Overview of Generic Drug Policy and Introduction of its Review Points/BE Guideline in Japan

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• Overview of Japan’s Policy

• Introduction of Review Points and BE Guidelines

• Quick overview of review process
Overview of Japan’s Policy
Goal of share in volume (Basic Policy in 2017)

By September 2020, the ratio of generic drugs use in volume should be 80% and further promoting measures are studied to enable the goal as early as possible.

Goal 80%

DATA source: MHLW
MHLW implements two main projects:

- Promoting information provision in collaboration with academia
- Certifying quality in the market as a part of inspection
Information Package of Quality of Prescription Drugs (Blue Book)

- “Blue Book” has been published since March 2017.

(URL) Blue Book
http://www.nihs.go.jp/drug/ecqaged/bluebook/list.html

(URL2) Database collaborated with Blue Book, implemented by JAPIC
http://www.bbdb.jp/generic/toppage.aspx

- The Blue Book website publishes on quality-related information such as similarity of dissolution behavior, bioequivalency and collaborative development of generic drugs.
Introduction of Review Points and BE Guidelines
What are generic drugs?

Comparing with the original, brand drug, generic drug have the same:

• API (active pharmaceutical ingredients)
• Strengths
• Route of administration
• Dosage form
• Dose and administration
• Indications
Requirements for application/approval of generic drugs

• Expiration of re-examination period of the original product
• No valid patent (substance/utility patent for the active ingredient) at the time of approval
• Warranty of equivalent quality and bioequivalence to the original product
## Requirements of data in application in Japan

<table>
<thead>
<tr>
<th>Documents</th>
<th>Originator</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a. Origin or background of discovery, condition of use in foreign countries</strong></td>
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<tr>
<td>1. Origin or background of discovery</td>
<td>○</td>
<td>×</td>
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<td>2. Conditions of use overseas</td>
<td>○</td>
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<td>3. Special characteristics, comparisons with other drugs etc.</td>
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<tr>
<td><strong>b. Manufacturing methods, specification and test methods</strong></td>
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<tr>
<td>1. Chemical/physical characteristics and structure property</td>
<td>○</td>
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<tr>
<td>2. Manufacturing methods</td>
<td>○</td>
<td>△</td>
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<tr>
<td>3. Specification and test methods</td>
<td>○</td>
<td>○</td>
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<tr>
<td><strong>c. Stability</strong></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>
<td>○</td>
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<tr>
<td>3. Accelerated tests</td>
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<td><strong>d. Pharmacological action</strong></td>
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<tr>
<td>1. Tests to support efficacy</td>
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<td>×</td>
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<tr>
<td>2. Secondary pharmacology, safety pharmacology</td>
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<tr>
<td>3. Other pharmacology</td>
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<tr>
<td><strong>e. Absorption, distribution, metabolism, and excretion</strong></td>
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<tr>
<td>1. Absorption</td>
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<td>2. Distribution</td>
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<td>3. Metabolism</td>
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<td>4. Excretion</td>
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<td>5. Bioequivalency</td>
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<tr>
<td>6. Other pharmacokinetics</td>
<td>△</td>
<td>×</td>
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<td><strong>f. Acute/sub acute/chronic toxicity, teratogenicity, and other type of toxicity</strong></td>
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<tr>
<td>1. Single dose toxicity</td>
<td>○</td>
<td>×</td>
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<tr>
<td>2. Repeated dose toxicity</td>
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<td>×</td>
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<tr>
<td>3. Genotoxicity</td>
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<tr>
<td>4. Carcinogenicity</td>
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<td>5. Reproductive toxicity</td>
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<tr>
<td>6. Local irritation</td>
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<td>7. Other toxicity</td>
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<td><strong>g. Clinical trials</strong></td>
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<tr>
<td>1. Results of clinical trials</td>
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<td><strong>h. Package inserts</strong></td>
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<tr>
<td>1. Points to consider of package inserts</td>
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</table>

Note) ○ means necessary, × means not necessary, and △ means to depend on each product
Data evaluated for approval

1. Manufacturing methods, specifications and test methods
   (1) Specifications and analytical procedures
   (2) Manufacturing methods

2. Stability
   - Accelerated tests (long-term storage tests and tests under severe conditions, in some cases)

3. Absorption, Distribution, Metabolism, and Excretion
   - Bioequivalence

4. Package insert
1(1). Specifications and analytical procedures

• The following tests are also considered generally applicable to generic drugs
  ➢ Limits of the content of ingredient(s) and/or the unit of potency, Description, Identification tests, etc.

• Assay
  ➢ Set acceptance criteria assuring the equal efficacy and safety based on the batch data and stability data, etc.

• Impurities
  ➢ Equal or tighter acceptance criteria than that of the original drug in principle
  ➢ Review based on ICH guidelines (Q3A, Q3B, Q3C) about impurities which are not detected in the original drug
1(2). Manufacturing methods

• The Marketing Approval Document includes all processes from starting material(s) to packaging process
  Starting materials, Intermediates, Critical steps, In-process control, Container closure system, etc.

• Applicants should demonstrate the manufacturing process is capable of consistently producing drug substance and drug product of the intended quality
2. Accelerated tests

• Applicants should submit accelerated stability data for 6 months
  ➢ At 40°C, RH 75%, 3 lots, for 6 months

• In some cases, applicants should also submit the following stability data at the time of submission
  ➢ Long-term storage tests
    At 25 °C, RH 60%, 3 lots, for 12 months at least
  ➢ Tests under severe conditions
    Photostability, etc.
3. Bioequivalence

• Assure therapeutic equivalence of a generic drug to its original drug
• Compare the bioavailability between a generic drug and its original drug
List of the BE guidelines (1)

- Guideline for Bioequivalence Studies of Generic Products + Q&A (February 29, 2012)
- Guideline for Bioequivalence Studies of Generic Products for Different Strengths of Oral Solid Dosage Forms + Q&A (February 29, 2012)
- Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms + Q&A (February 29, 2012)
- Guideline for Bioequivalence Studies for Different Oral Solid Dosage Form + Q&A (February 29, 2012)
- Bioequivalence Studies for Different Strengths of Ethical Combination Drug Products and formulation Changes of Ethical Combination Drug Products (February 29, 2012)

List of the BE guidelines (2)

- Basic Concept of Bioequivalence Studies of Generic Products of Dry Powder Inhalers (March 11, 2016)
- Basic Concept of Bioequivalence Studies of Generic Products of Aqueous Ophthalmic Solutions (March 11, 2016)

(Ref) PMDA website (Japanese only): [http://www.pmda.go.jp/review-services-drug-reviews/about-reviews/p-drugs/0008.html](http://www.pmda.go.jp/review-services-drug-reviews/about-reviews/p-drugs/0008.html)
Quick Overview of Review Process
PMDA’s Consultation

1. Pre-Consultation (free)
2. Face to Face Consultation (charge):
   – On Bioequivalence
   – On Quality

(URL) PMDA Websites (Japanese only)
1: https://www.pmda.go.jp/review-services/f2f-pre/consultations/0001.html
2: https://www.pmda.go.jp/review-services/f2f-pre/consultations/0018.html
Timeline of Newly Applied Generic Products

New Application

First inquires (major discussion points)

Review of equivalence

Additional inquiries

Replies

Conformity to reliable criterial, GLP and GCP

Compliance of manufacturers with GMP (GMP Inspection)

Notification of the application result

Marketing Approval

1 Months

Twice a year
In February/August

12 Months (FY29)

4 Months

1 - 5 Months

-2 Months

1 - 2 Weeks
We welcome your applications

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Thank you for your attention

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