Approval Review of Generic Drugs

Office of Generic/OTC Drugs, PMDA
Kazuyuki SAITO, Ph.D.
Outline of Presentation

- Introduction

- Approval Review of Generic Drugs
  - Equivalency review
  - Conformity audit

- Conclusion
Japan’s Drug Regulations

• Ministry of Health, Labor and Welfare
  Ultimate Responsibilities in policies & administrative measures
  e.g. • Final judgment on approval
       • Product withdrawal from market

• Pharmaceuticals and Medical Devices Agency
  Actual review, examination, data analysis, etc. to assist MHLW’S measures
  e.g. • Approval Review of Drugs and MDs
       • GMP/GLP/GCP inspection
       • Collection, analysis, & provision of ADR info

• Local Government (47 Prefectures)
  pharmaceutical administration on consignment from MHLW
  e.g. • supervise license holders
       • GMP Inspection
Ministry of Health, Labor & Welfare (MHLW)
Pharmaceuticals & Medical Devices Agency (PMDA)

Imperial palace

Ministry H. L. W.
PMDA
Diet
Other Ministries

10 min. walk

2012/12/4
15th Annual IGPA Conference in Kyoto
Office of PMDA

PMDA Office
New Kasumigaseki Bldg.
3th, 6th-14th, 18th FLOOR
Tokyo, JAPAN

http://www.pmda.go.jp/
What are generic drugs?

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

Can be used as same as original 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

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### Requirements in Japan (Data to be submitted with an application for approval)

<table>
<thead>
<tr>
<th>Origin or background of discovery, conditions of use in foreign countries</th>
<th>Origin or background of discovery</th>
<th>Conditions of use in foreign countries</th>
<th>Special characteristics, comparisons with other drugs, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○</td>
<td>×</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manufacturing methods, standards and test methods</th>
<th>Chemical structure and physicochemical properties, etc.</th>
<th>Manufacturing methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>×</td>
</tr>
</tbody>
</table>

#### b. Manufacturing methods, standards and test methods

- **3 Specifications and test methods**
  - | ○ |

#### c. Stability

- Long-term storage tests
- Tests under severe conditions

#### d. Pharmacological action

- Test to support efficacy
- Secondary Pharmacology, Safety pharmacology
- Other pharmacology

#### e. Absorption, distribution, metabolism and excretion

- Absorption
- Distribution
- Metabolism
- Excretion

#### f. Acute, sub acute, and chronic toxicity, teratogenicity, and other type of toxicity

- Single dose toxicity
- Repeated dose toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive toxicity
- Local irritation
- Other toxicity

#### g. Clinical Study

- Clinical trial results

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- Conclusion
Approval Review of Generic Drugs

Approval of New generic drugs: twice a year
(listing in the drug price list: twice a year)

- February
- August

More than Ca. 1,000 applications

Reviewing period for approval review: one year

Marketing approval application for pharmaceutical product

- Inquiries concerning product
- Notification concerning Master File

PMDA

Pharmaceutical product applicant
using drug substance with registered MF

Reply

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Approval Review of Generic Drugs

What shall we check?

1. Equivalency review

Same to the originator?

required data

① Specifications and test methods
② Stability
③ Bioequivalence studies

etc.
What shall we check?

Equivalency review (1)

① Specifications and test methods

Drug substance and Drug product

- Set up for a certain range: the content of the ingredient(s) and the unit of potency
- Set up for upper limit: Impurities
- Set up for lower limit: dissolution test

※ Related impurities which are not detected in originators (review based on manufacture method, product formula)
Ref. ICH GL (Q3A, Q3B)
# Typical Setting of Specifications

<table>
<thead>
<tr>
<th>Items</th>
<th>Drug Substance</th>
<th>Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Name</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2. Structural formula or empirical formula</td>
<td>△</td>
<td>✗</td>
</tr>
<tr>
<td>3. Molecular formula and molecular mass</td>
<td>○</td>
<td>✗</td>
</tr>
<tr>
<td>4. Origin</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>5. Limits of the content of the ingredient(s) and/or the unit of potency</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>6. Description</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>7. Identification</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>8. Specific physical and/or chemical values (Physicochemical properties, etc)</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>9. Impurities</td>
<td>○</td>
<td>△</td>
</tr>
<tr>
<td>10. Water content (Water or loss on drying)</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>11. Residue on ignition, total ash and/or acid-insoluble ash</td>
<td>△</td>
<td>✗</td>
</tr>
<tr>
<td>12. Tests for preparations</td>
<td>✗</td>
<td>○</td>
</tr>
<tr>
<td>13. Special tests</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>14. Others (including Microbial limits, Particle size)</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>15. Assay</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>16. Reference standard</td>
<td>△</td>
<td>△</td>
</tr>
<tr>
<td>17. Reagents, test solutions</td>
<td>△</td>
<td>△</td>
</tr>
</tbody>
</table>

Typical Setting of Specifications

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<table>
<thead>
<tr>
<th>Type of formulation</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powders and Granules</td>
<td>Uniformity of Dosage Units, Dissolution Test or Disintegration Test</td>
</tr>
<tr>
<td>Tablets, Pills, Capsules, Troches</td>
<td>Uniformity of Dosage Units, Dissolution Test or Disintegration Test</td>
</tr>
<tr>
<td>Injections</td>
<td>Foreign Insoluble Matter Test, Test for Extractable Volume, Uniformity of Dosage Units, Sterility Test, Insoluble Particulate Matter Test, Bacterial Endotoxins Test, Release Test, Particle Size Test</td>
</tr>
<tr>
<td>Aerosols (which requires quantitative accuracy)</td>
<td>Relationship between spray time and spray amount, Particle Size Test (Suspension type only)</td>
</tr>
<tr>
<td>Elixirs, Spirits, Tinctures, Fluidextracts</td>
<td>Alcohol Number Determination</td>
</tr>
<tr>
<td>Ophthalmic Ointments</td>
<td>Test for Metal Particles, Sterility Test, Release Test, Particle Size Test, Ductility Test</td>
</tr>
<tr>
<td>Transdermal Systems (Plasters, etc.)</td>
<td>Adhesiveness test, Release Test</td>
</tr>
<tr>
<td>Suppositories</td>
<td>Melting Point Test, Release Test, Softening Point</td>
</tr>
<tr>
<td>Ophthalmic Solutions</td>
<td>Foreign Insoluble Matter Test, Sterility Test, Release Test, Particle Size Test</td>
</tr>
</tbody>
</table>
What shall we check?

Equivalency review (2)

Stability

- Accelerated test
  - The rate of chemical degradation or physical change of a drug substance or drug product.
  - at 40 (±1) °C, RH 75% (±5%)
  - 3 lots, for 6 months
  - The data from the studies can be used to assess longer term chemical effects at non-accelerated conditions
What shall we check?

Equivalency review (3)

③ Bioequivalence studies

Dosing

Absorption etc.

Analysis and Evaluation

Intestinal epithelial cell

Vessel

Plasma level of drug

Time

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Guideline

For Bioequivalence Studies of Generic Drugs
(Notification by MHLW in Dec. 1997 was revised in Nov. 2006) and Feb. 2012)
– assure therapeutic equivalence of generic drugs to the originators.
– compare the bioavailability between a generic drug and its originator.

Bioequivalence tests: started to be required since 1980 under the GCP standards and also regulated as clinical trials by the Pharmaceutical Affairs Law
Procedure for Bioequivalence Evaluation

- Selection of an originator product batch (reference product batch)
- Evaluation of dissolution behavior
- Pilot bioequivalence study in humans
- Main bioequivalence study in humans
- Statistical analysis
Bioequivalence studies

Design
- Crossover studies with random assignment of individual subjects to each group and open-labeled studies

Number of subjects
- A sufficient number of subjects for assessing bioequivalence
- Minimum of 12 subjects (WHO Guideline)

Selection of subjects
- Healthy adult volunteers
Parameters to be assessed

- Blood samples
  - single dose: $AUC_t, C_{max}$
  - multiple dose: $AUC_{\tau}, C_{max}$
- AUC, $t_{max}$, MRT, $k_e$ (reference)

- Urine samples: $Ae_t, Ae_{\tau}, Ae_{\infty}, U_{max}$ and $U_{\tau}$
The 90% confidence interval of the difference in the average values of logarithmic AUC:

\[ \log(0.8) \sim \log(1.25) \cdot \cdot \cdot \text{acceptable range} \]

For \( C_{\text{max}} \), the same acceptable range.
Cases prone to Exhibiting Differences in Bioequivalence

1. Insoluble compounds
   - Dissolution controls absorption. Differences in the particle size of API affect bioavailability in some compounds.

2. Lipid-soluble compounds
   - Solubilization by bile acid controls bioavailability (potent effect of food) in some compounds.

3. Highly variable drugs
   - Bioavailability will not be within the confidence interval in the standard sample size (approx. 20 patients) as the pharmacokinetics (e.g. metabolic clearance) is highly variable.
4. Enteric-coated drugs

- Acid resistance and drug dissolution affect bioavailability. The gastric emptying rate (GER) is highly variable.

5. Sustained-release drugs

- Differences in bioavailability related to differences in the mechanism for sustained-release (equivalency in dissolution is required).
- GER is highly variable (the guidelines require that fasted and fed bioequivalence studies be performed).

6. Cases related to assays

- Nonspecific assays may result in incorrect determinations for the concentrations of unchanged substances.
Other application of bioequivalence studies

**Original drug**
Confirmed to have therapeutic efficacy and safety

**Generic drug**
For originator

**Formulation change**
Different strength
Different in dosage form
For original drug

**Formulation change**
Different strength
Different in dosage form
For drug in clinical development

Same in terms of Transition of therapeutic information
What shall we check?

Conformity audit

The reliability is also important point,

- Check the conformity to the standards in application data
  - 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
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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.

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Face-to-Face Consultation Service

- short consultation (kan-i-sodan) : already practiced by satisfactory entry in specification / MF (fee/application: ¥ 21,800)

A new trial consultation : starting in 2012. 1 ~ to give guidance and advice of application materials before the submission

- Quality (fee/application: ¥ 491,800)
- Bioequivalence study (fee/application: ¥ 997,500)
Thank you for your attention!

Office of OTC/Generic Drugs
Pharmaceuticals and Medical Devices Agency

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