Approval Review of Generic Drugs in Japan

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Second International Generic Drug Regulators Meeting at College Park, MD
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
<table>
<thead>
<tr>
<th>Requirements in Japan (Data to be submitted with an application for approval)</th>
<th>originator</th>
<th>generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Origin or background of discovery, conditions of use in foreign countries</td>
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</tr>
<tr>
<td>1 Origin or background of discovery</td>
<td>○</td>
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<tr>
<td>2 Conditions of use in foreign countries</td>
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<tr>
<td>3 Special characteristics, comparisons with other drugs, etc.</td>
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<tr>
<td>b. Manufacturing methods, standards and test methods</td>
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<tr>
<td>1 Chemical structure and physicochemical properties, etc.</td>
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<tr>
<td>2 Manufacturing methods</td>
<td>○</td>
<td>△</td>
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<tr>
<td>3 Specifications and test methods</td>
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<td>○</td>
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<tr>
<td>c. Stability</td>
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<tr>
<td>1 Long-term storage tests</td>
<td>○</td>
<td>×</td>
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<tr>
<td>2 Tests under severe conditions</td>
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<td>×</td>
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<tr>
<td>3 Accelerated tests</td>
<td>○</td>
<td>○</td>
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<tr>
<td>d. Pharmacological action</td>
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<tr>
<td>1 Test to support efficacy</td>
<td>○</td>
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<tr>
<td>2 Secondary Pharmacology, Safety pharmacology</td>
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<td>×</td>
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<tr>
<td>3 Other pharmacology</td>
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<tr>
<td>e. Absorption, distribution, metabolism and excretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Absorption</td>
<td>○</td>
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<tr>
<td>2 Distribution</td>
<td>○</td>
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<tr>
<td>3 Metabolism</td>
<td>○</td>
<td>×</td>
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<tr>
<td>4 Excretion</td>
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<td>×</td>
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<tr>
<td>5 Bioequivalence</td>
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<td>○</td>
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<tr>
<td>6 Other pharmacokinetics</td>
<td>△</td>
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<tr>
<td>f. Acute, sub acute, and chronic toxicity, teratogenicity, and other type of toxicity</td>
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<tr>
<td>1 Single dose toxicity</td>
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<tr>
<td>2 Repeated dose toxicity</td>
<td>○</td>
<td>×</td>
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<tr>
<td>3 Genotoxicity</td>
<td>○</td>
<td>×</td>
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<tr>
<td>4 Carcinogenecity</td>
<td>△</td>
<td>×</td>
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<tr>
<td>5 Reproductive toxicity</td>
<td>○</td>
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<tr>
<td>6 Local irritation</td>
<td>△</td>
<td>×</td>
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<tr>
<td>7 Other toxicity</td>
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<td>g. Clinical Study</td>
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<td>Clinical trial results</td>
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</tbody>
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- Introduction (What are generic drugs?)
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  - Equivalency review
  - Conformity audit
- Conclusion
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

Agent in Japan

MF registrant

Pharmaceutical product applicant using drug substance with registered MF

PMDA

MF registration

Inquiries concerning MF contents

Reply

Notification concerning MF

Inquiries concerning pharmaceutical product

Reply

Marketing approval application for pharmaceutical product
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

① Specifications and test methods
② Stability
③ Bioequivalence studies etc.
What shall we check?

Equivalency review

① Specifications 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.

② Stability

**Accelerated test**

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

③ Bioequivalence 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, $C_{\text{max}}: \log(0.8) \sim \log(1.25)$
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

<table>
<thead>
<tr>
<th>Year</th>
<th>Application</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY 2006</td>
<td>2,631</td>
<td>2,152</td>
</tr>
<tr>
<td>FY 2007</td>
<td>3,729</td>
<td>3,278</td>
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<td>FY 2008</td>
<td>3,893</td>
<td>1,980</td>
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<td>FY 2009</td>
<td>2,354</td>
<td>3,271</td>
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<td>FY 2010</td>
<td>3,062</td>
<td>2,633</td>
</tr>
</tbody>
</table>

- No. of Reviewer for Generic Drugs: 19 persons
- New approval of generic drugs and Partial change of approval items
- Reviewing period: 1 year (Y) or ca. 6 M or 1 Y
Thank you!

Contact information:
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Pharmaceuticals and Medical Devices Agency
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Yumiko Osa (osa-yumiko@pmda.go.jp)