SCIENTIFIC APPROACHES TO ASSESS QUALITY AND PERFORMANCE OF TOPICAL PRODUCTS

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Product Quality
Product Performance Tests
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USP Spalding Auditorium, Rockville, MD
USP Standard of Quality

USP – The Standard of Quality

USP Standards of Quality:

- Utilized Globally by many countries
- Developed and Developing Countries
USP Topical/Transdermal Performance Test Advisory Panel

- Kris Derdzinski, Ph.D.
- Gary Ewing, Ph.D.
- Gordon Flynn, Ph.D.
- Howard Maibach, M.D.
- J. Howard Rytting, Ph.D.*
- Steve Shaw

- Kailas Thakker, Ph.D.
- Avi Yacobi, Ph.D., M.Pharm.
- Margareth Marques, Ph.D.
- Vinod Shah, Ph.D.
- Clarence Ueda, Pharm.D., Ph.D (Chairperson)

- Initial Panel meeting – December 17, 2004

*Deceased
USP Topical/Transdermal Performance Test Advisory Panel

Goals

• Identify and define essential product characteristics critical to dosage form/drug product performance.
• Review and evaluate drug release tests used by topical/transdermal drug product manufacturers.
• Identify and evaluate apparatus for use for in vitro drug release testing.
• Investigate linking in vitro drug release testing to in vivo drug performance when applicable, or as appropriate.
• Recommend Performance Verification Test (PVT) Methods
USP Chapters <3> and <1724>


USP Chapter <3> ‘Product Quality Tests’ and
USP Chapter <725> ‘Product Performance Test’

“Background, Development and Rationale”

Drug products topically administered via the skin fall into two general categories, those applied for local action and those for systemic effects.

- Local actions products include creams, gels, ointments, pastes, suspensions, lotions, foams, sprays aerosols, and solutions.
- Systemic effect products typically include transdermal products.
Semisolid Products- Quality and Performance

Why Test for Quality of Semi-solid Products?

To provide assurances of batch-to-batch quality, reproducibility, reliability and performance throughout shelf life.

- Product quality tests - assay, identification, content uniformity, pH, microbial limits and minimum fill
- Product performance tests - to assess drug release from the finished dosage form
Semisolid Products- Quality

What is Quality of Semi-Solid Products?

- Product maintains its physical integrity throughout shelf life.
- Product keeps chemical & microbiological stability during shelf life.
- Container closure integrity/compatibility intact throughout shelf life.
Semisolid Products - Quality

Physical Integrity Test Parameters

- Visual separation vs chemical separation
- Color change
- pH
- Crystals
- Appearance - lumps, air, smell, etc.
- Viscosity
- Spreadability
Semisolid Products- Quality

- Physical Integrity Test Parameters
  - Visual Separation
    - Physical deterioration
    - Visible signs of separation - oil, water, etc.
Semisolid Products - Quality

- Chemical Stability
  - Assay/potency
  - Tube/container uniformity
  - Preservatives - assay/potency
  - Degradation products -
    - Generated during manufacturing processes
    - Shelf life
  - Impurities
    - API
    - Inactive ingredients
    - Product
Semisolid Products - Quality

**Microbiological Stability**

**Microbial Limit Test**
- Total Aerobic Microbial Count
- Total Yeast & Mold count
- Test for specified Microorganisms (*S. aureus* & *P. aeruginosa*)

**Preservative Effectiveness Testing**
- Testing at 100% and at lower specification limit to ensure product is preserved at in the specification range.
- Testing at the end of shelf life
Semisolid Products- Quality

Container closure incompatibilities
- Peeling: labels, lamination
- Leakage: vehicles, solvents
- Migration: actives, inactive materials
- Penetration: moisture, oxygen etc.
- Color change: due to instability, degradation, oxidation, etc.
- Adherence: container closure, tubes, etc.
- Package deformation: swelling, opening of crimp, bulges in the tube
There is now an official acceptance criteria for analytical tube uniformity testing.

This is now a requirement as described in chapter <3>.
Performance Test

Product Performance Test

- Drug dissolution (Solid dosage forms)

- In vitro drug release (Semisolid dosage forms)
Semisolid Products-Performance

In-vitro Release Testing

SUPAC requirements

- Required to demonstrate product sameness to the approved product:
  - Not needed for filing a new product
  - Change of structural forming ingredient(s)
  - Change of API (particle size for suspension products)
  - Change in the manufacturing process(es) and manufacturing sites
  - Other changes impacting product quality and efficacy.
Semisolid Products-Performance

FDA’s New Draft Guidance

Acyclovir Cream and Ointment
- Generic product approval based on:
  - Q1 analysis, qualitative similarity
  - Q2 analysis, quantitative similarity
  - Q3 (micro structure) in vitro test to demonstrate similarity to the approved product

Does this development offer an opportunity to reassess the potential use of in vitro release test for the evaluation of individual commercial batches of semisolid products in a similar way the dissolution test is used for oral products?
Semisolid Products- Performance

- In-vitro Release Testing
  - Good measure to ascertain performance of the product
    - Offers standard for comparing a semi-solid product manufactured across industry.
    - Monitors consistency of product manufactured.
    - May assist in the development of product.
    - Can provide an idea for bioequivalence performance of the product.
USP Standards and USP Products

To claim a product to be USP, all tests will need to be completed and standards are met. This applies globally.

For example, “Hydrocortisone Cream USP” will need to meet the new requirements of <3>.

These standards will apply to all products in the market and not limited to newly approved products; brand and generic.

The standards apply to all products produced for the US market and often they will apply to markets in which the products produced.
Conclusions

USP is The Standard of Quality utilized Globally by many countries.

Standards specified in <3> are reasonable and should be implemented for all products.

In vitro release test is a reasonable test that may be considered as a batch-to-batch uniformity test, same way as dissolution test.