GUIDANCE ON MASTER FILE SYSTEM

Pharmaceuticals and Medical Devices Agency
Office of Review Administration
Review Planning Division
Master File Management Group

INTRODUCTION

Applicable law for the Master Files

The Pharmaceutical Affairs Law first paragraph of Article 14-11

"A person who manufactures active pharmaceutical ingredients etc. (including those who manufacture in foreign countries) may register in a drug master file the matters specified by MHLW Ministerial Ordinance, including the name, ingredients (in the case of an unknown ingredient, its essence), manufacturing methods, properties, quality or storage of the active pharmaceutical ingredient etc."

What is the Master File System?

Manufacturers of drug substances, etc. can register information on their manufacturing process of drug substances, etc. Registered information is called Drug Master Files.

In applying for marketing approval, applicants shall quote the registration number of drug substances used in their pharmaceutical products so that the regulatory authority proceed with their scientific review by referring the detailed information registered in MFs.

In this way, the manufacturers can protect their technical know –how relating to manufacturing process of drug substances, etc.

Outline of Master File system

①MF registrant : A manufacturer of drug substances, etc.

②Documents required : Application form , supporting data

③When to submit : As needed

④Benefits of using MFs:

- Protection of manufacturers' intellectual properties and keep their business competitiveness (avoid troubles)
- Smooth operation of regulatory marketing approval process

Outline of Master File (MF) system

⑤Other features:

- MF Registration is not mandatory. It may be done on a voluntary basis.
- PMDA does not conduct scientific review over the application. PMDA shall only examine whether it is written in the correct format or not.
- Registration certificate shall be issued.
- Names of MF holders shall be made public.

DMF Related Notifications

・Notification of Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW*; yakushoku shinsa-hatsu No.0210004, February 10 2005
「Guideline for details of the use of DMF procedure」
・Notification of Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; yakushoku shinsa-hatsu No.0310002, March 10 2005
「Guidance on the application for the registration of DMF before the implementation of the Revised Pharmaceutical Affairs Law」
・Notification of Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; yakushoku shinsa-hatsu No.0325003, March 25 2005
「Guidance on handling of TSE documents in the implementation of the Revised Pharmaceutical Affairs Law」
・PMDA's** Notification, yakki-hatsu No.0330003, March 30 2005
「Guidance on acceptance of applications and notifications in PMDA's review operation」
・Notification of Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; yakushoku shinsa-hatsu No.0331023, March 31 2005
「Guidance on handling of applications submitted on flexible disk etc.」
・ Notice of Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; jimu renraku,July, 28 2005
「Q&As on DMF Registration System」
・ Notice of Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; jimu renraku,December 20 2005
「Q&As on DMF Registration System, PartⅡ 」
・ Notification of Evaluation & Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; yakushoku shinsa-hatsu No.0208003, February 8 2006
「Guidance on deletion of a DMF」

*MHLW ・・・The Ministry of Health, Labour and Welfare
**PMDA ・・・The Pharmaceuticals and Medical Devices Agency

Items targeted for Master File Registration

- Drug substances, intermediates
- Pharmaceutical product materials
  (materials of pharmaceutical products with special dosage form, etc.)
- Excipients (new excipients , new pre-mix excipients)
- Materials for medical devices.・・・Now under review
- Containers, packaging materials. ・・・Now under review

Drug substances used in OTC drugs

- Drug substances, intermediates and pharmaceutical product materials used in OTC drugs (excluding OTC with new active ingredients or those with their active ingredients still in the reexamination period) are not appropriate for registration in MFs, as it is considered that their quality and safety are already clarified even in existing specifications and analytical procedures.

Details registered in Master Files

- Name of the manufacturing establishment and other information to be stated in the registration certificate
- Manufacturing process, manufacturing process control and quality control test
- Specification and test method and information on stability and safety
- Data on non-clinical study (mainly for new excipients)
- Country of origin and data on inspection/certification of bovine-derived raw materials
- Information requested by the reviewing authority for which the registration of DMF is appropriate

Example of how to describe a quoted drug substances in the approval application form

▲▲▲▲（MF Registration Number：xxxxxYY/MM/DD）
Version Number ■ of MF Registration）Method ○○○
e.g. MF Registration No.: 217MF1YYMMDD

The name of drug substances etc.

The latest Issued date of registration certificate

If there are more than one manufacturing process in a MF, it should be specified which process is used by marking or numbering.

- ■: Number.

Amendment of MF requires new registration
(Minor amendment doesn't)

Information disclosed to the applicants of marketing approval

- MF registrant must notify each applicant of the detailed information registered in MF or even any changes made to their registered items in advance.
- If any changes are made, it should be properly discussed whether those will affect the quality of pharmaceutical products or not to assure product safety, among MF registrant, applicants or marketing approval holders who quote the MF. (In order to avoid troubles)

Notes on registration of MFs①

The application for registration

- Application date shall be the date of submission
- The applicants shall submit application forms by giving original sheet and duplicate sheet.

(Photocopies are not acceptable)

Document submitted by flexible disk

【Manufacturer code】:In case the manufacturer does not have the code, obtaining one before submission shall be required.

【Resubmission Information】: Regardless of in-advance application, it shall be stated as (1) original submission. (If it is a replacement document, it should be stated as (2) resubmission.)

Notes on registration of MFs ②

Document submitted by flexible disk

- 【Name of drug substances, etc.】: Both of generic name and brand name shall be stated.

- Section of components, quantity and entity

  Components・・・specifications（if the approval number has been issued, the section may be left blank）、component code（If there is no ingredient code, enter 999999）、name of the component

  Text field shall be filled as needed.

Notes on registration of MFs ③

Document submitted by flexible disk

・For the description of【manufacturing process】,
please refer to MHLW/PFSB/ELD Notification No.02100001
dated February 10,2005

・Regarding other items, the applicant should state what they actually does.

・Please refer to Notifications for applications by flexible disk and MHLW /PFSB/ELD Notification No.0331023 dated March 31,2005.

Notes on registration of MFs ④

Before MF system, there was a similar system called Advanced Registration system.

With the introduction of the MF system, all the information previously registered under the AR system have to be re-registered to MFs.

In the re-registration process, sections previously stated as “No Information” under the AR system should be left blank (the same section of the registration certificate will be left blank as well).

However, if there is new data to fill the section, it could be stated (In that case, appropriate supporting data should be submitted).

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If a section is left blank, it means that no information is registered.

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The registrant must notify each affected person who has quoted information in MFs and obtained approval of any change in the MFs.

Operating Procedure for submission and correspondence

（PMDA's Notification, yakki-hatsu No.0330003, March 30,2005）

・MF submission and correspondence should be addressed to:

Incorporated Administrative Agency-
Pharmaceuticals and Medical Devices Agency (PMDA)

Office of Review Administration, Review Operation Division
Shin-Kasumigaseki Building 6th floor,
3-3-2 Kasumigaseki, Chiyoda-ku,
Tokyo 100-0013 Japan

TEL:03-3506-9437
FAX:03-3506-9442

・Office hours
9:30～12:00 and 13:30～17:00

Operating Procedure
for submission and correspondence

- No registration fee shall be charged.
  Application form shall be submitted as needed.

- As for forms and instructions in registration procedure,
  please refer to “the checklist for application forms ”

- Registration certificate shall be sent back with duplicate sheet of application form.

- Please enclose a self-addressed stamped envelope for recorded delivery.
  (Please include the weight of the duplicate sheet in the return postage.)

Points to remember for MF registration ①

The MFs may be registered on a voluntary basis at any time since it is not an obligation. The application shall be examined to see if it meets minimum requirements in the point of its format. PMDA shall acknowledge its receipt and assign MF registration number. This does not mean PMDA conduct scientific review over the items written in the application form. Registration certificate does not mean the approval of normal review procedure.

Points to remember for MF registration②

A person who manufactures drug substances, etc. in foreign country and wish to apply for MF registration in Japan, shall appoint a person who is engaged in services of the MF registration in Japan (referred to as “MF registered in-country caretaker”) from those who has address in Japan (including representatives of foreign companies with their offices in Japan).

Figure1 Master File System

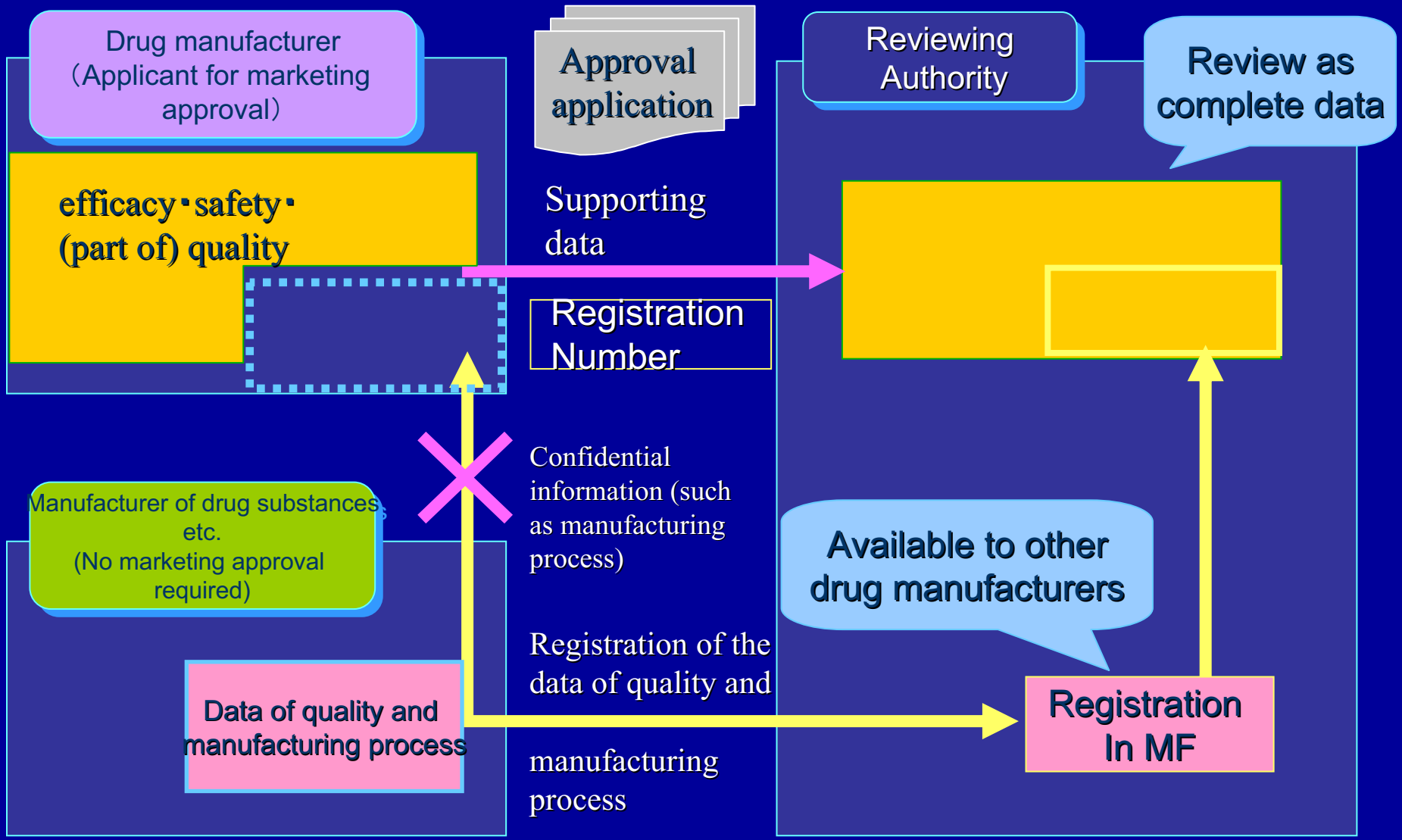
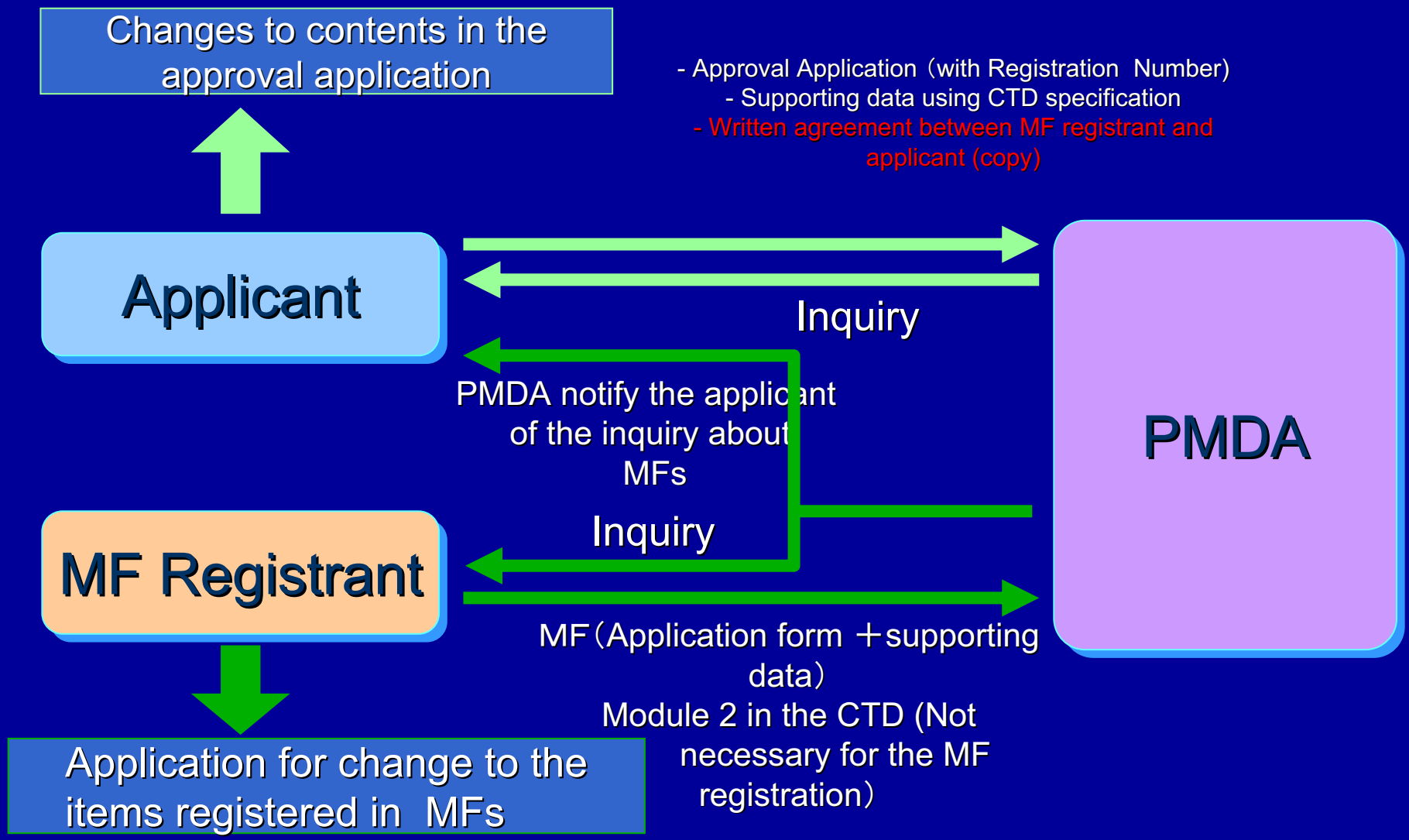


Figure2 Flow of Regulatory Review of MFs



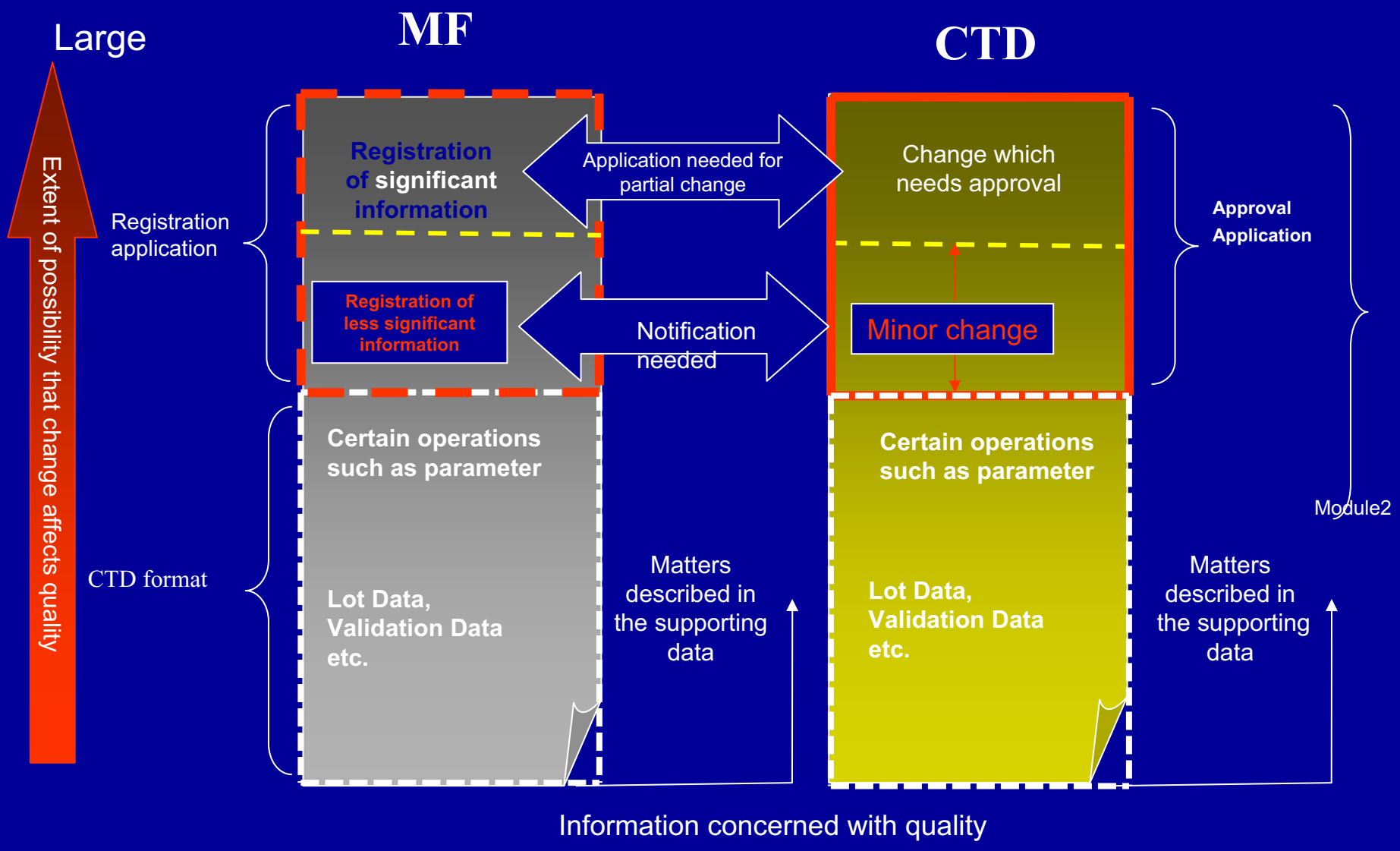


Figure 3 MFs and CTD

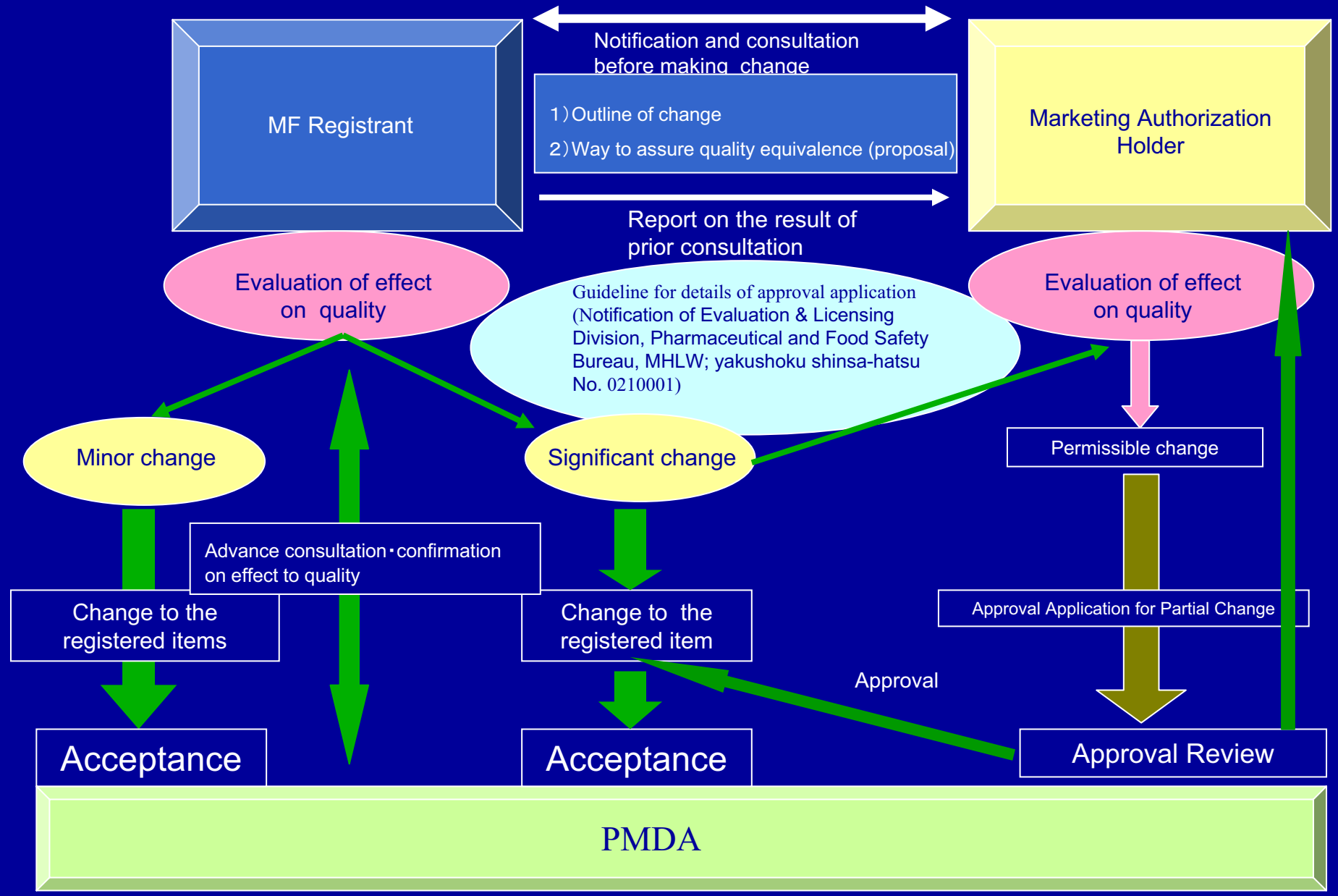


Figure 4 Procedure for change to MFs