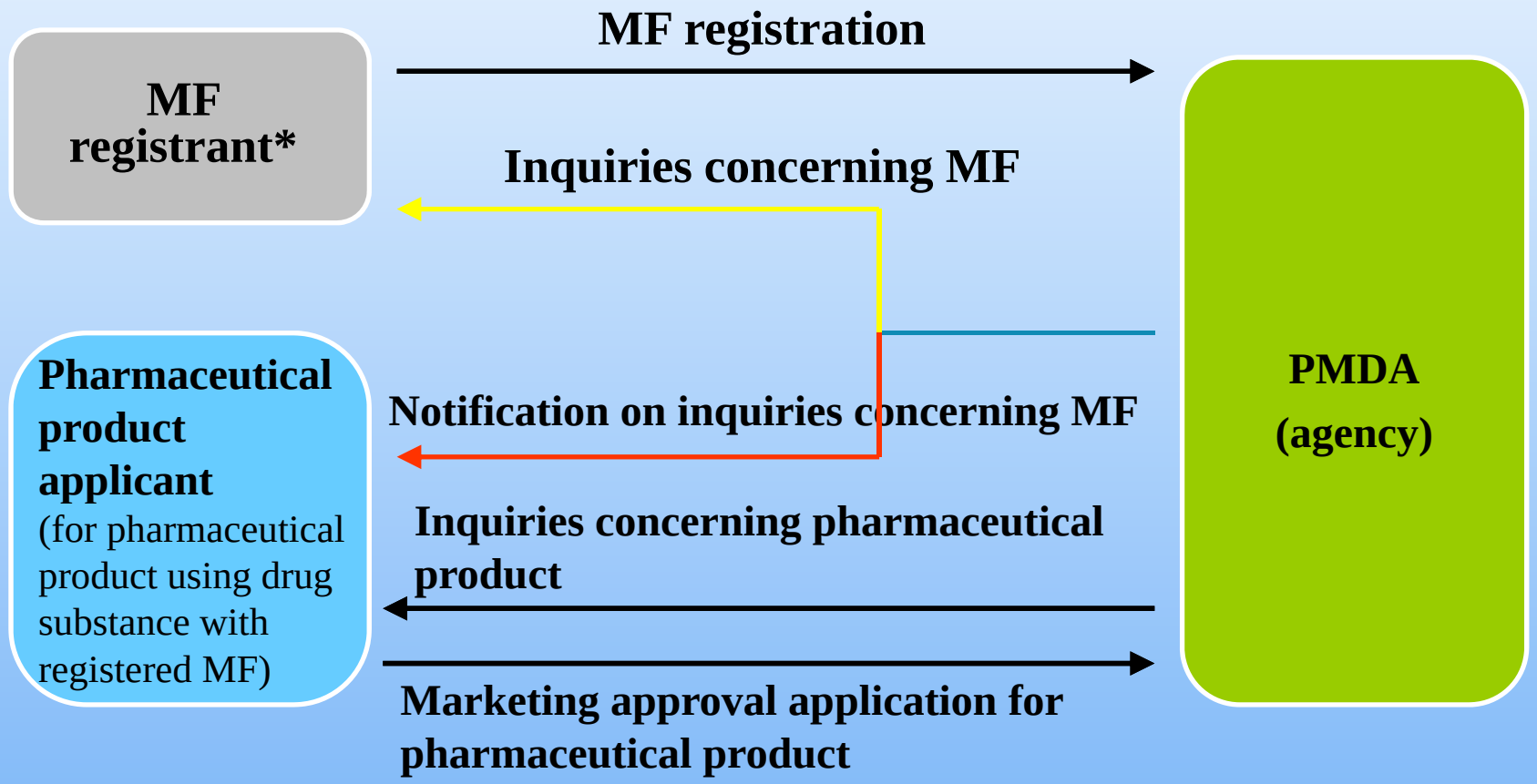
(Reference Notification) Notification of Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, MH LW; Notification No.0210004 of the PFSB, February 10, 2005

Information that MF registrant shall disclose to pharmaceutical product approval applicant etc.

	Applicant (disclosed) part	Restricted part
3.2.S.1 General information	Applicable	
3.2.S.2 Manufacturing		
3.2.S.2.1 Manufacture	Applicable	
3.2.S.2.2 Manufacturing method and process control	Applicable	Applicable
3.2.S.2.3 Raw material control		Applicable
3.2.S.2.4 Key process / key intermediate control		Applicable
3.2.S.2.5 Process validation/ process evaluation		Applicable
3.2.S.2.4 History of manufacturing process development		Applicable
3.2.S.3 Characteristics		
3.2.S.3.1 Clarification of structure and other characteristics	Applicable	
3.2.S.3.2 Impurities	Applicable	
3.2.S.4 Drug substance control		
3.2.S.4.1 Specification and testing method	Applicable	
3.2.S.4.2 Testing method (analytical method)	Applicable	
3.2.S.4.3 Testing method (analytical method) validation	Applicable	
3.2.S.4.4 Batch analysis	Applicable	Applicable
3.2.S.4.5 Reasonability of specification and testing method (rationale for setting)	Applicable	Applicable
3.2.S.5 Reference standard or standard substance	Applicable	
3.2.S.6 Container and sealing system	Applicable	
3.2.S.7 Stability	Applicable	

When Applicable is put to both the columns, the item concerned is handled as a disclosed item. But, the information related to the MF registrant's intellectual property can be handled as the restricted part.

Overview of pharmaceutical product quoting MF



MF registrant*: If the registrant is an overseas manufacturer, inquiries are made by way of in-country caretaker for drug substances (APIs) etc.

Drug Substance Master File (MF) Positioning of registered item

○ **Information registered in MF**

- **Information partially alternative to drug product manufacturing/marketing approval application dossier**
- **Information partially alternative to Attached Data on filing drug product approval application**

○ **In the regulatory review of the drug product utilizing the MF concerned, at the time of review related to the registered item, the data corresponding to CTD Module 2 (outline of attached data) is necessary in addition to the data of Module 3.**

Items to be kept in mind by MF registrant

- MF registration can be performed voluntarily, but the review authority will check at the time of registration only whether the necessary style is met and whether the necessary data are attached.
- At the time of registration, reasonability of registered contents is not reviewed by the regulatory authority. In other words, even when the MF registration is accepted, it does not mean that approval of the review authority is obtained.

- **When the registered item is changed (even when a minor change notification is performed),** the MF registrant (domestic care taker in case of foreign manufacturer of drug substance, etc.) must make **notification to the approval applicant and the approval holder of the relevant drug product.**

Thank you for your attention.