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

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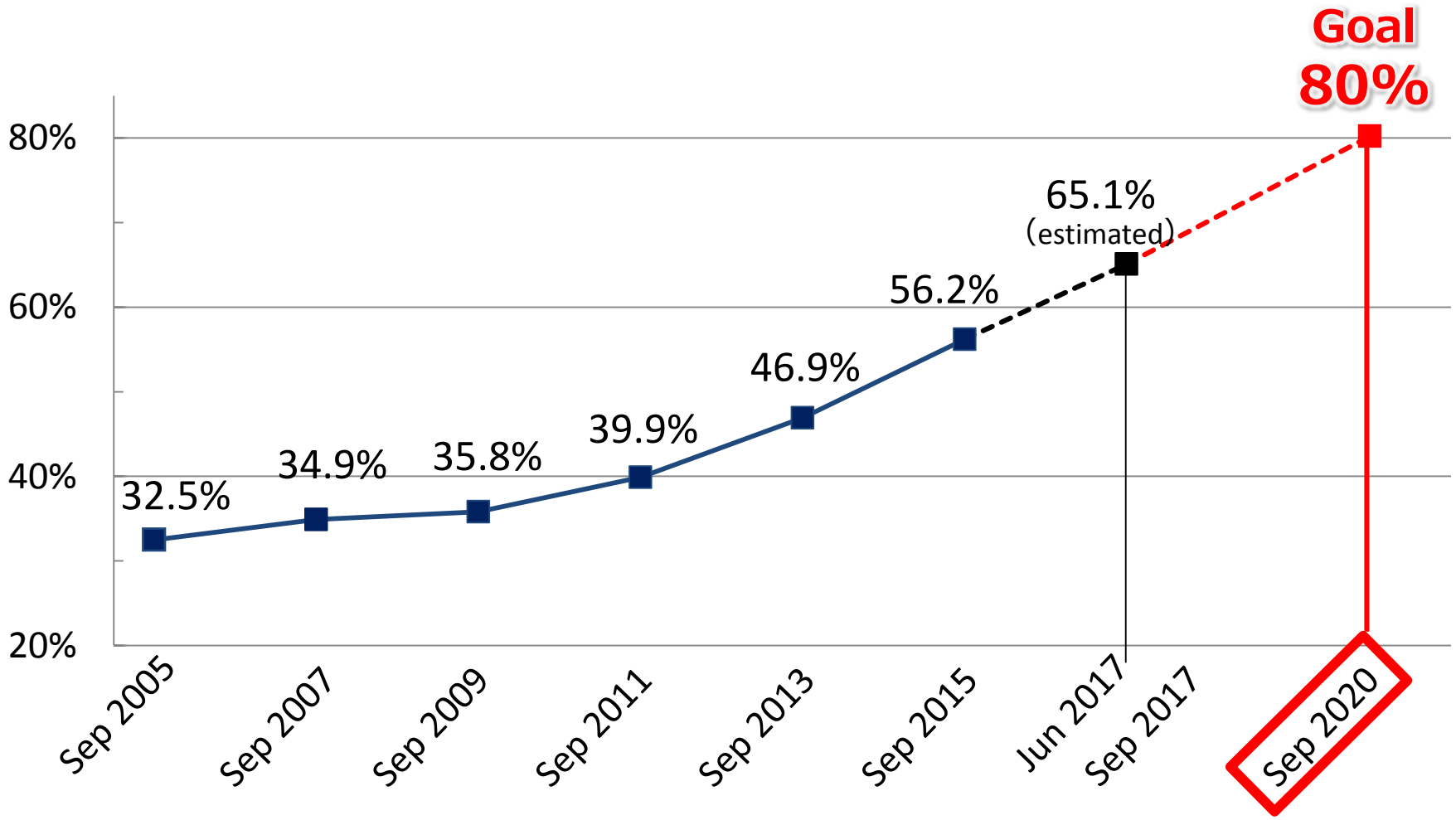
Overview of Japan's Policy

Transition of Generic Drugs Market Share in Volume and its Goal

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



DATA source: MHLW

Joint Projects of Strengthening Quality Certification in Collaboration with Academia/Inspection

MHLW implements two main projects:

- Promoting information provision in collaboration with academia
- Certifying quality in the market as a part of inspection

Project of Promoting Information Provision

Concerns from nationals/academia/medical workers

PMDA
Consultation service

MHLW

NIHS
Quality Information Committee

Local Health Centers

Project of Certifying Quality

MHLW

Results

NIHS
NIID

Products under test

Results

Local Prefectures

Local Health Centers

Inspection

Voluntary sample provision

Marketing Authorization Holders

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

Documents		Originator	Generic
a. Origin or background of discovery, condition of use in foreign countries	1 Origin or background of discovery	○	×
	2 Conditions of use overseas	○	×
	3 Special characteristics, comparisons with other drugs etc.	○	×
b. Manufacturing methods, specification and test methods	1 Chemical/physical characteristics and structure property	○	×
	2 Manufacturing methods	○	△
	3 Specification and test methods	○	○
c. Stability	1 Long-term storage tests	○	×
	2 Tests under severe conditions	○	×
	3 Accelerated tests	○	○
d. Pharmacological action	1 Tests 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 Bioequivalency	×	○
	6 Other pharmacokinetics	△	×
f. Acute/sub acute/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 trials	1 Results of clinical trials	○	×
h. Package inserts	1 Points to consider of package inserts	○	○

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℃, 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 ℃, 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)

(Ref) English documents on NIH website: http://www.nihs.go.jp/drug/DrugDiv-E.html

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

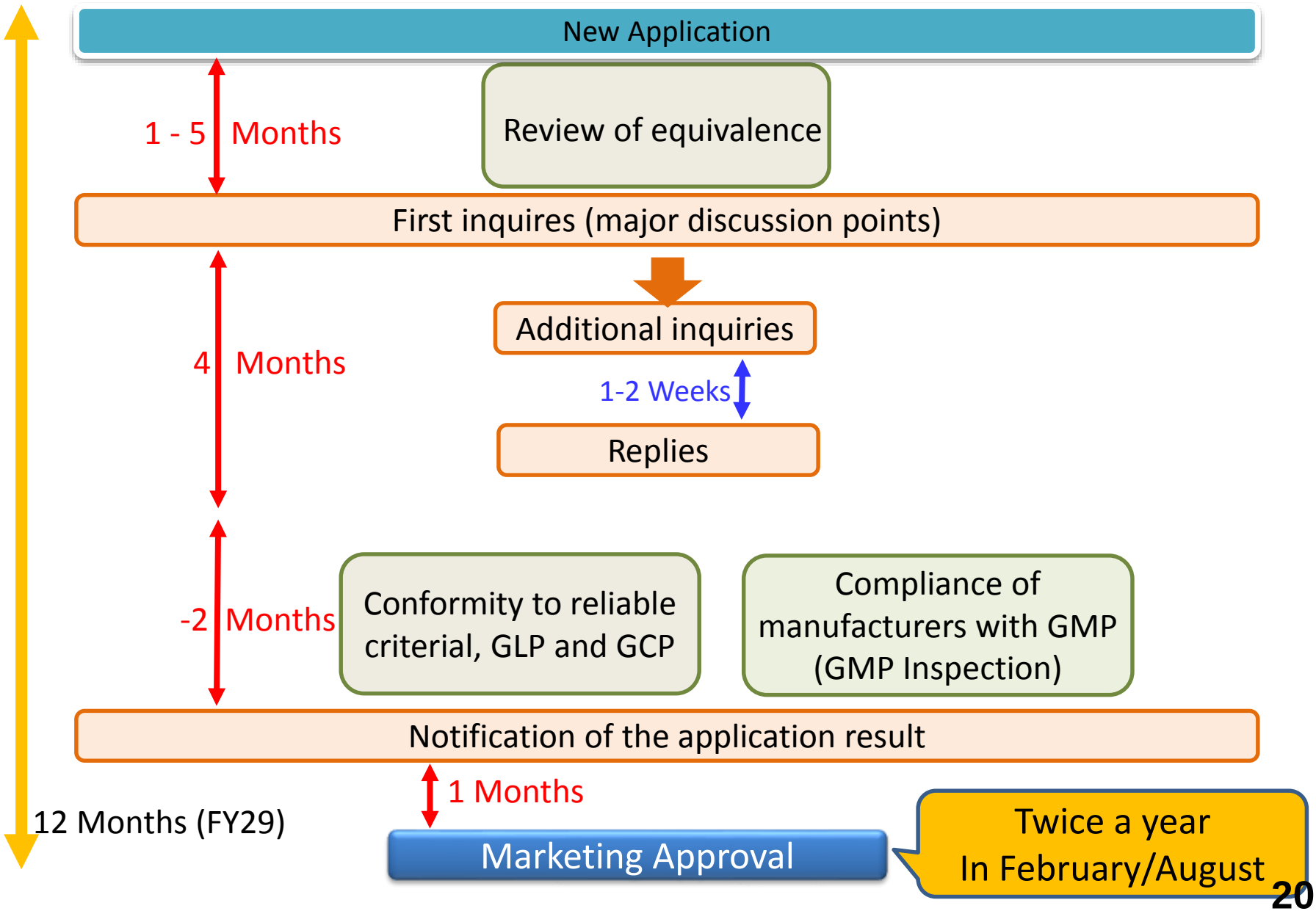
Quick Overview of Review Process

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



We welcome your applications

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Thank you for your attention

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