Overview of Current Science-Based Regulatory Standards

Complex Generic Drug Product Development Workshop

Session 5: Complex Route of Delivery/Dosage Forms
Topical (Dermatological) and Transdermal

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Equivalence of Complex Generics

- Topical and transdermal reference listed drug (RLD) products are typically complex, often in multiple ways
- There are unique considerations impacting equivalence for complex generic topical and transdermal products
- Let us discuss these considerations independently for:
  - **Topical products**
  - **Transdermal Delivery System (TDS) products**

Topical Dermatological Drug Products

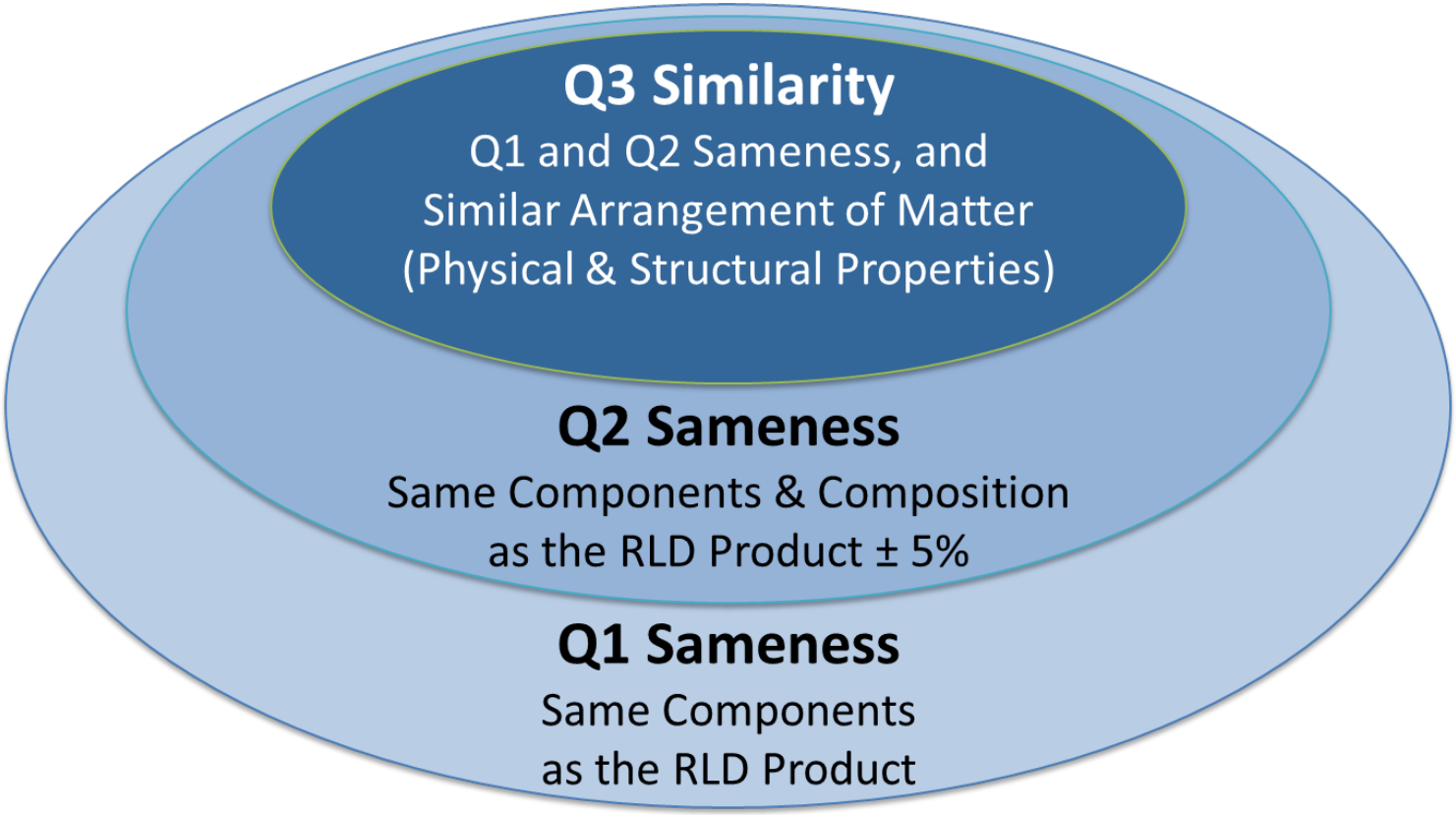
Topical Dermatological Formulations

- The formulation of a topical product matters greatly
- The components and composition modulate the physical and structural arrangement of matter
- The resulting topical product characteristics can influence metamorphosis and bioavailability

Topical Dermatological Formulations

- Components, composition, physical and structural properties of a topical product can influence:
  - The drug state(s) and phase(s) of the dosage form
  - The distribution of the drug in the dosage form
  - Drug diffusion within the dosage form
  - Drug partitioning from the dosage form into the skin barrier
  - The structure and chemistry of the skin barrier
  - Drug diffusion within the skin itself
  - Drug delivery & bioavailability at the target site
  - Skin (de)hydration, irritation or damage
  - The metamorphosis of the dosage form on the skin

Topical Dermatological Formulations



Q1/Q2 Sameness of Topical Generics

- Q1/Q2 Sameness (Components and Composition)

  Mitigates the risk of known failure modes related to:

  - Irritation and sensitization
  - Formulation interaction with diseased skin
  - Stability, solubility, etc. of the drug
  - Vehicle contribution to efficacy

Q3 Similarity of Topical Generics

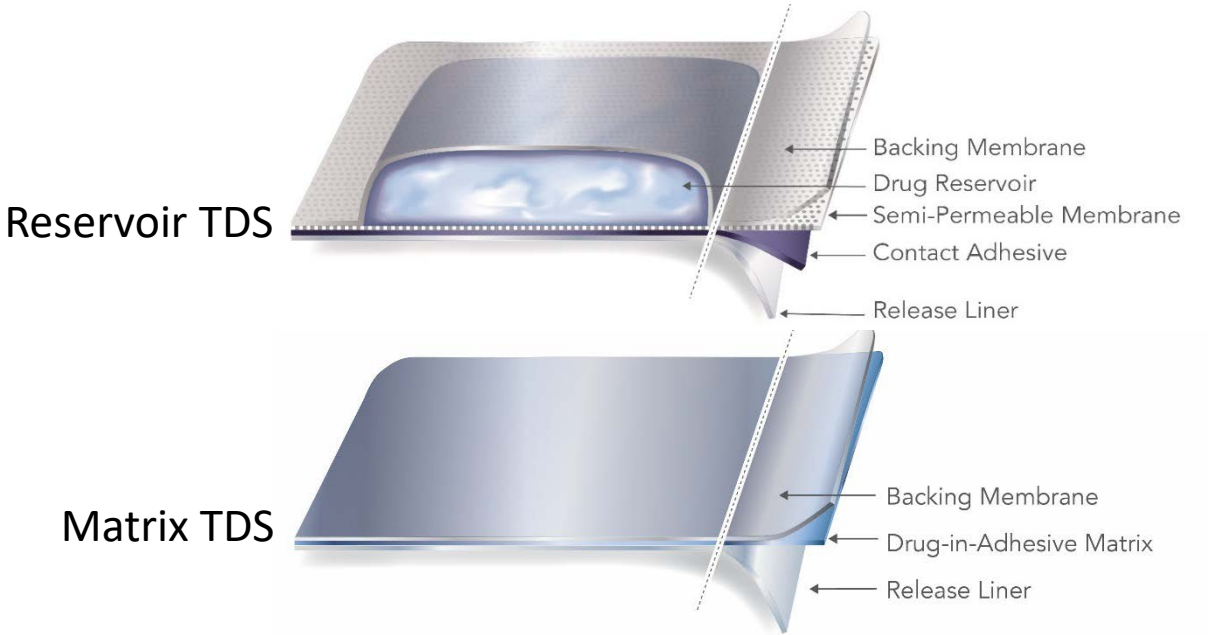
- Q3 Similarity (Arrangement of Matter)

  Mitigates the risk of potential failure modes related to:

  - Differences in Q1/Q2 sameness (± 5% tolerances)
  - Differences in pH that may sting or irritate diseased skin
  - Differences in the polymorphic form of the drug
  - Differences in rheology that alter the spreadability, retention, etc.
  - Differences in entrapped air and drug amount per dose
  - Differences in phase states and diffusion, partitioning, etc.
  - Differences in metamorphosis and drying rates

Evaluation of BE for Topical Products

- A Modular Framework for In Vitro BE Evaluation
  - **Q1/Q2** sameness
  - **Q3** similarity
  - **IVRT** (In Vitro Release Test)
  - **IVPT** (In Vitro Permeation Test)
- Multiple Approaches for BE Evaluation
  - **In Vivo Pharmacokinetic** studies
  - **In Vivo Pharmacodynamic** (Vasoconstrictor) studies
  - **In Vivo Clinical Endpoint BE** studies
  - **In Silico** Quantitative Methods, Modeling and Simulation



Transdermal Delivery System Products

Generic TDS products

- Compared to the RLD product, a generic TDS may have
  - Different product design
    - Reservoir or Matrix TDS designs
  - Differentiated failure modes related to the product design
    - Leakage (bursting) or cold flow
    - Release liner removal issues
    - Abuse potential
    - Crystallization
    - Heat effects
    - Adhesion

Generic TDS products

- Compared to the RLD product, a generic TDS may have
  - Different drug load
  - Different residual drug excess
  - Different product size and/or shape
  - Different strength when evaluated by different methods
  - Different heat effects due to different drug load and design

Generic TDS products

- Compared to the RLD product, a generic TDS may have
  - Different “inactive” ingredients
    - Adhesives, impurities, penetration enhancers
  - Different level of exposure to adhesive impurities
  - Different irritation/sensitization potential
  - Different adhesion characteristics
  - Different heat effects due to product composition

Evaluation of BE and Quality for TDS

- In Vivo Studies With Which to Demonstrate BE for TDS
  - A comparative BE study with pharmacokinetic endpoints
  - A comparative study of the adhesion performance of the TDS
  - A comparative study of the irritation/sensitization potential of the TDS
- An In Vitro Study to Compare the Effects of Heat on TDS
  - A study evaluating the quality of prospective generic TDS, comparing how heat alters the rate and extent of transdermal drug delivery

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