Overview of Breakout Session on Topical Drug Products

Workshop on Complex Generic Drug Products (CGDPs)

Association for Accessible Medicines - GRx+Biosims 2020

November 10, 2020

Sam Raney, PhD
Office of Research and Standards
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.

Patient Access to Generic Drugs

- Generic drugs must demonstrate bioequivalence (BE)
  - Per 21 CFR 314.3: *BE is the absence of a significant difference in the **rate and extent to which the active ingredient** or active moiety in pharmaceutical equivalents or pharmaceutical alternatives **becomes available at the site of drug action** when administered at the same molar dose under similar conditions in an appropriately designed study.*
- For systemically acting drug products, it is **efficient** to demonstrate BE by pharmacokinetics (PK) based studies
- For locally acting drug products, it has been **challenging** to directly assess the rate and extent to which the active ingredient becomes available at the site of action

The AAM Reports

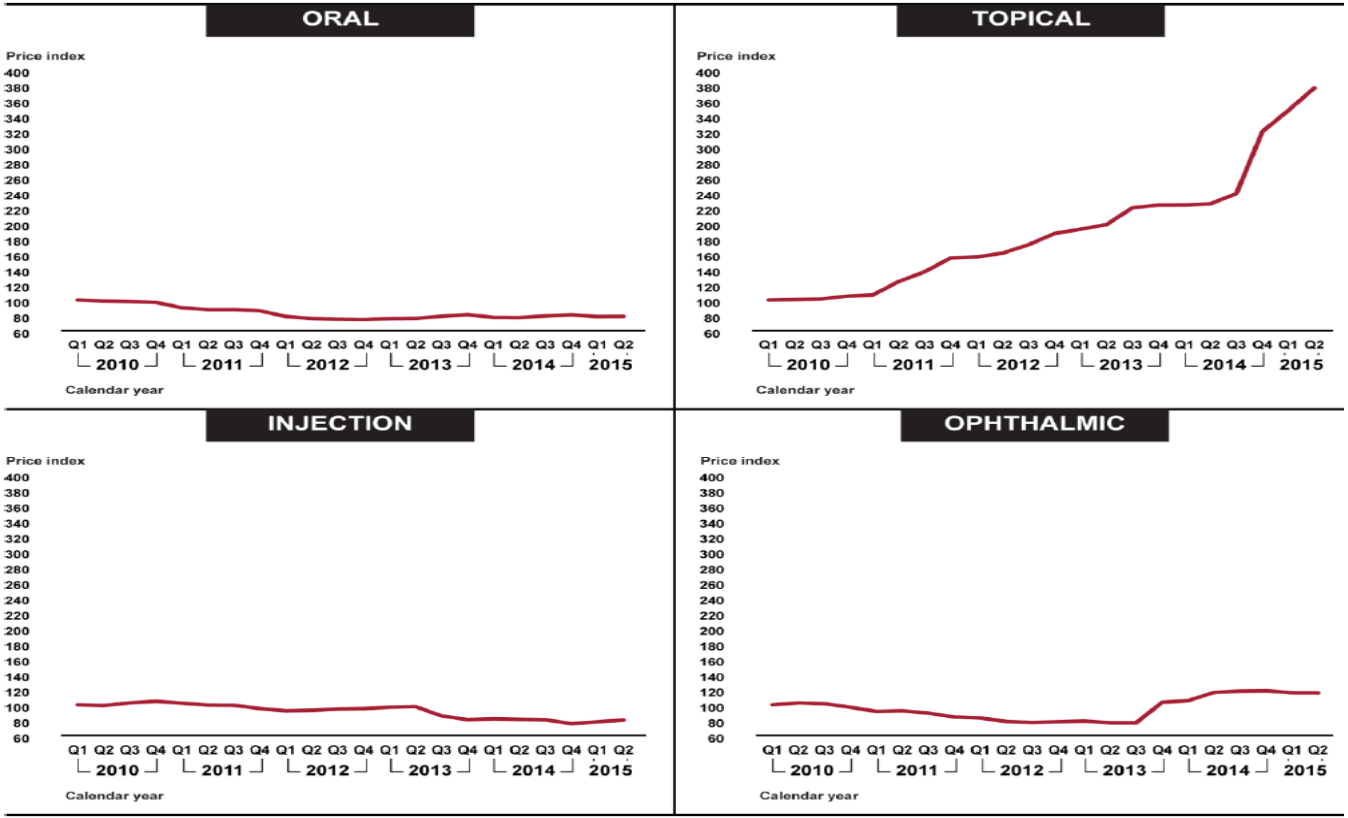
- The Association for Accessible Medicines (AAM) 2017[1] and 2020[2] Generic Drug Access & Savings Reports have documented the ***overall*** success of generic drugs
- **90%** of the of the prescriptions filled in the U.S. during 2019 were dispensed as generics, up from 89% in 2016
- **95%** of generic prescriptions were filled at ≤ $20, up from 90% in 2016; the average generic copay in 2019 was **$6.97**
- ***Overall***, this represented **exceptional patient access** to high quality, safe, effective, affordable medicines, even in 2016

[1] AAM Report: 2017 Generic Drug Access & Savings in the U.S. (https://accessiblemeds.org)
[2] AAM Report: 2020 Generic Drug & Biosimilars Access & Savings in the U.S. (https://accessiblemeds.org)

The GAO Report

- The U.S. Government Accountability Office (GAO) Report (GAO-16-706; August 2016) had analyzed a period spanning Quarter 1 of 2010 through Quarter 2 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 Topical Products

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

- Most topical dermatological drug products had fewer than three generic competitors; for many products no generics were available at all
- This may have been attributable to the historical challenges impacting the development of topical dermatological generic drug products, possibly including
  - Absence of efficient PK-based approaches by which to demonstrate BE
  - Inefficiency of high risk, costly, comparative clinical endpoint BE studies
  - The complex nature of topical formulations
- FDA had begun research to develop more efficient ways to demonstrate BE for complex generics, including topicals

Concept of BE for Topical Products

- **In Vitro** Methods to Support a Demonstration of BE
  - **Qualitative (Q1) and Quantitative (Q2)** Sameness or '*No Difference*'
  - **Physicochemical and Structural (Q3)** Sameness/Similarity
  - **IVRT** (In Vitro Release Test)
  - **IVPT** (In Vitro Permeation Test)
- **In Vivo/In Silico** Methods to Support a Demonstration of BE
  - **In Vivo Pharmacokinetic (PK)** Studies
  - **In Vivo Pharmacodynamic** (Vasoconstrictor) Studies
  - **In Vivo Comparative Clinical Endpoint BE** Studies
  - **In Silico** Quantitative Methods, Modeling and Simulation

Topical Products Breakout Session

Part I: Rapid Review Modules

Qualitative (Q1) and Quantitative (Q2) Assessments
Dr. Megan Kelchen

Physicochemical and Structural (Q3) Assessments
Dr. Hailing Zhang

IVRT Studies
Dr. Mengmeng Niu

IVPT Studies
Dr. Priyanka Ghosh

In Silico Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation
Dr. Eleftheria Tsakalozou

Topical Products Breakout Session

Part II: Interactive Generic Product Development Exercise

Introduction to a Hypothetical Reference Product (*RHEOMACREAM*)
Dr. Tannaz Ramezanli

Interactive Scenarios on Formulation Development and BE Strategies
Dr. Priyanka Ghosh, Dr. Wendy Good, Dr. Megan Kelchen, Dr. Markham Luke, Dr. Mengmeng Niu, Dr. Tannaz Ramezanli, Dr. Sam Raney, Dr. Eleftheria Tsakalozou, Dr. Hailing Zhang

Simulated (Mock) Pre-ANDA Product Development Meeting
Dr. Priyanka Ghosh, Dr. Wendy Good, Dr. Megan Kelchen, Dr. Markham Luke, Dr. Mengmeng Niu, Dr. Tannaz Ramezanli, Dr. Sam Raney, Dr. Eleftheria Tsakalozou, Dr. Hailing Zhang

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- Andrew Babiskin, PhD
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- Richard Chang, PhD
- Pahala Simamora, PhD
- Bing Cai, PhD
- Markham C. Luke, MD, PhD
- Liang Zhou, PhD
- Lei Zhang, PhD
- Robert Lionberger, PhD

U.S. FOOD & DRUG ADMINISTRATION

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Part I: Rapid Review Modules

Qualitative (Q1) and Quantitative (Q2) Assessments

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Megan Kelchen, PhD

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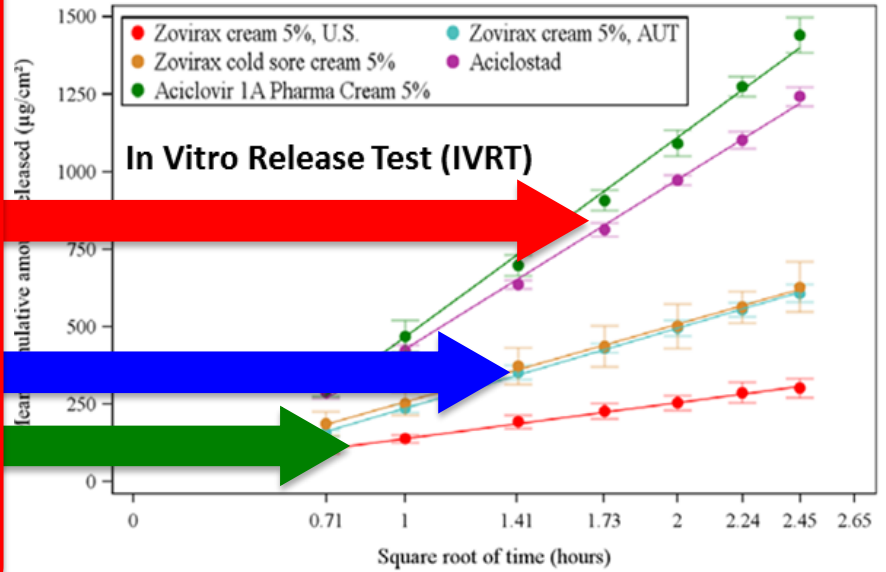
Topical Dermatological Formulations

- 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

Quality and Performance (Acyclovir)

	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 alcohol	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		
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate		
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8				
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***

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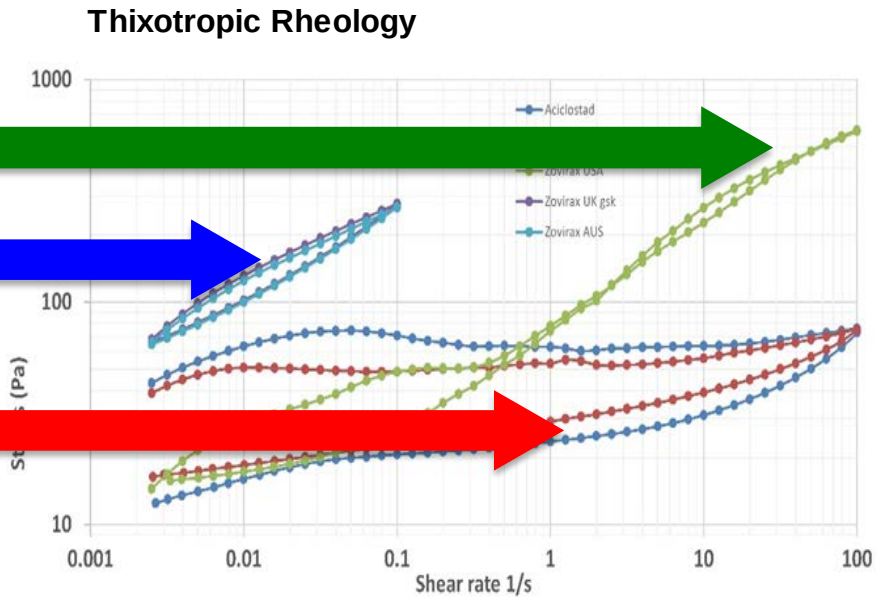
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum				
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20		
		Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Polyoxyethylene stearate	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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In Vitro Cutaneous PK (Acyclovir)

In Vivo Cutaneous PK Study

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	Water	Water	Purified water	Water	Water
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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
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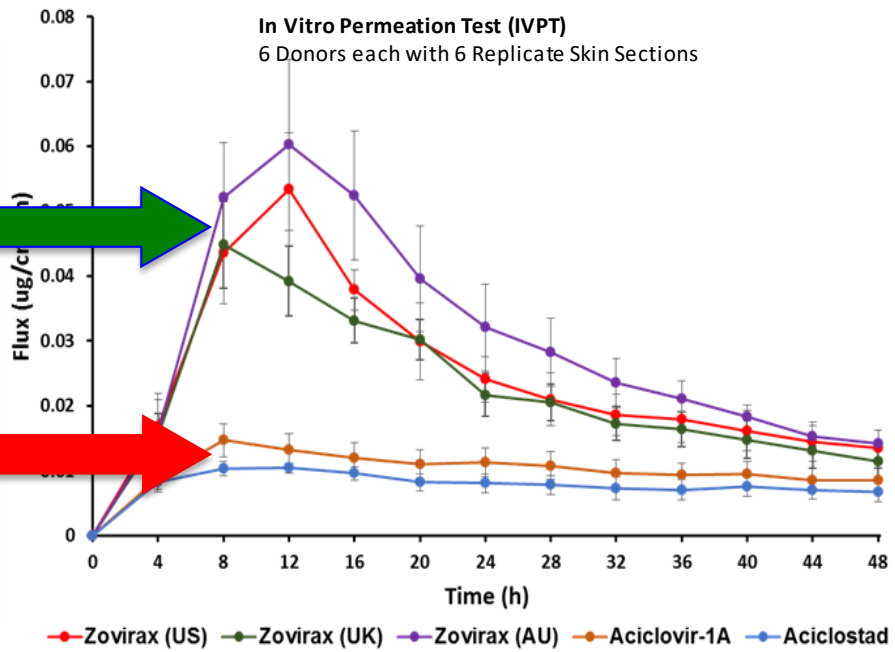
Water Activity	0.75	0.73	0.74	0.95	0.95



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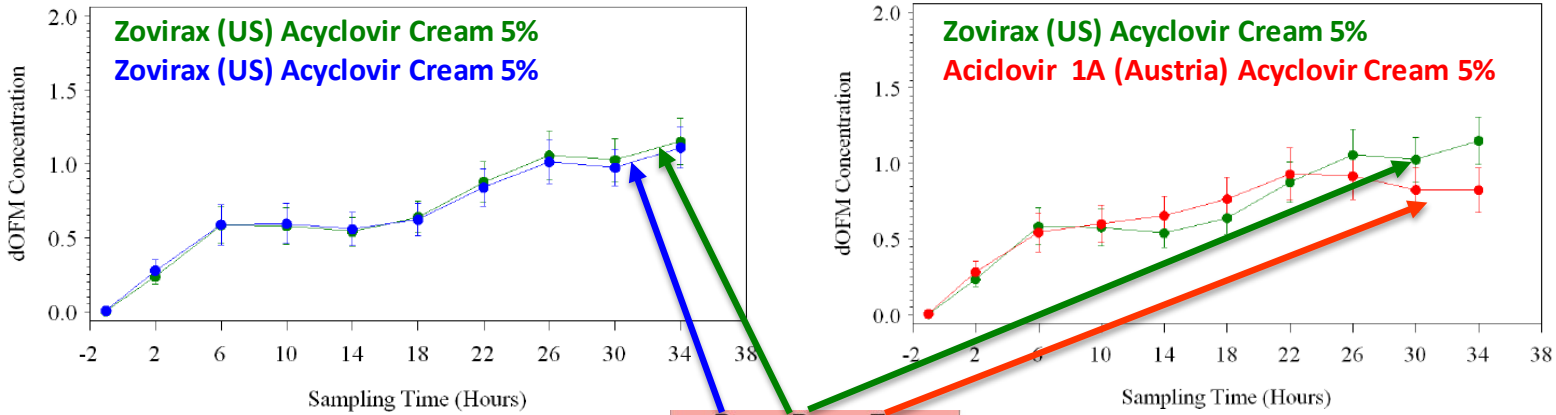
In Vivo Cutaneous PK (Acyclovir)



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)

Waiver of In Vivo Evidence of BE

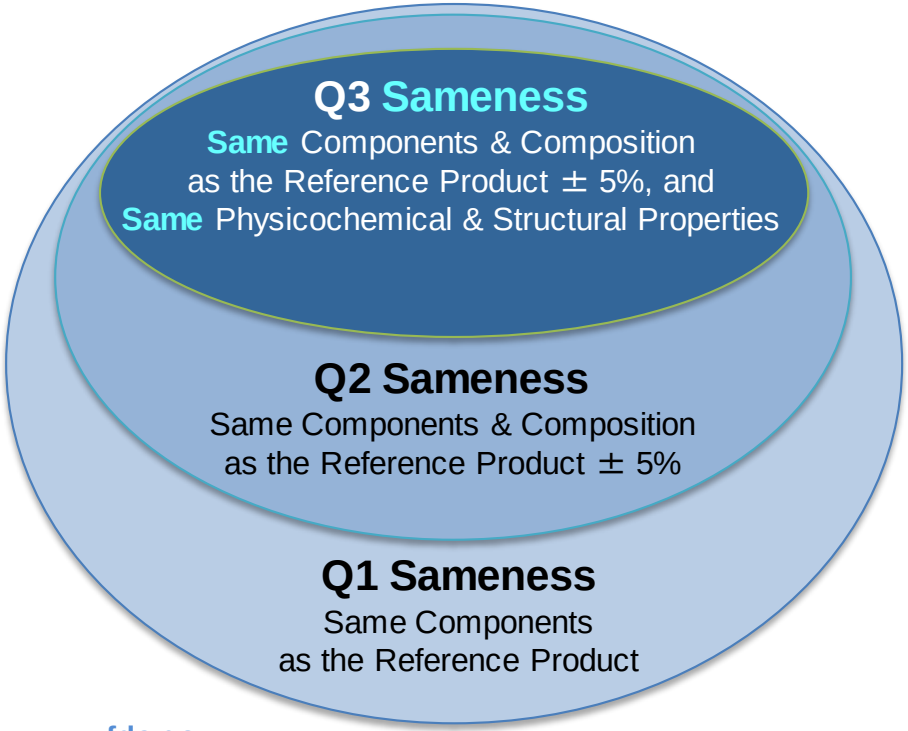
Title 21 of the Code of Federal Regulations, Section 320.22 [21CFR320.22(b)]

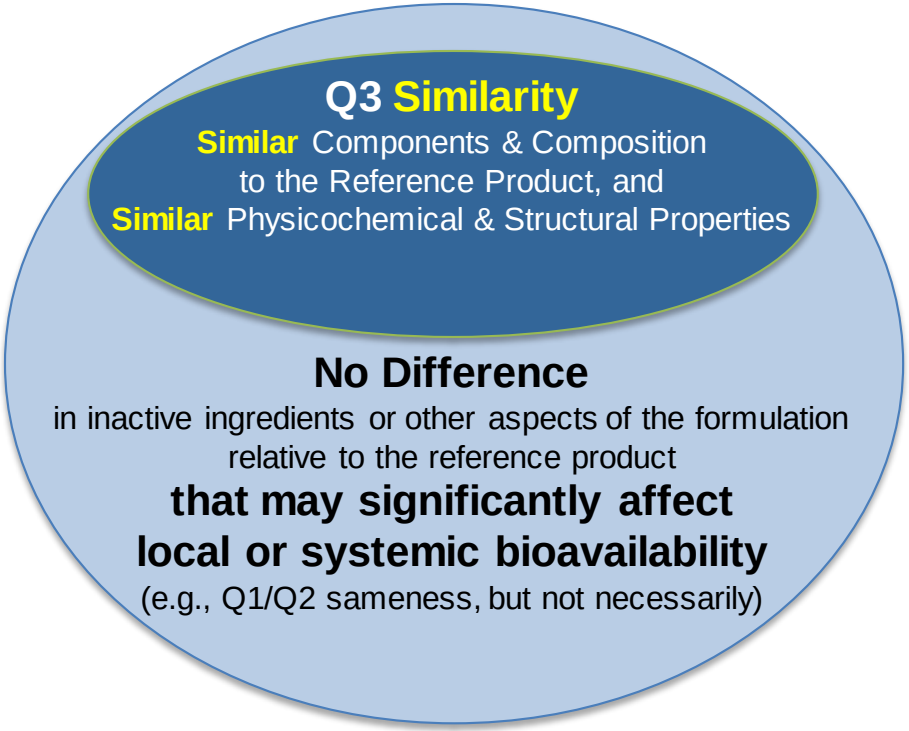
- **Parenteral solutions for injection or ophthalmic or otic solutions**
  - ⇨ Should contain "*the same active and inactive ingredients in the same concentration*" as the reference product
  - ⇨ **Q1 and Q2 sameness**

- **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**

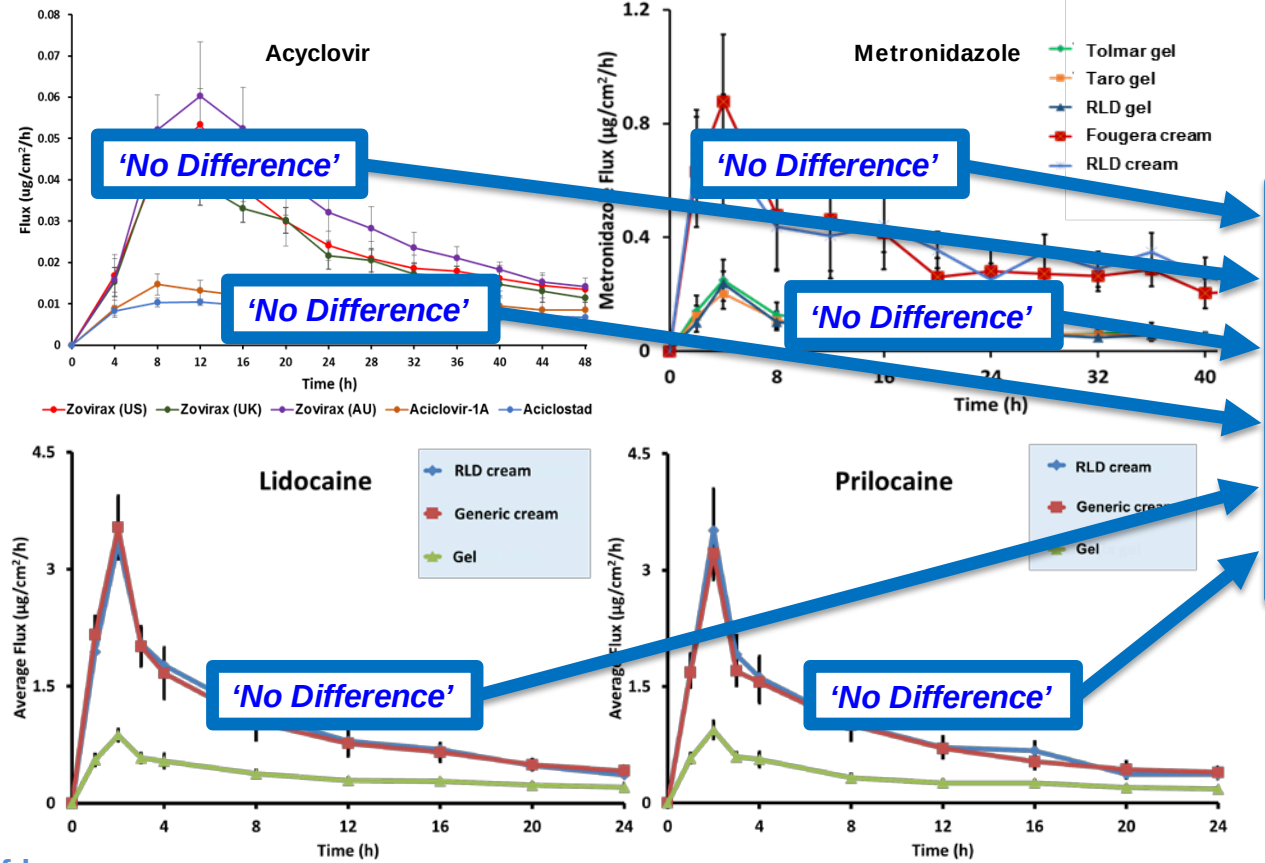
Q3 Sameness vs. Similarity

- An evolving concept *for topical dermatological products*





Q1/Q2 Sameness vs. 'No Difference'



Not necessarily
Q1 & Q2 the same

~

No significant impact on bioavailability

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

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
    - 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

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- Lei Zhang, PhD
- Robert Lionberger, PhD

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  University of Mississippi

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- Frank Sinner, PhD
  Joanneum Research

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Physicochemical and Structural (Q3) Assessments

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Hailing Zhang, PhD

Office of Lifecycle Drug Products

Office of Pharmaceutical Quality

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Physicochemical & Structural Characterization

Physicochemical and structural (Q3) characterizations describe the essential properties of the product which may be critical to its performance.

- Q3 characteristics collectively represent the arrangement of matter in the dosage form
- Q3 characteristics may potentially be critical to product performance under relevant conditions

Comparative Q3 characterization between a test & reference topical dermatological product is critical

- to demonstrate that a test product and its reference product are the same dosage form
- to evaluate whether there are Q3 differences between the test and reference products that may affect BE.

Totality of Q3 characterization is critical to compare test and reference topical dermatological products.

Q3 Characterization in a Topical Dermatological Product ANDA – Points to Consider

It is recommended to perform Q3 characterization to demonstrate that a proposed topical dermatological product is pharmaceutically equivalent and/or bioequivalent to the reference product.

It is recommended that relevant comparative characterizations should be performed with a minimum of three batches of the test product and three batches (as available) of the reference product.

The particular Q3 characteristics that should be assessed for a specific proposed generic topical dermatological product will depend on the nature and complexity of its reference product.

Q3 Characterization in a Topical Dermatological Product ANDA

General recommendations on the characterizations:

1. Characterization of appearance and texture

2. Characterization of phase states – to support the drug is dissolved in the dosage form, and/or single-phase dosage form (as relevant)

3. Characterization of structural organization of matter – to assess particle size distribution and crystal habit, and/or emulsion globule size distribution (as relevant)

4. Characterization of polymorphic form(s) of the active ingredient(s)

5. Characterization of rheological behavior

- Complete flow curves (plotted as both, shear stress vs. shear rate and viscosity vs. shear rate) should consist of multiple data points across the range of attainable shear rates, typically until low or high shear plateaus are identified;
- Yield stress values should be reported if the material tested exhibits plastic flow behavior; and
- The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.

Q3 Characterization in a Topical Dermatological Product ANDA

General recommendations on the characterizations –continued

6. Characterization of water activity and/or drying rate

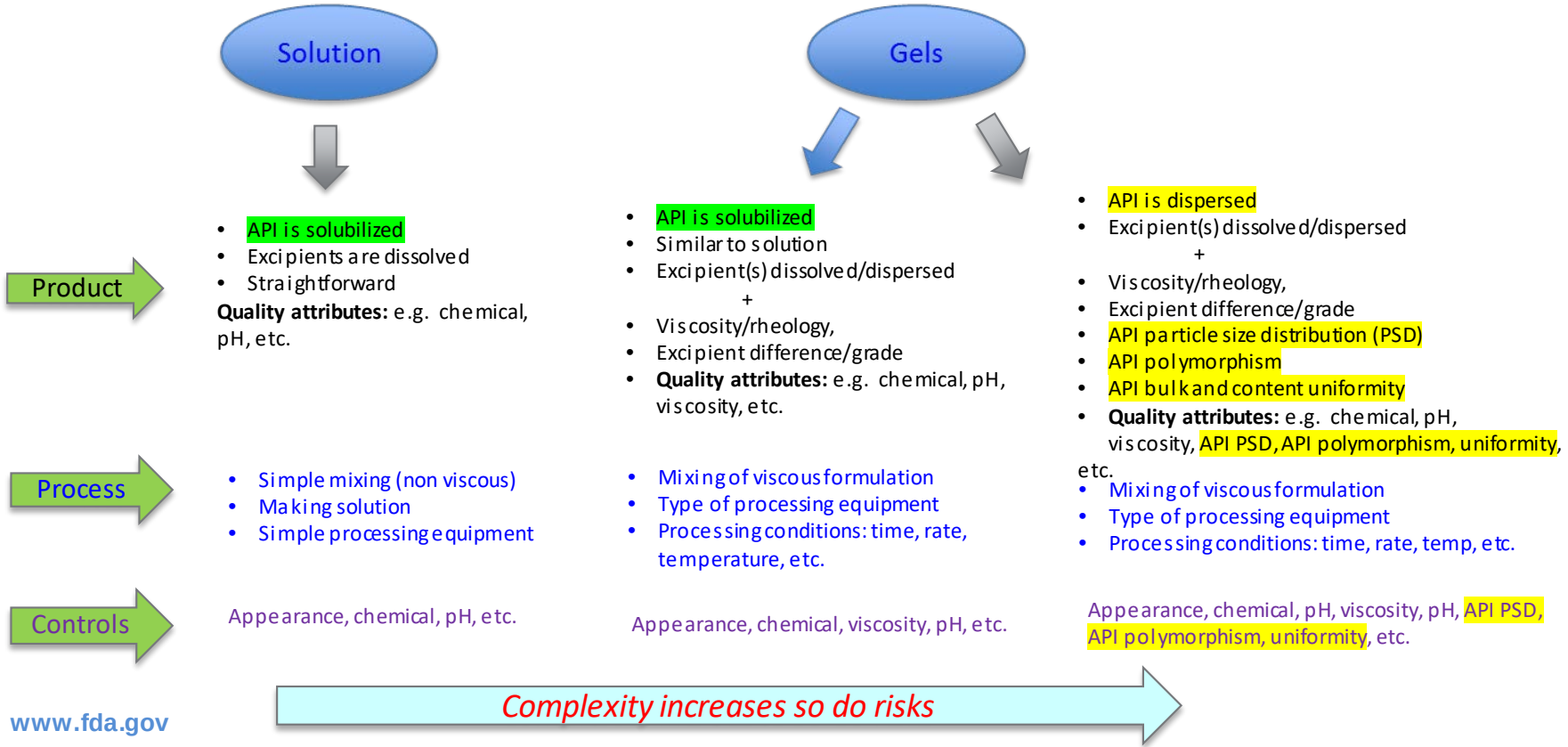
7. Characterization of pH and buffer capacity

8. Characterization of alkalinity and acidity

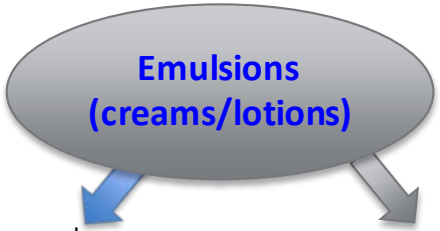
9. Characterization of specific gravity

10. Characterization of metamorphosis-related changes

Single/Multi Phase System (e.g., solution, gels)



Multi Phase System (Emulsions)



Product

- API is solubilized
- Excipient(s) dissolved/dispersed
  +
- Viscosity/rheology,
- Excipient difference/grade
- Globule size
- **Quality attributes:** e.g. chemical, pH, viscosity, globule size, etc.

Process

- Mixing of viscous formulation
- Type of processing equipment - emulsification
- Processing conditions: time, rate, temperature, etc.
- Impact of processing conditions on the quality attributes/product quality?

Controls

Appearance, chemical, viscosity, pH, globule size, etc.

- API is dispersed
- Excipient(s) dissolved/dispersed
  +
- Viscosity/rheology,
- Excipient difference/grade
- API PSD
- API polymorphism
- API bulk and content uniformity
- Globule size
- **Quality attributes:** e.g. chemical, pH, viscosity, API PSD, API polymorphism, uniformity, globule size, etc.

- Mixing of viscous formulation
- Type of processing equipment - emulsification
- Processing conditions: time, rate, temp, etc.
- Impact of processing conditions on the quality attributes/product quality?

Appearance, chemical, pH, viscosity, pH, API PSD, API polymorphism, uniformity, globule size, etc.

Complexity increases so do risks

Summary

- It is recommended to consult relevant product-specific guidances (as applicable and when available) when considering the design and conduct of Q3 characterization tests.
- The extent of physicochemical and structural (Q3) characterizations is dependent on the complexity of the dosage form/drug product.
  - As the complexity increases so do the risks
- It is of importance to evaluate the Q3 characterization test results from the totality of the data.

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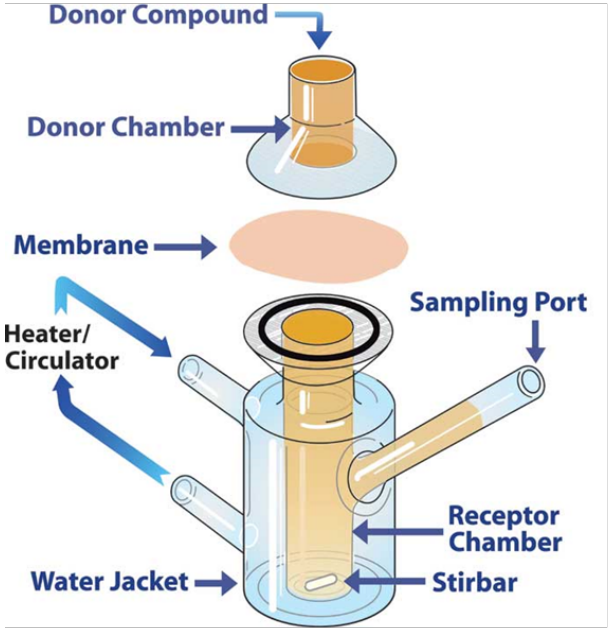
IVRT Studies



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Information in this edition of USP–NF remains official until May 1, 2017	Information in this edition of USP–NF will become official on May 1, 2017	Information in this edition of USP–NF will become official on August 1, 2017
	Before May 1, 2017, use this information to prepare for compliance.	Before August 1, 2017, use this information to prepare for compliance.

⟨1724⟩ SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

General Chapters

SCOPE

The scope of this general chapter is to provide general information for performance testing of semisolid drug products, various types of equipment employed for such testing, and potential applications of the performance testing.

PURPOSE

This chapter provides general information about performance testing of semisolid drug products, the theory and applications of such testing, information about the availability of appropriate equipment, and likely developments in performance testing of semisolid drug products. General chapter *Topical and Transdermal Drug Products—Product Quality Tests* ⟨3⟩ provides information related to product quality tests for topical and transdermal dosage forms, *Drug Release* ⟨724⟩ provides procedures and details for testing drug release from transdermal systems, and this chapter ⟨1724⟩ provides procedures for determining drug release from semisolid dosage forms.

INTRODUCTION

This chapter provides general information for in vitro testing of semisolid drug products. Semisolid dosage forms include creams, ointments, gels, and lotions. Semisolid dosage forms may be considered extended-release preparations, and their drug release depends largely on the formulation and manufacturing process. The release rate of a given product from different manufacturers is likely to be different.

DRUG PRODUCT QUALITY AND PERFORMANCE TESTS

A USP drug product monograph contains tests, analytical procedures, and acceptance criteria. Drug product tests are divided into two categories: (1) those that assess general quality attributes, and (2) those that assess product performance, e.g., in vitro release of the drug substance from the drug product. Quality tests assess the integrity of the dosage form, but performance tests, such as drug release, assess attributes that relate to in vivo drug performance. Taken together, quality and performance tests are intended to ensure the identity, strength, quality, purity, comparability, and performance of semisolid drug products.

Details of drug product quality tests for semisolid drug products can be found in chapter ⟨3⟩. Product performance tests for semisolid drug products are conducted to assess drug release from manufactured pharmaceutical dosage forms. In vitro performance tests for semisolid products do not, however, directly predict the in vivo performance of drugs, as the primary factor that impacts bioavailability and clinical performance are the barrier properties of the epithelia to which the product is applied (epidermal or mucosal tissues). Although product performance tests do not directly measure bioavailability and relative bioavailability (bioequivalence), they can detect in vitro changes that may correspond to altered in vivo performance of the dosage form. These changes may arise from changes in physicochemical characteristics of the drug substance and/or excipients or to the formulation itself, changes in the manufacturing process, shipping and storage effects, aging effects, and other formulation and/or process factors.

At present, a product performance test is available to evaluate in vitro drug release for creams, ointments, lotions, and gels. Several available apparatus can be used for this evaluation, including the vertical diffusion cell, immersion cell, and a special cell used with USP *Apparatus 4*. Because of the significant impact of in vitro test parameters, such as release media, porous membrane and dosing, and the interaction of these parameters with a given drug product, the primary use of in vitro drug

IVRT Studies

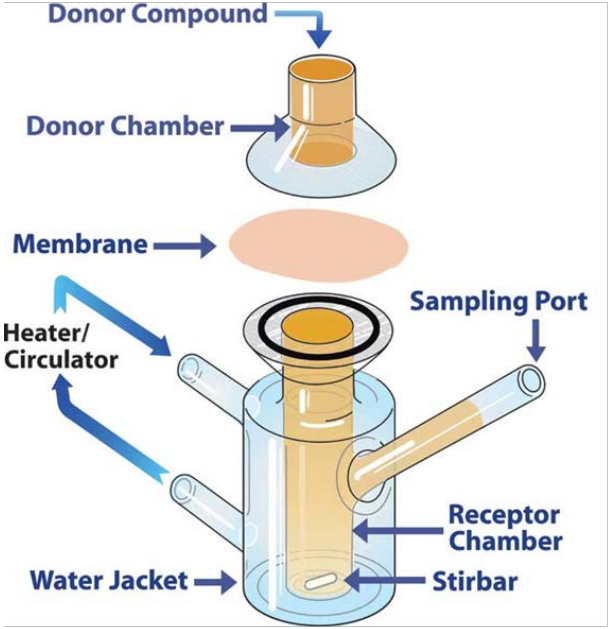
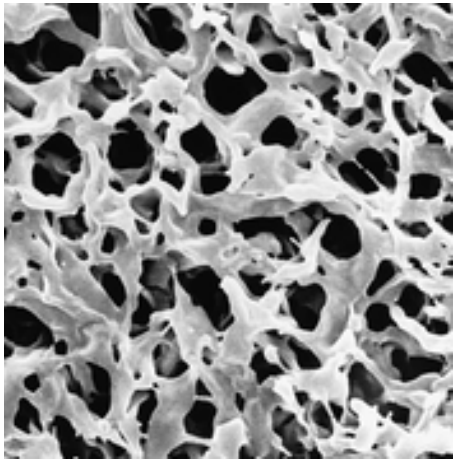
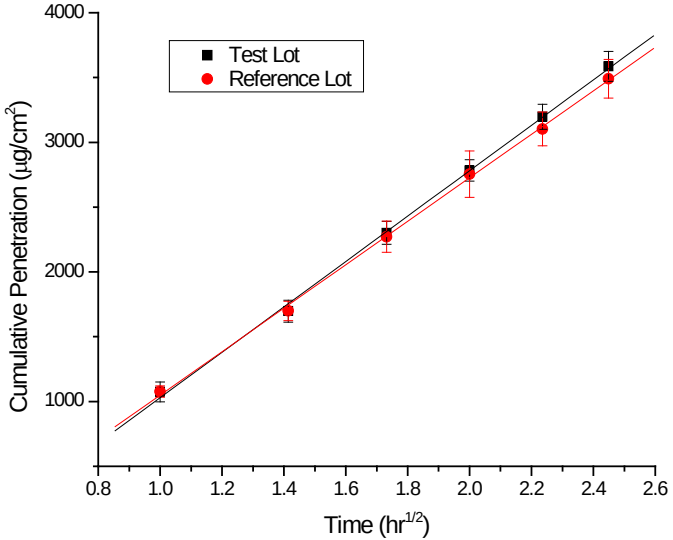


Image courtesy of PermeGear



IVRT Study Results



Reference Product	Test Product	Lower Limit	Upper Limit	Pass/Fail
(Details Redacted)	(Details Redacted)	100.881 %	109.068 %	Pass

IVRT Studies

- Major IVRT Study Phases
  - IVRT method development
  - IVRT method validation
  - IVRT pivotal study
- Common misconceptions and/or development challenges
  - 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

Acknowledgements

U.S. Food & Drug Administration

- Sam Raney, PhD
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- Robert Lionberger, PhD

U.S. FOOD & DRUG ADMINISTRATION

Breakout Session on Topical Drug Products

Part I: Rapid Review Modules

In Vitro Permeation Test (IVPT) Studies

Workshop on Complex Generic Drug Products (CGDPs)

Association for Accessible Medicines - GRx+Biosims 2020

November 10, 2020

Priyanka Ghosh, PhD
Office of Research and Standards
Office of Generic Drugs
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IVPT Studies

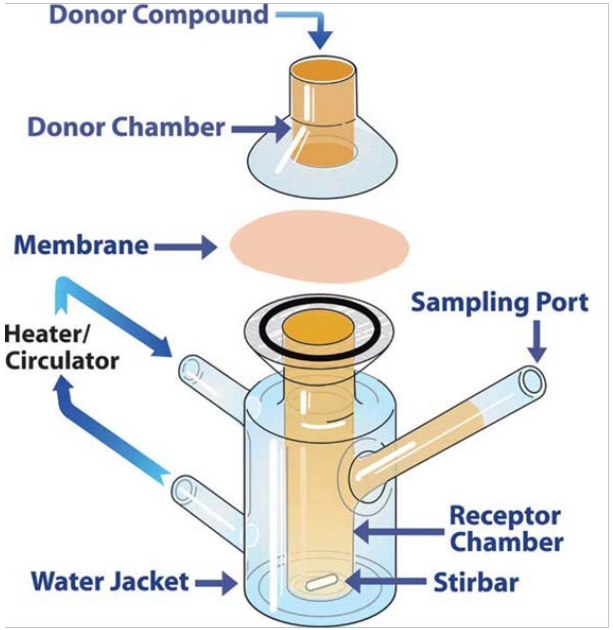
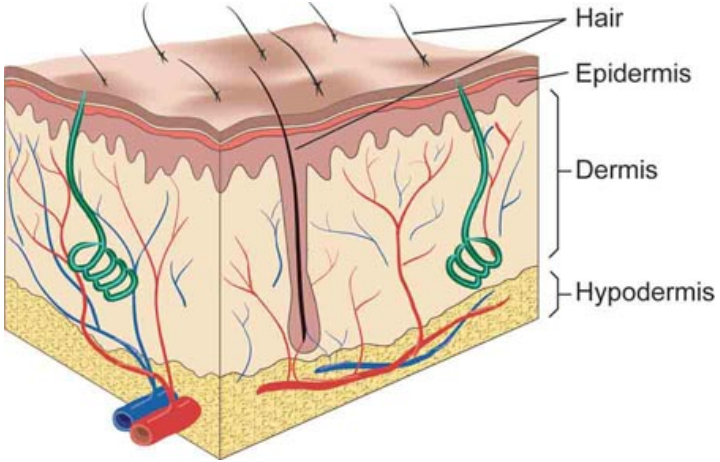
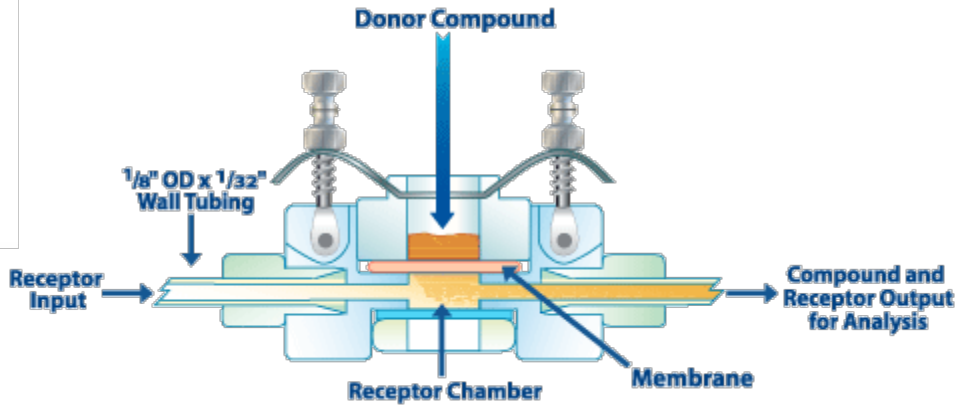


Image courtesy of PermeGear





IVPT vs. IVRT Studies

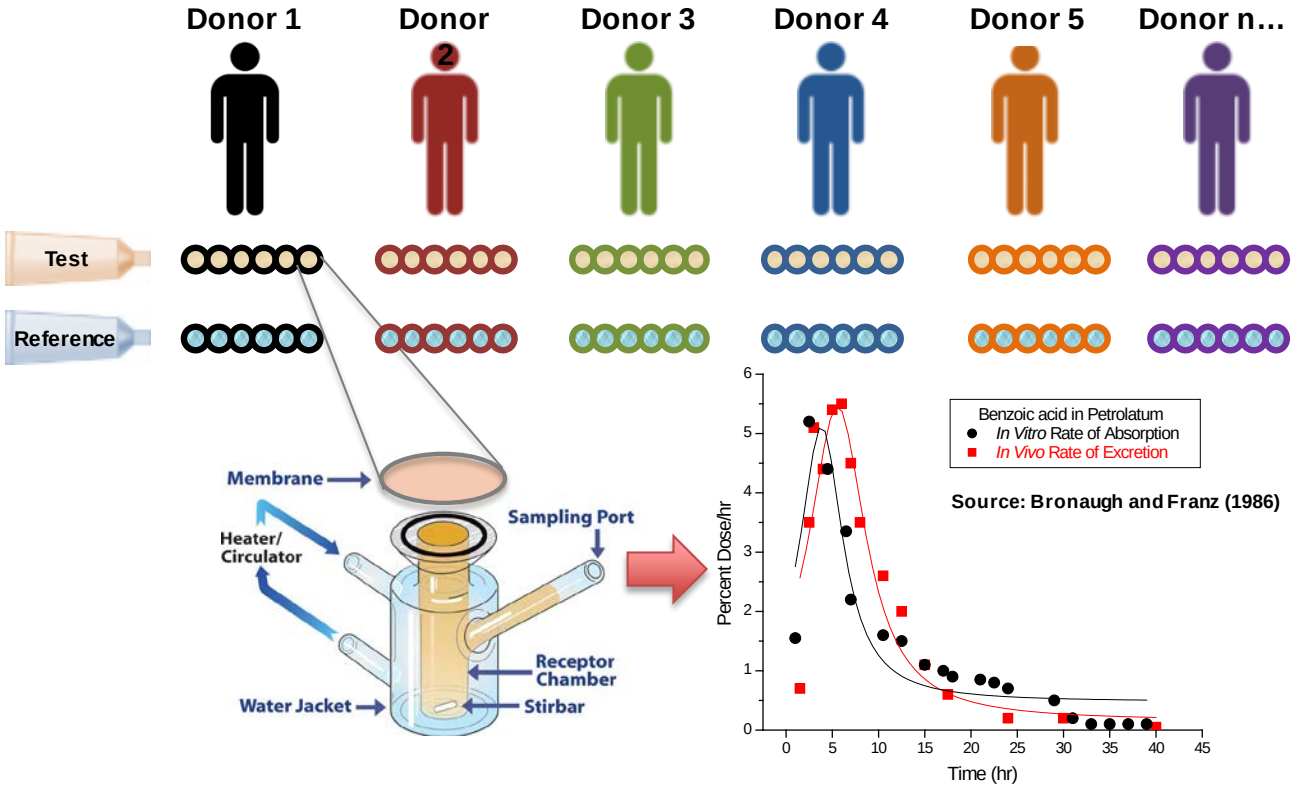
IVPT (Permeation)

- **Human Skin**
- Unoccluded Dose
- Finite Dose
- Flux Profile (J_{max}, etc.)
- Physiological Media
- pg to ng Range
- Product stays 'dry'
- *IVIV* Correlation
- Donor Variability

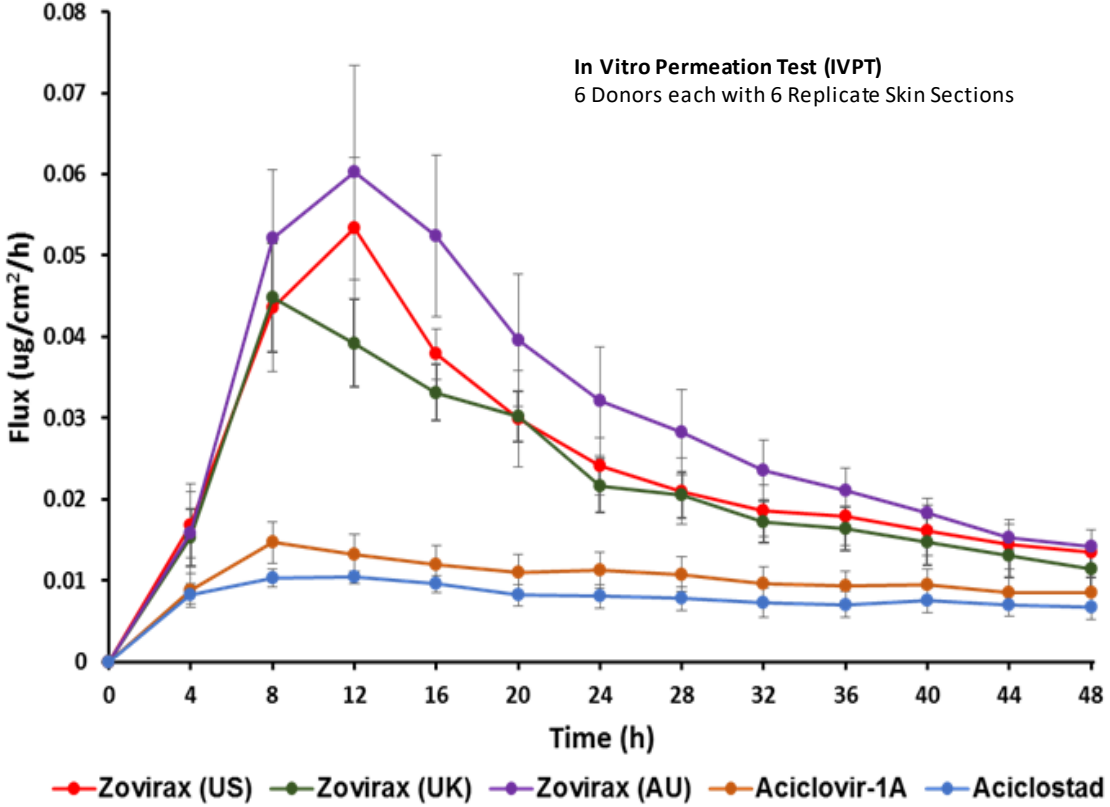
IVRT (Release)

- **Synthetic Membrane**
- Occluded Dose
- Infinite Dose
- Release Rate (slope)
- Alcoholic Media
- µg to mg Range
- Product-Media Interface
- Specific to the Formulation
- Relative Consistency

IVPT Study Design



IVPT Study Results



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

IVPT Studies

- Major IVPT Study Phases
  - IVPT method development
  - IVPT method validation (and pilot study)
  - IVPT pivotal study
- Common misconceptions and/or development challenges
  - 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

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U.S. FOOD & DRUG ADMINISTRATION

Breakout Session on Topical Drug Products

Part I: Rapid Review Modules

Dermal PBPK Modeling and Simulation

Workshop on Complex Generic Drug Products (CGDPs)

Association for Accessible Medicines - GRx+Biosims 2020

November 10, 2020

Eleftheria Tsakalozou, PhD

Office of Research and Standards

Office of Generic Drugs

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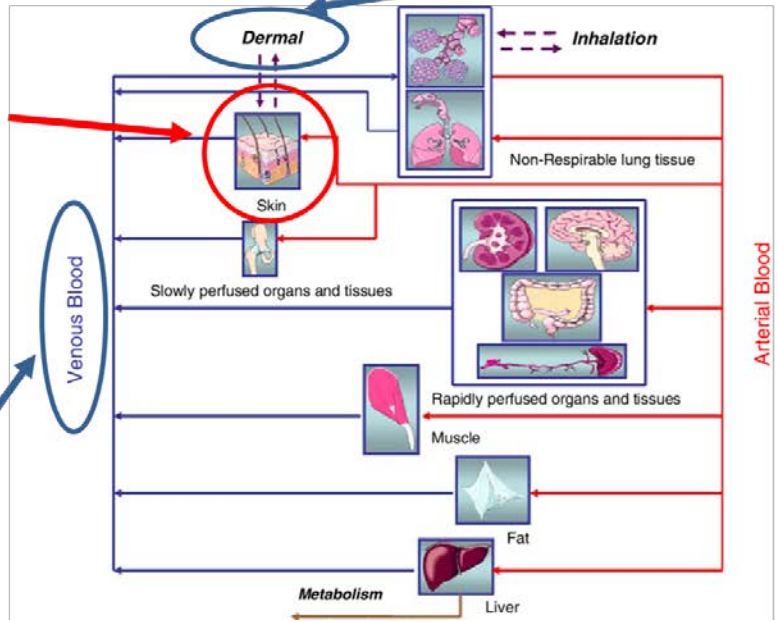
Dermal PBPK models

- Dermal PBPK models relate what we can measure to what we want to know

What we can measure:
-Formulation in vitro performance

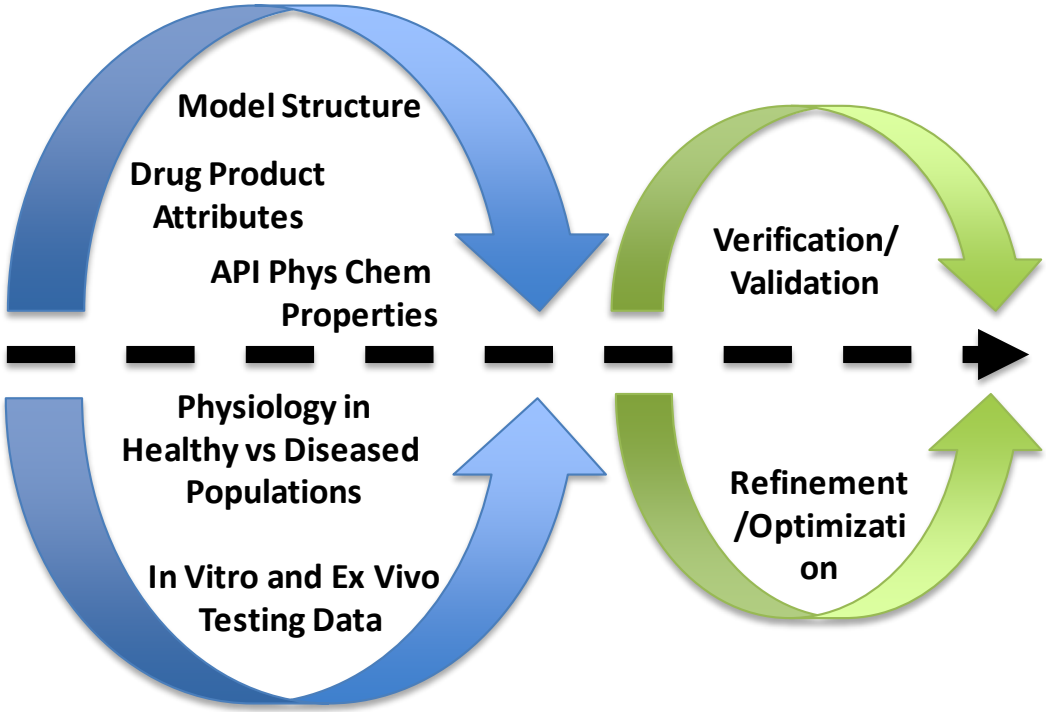
What we would like to know:
-local drug concentrations

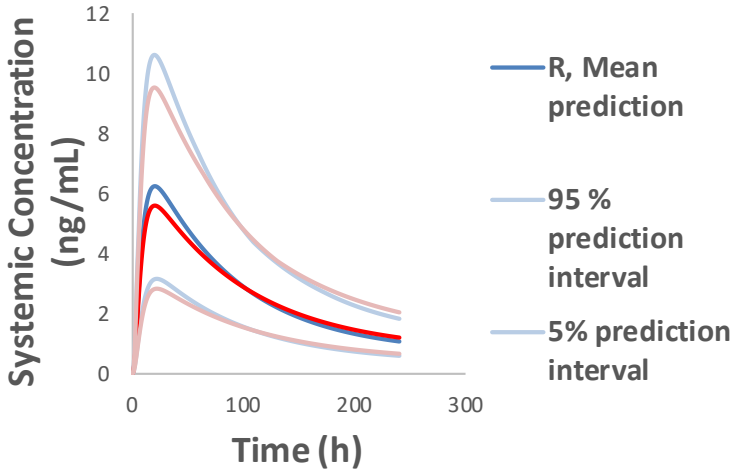


What we can measure:
-Systemic drug exposure

Source: Environ Geochem Health (2009) 31:165–187

PBPK modeling for generic locally-acting drug products to support a regulatory decision

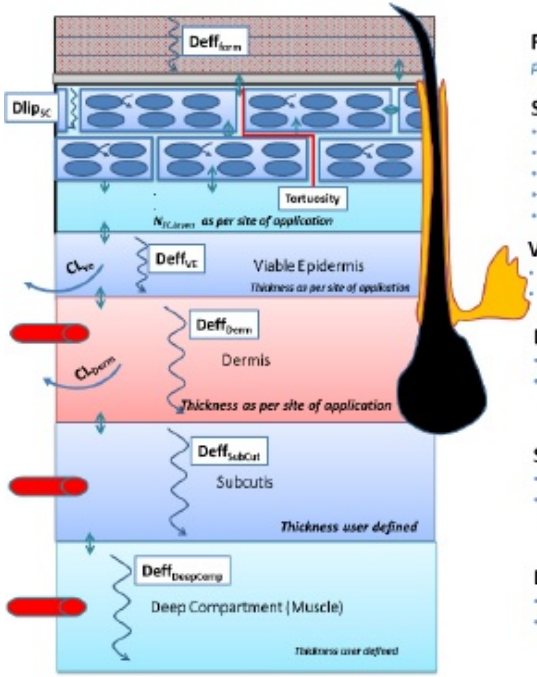




Are R and T bioequivalent?

R: Reference, T: Test

Dermal PBPK model supporting ANDA 211253 approval



Formulation *(Gel, cream, lotions, paste, patch, ointments, etc.)*

Stratum Corneum (SC)
- *Define cell shape and size*
- *Cell membrane permeability*
- *Keratin bonding kinetics*
- *Tortuosity and diffusivity*
- *Hair follicle density and size*

Viable Epidermis (VE)
- *Thickness, diffusivity*
- *Metabolism*

Dermis
- *Thickness, diffusivity*
- *Metabolism, blood flow*

Subcutis
- *Thickness, diffusivity*
- *Blood flow*

Deep Tissue
- *Thickness, diffusivity*
- *Blood flow*

- Diclofenac sodium topical gel, 1%
- Dermal PBPK model to support an alternative BE approach for the Q1/Q2/Q3 formulation
- The alternative BE approach did not include the PSG-recommended in vivo comparative clinical endpoint BE study
- Dermal PBPK model leveraged for virtual BE assessments on predicted systemic and local exposure

PSG: Product-Specific Guidance

Tsakalozou, E. Physiologically-based pharmacokinetic modeling and simulation approaches: best practices for regulatory applications related to locally-acting generic drugs. Presented at Regulatory Education for Industry: 2019 Complex Generic Drug Product Development Workshop, Maryland, USA.

Utility of dermal PBPK models

- Generic drug development
  - Estimate impact of variations in product quality on product performance
  - Define a design space for critical quality attributes of topical formulations
  - Guide the selection of in vitro and/or in vivo study design parameters
- Generic drug approval
  - Support a demonstration of BE and regulatory decision-making
  - Extrapolate BE assessments from healthy to diseased subpopulations

Dermal PBPK models

- Challenges of dermal PBPK models for regulatory decision-making
  - Need to develop and refine quantitative modeling tools that adequately describe formulation attributes, drug properties, skin physiology and/or disease states
    - Knowledge gaps currently exist
  - Need to verify/validate dermal PBPK models by utilizing observed local (skin) and systemic concentrations of the drug
    - It may not always be feasible (or ethical) to determine local concentrations
    - No correlation may be evident in many cases
  - Need to verify/validate dermal PBPK models that capture inter- and intra-subject variability under a fit-for-purpose modeling strategy
    - Leverage data on local concentrations from literature/FDA-funded research sources

Acknowledgements

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Breakout Session on Topical Drug Products

Part II: Interactive Generic Product Development Exercise

A Hypothetical Reference Product (*RHEOMACREAM*)

Workshop on Complex Generic Drug Products (CGDPs)

Association for Accessible Medicines - GRx+Biosims 2020

November 10, 2020

Tannaz Ramezanli, PharmD, PhD

Office of Research and Standards

Office of Generic Drugs

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Hypothetical Reference Product

Relevant sections of the product labeling:

This is fictional drug labeling for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY. This fictitious labeling is not representative of a complete and accurate FDA approved drug labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RHEOMACREAM™ Cream safely and effectively. See full prescribing information.

RHEOMACREAM™ Cream (Tanasone; Ardamethacin) topical cream, For topical use only

---------- **INDICATIONS AND USAGE** ----------

RHEOMACREAM™ Cream is a combination of Tanasone, and Ardamethacin, and is indicated for relief of signs and symptoms of rheumatoid arthritis in adults.

---------- **DOSAGE AND ADMINISTRATION** ----------

Apply a thin layer of the RHEOMACREAM™ Cream to the affected area twice daily.

---------- **DOSAGE FORMS AND STRENGTHS** ----------

RHEOMACREAM™ Cream exists in one strength: 0.1% Tanasone; 0.5% Ardamethacin

---------- **WARNING** ----------

RHEOMACREAM™ can cause serious skin adverse events such as exfoliative dermatitis and toxic epidermal necrolysis (TEN), which can be fatal. RHEOMACREAM™ Cream should be discontinued if rash or other signs of local skin reaction occur.

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions during application of RHEOMACREAM™ Cream in clinical trials were application site reaction and drowsiness.

See below for FDA-approved patient labeling

Revised: 10/2018

Hypothetical Reference Product

Relevant sections of the product labeling:

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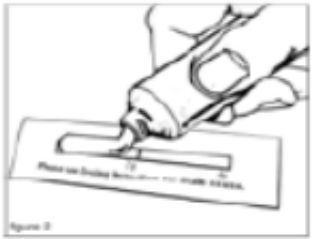
1 INDICATIONS AND USAGE

RHEOMACREAM™ Cream is a combination of Tanasone and Ardamethacin and is indicated for relief of signs and symptoms of rheumatoid arthritis in adults.

2 DOSAGE AND ADMINISTRATION

The proper amount of RHEOMACREAM™ Cream should be measured using the dosing card supplied in the drug product carton. The dosing card should be used for each application of drug product. The cream should be applied within the oblong area of the dosing card up to the 2 gram or 4 gram line. The dosing card can be used to apply the cream to the affected areas. The hands should then be used to gently rub the cream into the skin. Apply a thin layer of the cream to the affected area twice daily. Do not apply more than 6 g daily to any affected area. RHEOMACREAM™ Cream is not for oral, ophthalmic, or intravaginal use.



Hypothetical Reference Product

Relevant sections of the product labeling:

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3 DOSAGE FORMS AND STRENGTHS

0.1% Tanasone; 0.5% Ardamethacin in a topical cream

4 DESCRIPTION

RHEOMACREAM™ is an opaque, white oil in water emulsion-based cream, consisting of benzyl alcohol as a preservative, ceteareth-30, cetostearyl alcohol, mineral oil, phosphoric acid, propylene glycol, purified water, sodium phosphate monobasic monohydrate, and white petrolatum.

- Ardamethacin is an odorless, white crystalline powder, insoluble in water and soluble in ethanol.
- Tanasone is a white to creamy-white, odorless crystalline powder, insoluble in water. Tanasone is the R-enantiomer and contains one chiral center.

Hypothetical Reference Product

Relevant sections of the product labeling:

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5 CLINICAL PHARMACOLOGY

5.1 Mechanism of Action

Ardamethacin inhibits an enzyme that reduces the formation of prostaglandins. Tanasone is a corticosteroid with anti-inflammatory, and anti-pruritic properties. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. The exact mechanisms of action for the therapeutic efficacy of both drugs are not understood, and there is some evidence to suggest a mechanism of action for Ardamethacin in this indication via the central nervous system.

5.2 Pharmacodynamics

Ardamethacin has analgesic and anti-inflammatory effects and Tanasone has anti-inflammatory, and anti-pruritic properties.

Hypothetical Reference Product

Relevant sections of the product labeling:

This is fictional drug labeling for a fictitious drug, designed for EDUCATIONAL PURPOSES ONLY. This fictitious labeling is not representative of a complete and accurate FDA approved drug labeling.

5.3 Pharmacokinetics

The pharmacokinetics of RHEOMACREAM™ Cream were assessed in healthy volunteers following repeated applications during 7 days of RHEOMACREAM™ Cream to 2 wrists (2 x 4 g per day). The average peak plasma concentration (C_{max}) and the average area under the curve (AUC) for Ardamethacin were 45 ng/mL and 766 ng*h/mL and for Tanasone were 2.1 ng/mL and 56 ng*h/mL respectively.

6 HOW SUPPLIED

RHEOMACREAM™ Cream is available in tubes containing 50 g of the topical cream and pumps containing 70 g of the topical cream.

Acknowledgements

U.S. Food & Drug Administration

- Sam Raney, PhD
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- Mengmeng Niu, PhD
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- Andrew Babiskin, PhD
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U.S. FOOD & DRUG ADMINISTRATION

Breakout Session on Topical Drug Products

Part II: Interactive Generic Product Development Exercise

Interactive Scenarios: Formulation Development and BE Strategies

Workshop on Complex Generic Drug Products (CGDPs)

Association for Accessible Medicines - GRx+Biosims 2020

November 10, 2020

Office of Generic Drugs & Office of Pharmaceutical Quality

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Outline

- Considerations related to the formulation of the test product
- Considerations related to the bioequivalence (BE) approaches
- Considerations related to physicochemical and structural (Q3) characterizations and the packaging configurations

Formulation of the Test Product

- Steps to identifying an appropriate formulation
  - Deformulation (reverse engineering) of the reference product
  - Understanding limitations of information in the reference listed drug (RLD) labeling and FDA's inactive ingredient database (IID)
  - Developing a thorough understanding of the product by characterizing multiple (fresh and aged) batches of the reference product
  - Formulating the test product to match the reference product, determining critical quality attributes (CQAs), and failure modes for BE

Deformulation and Characterization

- Hypothetical RLD:

- Topical cream with two drug molecules
- Oil in water emulsion
- In the finished product ardamethacin is completely dissolved and tanasone is partially dissolved
- The pH of the finished product is 5.5
- The RLD is available in tubes and non-metered pumps

Reverse engineering of the RLD

Ingredients	Function	% W/W
Tanasone,	Active ingredient	0.1
Ardamethacin,	Active ingredient	0.5
White Petrolatum	Emollient, oil phase	15.0
Mineral Oil	Emollient, oil phase	2.0
CetoStearyl Alcohol	Stiffening agent, emulsifier	12.5
Propylene Glycol	Solvent, humectant	10.0
Ceteareth-30	Emulsifier	1.8
Sodium Phosphate Monobasic Dihydrate,	Buffering agent	0.30
Sodium Hydroxide	pH adjuster	0.002
Phosphoric Acid	pH adjuster	0.006
Benzyl alcohol	Preservative	1.00
Purified water	Vehicle	57.79

Seeking Acceptability of a Formulation

Assessment of qualitative (Q1) and quantitative (Q2) sameness

✓ Assessment of acceptability of a test formulation for the proposed BE approach

- When the product-specific guidance (PSG) recommends that test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient.
  - Via a controlled correspondence
- When there is no PSG for the RLD.
  - Via a pre-abbreviated new drug application (pre-ANDA) meeting request in parallel with proposing a specific BE approach

Acceptability of a Test Formulation

- Is the following formulation acceptable for the in vitro BE approach?
  - May not be acceptable

Test Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
Petrolatum, USP	15.00
Mineral Oil, USP	**1.70**
CetoStearyl Alcohol, NF	**12.5 (The IID limit is 12%)**
Propylene Glycol, USP	10.00
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	**0.004 (QS to target pH 5.5)**
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	56.10

RLD Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
White Petrolatum, USP	15.00
Mineral Oil, USP	**2.00**
CetoStearyl Alcohol, NF	12.00
Propylene Glycol, USP	10.50
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	**0.002**
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	57.00

Acceptability of a Test Formulation

- How would you change your test formulation table below before submitting it to the Agency for an assessment?

Ingredients	Function	% W/W
Tanasone, USP	Active ingredient	0.1
Ardamethacin, USP	Active ingredient	0.5
White Petrolatum	Emollient, oil phase	15
Mineral Oil, USP	Emollient, oil phase	2
Cetyl alcohol plus stearyl alcohol	Stiffening agent, emulsifier	12
Propylene Glycol, USP	Solvent, humectant	10
Ceteareth-30	Emulsifier	1.8
Sodium Phosphate Monobasic Dihydrate, USP	Buffering agent	0.35
Sodium Hydroxide, NF	pH adjuster	QS to 100
Phosphoric Acid, NF	pH adjuster	QS to 100
Benzyl alcohol, NF	Preservative	1.0
Water, USP	Vehicle	QS to 100

Acceptability of a Test Formulation

- Quantitative nominal amount for each (and every) ingredient in the composition table.
- Quantitative nominal amount specified to the same number of decimal places (at least two)
- The correct compendial grades and names of each excipient should be specified.

Ingredients	Function	% W/W
Tanasone, USP	Active ingredient	0.10
Ardamethacin, USP	Active ingredient	0.50
White Petrolatum, USP	emollient, oil phase	15.00
Mineral Oil, USP	emollient, oil phase	2.00
Cetyl alcohol plus stearyl alcohol (Stenol® I665)	stiffening agent, emulsifier	12.00
Propylene Glycol, USP	solvent, humectant	10.00
Ceteareth-30 (EUMULGIN® B 3)	Emulsifier	1.77
Sodium Phosphate Monobasic Dihydrate, USP	buffering agent	0.35
Sodium Hydroxide, NF	pH adjuster	0.003^
Phosphoric Acid, NF	pH adjuster	0.006^
Benzyl alcohol, NF	preservative	1.00
Purified Water, USP	Vehicle	58.00
^ QS to pH 5.5		

BE Strategy

Hypothetical RLD:

- The RLD is indicated for relief of signs and symptoms of rheumatoid arthritis in adults.
- Ardamethacin inhibits an enzyme that reduces the formation of prostaglandins. Tanasone is a corticosteroid with anti-inflammatory, and anti-pruritic properties.
- Potential BE approaches for the hypothetical product:
  - Comparative clinical endpoint BE study and vasoconstrictor (VC) studies
  - In vitro characterization-based BE approach (and systemic pharmacokinetic study)
  - Combination of the In vitro characterization-based BE and in silico approach

In vitro BE Studies

Identifying the complexities of the RLD:

- Formulation: solution, semisolid single-phase, semisolid multi-phase
- Solubility of the drug in the formulation: dissolved …. undissolved
- Site/mechanism of action: local ….. local + systemic

Considerations for BE Approach

Scenario 1: There is a PSG for this product and it recommends two types of studies: 1) VC studies and 2) a comparative clinical endpoint BE study. The primary endpoint for the comparative clinical endpoint BE study is after 24 weeks of treatment.

- You want to conduct the comparative clinical endpoint BE study and assess the therapeutic equivalence of your test product after 6 weeks of application instead of the 24 weeks recommended in the PSG. How do you solicit the FDA's feedback on the acceptability of your proposed BE study?
  - As part of a pre-ANDA meeting, for example, an applicant might demonstrate that a 6 week study is appropriately sensitive, that it can differentiate formulation differences, and that the proposed study duration is clinically relevant.

    You can use modeling and simulation methods to support the earlier endpoint.

Considerations for BE Approach

Scenario 2: There is no PSG for this RLD. If you propose a characterization-based BE approach, what studies would you include for this approach?

- Formulation sameness as the reference product (no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient)
- Similar physical/structural properties (Q3)
- Equivalent drug release rate through a validated in vitro release test (IVRT) for both of the active ingredients
- Equivalent rate and extent of permeation through human skin using a validated in vitro permeation test (IVPT) for both of the active ingredients

Considerations for BE Approach

Scenario 3: The PSG recommends an in vitro characterization-based BE approach (formulation sameness, Q3, IVRT and IVPT) + an in vivo pharmacokinetic (PK) study with a single-dose, two-way, crossover design.

1) You are proposing to establish BE using a Q1/Q2 formulation by showing Q3 similarity, IVRT, and in vivo PK. Are you eligible for a pre-ANDA product development meeting with the Agency for an alternative BE approach?

- You may be eligible if you submit sufficient justifications and propose alternative studies to provide relevant information about the cutaneous PK of the drug product in order to support the proposed BE approach for your test product.

Physicochemical & Structural Characterization

1) What Q3 tests are recommended as part of the characterization-based BE approach for this product?

Note:

- The RLD is an O/W emulsion cream.
- In the finished product ardamethacin is completely dissolved and tanasone is partially dissolved.

RLD Formulation	
Ingredients	% W/W
Tanasone, USP	0.10
Ardamethacin, USP	0.50
White Petrolatum, USP	15.00
Mineral Oil, USP	2.00
CetoStearyl Alcohol, NF	12.00
Propylene Glycol, USP	10.50
Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	0.002
Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00
Purified water, USP	57.00

Physicochemical & Structural Characterization

1) What Q3 tests are recommended as part of as part of the characterization-based BE approach for this product?

   – The recommended Q3 tests may include, but are not limited to, assessment of appearance, microscopic images at multiple magnifications, pH, particle size distribution of tanasone, globule size distribution, polymorphic form and crystal habit of tanasone, and rheological behavior of the cream product.

   – Modeling and simulation may be used to justify variations in product quality on product performance should these exist between the reference and the test product.

Physicochemical & Structural Characterization

2) You are developing a generic version of the hypothetical product with only one packaging configuration (pump). What data would be needed to support that your test product is BE to both packaging configurations of the RLD?

   - You would perform the comparative Q3 tests of the formulation inside the tube and pump and compare the formulation dispensed from the pump for both the reference and your test product.

Conclusions

- A good Pre-ANDA product development meeting package
  - Should clearly characterize the complexity of the drug product
  - Should contain the formulation composition of the test product
  - Should provide clear and concise information about how the proposed approach can systematically mitigate concerns related to potential failure modes for BE
  - Should contain sufficient data and rationale to support the questions
  - Should include the information to support the feasibility of any proposed novel techniques
  - If modeling is involved, should contain a clear presentation of how the model will be used and how the model will be verified

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U.S. FOOD & DRUG ADMINISTRATION

Breakout Session on Topical Drug Products

Part II: Interactive Generic Product Development Exercise

Simulated (Mock) Pre-ANDA Product Development Meeting

Workshop on Complex Generic Drug Products (CGDPs)

Association for Accessible Medicines - GRx+Biosims 2020

November 10, 2020

Office of Generic Drugs & Office of Pharmaceutical Quality

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