The Matter of Medicine

Does Form Follow Function or Vice Versa?

May 24th, 2016
Rutgers University, New Jersey
Center for Dermal Research

Sam Raney, PhD
Scientific Lead for Topical & Transdermal Drug Products
Division of Therapeutic Performance
Office of Research & Standards
Office of Generic Drugs, U.S. Food and Drug Administration

Disclaimer

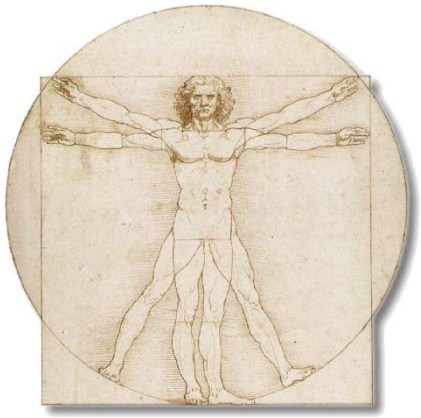
1. The information communicated in this presentation is my personal view and opinion.
2. The presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred.
3. The material presented in my slides is based upon information available in the public domain.
4. I do not have any financial interest or conflict of interest with any pharmaceutical companies.

Form Follows Function

*"It is the pervading law of all things organic and inorganic… that **form ever follows function**."*

- Louis Henry Sullivan, 1896
  (American architect)

- Concept attributed to Marcus Vitruvius Pollio's *De Architectura*
  (Ancient Roman architect & engineer)



Leonardo Da Vinci's Vitruvian Man

Prologue

- Specifications on semisolid drug products may encompass some common quality attributes:
  - Appearance
  - Viscosity
  - Particle size
  - pH
  - Component identity & assay tests, homogeneity, content uniformity, minimum fill, microbial tests, residual solvents, related compounds, etc.
- Are traditional measures of quality complete?
- How well are specification ranges justified?

Prologue

- Specifications on semisolid drug products may encompass some common quality attributes:
  - Appearance
  - Viscosity
  - Particle size
  - pH
  - Component identity & assay tests, homogeneity, content uniformity, minimum fill, microbial tests, residual solvents, related compounds, etc.
- Are traditional measures of quality complete?
- How well are specification ranges justified?

Prologue

- Is a Quality by Design (QbD) approach implemented consistently during product development?
- What role does quality risk management play to support process development and to identify control strategies to mitigate risk?
- How do we attain product and process understanding
  - Where semisolid complexity is adequately characterized
  - Where potential failure modes are adequately understood
  - Where the critical range of each quality attribute is adequately well- established in a relevant design space
  - Where quality attributes that might matter are adequately controlled
- Let us consider what may matter, and why…

Diffusion of Topical Compounds

Katz & Poulsen, 1971 (Fick's Law of Diffusion)

$$J = \frac{P \times D \times \Delta C}{l}$$

J = Flux (e.g. µg/cm^2/hour)
P = Partition Coefficient
D= Diffusion Coefficient
C = Concentration
l = Length of Travel

Qualities of Topical Dosage Forms

Inactive Ingredient Qualities

- What functions do inactive ingredients have in the drug product, individually and in combination?
- Can differences in inactive ingredient quality impact the physicochemistry, microstructure, functioning and/or robustness of the drug product?
- Can some inactive ingredients themselves penetrate skin and alter the structure and chemistry of the skin?
  - Alter the solubility of the active ingredient(s) in stratum corneum (SC) intercellular lipids
  - Alter the ordered structure of SC intercellular lipids
  - Impact diffusion of active and inactive ingredients through the SC
  - Influence partitioning, diffusion, other parameters

Qualities of Topical Dosage Forms

Penetration Enhancer (Modifier) Qualities

- Some "inactive" ingredients may significantly impact bioavailability
- Penetration modifiers can have contextually complex mechanisms of action
- Increase of drug solubility in a formulation can alter the amount of drug available for partitioning into the stratum corneum (SC), as well as other factors
- Solubility enhancement in the vehicle may increase bioavailability of a drug from a formulation and be interpreted as generalized penetration enhancement

Linking Quality to Clinical Performance

What qualities of a topical product influence:

- The composition of matter in the product
- The states of matter in the product
- The arrangement of matter in the product
- Drug diffusion within the dosage form
- Drug partitioning from the dosage form into the SC
- Alteration of skin structure and chemistry
- Drug diffusion within the skin itself
- Drug delivery & bioavailability at the target site
- Skin (de)hydration, irritation or damage
- Metamorphosis of the dosage form on the skin

Linking Complexity to Failure Modes

Consider a typical solution

- Simple solvent, single drug, fully dissolved
- Single phase drug product
- Robust to broad ranges of manufac. process variables
- Quality attributes like pH may be critical
- Failure modes do exist, but are relatively few
  - Simple composition of matter in the product
  - Simple state of matter in the product
  - Simple arrangement of matter in the product
  - Simple drug diffusion within the dosage form

Linking Complexity to Failure Modes

Consider a typical cream

- Immiscible mixture of several inactive ingredients
- Partially dissolved, partially dispersed drug(s)
- Multiple phases in the drug product
- Complex arrangement of matter
- Potentially complex/dynamic distribution of drug
- Relatively sensitive to manufacturing process variables
- Numerous quality attributes may be critical
- Numerous failure modes may exist
  - Complex composition of matter in the product
  - Complex state of matter in the product
  - Complex arrangement of matter in the product
  - Complex drug diffusion within the dosage form

Linking Complexity to Failure Modes

As the complexity of a dosage form increases, so do the potential failure modes for the drug product.

Linking Complexity to Failure Modes

- To ensure target performance of the drug product what must we understand about:
  - The complexity of the drug product
  - The potential failure modes
  - The critical ranges for all relevant quality attributes
  - The influence of manufacturing process variables

- Can the risk of failure modes be mitigated by:
  - More comprehensive product quality characterization
  - Well-characterized product and process understanding
  - Appropriate product and process controls and tests

Topical Product Quality Tests

- Q1: Qualitative Composition
- Q2: Quantitative Composition (and Q1)
- Q3: Physicochemical Attributes (and Q1/Q2)
  - Rheological Characteristics
  - Drug Polymorphic Form
  - Drug Release Rate
  - Globule Size
  - pH
  - Etc.

- Which Q1/Q2/Q3 Attributes are Critical?
  - In what range of values is a quality attribute robust?

Understanding Drug Product Complexity

What are the limitations on industry to:

- Advance our understanding of the complexity and potential failure modes of semisolid dosage forms
- Advance pharmaceutical technology and expand our compendial toolkit of product quality tests
- Enhance the level of detail for the specific quality attributes that are designed into drug products

Critical Quality Attributes (CQAs)

- Can differences in individual attributes of a product quality profile be directly associated with significant differences in product performance?
- Once potential CQAs have been identified, what are the limitations on implementing a QbD approach to establish critical ranges for each attribute in a larger design space?

Topical Product Quality Tests

1. Do we understand adequately how differences in composition and/or manufacture impact:
   - The states of matter in the drug product
   - The arrangement of matter in the drug product
   - The complex/dynamic distribution of drug
   - The metamorphosis of the semisolid on the skin

2. Can we study qualitative differences and observe
   - When a quality attribute is critical
   - When a potential failure mode may be at risk
   - How qualities and failures are multi-factorial effects

Failure Modes related to Quality Attributes

For example, consider that pH alone can influence

- Ionization state of the drug substance
- Polymorphic state of the drug substance
- Stability of the drug substance in the drug product
- Solubility of the drug substance
- Ratio of dissolved to undissolved drug
- Distribution of drug in the product microstructure
- Amount of drug in the phase in contact with the skin
- Rheology of the semisolid product
- Dose application, spreading, product transfer
- Patient perception of cosmetic acceptability and quality

Failure Modes related to Quality Attributes

Do we have the necessary tools to measure pH?

- What does it mean to measure the bulk pH of a cream
- Does it matter what kind of probe/technology is used
- Is it important to independently measure the pH of the aqueous component of an emulsion
- How might these measures of pH change following application to the skin
- Is the formulation adequately buffered, if pH is critical
- Petrolatum, USP has specifications related to alkalinity and acidity; what ramifications might extremes of the range within the grade have for the final drug product and is there an appropriate way to characterize this?

Failure Modes related to Quality Attributes

- In complex products, consider how failure modes arise from and convolute among multiple quality attributes
- Consider how the risk of failure modes can be mitigated once the associated (individual and collective) quality attributes are designed into the product and controlled within a well-characterized design space
- Consider which qualities to characterize, what measurement techniques to use, and how to interpret the results

Broad Considerations for Quality Attributes

Consider the patient impact

- Consider quality attributes that relate to
  - Storage, dispensing and re-dispensing
  - Dose application, maintenance and removal
  - Patient perceptions of quality and acceptability
  - Robustness of therapeutic effect in the real world
- Consider how the product quality changes during dose application and during subsequent metamorphosis
- Consider how the vehicle impacts the skin (hydrating or dehydrating effects, irritancy, burning sensation)
- Consider how product quality attributes at the limits of stability specifications impact these factors

Characterizing Quality Attributes

Consider the target rheological profile, for example

- Anticipate the forces the dosage form experiences
  - When being dispensed from the container closure system
  - When being applied throughout the affected area of skin
- Consider the contact of the semisolid with the skin
- Consider the effect of skin surface temperature(s) on the rheological properties of the semisolid product
- Consider the rheology across a the entire relevant range of shear rates and shear stresses at relevant temperatures
  - What are the relevant characteristics to monitor?
  - Yield stress, thixotropy, other relevant characteristics?
- Consider the sensorial properties for the patient and the tenderness of the skin upon which the product is spread

Characterizing Quality Attributes

Consider the complexity of the dosage form

- A single phase with fully dissolved drug
- A suspension of particles and some partially dissolved drug
- A multi-phase emulsion with the drug predominantly dissolved in the oil phase
  - Oil-in-water; water-in oil; micro or nano emulsion
- Preservatives, antioxidants, colors, fragrances
- Distribution of drug in the dosage form
- Component volatility, water activity, metamorphosis rate
- Dosage form shrinkage, phase separation/breaking
- Drug solubility, stability, polymorphs, precipitation/caking
- Drug particle size distribution, crystal growth
- Polymerization; response to pH, temperature, etc.

Characterizing Quality Attributes

Consider the critical ranges for quality attributes

1. A suspension of particles and partially dissolved drug
   - How critical is particle size distribution
   - How critical is the concentration of dissolved drug
   - How critical is the rate of metamorphosis on the latter

2. A multi-phase emulsion with the drug predominantly dissolved in the oil phase
   - How critical is globule size distribution
   - How does globule size distribution change in response to shear stresses of dose application
   - How does the microstructure, drug solubility, drug distribution, etc. change at different relevant temperatures

Characterizing Quality Attributes

Consider criticality of product/process parameters

- How critical is the composition of inactive ingredients
- How critical is the grade of each inactive ingredient
- How critical is the sequence of mixing
- How critical are mixing rates and durations
- How critical are temperatures and rates of change
- How critical are the orifice diameters, tube lengths, pressures, etc. during transfer, holding, packaging
- How critical is the inertness of the container closure system (e.g. are there adsorption/absorption issues)
- How critical are the product dispensing stresses/forces

Characterizing Quality Attributes

In what contexts should CQAs be characterized?

- Are there failure modes that are not apparent in the product within the container closure system, but which manifest once the product is dispensed or applied?
- What specific test methods must be developed to better characterize physicochemical and microstructural complexity?
- To what degree should a topical semisolid product development program characterize CQAs
  - Through iterative product development QbD cycles
  - Including simulated stresses of patient use scenarios
- How can clinical experience with the drug product be linked to a satisfactory profile of CQAs?

Characterizing Quality Attributes

Summary Considerations:

- Consider the patient's needs and expectations
- Consider how to appropriately characterize the Q1/Q2/Q3 attributes and complexity of the semisolid drug product
- Consider the dynamic ranges of conditions during formulation, manufacture, packaging, storage, dispensing, dosing, and metamorphosis
- Consider the relationship between quality attributes and potential failure modes, individually and collectively
- Consider the appropriate test methods for specific product qualities in relevant contexts, throughout QbD and as part of a quality risk management approach

Thank You for Your Consideration

The Matter of Medicine

Does Form Follow Function or Vice Versa?

May 24th, 2016
Rutgers University, New Jersey
Center for Dermal Research

Sam Raney, PhD
Scientific Lead for Topical & Transdermal Drug Products
Division of Therapeutic Performance
Office of Research & Standards
Office of Generic Drugs, U.S. Food and Drug Administration