Use of Q3 Characterization Tests for Topical Semisolid Drug Products

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Session 6: Complex Generics: Topical Products, Part 1

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September 22, 2021

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The Concepts of Q1, Q2, Q3

- Q1: Components in a product
  - Q1 characterization of a reference product provides a profile of the qualitative components (ingredients) in that reference product
- Q2: Composition of a product
  - Q2 characterization of a reference product provides a profile of the quantitative formulation composition of that reference product
- Q3: Arrangement of matter in a product
  - Q3 characterization of a reference product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that reference product

Q3 Characterization

1. Characterization of appearance and texture
2. Characterization of phase states
3. Characterization of structural organization of matter
4. Characterization of polymorphic form of the active ingredient
5. Characterization of rheological behavior
6. Characterization of water activity and/or drying rate
7. Characterization of pH and buffering
8. Characterization of oleaginous components
9. Characterization of specific gravity
10. Characterization of metamorphosis-related changes

Basic Q3 Characterization

1. Characterization of appearance and texture
2. Characterization of phase states
3. Characterization of structural organization of matter
4. Characterization of polymorphic form of the active ingredient
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6. Characterization of water activity and/or drying rate
7. Characterization of pH and buffering
8. Characterization of oleaginous components
9. Characterization of specific gravity
10. Characterization of metamorphosis-related changes

Comprehensive Q3 Characterization

1. Characterization of appearance and texture
2. Characterization of phase states
3. Characterization of structural organization of matter
4. Characterization of polymorphic form of the active ingredient
5. Characterization of rheological behavior
6. Characterization of water activity and/or drying rate
7. Characterization of pH and buffering
8. Characterization of oleaginous components
9. Characterization of specific gravity
10. Characterization of metamorphosis-related changes

Utility of Q3 Characterization

1. To support a demonstration of **pharmaceutical equivalence**:
    - **Basic** Q3 characterizations for both the test and reference products can demonstrate that a test topical product and its reference product are the same dosage form (e.g., have the same number, type, and structural arrangement of phases)

Utility of Q3 Characterization

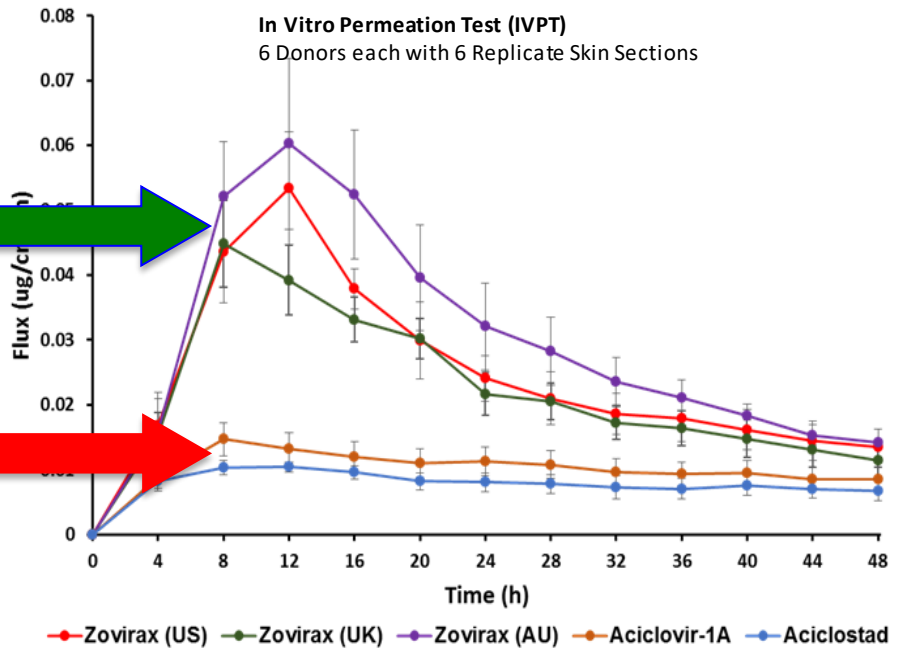
2. To support a demonstration of **bioequivalence**:

   - **Comprehensive** Q3 characterizations for both the test and reference products establishes a detailed profile of measurements for Q3 attributes that may potentially be critical to product performance, under relevant conditions. Matching the detailed profile of Q3 attributes for the test product to the detailed profile of Q3 attributes for the reference product substantially mitigates the risk of potential failure modes for bioequivalence.

In Vitro Cutaneous PK (Acyclovir)

In Vivo Cutaneous PK Study

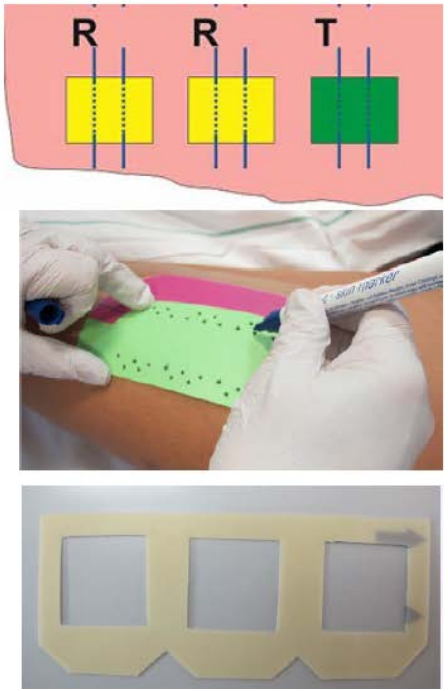
	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	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

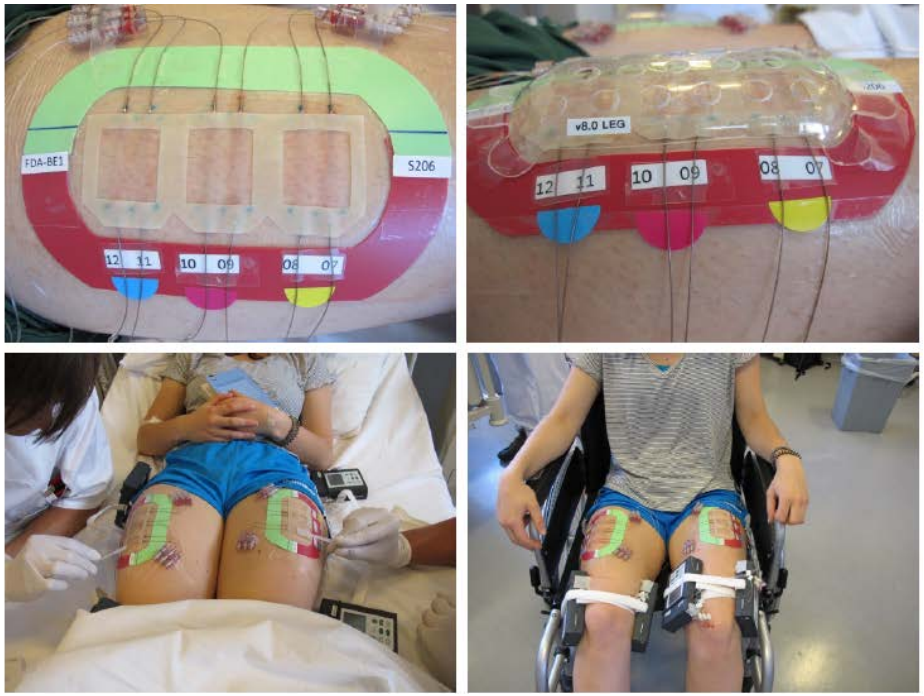


Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

In Vivo Cutaneous PK (Acyclovir)

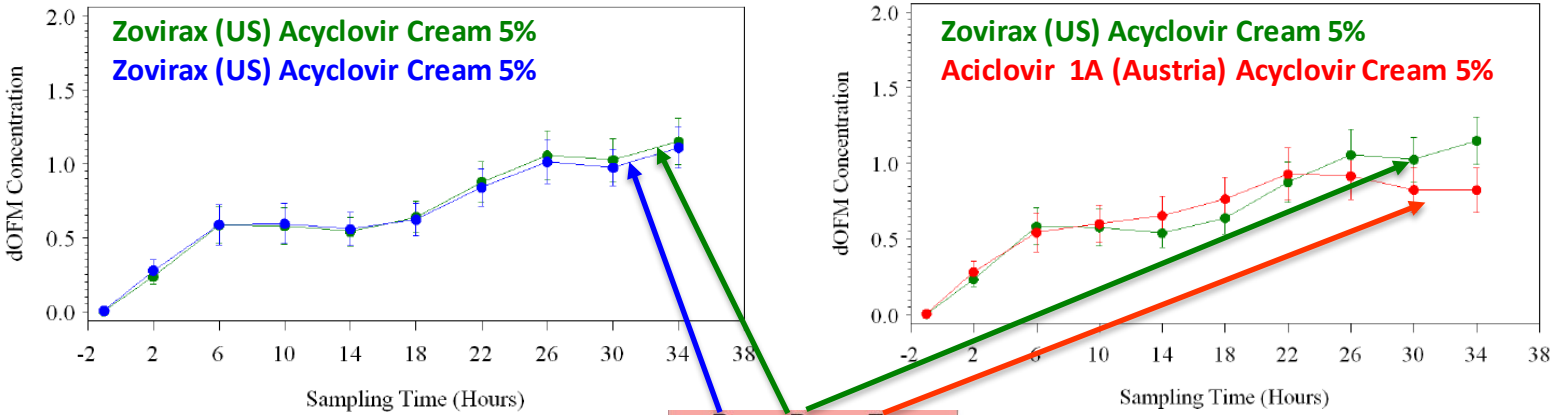
- dOFM: Testing Positive and Negative Controls for BE





 Images provided courtesy of Dr. Frank Sinner (Joanneum Research) ***FDA Award U01-FD004946*** dOFM = dermal Open Flow Microperfusion

In Vivo Cutaneous PK (Acyclovir)



Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]
log(C_{max})	[-0.155 ; 0.190] or [85.7 % ; 120.9%]

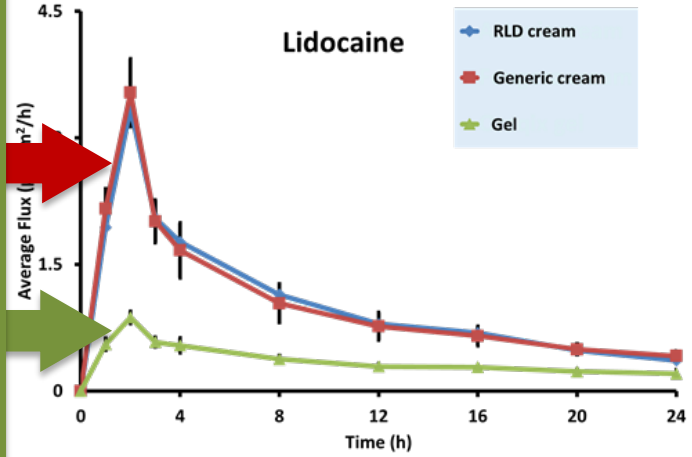
Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
log(C_{max})	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

Data provided courtesy of Dr. Frank Sinner (Joanneum Research) ***FDA Award U01-FD004946***

Bodenlenz et al. (2017) Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence. Clin Pharmacokinet. 2017 Jan;56(1):91-98. doi: 10.1007/s40262-016-0442-z (FREE Full Text Article)

In Vitro Cutaneous PK (Lidocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved				the formulation
Globule Size, d50 (µm)	3.30		3.00		
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.2	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223*** (RLD = Reference Listed Drug)

In Vivo Cutaneous PK (Lidocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocai		e completely dissolved		the formulation
Globule Size, d50 (µm)	3.30		3.00		---
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06			---
	Prilocain e	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.22	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
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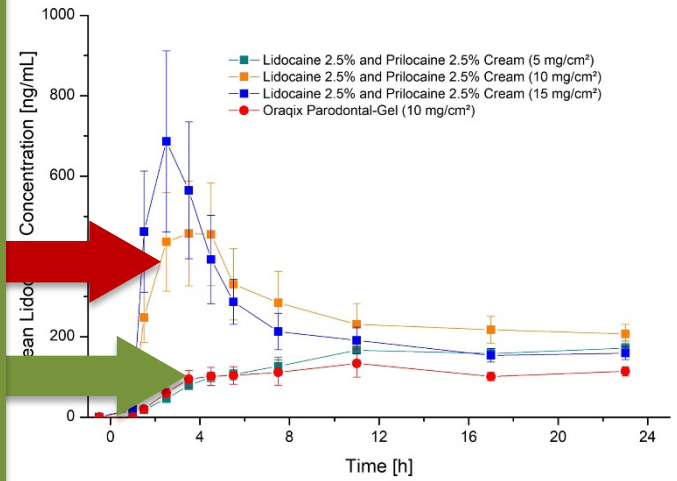
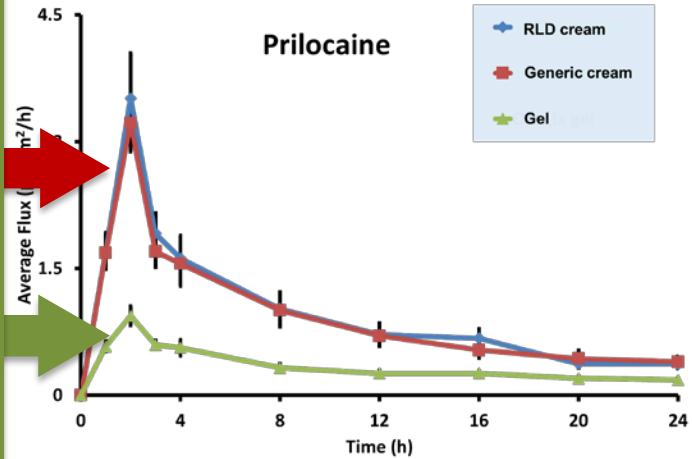


Data provided courtesy of Dr. Frank Sinner (Joanneum Research) ***FDA Award U01-FD005861***

In Vitro Cutaneous PK (Prilocaine)

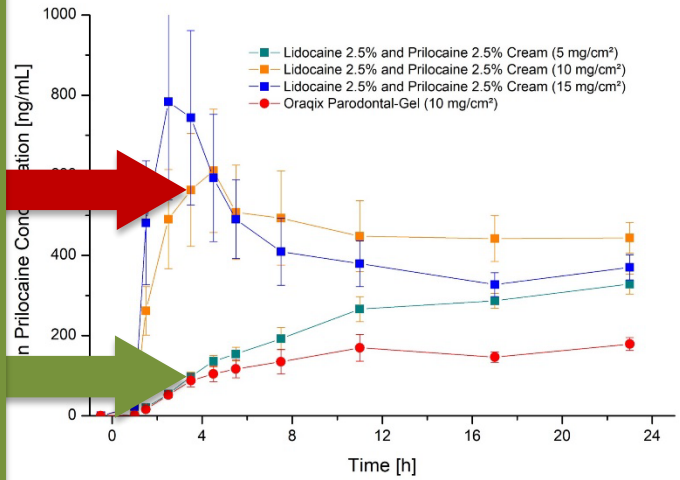
Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved				the formulation
Globule Size, d50 (µm)	3.30		3.00		
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.2	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223*** (RLD = Reference Listed Drug)

In Vivo Cutaneous PK (Prilocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocai		e completely dissolved		the formulation
Globule Size, d50 (µm)	3.30				
Drug in Aqueous Phase (µg/g)	idocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocain e	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	idocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	rilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.22	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3

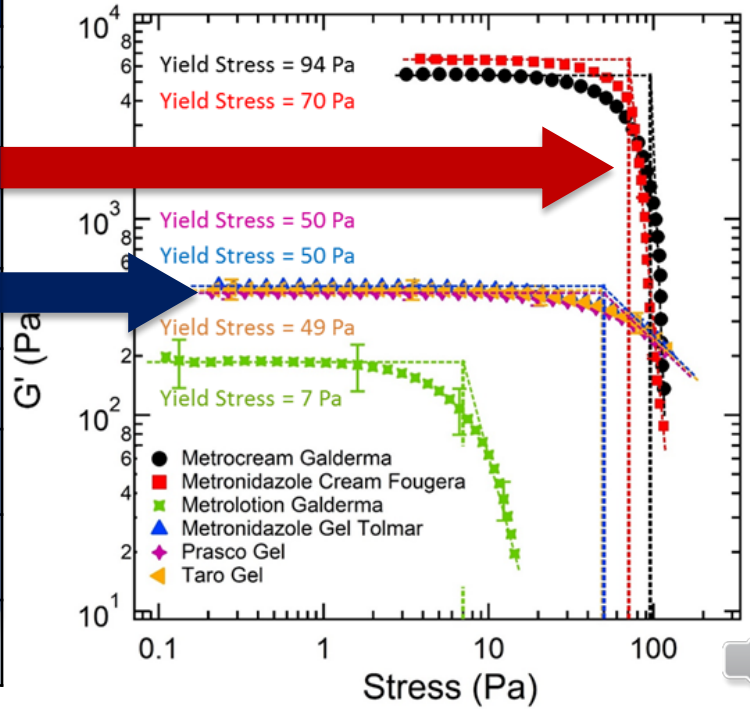


Data provided courtesy of Dr. Frank Sinner (Joanneum Research) ***FDA Award U01-FD005861***

In Vitro / In Vivo (Metronidazole)

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			
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***

In Vitro / In Vivo (Metronidazole)

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	---	---	---
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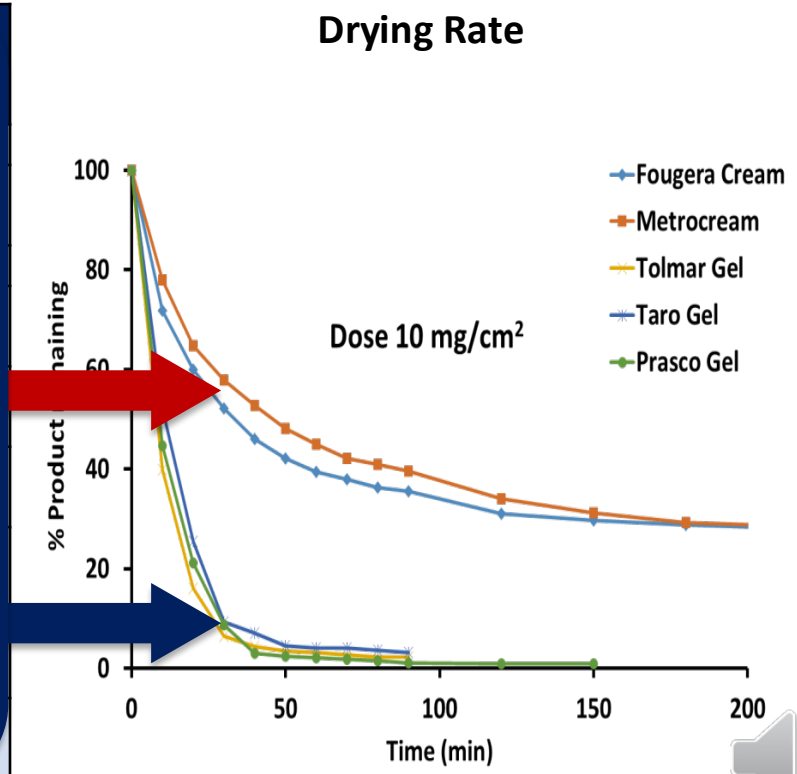
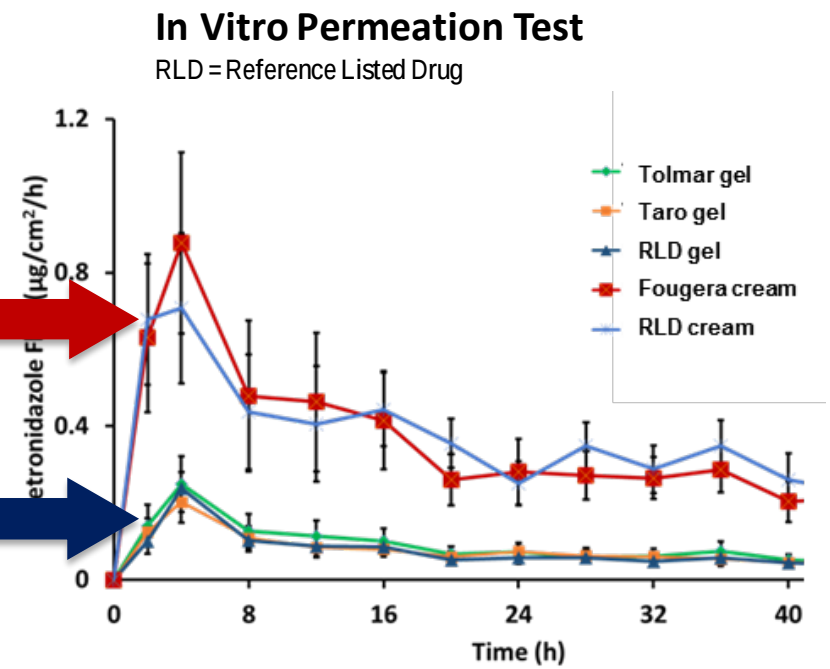


Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

In Vitro / In Vivo (Metronidazole)

Quality Attribute	MetroCream® (RLD Cream)	Generic Cream (Fougera)	Metrogel® (RLD Gel)	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



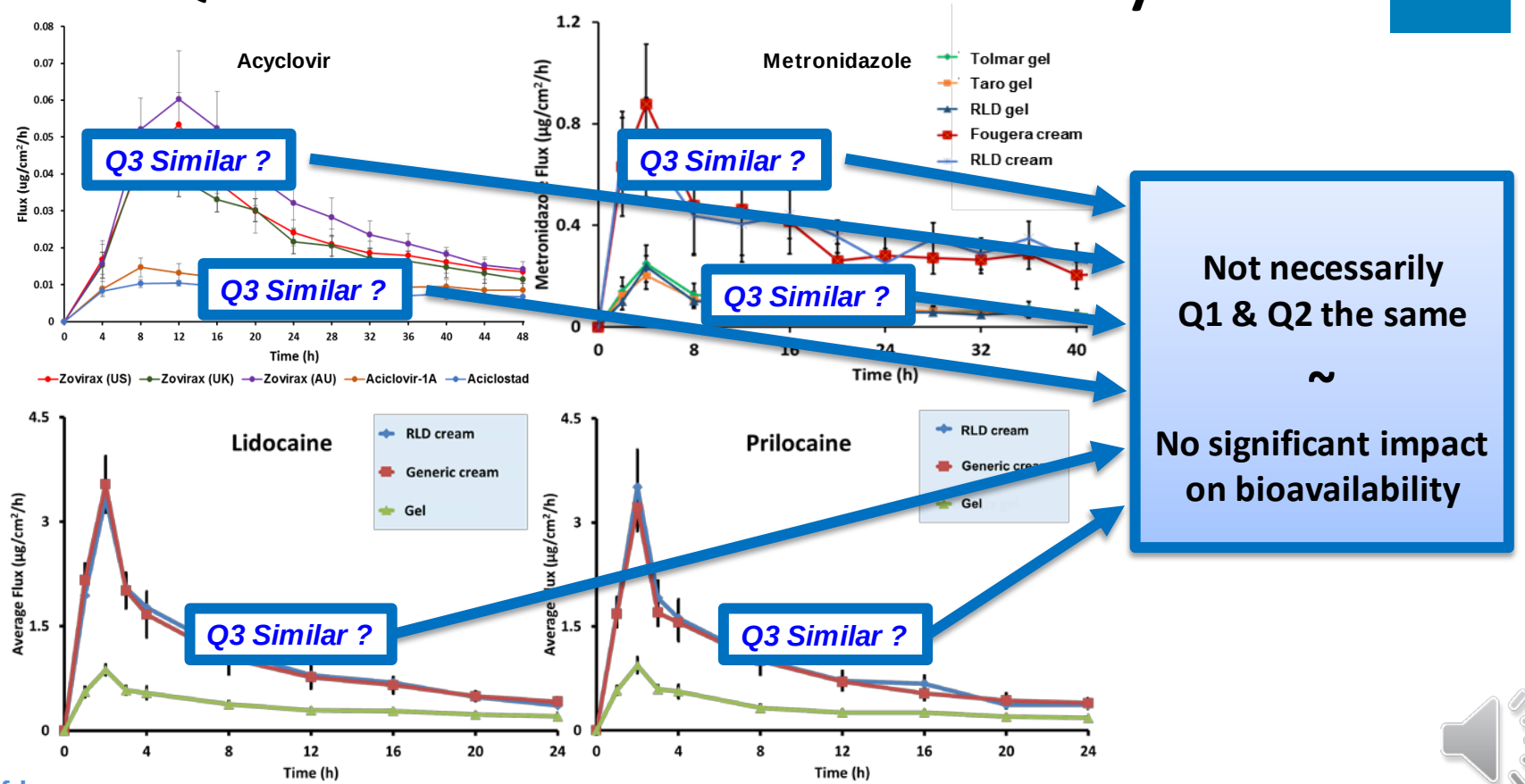
Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

Topical Dermatological Formulations

- Clinical evidence has demonstrated the bioequivalence 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 …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?***

Q3 Sameness vs. Similarity



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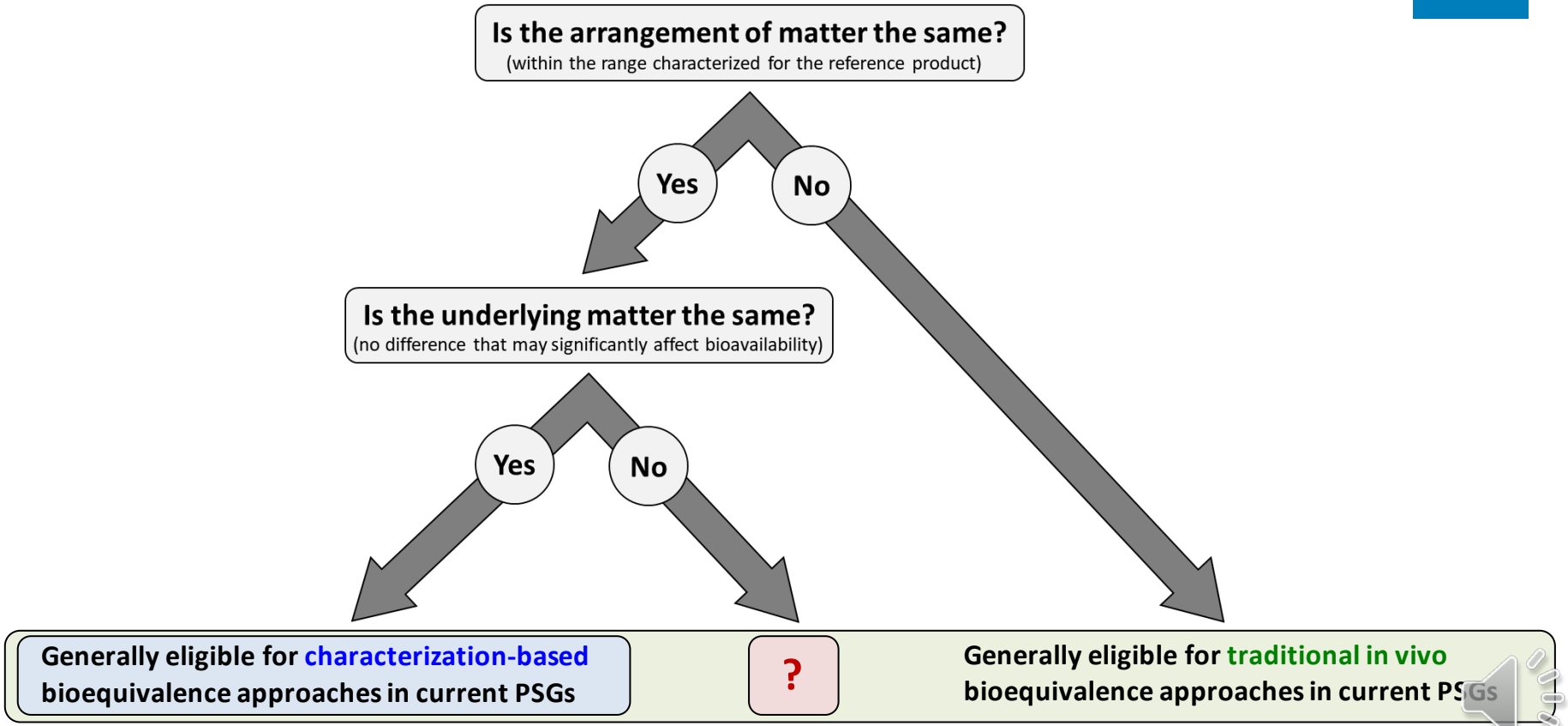
Product-Specific Guidances (PSGs)



Communication with FDA

- Applicants intending to submit an abbreviated new drug application (ANDA) for a topical product that relies upon a Q3-characterization-based bioequivalence approach, for which relevant recommendations have not been published in a PSG, are encouraged to request a pre-ANDA meeting with the FDA to discuss their proposed BE approach
- A pre-ANDA meeting request should include sufficient Q3 characterization to determine the number, type, and arrangement of phase states in the reference product, and product characterizations relevant to the nature, complexity, and identification of potential (therapeutic) failure modes for the test product

Conclusions

- Q3 characterization of a reference product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that reference product; these attributes may potentially be critical to product performance
- Basic Q3 characterization can demonstrate that a test and reference product are the same dosage form, and thereby, support a demonstration of pharmaceutical equivalence
- Comprehensive Q3 characterization establishes a detailed profile of measurements for Q3 attributes that may be critical to product performance; when these are the same for a test and reference product, it can support a demonstration of bioequivalence

Challenge Question

Which of the Following Statements is True:

A. Q3 characterization of a reference product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that reference product.

B. Basic Q3 characterizations can demonstrate that a test topical product and its reference product are the same dosage form, supporting a demonstration of pharmaceutical equivalence.

C. Comprehensive Q3 characterizations matching the detailed profile of Q3 attributes for the test product to the detailed profile of Q3 attributes for the reference product substantially mitigates the risk of potential failure modes for bioequivalence, supporting a demonstration of bioequivalence.

D. All of the above.

Challenge Question

Which of the Following Statements is True:

A. Q3 characterization of a reference product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that reference product.

B. Basic Q3 characterizations can demonstrate that a test topical product and its reference product are the same dosage form, supporting a demonstration of pharmaceutical equivalence.

C. Comprehensive Q3 characterizations matching the detailed profile of Q3 attributes for the test product to the detailed profile of Q3 attributes for the reference product substantially mitigates the risk of potential failure modes for bioequivalence, supporting a demonstration of bioequivalence.

D. All of the above.

Acknowledgements

U.S. Food & Drug Administration

- Bing Cai, PhD
- Pahala Simamora, PhD
- Richard Chang, PhD
- Mindy Ehrenfried, JD
- Priyanka Ghosh, PhD
- Tannaz Ramezanli, PharmD, PhD
- Markham C. Luke, MD, PhD
- Robert Lionberger, PhD

Research Collaborators

Funding for studies for which results were shown was made possible, in part, by U.S. FDA through:

FDA Award U01 - FD005223

Prof. Narasimha Murthy, PhD
The University of Mississippi

FDA Award U01 - FD004946/5861

Dr. Frank Sinner, PhD
Joanneum Research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U.S. FOOD & DRUG
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