EDQM Conference
Quality of Medicines in a Globalised World: Dreams and Reality
14-15 October 2010
Prague, Czech Republic

Plenary Session
Dr Roger L. Williams
Dr Toru Kawanishi
Dr G. N. Singh
Dr Gerson Pianetti
International Perspectives: Pharmacopoeias

Roger L. Williams, M.D.
CEO/Chair, Council of Experts

Topics

- The Monograph Today
- Performance Based Monographs (PBMs)
- Biologics—Horizontal Standards
- Summary
- References
Drug Product Monographs and General Chapters

A PBM can include:
- Specified tests
  - Identification, Assay, others
- Specific acceptance criteria
  - 97%-103%, NMT 0.1%, others
- Criteria-based procedures with:
  - Procedure Performance Measures (Precision, accuracy, others)
  - Procedure Performance Acceptance Criteria (% RSD, Bias, $R^2$, others)
PPMs and PPACs

- **USP General Chapter Validation of Compendial Procedures <1225>** defines the critical validation parameters necessary to validate a procedure.
- Pre-set criteria assure that an acceptable procedure will reliably assess whether an article meets acceptance criteria of its Tests.
- USP now terms these criteria as *Procedure Performance Measures* (PPM) and the *Procedure Performance Acceptance Criteria* (PPAC).
- PPM and PPAC may be used to determine suitability of multiple acceptable procedures.

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**Glutathione Example: Assay**

- **ASSAY**
- **Standard solution:** USP Glutathione RS in an appropriate diluent [Note: base determination may be substituted where appropriate]
- **Sample solution:** Glutathione in an appropriate diluent [Note: base determination may be substituted where appropriate]
- **Analytical System:** Use a procedure validated as described in USP *General Procedure for Procedure Performance Measures (PPM)* and the *Procedure Performance Acceptance Criteria (PPAC)*
- **Suitability:** Use the following calculations to determine the suitability of the procedure:
  - **Acceptance criteria:** 97.0% - 103.0% of USP Glutathione RS
Biologics: Horizontal Standards

Public

First Entry

- Safety
- Efficacy
- Quality (Control Specifications)
- Private

Biologics

- Harmonize horizontal standards
- These can include procedures with reference materials
- Monographs/PBMs come later

Summary

- Performance Based Monographs: Chemical Drugs
  - Agree on Tests
  - Agree on acceptance criteria
  - Allow different procedures
  - Designate one for compliance purposes if necessary

- Biologics
  - Harmonize horizontal standards
  - Monographs/PBMs come later
References


Thank You
Japanese Pharmacopoeia

Toru KAWANISHI
Head of Division of Drugs, National Institute of Health Sciences, & Chair of Expert Committee in PMDA

EDQM International Conference, 14th October, 2010

Outline of the Presentation

• History of JP
• Legal Status of JP
• Council / Expert Committee and JP Establishing Process
• Introduction of JP 16
• What is the next?
History of JP

• First published on June 25, 1886
• and Implemented from July 1, 1887
Legal Status of JP


Article 41, Paragraph 1
- To standardize and control the properties and quality of drugs, the MHLW shall establish and publish the Japanese Pharmacopoeia (JP), after hearing the opinion of the Pharmaceutical Affairs Food Sanitation Council (PAFSC).

Council Committee in MHLW and Expert Committees in PMDA on JP

<MHLW>
JP Committee under the Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

<PMDA>
15 Expert Committees, 1 sub-Committee, 3 Working Groups
Membership
- experts from National Institutes, Universities, etc.
- representatives from industry associations & other interested parties
Frequency
- every two months
**System of Establishing JP**

**MHLW, JP Committee / PAFSC**
- Basic Policies
- Determination of Drugs to be listed in JP

**PMDA**
- Company’s Draft
- Secretariat’s Draft
- Expert Committees
  - Review
- JP Draft

**MHLW, JP Committee / PAFSC**
- Adoption and Promulgation of JP
- Publication of JP (English Translation)

**Organization of JP Expert Committees**

**Expert Committee**
- Com. on Chemicals (1), (2)
- Com. on Antibiotics
- Com. on Biologicals
- Com. on Crude Drugs (B)
- Com. on Crude Drugs (A)
- Com. on Excipients
- Com. on Drug Formulation
- Com. on Physicochemical Methods
- Com. on Physical Methods
- Com. on Biological Methods
- Com. on Nomenclature for pharmaceuticals
- Com. on International Harmonization
- Com. on Pharmaceutical Water
- Com. on Reference Standards

**Sub-expert Com.**
- Dissolution WG
- Inhalation WG
- Chromatography WG
- Aseptic process WG
JP16: Schedule to the Notification

- Submission of the final draft from the PMDA to the MHLW at the last of August, 2010
- Adoption of the draft by JP committee in the Pharmaceutical Affairs and Food Sanitation Council in September, 2010
- Public comment by the MHLW in October, 2010
- Notification at the last of March, 2011

Main Policies on Preparation of JP16

- Complete entries of all drugs important in healthcare and medical treatments
- Active introduction of up-to-date Science and Technology
- Promotion of international harmonization
- Prompt partial revisions as required and smooth application based on government policies
- Ensuring transparency of the revision process and widespread application of JP to the public
Increased Numbers of Official Monographs on Drugs in JP

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Key points in revisions in JP16

- Wholly revision of “General Rules for Preparations”
- Revision of General Notices, Monographs and General Information on pharmaceutical waters.
- Change of “component determination tests” to “assays” in Monographs of Crude Drugs
- Revision of Names of Reagents and Test Solutions
- Revision of dissolution tests in Monographs of JP Preparations
**Basic Concept on the revision of "General Rules for Preparations"**

- General Rules for Preparations
  - (1) classify preparations commonly used for medical treatments,
  - (2) give their definitions,
  - (3) present manufacturing procedures, tests, container and storage, etc. to insure the quality.
- Revision should be carried out in order to answer the current medical needs, by means of incorporating the new technologies and dosage forms, considering international harmonization.
- The General Rules for Preparations is the fundamental rules for pharmaceuticals, including the newly developed ones, the generics, and OTC drugs.

**Major changes in the revised General Rules for Preparations**

- Dosage forms are classified first by the administration route and/or application sites, second by the forms, third by functions, and characteristics of the preparations.
- Independent categories of Crude Drugs (herbal drugs and/or drugs for traditional chinese medicine)
- 28 dosage forms → 71 dosage forms
- Change of definition on granules and powders
- Creams are separated from Ointments
- General Notices refer to the definition, typical manufacturing procedures, the characteristics of individual pharmaceutical preparations, their corresponding tests, container and storage, etc.
Dosage Forms listed in “the General Rules for Preparations” in the JP 16

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### Monographs on Pharmaceutical Waters

**JP15**
- Water
- Purified Water
- Sterile Purified Water
- Water for Injection

**JP16**
- Water
- Purified Water
- Sterile Purified Water
- Water for Injection

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**JP15**
- Water
- Purified Water
- Sterile Purified Water
- Water for Injection

**JP16**
- Water
- Purified Water
- Sterile Purified Water
- Water for Injection
Purity tests of Pharmaceutical Waters

**JP15**
- Purified Water
  - Sterile Purified Water
  - Water for Injection
- (1) Acidity or alkalinity
- (2) Chloride
- (3) Sulfate
- (4) Nitrogen from nitrate
- (5) Nitrogen from nitrite
- (6) Ammonium
- (7) Heavy metals
- (8) KMnO$_4$-reducing substances
- (9) Residue on evaporation

**JP16**
- Purified Water
  - Sterile Water for Injection
- (1) Conductivity
- (2) Total Organic Carbon
- Purified Water in Containers
  - Sterile Purified Water in Containers
  - Sterile Water for Injection in Containers
- (1) Conductivity
- (2) KMnO$_4$-reducing substances

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What is the next?

- Continue to follow the main policies in preparation of JP16

Specifically,
- Prompt publication of JP English Edition
- Further improvement of the JP Home Page - to more informative for users -
- Follow-up the revision of “General Rules for Preparations” in JP16: General quality tests for preparations would be newly set, as follows:
  - Release test from transdermal preparations
  - Release test from suppository
  - Release test from implants
  - etc.
- Revision about Containers and storage
Thank you for your attention !!

(http://www.std.pmda.go.jp/jpPUB/index_e.html)

“You can have freely access to JP by opening this HP !! ”
INDIAN PHARMACOPOEIA PERSPECTIVES

Current and new issues concerning global markets and the quality of medicines: challenges and opportunities

14 October 2010

Dr G. N. Singh
Secretary-cum-Scientific Director
Indian Pharmacopoeia Commission
• The Indian Pharmacopoeia Commission is the Standards Setting Institution for Drugs in India

• It is an autonomous body under the Ministry of Health & Family Welfare, Govt. of India, New Delhi

Indian Pharmacopoeia Commission

Vision
To promote the highest standards of drugs for use in humans and animals within practical limits of the technologies available for manufacturing and analysis

Mission
To promote public health in India by bringing out authoritative and officially accepted standards for quality of drugs including APIs, excipients and dosage forms, used by health professionals, patients and consumers
### Mandates of the Commission

- Publication of Indian Pharmacopoeia, the book of standards for Drugs in India
- Bringing out the National Formulary of India, the reference book for healthcare professionals
- Providing IP Reference Substances
- Nodal agency for establishing national/international collaboration with similarly placed bodies

### Industry Perspective

- **Global ranking-**
  - 3rd - Volume
  - 14th - Value
- **India is a recognized for supplying quality medicines**
  - Anti TB segment
  - Antiretrovirals
  - Vaccines
  - Herbal drugs
- **Manufacturing Capability for conventional and current drugs delivery systems**
  - 60,000 Formulations in 60 categories
## Indian Strength

- Contract research and manufacturing (CRAM) sector is growing at 18%
- A company moving R&D to India could save cost as much as 30% to 50%
- Thus, Indian companies have capability to produce pharmaceuticals
  - less than half of what it costs overseas
  - conduct clinical trials at less than one tenth of US costs
  - conduct research at less than one eighth of what it cost abroad

## Global Acceptance


The Organization for Economic Co-operation and Development (OECD) has forecasted the Indian Economy to grow 8.6% this year
Government Initiatives

- Independent Standards Setting Institution of drugs
- Transparent and Accountable Regulatory System
- Trained and Talented Manpower
- Special Economic Zones for Pharma Sector

Highlights of IP 2010 (6th Edition)

- Total monographs ~2000
- New monographs – 287
- Updated monographs > 600
- Harmonized the monographs on:

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<td>06</td>
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<td>Excipients</td>
<td>31</td>
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Most of existing assay and related substance tests are updated by liquid chromatography

Focus on Liposomal technology

Special emphasis:
- Antimalarials
- Antiretroviral (drugs for AIDS and Swine Flu)
- Anticancer drugs
- Excipients
- Anticoagulant (Heparin)
- Appendices

On user friendly format

Updated General Chapter
- Microbiology
  Effectiveness of antimicrobial preservatives, microbial contamination in pharmaceutical preparation and identification of *Shigella boydii* strain, first time has been introduced
- Biotechnology
- Vaccines & Sera
- Chemicals and Reagents
- Analytical Methods
# National Formulary of India 2010

- To Promote rational use of medicines
- Contains 350 monographs of medicines
- Special focus on Interactions
  - Drug – Drug
  - Drug – Food
  - Drug – Contraceptive
  - Drug – Alcohol
- Emphasis on medicines safety during pregnancy
- Focus on Therapeutic Drug Monitoring, Dose calculation for renal impairment etc.

## Challenges

- Acquisition of
  - Monographs
  - Candidate materials (RS)
  - Training
    - Trained Manpower
    - Application by stakeholders
  - Surveillance
Concluding Remarks

- Sharing of information on
  - Monographs
  - Reference Substances
  - Training

Harmonization of standards: improve the quality and reduce the cost of medicines

Thank You
Quality of medicines in globalised word: Dreams and reality
Internacional Conference, EDQM – Council of Europe
14 – 15 October 2010, Prague, Czech Republic

National Health Surveillance Agency (ANVISA) and the challenges for the construction of MERCOSUR Pharmacopoeia

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Brazilian Health Surveillance System

- Part of the Unified Health System
- Formed by the tree levels of government (federal, state, and municipal)
- Co-ordinated by ANVISA
- Articulated and decentralised activities

Source: IBGE 2009
Unified Health System (SUS)

- Federal Constitution of 1988: “health is a right of all and a duty of the State”.
- **SUS** legal principles: universal access, full assistance, equality, community participation, political-administrative decentralisation with a single direction at each government level.
- **SUS**: one of the largest public health systems worldwide, including from a simple ambulatory health care up to organ transplantation. This ensures full, universal and free access to the whole population in the country (over 190 million people).

Brazilian Health Surveillance Agency (ANVISA)

- State company under a special regimen: administrative independence and financial autonomy
  - officially related – not subordinated – to the Ministry of Health;
  - annual signature of the Management Contract (indicators and goals);
  - stability of its directors (mandate);
  - technical criteria for decision making;
  - predictability and transparency of the regulatory process.
- Co-ordinates the Brazilian Health Surveillance System
- Regulates products and services subjected to health surveillance
- Since its creation (1999), its competences included “TO PROMOTE THE PERIODICAL PHARMACOPOEIA REVIEW AND UPDATE”.

Brazilian Regulation System

- Food
- Drugs
- Sanitising products
- Tobacco
- Toxicology
- Health services
- Cosmetics
- Health products
- Laboratories
- Blood, tissues and organs
- Advertising
- Ports, airports and borders
- International
- SNVS Co-ordination

Brazilian Pharmaceutical Market

- 450 drug industries
- 2,000 drug distributors
- 65,000 private drug stores
- 2.5 billion drug units / year

Brazil is now the tenth largest pharmaceutical consumer market worldwide – US$14.5 billion in sales. Branded and OTC drug sales accounted for 57% and 27%, respectively, of total sales in 2009. The generic drugs have a significantly increased participation in total sales, and accounted for the remaining 16%. (Source: IMS Health, 2010.)
**Brazilian Pharmacopoeia**

**Mission**
To promote the population's health protection, establishing quality requirements – specifications, limits and procedures to health strategic inputs, particularly drugs, supporting health regulation actions in this area, and inducing the Brazilian technical development.

**Vision**
To be a technical-scientific reference in Brazil and acknowledged internationally.

**Operation**
- Brazilian Pharmacopoeia Commission – CFB – 17 members;
- Theme technical committees (18) – 130 members;
- Brazilian Pharmacopoeia Co-ordination (COFAR – ANVISA).

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**Foreign Relations**

**RDC Nº 37/2009 – ANVISA: admissibility of pharmacopoeias**

- **Article 1.** In the absence of an official monograph of raw material, dosage forms, correlates, and general methods in the Brazilian Pharmacopoeia, the official monograph of the latest edition of the following international compendia may be adopted:

- **Article 2.** In the absence of chemical reference substances certified by the Brazilian Pharmacopoeia, the CRS certified by the Pharmacopoeias referred to in Article 1 may be used.
Foreign Relations
Brazil – Argentina → MERCOSUL

- Brazilian Health Surveillance Agency (ANVISA) and Argentine Administration of Drug, Food and Medical Technology (ANMAT): important step towards exchange in the area of drugs and APIs, in October 2007;
- the health authorities signed an understanding memorandum for the exchange of experiences and knowledge on Pharmacopoeia, in order to develop and increase the list of Chemical Reference Substances;
- the subject was included in the Brazil / Argentina Integration and Co-operation Mechanism, coordinated by the presidents of those countries, who strongly recommended ANVISA and ANMAT to continue the cooperation project, aiming at strengthening Brazil and Argentina Pharmacopoeias;
- start of work on technical cooperation between Brazil and Argentina Pharmacopoeias.

OBJECTIVES

- Seek technical, methodological and procedure convergences;
- Strengthen the pharmacopoeias of these countries through the effective bilateral co-operation and the exchange of technological knowledge to increase the local production of reference chemical substances and, as a result, contribute towards reducing the technological dependence on RCS imports, which reflects on cost reduction for Brazilian companies;
- Identify and characterise the APIs initially produced in each country, as well as their related substances;
- Promote the Brazilian production of APIs and, at the same time, work on the development of Reference Substances for both countries;
- Promote the development of pharmacopoeia subject in the context of MERCOSUR.
Perspectives

- The MERCOSUR Common Market Group (GMC) recommended SGT11 to work on a strategy to create the MERCOSUR Pharmacopoeia;
- Joint project for the institutional strengthening of health authorities in the pharmacopoeia area for the development of RCS, thus contributing towards the future creation of the block’s Pharmacopoeia;
- Promotion of standards/requirements needed to API good quality, high safety and low cost of API acquisition; Brazil becomes a respectful buyer;
- Reduction of Brazilian vulnerability;
- Development of the Brazilian API production;
- Strengthening of MERCOSUR block (Argentina, Brazil, Paraguay, and Uruguay) and Latin American pharmacopoeias.

Conclusions

MERCOSUR Pharmacopoeia may lead to less dependence on imports of chemical reference standards from other pharmacopoeias, resulting in less cost when acquiring those substances, with a positive impact on the State Parties, in addition to being a priceless instrument for regulating the quality of pharmaceutical-chemical and pharmaceutical products, as well as promoting scientific and technologic development. In summary, it contributes towards strengthening the region’s economy and increasing the population’s quality of life.
Brazilian Pharmacopoeia

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