Advances in Topical Bioequivalence Assessments: Characterization-Based Approaches

Topical Drug Development - Evolution of Science and Regulatory Policy II

Challenges in Topical Drug Development – Harnessing In Vitro Methods

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)

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CDER | U.S. FDA

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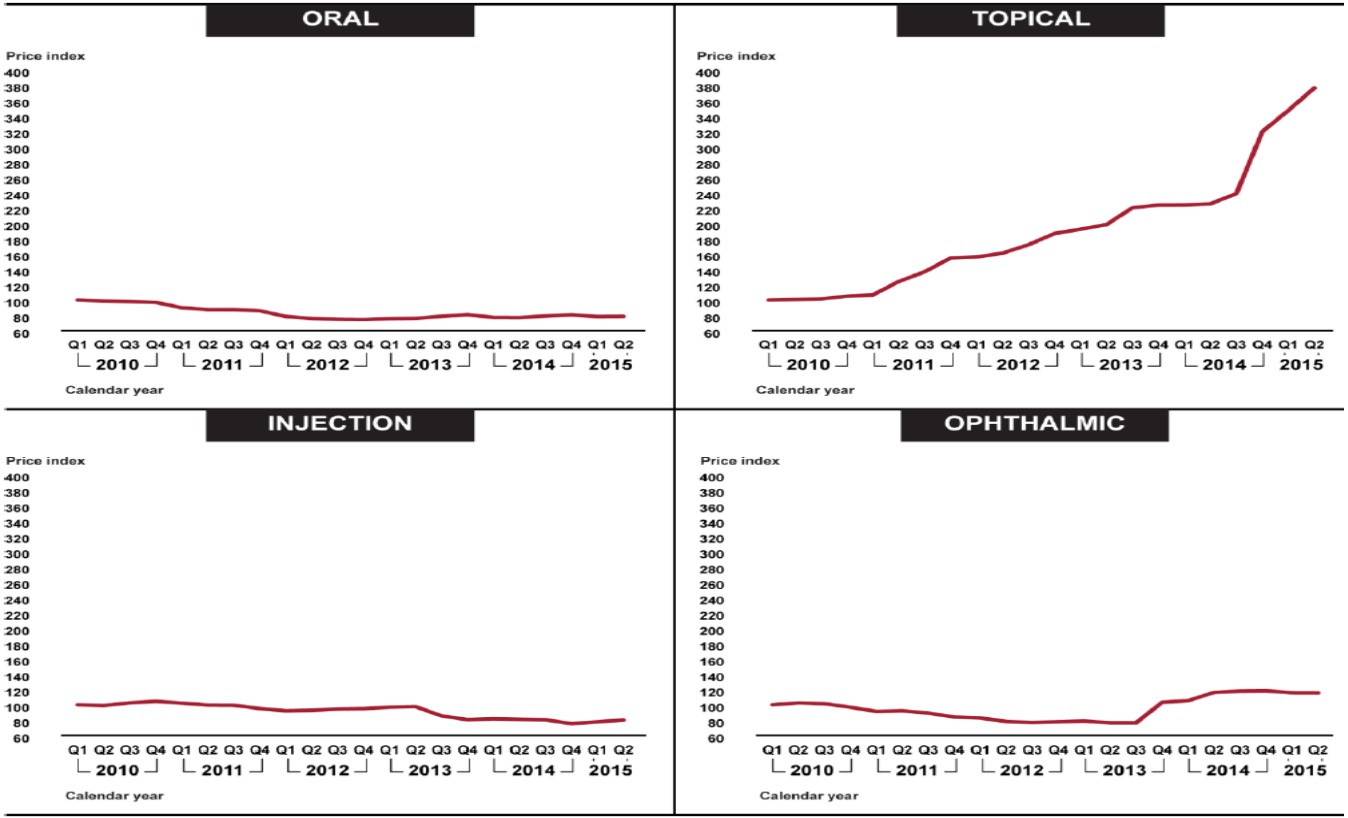
This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

The GAO Report (GAO-16-706)

- The U.S. Government Accountability Office (GAO) Report in August 2016 analyzed a period spanning Q1 of 2010 through Q2 of 2015
- **57%** of the topical drug products experienced an extraordinary price increase in that period
- The average price of topical generic drugs was **276% higher** by the end of the period analyzed
- Manufacturers and other stakeholders reported that market **competition**, influenced by various factors, drives generic drug prices

The GAO Report (GAO-16-706)



Source: GAO analysis of Medicare Part D prescription drug event data. | GAO-16-706

Retail Prices for Dermatologic Drugs

Drug	Type	Price, US $ 2009	2011	2014	2015	Absolute Change, 2009-2015	% Change, 2009-2015
Altabax, 15 g	I	92.50	106.18	168.75	196.86	104.36	112.82
Benzaclin, 50 g	A	166.79	205.80	451.29	503.85	337.06	202.08
Carac cream, 30 g	N	159.40	227.16	2939.68	2864.70	2705.30	1697.18
Clobex spray, 4 oz	S	389.57	500.29	827.11	958.01	568.44	145.91
Cloderm cream, 30 g	S	96.47	132.92	220.75	360.02	263.55	273.19
Cutivate lotion 120 mL	S	305.00	493.92	918.63	1067.25	762.25	249.91
Derma-Smoothe FS oil, 4 oz	S	45.70	47.23	247.84	322.67	276.97	606.06
Finacea, 50 g	A	124.42	185.42	288.92	284.30	159.88	128.51
Olux-E foam, 100 g	S	307.58	382.79	750.79	841.76	534.18	173.67
Oracea, 40 mg (30 tablets)	A	439.01	416.09	632.80	702.46	263.45	60.01
Oxistat cream, 30 g	I	76.50	119.25	399.00	544.66	468.16	611.97
Oxsoralen-Ultra, 10 mg (50 capsules)	P	1227.32	2150.49	4568.54	5204.31	3976.99	324.04
Retin-A Micro, 0.1%, 50 g	A	178.05	335.73	791.47	914.52	736.47	413.64
Solaraze gel, 100 g	N	442.89	618.56	1738.91	1883.98	1441.09	325.38
Soriatane, 25 mg (30 capsules)	P	757.75	958.50	1452.50	1595.27	837.52	110.53
Taclonex, 60 g	P	465.99	522.58	848.21	962.90	496.91	106.64
Targretin gel, one 60-g tube	N	1686.78	1787.97	15 708.40	30 320.12	28 633.34	1697.51
Tazorac cream, 0.1%, 60 g	A	266.18	464.96	656.20	722.27	456.09	171.34
Xolegel, 30 g	I	212.50	278.00	389.25	641.96	429.46	202.10

Abbreviations: A, acne and rosacea; I, antiinfective; N, antineoplastic; P, psoriasis; S, corticosteroid.

Source: Miranda E. Rosenberg, BA and Steven P. Rosenberg, MD (2016) *Changes in Retail Prices of Prescription Dermatologic Drugs From 2009 to 2015*. JAMA Dermatology. 152(2):158-163. doi:10.1001/jamadermatol.2015.3897

Patient Access to Topical Products

- Approximately 80% of topical dermatological drug products have fewer than three generic competitors; for many products no generics are available at all
- This may have been attributable to the historical barriers to the development of topical dermatological drug products, possibly including
  - Difficulty/issues with comparative clinical endpoint bioequivalence (BE) studies
  - The complex nature of topical formulations

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 and bioavailability at the target site
  - Skin (de)hydration, irritation, or damage
  - The metamorphosis of the dosage form on the skin

Failure Modes (BE) – Drug Substance

Is the Drug Substance **Dissolved** in the Formulation?

- Isomers of the drug
- pKa(s) of the drug
- pH of the formulation

Is the Drug Substance **Suspended** in the Formulation?

In addition to the potential failure modes identified on the left….

- Polymorphic forms of the drug
- Particle size distribution of the drug (and crystalline habit)

Failure Modes (BE) – Dosage Form

Is the Formulation a **Single Phase** System? *e.g., solution, gel*

- Excipient differences
- Viscosity/Rheology
- pH

Is the Formulation a **Multi Phase** System? *e.g., lotion, cream*

In addition to the potential failure modes identified on the left….

- Phases and arrangement of matter
- Distribution/localization of drug

Note: The packaging configuration itself may impact bioavailability

Mechanism and/or Site of Action

Is the Mechanism/Site of Action **Well Understood?**

- Acyclovir Topical Cream
- Benzyl Alcohol Topical Solution

An in vitro characterization based approach may be recommended

Is the Mechanism/Site of Action **Not Well Understood?**

- Dapsone Topical Gel
- Ivermectin Topical Cream

If the mechanism and/or site of action may be (partially) systemic, an in vivo PK study may also be recommended

Formulation of Topical Generics

- Sameness or '*No Difference*' in the topical formulation **Q1** (components) and **Q2** (composition)

  Mitigates the risk of failure modes related to:

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

Formulation of Topical Generics

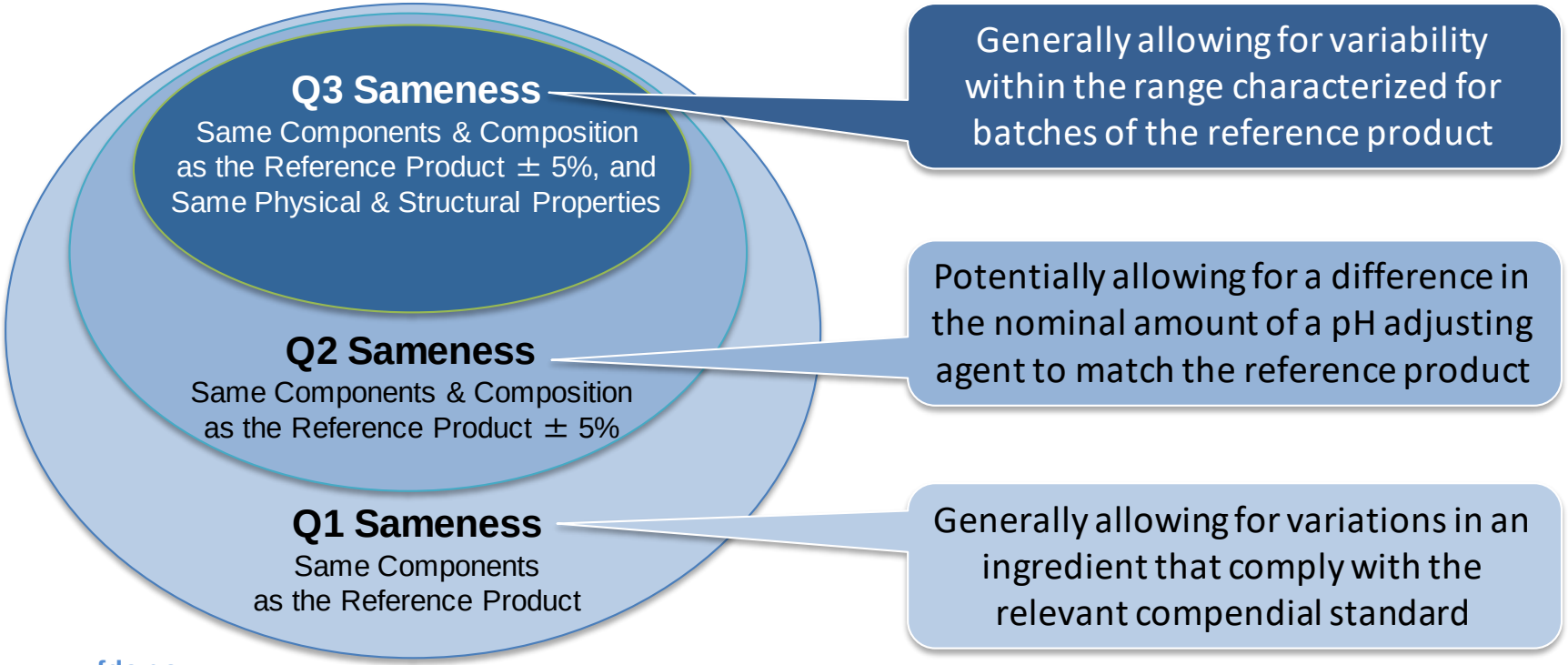
- Q3 Similarity (Arrangement of Matter)

  Mitigates the risk of failure modes related to differences in:

  - Q1/Q2 sameness (± 5% tolerances)
  - pH that may sting or irritate diseased skin
  - Polymorphic form of the drug
  - Rheology that alter the spreadability, retention, etc.
  - Entrapped air and drug amount per dose
  - Phase states and diffusion, partitioning, etc.
  - Metamorphosis and drying rates

Q3 Sameness for Topical Products

- An evolving concept *for topical dermatological products*



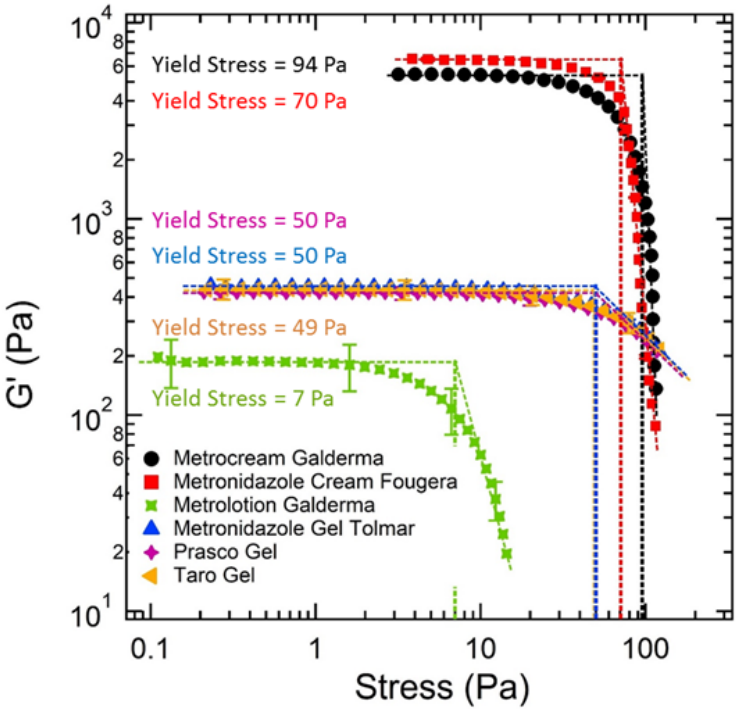
Evaluation of BE for Topical Products

- A Modular Framework for In Vitro BE Evaluation
  - **Qualitative (Q1) and Quantitative (Q2)** Sameness or '*No Difference*'
  - **Physical and Structural (Q3)** Sameness/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 Comparative Clinical Endpoint BE** Studies
  - **In Silico** Quantitative Methods, Modeling and Simulation

Metronidazole, 0.75% **In Vitro** 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***

Metronidazole, 0.75% **In Vitro** 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				
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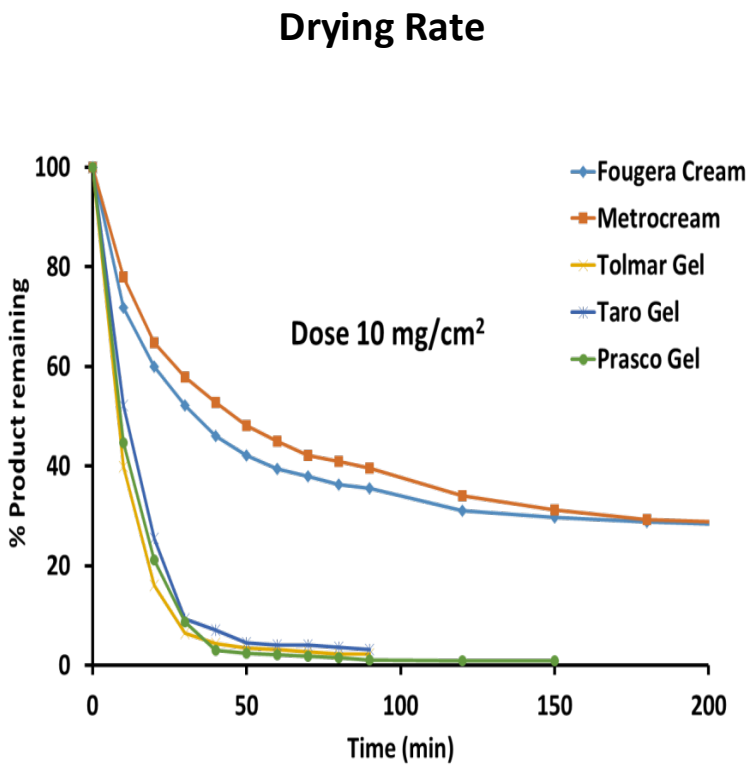

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pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
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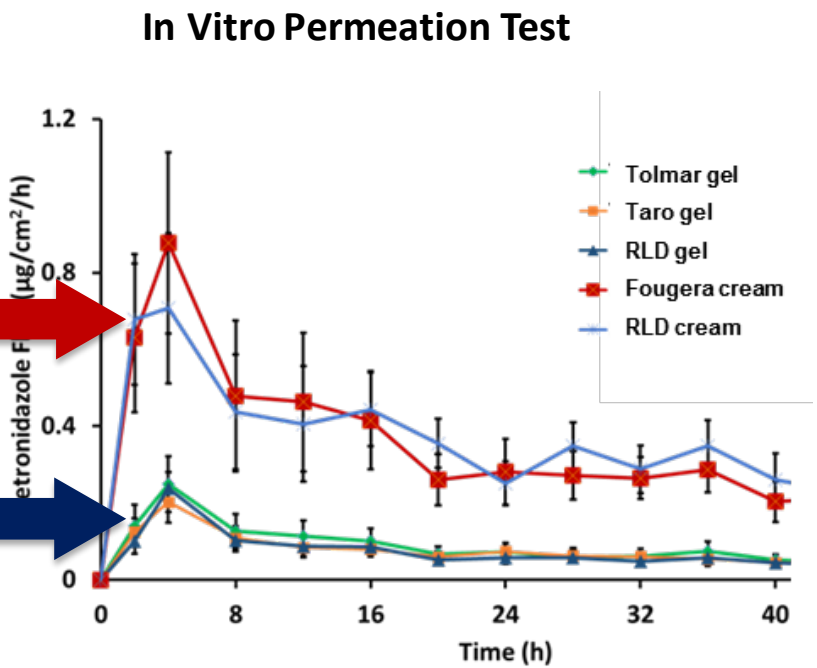

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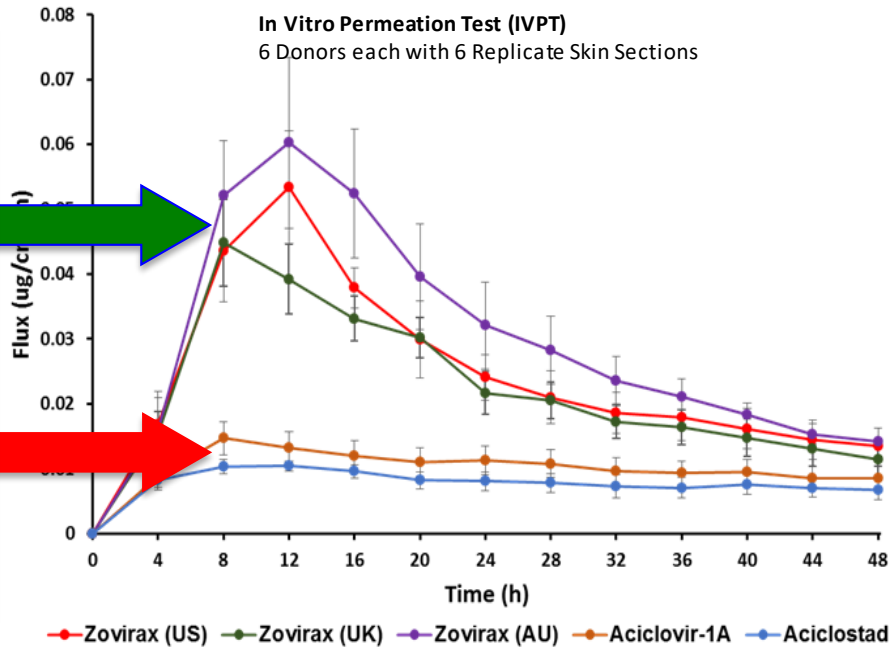
Product Quality and Performance

	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



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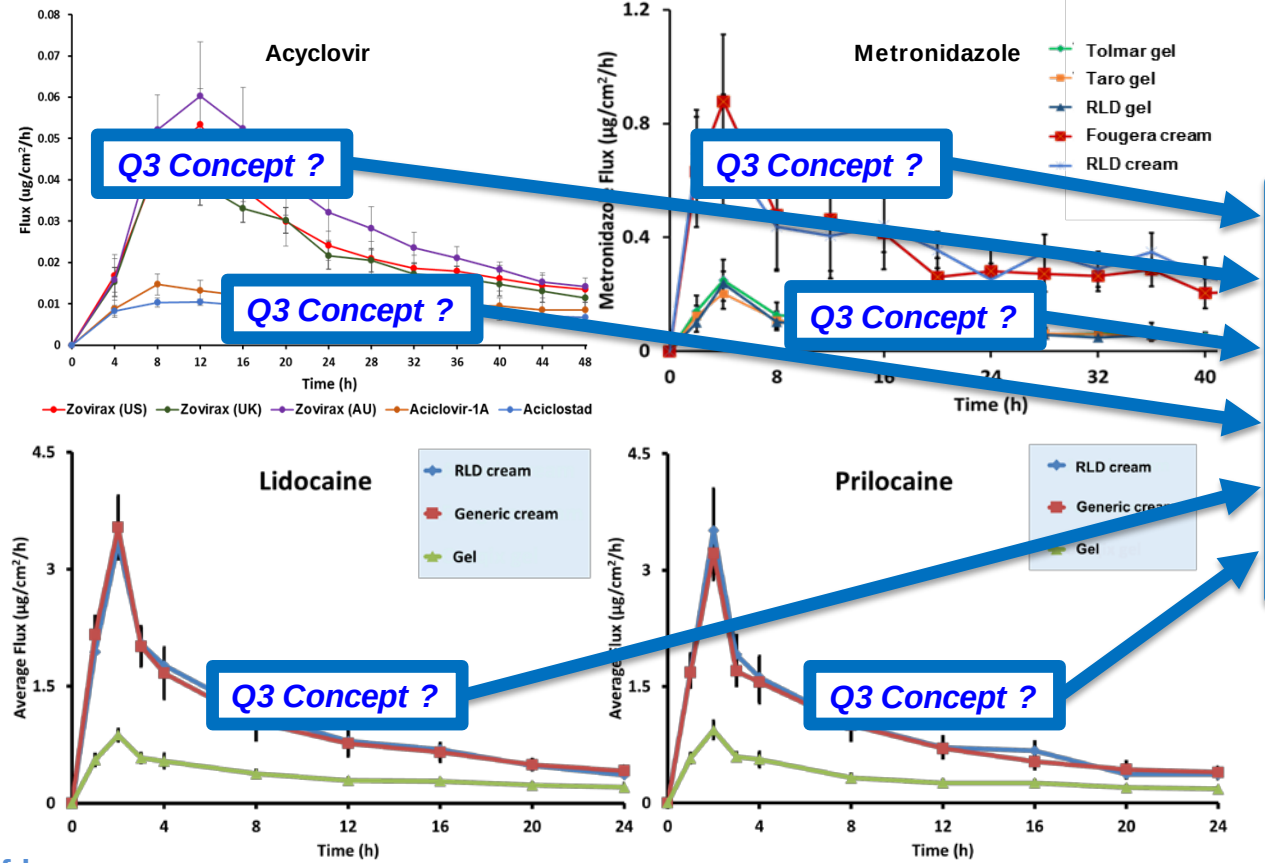
Product Quality and Performance



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

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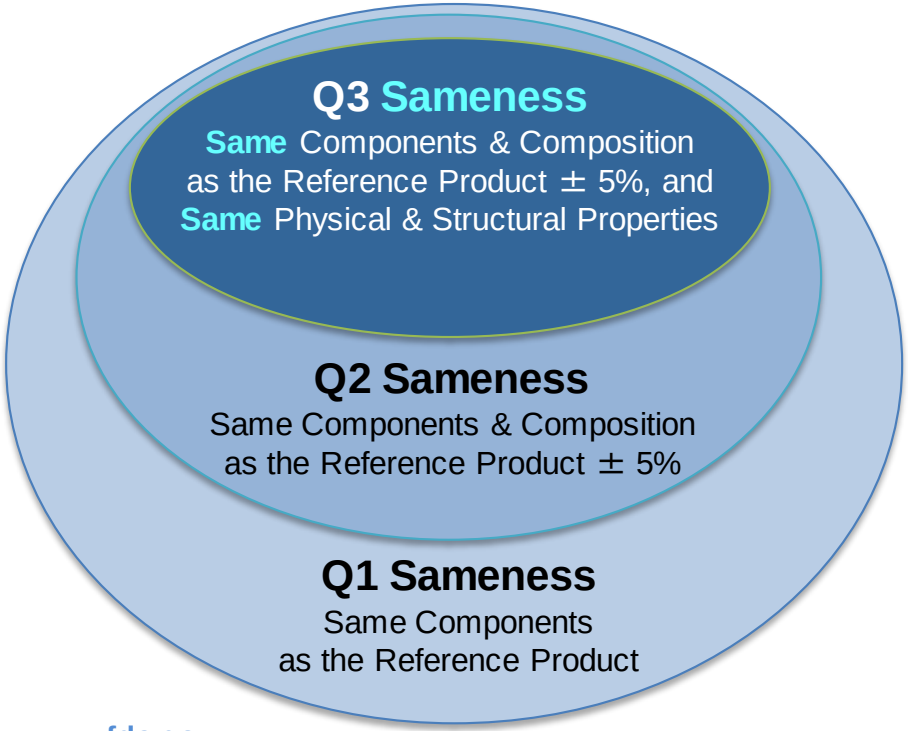
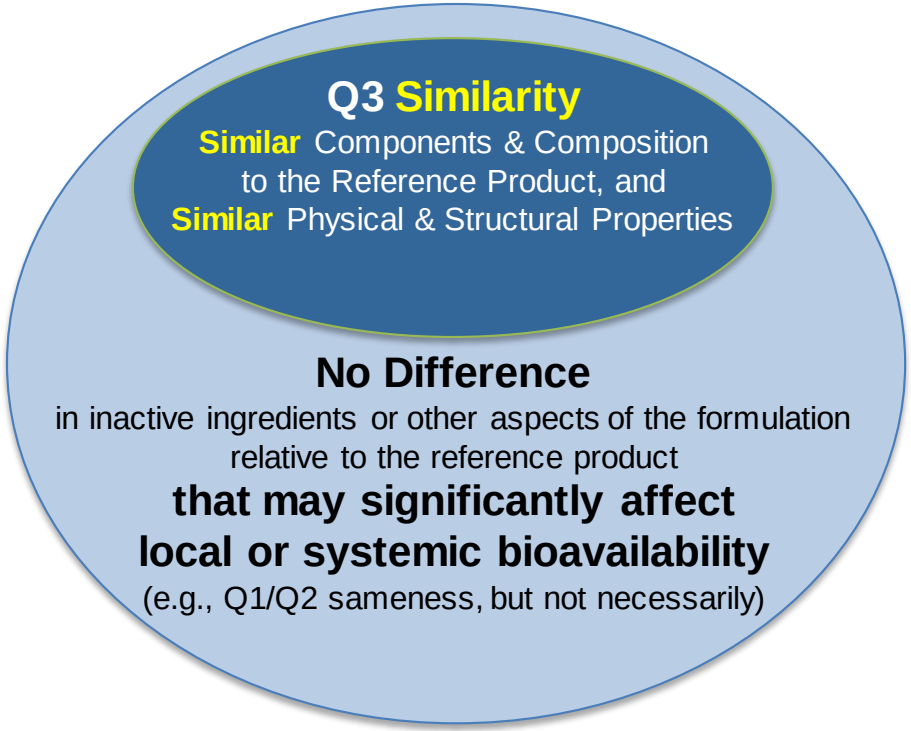
Q3 Sameness vs. Similarity

- An evolving concept *for topical dermatological products*





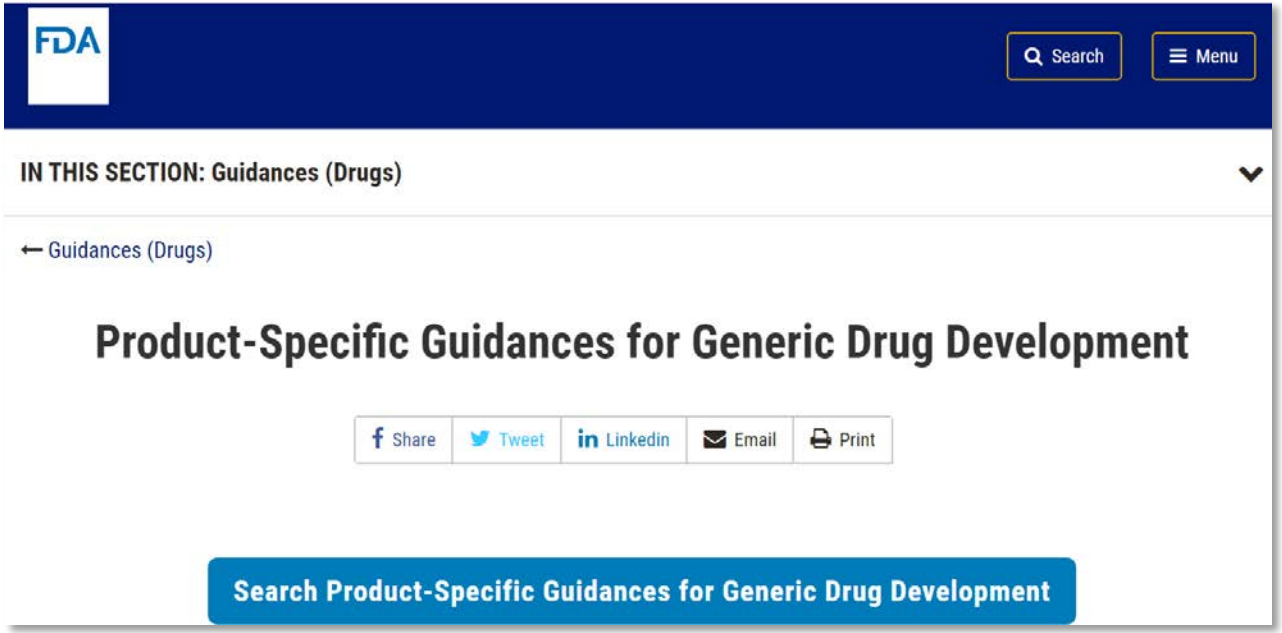
Alternative BE Approaches

- 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 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.

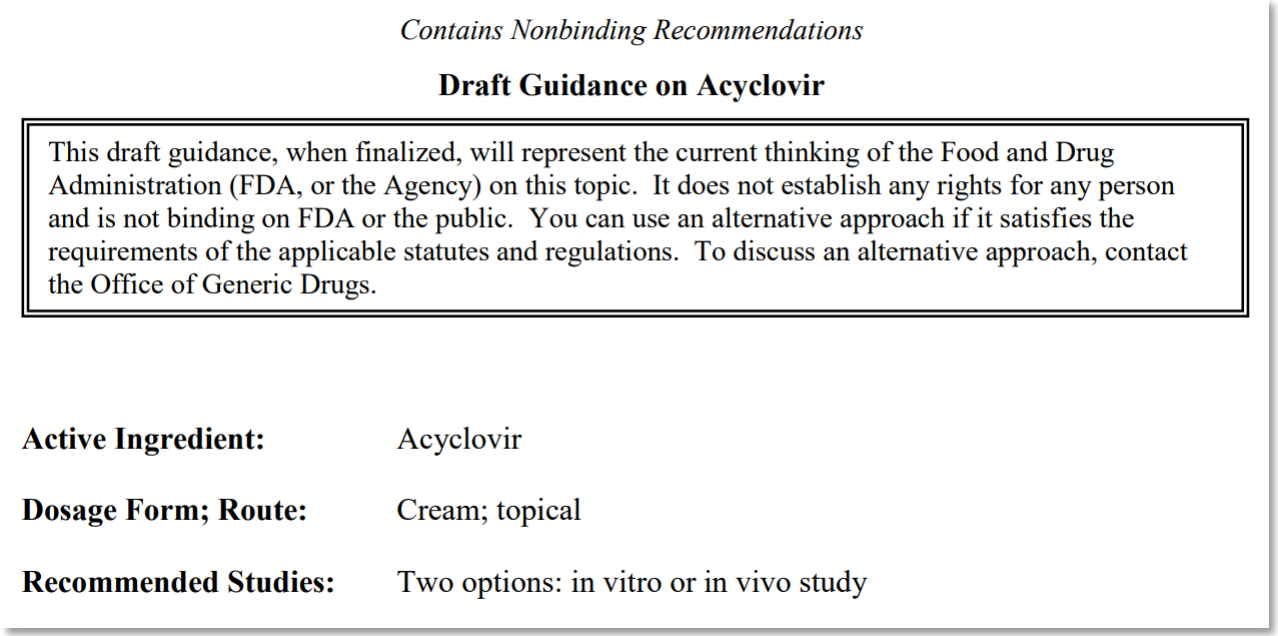
FDA Product-Specific Guidance (PSG)

- Product-Specific Guidances for Generic Drug Development (*Searchable*)
  https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development



FDA Acyclovir Cream PSG

- Draft Guidance on Acyclovir (*Recommended Dec 2014; Revised Dec 2016*)
  https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%2021478_RV12-16.pdf



Contains Nonbinding Recommendations

Draft Guidance on Acyclovir

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:	Acyclovir
Dosage Form; Route:	Cream; topical
Recommended Studies:	Two options: in vitro or in vivo study

Next Steps

- **Q3 Characterization**

  Developing compendial methods for Q3 characterization

  - What instrumentation to utilize (e.g., for polymorphs)
  - How many samples to analyze (e.g., number of particles)
  - How many replicates to use (e.g., rheological measurements)
  - How to report results (e.g., viscosity at low/mid/high shear)
  - Other considerations

Next Steps

- **IVRT Studies**

  Improving general understanding of IVRT principles and practices

  - Pseudo-infinite dose kinetics
  - Steady state release rate for a suitably sustained duration
  - Appropriate linearity of steady state region
  - Misconceptions surrounding a dose depletion exceeding 30%
  - Issues related to specific apparatus and/or metamorphosis
  - Issues related to studies with certain synthetic membranes

Next Steps

- **IVPT Studies**

  Improving general understanding of IVPT principles and practices

  - Finite dose kinetics, dose depletion, and metamorphosis
  - Diffusion cell apparatus and sampling of the receptor solution
  - Considerations relating to skin type, preparation, and storage
  - Barrier integrity assumptions, testing, and acceptance criteria
  - Study designs and data analyses (appropriate to context of use)
    - Dose duration vs. study duration; number of donors vs. replicates
    - Questions/Issues related to “outlier” or aberrant data

Future Research & Discussion

- Further develop standard (compendial) test methods for:
  - **Q3 Characterization**
- Enhance the overall level of investigator experience with principles and technical considerations for:
  - **IVRT Studies**
- Evolve/Establish best practices, study designs, qualified apparatus, and compendial methods for:
  - **IVPT Studies**

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