When Do Formulation Differences in Topical Dosage Forms Impact Their Function: Emerging Insights and Implications for Bioequivalence Approaches

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 3: Future Directions, Emerging Technology, and Current Thinking on Alternative BE Approaches

Topic 2: Topical Dermatologic Products

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Disclaimer

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Topical Dermatological Formulations

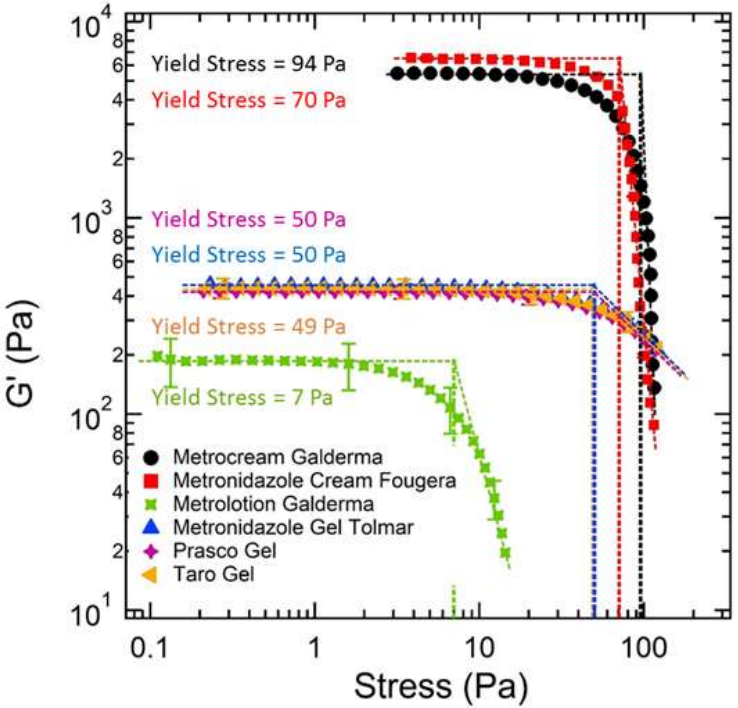
- The components (Q1) and quantitative composition (Q2) of a topical product (and how it is manufactured) can modulate its physical and structural arrangement of matter (Q3)
- These Q3 characteristics influence molecular interactions that control the rate and extent of topical bioavailability
- One approach to developing generic topical products is to:
  - Characterize the complexity of the reference product
  - Match the Q1, Q2, and Q3 characteristics of the reference product

➲ ***How closely should test and reference products be matched?***

Clinical and Pharmacokinetic Data

Quality Attribute	Metrocream®	Generic Cream (Fougera)	Metrogel®	Generic Gel (Tolmar)	Generic Gel (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingredient is completely dissolved				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
Drug in Oil (mg/g)	2.58	3.94	---	---	---
Solvent Activity	0.977	0.974	0.992	0.994	1.002
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drying, T_{30}(min)	17	11.4	5.5	4.7	6.5

Rheology



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

Clinical and Pharmacokinetic Data

Quality Attribute	Metrocream®	Generic Cream (Fougera)	Metrogel®	Generic Gel (Tolmar)	Generic Gel (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
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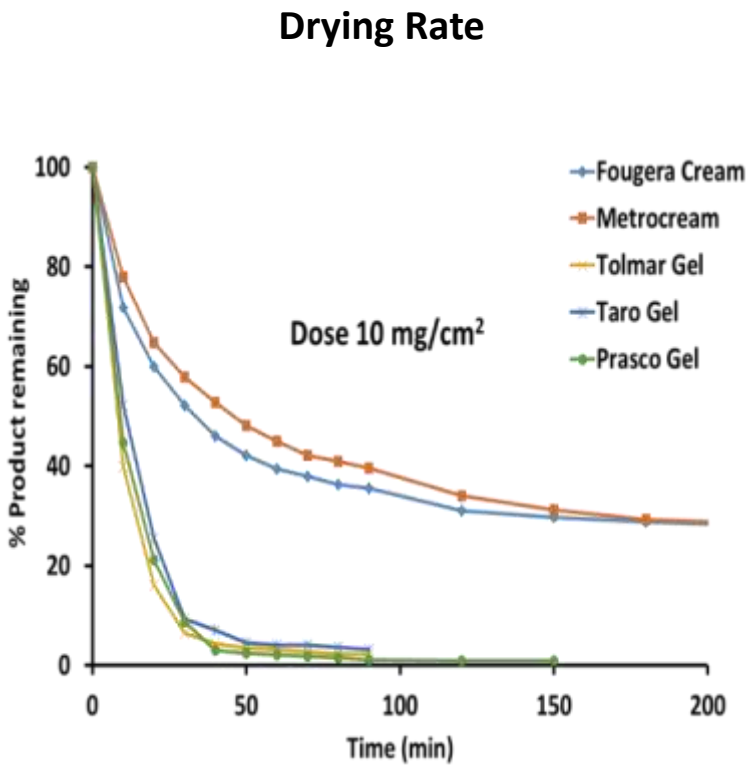

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

Clinical and Pharmacokinetic Data

Quality Attribute	Metrocream® (RLD Cream)	Generic Crear (Fougera)	Metrogel® (RLD Gel)	Generic Gel (Tolmar)	Generic Ge (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
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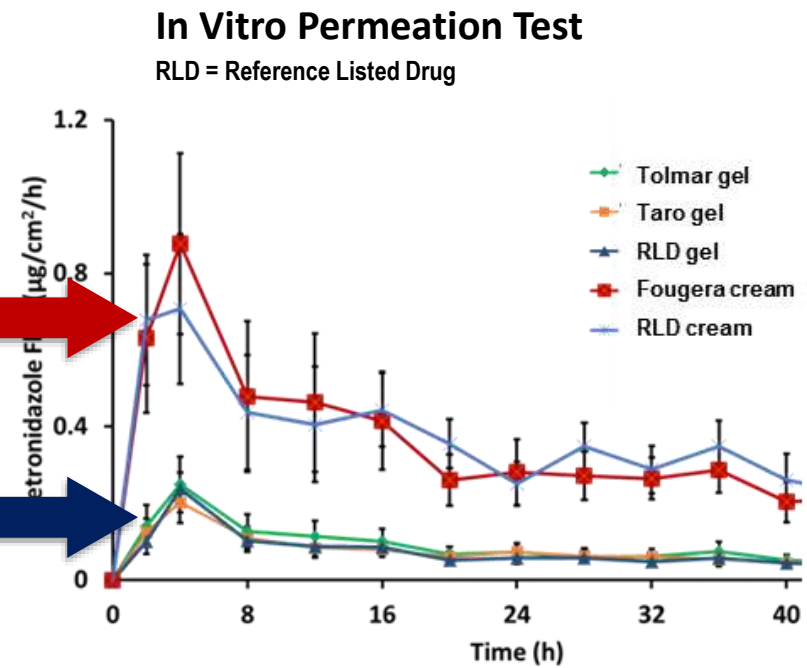

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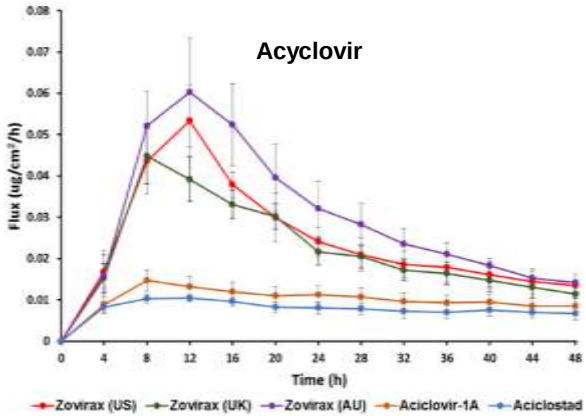

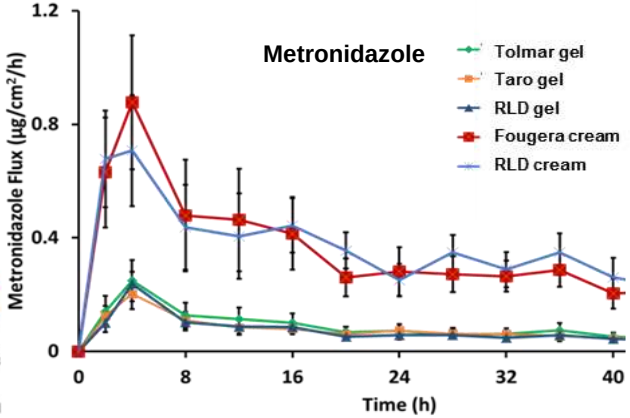

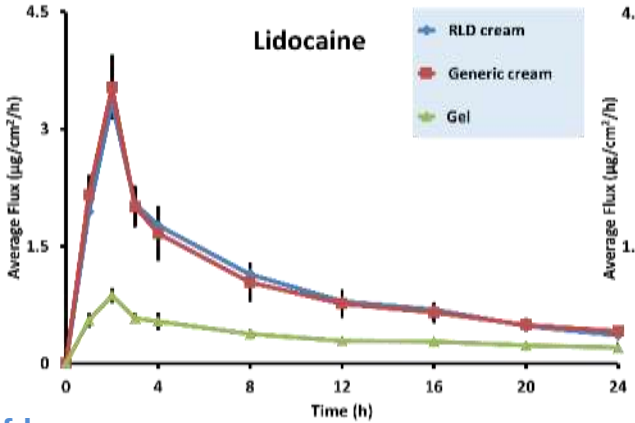

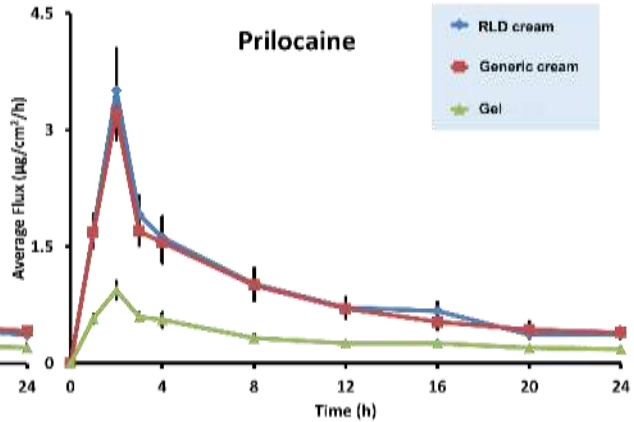

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Topical Dermatological Formulations

- Clinical evidence has demonstrated the bioequivalence (BE) of several topical generics that are not necessarily Q1, Q2, or Q3 the same as the reference product
- An expanding body of evidence has demonstrated that these topical generics exhibit comparable cutaneous pharmacokinetics (PK) …not only comparable clinical efficacy

➲ ***When do Q1, Q2, or Q3 differences impact the BE of topical products, and what may be acceptable differences between a test and reference product formulation?***

Waiver of In Vivo Evidence of BE

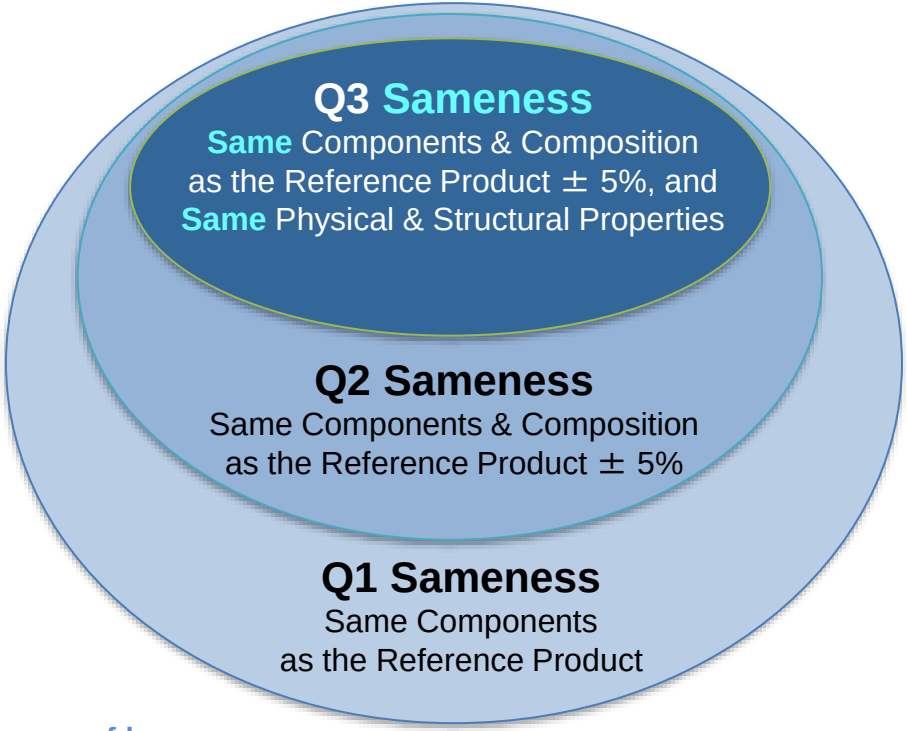
Title 21 of the Code of Federal Regulations, Section 320.22 [21CFR320.22(b)]

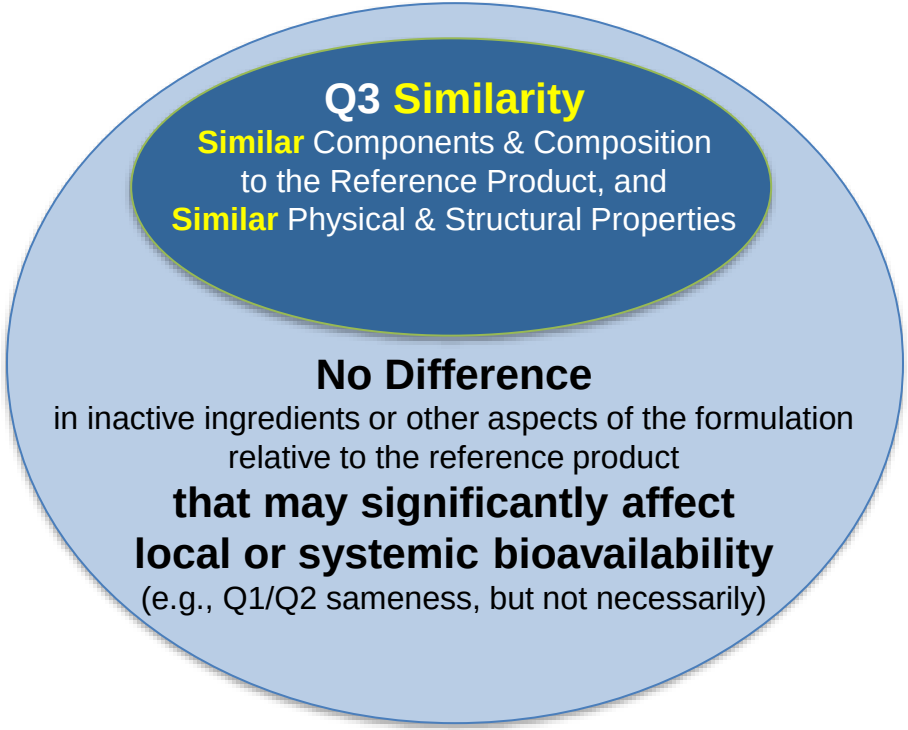
- **Parenteral solutions for injection or ophthalmic or otic solutions**
  - ⇨ Should contain "*the same active and inactive ingredients in the same concentration*" as the reference product
  - ⇨ **Q1 and Q2 sameness**

- **Topical solutions or solution-based foam aerosols**
  - ⇨ Should contain "*no inactive ingredient or other change in formulation …that may significantly affect systemic or local availability*"
  - ⇨ **Not necessarily Q1 and Q2 sameness**

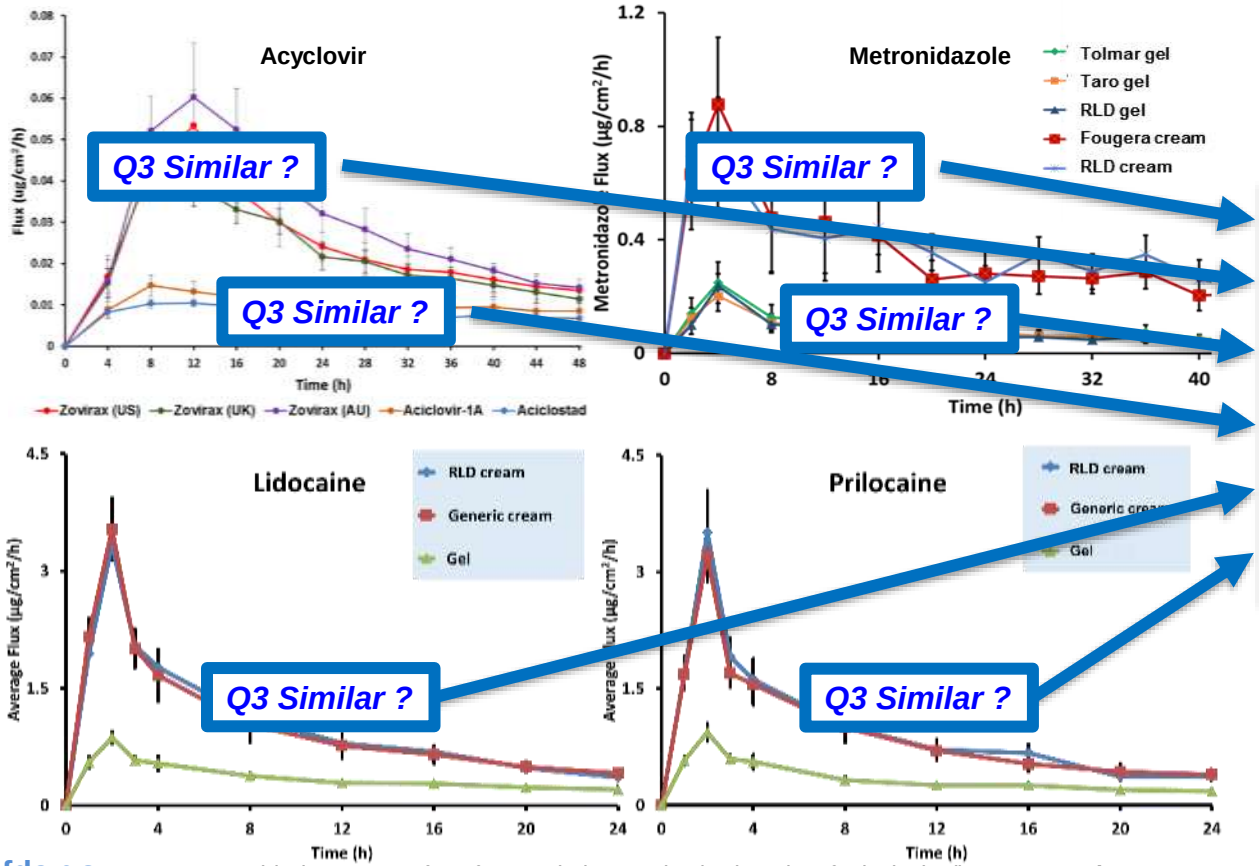
Q3 Sameness vs. Similarity

- An evolving concept *for topical dermatological products*





Q3 Sameness vs. Similarity



Not necessarily
Q1 & Q2 the same

~

No significant impact on bioavailability

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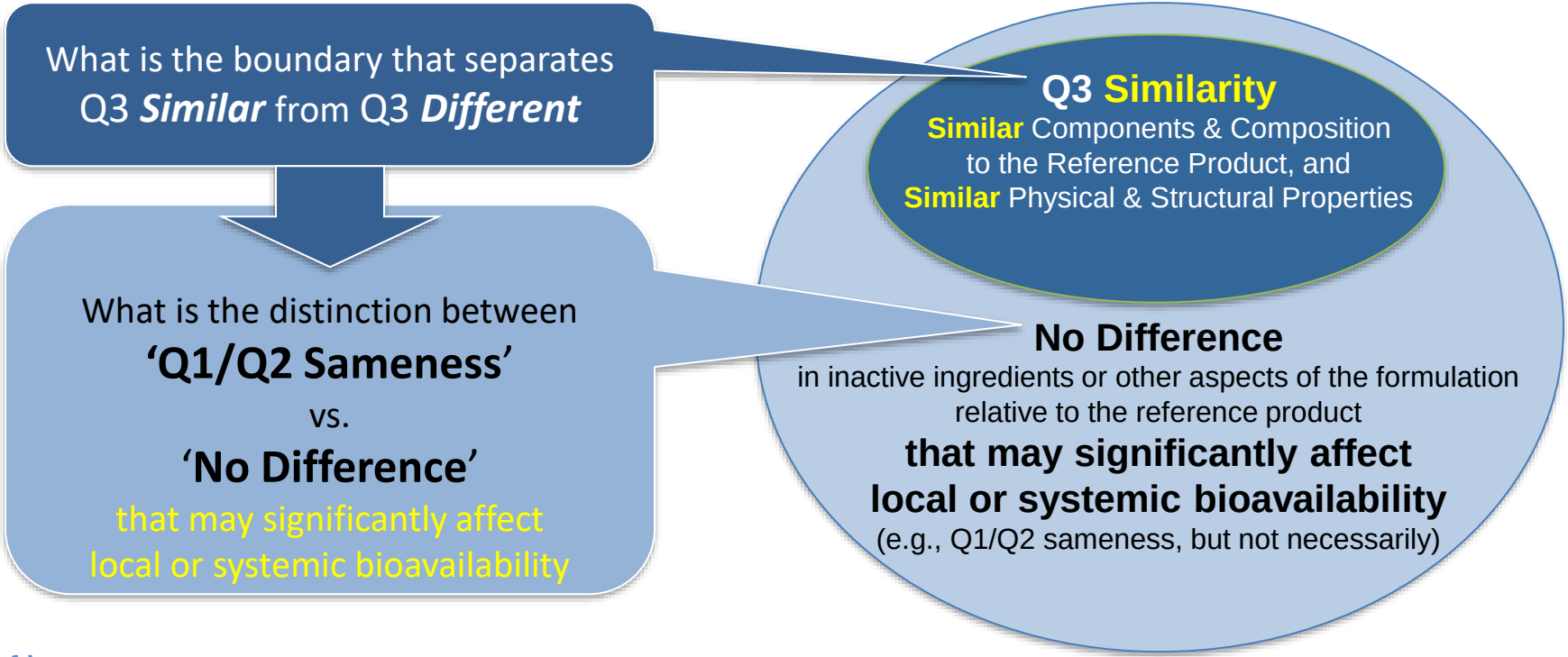
What Do These Concepts Mean?

- An evolving concept *for topical dermatological products*



Q1/Q2 Sameness vs. ‘No Difference’

- Determining the suitability of proposed test product formulations to demonstrate BE by a characterization-based approach:
  - An assessment of ‘No Difference’ in formulation is based upon the same principles as assessing Q1/Q2 sameness, including tolerances of ±5%
  - An assessment of ‘No Difference’ for topical dermatological products evaluates whether certain components and compositions may be acceptable for a proposed generic product, based upon information available to the Agency and/or based upon evidence submitted in an abbreviated new drug application (ANDA); i.e., evidence that there is no difference between the test and reference products in the local or systemic availability of the active ingredient

Evaluation of BE for Topical Products

- A Modular Framework for Characterization-Based BE
  - **Qualitative (Q1) and Quantitative (Q2)** Sameness or '***No Difference***'
  - **Physical and Structural (Q3)** Sameness or '***Similarity***'
  - **IVRT** (In Vitro Release Test)
  - **IVPT** (In Vitro Permeation Test)
- Other Types of Evidence to Support a Demonstration of BE
  - **In Vivo Pharmacokinetic** Studies
  - **In Vivo Pharmacodynamic** (e.g., Vasoconstrictor) Studies
  - **In Vivo Comparative Clinical Endpoint BE** Studies
  - **In Silico** Quantitative Methods, Modeling and Simulation

Conclusions

- Generic topical products are not required to be Q1/Q2 the same compared to the reference product
- Generic topical products should contain ‘No Difference’ in inactive ingredients or in other aspects of the formulation that may significantly affect local or systemic bioavailability
- Certain components and compositions may be acceptable for a proposed generic product, based upon information available to the Agency and/or based upon evidence submitted in an ANDA
- When the Q3 attributes of such a product match those of the reference product, but the underlying matter is not the same, it would not be considered Q3 the same, but rather, ‘Q3 Similar’

Challenge Question

- Differences in inactive ingredients or in other aspects of a proposed test product formulation (relative to the reference product) may be acceptable when:
  A. Differences are ***never*** acceptable
  B. Differences are fine; ***anything goes*** for topical products
  C. Information available to the Agency indicates that certain components and compositions of a proposed formulation may be acceptable
  D. Evidence submitted in an ANDA demonstrates that specific differences between a test and reference product do not alter local or systemic bioavailability
  E. C and D

Challenge Question

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  E. C and D

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