Research Activities, Scientific Advances, & Modernization of Bioequivalence Standards for Generic Topical and Transdermal Products

Complex Generic Drug Product Development Workshop

Session 2: Scientific and Regulatory Advances for Generic Topical and Transdermal Product Development

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Office of Generic Drugs

CDER | U.S. FDA

Disclaimer

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

Goals of GDUFA Research Programs

Enhance patient access to generic drug products

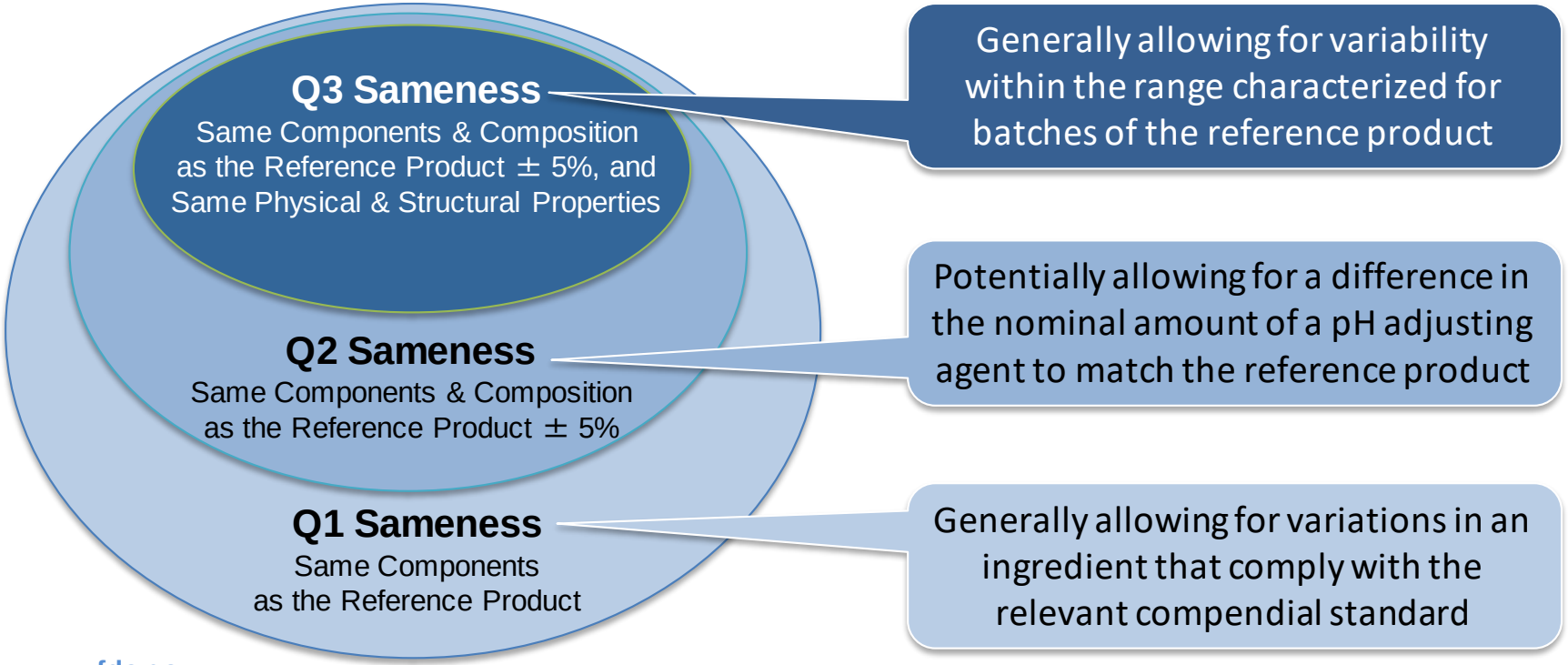
- Overcome barriers limiting generic drug development
- Utilize scientific evidence to establish efficient, modern bioequivalence (BE) standards
- Continually study, learn, evolve, refine, and harmonize

Evaluation of BE for Topical Products

- A Modular Framework for In Vitro BE Evaluation
  - **Qualitative (Q1) and Quantitative (Q2)** Sameness
  - **Physical and Structural (Q3)** Sameness
  - **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 Comparative Clinical Endpoint BE** Studies
  - **In Silico** Quantitative Methods, Modeling and Simulation

Q3 Sameness for Topical Products

- An evolving concept *<u>for topical dermatological products</u>*

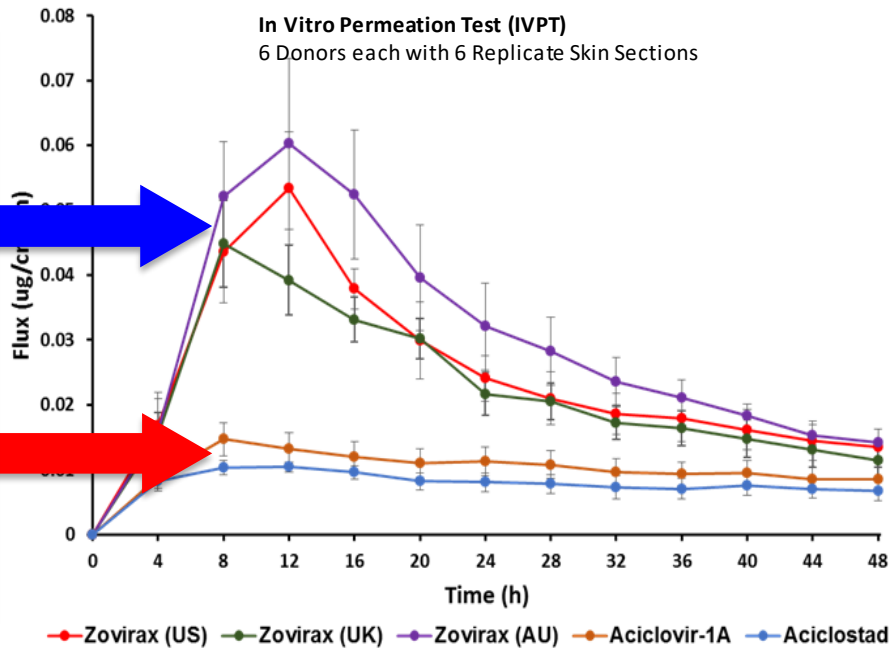


Quick Note on ‘Reference’ Product

- Bioequivalence is implicitly demonstrated with respect to the reference listed drug (RLD) product
- Topical dermatological test products may be compared to the designated reference standard (RS) product to support a demonstration of BE
- This applies to in vitro and/or in vivo characterizations of topical dermatological product quality or performance that support a demonstration of BE

Product Quality and Performance

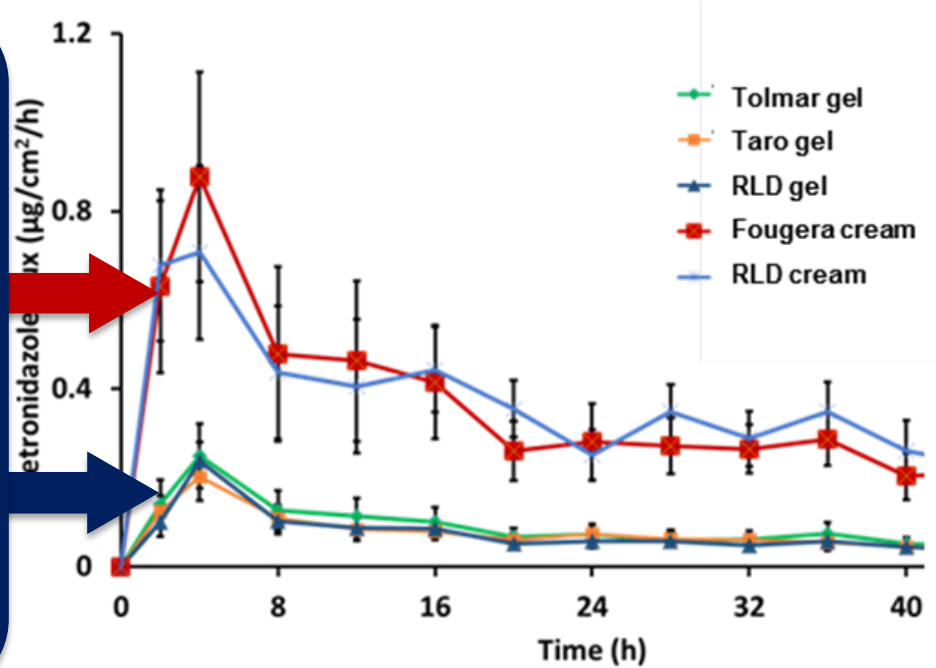
	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcoh	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol Stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95



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

Product Quality and Performance

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 ingred				
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



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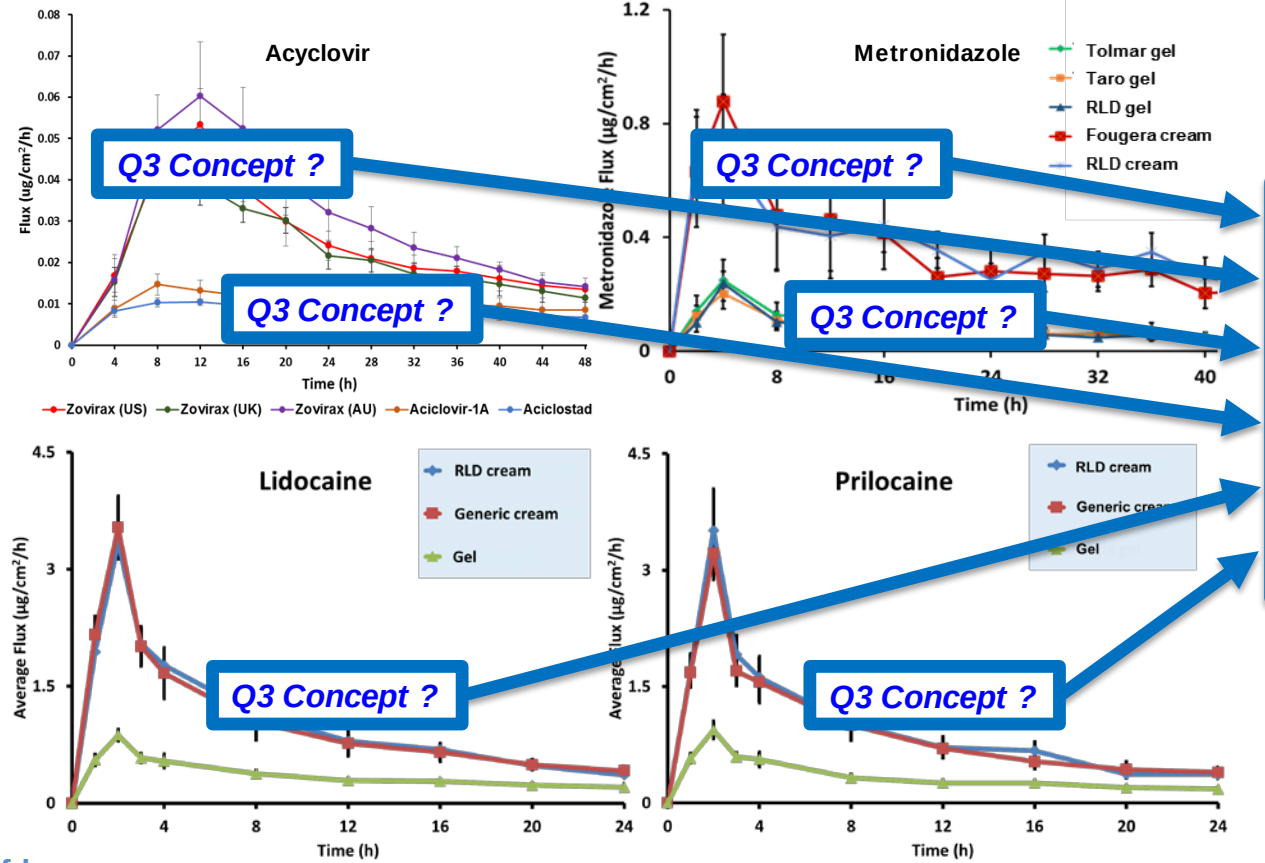
Product Quality and Performance



Not necessarily
Q1 & Q2 the same
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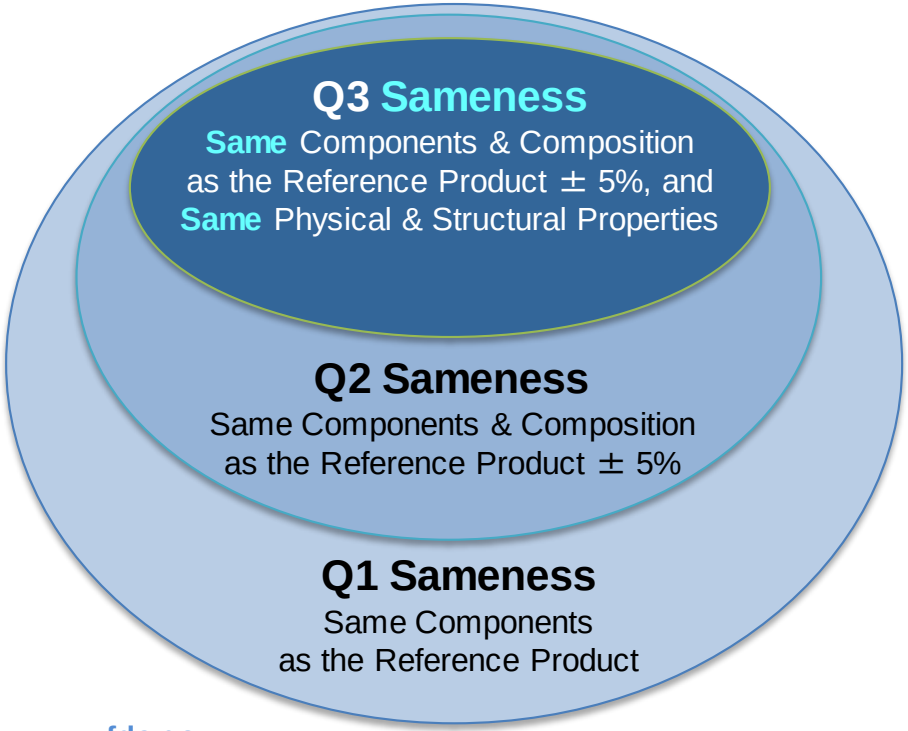
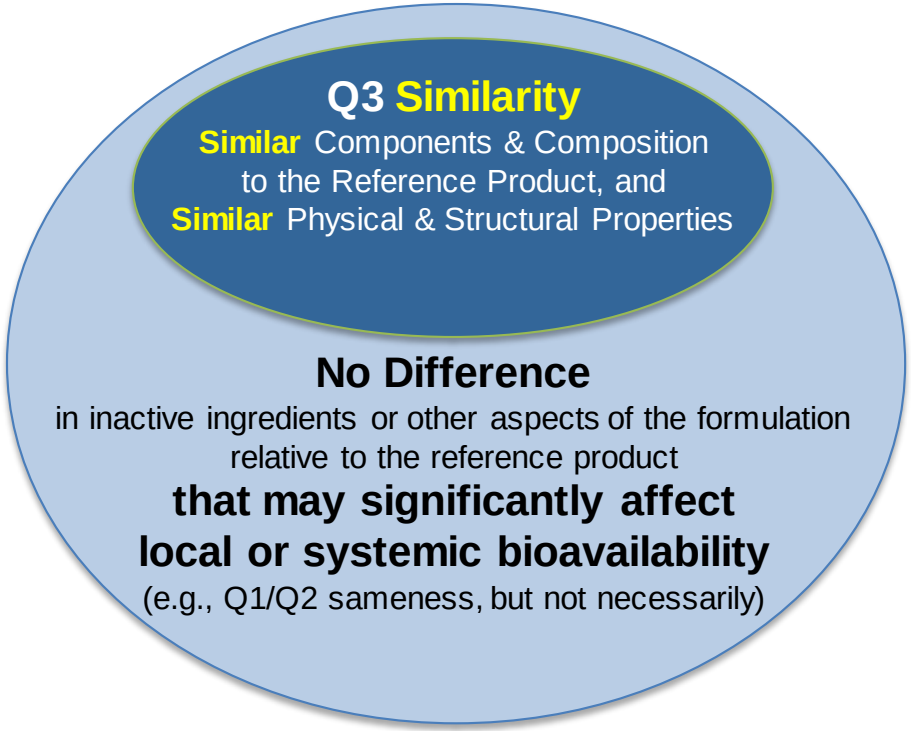
No significant impact on bioavailability

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

Q3 Sameness vs. Similarity

- An evolving concept *for topical dermatological products*



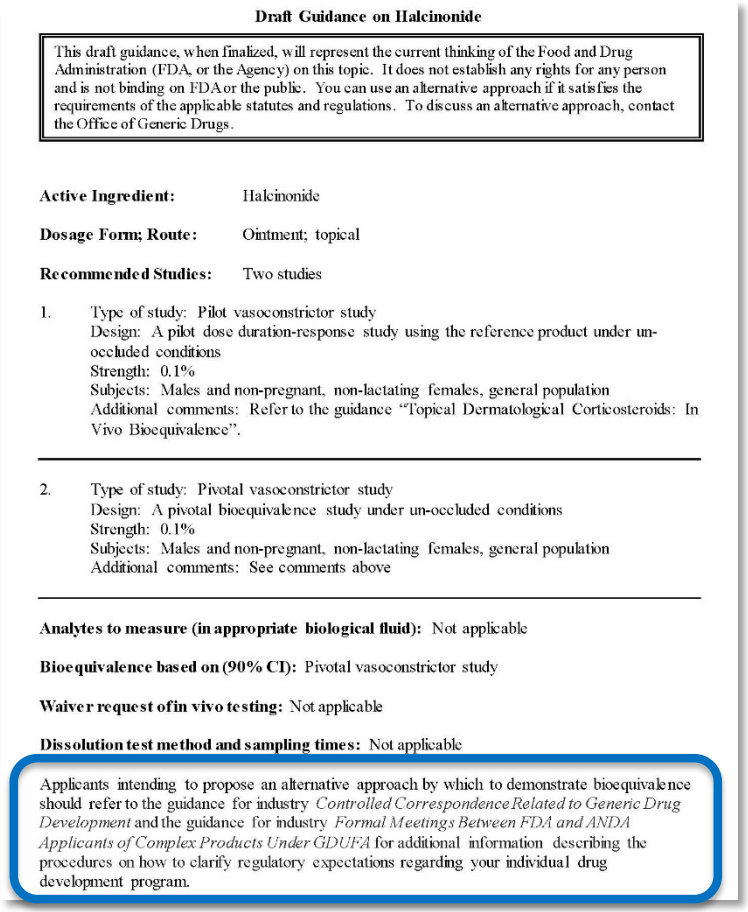


Alternative BE Approaches

- Certain BE approaches may **generally** be alternatives for topical dermatological drug products
  - In vitro (characterization based) BE approach
  - In vivo (comparative clinical endpoint) BE approach
- Product specific guidances may specifically state:

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry Controlled Correspondence Related to Generic Drug Development and the guidance for industry Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Alternative BE Approaches



Draft Guidance on Halcinonide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Halcinonide

Dosage Form; Route: Ointment; topical

Recommended Studies: Two studies

1. Type of study: Pilot vasoconstrictor study
   Design: A pilot dose duration-response study using the reference product under un-occluded conditions
   Strength: 0.1%
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Refer to the guidance "Topical Dermatological Corticosteroids: In Vivo Bioequivalence".

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2. Type of study: Pivotal vasoconstrictor study
   Design: A pivotal bioequivalence study under un-occluded conditions
   Strength: 0.1%
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above

Analytes to measure (in appropriate biological fluid): Not applicable

Bioequivalence based on (90% CI): Pivotal vasoconstrictor study

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

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FY 2018 Research Priority

- Expand characterization-based BE methods across all topical dermatological products

Topical & Transdermal Product Types

Topical

- Solutions and Sprays
- Creams and Lotions
- Ointments and Oils
- Gels and Jellies
- Shampoos
- Aerosol Foams
- Patches, Tapes, and Films
- Suppositories and Enemas
- Rectal and Vaginal Tablets and Inserts

Transdermal

- Transdermal Delivery Systems
- Ointments
- Gels

Scientific Issues Impacting BE

EXAMPLE #1: Solution-Based Dosage Forms

- Some topical **solutions** or **solution-based foam aerosols** may qualify for a waiver of in vivo evidence of BE

Title 21 of the Code of Federal Regulations, Section 320.22 [21CFR320.22(b)(3)]

…A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if…the drug product…

(i) is a solution for application to the skin…

(ii) contains an active drug ingredient in the same concentration and dosage form…

*(iii) contains **no inactive ingredient or other change in formulation** from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or **that may significantly affect systemic or local availability** for products intended to act locally.*

Scientific Issues Impacting BE

EXAMPLE #1: Solution-Based Dosage Forms

- Some topical **solutions** or **solution-based foam aerosols** may qualify for a waiver of in vivo evidence of BE
- However, **compositionally different** solution-based products can have complex BE issues related to
  - Formulation components and composition (irritant potential)
  - Product quality attributes (pH, rheology, drug solubility, etc.)
  - Product performance (metamorphosis, drug delivery, etc.)
  - Container closure system (physical stability, dispensing, etc.)

Research to Address the BE Issues

EXAMPLE #1: Solution-Based Dosage Forms

- **Research Funded by RFA-FD-14-010**:
  - Currently characterizing the critical properties that modulate the metamorphosis and physical stability of topical foams
- **Research Funded by RFA-FD-18-010**:
  - Currently characterizing thermodynamic properties that modulate BE for compositionally different topical products
    - Research initially focuses on simple solutions and solution-based dosage forms
    - Research will progress into compositionally different semisolid dosage forms

Scientific Issues Impacting BE

EXAMPLE #2: Petrolatum-Based Ointments

- Some topical ointment formulations are comprised predominantly of (White) Petrolatum, USP
- However, despite an apparent compositional simplicity, these products can have complex BE issues related to
  - Compositional heterogeneity of (White) Petrolatum, USP
  - Failure modes for BE depending upon petrolatum composition
  - Broad overlapping compendial specifications for petrolatums

Research to Address the BE Issues

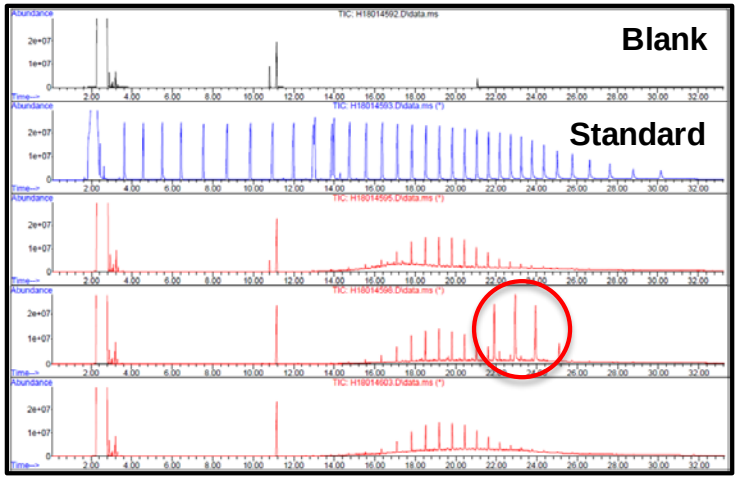
EXAMPLE #2: Petrolatum-Based Ointments

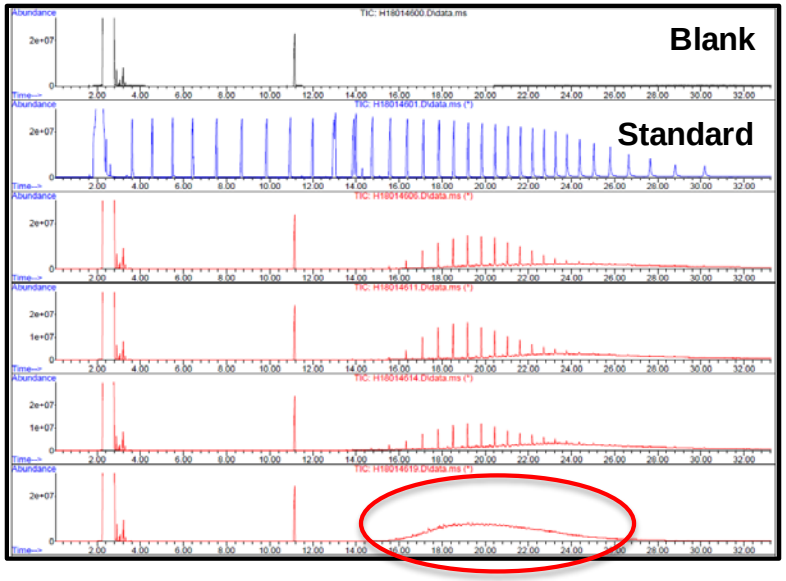
- **HHSF223201610125C**: Assessment of the In Vitro Percutaneous Absorption, In Vitro Rate of Release, and Physicochemical Properties of Selected Commercially Available AT Rated Ointment Formulations
  - Currently evaluating tests to characterize the compositional heterogeneity and physical properties of petrolatum based topical ointments that may have the potential to influence BE

Research to Address the BE Issues

EXAMPLE #2: Petrolatum-Based Ointments

- Gas Chromatography Mass Spectrometry (GC/MS) characterization of petrolatum based topical ointments





*Results from QPS Contract **HHSF223201610125C***

Scientific Issues Impacting BE

EXAMPLE #3: Topical/Transdermal Delivery Systems (TDS)

- Studies performed to support a demonstration of BE varied substantially for different TDS products
- Some aspects of study designs confounded the ultimate assessment of comparability in clinical performance
- Statistical analyses utilized to evaluate non-inferiority exhibited low power, and required large subject populations to meet statistical endpoints

Research to Address the BE Issues

EXAMPLE #3: Topical/Transdermal Delivery Systems (TDS)

- The Agency comprehensively reviewed, (re)considered, updated, revised, clarified, and standardized BE recommendations for all TDS products
  - New and revised guidances for industry (GFIs)
  - New and revised product-specific guidances (PSGs)
  - More powerful statistical analyses
  - Enhanced flexibility to utilize alternative scales
  - More efficient and better controlled in vivo study designs

Conclusions

- The Agency is committed to:
  - Identifying opportunities for strategic research to support the development of evidence based, efficient BE standards
  - Reviewing, revising, and modernizing BE recommendations to ensure that they reflect the Agency's current thinking, based upon continually advancing scientific knowledge
  - Harmonizing BE standards within classes of topical and transdermal drug products, to improve the consistency and predictability of regulatory expectations

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