# Japan Drug Regulatory Overview

# 2014


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# Japanese Pharmaceutical Laws (PAL)

Pharmaceutical administration in Japan is based on various laws and regulations, consisting mainly of:

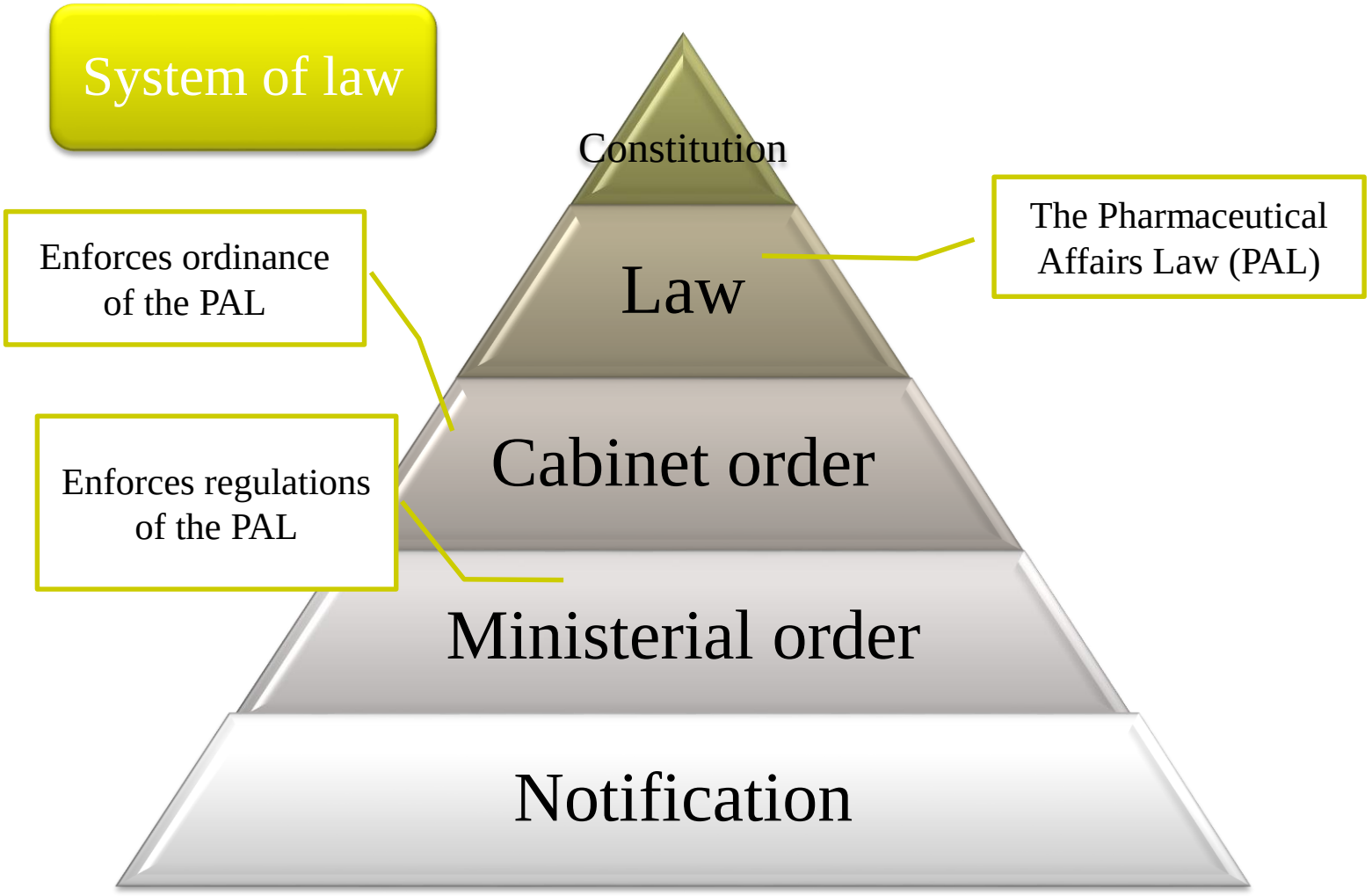
- (1) the Pharmaceutical Affairs Law,
- (2) Pharmacists Law,
- (3) Law Concerning the Establishment for Pharmaceuticals and Medical Devices Organization,
- (4) Law Concerning Securing Stable Supply of Blood Products,
- (5) Poisonous and Deleterious Substances Control Law,
- (6) Narcotics and Psychotropics Control Law,
- (7) Cannabis Control Law,
- (8) Opium Law, and
- (9) Stimulants Control Law

# Japanese Pharmaceutical Affairs Law (PAL)

The Pharmaceutical Affairs Law has 11 chapters and 91 articles.

- Chapter 1: General provisions (Articles 1 and 2) (Purpose and definitions of drugs, quasi-drugs, cosmetics, and etc.
- Chapter 2: Prefectural pharmaceutical affairs councils (Article 3)
- Chapter 7: Handling of drugs
- Chapter 9-2: Handling of designated drug substances
- Chapter 9-3: Designation of orphan drugs

# Pharmaceuticals Affairs Law (PAL)



# Revision of the Pharmaceutical Affairs Law

| | |
|---|---|
| Change of the name | • Legislation concerning securement of quality, efficacy and safety of pharmaceuticals, medical devices, etc. |
| Main amendment | • Enforcement of safety measures for pharmaceuticals, medical devices, etc.<br>• "Regenerative medicine products" are added to subjects of regulation of the PAL<br>• Regulation of medical devices and in vitro diagnostics based on their characteristics |
| Enforcement date | • Within a year after the date of promulgation (November 27, 2013) |

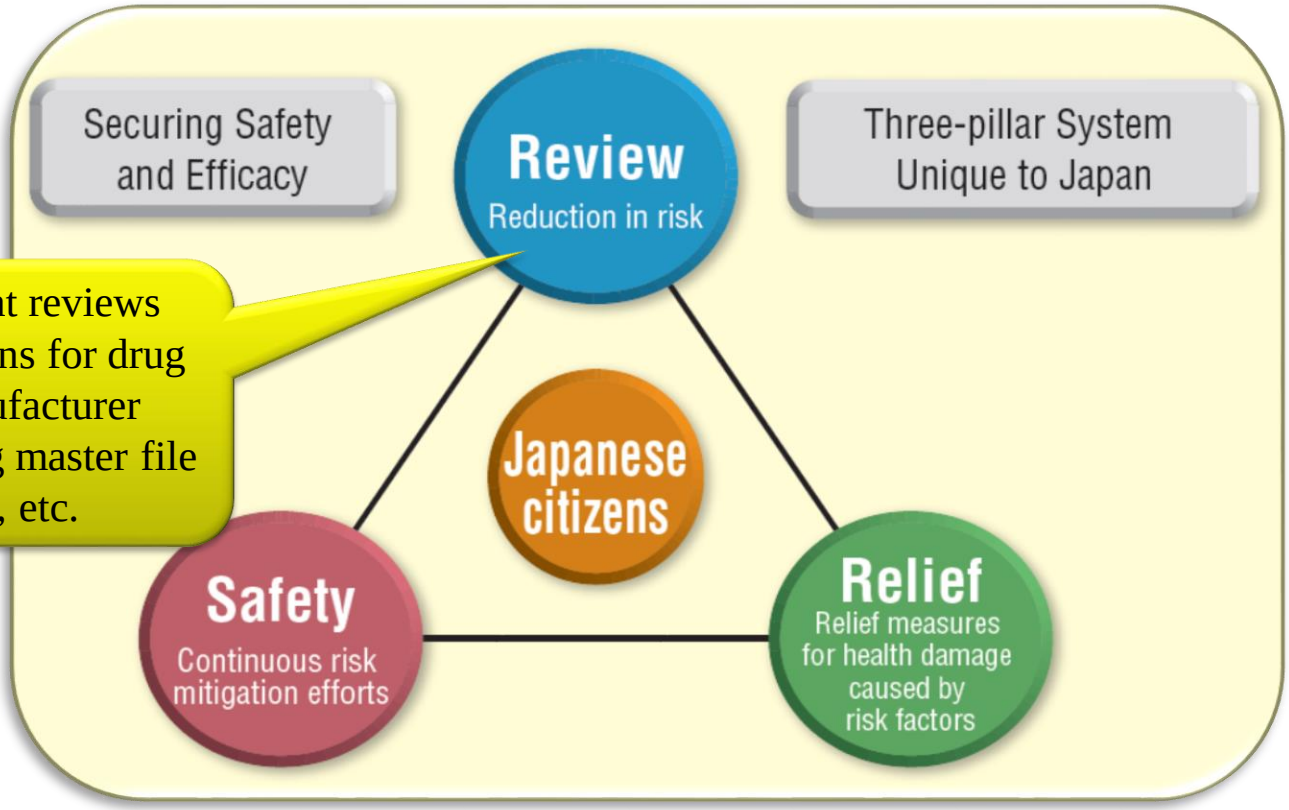
# MHLW/PMDA

- The Ministry of Health, Labour and Welfare (MHLW) in Japan is an administrative organization equivalent to the Department of Health and Human Services (DHHS) in the US.
- PMDA is an organization established in the *Pharmaceuticals and Medical Devices Agency Law (Agency Law)* based upon the Reorganization and Rationalization Plan for Special Public Corporations approved by the Cabinet in December 2001.

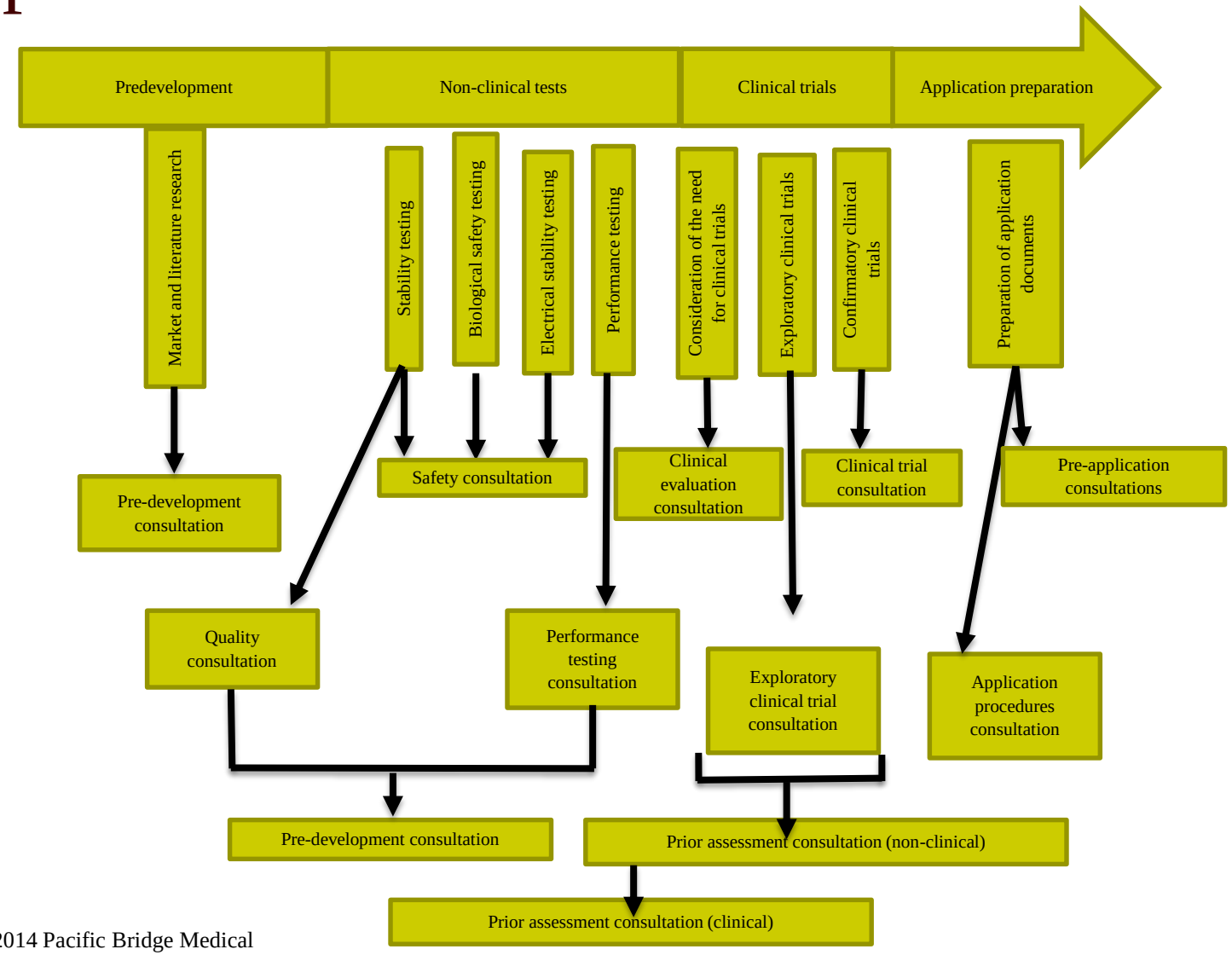
# Pharmaceuticals and Medical Devices Agency

http://www.pmda.go.jp/english/index.html

PMDA is the agency that reviews submissions of applications for drug approval, foreign manufacturer accreditation (FMA), drug master file (DMF) registration, etc.



# Japanese PMDA Consultation Sessions



# Consulting Services by the PMDA for Clinical Trials

## Face-to-face consultation by the PMDA

The PMDA provides guidance regarding clinical trials and required information for approval applications, etc. Using the face-to face consulting services can aid the application process.

**Fees for face-to-face consultation（abstract）**

| Description | Fee（yen） |
|---|---|
| Consultation before starting Phase I study | 4,360,500<br>（excluding orphan drug） |
| Consultation before starting preceding period of Phase II study | 1,669,400<br>（Excluding orphan drug） |
| Consultation before starting later period of Phase II study | 3,114,900<br>(Excluding orphan drug） |
| Consultation after completion of Phase II study | 6,183,300<br>（Excluding orphan drug） |

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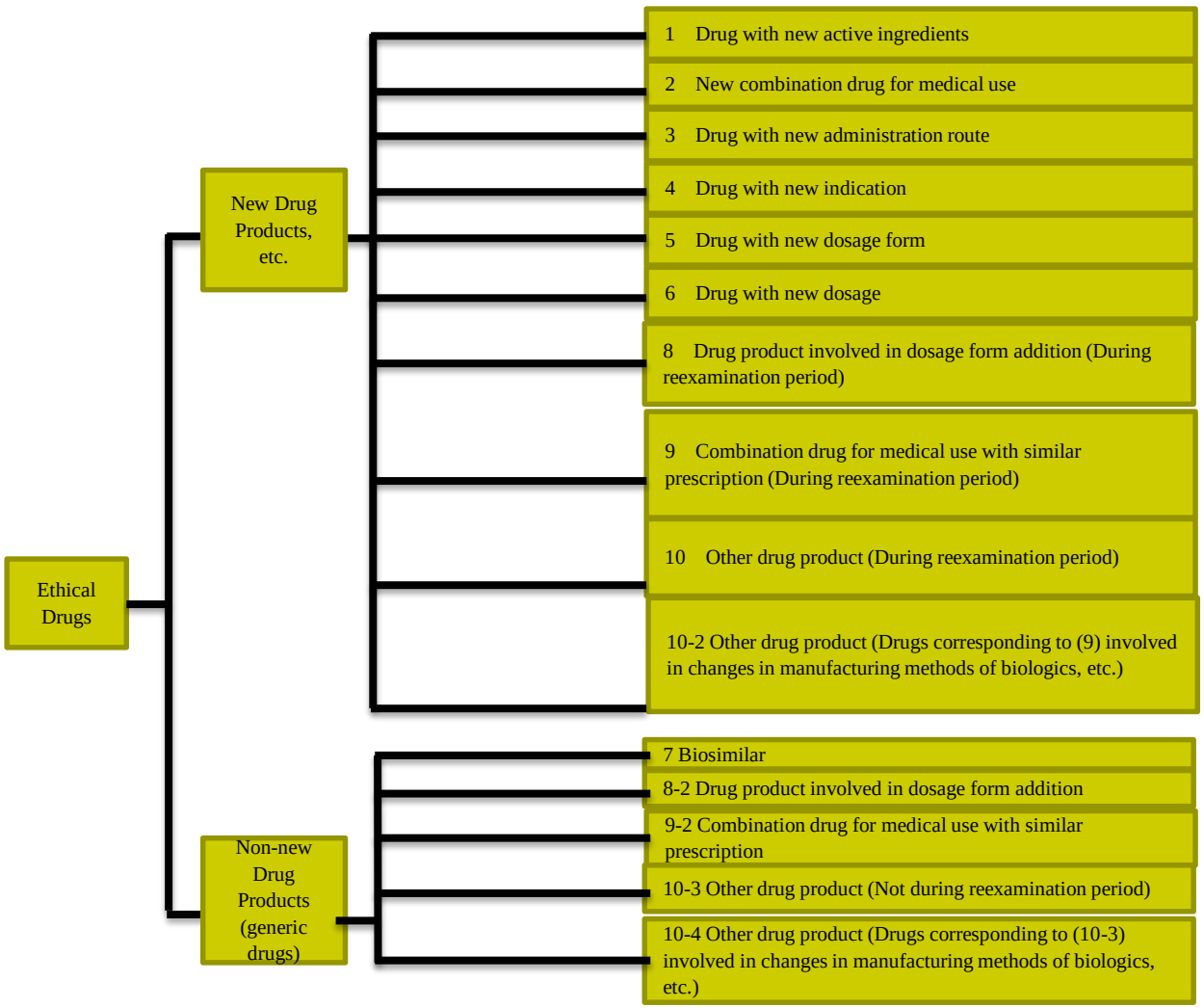
# Classification of Drug Products

- Ethical Drugs
- Prescription Drugs
- OTC Drugs
  - Class I Drug Products
  - Class II Drug Products
  - Class III Drug Products
- Orphan Drugs

# Classification of Ethical Drugs



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# Approval Application for Marketing a Drug

When marketing a drug, it is necessary to obtain approval for each product by receiving examinations on both its efficacy and safety.

- Only a MAH license holder can submit an approval application for a product.
- To obtain product approval, the manufacturer in Japan needs to be licensed. For a foreign manufacturer, a Foreign Manufacturer Accredited Certificate (FMA) is required.
- The application is sent to the PMDA and further examination is mainly conducted by this agency.

Application fee for a new drug

| Description | Total fee（yen） |
|---|---|
| Drug containing new ingredient, drug for a new route of administration, drug with a new combination, biotechnology based existing drug (excluding an orphan drug) | 31,068,900 |
| Drug containing new ingredient, drug for a new route of administration, drug with a new combination, biotechnology based existing drug (orphan drug) | 23,847,800 |
| Drug with a new indication, drug with a new dosage form, drug for new dosage and drug with similar formulation (excluding an orphan drug) | 14,230,600 |
| Drug with a new indication, drug with a new dosage form, drug for new dosage and drug with similar formulation (orphan drug) | 10,957,300 |

# Required Documents for IND Application

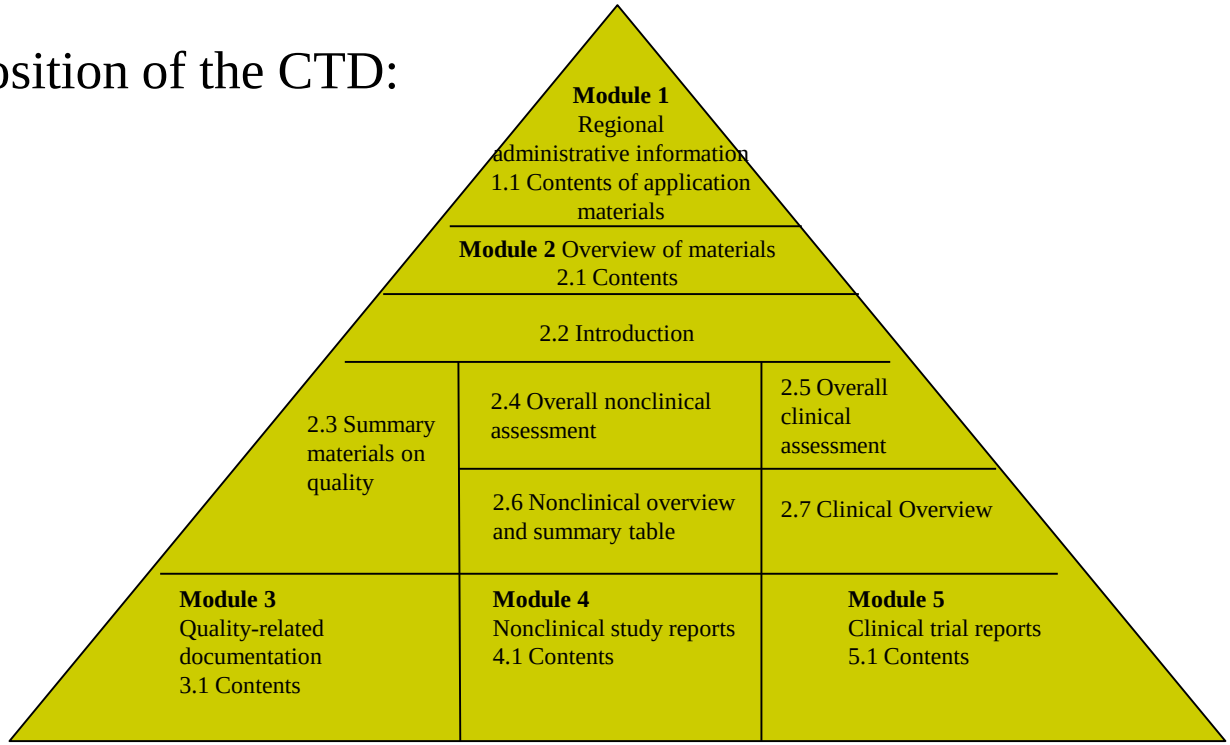
In order to protect public health, it is mandatory to submit a IND application to the Ministry of Health, Labor and Welfare.

| Document | Language |
|---|---|
| Application Form (written) | Japanese |
| Application Form (XML) | Japanese |
| Protocol | Japanese |
| Case Report Form | Japanese |
| IB | Japanese |
| ICF | Japanese |
| Written reason with appropriate requests for clinical trial | Japanese |

# Documents Required for Approval Application

- Application documents for a new drug should be prepared in the Common Technical Document (CTD) format following the ICH-M4 guideline.

- Composition of the CTD:

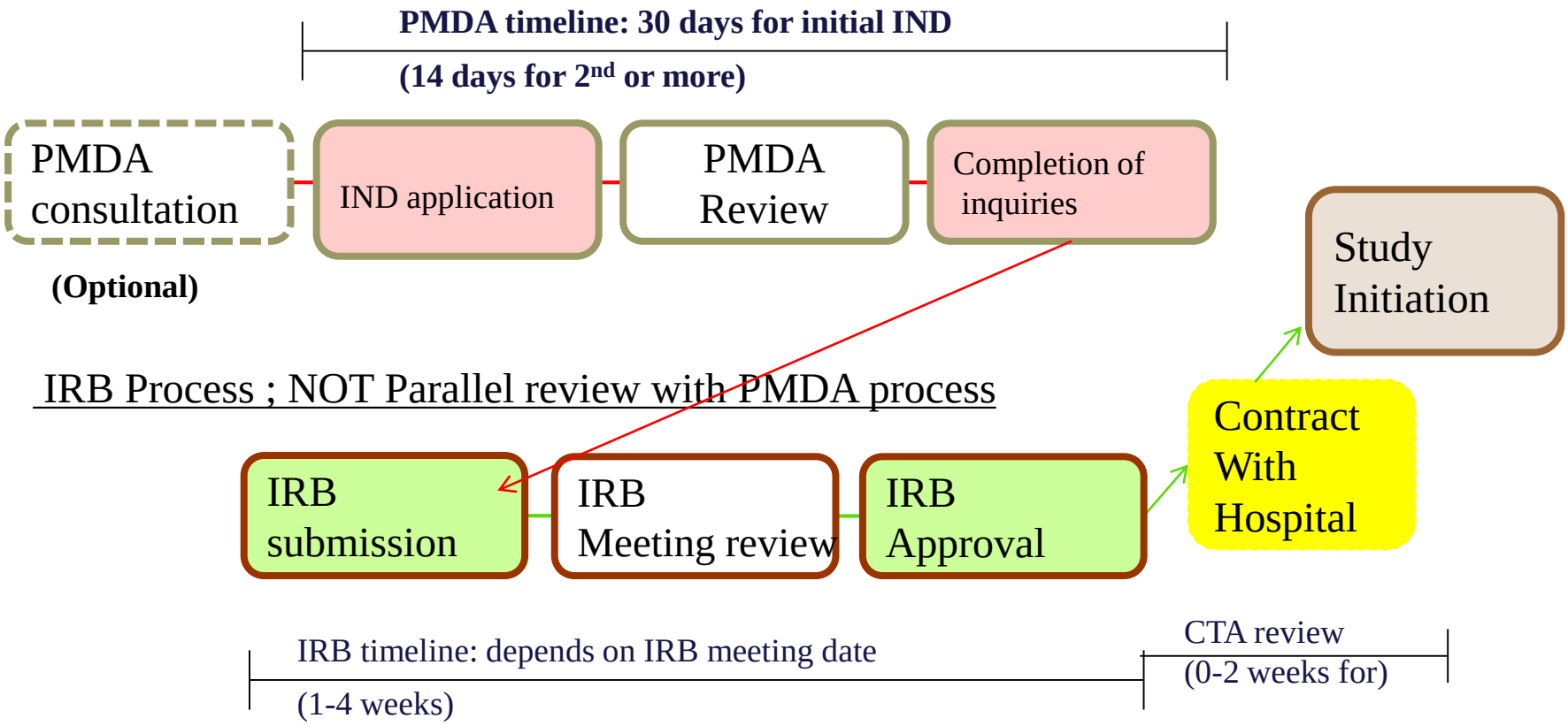


# Documents Required for Approval Application

| Required documents | | Contents | Corresponding CTD Module | |
|---|---|---|---|---|
| a | Documents on origin or course of discovery and usage status overseas | Status of development and approvals overseas, comparison of package inserts with similar drugs | Module 1 | |
| b | Documents on manufacturing method and standards and test methods | Structure determination and physical-chemical property | Module 3 | Module 2 |
| c | Documents on stability | Long term stability test, accelerated test and stress test | | |
| d | Documents on pharmacological action | Tests supporting efficacy, secondary pharmacology/safety pharmacology | Module 4 | |
| e | Documents on absorption, distribution, metabolism and excretion | In vivo disposition study | | |
| f | Acute, subacute and genetic toxicity, teratogenicity and other toxicities | Single dose toxicity, repeated dose toxicity, genetic toxicity, carcinogenicity study, reproduction toxicity, local irritation study and other toxicity study | | |
| g | Documents on clinical test results | Phase I, Phase II and Phase III | Module 5 | |

# IND approval process

- PMDA & IRB Approval Process




- IRB Process ; NOT Parallel review with PMDA process

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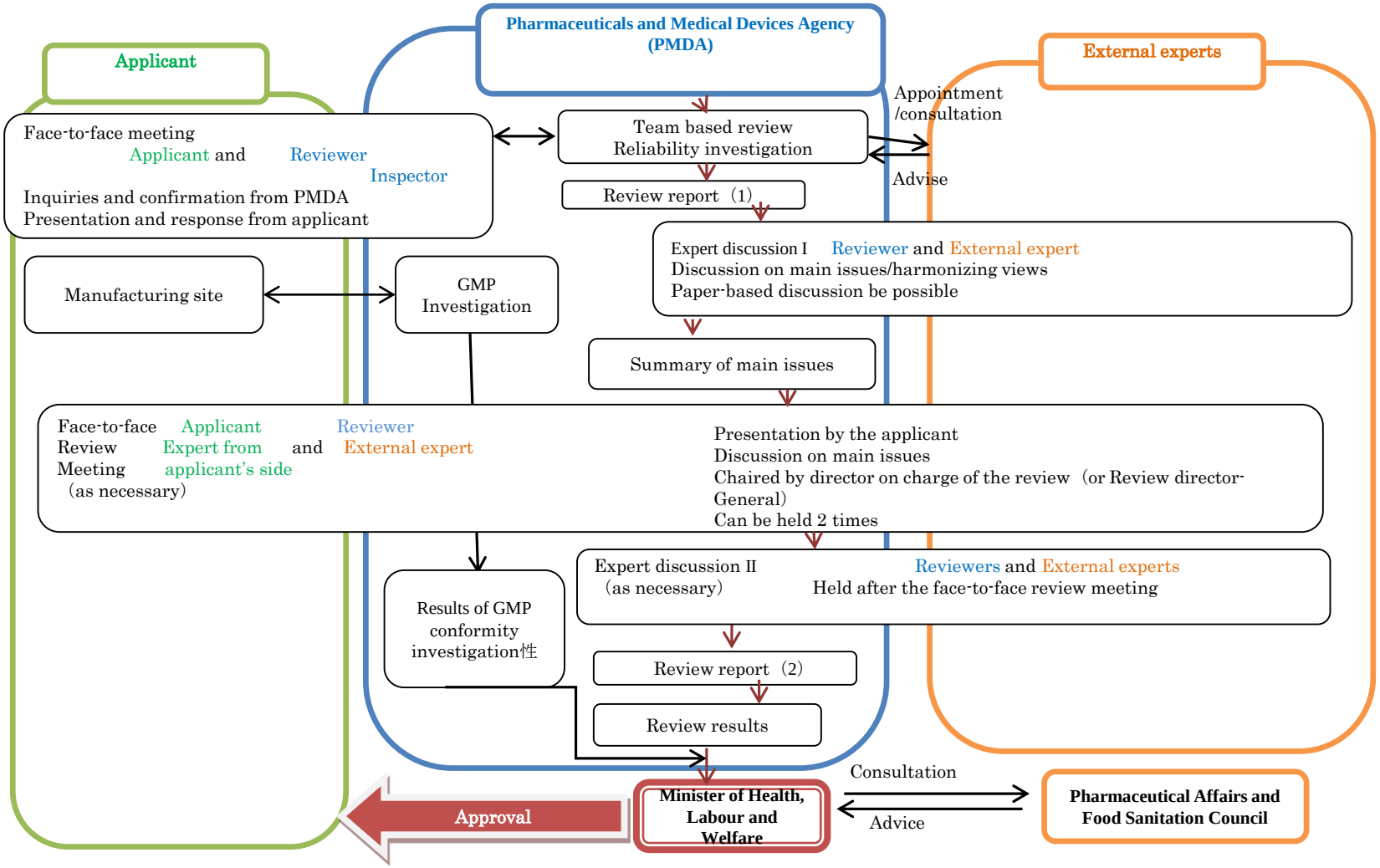
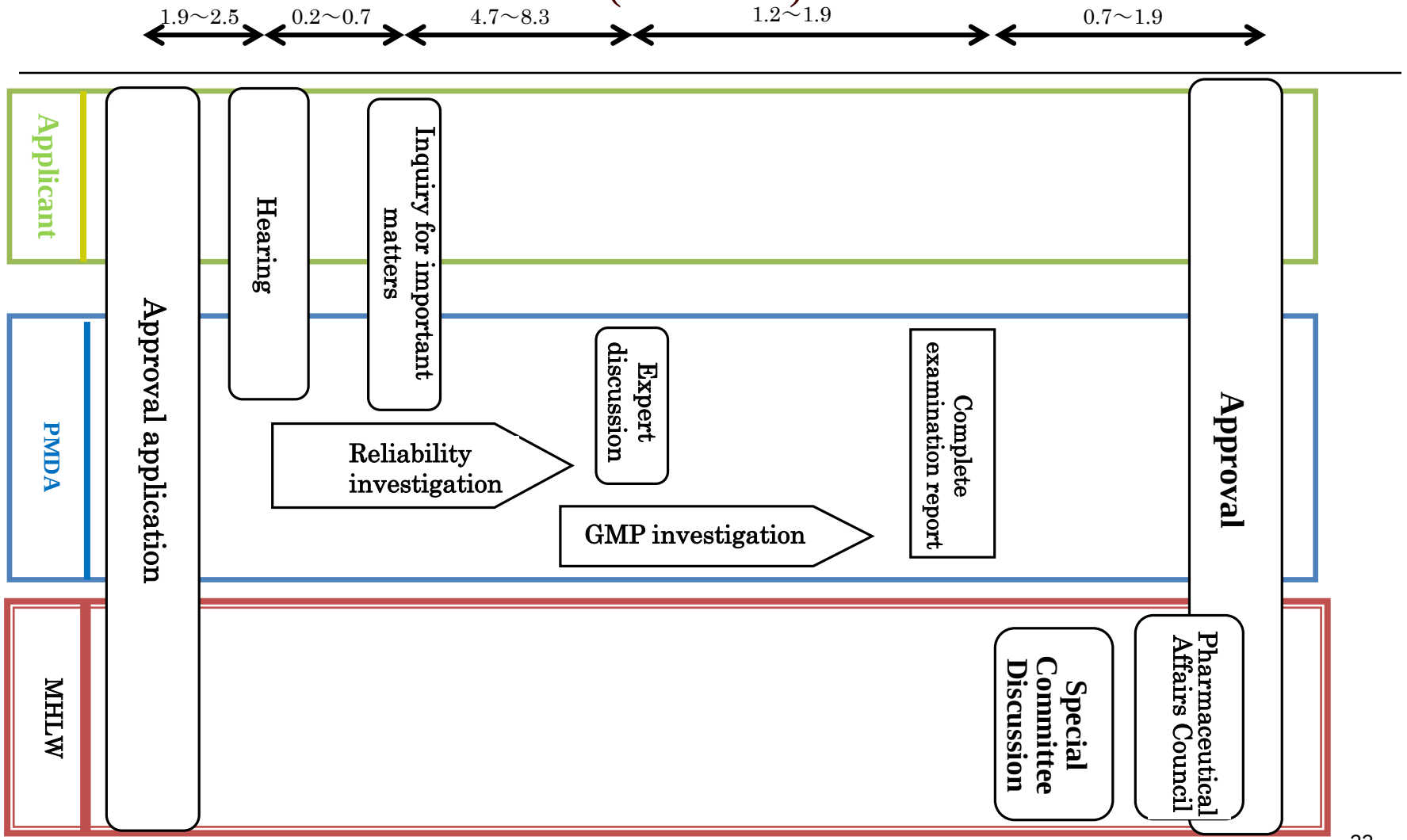
# Registration Flow Chart



# Standard Timeline for Approval of a New Drug



# Approval and Publication of Information

## ❑ Approval

When deliberation by the Pharmaceutical Affairs and Food Sanitation Council is completed, the new drug that the Ministry of Health, Labor and Welfare reports as being acceptable will be approved after a GMP conformity investigation and through routine procedure within the MHLW. A drug designated as a poisonous or powerful drug or biological products appears in the government gazette.

Approval certificate is delivered by the Evaluation and Licensing Division after the date of approval. For drugs processed by the bureau, approval certification is delivered through the PMDA.

## ❑ Publication of Information

As for a new drug, an Assessment Report is published right after the approval and the outline of application documents (Module 1 (partially) and 2 of CTD) is published 3 months after the approval.

# The Drug Lag Problem

- Despite the fact that Japan is the world's second-largest pharmaceutical market and a center for cutting-edge life-science research, it has a deplorably slow approval process for new drugs. This otherwise advanced nation has become known for its "drug lag".

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# Orphan Drugs

**Drugs that meet the following standards can be regarded as an orphan drug:**

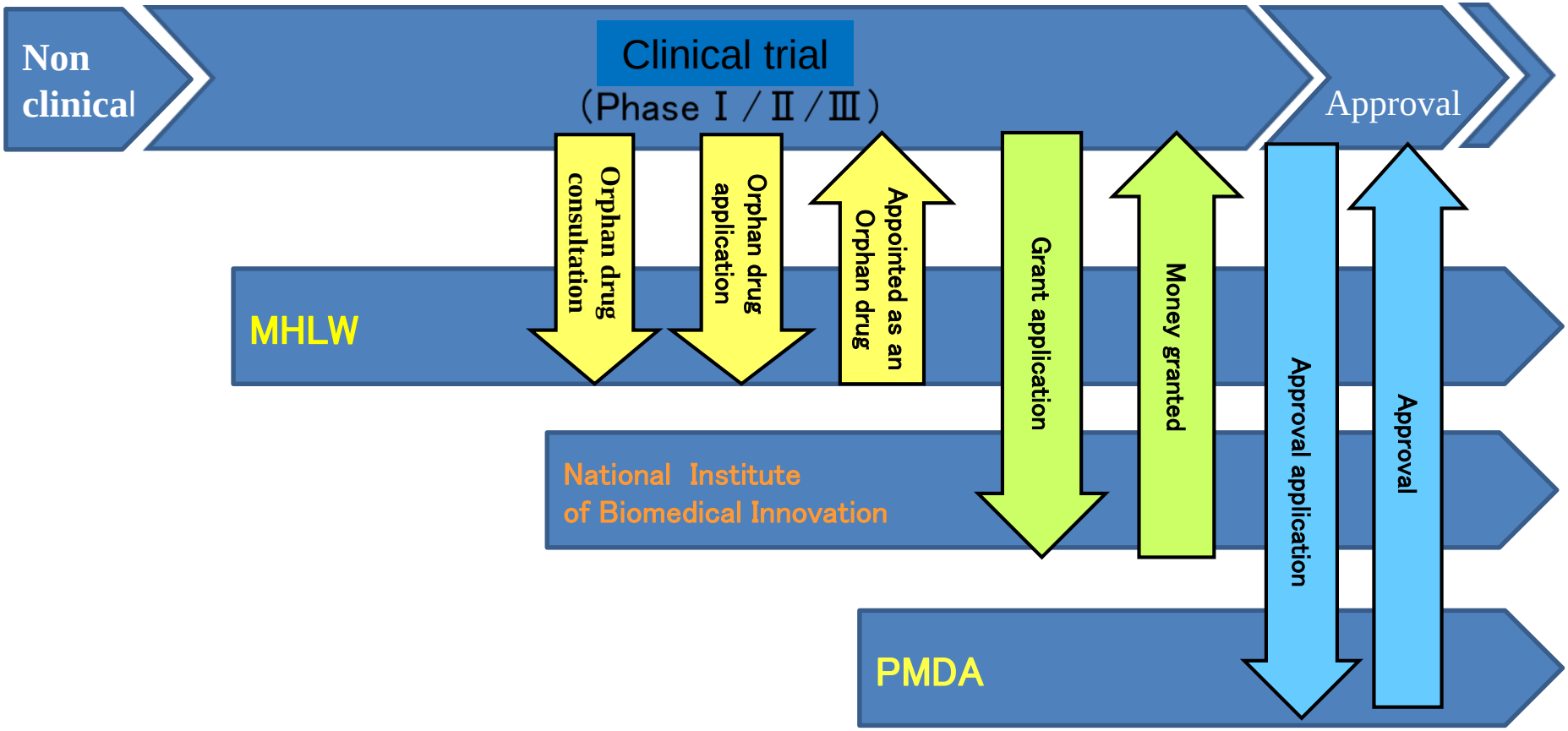
- The number of patients for the product is less than 50,000.
- The medical need is especially high and the intended use is for severe diseases such as intractable diseases. In addition, the following conditions must be met:
  - No other drug or medical treatment is available for the disease of concern.
  - Significantly high efficacy and safety are expected from the product.
- There should be a strong rationale for the use of the product. The development plan of the product should also be valid.
- There are key issues to consider with orphan drugs such as government funding, prioritized guidance and advice by the PMDA, priority review, tax breaks and exclusive marketing periods.

# Priority Review System and Designation of Drug Products for Priority Reviews

- Drug approval reviews are normally processed in the order that the application forms are received.
- For drugs designated as orphan drugs and other drugs considered to be especially important from a medical standpoint, the drug product may be chosen for priority review after an evaluation of the seriousness of the targeted disease and the clinical usefulness of the product (Article 14-(7) of the Pharmaceutical Affairs Law).

# Product Registration Process for Orphan Drugs in Japan

Outline for an approval of an orphan drug



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# Biological Products and Specified Biological Products

Biological Products

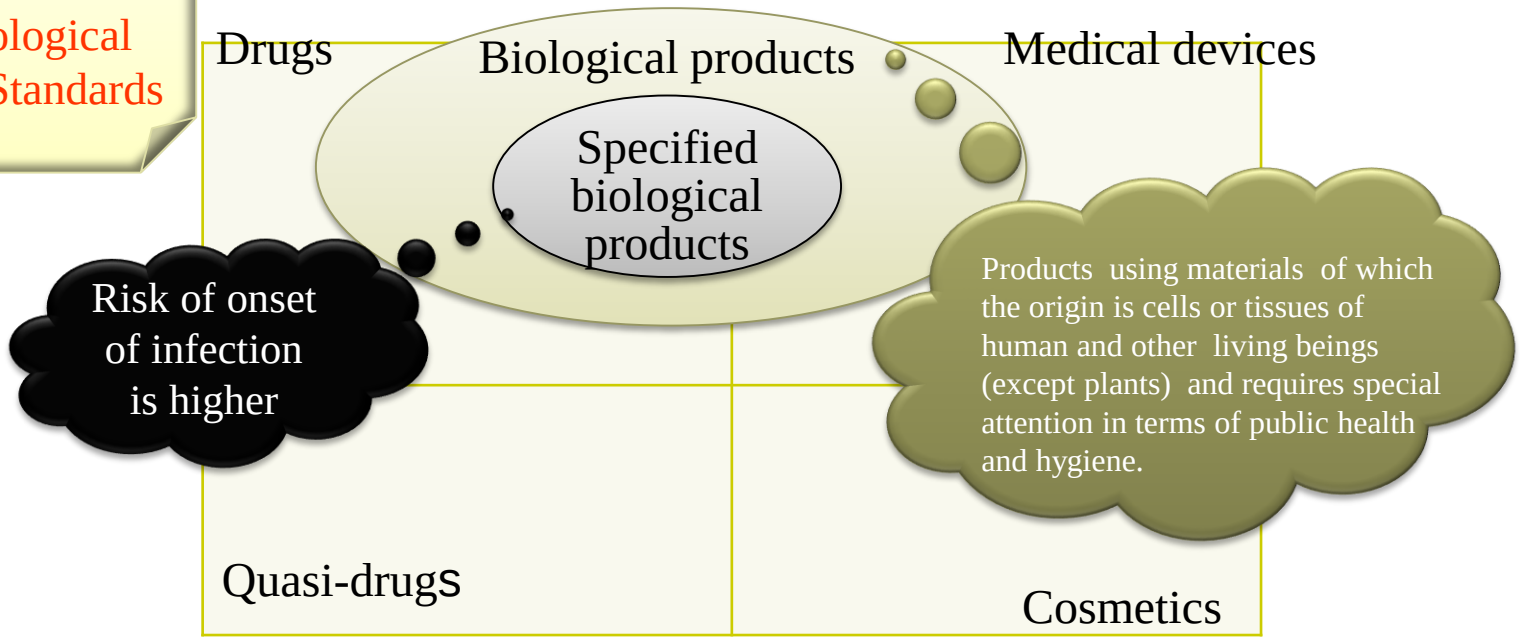
- Drugs, quasi-drugs, cosmetics, or medical devices using materials manufactured from humans or other organisms (excluding plants) as raw materials or packaging materials, which are designated as requiring special precautions in terms of public health and hygiene.

Specified biological products

- Biological products designated as requiring measures to prevent the onset or spread of risk to public health and hygiene due to the biological product after it is sold, leased, or distributed.

# Biological Products and Specified Biological Products

Raw materials of biological products need to conform with Biological Material Standards




For the approval application, documents for designation of biological/specified biological products may be requested.

# Regulation for Biotechnology-Based Drugs

## ICH quality guidelines for biotechnology-based drugs

Many of ICH guidelines for quality are incorporated as Japanese regulations.

| Topic | Name of the guideline |
|---|---|
| Q5A | Viral safety evaluation of biotechnology-based drugs derived from cell lines of human or animal |
| Q5B | Analysis of the expression construct in cells used for production of r-DNA derived protein products |
| Q5C | Stability testing of biotechnological/biological products |
| Q5D | Derivation and characterization of cell substrates used for production of biotechnological/biological products |
| Q5E | Comparability of biotechnological/biological products subject to changes in their manufacturing process |
| Q6B | Specifications: Test procedures and acceptance criteria for biotechnological/biological products |
| Q7A | GMP guide for active pharmaceutical ingredients |

# Regulations on Genetically Engineered Drugs

- For regulations on genetically engineered drugs, refer to the table on the previous slide.
- Points to consider for biosimilar, refer to the table of notifications issued by the MHLW below.
- Category of application for a new genetically engineered drug is “Class I: Drugs containing new active ingredients” whereas biosimilar is “Class VII: biosimilar”

**Notifications concerning biosimilar**

| Name of notification | Date and number |
|---|---|
| Approval application for biosimilar | 2009.3.4<br>YAKUSHOKUHATSU0304004 |
| Guideline to ensure quality, safety and efficacy of biosimilar | 2009.3.4<br>YAKUSHOKUSHINSAHATSU0304007 |
| Generic name and proprietary name regarding biosimilar | 20013.2.14<br>YAKUSHOKUSHINSAHATSU02141 |
| Points to consider  at a time of approval application for biosimilar | 2009.3.4<br>YAKUSHOKUSHINSAHATSU0304015 |
| Q & A on Guideline to ensure quality, safety and efficacy of biosimilar | 2009.7.21<br>From Evaluation and License Div |
| Q & A on Guideline to ensure quality, safety and efficacy of biosimilar | 2010.3.31<br>From Evaluation and License Div |

# Regulations on Cells/Tissues Processing Drugs

For cells/tissues processing drugs, submission of an application for confirmation is required before the first IND application.

Application for confirmation → Confirmation by the Minister → IND application → Approval application

**MHLW Notifications concerning cells/tissues processing drugs**

| Name of notification | Date and number |
|---|---|
| Changes in handling cells/tissues processing drugs or medical devices due to implementation of consultation for regulatory strategies | 2011.6.30<br>YAKUSHOKUHATSU 0630-2 |
| Changes in procedures to ensure quality and safety of cells/tissues processing products | 2007.3.30<br>YAKUSHOKUHATS 0330030 |
| Partial amendment of "Ensure quality and safety of cells/tissues processing medical devices or drugs" | 2010.11.1<br>YAKUSHOKUHATSU 1101-3 |
| Quality and safety of drugs manufactured using materials of human or animal origin | 2007.3.30<br>IYAKUHATSU 1314 |
| Securement of human derived (autologous) cells/tissues processing drugs of medical devices | 2008.2.8<br>YAKUSHOKUHATS 0208003 |
| Securement of human derived (homologous) cells/tissues processing drugs of medical devices | 2008.9.12<br>YAKUSHOKUHATSU 0912006 |
| Q & A on the guideline for Securement of human derived (autologous) cells/tissues processing drugs of medical devices | 2008.3.12<br>From Evaluation & Licensing Div. |
| Q & A on the guideline for Securement of human derived (homologouss) cells/tissues processing drugs of medical devices | 2008.10.3<br>From Evaluation & licensing Div. |
| Manufacturing and quality control for human derived (autologous) cells/tissues processing drugs of medical devices | 2008.3.27<br>YAKUSHOKUKANMAHATSU 0327025 |

# Regulation Related Cartagena Protocol

- Cartagena Protocol is a regulation for the use of genetically-modified organisms
- For those products, application should be submitted after consultation with the PMDA about containment measures and use rules.
- It is required to obtain confirmation or approval from MHLW or Ministry of Environment before starting manufacture or clinical trial.

## MHLW Notification on Cartagena protocol

| Name of notification | Date and number |
|---|---|
| Partial amendment of "Enforcement of the law for securement of biotic diversity through regulations on the use of genetically-modified organisms" | 2013.7.1 YAKUSHOKUHATSU 0701-10 |
| Diffusion prevention measures in manufacturing drugs using genetically-modified organisms | 2004.2.19 YAKUSHOKUHATSU 0219011 |
| Procedures after enforcement of the law for securement of biotic diversity through regulations on the use of genetically-modified organisms | 2004.3.19 YAKUSHOKUSHINSAHATSU 0319001 |

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# What are Generic Drugs?

- Compared with the original drugs (brand drugs), generic drugs have the same:
  - Active ingredient(s)
  - Quantities
  - Route of administration
  - Dosage form
  - Direction and dose
  - Indications and effects
- Can be used in the same way as brand drugs.

# Main Data Required for the Approval of Generic Drugs

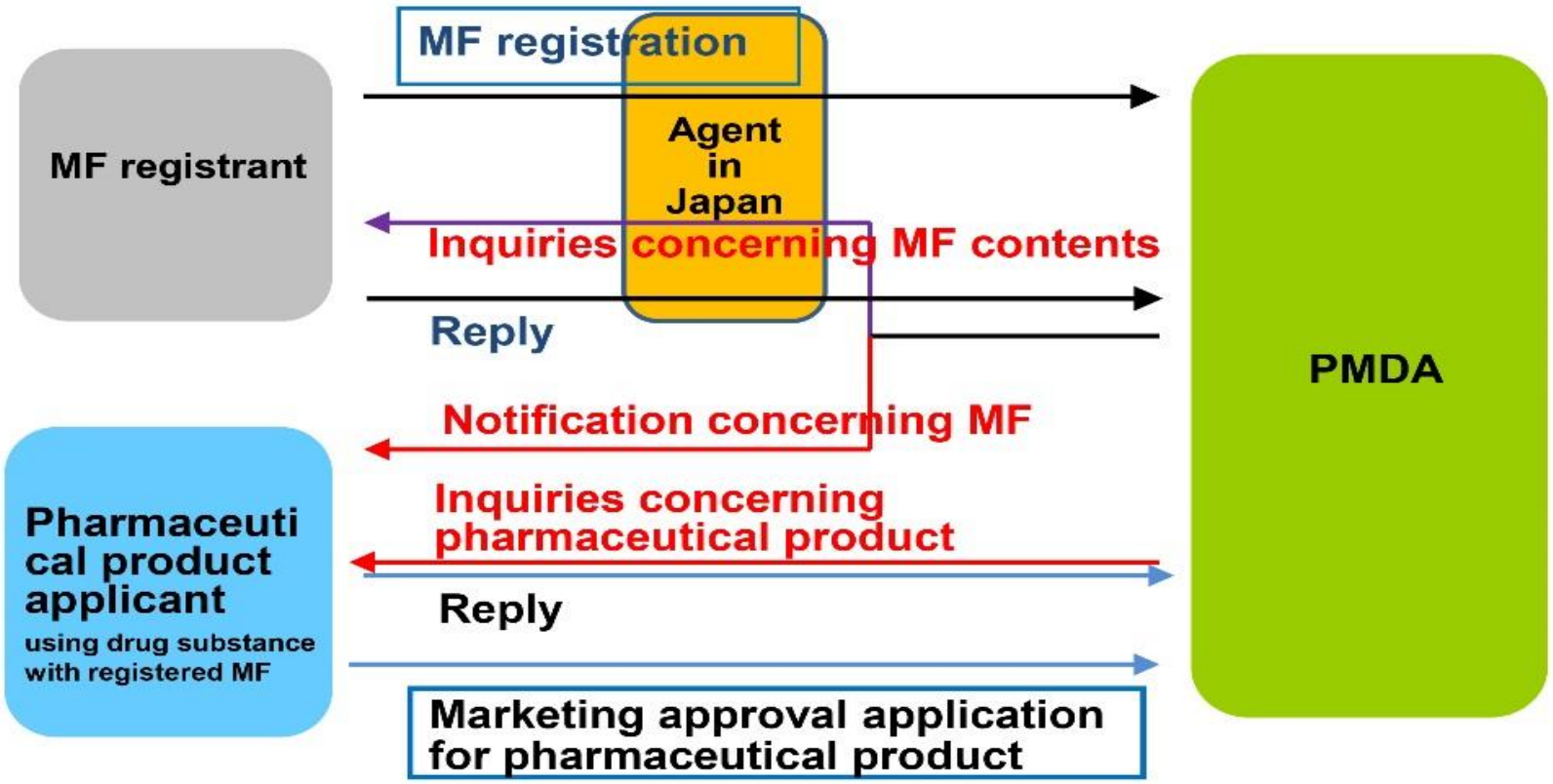
- The manufacturing methods, standards, and test methods, which are used for evaluations of specifications and test methods (and manufacturing methods, in some cases).
- Stability data, which is used to conduct accelerated tests.
- Absorption, distribution, metabolism, and excretion data, which are used in bioequivalence evaluations.

| 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 | ○ | Δ |
| | 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 | Δ | × |
| e. Absorption, distribution, metabolism, and excretion | 1 Absorption | ○ | × |
| | 2 Distribution | ○ | × |
| | 3 Metabolism | ○ | × |
| | 4 Excretion | ○ | × |
| | 5 Bioequivalence | × | ○ |
| | 6 Other pharmacokinetics | Δ | × |
| 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 | Δ | × |
| | 5 Reproductive toxicity | ○ | × |
| | 6 Local irritation | Δ | × |
| | 7 Other toxicity | Δ | × |
| g. Clinical study | Clinical trial results | ○ | × |

# Approval Review of Generic Drugs

- Master file (MF) scheme for active ingredients
  - Mainly provides information on the quality and manufacturing method for active ingredients to be used in drug products (active ingredient = drug substance).
  - 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 only be used for contracted multiple users.

# Generic Drugs: Approval Review for Pharmaceutical Product Quoting from MF



# Approval Review of Generic Drugs

**Equivalency review**

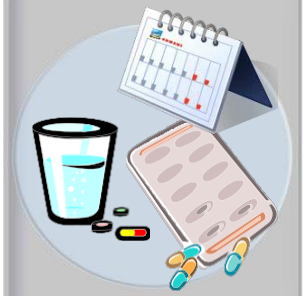
## What shall we check?

Active ingredient(s)

Quantities

Route of administration

Dosage form



Direction and Dose

Indications and Effects

Required data:

- Specifications and test methods
- Stability
- Bioequivalence studies, etc.

# Generic Drugs: 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)

# Generic Drugs: Procedure for Bioequivalence Evaluation

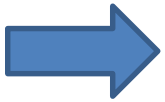
**Evaluation of dissolution behavior**

as reference product batch····

Selection either from another manufacturer's product batch or an originator product batch

**Bioequivalence study in humans**

valuation : The 90% confidence interval of the difference in the average values of logarithmic AUC, Cmax : log(0.8) ~ log(1.25)



**bioequivalence**

# Generic Drugs: Conformity Audit

- Reliability is also an important point:
  - Check the application data for conformity to the standards.
    - Check the consistency between application materials and raw data.
    - If necessary, conduct on-site GCP audits to check the compliance of sponsors and clinical trial facilities.
  - Check the manufacturing and quality control for conformity to the standards.
    - Conduct GMP inspections of the manufacturing sites.
    - In addition to the pre-approval GMP inspection, periodical GMP inspections are also required after approval.

# Recent Data on PMDA Reviews of Generic Drugs

| 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 |

↓

| | | Reviewing Period |
|---|---|---|
| New approval of generic drugs | → | 1 year |
| and | | |
| partial change of approval items | → | ca. 6 months or 1 year |

# Generic Drugs: Conclusion

- Generic drugs
  - In reviewing generic drugs:
    - Specifications and test methods
    - Accelerated tests
    - Bioequivalence
  - Generic drugs are substitutes for the originators
- Generic drugs are able to be approved without clinical trials to confirm their efficacy and safety
  - Generic drugs provide economical efficiency for patients' co-payment and total medical expenditure

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# Standards for Good Clinical Practice

- Clinical trials in Japan are governed by country specific standards for Good Clinical Practice (J-GCP). The standards are generally consistent with the international standard (ICH-GCP), but are more comprehensive and include additional requirements that often slow the development process. The two main differences between J-GCP and ICH-GCP are:
  - Under most circumstances, each site needs to have its own institutional review board (IRB)
  - Site heads (e.g., the chief executive officer of a hospital or clinic) must take responsibility for signing financial contracts and overseeing the conduct of the study. As the size of an institution increases, this approach quickly becomes untenable and can be demotivating both for sites and investigators.

# Comparison of ICH-GCP and J-GCP

| | ICH-GCP | J-GCP |
|---|---|---|
| Responsibilities of the site head (leader of institution) | Not mentioned | Many specific roles and responsibilities |
| Sign contracts | Investigator and site | Site head |
| Ensure site qualifications | Not mentioned (but implied to be the investigator's responsibility) | Numerous necessary conditions, including assignment of responsible person to handle the administrative process of clinical trial management |
| Ensure compliance with SOPs and confidentiality laws | Not mentioned | Site head |
| Provision of IMP | Investigator | Site head |
| Record keeping | Investigator | Site head (can assign duties to a responsible person) |
| Establishment of IRB | Not mentioned | Under most circumstances, each site must have its own IRB |
| Obtain IRB approval and follow guidance | Investigator | Site head |

ICH-GCP = International Conference on Harmonization on Good Clinical Practice; IMP = investigational medical product; IRB = institutional review board; J-GCP = Japanese Good Clinical Practice; SOP = standard operating procedures

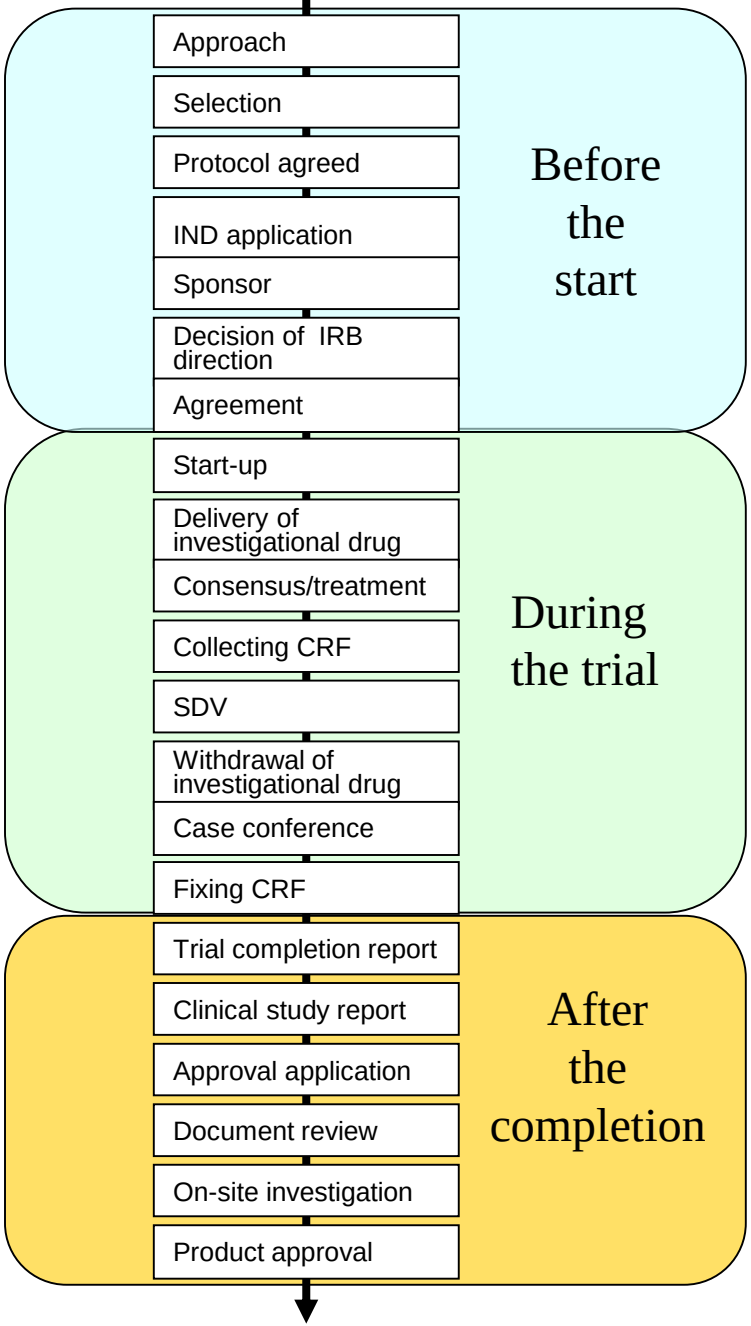
# Key Clinical Trial Issues

- Limited recognition of the value of clinical research
- Limited availability of investigators
- Limited incentives for investigators
- Limited incentives for patients
- Different ways of working
- Language barrier
- Higher costs

# Planning Ahead

- Although clinical trial infrastructure has improved and review times have shortened significantly, advanced planning, reforms from the Japanese government and a contract research organization (CRO) with experience in Asia, are necessary to reducing the drug lag.
- Keeping the following things in mind will help in making the drug available to the Japanese pharmaceutical market 18 to 24 months earlier than was possible 10 years ago (approximately 12 months after approval in the U.S.):
  - ✓ The need for data on the Japanese population.
  - ✓ Initiate Phase I studies in Japan when the drug enters Phase II studies elsewhere in the world.
  - ✓ Design the Phase III program to include Japanese and other East Asian populations.
  - ✓ Meet with PMDA twice to discuss regulatory strategies for the Japanese market.
  - ✓ Submit a new drug application (NDA) to PMDA approximately nine months after documents are filed in the U.S. and EU.

# Flow of Clinical Trial



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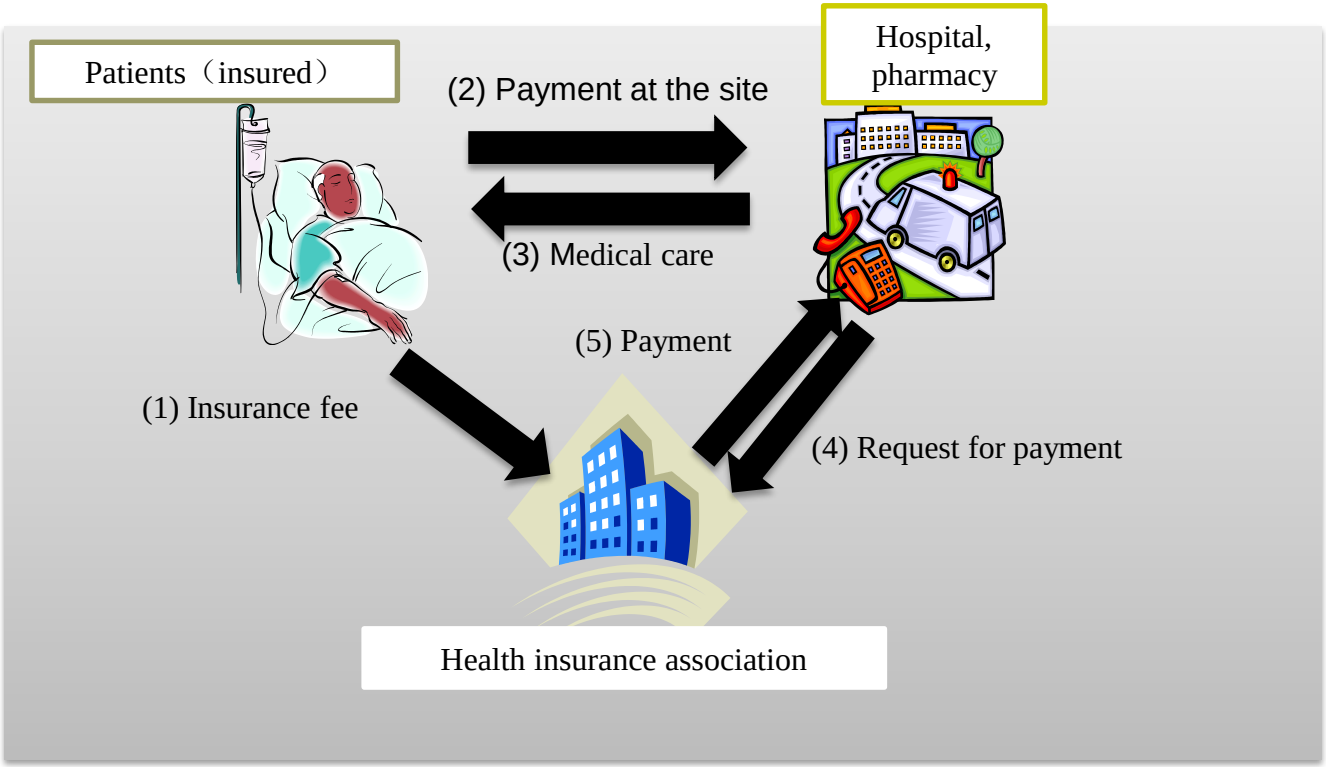
# Insurance System in Japan

The Japanese have either corporate health insurance or national health insurance. They can receive health insurance through the public health care insurance system by paying an insurance fee to the health insurance association. A portion of the medical fee is paid by the patient and the rest is covered by the health insurance association.

※ Insurance covers the expenses of medical care such as the initial visit, follow-up visits, base cost of hospitalization, laboratory tests, injections, drugs, treatments, operations, etc.



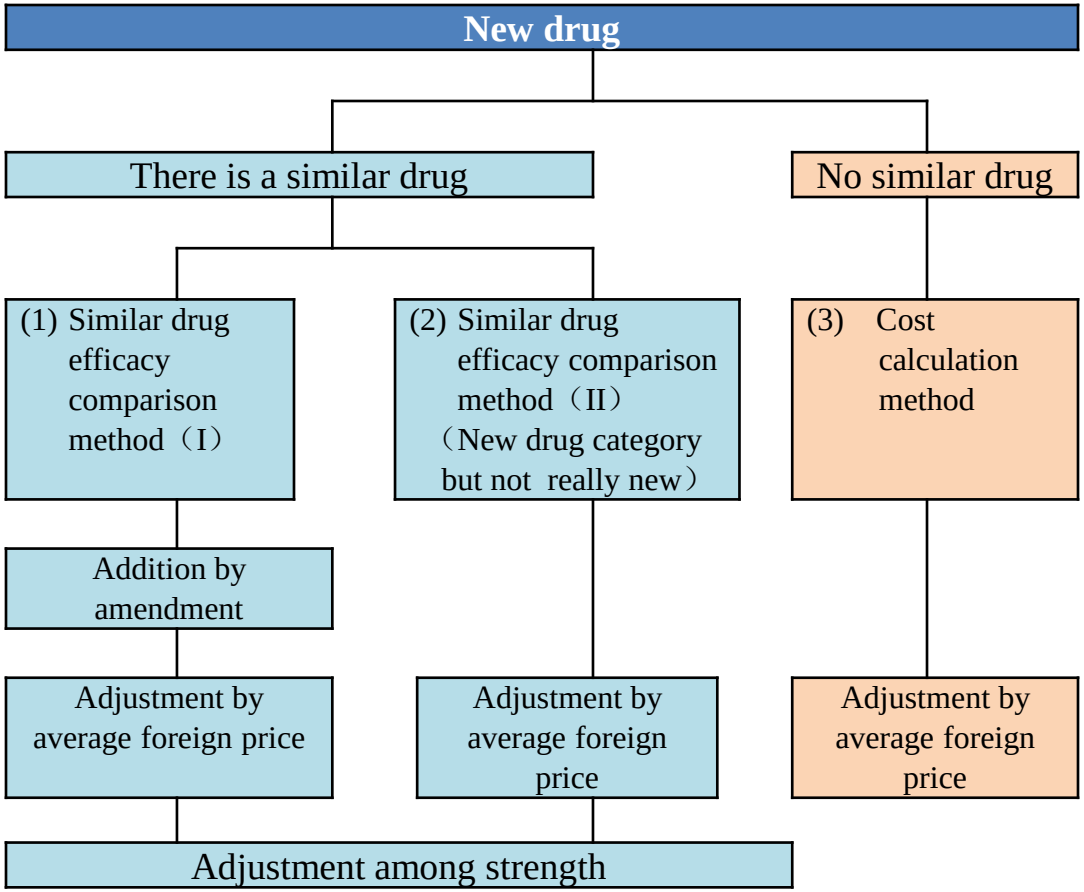

The medical fee is set by the Ministry of Health Labor and Welfare (MHLW) which hears the opinions of the Central Social Insurance Medical Council.
The MHLW also determines the prices of drugs used for treatment.
The Pharmaceutical company cannot decide drug prices on its own.

The public price determined for each drug is called the "National health insurance (NHI) price"

# NHI Price Listing

- After an approval for a new drug is received, the applicant needs a NHI Drug Price Standard. The applicant will submit a document called, “Hope statement for NHI price” to the Economic Affairs Division of the Health Policy Bureau, MHLW. The basis or rationale for the calculation of the NHI price should be attached to the statement.
- A draft for calculation of the NHI price is prepared.
- If the MHLW agrees with the price calculation, the drug is listed through the Central Social Insurance Medical Council.
- If the applicant is unsatisfied with the draft, the applicant can submit an unsatisfactory statement and the draft is reviewed again.

# Calculation of NHI Price for a New Drug




Similar drug

In principle, drug that was added to the NHI Price List within the past 10 years and has no generic versions listed.

The prices of Medicines Company's products are calculated based on the current NHI prices of similar drugs. NHI prices are revised every 2 years (mainly reduction). Range of revision is affected by current market prices, replacement rate by generic drugs and profitability. Currently, yearly revisions are discussed. When The Medicines Company's products are introduced into the Japanese market, it is possible that their NHI price will decrease. On the other hand, the TPP negotiation may lead higher NHI prices for Medicine' Company's products.

# Calculation of NHI Price

- Similar drug comparison method

In the case that there is a similar drug, NHI price of a new drug is matched with the price of the existing drug. If the new drug is recognized as being more useful, a higher price is given (corrective addition).

  - Drug to be compared is a new drug listed in the NHI price standard within 10 years and no generic drugs are listed.

Example of 1 day NHI price matching

Similar drug: 50 yen/ tablet, administered 3 times  a day
Subject new drug:  X yen/tablet, administered 2 times a day
50 x 3 = X x 2 (1 day)
X = 75 yen

# Corrective Addition

| | |
|---|---|
| Addition for breakthrough nature (70 – 120%) | Marketability addition (I) (10 – 20%) |
| Addition for usefulness (I) (35 – 60%) | Marketability addition (II) (5%) |
| Addition for usefulness (II) (5 – 30%) | Addition for pediatric use (5 – 20%) |

| | |
|---|---|
| Addition for breakthrough nature | New mechanism, high efficacy and safety, improvement of treatment of diseases, etc. |
| Addition for usefulness | High efficacy and safety, improvement of treatment of diseases, etc. |
| Addition for usefulness | Orphan drug, etc. |
| Addition for pediatric use | Dosage and administration for children are included expressly., etc. |

# Comparable Drug Method for Price Determination

This is a calculation method applied to drugs that has little novelty. The lowest price is set by comparing NHI prices of similar drugs listed in the  past few years. This method is applied to those that meet the following 3 conditions:

- Exempted from the corrective addition
- 3 or more drugs of similar pharmacological mechanism
- 3 or more years since the oldest similar drug was listed to the NHI

# Cost Accounting System

In the case that there is no similar drug, raw material cost, manufacturing cost, etc. are accumulated.

(1) Manufacturing (import) cost (Industry average: 199 yen)
(2) Selling cost, research expense, etc. (= ((1)+(2)+(3)) x 0.377 (Industry average: 174 yen)
(3) Business profit (=((1)+(2)+(3)) x 0.192 (Industry average 89 yen)
(4) Distribution cost (=((1)+(2)+(3)+(4)) x 0.076 (Industry average: 38 yen)
(5) Consumption tax (8%) (40 yen)

Calculated NHI price = (1)+(2)+(3)+(4)+(5) (Industry average 540 yen)

# Adjustment by Foreign Prices

In the case there is a big discrepancy from foreign prices, an adjusted foreign price is applied.

Foreign price average： Either adjustment described below is performed against average of prices in US, UK, Germany and France,

(1) When the calculated price is 1.5 times or more than the foreign price average
→Reduction adjustment

( 1/3 x calculated price/foreign price average +1) x foreign price average

(2) When the calculated price is below 0.75 times of the foreign average price
→Raising adjustment

(1/3 x calculated price/foreign price average + 1/2) x foreign price average

* Upper limit is 2 times of calculated price

Similar drug comparison method has no raising adjustment.

# Adjustment Between Strength

In cases of similar drug comparison methods (I) and (II), NHI price of non-general use strength is calculated from the calculated price of general use strength by using the ratio between strengths.

Calculated price of general use strength (5mg) of Tablet A: 174.60 yen

- NHI price of similar drug (Tablet B):
  10mg tablet: 158.30 yen (general use strength)
  5mg tablet: 82.50 yen (non-general use strength)
- Ratio between strength of similar drug (Tablet B):
  log (158.30/82.50) / log (10/5) = 0.9402
- Calculated price of non-general use strength (2.5 mg and 10mg) of Tablet A:
  2.5mg tablet: 174.60 yen x $(2.5/5)^{0.9402}$=91.00 yen
  10mg tablet: 174.60 yen x $(10/5)^{0.9402}$=335.00 yen

# Reimbursement Price

- The reimbursement prices are determined by calculating weighted means of sales prices of all existing package sizes by brand and adding a certain percentage of the current reimbursement prices (within a specified price range) to the weighted mean prices obtained. However, the new reimbursement prices must never be higher than the current prices.

# Drug Reimbursement

- When the brand drug is already entered in the list and a generic drug identical to the brand drug is entered for the first time, the price of the generic drug is obtained by multiplying the brand drug price by a factor of 0.7. The factor is 0.6 for oral preparations, in the case that more than 10 brands are already on the market.
- When both the brand and generic drugs are already entered, the price of the newly entered generic drug is the same as the lowest of the generic prices.

# Drug Reimbursement

- When there are many brands with the same standard, i.e., when the number of products entered and to be entered exceeds 20, the price of the generic drug to be entered is obtained by multiplying the lowest among all products entered by a factor of 0.9.
- A special formula was introduced for biosimilar products. A premium (maximally 10/100 of the standard) is added to the standard price depending on qualitative and quantitative data obtained from clinical trials.

# Determination of Reimbursement Prices for New Drugs

- It was recommended that the reimbursement price of new drugs be determined by comparing the new drugs to existing drugs from the same category while marking up using premiums for innovation, usefulness, and market size. The requirements for each premium should be clearly defined.

# Reimbursement Price Revisions

- Reimbursement price revisions cover the drugs sold in the month of September of a previous year. A survey of all products in the NHI Drug Price List is conducted on about 4,000 sellers, all first-class wholesalers, and about 3,400 purchasers consisting of hospitals, clinics, and pharmacies selected at random using specified sampling fractions in each case.

# Calculation of New Reimbursement Price

The new reimbursement price is calculated by adding a reasonable adjustment zone (R) to the weighted average marketing price obtained from surveys of products in the NHI Drug Price List (must consider consumption tax).

Calculation formula:

New drug price =

| | | | | | | |
|---|---|---|---|---|---|---|
| weighted average value of market price in survey | x | 1+ consumption tax rate | + | current reimbursement price | x | R/100 |

*However, the new price shall not exceed the current reimbursement price.

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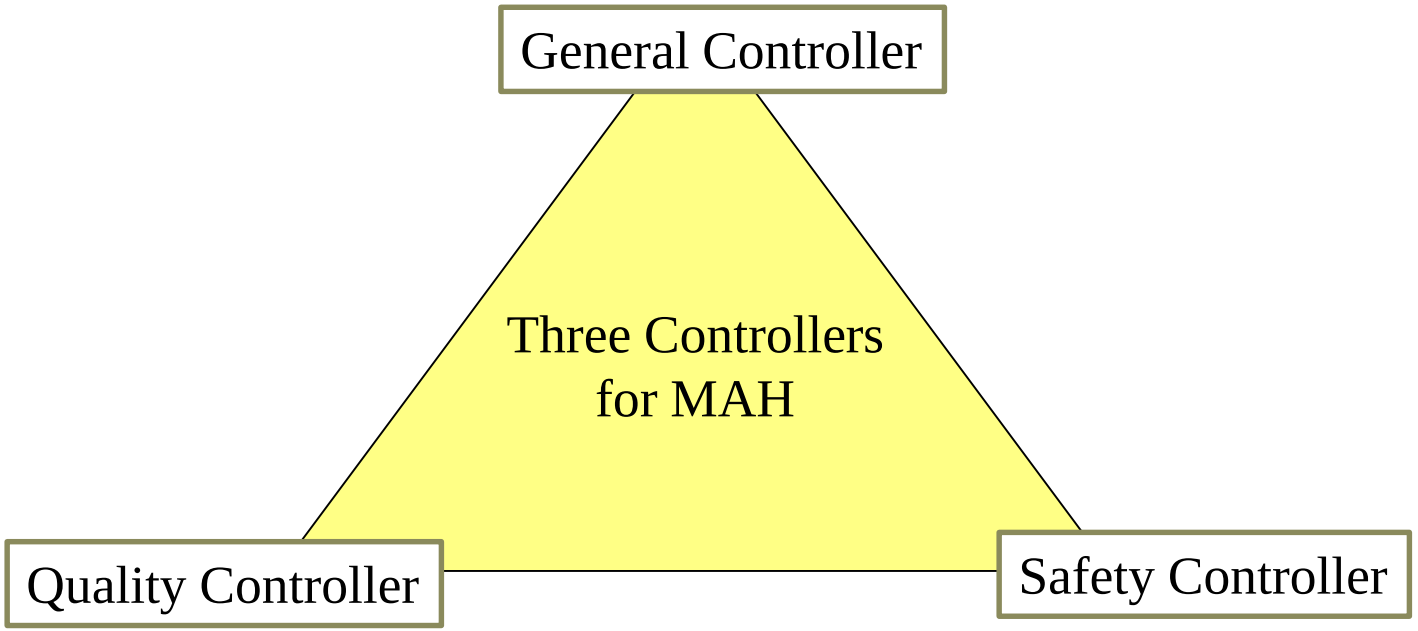
# Marketing Authorization Holder (MAH)

Relationship of Three Controls Within MAH



# Marketing Authorization Holder (MAH)

Foreign restrictive approval system

It is a system that a foreign company who does not have its own corporation in Japan can utilize when marketing a drug in Japan.

**Assign a Designated Marketing Authorization Holder (DMAH)**

- It is necessary for a foreign company to assign a Japanese MAH (Designated Marketing Authorization Holder) who has the appropriate licenses.
- Approval is granted under the condition that a designated MAH conducts safety management on behalf of the foreign company.
- In addition to safety management, a designated MAH should also perform various procedures such as submission of the drug application, post-market surveillance (PMS), etc.

# License for Marketing Authorization Holder (MAH)

License application for the Marketing Authorization Holder is submitted to the prefectural government in which the main office of the applicant in Japan is located

| Type of license | Product range |
|---|---|
| Type 1 drug MAH ※ | Prescription drugs |
| Type 2 drug MAH | Drugs other than prescription drug |

※ Registration fee: 146,200 yen,
Standard processing period: 35 days
(In case of Tokyo)

- 1 MAH license per corporation is necessary
- MAH licenses are valid for 5 years.

## Requirements for MAH license

- Conformity with GQP (Good Quality Practice)
- Conformity with GVP (Good Vigilance Practice)
- Presence of a marketing supervisor to take responsibility for quality assurance and post marketing safety control

# Foreign Manufacturer Accreditation (FMA)

- An individual company who intends to manufacture drug products, quasi-drugs, cosmetics or medical devices overseas and import them into Japan is referred to as a foreign manufacturer and must acquire a Foreign Manufacturer Accreditation (FMA) from the Ministry of Health, Labour and Welfare to provide such products to the market.

# Foreign Manufacturer Accreditation (FMA)

- Type of manufacturer and requirements for FMA accreditation are the same as those for a manufacturing license.
- There are 2 ways to determine FMA – document review and on-site investigation. Most reviews are done by document review and on-site investigation is performed as necessary.
- FMA application is applied to the Pharmaceuticals and Medical Devices Agency (PMDA).

Government fees to obtain a FMA license is 149,700 yen (document review) and standard processing period is about 5 months.

# Drug Master File (DMF) Registration

Drug master file registration system

A DMF is a system to register confidential data on quality, manufacturing methods, etc. of a drug substance used for a drug. Domestic and foreign drug manufacturers register their DMFs to the PMDA on a voluntary basis.

Advantages of DMF registration

- The manufacturer of the drug substance can be reviewed by the competent Japanese authority without sharing information containing details on its manufacturing methods, production management and quality control with the manufacturers of the drug product.
- The examiner at the competent authority is able to manage drugs using the same drug substance by its MF registration number.

**In-country care taker of drug substance**

It is necessary to assign an in-country care taker in Japan when a foreign manufacturer is to register a DMF.

Tasks of in-country care taker

- Registration application（New registration, change registration, minor change notification)
- Interaction with the PMDA (Submission, answering to inquiries, etc.）
- Other tasks that a foreign manufacturer should do

# Good Manufacturing Practice (GMP)

- GMP specifies that compliance with the Regulations for Buildings and Equipment of Pharmacies, etc. that specify standards for structures and equipment in manufacturing plants (for each manufacturing category without relation to the products manufactured) is a requirement for a manufacturing business license.

- Compliance with the GMP ordinance that specifies standards for structures and equipment required for the product concerned as well as standards for manufacturing and quality control for each manufactured product is a condition for approval of the drug concerned.

# GMP Conformity Investigation

**[Pharmaceutical Affairs Law]**

**Article 14-6** A person intending to obtain the approval specified in Paragraph 1 or a person obtaining the approval specified in the same paragraph, shall be subjected to an examination in writing or an on-site examination performed by the Minister as to whether a method of manufacturing control or quality control of it in the manufacturing establishment complies with the standards specified by Ministerial Ordinance MHLW (Abstract)

It is the investigation to determine whether manufacturing control and quality control are complied with the Ministerial Ordinance. GMP conformity of the manufacturing site is required for product approval.

# GMP Conformity Investigation

**Range of drugs subject to GMP Conformity Investigation**
**Drugs and active pharmaceutical ingredients other than those A – G below**（API for non-prescription drugs are exempted)

A. Drugs exclusively used for the extermination or prevention of rats, flies, mosquitoes, fleas or other similar species, which are not directly applied to the human body
B. Drugs exclusively used for the sterilization or disinfection which are not directly applied to the human body
C. Drugs as active pharmaceutical ingredients which are exclusively used for manufacture of the drugs indicated in 1) and 2) above
D. Drugs manufactured in the manufacturing sitet which undergo only powering and cutting operations
E. Drugs manufactured in pharmacies
F. Gases used for medical treatment which are designated by the Minister
G. Drugs listed in the Japanese Pharmacopoeia other than those indicated in 1) – 6) above, which are designated by the Minister as having a mild effect to the human body

# GMP Conformity Investigation

**Facilities subject to GMP conformity investigation**

- All the manufacturing sites described in the approval application (including external testing and inspection agency)
- For ethical drugs, in addition to the manufacturing sites of drug preparations, active pharmaceutical ingredients, drug substance intermediates, facilities for packaging, labeling and storage and external testing and inspection agencies are the subjects to GMP conformity investigation.

GMP conformity investigation on foreign manufacturers is conducted by PMDA upon application by the marketing authorization holder who submits approval application or obtains approval. PMDA shall request documents and information from the foreign manufacturer through the marketing authorization.

# Manufacturer License

The license application is submitted to a prefectural government.
For certain drugs*1 the government office submits the paper to a local department of human services which has the licensing authority.

Type of license for manufacturer

| | | |
|---|---|---|
| I | Biological drugs | License for manufacturing process for biological drugs, recombinant drugs genetic recombinant drugs, either in whole or in part |
| II | Radioactive drugs | License for manufacturing process for radioactive drugs (excluding I above), either in whole or in part |
| III | Sterile drugs | License for manufacturing process for sterile drugs (excluding I and II above), either in whole or in part |
| IV | General drugs *2 | License for manufacturing process for drugs other than I, II, and III above, either in whole or in part |
| V | Packaging *3 | License for manufacturing process of only packaging, labeling and storage for drugs of III and IV above |

*1 Biological drugs, radioactive drugs, specific biological drugs, etc.
*2 Application fee: 83,400 yen, standard processing period: 35 days
*3 Application fee: 46,500 yen, standard processing period: 35 days (In case of Tokyo)

# Manufacturer License

Requirements for manufacturer license

- The building and facility of the manufacturer conforms with the standard defined by Regulations for Buildings and Facilities of Pharmacies, etc.
- Placement of manufacturing controller

- Manufacturer license is required for each manufacturing site
- License is valid for 5 years. Renewal application is required in every 5 years.
- Application for changing type of license or additional license is required when other type of license than the current license is necessary.

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# Recommendations: Factors for Success with Clinical Development in Japan

- Consultation Sessions on Clinical Trials with the PMDA

PMDA will evaluate documents submitted and provide advice regarding the adequacy of the study design and protocol. The consultation requires a fee but it is highly recommended to utilize it before advancing to a major step.

- Selection of Institution

By selecting an institution that has many cases of the subject disease and is accustomed to conducting clinical trials, quality data can be collected more efficiently. There will be less deviation from the protocol and will shorten the study period. The first study in Japan should be conducted at a University hospital or another institution of the same level.

- Key Opinion Leader (KOL)

It is essential to retain KOL for an appropriate advice as an expert of the area and for building consensus with an expert of the PMDA side at an occasion of PMDA consultation, etc.

# Recommendations: Registration File

- If tests are performed according to the ICH guidelines and the results are summarized in CTD, English files on Modules 3 – 5 can be submitted as a registration file (Table of Contents should be prepared in Japanese).
- Module 1 and Module 2 requires Japanese translation (English is acceptable for figures and tables).
- If ethnic differences between Americans and Japanese are shown to be small by bridging the study for pharmacodynamics, etc., foreign data can be used which would allow the scale of clinical study in Japan to be reduced significantly.

# Recommendations: NHI Price

There are 3 methods for the calculation of NHI prices, namely 1) Price determination by comparable drug (I), 2) Price determination by comparable drug (II) and 3) Cost accounting system. To assume more accurate prices, information on foreign prices and cost of import are needed.

- Although there are no similar drugs in Japan for now, at the time of approval of the products, there is a possibility that similar drugs are listed in the NHI price standard. In such cases, the price of the product under development would be equal to the similar drugs.
- Due to the suppression of medical expenses of public health insurance, the NHI price standard is reviewed every year and so the NHI price at the time of approval will be reduced for a long term.
- Moreover, in the case that the scope of the public health insurance is narrowed and liberalization of NHI prices is introduced after TPP, there is a possibility that higher NHI price will be granted.
- It is necessary to pay attention to changes in both the NHI price system and the status of development of similar drugs.

# Thank you for your consideration!

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