PQRI-FDA Workshop on Process Drift: Detection, Measurement and Control in the Manufacturer of Pharmaceuticals

Topical Semisolid Dosage Forms

Product Quality and Product Performance Testing

Clarence T. Ueda, Pharm.D., Ph.D.
University of Nebraska Medical Center
College of Pharmacy
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Background

In 2004, USP Biopharmaceutics Expert Committee established Topical Products Performance Tests Advisory Panel.

Panel Members

Kris Derdzinski, Ph.D.                        Kailas Thakker, Ph.D.
Gary Ewing, Ph.D.                            Avi Yacobi, Ph.D.
Gordon Flynn, Ph.D.                           Margareth Marques, Ph.D.
Howard Maibach, M.D.                          Vinod Shah, Ph.D.
J. Howard Rytting, Ph.D.*                    Clarence Ueda, Pharm.D., Ph.D.
Steve Shaw

* Deceased
USP Topical Products Performance Tests Advisory Panel

Primary Objective/Guiding Principle

“Provide measures for assuring optimal product quality of manufactured topical drug products.”
USP Topical Products Performance Tests Advisory Panel

Goals

• Identify and define essential product characteristics critical to the dosage form and drug product performance.

• Review and evaluate drug release tests used by topical drug product manufacturers.

• Identify and evaluate apparatus for use for in vitro drug release testing.

• Recommend Performance Verification Test (PVT) Methods

* Note: Panel considered all topically applied drug products including transdermal patches.
The quality of a finished drug product is inextricably linked to:

a. Quality of the ingredients that go into the manufacture of the product,
b. Quality of the ingredients and components within the product, and
c. Performance of the finished drug product, i.e., drug release.

Thus, product quality may be assessed in terms of:

- Quality of the physicochemical make-up of the finished product *and*
- Physical performance of the finished product
Product quality testing separated into two separate groups of tests:

- Product Quality Tests
- Product Performance Tests
Background (Cont.)

Work of the Advisory Panel resulted in the preparation and submission of the following documents to the 2005-2010 USP Biopharmaceutics Expert Committee and to USP Staff.


Topical Drug Products - Product Quality Tests

Three Test Categories for Semisolids:

I. Universal Tests

II. Specific Tests (as appropriate/applicable)

III. Specific Tests for Topical Semisolid Products
I. Product Quality Testing - Universal Tests

- Tests that assess applicable general product quality attributes.
- See ICH Guidance Q6A - Specifications; Test Procedures and Acceptance Criteria; Chemical Substances - www.ich.org

A. Description - Qualitative description of the drug product. Acceptance criteria include final appearance of the finished dosage form. Visual examination should identify changes in color, separation(s), crystallization, etc. that are specific to the drug product. The description should specify the content or label claim of the product.

B. Identification - Identification tests are discussed in *USP General Notices and Requirements, 5.40*. Identification tests (e.g., IR, NIR, Raman spectroscopy, chromatography) establish the identity of and should be specific for the drug(s) present in the product.
C. **Assay** - A specific and stability-indicating test should be used to determine the strength (content) of the drug product.

D. **Impurities** - Process impurities, synthetic by-products, residual solvents, elemental impurities and other inorganic and organic impurities used in the manufacture of the drug product, and impurities arising from degradation of the drug substance and during the manufacturing process of the drug product should be assessed and controlled.
II. Product Quality Testing - Specific Tests

• Drug product/formulation specific tests that should be considered on a case-by-case basis (as appropriate/applicable).
• Testing performed at time of batch release and for shelf-life monitoring.

A. Physicochemical Properties - e.g., pH <791>; Specific gravity <841>; Apparent viscosity <912>

B. Uniformity of Dosage Unit (for dosage forms packaged in single-unit containers) - Uniformity of Dosage Units <905>

C. Water Content - Water Determination <921>

D. Microbial Limits - Microbiological Examination of Nonsterile Products <61>,<62> and <1111>

E. Antimicrobial Preservative Content - Antimicrobial Effective Testing <51>
II. Product Quality Testing - Specific Tests (Cont.)

F. Antioxidant Preservative Content - New

G. Sterility - <71>

H. pH - <791>

I. Particulate Size - New; Examples:
   - Particle size of API
   - Alteration of API crystalline form (crystal type or habit)
   - Aggregation of API

J. Specific Tests for Ophthalmic Dosage Forms
   - Sterility Tests <71>
   - Ophthalmic Ointments <771> (e.g., Added substances, leakage, metal particles)
III. Product Quality Testing - Topical Semisolid Drug Products

A. Visual Inspection - Physical Appearance

**Phase Separation**

**Lumps and Phase Separation**

*Photographs courtesy of Drs. Satish Asotra and Avi Yacobi, Taro Pharmaceuticals, Inc.*
III. Product Quality Tests - Specific Tests for Topical Semisolid Drug Products

A. Apparent Viscosity - New

1. Measurement procedures developed as outlined in <912> - Non-Newtonian Rheology.

2. Testing performed at time of batch-release and initially at designated stability time points to set specifications for batch-to-batch and shelf-life monitoring.

3. For some products, may be desirable to have apparent viscosity specifications for more than one set of conditions (e.g., bulk in-process stage, final packaged product, different temperatures)
B. Uniformity in Containers - New

1. Products Packaged in Tubes
   a. Multiple-dose Products containing 5 Grams or more

Procedure
1. Expose product in tube.
2. Visually inspect product (e.g., phase separation, change in physical appearance, texture and other properties described in Product Description Test.
3. Remove sample of product from top, middle and bottom portions of the tube and assay each for API.
4. Evaluate test results according to Acceptance Criteria.
5. Assay results within range of 90-110% of product label claim and RSD not more than 6%, or as specified in the product specification or compendial monograph.
B. **Uniformity in Containers** (Cont.)

1. Products Packaged in Tubes
   a. Multiple-dose Products containing 5 Grams or more
   b. Multiple-dose Products containing less than 5 Grams

**Procedure**

1. Expose product in tube.
2. Visually inspect product.
3. Remove sample of product from top and bottom portions of the tube and assay each for API.
4. Evaluate test results according to *Acceptance Criteria*.
5. Assay results should be within range of 90-110% of product label claim, or specified in product specification or compendial monograph.
2. Products Packaged in Containers Other Than Tubes
   a. Other samplings methods are acceptable
   b. Example: Jar

**Procedure**
1. Select a suitable syringe that will reach the bottom of the container.
2. Remove plunger and cut off bottom of syringe barrel.
3. Sample from one side of the container by slowly inserting the syringe barrel into the container until it reaches the bottom.
4. Twist the syringe barrel containing the sample core and remove the barrel.
5. Insert the syringe plunger and carefully extrude three equal portions representing top, middle and bottom of the container.
6. Assay and evaluate results as with Tubes.
Topical Drug Products – Product Performance Tests

I. In Vitro Semisolid Drug Product Drug Release Performance Tests

A. Vertical Diffusion Cell (VDC) Test Method

1. Methods and Procedures developed for creams, ointments, and gels.
2. Methods and procedures validated through a Collaborative Study.
3. Data analysis methods and Acceptance Criteria established.

* photograph and diagram courtesy of Hanson Research
Topical Drug Products – Product Performance Tests

I. In Vitro Semisolid Drug Product Drug Release Performance Tests

A. Vertical Diffusion Cell (VDC) Test Method

B. **Other Semisolid Drug Product Drug Release Test Methods**

   TBA
Summary and Conclusion

The quality of a topical semisolid drug product may be assessed by:

a. Examining the physical appearance of the finished drug product,
b. Testing the physicochemical make-up of the finished drug product, and
c. Testing the *in vitro* drug release, i.e., ‘performance’, of the finished drug product.

Quality testing of semisolid drug products is a ‘work in progress’. The work and recommendations of the 2005-2010 USP Topical Products Performance Tests Advisory Panel should be viewed as the ‘starting-off’ point for the continuous quality improvement of topical semisolid drug products.

When appropriately performed, product quality and product performance tests can be useful in detecting and addressing issues related to ‘process drift’ of manufactured semisolid topical products and avoiding product performance failure.
Thank you