Japanese Pharmacopoeia

- History and Prospect -

Takao Yamori, Ph.D.
Executive Director,
Pharmaceuticals and Medical Devices Agency
1. Introduction of MHLW and PMDA

2. History and legal status of the Japanese Pharmacopoeia

3. Actions for internationalization and dissemination of the Japanese Pharmacopoeia
MHLW and PMDA

Ministry of Health, Labour and Welfare (Pharmaceutical Safety and Environmental Health Bureau)

- Final decision on marketing approval, etc.
- Issue of guidelines
- Management of the Pharmaceutical Affairs and Food Sanitation Council
- Supervision of PMDA, etc.

Pharmaceuticals and Medical Devices Agency

- Reviews of pharmaceuticals and medical devices, Safety measures
- Judgment about and provision of relief compensation for sufferers from adverse drug reaction and infections
- GCP, GMP inspections
- Clinical trial consultation, etc.

Collaboration
MHLW and PMDA – the Japanese Pharmacopoeia

Japanese Pharmacopoeia (JP)

Notification

Outsource

Report

Consultation

Advice

Development of JP drafts

Division of Pharmacopoeia and Standards for Drugs, Office of Review Management

Request

Result

Consultation

Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

MHLW

JP Expert Committees
PMDA and the Japanese Pharmacopoeia

Development of pharmacopoeial drafts and review of pharmaceuticals at PMDA as an entity
2. History and Legal Status of the Japanese Pharmacopoeia
The Japanese Pharmacopoeia is an official standard that the MHLW stipulates for proper properties and quality of pharmaceuticals by seeking opinions from the PAFSC under Paragraph 1, Article 41 of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Act No. 145 of 1960).
Legal Status of the Japanese Pharmacopoeia (2)

Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices

Article 41

In order to ensure the proper properties and quality of pharmaceuticals, the MHLW will set forth and make public notice of the JP after gaining opinions from the PAFSC. The MHLW must consult with the PAFSC on any revisions to be made through discussions on all aspects of the JP made by the PAFSC at least every ten years.
The role of the pharmacopoeia is to note the principles regulating the quality level of pharmaceuticals supplied in our country...

“Document on the role assigned to the Japanese Pharmacopoeia” (October 6, 1880)
At that time, advanced countries already had their own pharmacopoeia for drugs used and had a certain criteria established for healthcare provided. As our country did not have regulations to prepare such manuals, healthcare was in disarray as the amount of the main ingredient included in drugs with the same name differed depending on which country it was being imported from and, in some cases, fraudulent or defective products were being circulated.

(Source: In commemoration of 100 years since the Japanese Pharmacopoeia was first published (October 1986)“)
Toward Establishment of the first edition of the Japanese Pharmacopoeia

- Sensai Nagayo, the Head of Health & Medical Bureau of the Ministry of Internal Affairs, commissioned Dr. A. J. C. Geerts, a Dutchman who instructed the pharmaceutical organization, to prepare a draft for pharmacopoeia.

- The draft was completed in 1877 referring to European and American pharmacopoeias, mainly the Dutch Pharmacopoeia.

Draft for the Japanese Pharmacopoeia (1877): National Institute of Health Sciences Library
Draft for the Japanese Pharmacopoeia (1877): National Institute of Health Sciences Library
Establishment of JP 1st Edition

The first edition of the JP was compiled and published in 1886 in cooperation with foreign teachers such as J.F. Eijkmsn, Geerts, and A. Langgard. The Latin version was published in 1888 and the overview was published in 1890.

Published as a separate volume to the Ordinance of the Home Ministry, No. 10 (Addendum for the Official Gazette No. 894) in 1886
- 2 columns, 78 pages of text, 8 pages of index
- 468 monographs, 10 general rules for preparations
- Publication of Latin version in 1888

The Health Department of the Home Ministry published “Overview of the Japanese Pharmacopoeia” in 1890
JP Revisions and Changes in Pharmaceutical Regulation

- Start of revisions by Japanese only with the 2\textsuperscript{nd} edition of the Japanese Pharmacopoeia
- Establishment of Dainippon Pharma. (Start of manufacturing of domestic pharmaceuticals)

- Publication of the Institutes of Health Sciences

- Establishment of private pharmacology school (Predecessor of Tokyo University of Pharmacy and Life Sciences)

- Publication of the Pharmaceutical Marketing and Handling Regulations

- Publication of JP 3\textsuperscript{rd} Edition
- Abolition of Latin version
- Release of English version
1948 - Promulgation of the Pharmaceutical Affairs Law (older version)
  - Publication of the “National Formulary” (predecessor of the latter Japanese Pharmacopoeia Section 2)
1961 - Implementation of the Pharmaceutical Affairs Law (newer version)
  - Publication of the Seventh Edition – consisting two main sections (prepared with the aim of making suitable to our country’s conditions given the rapid advancement of new pharmaceuticals and development of test methods, etc.)
  - Abolition of the National Formulary
History of JP revisions

- The Japanese Pharmacopoeia is revised at least every 10 years according to the Article 41 of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices.

- In recent years, JP is revised every 5 years and two supplements are published between each revision.

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Schedule of Publication toward JP 18th Edition

17th Edition of the Japanese Pharmacopoeia
Published in March 7, 2016

Supplement I to JP17
Published in December 1, 2017

Supplement II to JP17
Published in June 28, 2019

- Basic Principles for Preparation of JP (Five pillars)
  Published in October 2016

- Guideline for Preparation of JP18 Draft
  Published in January 2017

18th Edition of the Japanese Pharmacopoeia
To be published in 2021
Content of the Japanese Pharmacopoeia (1)

2. General Rules for Crude Drugs - specification of general rules for crude drugs: 10 paragraphs
   General Rules for Preparations, general notices for preparations, general notices for packaging of preparations, monographs for preparation, monographs for preparations related to crude drugs
3. General Tests - 8 categories (General tests: 85)
4. Official Monographs - 2008 articles
5. Reference Spectra - Ultraviolet-visible: 554 articles, Infrared: 638 articles
6. General Information
7. Appendix
   (As of September, 2019)
The General Information is the relevant references necessary for quality assurance of pharmaceuticals and the referential test methods on pharmaceuticals listed in JP. It does not serve as the criteria for pharmaceuticals listed in JP.

(Notification of Pharmaceutical Safety and Environmental Health Bureau, MHLW)
<table>
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* General methods only
# Outline of Supplement II to JP17

## New General Tests

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<td>2.26 Raman Spectrophotometry</td>
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<td>2.66 <strong>Elemental Impurities — Procedures</strong></td>
<td>ICH-Q3D related</td>
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<td>6.16 Rheological Measurements for Semi-solid Preparations</td>
<td>Spreadability test / Penetrometry</td>
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<td>6.17 Insoluble Particulate Matter Test for Therapeutic Protein Injections</td>
<td>Light obscuration particle count test for insoluble particulate matters in injections</td>
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## New General Information

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<td><strong>Control of Elemental Impurities in Drug Products</strong></td>
<td>ICH-Q3D related</td>
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<td>Host Cell Protein Analysis</td>
<td>Sandwich immunoassay using antibodies</td>
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<td>Concept on Impurities in Chemically Synthesized Drug Substances and Drug Products</td>
<td>ICH-Q3A/B related</td>
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<td>Glossary for Quality by Design (QbD), Quality Risk Management (QRM) and Pharmaceutical Quality System (PQS)</td>
<td>ICH Q quartet related</td>
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### Incorporation of ICH (Quality)

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<td>Control of impurities</td>
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<td>Q3C: Residual solvents</td>
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<td>Q9: Quality risk management</td>
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* 1: Incorporated into Supplement I to JP 17th Edition
* 2: Partially incorporated into Supplement I to JP 17th Edition
* 3: Incorporated into Supplement II to JP 17th Edition
Basic Principles for Preparation of JP 18 - Five pillars

1. Including all drugs which are important from the viewpoint of health care and medical treatment;
2. Making qualitative improvement by introducing the latest science and technology;
3. Promoting internationalization corresponding to globalization of pharmaceuticals;
4. Making prompt partial revision as necessary and facilitating smooth administrative operation; and
5. Ensuring transparency regarding the revision, and disseminating the JP to the public.

3. Actions for Internationalization and Dissemination of the Japanese Pharmacopoeia
Basic Principles for Preparation of JP 18

Actions for Internationalization (1)

1. Roles and characteristics of the Japanese Pharmacopoeia – official, public, open pharmaceutical quality standards

In addition, the JP shall be a list of pharmaceuticals which are important from the viewpoint of health care and medical treatment in this country and is expected to play an appropriate role of and to contribute maintaining and securing advancedness as well as international consistency in the international community for quality assurance of pharmaceuticals beyond the country level.
2. Basic principles for preparation of the Japanese Pharmacopoeia – Five pillars

1) Including all drugs which are important from the viewpoint of health care and medical treatment;

2) Making qualitative improvement by introducing the latest science and technology;

3) Promoting internationalization corresponding to globalization of pharmaceuticals;

4) Making prompt partial revision as necessary and facilitating smooth administrative operation; and

5) Ensuring transparency regarding the revision, and disseminating the JP to the public.

Vision II.
Maximization of common benefits with other countries and regions

PMDA will improve communication and facilitate regulatory harmonization and cooperation with each countries in the world in order to provide more effective and safer pharmaceuticals, medical devices and regenerative medical products for patients in the world more quickly.
Strategy 2.

Internationalization of regulatory affairs and promotion of international collaboration

1. Promotion of internationalization of the Japanese Pharmacopoeia

① Further promote pharmacopoeial harmonization among the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia through Pharmacopoeial Discussion Group (PDG)

② Positively incorporate the concept of quality assurance based on the latest science and technology, encourage use of JP as a reference pharmacopoeia in other countries and regions and contribute to quality improvement of pharmaceuticals that are distributed in the world

Based on the “International Pharmaceutical Regulatory Harmonization Strategy – Regulatory Science Initiative” of MHLW
International Meeting of World Pharmacopoeias

[Purpose]
Exchange of information and discussion on international collaboration and harmonization among pharmacopoeias around the world

[Main Activities]
● Development of Good Pharmacopoeial Practices: GPhP
  Aiming harmonization and acceptance of pharmacopoeial standards with deep understanding and global cooperation from stakeholders about development of pharmacopeia
● The 7th IMWP was held in Tokyo in September, 2016, participated by about 50 representatives from WHO and 14 regions.
● The draft of white paper about collaboration among pharmacopoeias and significance of pharmacopoeia. (The 10th IMWP was held in Geneva in March, 2019.)
Harmonization in the Pharmacopoeial Discussion Group

- **Purpose of activities**
  - Standardize the test procedures and acceptance criteria that differ among pharmacopoeias
    - → Reduce manufacturers’ burden of performing analytical procedures
  - Standardize excipient monographs commonly used in manufacturing drugs
  - Maintain an optimal level of science

- **Items to harmonize**
  - General Chapters (Physico-chemical, Drug formulation, Physical Methods, Microbial, Biological)
  - Excipient Monographs
JP’s expectations for PDG

• Promotion of Internationalization of JP is one of topics of the PMDA International Strategic Plan 2015.

• Standardization of test methods and monographs in response to comments from stakeholders in Europe and the U. S. leads to Internationalization of JP.

• PDG activity, which can reflect opinions from representative of Europe and the U.S., is very important for internationalization of JP.
Transparency in drafting JP (1)

Basic principles for preparation of the JP – Five pillars

1) Including all drugs which are important from the viewpoint of health care and medical treatment;
2) Making qualitative improvement by introducing the latest science and technology;
3) Promoting internationalization corresponding to globalization of pharmaceuticals;
4) Making prompt partial revision as necessary and facilitating smooth administrative operation; and
5) Ensuring transparency regarding the revision, and disseminating the JP to the public.

Publication of the Basic principles for preparation of the JP, Experts from various background, Publication of English version of JP and Public consultation in English, etc.
Good Pharmacopoeia Practices (GPhP)

6.1.2 Open and transparent process
Pharmacopoeial standards are based on current scientific knowledge and reflect the quality of pharmaceutical substances and FPPs available. Pharmacopoeias ensure openness and transparency throughout the development and revision of monographs and other texts, which includes...

(WHO_TRS_996_Annex1)
Collaboration with various related parties

JP Expert Committees

Request for review

Result

Established in PMDA and mainly composed of outside experts

JP Expert Committees

Public Consultation

Coordinate views

Citizen • interested parties

Universities

Research Institute

Industry

Participate as experts

Experts of PMDA

Experts for review of new drugs

Professor in University/Institute

Experts from Industry

Example of Constitution of JP Expert Committee

Appointed based on recommendation from Industry group

October 3, 2019 The PDG 30th Anniversary Symposium
Organization of JP Expert Committees

JP Expert Committees
(As of September, 2019)

Number of Experts: about 260

Standing Committee

Sub-Standing Com.
Sub-Com. On Manufacturing Process-related Matters
Chromatography WG

Com. on Chemicals (1) and (2)
Com. on Antibiotics
Com. on Biologicals
Com. on Crude Drugs (B)
Com. on Excipients
Com. on Physico-Chemical Methods
Com. on Drug Formulation
Com. on Physical Methods
Com. on Biological Methods
Com. on Nomenclature for Pharmaceuticals
Com. on International Harmonization
Com. on reference Standards

Com. on Crude Drugs (A)
Sterile Water for Injection in Containers WG
Dissolution WG
Inhalation WG
Packaging Integrity for Aseptic Products WG
Nasal Preparation WG
qNMR WG

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Publication of English version of JP

After publication of Japanese version of JP, English version would be published about half a year later.

Free download from PMDA website

http://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0019.html
Public Consultation in English

- Public consultation for JP is published on PMDA website.
- Since 2015, Public consultation in English has been started as a trial at the same time of it in Japanese.

JP Drafts (September 2, 2019)

**New General Test**
- **2.05 Size Exclusion Chromatography** (001-1909-1eng.pdf)

**JP drafts for public comments, September 2 - 30, 2019**

**Revised General Test**
- **2.66 Elemental Impurities** (002-1909-1eng.pdf)

**Briefing on Proposed Revision**
- General Test "2.66 Elemental Impurities Procedures"

**New monographs**
- **Bicalutamide** (003-1909-1eng.pdf)
- **Celecoxib** (004-1909-1eng.pdf)
- **Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution** (005-1909-1eng.pdf)
Information on JP

Japanese Pharmacopoeia

Basic principles of preparation of the JP, Scheme of establishing JP, Schedule of publication of JP

PDF of the whole JP texts

Pharmacopoeial Harmonization

Related information on revision
Column Information

Public consultation

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Thank you for your attention!!