Introduction of the Japanese Pharmacopoeia

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Today’s topics

- Legal Status and History of the Japanese Pharmacopoeia (JP)
- Content of JP
- Drafting and Publication of JP
- Key points of the JP, 18th Edition
- JP’s activity for transparency

The Japanese Pharmacopoeia (JP)

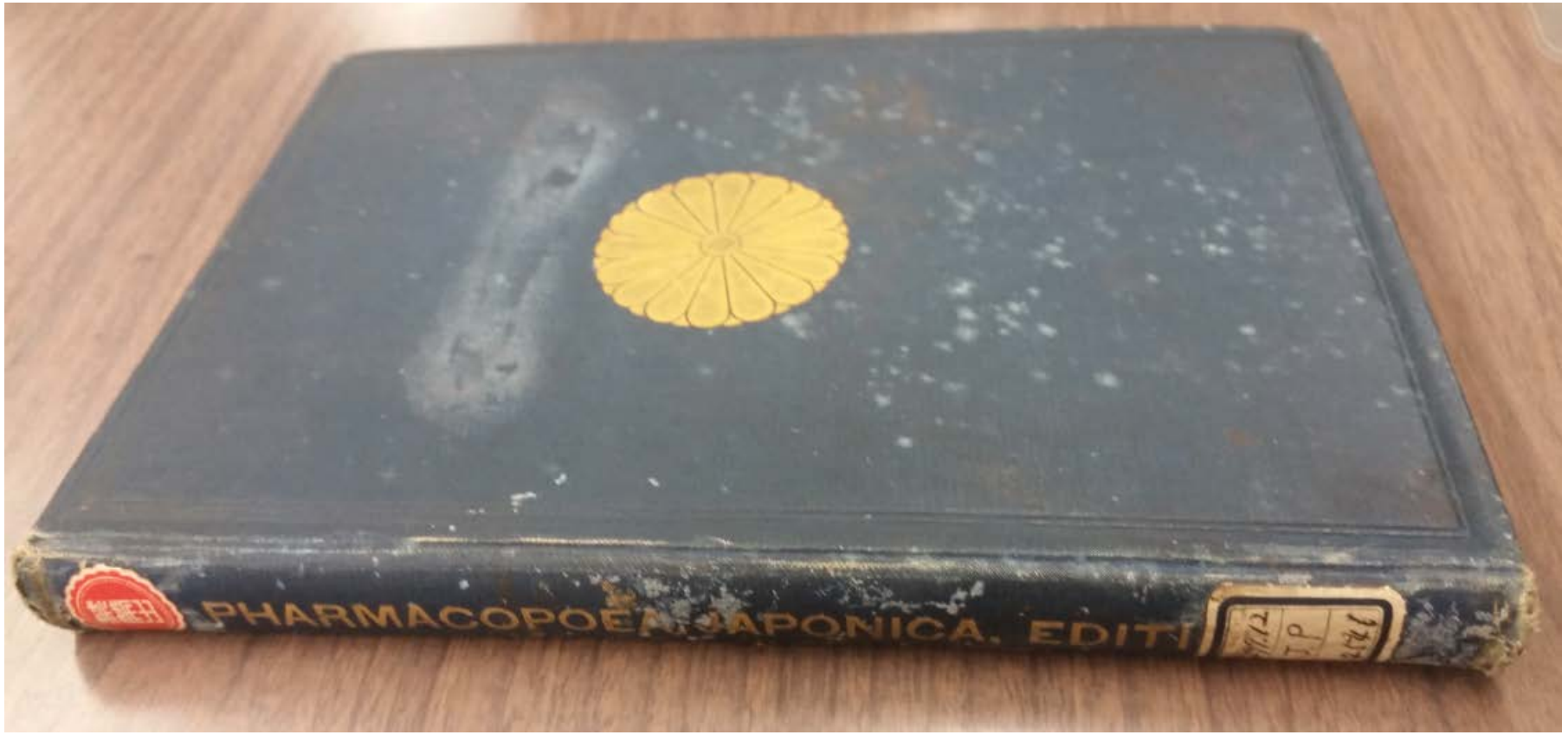
- Notified by Minister of Health, Labour and Welfare, based on Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices
- Publication:
  - First Edition: published in 1886
  - Current Edition: JP17 Supplement 2

- Full-fledged revisions have been made every 5 years, and a supplement has been promulgated twice in every 5 years.
  - JP18 was notified in June 7, 2021.
- FREE compendia available from website

  (English) https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0010.html

  (Japanese) https://www.pmda.go.jp/rs-std-jp/standards-development/jp/0004.html

JP1 in Latin in 1888



Crude Drug Specimens that were used as Reference for Listings in the JP1

Remained set, out of two sets (for current NIHS and Imperial Household Agency)

Legal recognition of JP

Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (Act No. 145 of 1960)

Article 2 (1)

The term "pharmaceutical" as used in this Act refers to the following items:

(i) items listed in the Japanese Pharmacopoeia (JP)

Article 41 (1)

In order to ensure the proper properties and quality of pharmaceuticals, the Minister of Health, Labour and Welfare will set forth and make public notice of JP after gaining opinions from the Pharmaceutical Affairs and Food Sanitation Council (PAFSC).

Article 56

Pharmaceuticals falling under any of the following items must not be sold, provided, or, for the purpose of the sale or provision thereof, manufactured, imported, stored, or displayed:

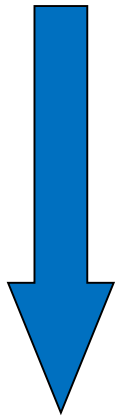
(i) pharmaceuticals listed in JP whose properties or qualities do not comply with the standards prescribed in JP.

The roadmap to JP18 and future

JP17
(Mar 7, 2016)

JP17 Supplement 1
(Dec 1, 2017)

JP17 Supplement 2
(Jun 28, 2019)



- Basic Principles for Preparation of JP18 (Five pillars)
  (Oct, 2016)
- Guideline for Preparation of JP18 Draft
  (Jan, 2017; Rev1: Oct, 2019; Rev2: Dec, 2020)

JP18
(Jun 7, 2021)

Under preparation

- Basic Principles for Preparation of JP19
- Guideline for Preparation of JP19 Draft

Contents of JP

1. General Notices:

specification of general rules: 49 paragraphs in JP18 (added 1 new paragraph)

2. General Rules for Crude Drugs:

specification of general rules for crude drugs: 10 paragraphs

3. General Tests

8 categories/86 General tests in JP18 (added 1 new General test) - Chemical Methods (15), Physical Methods (37), Powder Property Determinations (6), Biological/Biochemical/Microbial Tests (6), Tests for Crude Drugs (2), Tests for Preparations (17), Tests for Containers and Packing Materials (3), Reference Standards/Standard Solutions, Reagents, Test Solutions

4. Official Monographs:

2033 articles in JP18

5. Reference Spectra:

The Japanese Pharmacopoeia

6. General Information

62 chapters in JP18 (added 7 new chapters) - Physics and Chemistry (5), Solid-state Properties (4), Biotechnological/Biological Products (15), Microorganisms (10), Crude Drugs (8), Drug Formulation (4), Containers and Package (6), Water (2), Reference Standards (1), Others (7)

7. Appendix

Basic Principles for Preparation of JP18

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.

JP Expert Committee and related organization

JP

Notification

MHLW

Consultation

Advice

Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

Outsource

Report

Request

Development of JP drafts

Pmda

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

Request

Result

JP Expert Committees

NIHS

Reference Standards Distributer

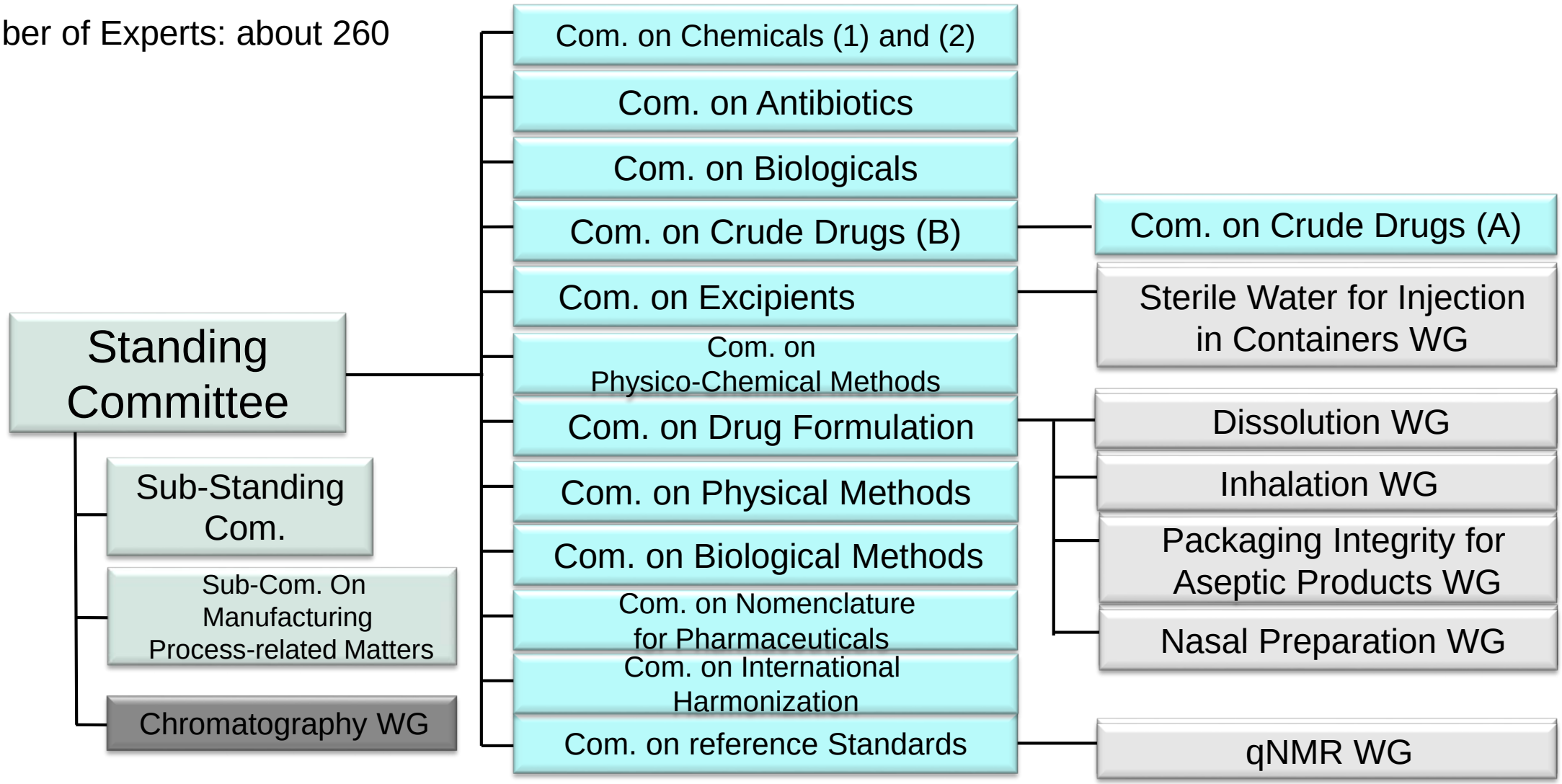
Pharmaceutical and Medical Device Regulatory Science Society of Japan

PMRJ

National Institute of Infectious Diseases

Organization of JP Expert Committees

Number of Experts: about 260



JP Expert Committee – Collaboration with stakeholders

Established in PMDA and mainly composed of outside experts

PMDA

Request for review

Result

JP Expert Committees

Public Consultation

Coordinate views

Universities

Research Institute

Industry

Citizen/Interested parties

Stakeholders
(Industry, Pharmacist Association)

Participate as experts

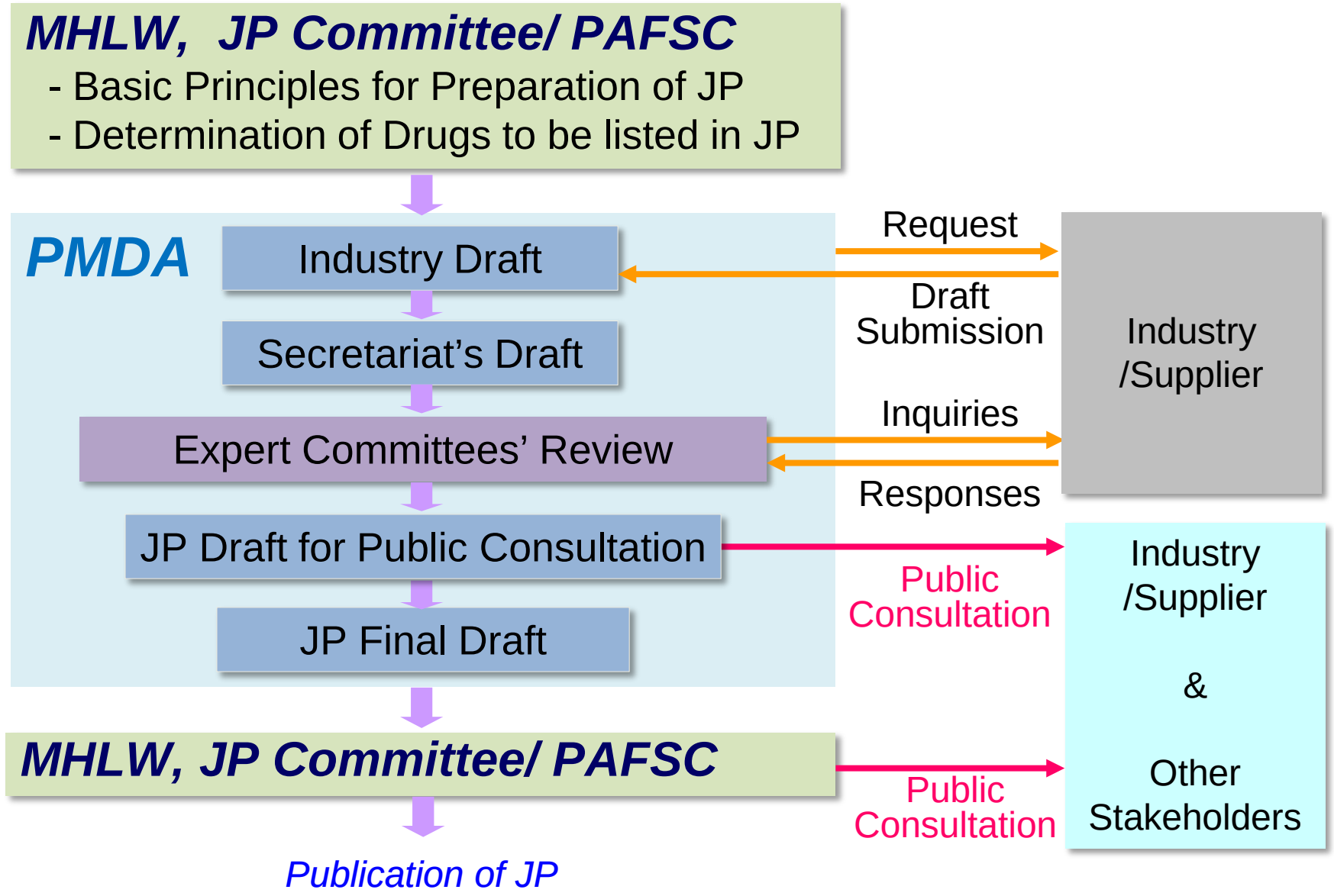
Experts from Industry

Appointed based on recommendation from Industry group

New drugs/Generic drugs reviewers (as Observers)

Professor in University/Institute

Publication process of JP



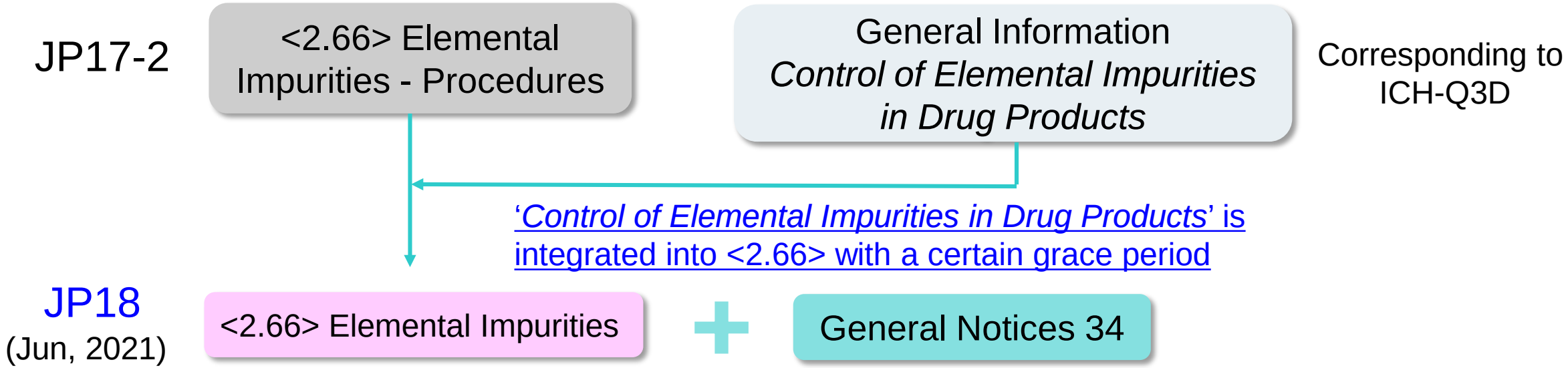
Key revisions in JP18

- Implementation of ICH-Q3D (Guideline for Elemental Impurities)
- New General Tests: <2.05> Size Exclusion Chromatography
- 7 New General Information (with new numbering system related to category)
  - <G3-1-180> A basic concept of the quality assurance on biotechnological products (biopharmaceuticals)
  - <G4-4-180> Bacterial Endotoxins Test and alternative methods using recombinant protein-reagents for endotoxin assay
  - <G5-8-180> Radioactivity Measurements Method for Crude Drugs
- 33 New Monographs
  - 27 chemical pharmaceuticals, 3 biopharmaceuticals, 1 additives, 2 crude drug products
- Removal of harmful reagents from 5 Official Monographs
  - Carbon tetrachloride
  - 1,2-Dichloroethane
  - 1,4-Dioxane

Including Eribulin Mesilate

Copovidone: PDG harmonized one

Implementation of ICH-Q3D



General Notices 34

In principle, the JP Drug Products are controlled appropriately according to the direction under <2.66> Elemental Impurities of the General Tests. When elemental impurities in the drug products are appropriately controlled in accordance with the direction, it is not necessary to perform the tests on elemental impurities such as heavy metals and arsenic in the monographs including but not limited to those of drug products, drug substances and excipients.

Time Table of Implementation of ICH-Q3D

JP17-2

<2.66> Elemental Impurities - Procedures

General Information
Control of Elemental Impurities in Drug Products

Corresponding to ICH-Q3D

'*Control of Elemental Impurities in Drug Products*' is integrated into <2.66> with a certain grace period

JP18
(Jun 7, 2021)

<2.66> Elemental Impurities + General Notices 34

In principle, the JP Drug Products are controlled appropriately according to the direction under Elemental Impurities of the general tests. --------

Elemental Specific Chapters in Monographs

grace period (3 years)

Control based on <2.66>

JP18 publication
(Jun 7, 2021)

JP18-1 publication

May, 2024

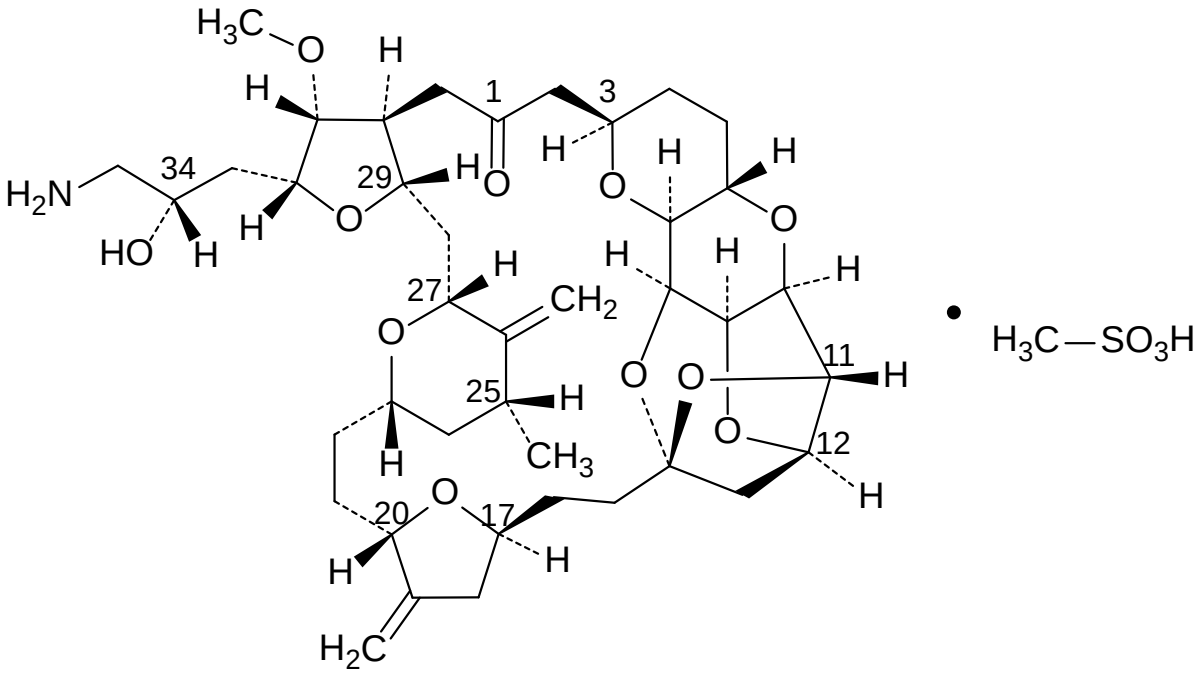
<G5-8-180> Radioactivity Measurements Method for Crude Drugs

Radioactivity Measurements Method for Crude Drugs <*G5-8-180*>

Crude drugs are natural products produced by harvesting cultivated plants/reared animals or collecting wild resources and processing them through washing and drying. This General Information describes the radioactivity measurement method of crude drugs that can be applied when there is a concern about the contamination of radioactive materials in more amounts exceeding that from natural origin. The measurement methods described here are procedures to measure radioactivity by γ-ray spectrometry, and target nuclides are ^{131}I, ^{134}Cs and ^{137}Cs.

This general information is based on the monitoring method of radioactivity of crude drugs harvested in east Japan after the Great East Japan Earthquake, although few crude drugs used in Japan is harvested around Fukushima area

Official Monograph ‘Eribulin Mesilate’



- 19 chiral carbons are existing
- Synthesized by 64 steps

$C_{40}H_{59}NO_{11}.CH_4O_3S$: 826.00

(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-2-[(2*S*)-3-Amino-2-hydroxypropyl]-3-methoxy-26-methyl-20,27-dimethylidenehexacosahydro-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2′,3′:5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one monomethanesulfonate

[441045-17-6]

Official Monograph ‘Eribulin Mesilate’ - Manufacture

Manufacture

Eribulin Mesilate has 19 chiral carbons, and its purity tests can not estimate all isomers derived from them. Therefore, based on sound science and the understanding of the product and the manufacturing process, control and manage the isomers and related substances during manufacturing process, and ensure the three-dimensional structure of eribulin mesilate. In the quality control strategy of Eribulin Mesilate, control the related substances including the principal isomers in the drug substance or starting materials and intermediates in upstream process. The acceptance value are not more than 0.22% and not more than 0.68% for the related substances B and C, which are the isomers at position C34 and controlled in the drug substance, and are not more than the threshold requiring identification (0.10%) for the related substances including other isomers. When Eribulin Mesilate is manufactured through the compounds 1 and 2, control as follows.

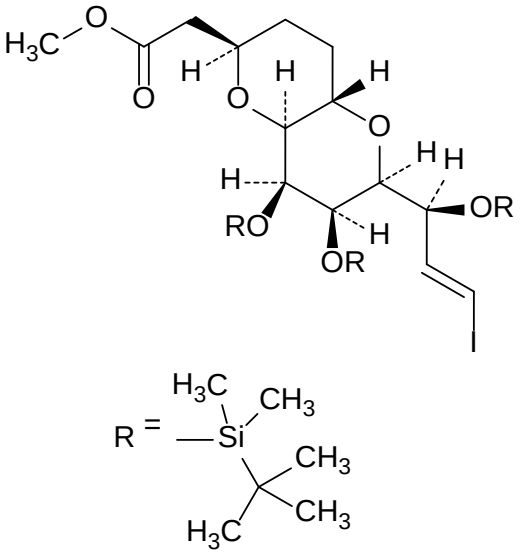
In the compound 1, control so that the isomers at positions C3 and C11, C12 *cis*-olefin, and other related substances are not more than the threshold requiring identification (0.10%). In the compound 2, control so that the isomers at positions C17 and C29 are not more than 0.30%, and the isomer at position C20 is not more than 0.50%, the isomer at position C25 is not more than 0.40%, and the isomers at positions C23, C27, C34 and C18/C19 *endo*-olefin and the other related substances are not more than the threshold requiring identification (0.10%).

Furthermore, ensure that the isomers at positions C17, C20, C25 and C29 are not more than the threshold requiring identification (0.10%) in the processes after the compounds 1 and 2, and the other related substances are not more than the threshold requiring qualification (0.15%).

When manufactured without reaction using the compounds 1 and 2, perform the control based on the control mentioned above.

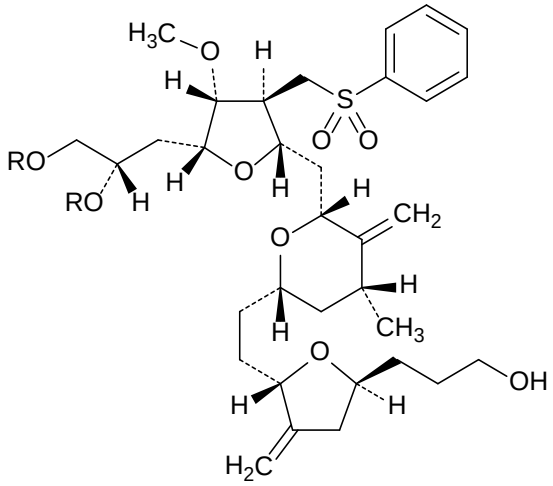
➡ ***Impurities too difficult to be qualified by release-testing, are controlled by manufacturing process.***

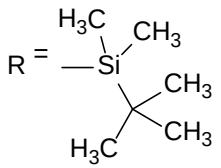
Official Monograph ‘Eribulin Mesilate’ – Compound 1 & 2



Compound 1

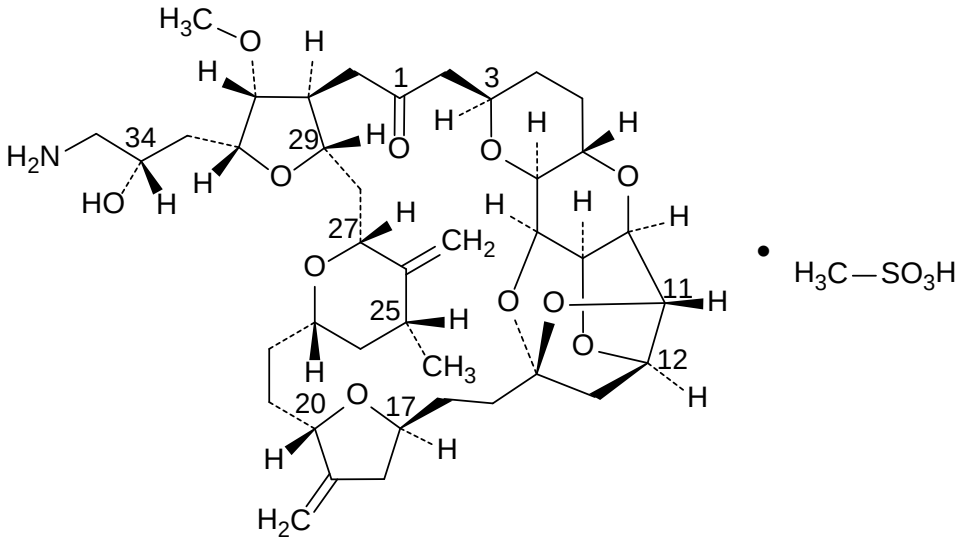
the isomers at positions C3 and C11, C12 *cis*-olefin, and other related substances are not more than the threshold requiring identification (0.10%)





Compound 2

the isomers at positions C17 and C29 are not more than 0.30%, and the isomer at position C20 is not more than 0.50%, the isomer at position C25 is not more than 0.40%, and the isomers at positions C23, C27, C34 and C18/C19 endo-olefin and the other related substances are not
more than the threshold requiring identification (0.10%).



the isomers at positions C17, C20, C25 and C29 are not more than the threshold requiring identification (0.10%) in the processes after the compounds 1 and 2, and the other related substances are not more than the threshold requiring qualification (0.15%)

Public Consultation in PMDA website

https://www.pmda.go.jp/rs-std-jp/standards-development/jp/pub-comments/jp/0096.html

ホーム > レギュラトリーサイエンス・基準作成調査・日本薬局方 > 基準作成調査業務 > 日本薬局方関連業務 > パブリックコメント > 日本薬局方

レギュラトリーサイエンス・基準作成調査・日本薬局方

- ⊞ レギュラトリーサイエンス推進業務
- ⊞ 科学委員会運営業務
- ⊟ 基準作成調査業務
  - 基準作成調査業務の概要
  - ⊟ 日本薬局方関連業務
    - ⊞ 日本薬局方
    - 日本薬局方(原案)
    - ⊞ 関連通知等
    - 技術情報
    - 新規収載要望
    - 改正要望
    - 薬局方の国際調和
    - ⊟ パブリックコメント
      - 日本薬局方

パブリックコメント(日本薬局方)

募集中

New/Update	掲載月	タイトル	募集期間
	2021年3月分	日本薬局方収載原案に関するご意見の募集について(令和3年3月分)	2021年3月1日 ～ 2021年5月31日

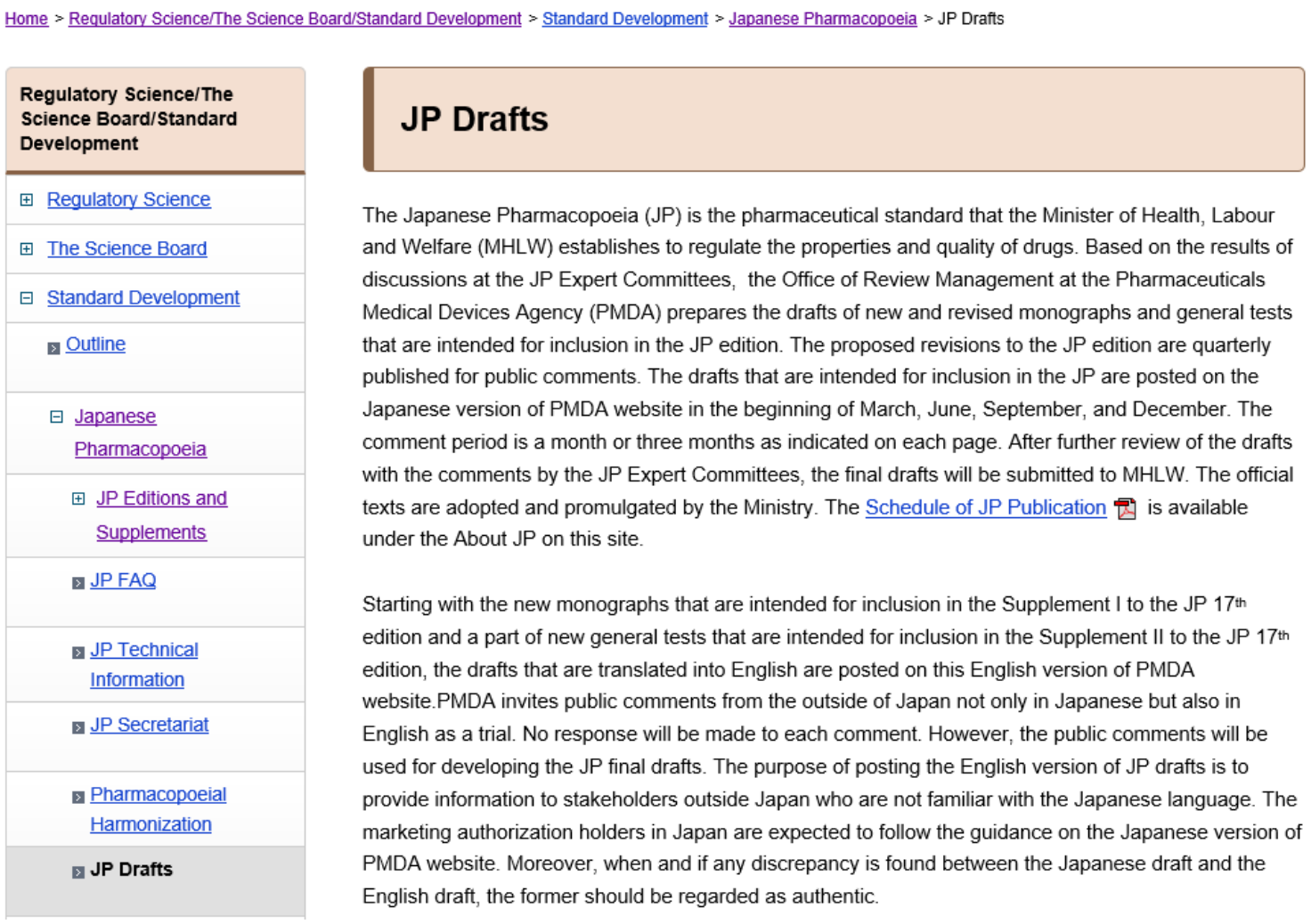
募集終了

New/Update	掲載月	タイトル	募集期間
現在、該当する情報はありません。			

- パブリックコメント(日本薬局方)(令和2年度)
- パブリックコメント(日本薬局方)(令和元年度)
- パブリックコメント(日本薬局方)(平成30年度)
- パブリックコメント(日本薬局方)(平成29年度)
- パブリックコメント(日本薬局方)(平成28年度)

Public Consultation in PMDA website in English

https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0013.html



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Regulatory Science/The Science Board/Standard Development

- ⊞ Regulatory Science
- ⊞ The Science Board
- ⊟ Standard Development
  - Outline
  - ⊟ Japanese Pharmacopoeia
    - ⊞ JP Editions and Supplements
    - JP FAQ
    - JP Technical Information
    - JP Secretariat
    - Pharmacopoeial Harmonization
    - **JP Drafts**

JP Drafts

The Japanese Pharmacopoeia (JP) is the pharmaceutical standard that the Minister of Health, Labour and Welfare (MHLW) establishes to regulate the properties and quality of drugs. Based on the results of discussions at the JP Expert Committees, the Office of Review Management at the Pharmaceuticals Medical Devices Agency (PMDA) prepares the drafts of new and revised monographs and general tests that are intended for inclusion in the JP edition. The proposed revisions to the JP edition are quarterly published for public comments. The drafts that are intended for inclusion in the JP are posted on the Japanese version of PMDA website in the beginning of March, June, September, and December. The comment period is a month or three months as indicated on each page. After further review of the drafts with the comments by the JP Expert Committees, the final drafts will be submitted to MHLW. The official texts are adopted and promulgated by the Ministry. The Schedule of JP Publication is available under the About JP on this site.

Starting with the new monographs that are intended for inclusion in the Supplement I to the JP 17th edition and a part of new general tests that are intended for inclusion in the Supplement II to the JP 17th edition, the drafts that are translated into English are posted on this English version of PMDA website.PMDA invites public comments from the outside of Japan not only in Japanese but also in English as a trial. No response will be made to each comment. However, the public comments will be used for developing the JP final drafts. The purpose of posting the English version of JP drafts is to provide information to stakeholders outside Japan who are not familiar with the Japanese language. The marketing authorization holders in Japan are expected to follow the guidance on the Japanese version of PMDA website. Moreover, when and if any discrepancy is found between the Japanese draft and the English draft, the former should be regarded as authentic.

FAQ on JP

https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0001.html

Regulatory Science/The Science Board/Standard Development

- ⊞ Regulatory Science
- ⊞ The Science Board
- ⊟ Standard Development
  - Outline
  - ⊟ Japanese Pharmacopoeia
    - ⊞ JP Editions and Supplements
    - **JP FAQ**
    - JP Technical Information
    - JP Secretariat
    - Pharmacopoeial Harmonization

JP Frequently Asked Questions

Q1
When will the latest edition of JP be available?

The "Schedule of JP Publication" is posted on the "About JP" at the Pharmaceuticals and Medical Devices Agency (PMDA)/Japanese Pharmacopoeia (JP) website. It shows the publication schedule of JP latest editions. The publication dates are updated as soon as confirmed. No estimated date is available.

Q2
When will the latest edition of JP be available in English?

The "Schedule of JP Publication" is posted on the "About JP" at the Pharmaceuticals and Medical Devices Agency (PMDA)/Japanese Pharmacopoeia (JP) website. It shows the publication schedule of JP latest editions. The JPs are originally prepared in Japanese and are translated to English after publication of Japanese version. The translation may take about a year depending on the volume of texts. The translated editions are uploaded as soon as possible. No estimated date is available.

The JP contents and preface in English may be available on the "JP Editions and Supplements" page prior to posting of the JP English edition.

Thank you for your attention.