

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



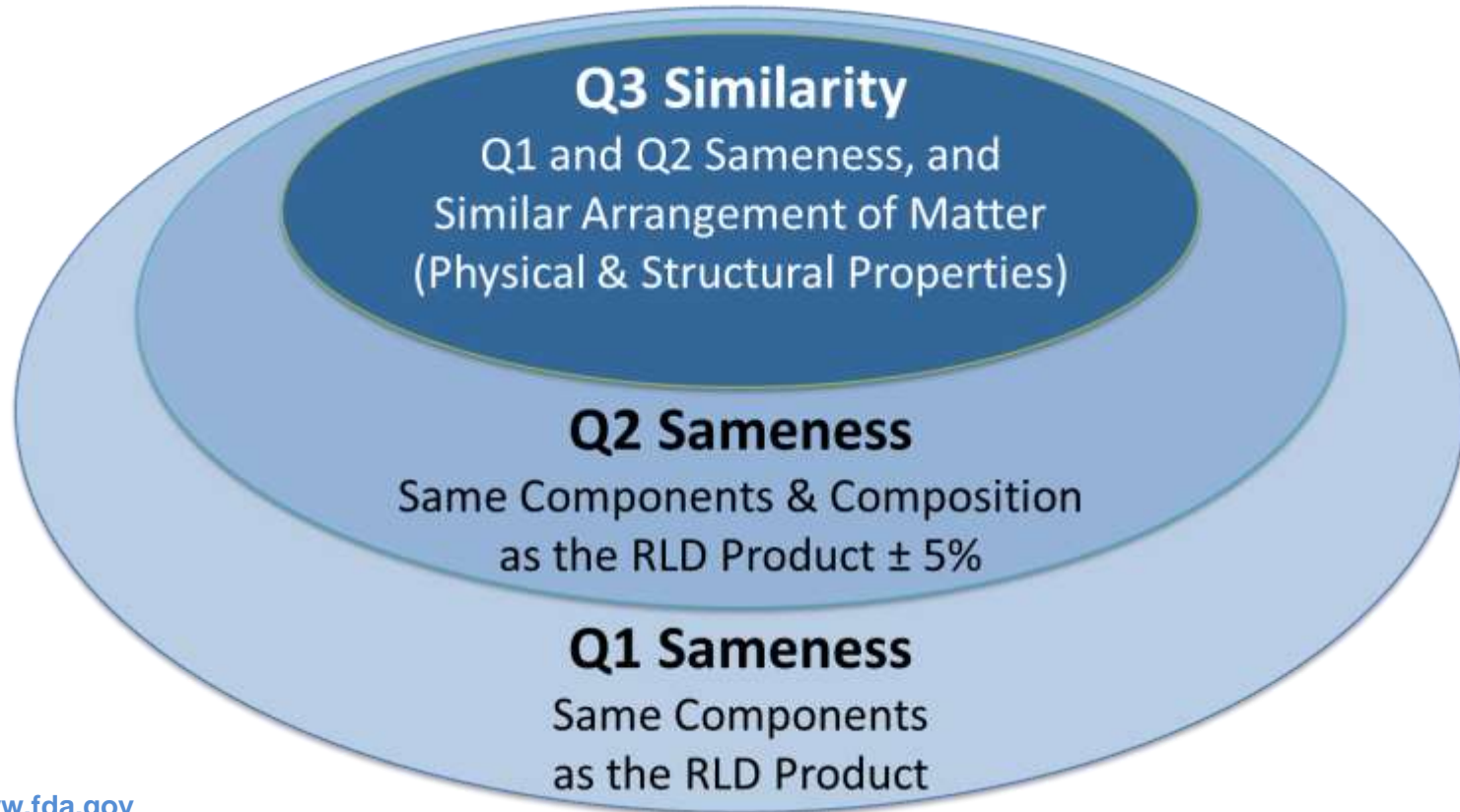
- The formulation of a topical product matters greatly
- The components and composition modulate the physical and structural arrangement of matter
- The resulting topical product characteristics can influence metamorphosis and bioavailability

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:

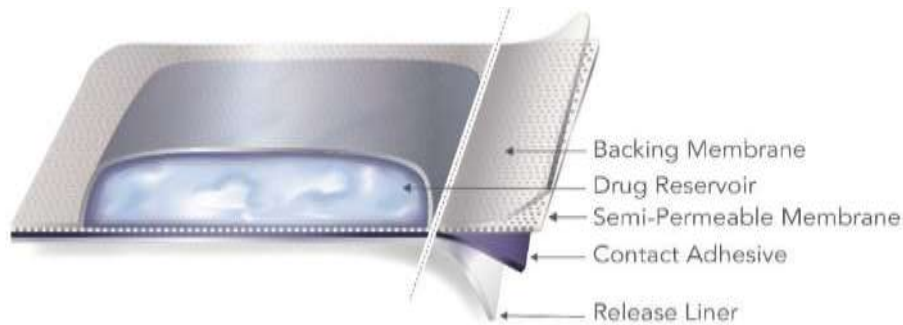
- Differences in Q1/Q2 sameness ($\pm 5\%$ tolerances)
- Differences in pH that may sting or irritate diseased skin
- Differences in the polymorphic form of the drug
- Differences in rheology that alter the spreadability, retention, etc.
- Differences in entrapped air and drug amount per dose
- Differences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

Evaluation of BE for Topical Products

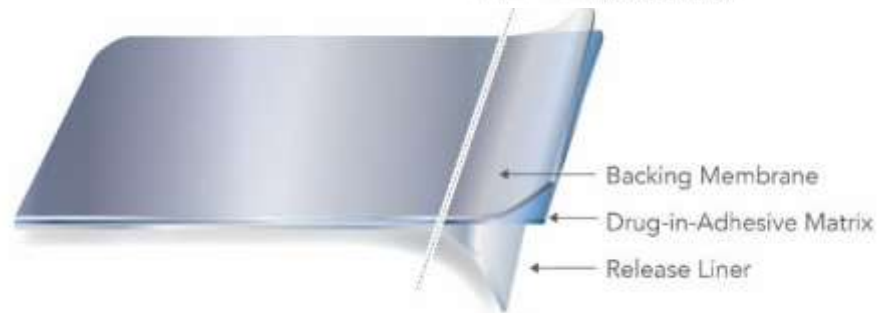


- A Modular Framework for In Vitro BE Evaluation
 - **Q1/Q2** sameness
 - **Q3** similarity
 - **IVRT** (In Vitro Release Test)
 - **IVPT** (In Vitro Permeation Test)
- Multiple Approaches for BE Evaluation
 - **In Vivo Pharmacokinetic** studies
 - **In Vivo Pharmacodynamic** (Vasoconstrictor) studies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

Reservoir TDS



Matrix TDS



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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