Approval Review of Generic Drugs in Japan

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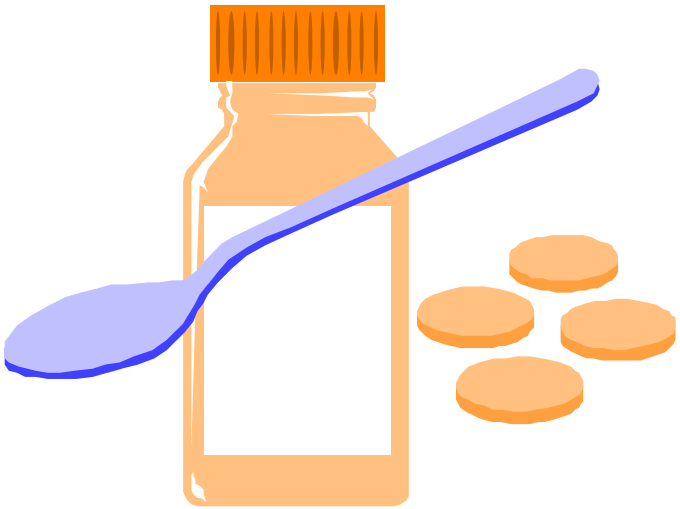
Outline of Presentation

- Introduction (What are generic drugs?)
- Approval Review of Generic Drugs
  - Master File (MF) scheme
  - Equivalency review
  - Conformity audit
- Conclusion

What are generic drugs?

- Compare with Original Drugs (Brand Drugs) to have the same
  - active ingredient(s)
  - quantities
  - route of administration
  - dosage form
  - direction and dose
  - indications and effects



Can be used as same as brand drugs

Main data required for Approval to Generic Drugs

Manufacturing methods, standards and test methods	• Specifications and test methods (and Manufacturing methods, in some cases)
Stability	• Accelerated tests
Absorption, distribution, metabolism, and excretion	• Bioequivalence

Requirements in Japan(Data to be submitted with an application for approval)		originator	generic
a. Origin or background of discovery, conditions of use in foreign countries	1 Origin or background of discovery	○	×
	2 Conditions of use in foreign countries	○	×
	3 Special characteristics, comparisons with other drugs, etc.	○	×
b. Manufacturing methods, standards and test methods	1 Chemical structure and physicochemical properties, etc.	○	×
	2 Manufacturing methods	○	△
	3 Specifications and test methods	○	○
c. Stability	1 Long-term storage tests	○	×
	2 Tests under severe conditions	○	×
	3 Accelerated tests	○	○
d. Pharmacological action	1 Test to support efficacy	○	×
	2 Secondary Pharmacology, Safety pharmacology	○	×
	3 Other pharmacology	△	×
e. Absorption, distribution, metabolism and excretion	1 Absorption	○	×
	2 Distribution	○	×
	3 Metabolism	○	×
	4 Excretion	○	×
	5 Bioequivalence	×	○
	6 Other pharmacokinetics	△	×
f. Acute, sub acute, and chronic toxicity, teratogenicity, and other type of toxicity	1 Single dose toxicity	○	×
	2 Repeated dose toxicity	○	×
	3 Genotoxicity	○	×
	4 Carcinogenecity	△	×
	5 Reproductive toxicity	○	×
	6 Local irritation	△	×
	7 Other toxicity	△	×
g. Clinical Study	Clinical trial results	○	×

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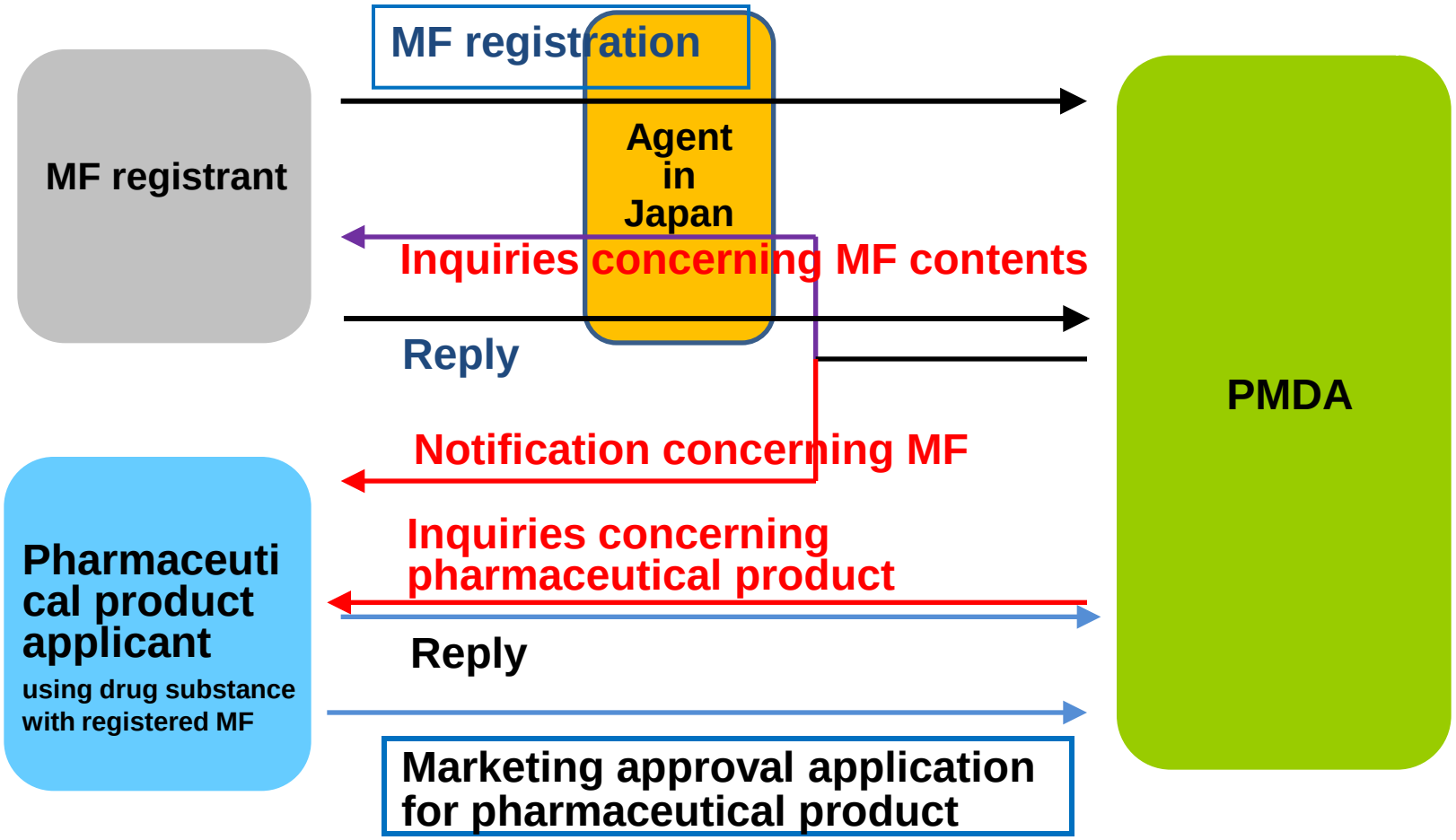
Master File (MF) Scheme for Active Ingredients

- The master file (MF) is allowed to register(s):
  - described mainly information on the quality and manufacturing method for active ingredients to be used in drug products
    - the manufacturing method is reviewed in detail
- The merit of MF registrations is to avoid the disclosure of data on the active ingredients to Pharmaceutical product applicants
- Registered data (MF data) can be used for only contracted multiple users

Active Ingredient = Drug Substance

Approval Review for Pharmaceutical Product Quoting from MF



Approval Review of Generic Drugs

What shall we check?

1. Equivalency review

Active ingredient(s)

Quantities

Route of administration

Dosage form

Direction and Dose

Indications and Effects

Same to the originator?

required data
- ①Specifications and test methods
- ②Stability
- ③Bioequivalence studies etc.

What shall we check?

Equivalency review

①Specifications and test methods

Drug substance and Drug product

Items:

Limits of the content of the ingredient(s) and/ or the unit of potency, Description, Identification, Specific physical and/or chemical value, Impurities, Water or loss on drying, Residue on ignition, Assay, and so on.

②Stability

Accelerated test

at 40 (±1) degree, RH 75% (±5%), 3 lots, for 6 months

③Bioequivalence studies

Guideline for Bioequivalence Studies of Generic Drugs

(Notification by MHLW in Dec. 1997 was revised in Feb. 2012)

Procedure for Bioequivalence Evaluation

・Evaluation of dissolution behavior

as reference product batch・・・・

Selection of from?? an originator product batch

・Bioequivalence study in humans

Evaluation : The 90% confidence interval of the difference in the average values of logarithmic AUC, C_{max} : log(0.8) ～ log(1.25)

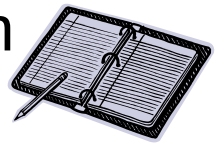
→ **bioequivalence**

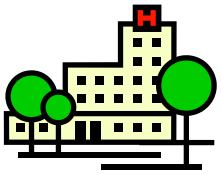
What shall we check?

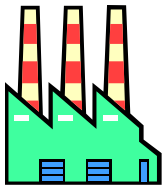
Conformity audit

The reliability is also important point,

- Check the conformity to the standards in application data
  - Check the consistency between application materials and raw data
  - On-site GCP audit, to check compliance of sponsors and clinical trial facilities, if necessary
- Check the conformity to the standards for manufacturing and quality control
  - GMP inspection to the manufacturing sites
  - In addition to pre-approval GMP inspection, periodical GMP inspection is also required after approval







Conclusion

In reviewing of generic :

- Specifications and test methods
- Accelerated tests
- Bioequivalence

Generic drug ：substitute for the originator

able to be approved without clinical trials for confirming their efficacy and safety

Generics!!

Economical efficiency for patients' co-payment and total medical expenditure.

Some Kind of Recent Data on Reviewing Generic Drugs in PMDA

No.	application	approval
FY 2006	2,631	2,152
FY 2007	3,729	3,278
FY 2008	3,893	1,980
FY 2009	2,354	3,271
FY 2010	3,062	2,633

No. of Reviewer for Generic Drugs : 19 persons

Reviewing period

New approval of generic drugs → 1 year (Y)

and

Partial change of approval items → ca.6 M or 1 Y

Thank you!

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