Development, Control and Current Status of JP Reference Standards

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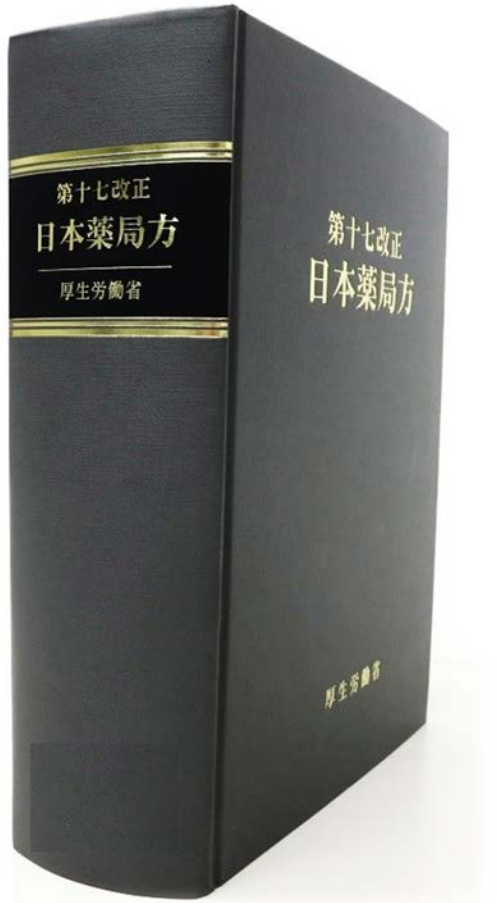
What's PMRJ

- **P**harmaceutical and **M**edical Device **R**egulatory Science Society of **J**apan
- Non-profit general incorporated foundation, founded in 1956
- Our objective is to **advance Regulatory Science** related to drugs and medical devices
  - ✓ *Head office's activities*: Organizing educational meetings, publishing journals of the technical information for JP, etc.
  - ✓ *Osaka office's activities*: Producing and distributing JP Reference Standards

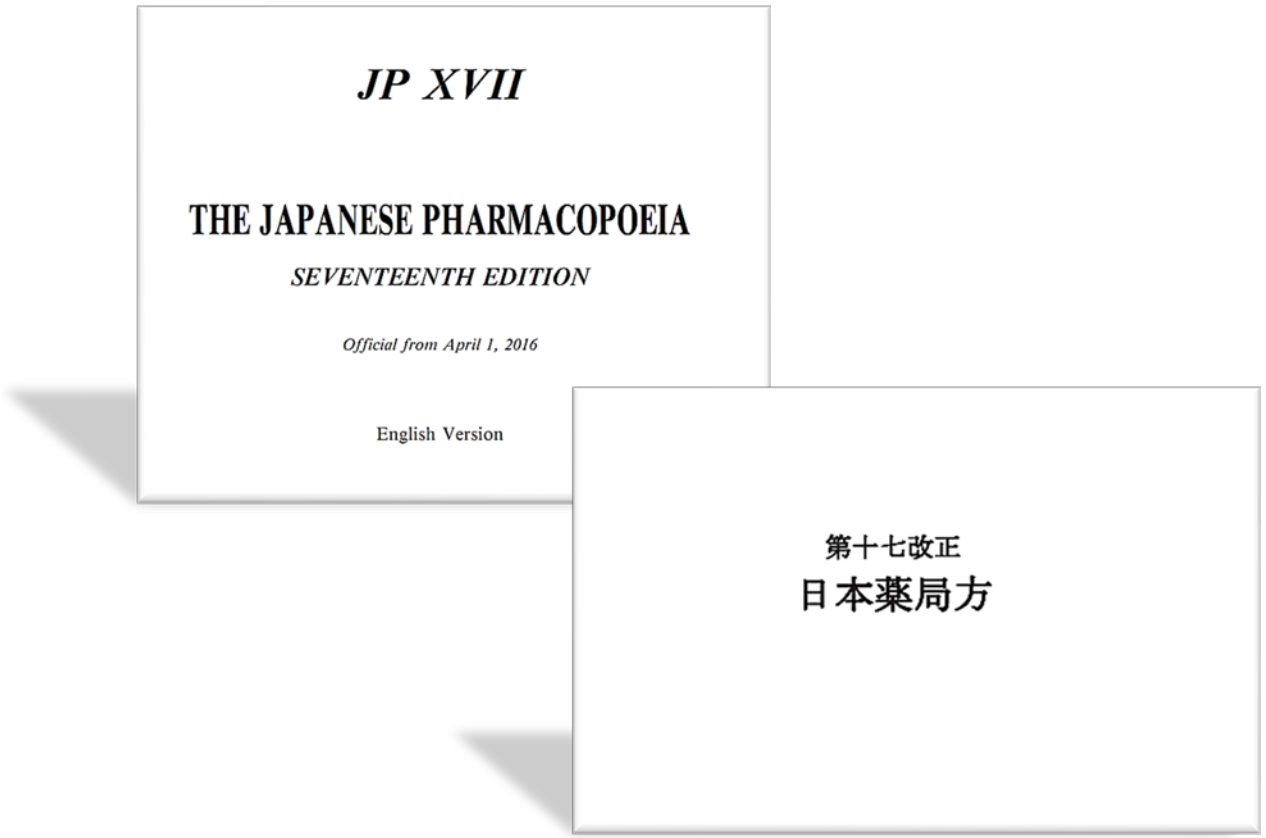
Today's Topics

1. Role of Japanese Pharmacopoeia (JP) and JP Reference Standards
2. Establishment of JP Reference Standards
3. Quality assurance of JP Reference Standards
4. Challenges
5. Specific Information

Role of Japanese Pharmacopoeia (JP) and JP Reference Standards



Japanese Pharmacopoeia 17th



Japanese Pharmacopoeia (JP)

- **Official document**
  - defines the specifications, criteria and standard test methods to properly assure the quality of drugs in Japan
- Established and published by the Japanese Government (MHLW) in accordance with the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices
- The current edition: the 17th edition (JP17), the supplement 1 & 2
  - The JP17 was published on March 7 and applied on April 1, 2016
    the supplement 1 in December 2017 and the supplement 2 in June, 2019
  - The JP18 will be published in June, 2021
- After the first edition was published in 1886,
  the JP was revised every 10 years, but recently has been revised every 5 years

Contents of the JP17 (including the supplement 1 and 2)

Mandatory Part

- **General Notices**
- **General Rules for Crude Drugs / for Preparations**
- **General Tests, Processes and Apparatus**
  - **85 general test methods**
  - **Reference Standards, Standard Solutions, Reagents, Test Solutions; Measuring Instruments, Appliances**
- **Official Monographs (2,008 monographs)**
- **Reference Spectra: Ultraviolet-visible / Infrared**
- General Information (56 General informations)
- Appendix

Definition of JP Reference Standards

JP17

General Tests, Processes and Apparatus in JP17

9.01 Reference Standards

Reference Materials

Substances employed as the standard for measuring chemical, physical and biological characteristics in a quantitative and qualitative manner, and also used for calibration and checking accuracy of apparatus for the tests of pharmaceuticals

Reference Standards

Reference materials used for quality tests of pharmaceuticals, prepared to constant quality, assured its level of quality by **official** organization, and **supplied officially**

JP Reference Standards

Reference standards used for the tests of drugs and for the General Tests specified in the Japanese Pharmacopoeia

Intended Use of JP Reference Standards

JP17

JP Reference Standards

Intended use

— Assay
— Identification
— Purity tests
— Calibration of apparatus
— System suitability (Analytical validation)

The application and use of the JP Reference Standards are directed in monographs and in the General Tests

Classification of JP Reference Standards

JP17

2. Classification of the JP reference standards by use

(1) Quantitative tests

For assays of active ingredients, indicator ingredients of crude drugs, and related substances

e.g.: Acetaminophen RS, Aciclovir RS, Heparin Sodium RS, Ginsenoside Rb1 RS

For quantitative assays specified in the General Tests.

e.g.: Endotoxin RS, Tyrosine for Digestion Test RS

Classification of JP Reference Standards

JP17

General Information *G9 Reference Standards*

Reference Standards and Reference Materials Specified in the JP

2. Classification of the JP reference standards by use

(2) Qualitative tests

For identification of products specified in the Monographs, the comparison of UV-visible absorption spectra, IR spectra, NMR spectra, retention time or Rf values in chromatography, and mobility in electrophoresis

e.g.: Anhydrous Lactose for Identification RS, Heparin Sodium for Identification RS, Montelukast Sodium for Identification RS

For identification of peaks or spots, or for limit tests of related substances, in purity of products specified in the Monographs

e.g.: Gitoxin for Purity RS, Adrenaline Bitartrate for Purity RS

Classification of JP Reference Standards

JP17

General Information *G9 Reference Standards*

Reference Standards and Reference Materials Specified in the JP

2. Classification of the JP reference standards by use

(3) System suitability

For system suitability test

e.g.: Entacapone Related Substance A for System Suitability RS

Montelukast for System Suitability RS

(4) Calibration and suitability confirmation of apparatus

For calibration of apparatus

e.g.: Calcium Oxalate Monohydrate for Calibration of Apparatus RS

For suitability confirmation of apparatus

e.g.: Acetanilide for Apparatus Suitability RS

Classification of JP Reference Standards

JP17

Kinds of RS	The number of RS (JP17 Supplement 2)
Chemical Drugs RS	231
Biologicals RS	29
Crude Drugs RS	9
RS for the General Tests	14
Antibiotics RS	121
Total	404

Producers of JP Reference Standards (RSs)

JP17

(1) PMRJ

produces and distributes all of the JP RSs except for antibiotics RSs*

* PMRJ has started distributing some JP RSs for antibiotics.

PMRJ was registered as the producer of the JP RSs by the MHLW according to the Ministerial ordinance

(2) National Institute of Infectious Diseases (NIID)

produces and distributes the JP RSs for antibiotics

The NIID is a research institute which belongs to the MHLW

Establishment of JP Reference Standards

Quality Requirements for JP Reference Standards

- Specified quality necessary with regard to their intended use.
- The JP RSs are provided with public assurance that the JP RSs have suitable quality for the specified use
- The required test items and test methods to assure the quality of JP RS are indicated in Written Standard of Quality Requirements for the JP RS
- The Drafts of monographs and the General Tests are reviewed and finalized by the JP expert committees. Simultaneously the drafts of Quality Requirements for the JP RS are also reviewed and finalized by the JP expert committee
- The JP RS producers are directed to produce new JP RS according to Quality Requirements for the JP RS by the MHLW

Establishment of a JP RS

MHLW

Direction to produce a JP RS with **Quality Requirement** for a JP RS

PMRJ

❶ **Review of Quality Requirement**

Requests

Pharmaceutical Company, etc.

Supply

❷ **Procurement of Raw Material for RS**

Decision of the purchase amount and requests of supply
Filling

Requests

External Laboratories

Reports

❸ **Quality Test**

Testing (Internal/external laboratory)

Evaluation

❹ **Approval**

Expert Committee for RS Evaluation

Approval for the reference standard

❺ **Production**

Labelling, Packaging

Shipping

Ordering

❻ **Customer Service**

Quality assurance of JP Reference Standards

Quality Evaluation Tests Chemical drugs JP RSs for quantitative use

Typical evaluation tests

- Spectroscopic (UV/Vis, IR) , H^1 NMR
- Chromatographic (HPLC, GC, TLC) related substances, residual solvents, other contaminants
- Water (KF) / Loss on drying
- Residue on ignition
- Dynamic vapor sorption (DVS)
- Specific rotation, melting points
- Thermal (TGA/DSC)
- Assay (if possible, an absolute quantification method such as titration)

Collaborative study for RS evaluation is carried out

Reference Standards must be suitable for their intended use

In Principle

Quantitative JP RSs have an assigned content/potency for the relevant requirements of the corresponding monograph(s)

Almost all chemical drugs JP RSs

Content is assigned as purity by mass balance approach

Mass Balance approach reflects Related impurities, Residual Solvents, Inorganic impurities (Residue on Ignition) , Other impurities, Water, Loss on Drying

Almost all biologicals JP RSs

Potency is determined by calibration to International Standard

Mass Balance Approach

Purities of USP RSs and EP RSs also are determined by mass balance approach

Generally, mass balance purity is calculated by deducting the measured impurities% from 100.0%

Purity (as is)

= 100% − (residue on ignition % + residual solvents %

+ water content % + related substances %)

Mass Balance Approach

- When the related substances % has been determined by chromatography rather than being based on mass fraction, purity is calculated as below

  Purity (as is)
  = {100% − (residue on ignition % + residual solvents % + water content %)}
  × (100% − related substances %) / 100

- When a JP Monograph directs that the JP RS is dried before use, or the RS content is used on the dried basis, on the anhydrous basis, and on the anhydrous and residual solvent–free basis, purity is determined by subtracting the measured impurities from 100.0% after drying the RS or performing the specified conversion.

  For example, purity on the anhydrous basis is calculated as below
  Purity (anhydrous basis)
  = {100% − (residue on ignition % + residual solvents %)}
  × (100% − related substances %) / 100

Role of Biologicals RS in JP

- Mainly used for potency assays

- General Notice No. 10 in JP17

The unit used for expressing the potency of the JP Drugs is recognized as the quantity of drug.

Usually it is expressed by a definite quantity of a definite standard substance which shows a definite biological activity, and differs according to each drug.

The units are determined, in principle, by comparison with each reference standard by means of biological methods. The term “Unit” used for the JP articles indicates the unit defined in the Japanese Pharmacopoeia.

- The units of the potency of the JP drugs are determined by comparison with each JP RS by biological methods
- Potency of JP biologicals RS is calibrated to WHO IS (International Standards) when available

— When not available, JP unit for a potency is defined based on the potency of the primary reference material when a new RS is adopted

WHO International Standards for Biological products

- Global standards for potency of biologicals
- Assigned International Unit (IU) for quantitative measurement of biological activity
- Established by ECBS (the WHO Expert Committee on Biological Standardization)
- The quality is assessed and the IU is assigned by international collaborative studies
- About 310 International Standards for biological products (as of March, 2019)

Lot-to-Lot Continuity / Traceability

- **To assure lot-to-lot continuity**

  Based on some results for an RS candidate, the assigned content/potency is confirmed to be traceable to the current / previous lots of the JP RS

Stability Monitoring

- **Stability monitoring program**

  A stability program is established and implemented to ensure the continued fitness-for-use of the JP RS

Reliability of Our Test Results

ISO/IEC 17025 laboratory accreditation

PMRJ, the Department of Reference Standards has obtained ISO/IEC 17025 laboratory accreditation, which serves as proof of the technical ability to carry out quality testing properly

Proficiency Testing

PMRJ, the Department of Reference Standards is participating in proficiency testing sponsored by EDQM to ensure that its ability in analytical technology is at the international level

Challenges

Challenges in JP Reference Standards

- **Change of JP RS establishment policy**
  - JP RSs have been mainly established as quantitative RSs
  - On the other hand, EP and USP have been actively establishing reference standards that have specific uses other than the use for quantitative tests

In the context of this global trend, JP needs to establish JP RSs for assay of impurities, for suitability of analytical systems, and for identification

Challenges in JP Reference Standards

- **Change of purpose to use JP RSs for biologicals**
  - Biopharmaceuticals produced by recombinant technology need physicochemical tests to assure the quality
  - Most important role of RSs for traditional biologicals is to be used for potency assays
  - JP RSs for biopharmaceuticals are used for:

    Quantitative tests (in vivo/ in vitro bioassay, protein content; HPLC)

    Qualitative tests (HPLC, Western blotting, Peptide mapping)

    System suitability (to verify that an analytical system is operated within the boundaries of its validation scope) — Importance of testing the relevant quality attributes with a robust method —

- **Establishment of common pharmacopoeia reference standards**

  EP, USP and JP are collaborating to develop a common reference standard for biopharmaceuticals with the same assigned content

Specific Information

PMRJ Pharmaceutical and Medical Device Regulatory Science Society of Japan (PMRJ)

Rev. June 1, 2020

PMRJ Reference Standards Catalog

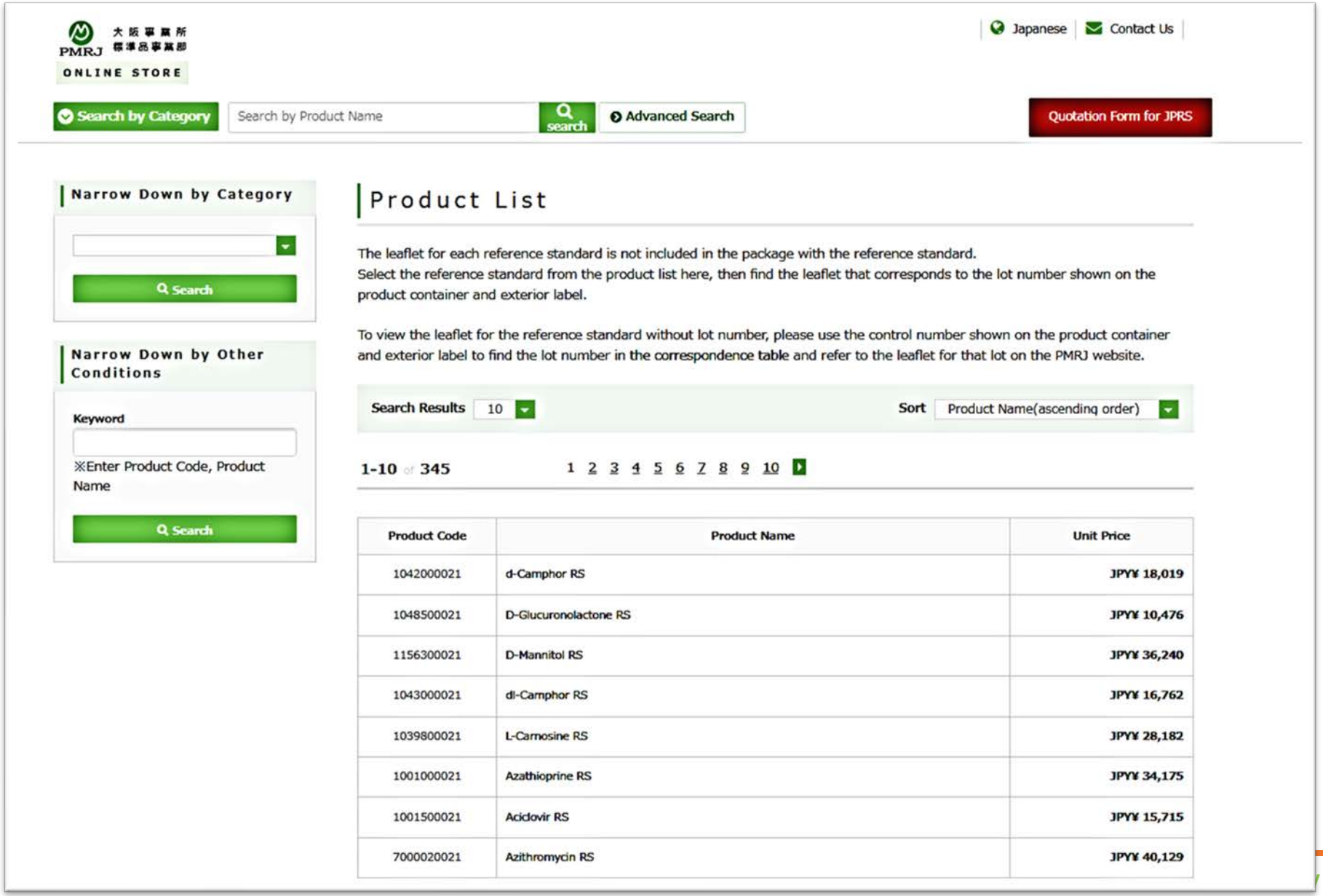
Please visit PMRJ Reference Standards Department website <https://www.pmrj-rs.jp/en> to check the ordering instruction.
In addition, please find a leaflet of each reference standard on the webpage for the reference standard prior to use.

1. Japanese Pharmacopoeia Reference Standards

Product Code	Reference Standard (RS)	Unit Quantity	Storage Temperature	Other Information Abbreviations	Price
1005000021	Acetaminophen RS	300 mg	≤25°C		JPY 18,334
1169000021	Acetanilide for Apparatus Suitability RS	200 mg	≤25°C		JPY 10,476
1170000021	Acetophenetidine for Apparatus Suitability RS	200 mg	≤25°C		JPY 10,476
1001500021	Aciclovir RS	100 mg	≤25°C		JPY 15,715
1006000021	Adrenaline Bitartrate for Purity RS	50 mg	≤8°C	SH	JPY 13,776
1011500021	Alendronate Sodium RS	150 mg	≤25°C		JPY 24,096
1011000021	Alprostadil RS	10 mg	≤5°C	SH	JPY 66,838
1114000021	*p*-Aminobenzoyl Glutamic Acid for Purity RS	500 mg	≤25°C		JPY 29,582
1008000021	Amitriptyline Hydrochloride RS	100 mg	≤25°C	SH	JPY 21,359
1012000021	Amlexanox RS	300 mg	≤8°C	SH	JPY 38,762
1010000021	Amlodipine Besilate RS	150 mg	≤25°C		JPY 68,096
7000110021	Ampicillin RS	100 mg	−20 – −30°C	AB SH	JPY 40,129
1106000021	Anhydrous Lactose for Identification RS	50 mg	≤25°C		JPY 12,815
1002000021	Ascorbic Acid RS	1 g	≤25°C		JPY 21,145
1003000021	Aspirin RS	300 mg	≤25°C		JPY 16,019
1005800021	Atorvastatin Calcium RS	150 mg	≤8°C	SH	JPY 17,809

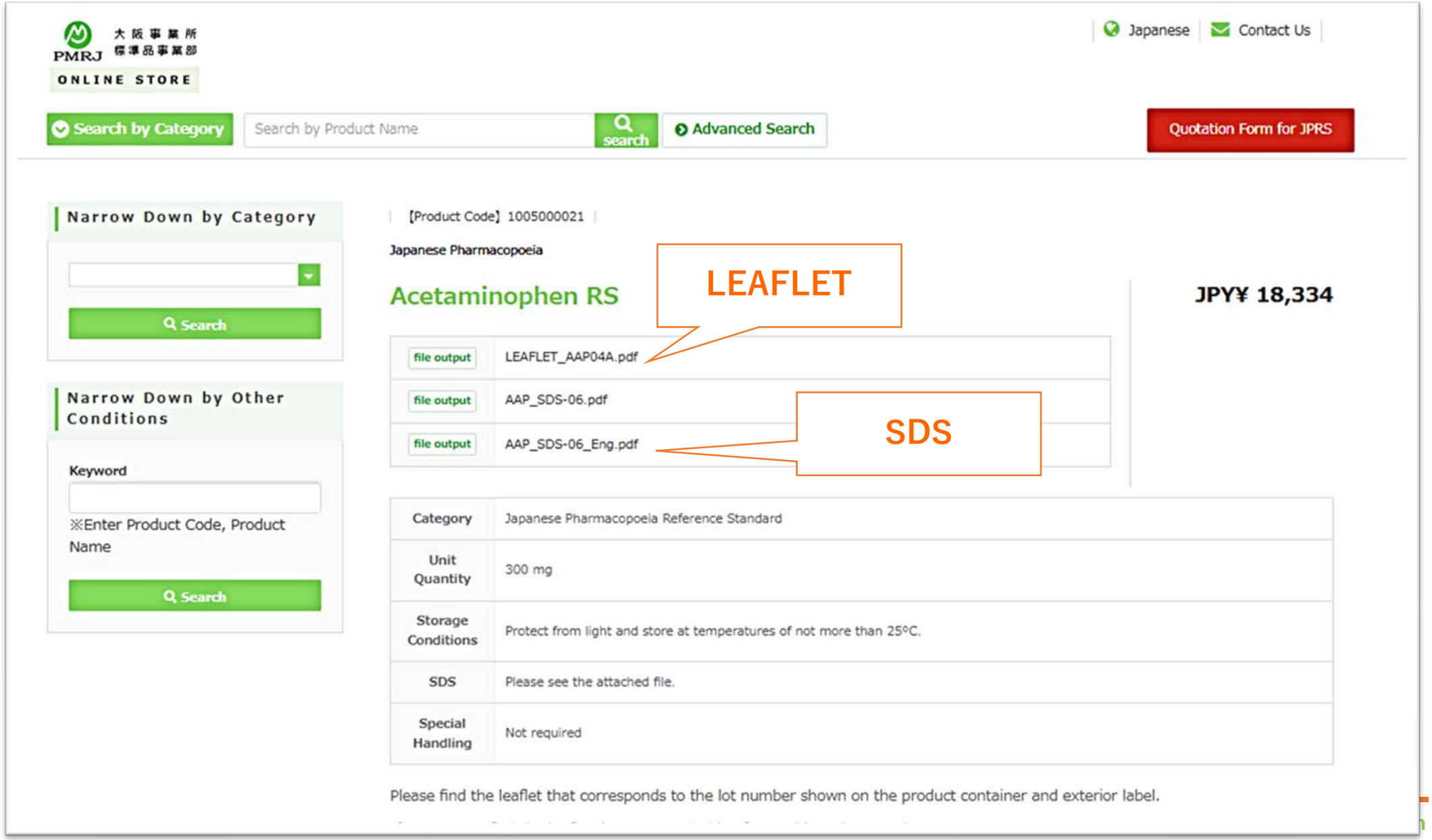
PMRJ online store

https://www.pmrj-ec.jp/aec/user/?lang=en



Product Code	Product Name	Unit Price
1042000021	d-Camphor RS	JPY¥ 18,019
1048500021	D-Glucuronolactone RS	JPY¥ 10,476
1156300021	D-Mannitol RS	JPY¥ 36,240
1043000021	dl-Camphor RS	JPY¥ 16,762
1039800021	L-Carnosine RS	JPY¥ 28,182
1001000021	Azathioprine RS	JPY¥ 34,175
1001500021	Aciclovir RS	JPY¥ 15,715
7000020021	Azithromycin RS	JPY¥ 40,129

Specific Information



Specific Information - Leaflet -

Date issued: April 1, 2019

PMRJ

Reference Standard – L E A F L E T

Japanese Pharmacopoeia

Entacapone Reference Standard

Lot ENT01A

《Unit Quantity》
approximately 210 mg

《Storage Conditions》
Protect from light and store in a refrigerator (not more than 8°C).

《Intended Uses》
Entacapone: Identification (Ultraviolet-visible Spectrophotometry, Infrared Spectrophotometry) and Assay (LC)
Entacapone Tablets: Uniformity of dosage units (LC), Dissolution (Ultraviolet-visible Spectrophotometry) and Assay (LC)

《Correction Information》
Loss on drying: 0.0%
Correction factor: 0.999(Assay (LC), Uniformity of dosage units (LC), on the dried basis)

Precautions

1. All the reference standards distributed by PMRJ are analytical reagents. They are not drugs or clinical

compendia. The specified uses are given in the Intended

as a correction factor to apply when the reference standard is used in quantitative tests. If a correction factor is provided in the Correction Information section of the leaflet for a reference standard, be sure to correct the weighed amount of reference standard by multiplying it by the correction factor when the reference standard is used in the official compendial quantitative tests following the correction factor. When quantitative tests

Product name
Lot#

Unit quantity
Storage condition

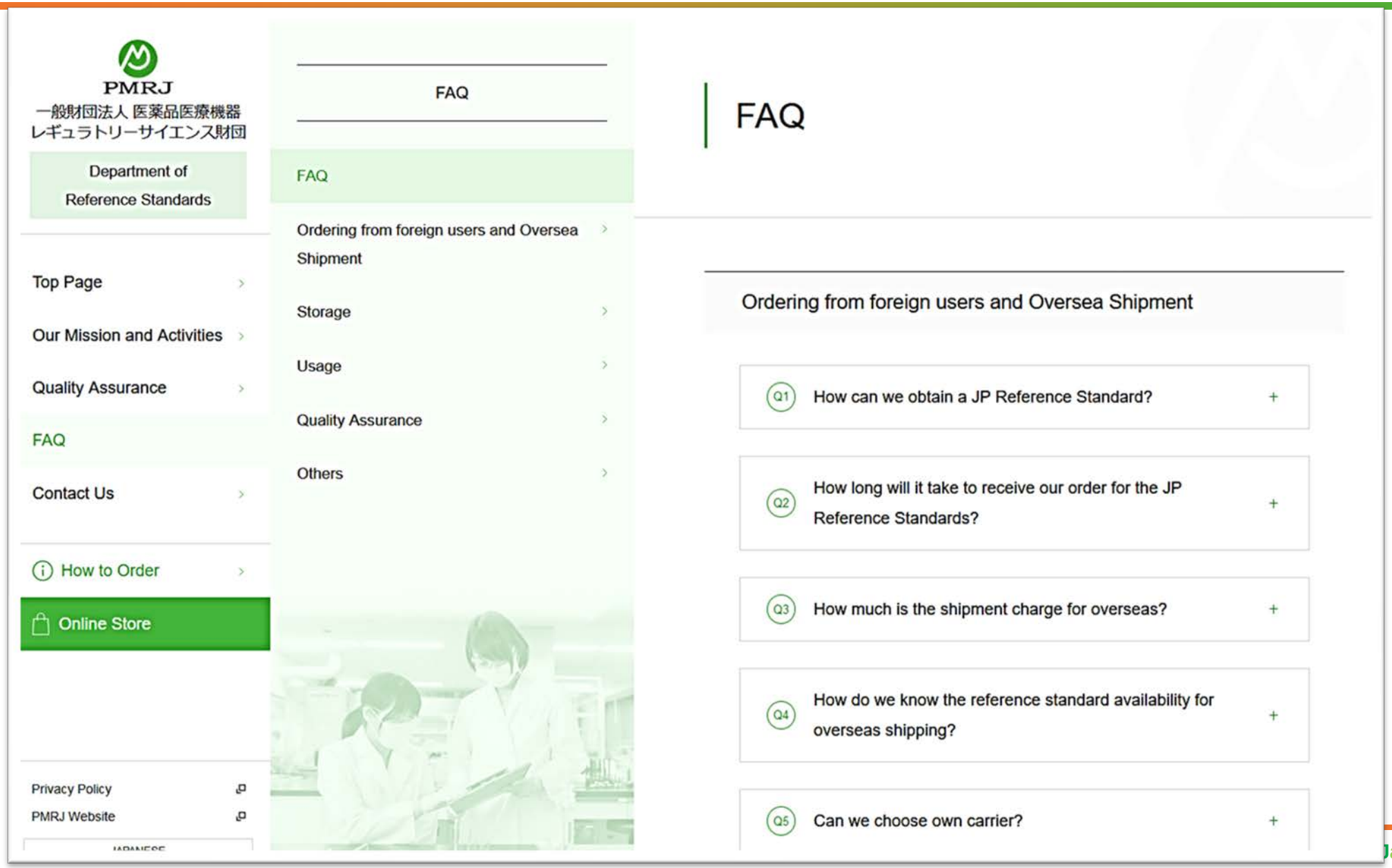
Intended use in JP

Correction Information
Water, LOD
Correction factor

Notes on the usage and storage

FAQ

https://www.pmrj-rs.jp/en/faq/



Conclusion

1. JP is the official document to properly assure the quality of drugs in Japan
2. JP RSs are used for the tests of drugs and for the General Tests in JP
3. JP RSs are assured to have suitable quality for the intended use
4. JP is working on establishing JP RSs for assay of impurities, for suitability of analytical systems, and for identification other than for quantitative tests of active ingredients

Thank you for your attention

Pharmaceutical and Medical Device Regulatory Science Society of Japan

PMRJ https://www.pmrj.jp/eng/index_e.html
Department of Reference Standards https://www.pmrj-rs.jp/en/