Globalization of JP's Reference Standards

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Disclaimer

The opinions expressed here do not necessarily reflect the official positions of neither PMRJ nor PMDA.

COI Statements

I serve as an expert in PMDA's International Harmonization Committee and as an associate-expert in Reference Standards Committee.

Themes of the Presentation

- Pivotal Turning Point for JP
- Characteristics of JP and the Policy for Establishing Reference Standards till Now
- Big Policy Changes of Establishing JP RSs
- Use of JP RSs outside Japan
- Challenges for JP's Reference Standards

Pivotal Turning Point for JP

- ✓ From "Domestically-oriented" JP (日本薬局方) to "Globally-oriented" Japanese Pharmacopoeia
- ✓ Proceed gradually but really began from JP XVII (2016)
  - —MHLW's and PMDA's International Strategic Plans

- ✓ Background :
  - —Globalization of medicines
  - —Globalization of manufacture and distribution
  - —Need to provide Reference Standards (RSs) outside Japan

Reality of JP RS

The Number of Monographs and RSs

	JP 17th (2016.4.1～)	EP 9th Ed. (2017.1.1～)	USP 39 (2016.5.1～)
Monograph	1,962	2,329	＞4,900
RS	394	2,708	＞3,500

An example of monographs and RSs of the three Pharmacopoeias

		JP	EP	USP
Monograph		Amlodipine Besilate Amlodipine Besilate Tablets	Amlodipine Besilate (describes information about impurities A, B, D, E, F,G and H)	Amlodipine Besylate Amlodipine Besylate Tablets Amlodipine Oral Suspension
RS	API	Amlodipine Besilate (for HPLC assay) (150 mg)	Amlodipine Besilate (for HPLC assay) (150 mg)	Amlodipine Besilate (for HPLC assay) (350 mg)
	Impurity		Amlodipine for Peak Identification (containing impurities D, E and F) Impurities A, B and G (10 or 15 mg each)	Amlodipine Related Compound A (25 mg)

JP's Policy of RS establishment till Now

✓Main use → Assay of Drug Substance

→ applied also to Identification test

but with Reference Spectra

✓Limited use

→ Related substances (Purity test) (Gitoxin RS)

→ Calibration of apparatus (Calcium Oxalate Monohydrate, 6 RSs for Apparatus Suitability (Melting point))

Big policy change -1-

✓ JP RSs have been mainly established for the Assay of Drug Substances

IS CHANGING !

In JP XVII (2016), three items of the new kinds of JP RSs were established :

(1) Montelukast RS for System Suitability

(2) Montelukast Racemate RS for System Suitability

(3) Montelukast Sodium RS for Identification

※ After JP XVII, JP will establish the impurity RSs but with the following general conditions;

Conditions of establishing RS for Purity test and Suitability of an analytical system -1-

1. When applied to specific related substance or impurity, in the case relative retention time cannot identify the substance and/or the limit cannot be specified by area normalization or by comparison with the sample solution, it is recommended to establish such RS.
2. If the system suitability cannot be adequately evaluated by conventional JP methods (determination of the number of theoretical plates and the symmetry factor, etc.), establish an RS for suitability of the system.

Conditions of establishing RS for Purity test and a Suitability of an analytical system -2-

3. Such RS should not be established if the continuous supply of the raw materials of the reference standard is uncertain.

Cf. Information on relevant texts of JP Monograph

(1) Major impurities: Names and structures shown at the end of the Monograph

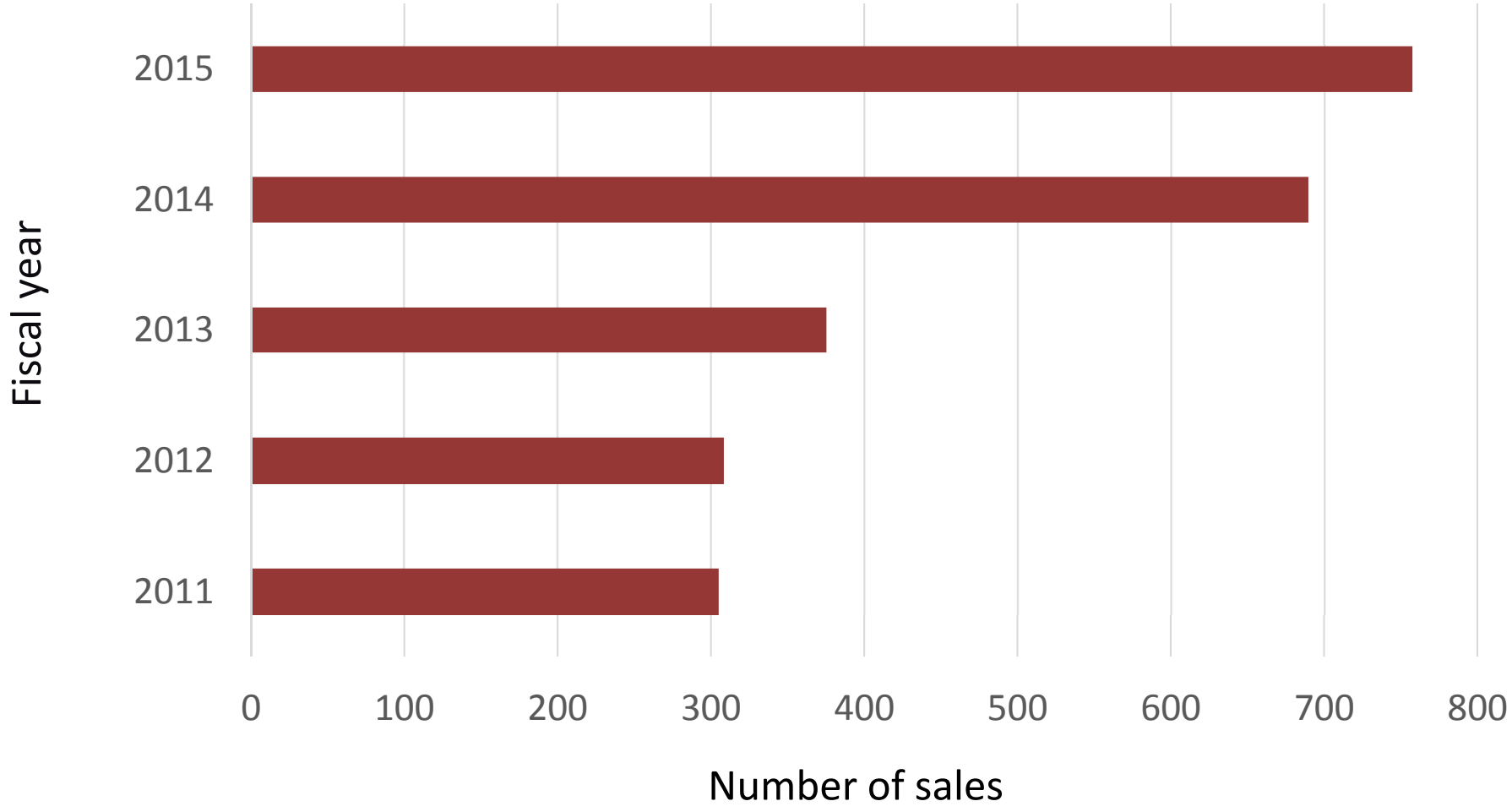
(2) When the existing procedure cannot be applied because of the difference of impurity profile, e.g. of manufacturing process, the second procedure may be established.

Big policy change -2-

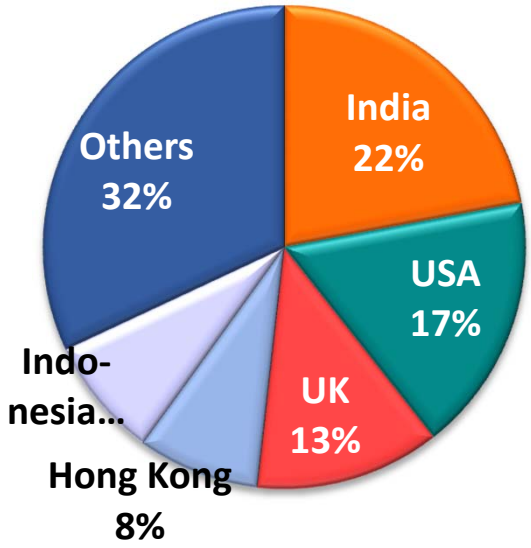
- ✓ Establishing the RS for the Identification is desirable, in principle, when the test is the comparison of IR spectra, UV spectra etc. unless the RS for Assay is applicable.

- ✓ There is a need to consider gradual establishment of the "reagents for assays (of Preparations)" as Reference Standards. In JP, when a Drug Substance does not involve RS (e.g. titration), no RS has been established for the assay of the Preparation.

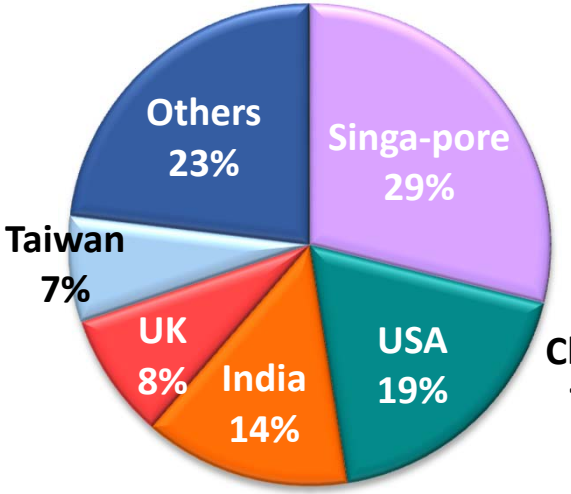
sales of JP Reference Standards outside JPN in the past five years（2011-2015）



JP Reference Standards Export by Destination



FY2015



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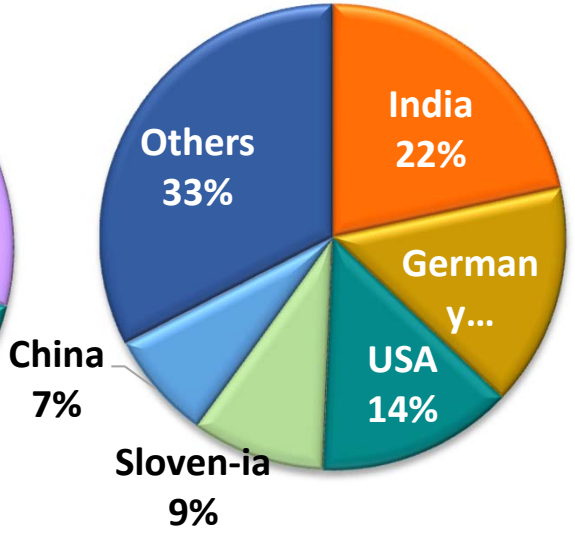

FY2013

JP's Challenges for the Future

- What is the role of JP in this changing global environment surrounding pharmaceuticals?
  — One of PDG's members (but the smallest)

1. To contribute to the world with this small entity
   - by showing the way how smaller Phs/ RAs may efficiently manage their Phs and review of application of generics
   - by proposing a new monograph (with/ without impurity RSs) which may fit to other smaller Phs/RAs

JP's Challenges for the Future

- What is the role of JP in this changing global environment surrounding pharmaceuticals?

2. Strengthening our distribution system for delivering JP Reference Standards outside Japan

3. Strengthening our system for establishing new types of Reference Standards by a number of ways, e.g., ensuring better coordination between relevant committees

Thank you for your attention!

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