



# FDA for the Dermatologist -

## The basics about FDA and advances in science and regulation of topical generic drugs

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# Disclaimer



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

# FDA Centers

Center For Drug Evaluation  
and Research

Center For Devices  
and Radiological Health

Center For Biological Evaluation  
and Research

Center For Food Safety  
and Applied Nutrition

Center For Veterinary Medicine

Center For Tobacco Products

National Center For  
Toxicological Research

## Most Relevant to Dermatology:

- **Center for Drug Evaluation and Research (CDER)**
  - Office of New Drugs (OND)
    - Division of Dermatology and Dental Drug Products
  - Office of Generic Drugs (OGD)
- **Center for Devices and Radiological Health (CDRH)**
- **Center for Biologics Evaluation and Research (CBER)**
- **Center for Food Science and Nutrition (CFSAN)**
  - Office of Cosmetics and Colors

# Dermatology Relevant 2022 New Drugs



Drug Name	Active Ingredient	Approval Date	FDA-Approved Use
NexoBrid	anacaulase	12/28/2022	To remove eschar in adults with deep partial thickness or full thickness thermal burns
Sotyktu	deucravacitinib	9/9/2022	To treat moderate-to-severe plaque psoriasis
Daxxify	daxibotulinumtoxinA	9/7/2022	To treat moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity
Spevigo	spesolimab	9/1/2022	To treat generalized pustular psoriasis flares
Vtama	tapinarof	5/23/2022	To treat plaque psoriasis
Opdualag	nivolumab and relatlimab	3/18/2022	To treat unresectable or metastatic melanoma
Cibingo	Abrocitinib	1/14/2022	To treat refractory moderate-to-severe atopic dermatitis

# Generic Drugs

- Why should generic drugs be important to dermatology patients?
- What are specific considerations for “topical drugs” that are applied to the skin?

# Generic Drug Access



- The Association for Accessible Medicines (AAM) 2022<sup>1</sup> Generic Drug Access & Savings Reports have documented the ***overall*** success of generic drugs
- **91%** of the prescriptions filled in the United States during 2021 were dispensed as generics, up from 90% in 2019
- **93%** of generic prescriptions were filled at  $\leq \$20$ , up from 90% in 2016; the average generic copay in 2021 was ***\$6.16***
- ***Overall***, this represented **exceptional patient access** to high quality, safe, effective, affordable medicines

<sup>1</sup> AAM Report: 2022 Generic Drug & Biosimilars Access & Savings in the U.S. (<https://accessiblemeds.org>)  
[www.fda.gov](http://www.fda.gov)

# 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

# First-time Generic Drug Approvals 2022 -

## Most Relevant to Dermatology (out of 90 total)

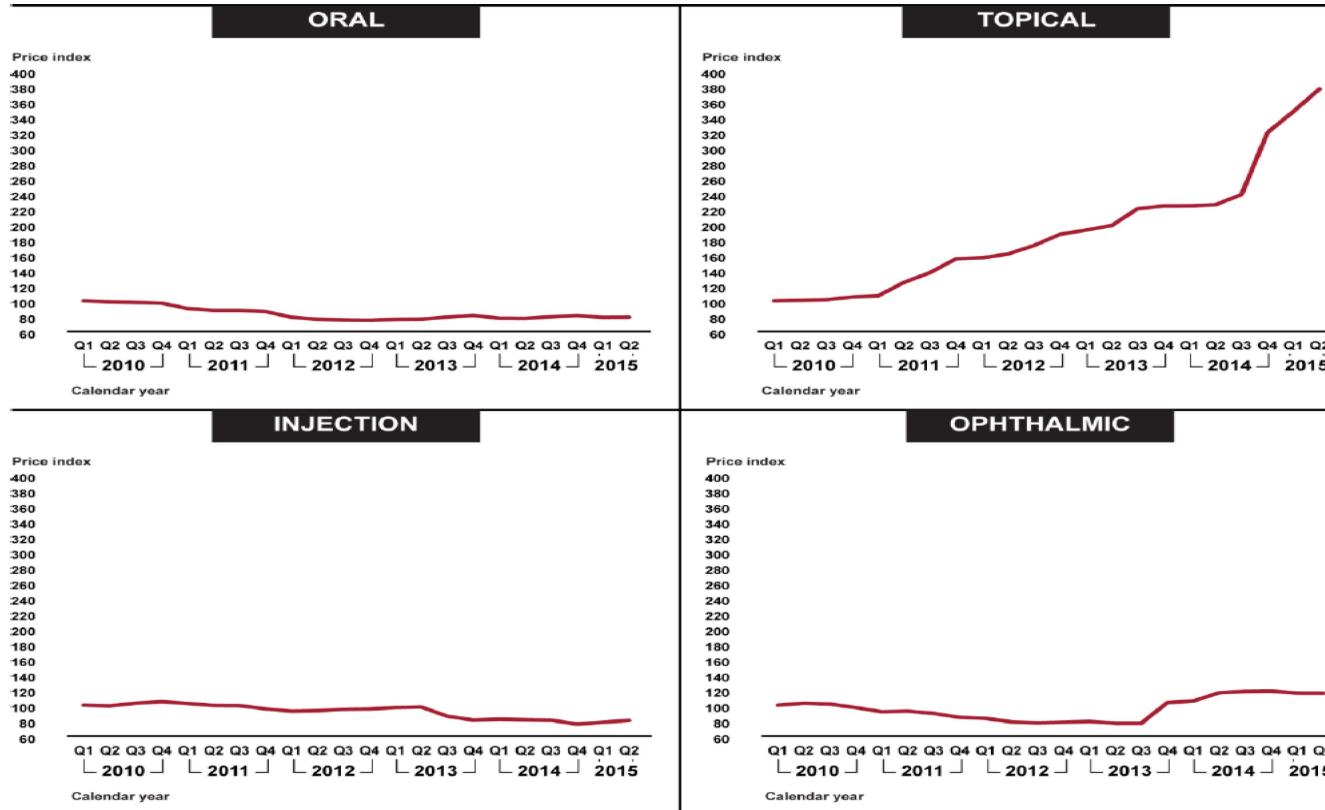


ANDA #	Generic Name	ANDA Applicant	Brand Name	ANDA Approval Date	ANDA Indication
212710	Penciclovir Cream 1%	Teva Pharma	Denavir	11/9/2022	Recurrent herpes labialis
215433	Tazarotene Gel 0.05%	Cosette Pharma	Tazorac	9/13/2022	Plaque psoriasis
208768	Posaconazole Injection	Par Sterile	Noxafil	5/25/2022	Prophylaxis of invasive Aspergillus and Candida
215398	Bexarotene Gel	Amneal Pharma	Targretin	4/27/2022	Cutaneous lesions of CTCL
214596 212424	Phytonadione Injectable Emulsion	Cipla	AquaMEP HYTOM	4/22/2022	Coagulation disorders caused by Vitamin K deficiency

# The 2016 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 \$					Absolute Change, 2009-2015	% Change, 2009-2015
		2009	2011	2014	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	
Soriatake, 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**

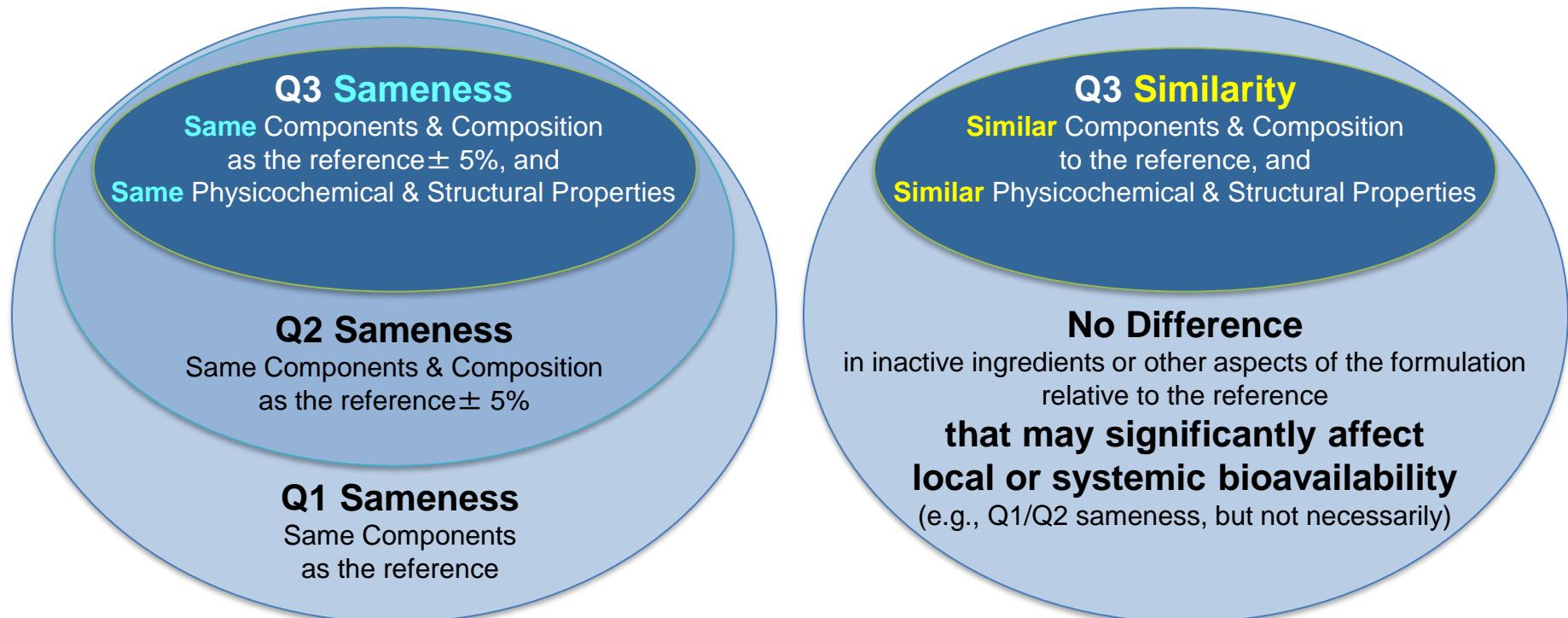
# Topical Dermatological Formulations



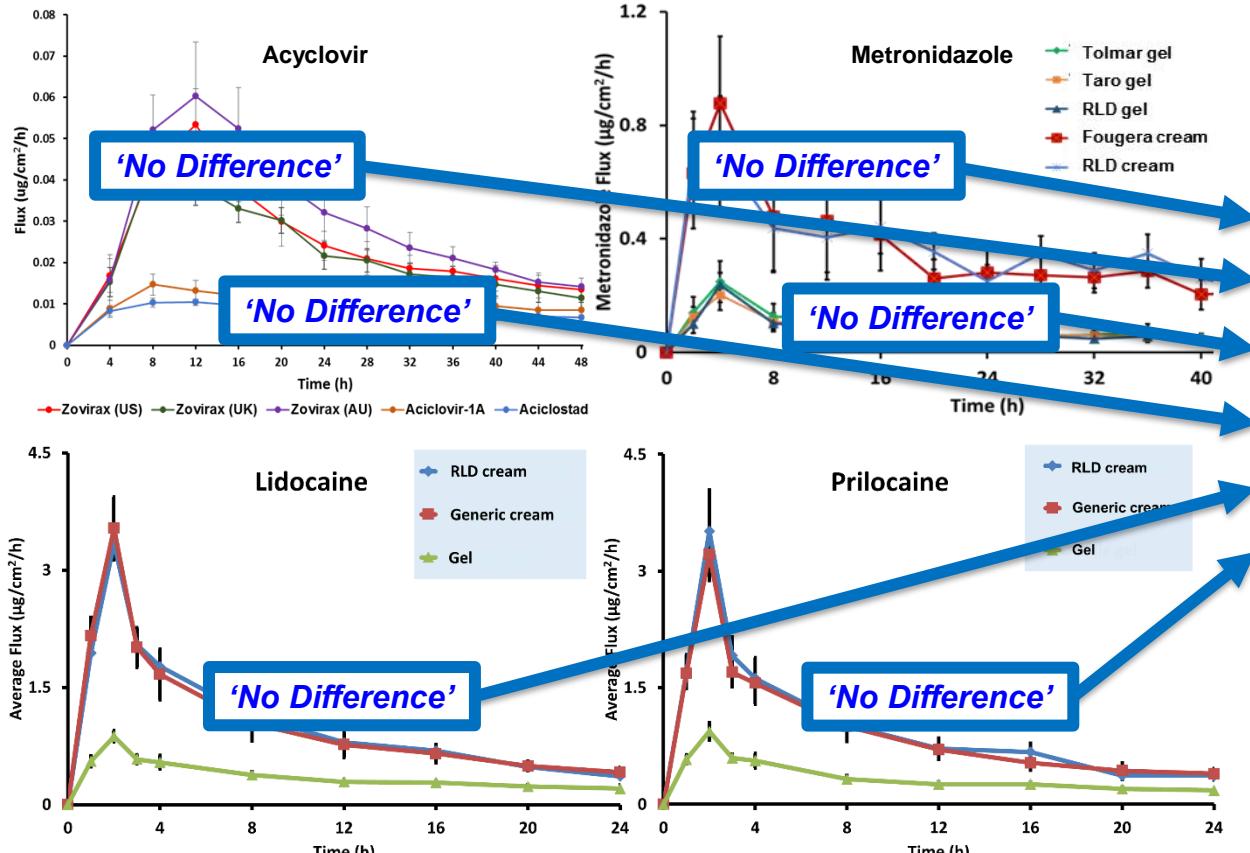
- The components (Q1) and quantitative composition (Q2) of a topical product (and how it is manufactured) can modulate its physical and structural arrangement of matter (Q3)
- These Q3 characteristics influence molecular interactions that control the rate and extent of topical bioavailability
- One approach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

# 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

# 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  $\pm 5\%$
  - 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 in the local or systemic availability of the active ingredient*

# Physicochemical 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 test and reference topical dermatological products 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



## General considerations on characterization:

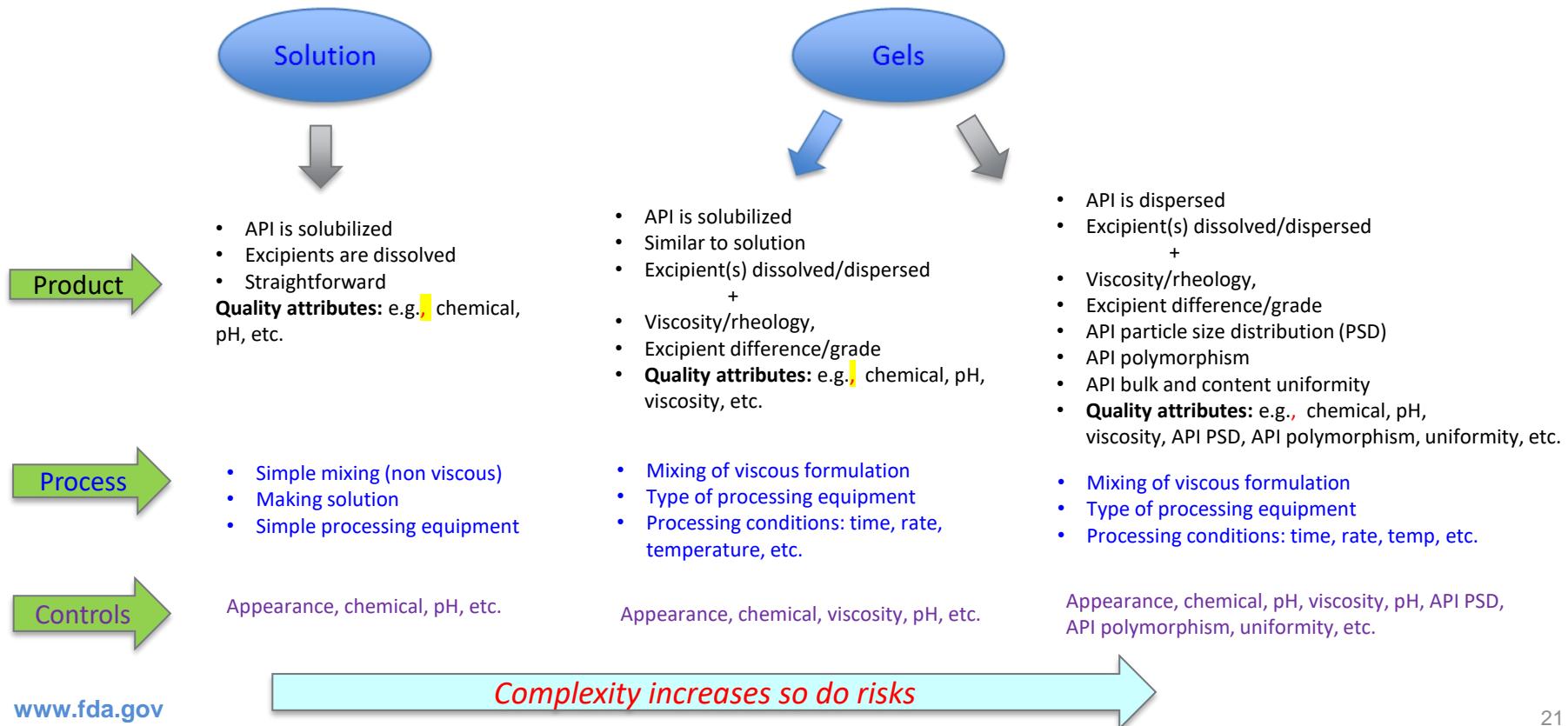
1. Characterization of appearance and texture
2. Characterization of phase states – to support the drug is dissolved in the dosage form, and/or single-phase dosage form (as relevant)
3. Characterization of structural organization of matter – to assess particle size distribution and crystal habit, and/or 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

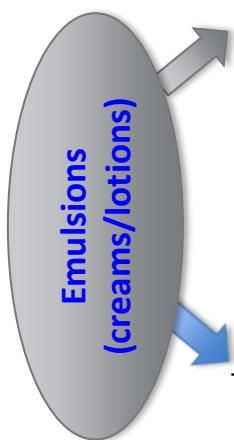
## General considerations on characterization (continued):

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)



- 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, temperature, etc.
- Impact of processing conditions on the quality attributes/product quality?
- Appearance, chemical, viscosity, pH, globule size, etc.

Product

Process

Controls

**Complexity increases so do risks**

## 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.

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.

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.

# IVRT Studies

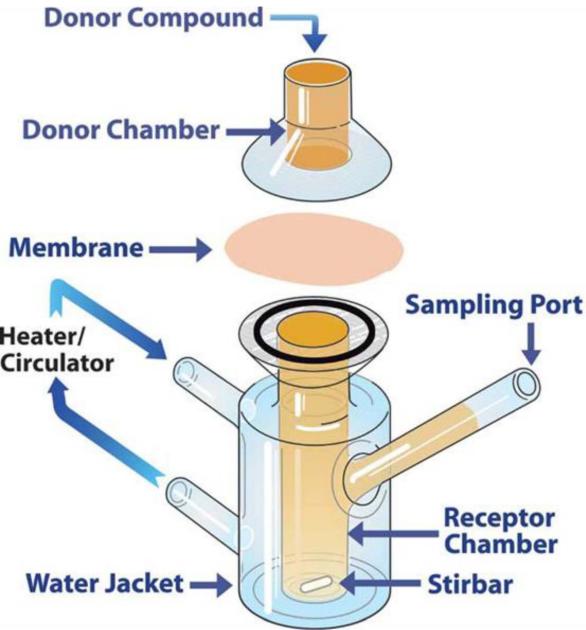


Image courtesy of PermeGear

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## (1724) SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

### 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 application of such testing, information on the use of appropriate equipment, and newly developed methods of performance testing for semisolid drug products. General chapter *Topical Transdermal Formulations* (1723) and *Product Quality Tests* (8) provides information related to product quality tests for topical and transdermal dosage forms. Drug Release (1724) 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

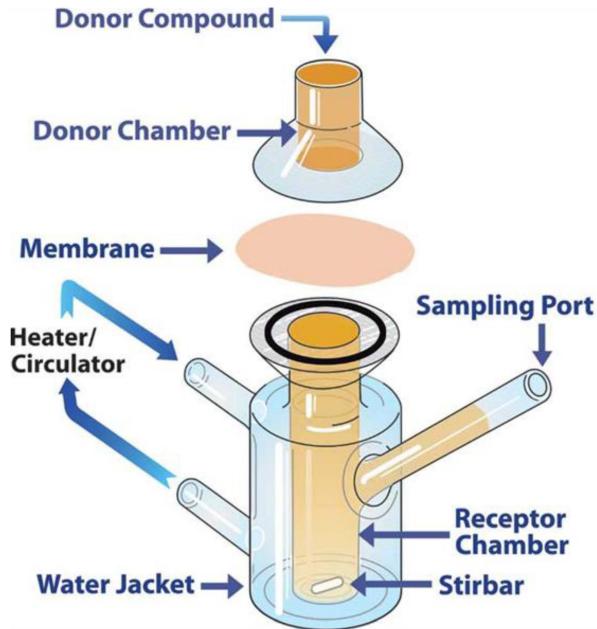
A USP drug product monograph contains tests, analytical procedures, and acceptance criteria. Drug product tests are divided into two categories: (1) those that assess general quality attributes, and (2) those that assess product performance, e.g., *in vitro* release of the drug substance from the drug 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 are used to predict the *in vivo* performance of the drug product. The *in vitro* performance tests 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.

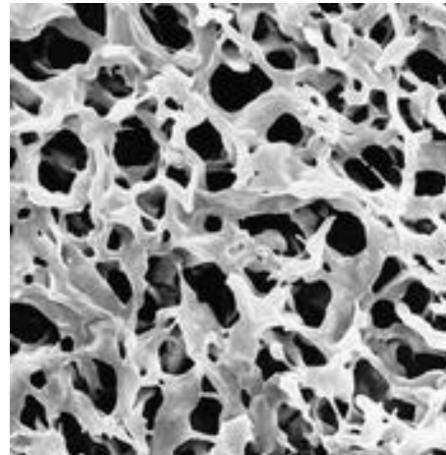
At present, a product performance test is available to evaluate *in vitro* drug release for creams, ointments, lotions, and gels. Semisolid drug products can be tested in this evaluation, including emulsions, suspensions, and pastes. A special cell used with USP Apparatus 2, because of the significant impact of *in vitro* test parameters, such as release media, permeable membrane and dosing, and the interaction of these parameters with a given drug product, the primary use of *in vitro* drug

General Chapters

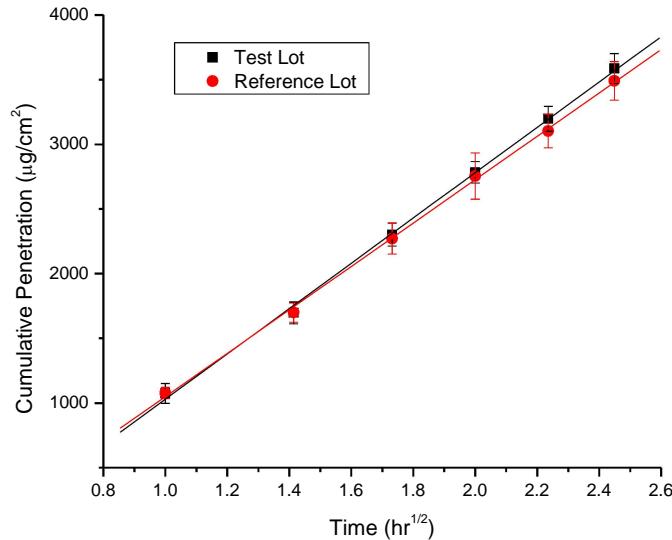
# IVRT Studies



*Image courtesy of PermeGear*



# IVRT Study Results

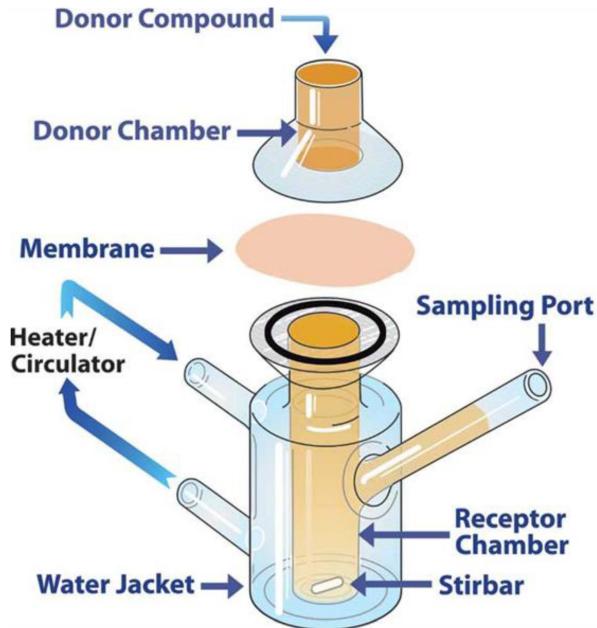


Reference Product	Test Product	Lower Limit	Upper Limit	Pass/Fail
(Details Redacted)	(Details Redacted)	100.881 %	109.068 %	Pass

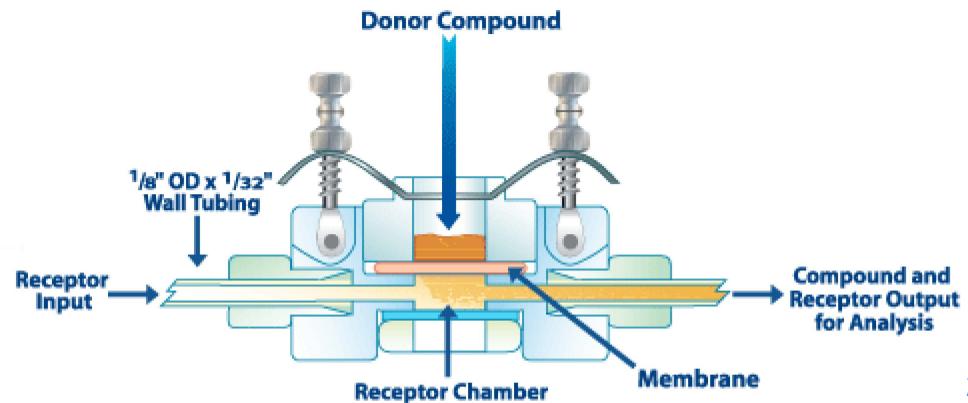
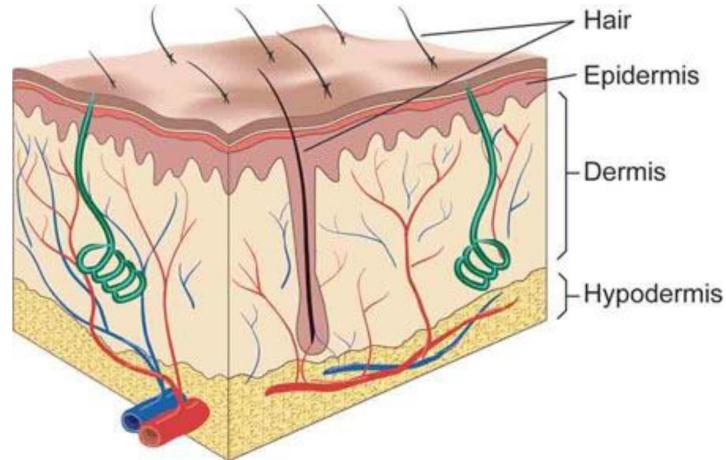
# IVRT Studies

- 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

# IVPT Studies



*Image courtesy of PermeGear*



# IVPT vs. IVRT Studies



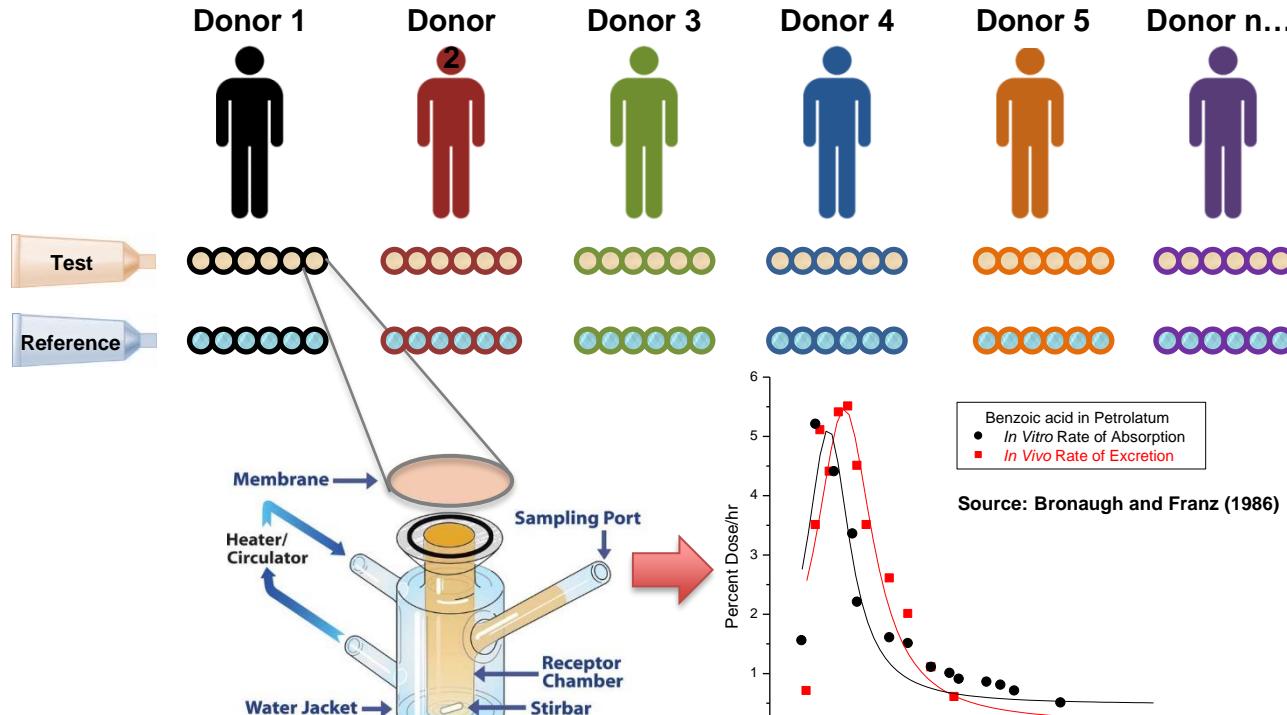
## IVPT (Permeation)

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

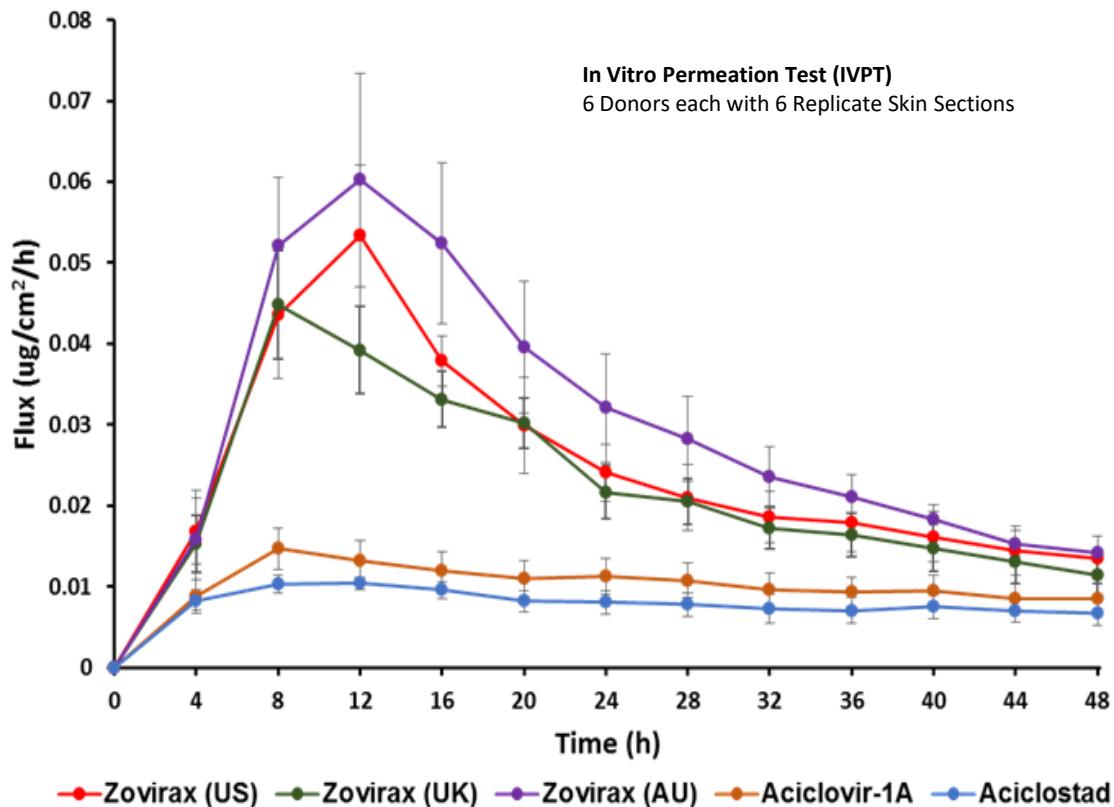
## IVRT (Release)

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

# IVPT Study Design



# IVPT Study Results



# IVPT Studies

- Major IVPT Study Phases
  - IVRT method development
  - IVRT method validation (and pilot study)
  - IVRT 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

# 2022 FDA Draft General Guidances



## Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs Guidance for Industry

### DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Susan Levine 240-402-7936.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

October 2022  
Generic Drugs

## In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs Guidance for Industry

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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

October 2022  
Generic Drugs

## In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs Guidance for Industry

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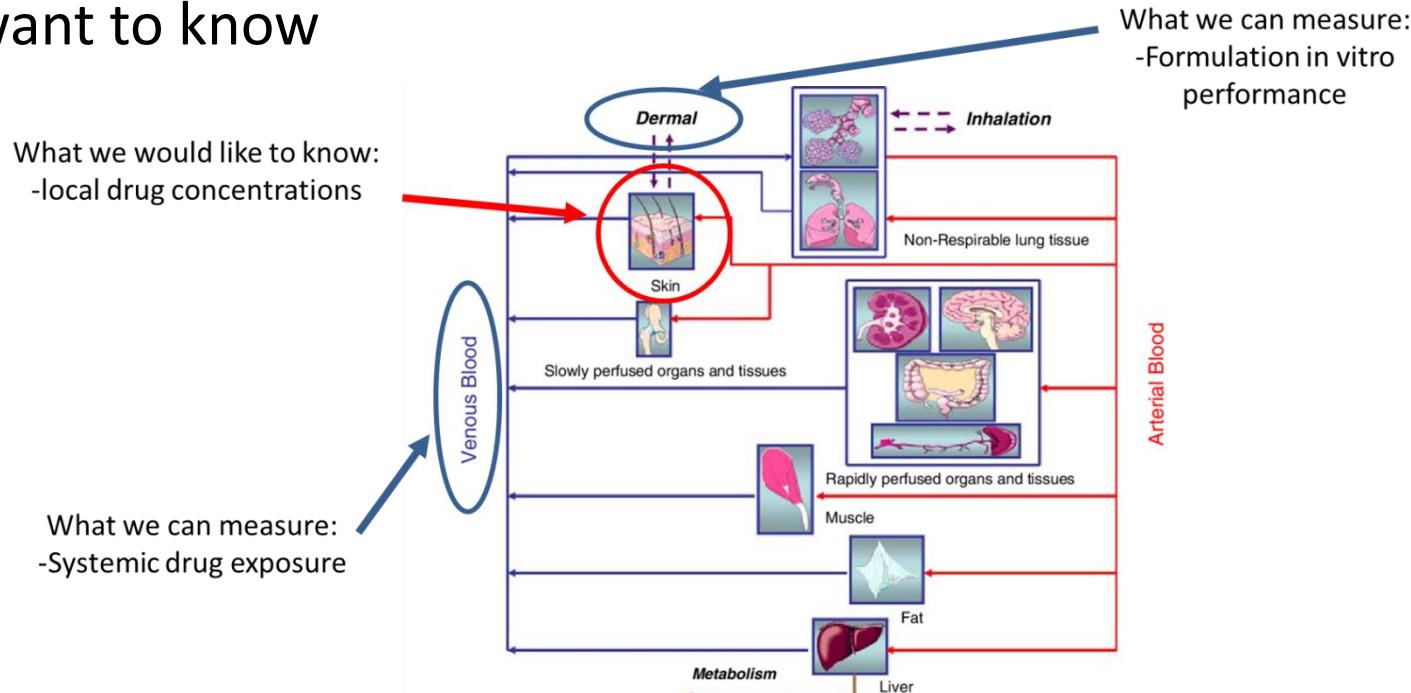
U.S. Department of Health and Human Services  
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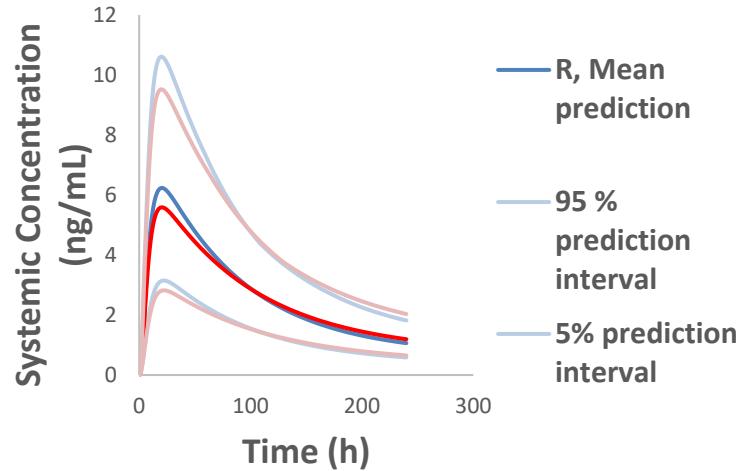
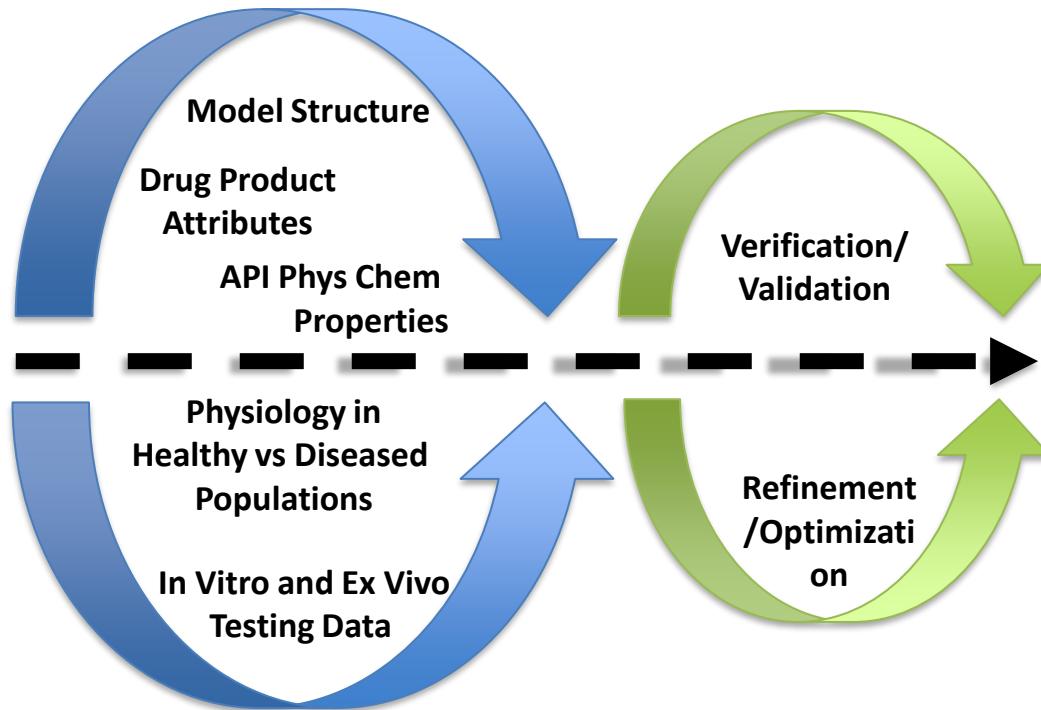
# Dermal PBPK models

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

What we can measure:  
Excretion in urine



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



Are R and T  
bioequivalent?

# 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

# Formulation of the Test Product



- **Test Product = Candidate Generic Drug**
- Steps to identifying an appropriate formulation
  - Deformulation (reverse engineering) of the drug to be compared with – usually the Reference Listed Drug (RLD)
  - Understanding limitations of information in the 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

FDA

- Hypothetical RLD:
- Topical cream with two drug molecules
- Oil in water emulsion
- In the finished product ardamethacin is completely dissolved and tanasonine 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 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		RLD Formulation	
Ingredients	% W/W	Ingredients	% W/W
Tanasone, USP	0.10	Tanasone, USP	0.10
Ardamethacin, USP	0.50	Ardamethacin, USP	0.50
<b>Petrolatum, USP</b>	<b>15.00</b>	<b>White Petrolatum, USP</b>	<b>15.00</b>
Mineral Oil, USP	<b>1.70</b>	Mineral Oil, USP	<b>2.00</b>
CetoStearyl Alcohol, NF	<b>12.5 (The IID limit is 12%)</b>	CetoStearyl Alcohol, NF	12.00
Propylene Glycol, USP	10.00	Propylene Glycol, USP	10.50
Ceteareth-30	1.80	Ceteareth-30	1.80
Sodium Phosphate Monobasic Dihydrate, USP	0.30	Sodium Phosphate Monobasic Dihydrate, USP	0.30
Sodium Hydroxide, NF	<b>0.004 (QS to target pH 5.5)</b>	Sodium Hydroxide, NF	<b>0.002</b>
Phosphoric Acid, NF	0.006	Phosphoric Acid, NF	0.006
Benzyl alcohol, NF	1.00	Benzyl alcohol, NF	1.00
Purified water, USP	56.10	Purified water, USP	57.00

# Acceptability of a Test Formulation



- Quantitative nominal amount for each (and every) ingredient in the composition table.
- Quantitative nominal amount specified to 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, <b>USP</b>	emollient, oil phase	15.00
Mineral Oil, USP	emollient, oil phase	2.00
Cetyl alcohol plus stearyl alcohol ( <b>Stenol® I665</b> )	stiffening agent, emulsifier	12.00
Propylene Glycol, USP	solvent, humectant	10.00
Ceteareth-30 ( <b>EUMULGIN® B 3</b> )	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
<b>Purified Water</b> , USP	Vehicle	58.00

<sup>^</sup> QS to pH 5.5

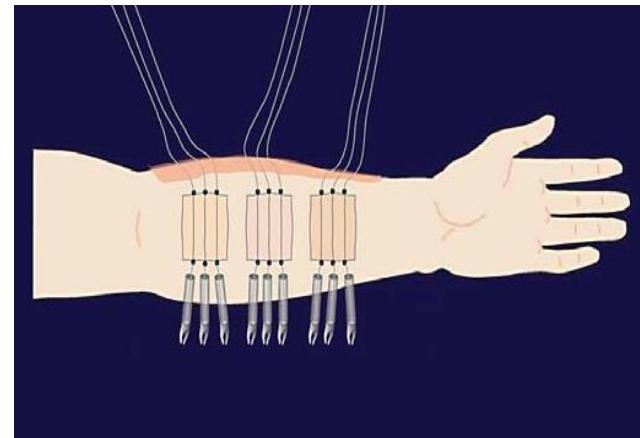
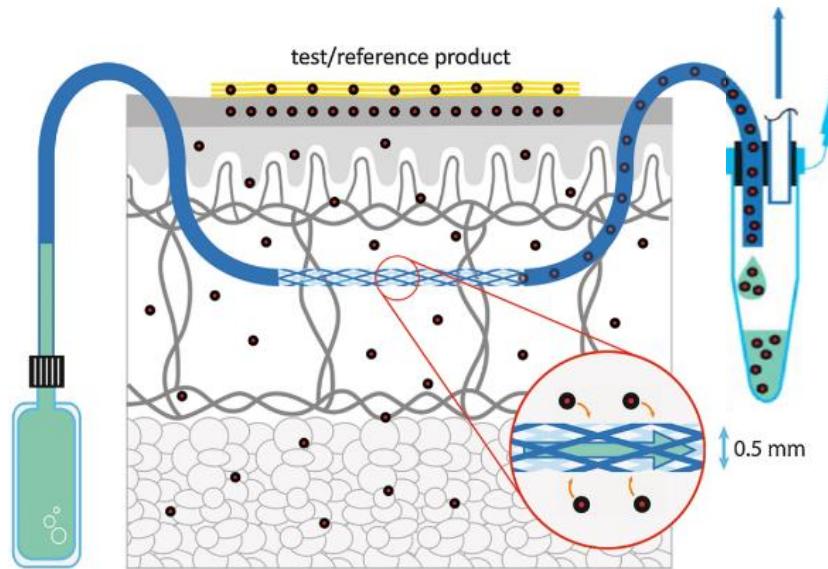
# Current Research



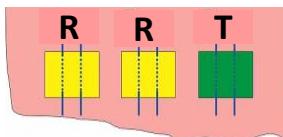
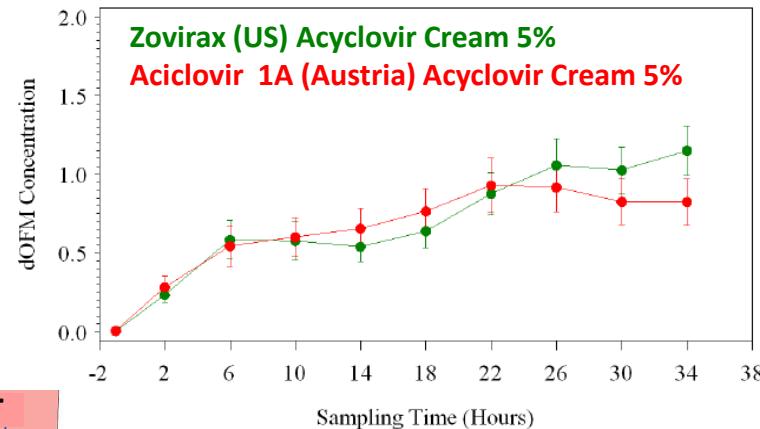
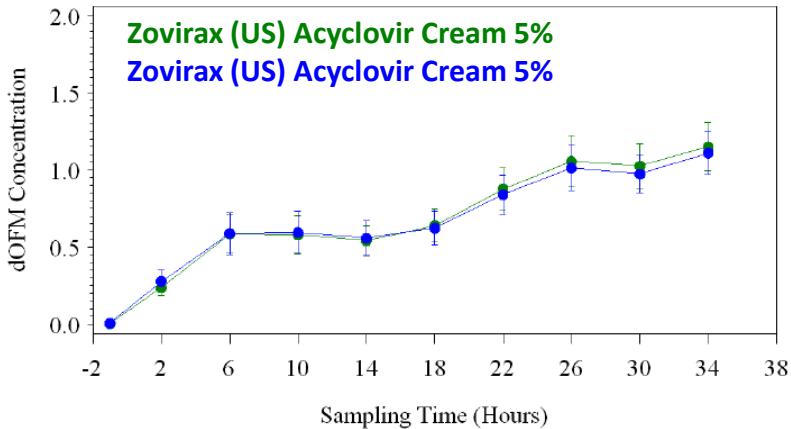
- Physical chemical characterization of topical formulations
  - Thermodynamics of topical drugs – rheology, solvent evaporation, and water uptake
  - Characterization of the impact of certain excipients in topical formulations
- Measuring drug concentrations in the skin
  - dermal Open Flow Microperfusion (dOFM)
  - Confocal Microscopic Raman Spectroscopy

# Cutaneous PK-Based Approaches

- dMD and dOFM directly measure the *in vivo* rate and extent of drug bioavailability at/near the site of action in the skin.



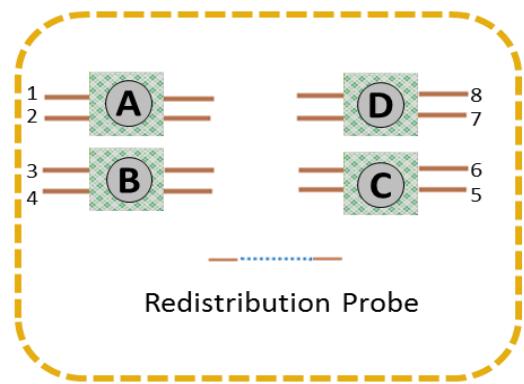
# Pivotal BE Study for Acyclovir Cream



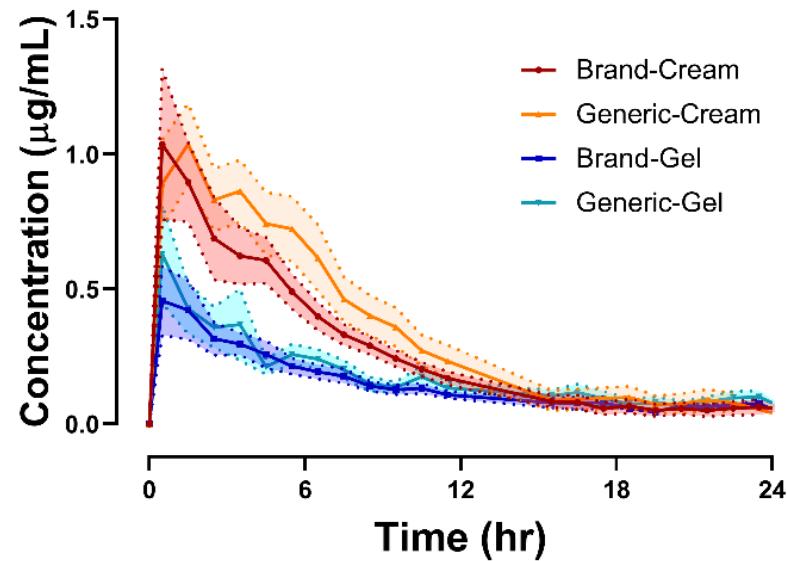
Outcome variable	CI <sub>90%</sub>	BE-limits	BE
log(AUC <sub>0-36h</sub> )	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]	[-0.223 ; 0.223] or [80% ; 125%]	<b>passed</b>
log(C <sub>max</sub> )	[-0.155 ; 0.190] or [85.7 % ; 120.9%]	[80% ; 125%]	<b>passed</b>

Outcome variable	CI <sub>90%</sub>	BE-limits	BE
log(AUC <sub>0-36h</sub> )	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]	[-0.223 ; 0.223] or [80% ; 125%]	<b>Failed</b>
log(C <sub>max</sub> )	[-0.498 ; 0.022] or [60.8 % ; 102.2%]	[80% ; 125%]	<b>Failed</b>

# Cutaneous PK of Metronidazole Products

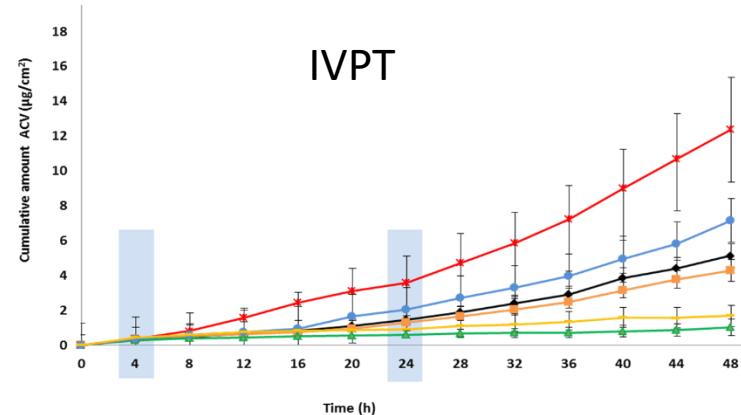
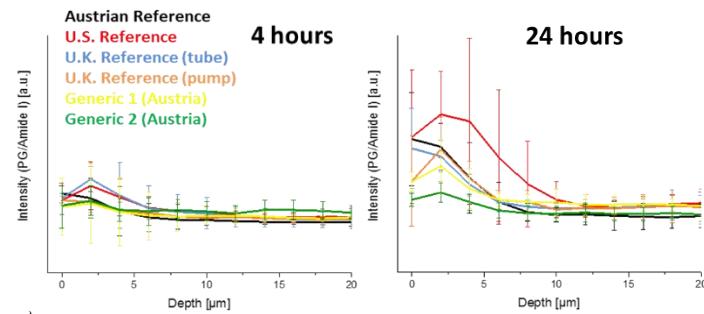
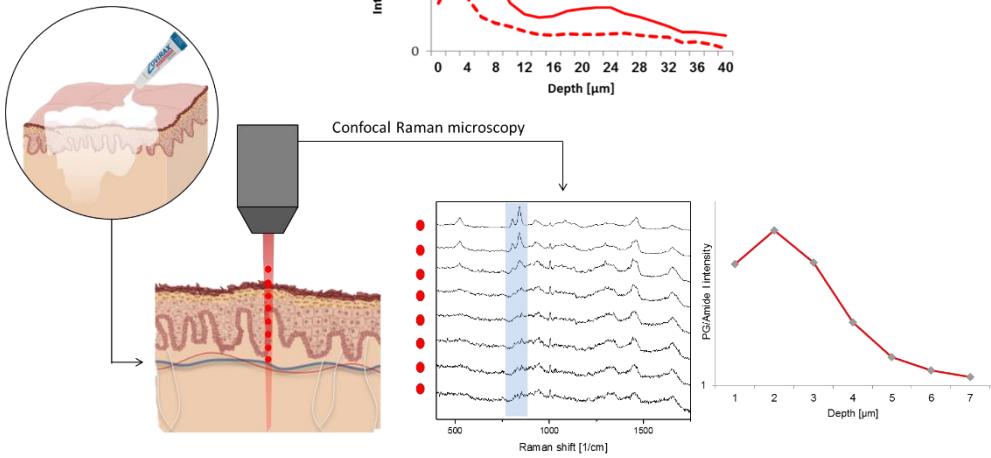


- MetroGel® topical gel, 0.75% “Brand Gel”
- Metronidazole topical gel, 0.75% “Generic Gel”
- MetroCream® topical cream, 0.75% “Brand Cream”
- Metronidazole topical cream, 0.75% “Generic Cream”



Average dermal concentration profiles using **dMD**,  
(mean  $\pm$  SEM, n=7), in rabbits

# Cutaneous PK: Non-Invasive Techniques



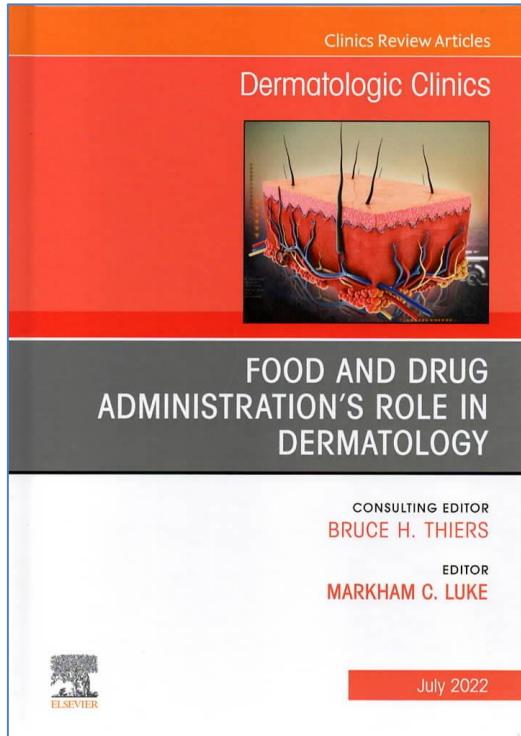
# Formulations Can Alter Bioavailability

- It is widely understood that the formulation of a topical semisolid dosage form can influence its performance
- It is now increasingly clear how excipients may exert their influence, by modulating the physicochemical and microstructural arrangement of matter in the dosage form
- The resulting physical and structural characteristics of topical dosage forms, and their metamorphic properties on the skin, can directly influence topical bioavailability

# Reiterating Q1, Q2, Q3

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

# July 2022 Dermatologic Clinics



Insightful articles on:

- The History of Dermatology at FDA
- FDA and Dermatologic Drug Development
- Postmarket Assessment for Dermatology Drugs and Cutaneous Adverse Reactions
- How does FDA Approve Generic Drugs
- Dermatology Drugs for Children
- Regulation of Medical Devices for Dermatology
- Regulation of Cosmetics in the United States
- Cutaneous Pharmacokinetic Approaches
- Measuring What Matters to Patients in Dermatology Drugs

# Concluding Summary



- FDA serves the U.S. dermatology patient community by –
  - Bringing new products to treat dermatologic disease (weighing balance between safety and efficacy)
  - Provide access to quality generic drug products
- These efforts involve applying knowledge gained from research and a practical approach to regulation

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Send your CV should you have interest in joining FDA team.

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Send your CV should you have interest in joining FDA team.