MHLW/PMDA-USP Workshop “Role of Quality in Pharmaceuticals “

June 17, 2021

New performance tests for formulations in Japanese Pharmacopoeia

Hiroyuki Yoshida

Drug Division, National Institute of Health Sciences

This presentation includes speaker’s personal opinion.

Contents

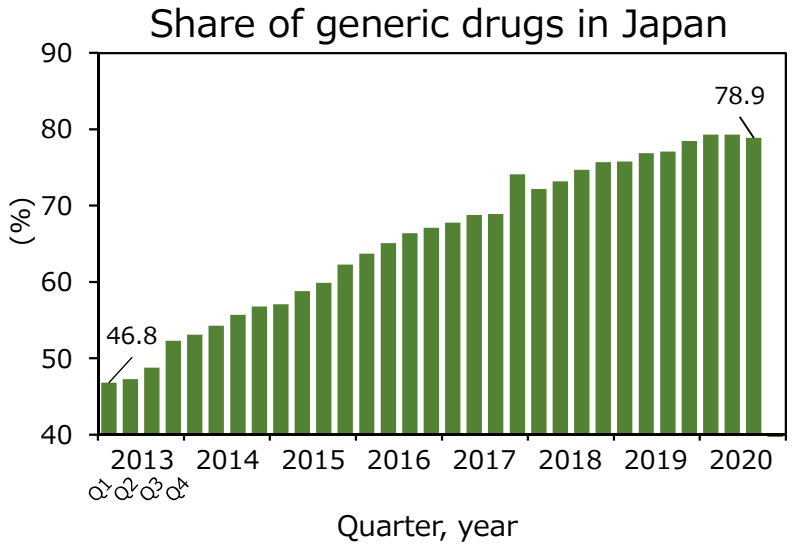
1. Role and setting of performance tests
2. New performance tests in JP
3. Future issues and conclusions

Role of performance tests for formulations in pharmacopoeia

- Safety and efficacy are assured by the product quality and consistency.
- Specifications (Test procedure and acceptance criteria) is one of one part of a total control strategy ensure product quality and consistency.
- Performance tests are specification tests to be set depending on the properties of drug products and drug substances.
- Wherever they are appropriate, pharmacopoeial procedures should be utilized (ICH-Q6A).

- Example of universal tests/criteria
  (Description, Identification, Assay, Impurities, etc.)
- Example of specific tests/criteria (e.g., Solid oral drug products)
  (Dissolution, Disintegration, Hardness/friability, Uniformity of dosage units, Water content, etc.)

Importance of performance tests



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with modification

- Share of generic drug products in Japan has been increasing in this decade.
- A wide variety of dosage forms and administration route are developed and listed in JP.

  No. of dosage forms in JP: 21 (JP15)
  63 (JP16)
  67 (~JP17-S2)

➢ Formulation performance tests play an important role to assure the consistency of bioavailability, bioequivalence, or interchangeability of multisource drug products.

Dosage forms and Performance tests in JP

- The Monographs for Preparations section re-categorized a wide variety of dosage forms in JP16.

Major category		Middle, Small category
• administration routes • application sites (e.g., Preparations for Oral Administration)	⇨	• forms (e.g., tablets, capsules) • Functions and characteristics (e.g., OD, chewable)

- Critical formulation properties for the function and characteristics are shown by citing the appropriate Performance tests in each dosage form.
(e.g., “Unless otherwise specified, Tablets meet the requirements of Dissolution Test <6.10> or Disintegration Test <6.09>.”)

- If appropriate performance tests are not specified in JP, formulation properties are described in Monographs for Preparations as follow:
“ xxx (dosage forms) have an appropriate yyy (formulation properties)”

Examples of formulation properties in Monograph for Preparations

Preparation type	Formulation properties	
	citing the General Tests, Processes and Apparatus	**specified as "■■(dosage forms) have an appropriate ●●"**
Tablets, Capsules	・Uniformity of Dosage Units ・Dissolution (except Effervescent Tablets and Soluble Tablets. If difficult, Disintegration should be specified)	・Disintegration (for Orally Disintegrating Tablets/ Orodispersible Tablets)
Ophthalmic Ointments	・Sterility ・Metal Particles	・Viscosity
Nasal preparations		・Uniformity of delivered dose（for metered-dose type preparations）

Contents of General Tests, Processes and Apparatus in JP

1. Chemical Methods
2. Physical Methods
3. Powder Property Determinations
4. Biological Tests/Biochemical Tests/Microbial Tests
5. Tests for Crude Drugs

6. Tests for Preparations

7. Tests for Containers and Packing Materials
9. Reference Standards; Standard Solutions; Reagents, Test Solutions; Measuring Instruments, Appliances, etc.

Organization of JP Expert Committees

- Standing Committee
  - Com. on
    - Chemicals (1) and (2)
    - Antibiotics
    - Biologicals
    - Crude Drugs (A) and (B)
    - Excipients
    - Nomenclature for pharmaceuticals,
    - Reference Standards For Monographs
    - **Drug Formulation**
      - 4 WGs
        - ・Dissolution
        - ・Inhalations
        - ・Packaging integrity
        - ・Nasal preparations
  - Physical Methods
    - Biological Methods
    - Physico-Chemical Methods
  - International Harmonization
- Sub-Standing Com.
- Sub-Com. on Manufacturing Process-related Matters

Contents

General Tests for Preparations in JP

6. Tests for Preparations		Revision history (2016~)
6.01	Test for Metal Particles in Ophthalmic Ointments	
6.02	Uniformity of Dosage Units	Revision (JP17, S1 to JP17)
6.03	Particle Size Distribution Test for Preparations	
6.04	Test for Acid-neutralizing Capacity of Gastrointestinal Medicines	Revision (S1 to JP17)
6.05	Test for Extractable Volume of Parenteral Preparations	Revision (JP17)
6.06	Foreign Insoluble Matter Test for Injections	Revision (JP17)
6.07	Insoluble Particulate Matter Test for Injections	
6.08	Insoluble Particulate Matter Test for Ophthalmic Solutions	
6.09	Disintegration Test	
6.10	Dissolution Test	
6.11	Foreign Insoluble Matter Test for Ophthalmic Liquids and Solutions	
6.12	Methods of Adhesion Testing	Newly added (JP17)
6.13	Release Test for Preparations for Cutaneous Application	Newly added (JP17)
6.14	Uniformity of Delivered Dose for Inhalations	Newly added (S1 to JP17)
6.15	Aerodynamic Particle Size Measurement for Inhalations	Newly added (S1 to JP17)
6.16	Rheological Measurements for Semisolid Preparations	Newly added (S2 to JP17)
6.17	Insoluble Particulate Matter Test for Therapeutic Protein Injections	Newly added (S2 to JP17)

Red letter: Harmonized in PDG(Pharmacopoeial Discussion Group)

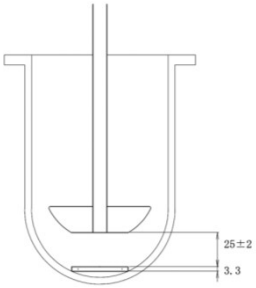
S#: Supplement No.

Newly listed testing (1): For Cutaneous application

6.12 Methods of Adhesion Testing

- These are testing methods to measure the adhesion of patches.
- The methods include peel adhesion testing, inclined ball tack testing, rolling ball tack testing, and probe tack testing.
- Although adhesion is not directly related to the efficacy and safety, constant adhesion between product lots should be maintained in each product.

6.13 Release Test for Preparations for Cutaneous Application



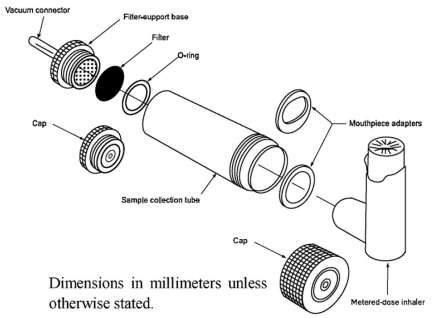
Paddle over disk apparatus

- This test describes the method to measure release profiles of active ingredients from preparations for cutaneous application.
- The methods include Paddle over disk method, Cylinder method, and Vertical diffusion cell method.
- Since the relation between efficacy and release profile depends on each characteristic of these preparations, this release test is an effective method for a quality control of each preparation.

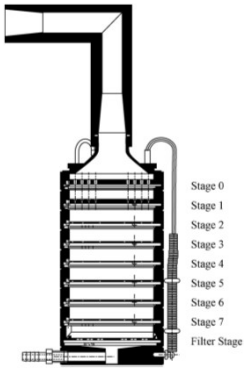
Newly listed testing (2): For Inhalations

6.14 Uniformity of Delivered Dose for Inhalations
6.15 Aerodynamic Particle Size Measurement for Inhalations

- These are the methods to confirm inhalers (except inhalation solution used with a nebulizer) have appropriate delivered dose uniformity and aerodynamic particle size distribution.
- Test procedures and apparatuses are similar to those in EP and USP.
- Harmonization work in PDG was withdrawn in 2017 because several issues such as different way of thinking about criteria were not resolved.
- Uniformity of Delivered Dose only is in working state for harmonization with EP.



An apparatus for 6.14

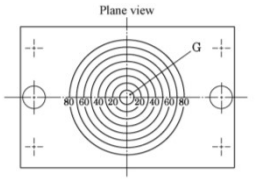


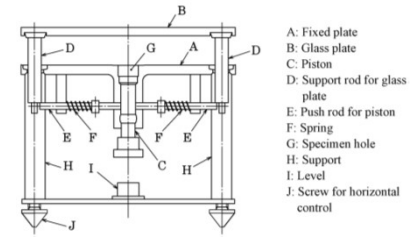
Apparatus 2 for 6.15

Newly listed testing (3): For Semisolid preparations

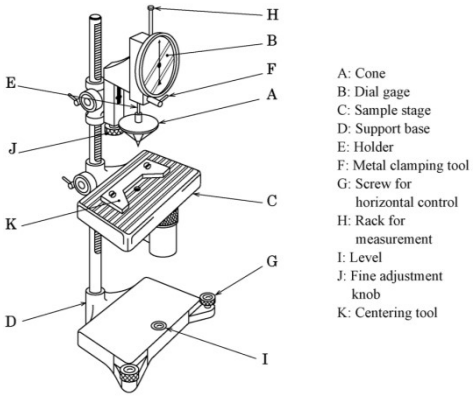
6.16 Rheological Measurements for Semisolid Preparations

- These are methods to measure fluidity and deformation of semisolid preparations for Oro-mucosal Application, Ophthalmic Ointments, Ointments, Creams and Gels, etc.
- There are two methods, spreadability test and penetrometry.
- These methods mainly aim to evaluate the physicochemical stability (structural stability) of a semi-solid preparation, so, it should be carefully handled not to break the structure of the semi-solid preparation while sampling.
- The measurement after breaking structure of a semi-solid preparation can provide data related to the usability of the preparations.





Example of spread meter



Example of penetrometer

Newly listed testing (4): For Therapeutic Protein Injections

6.17 Insoluble Particulate Matter Test for Therapeutic Protein Injections

- This test is applied to the injections whose active ingredients are peptides, proteins or their derivatives.
- The procedure uses the Method 1 (Light Obscuration Particle Count Test) in the “6.07 Insoluble Particulate Matter Test for Injections.
- The following points are the major modifications.
  - Procedures to avoid the generation of aggregates and bubbles due to improper operation of protein products are described.
  - No need to gather 10 or more units for small-volume parenteral (< 25 mL).
  - Measurement volume of 1 ~ 5 mL is allowed for the measurement. Volume of 0.2 ~ 1 mL is also allowed, if the validity is confirmed.

volume <<

- The above points in the “6.07 Insoluble Particulate Matter Test for Injections” are under discussion in the current PDG maintenance work (Q-09 / Particulate Contamination).

General Information on Drug formulation

- Test methods in the General information in JP can be used for ensuring the quality of drug products but not judge the conformity to the Japanese Pharmacopoeia.

G6 Drug Formulation	Revision history (2016~)
Tablet Friability Test	~~Revision (JP17)~~
Standard Procedure for Mechanical Calibration of Dissolution Apparatus	Newly added (JP17)
Aerodynamic Particle Size Measurement for Inhalations by Glass Impingers	Newly added (S1 to JP17)
Tablet Hardness Determinations	Addition scheduled (JP18)

Red letter: Harmonized in PDG(Pharmacopoeial Discussion Group)

S#: Supplement No.

Other recent works of Expert Com. on Drug formulation

- Addition of new dosage forms to the Monographs for Preparations
  - 1.8. Films for Oral Administration
  - 1.8.1.Orally Disintegrating Films
  - 3.1.4. Liposome Injections

- Revision of the Monographs for Preparations
  - 9.1. Suppositories for Rectal Application
  - 10.2. Suppositories for Vaginal Use

Appropriate drug release from suppositories for rectal application and vaginal use with lipophilic bases can be evaluated by meltability (Method 2 under Melting Point Determination <2.60>) instead of active substance release tests.

- Drafting some of the General Information on Containers and Package.
  - Leak tests for packaging of sterile products (G7-~~4~~5-180)
  - Packaging integrity evaluation of sterile products (G7-~~5~~4-180)

Contents

Domestic issues in JP Expert Com. on Drug Formulation

- Revision of the General Rules for Preparations according to the progress in formulation technology.
- New addition of performance test to evaluate “appropriate ●● (formulation properties)” specified in the Monographs for Preparations.
- Drafting dissolution test methods in the new Official Monograph (Dissolution WG)

Harmonization related issues in JP Expert Com. on Drug Formulation

- Maintenance of harmonized tests in PDG (Disintegration, Tablet Friability, Extractable Volume, Particulate contamination).
- Revision of Test for Glass Containers for Injections <7.01> to fill in the gap between JP and EP/USP.
- Harmonization of the Uniformity of Delivered Dose for Inhalations/Nasal preparations between EP and JP (Inhalation WG, Nasal preparation WG).

Conclusion

- ✓ Performance tests for formulations are intended to assure efficacy, safety, and quality of pharmaceutical products by evaluating formulation properties specified in each dosage forms.
- ✓ For the efficient addition/revision of dosage forms and functions to the Monograph for Preparations in JP, careful discussion about setting appropriate performance tests considering universal use, reproducibility, and international conformity is expected.

Thank you for your kind attention!