Dermatology Innovation Forum
an Advancing Innovation in Dermatology conference

FDA U.S. FOOD & DRUG ADMINISTRATION

Advancing the science of how topically applied drugs penetrate the skin and clinical relevance

- the viewpoint of an FDA dermatologist

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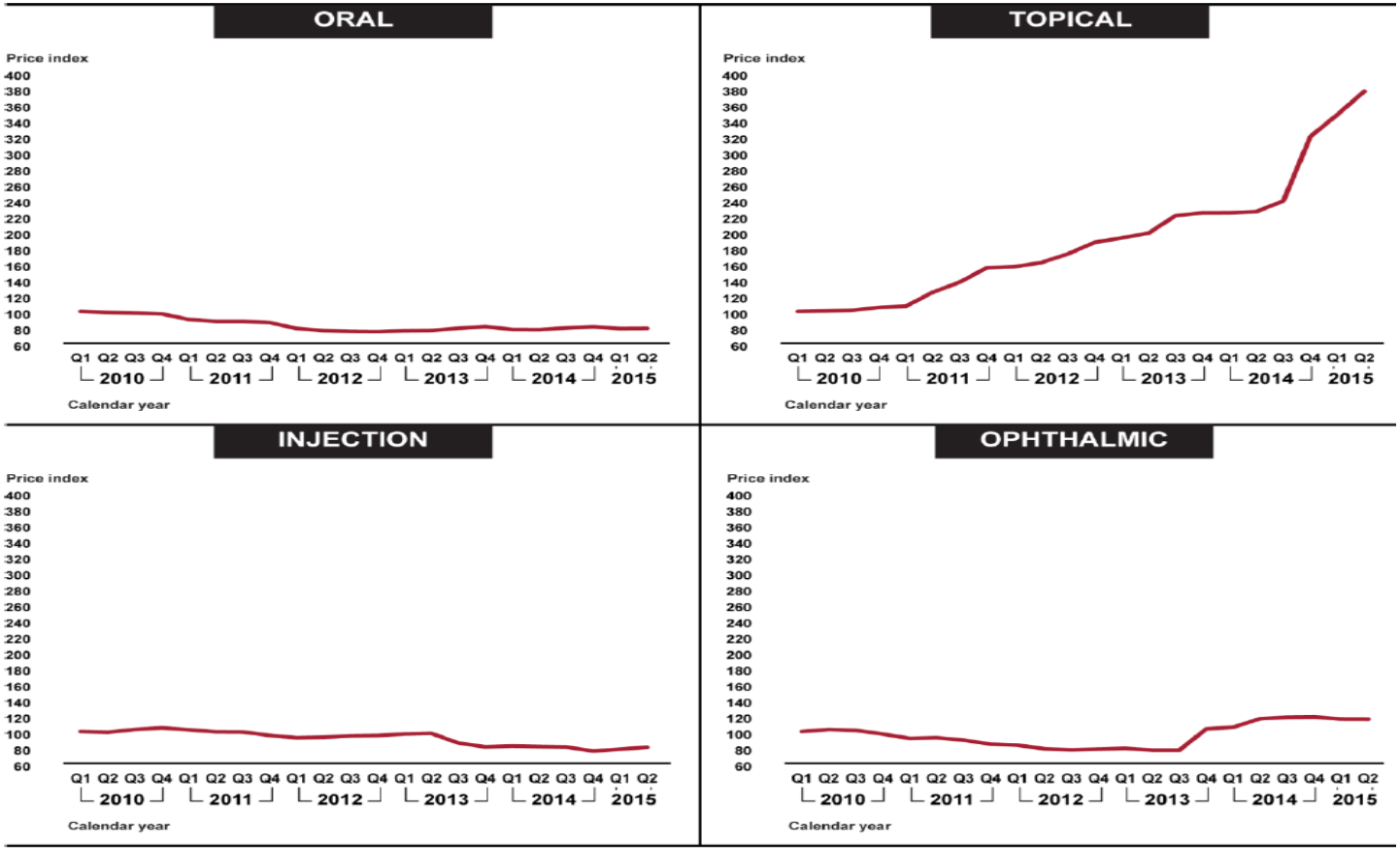
Disclaimer

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

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

Generic Drug Access

- 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)

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 pharmacokinetic (PK) 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

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

FDA Topical Drug 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

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

What are 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

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

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, 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

Q3 Characterization of Topical Products

1. Appearance and texture
2. Phase states – to support the drug is dissolved in the dosage form, and/or single-phase dosage form (as relevant)
3. Particle size distribution and crystal habit, and/or emulsion globule size distribution (as relevant)
4. Polymorphic form(s) of the active ingredient(s)
5. Rheological behavior
6. Water activity and/or drying rate
7. Absorption/miscebility of perspiration or other skin exudate
8. pH and buffer capacity
9. Specific gravity or density
10. Effect of temperature change on any of the above (e.g. as drug is applied to the skin)

IVRT Studies

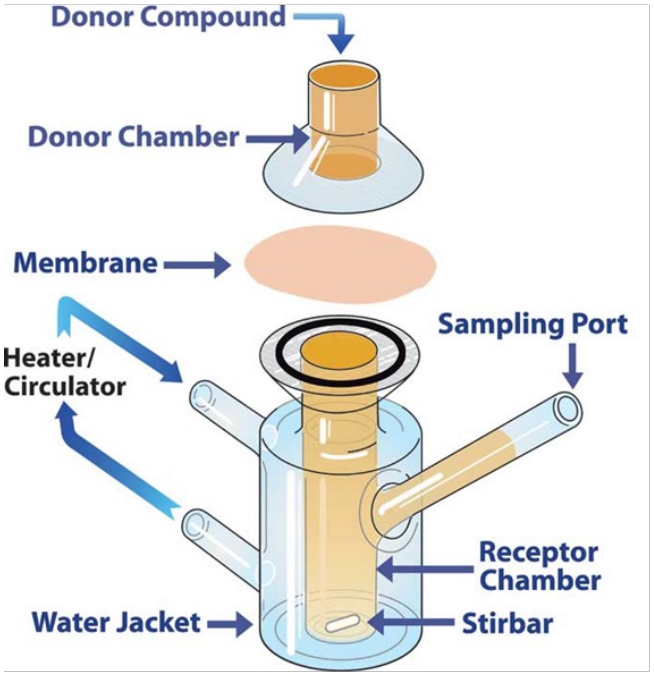
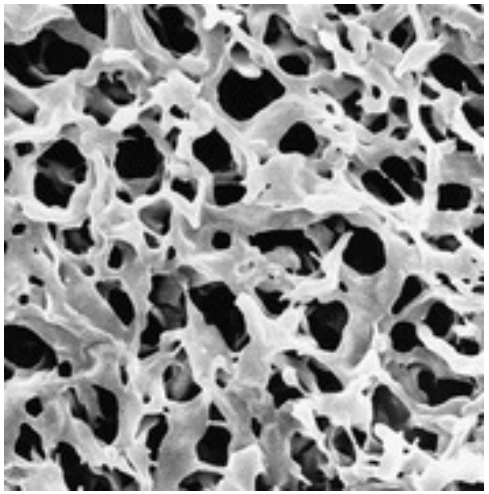
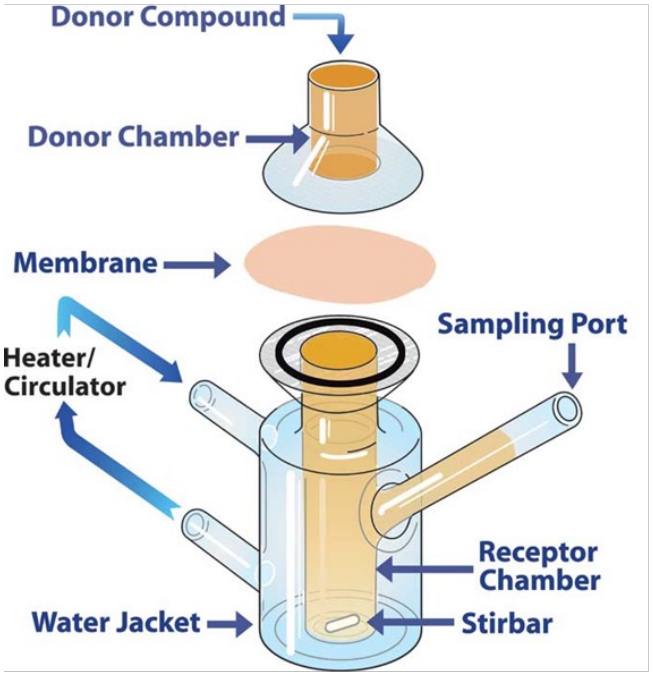


Image courtesy of PermeGear



IVRT Studies



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⟨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.

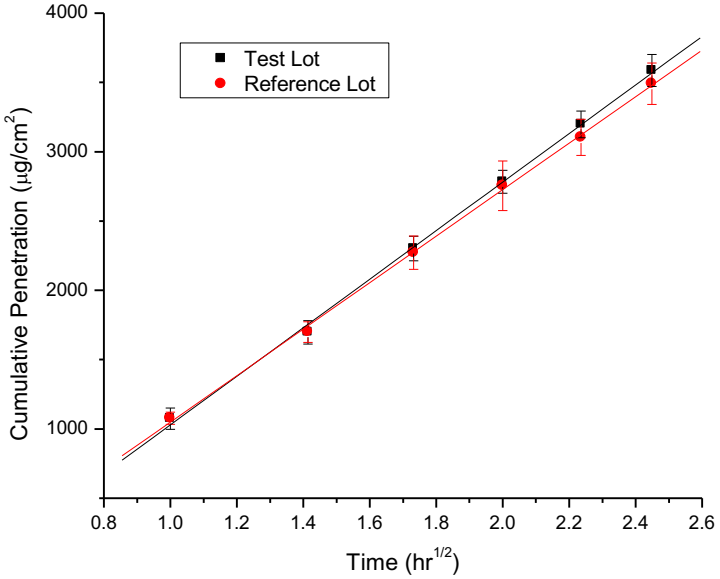
DRUG PRODUCT QUALITY AND PERFORMANCE TESTS

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 Study Results



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

IVPT Studies

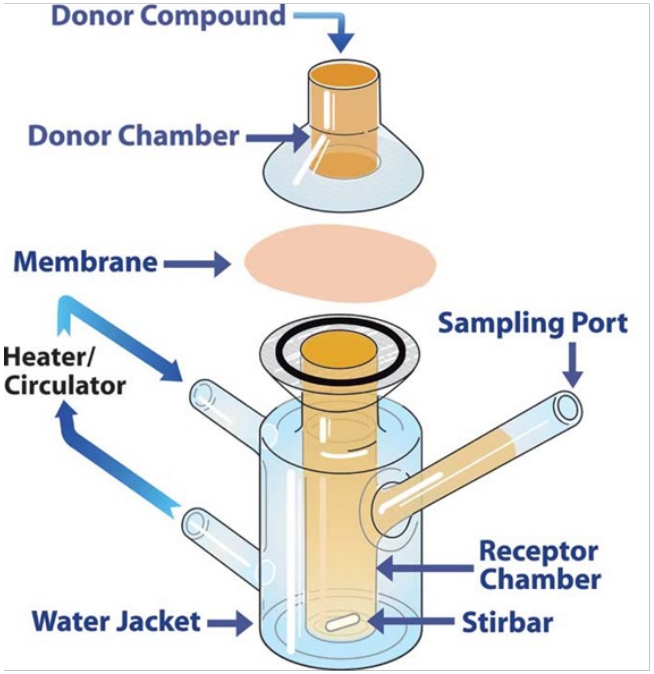
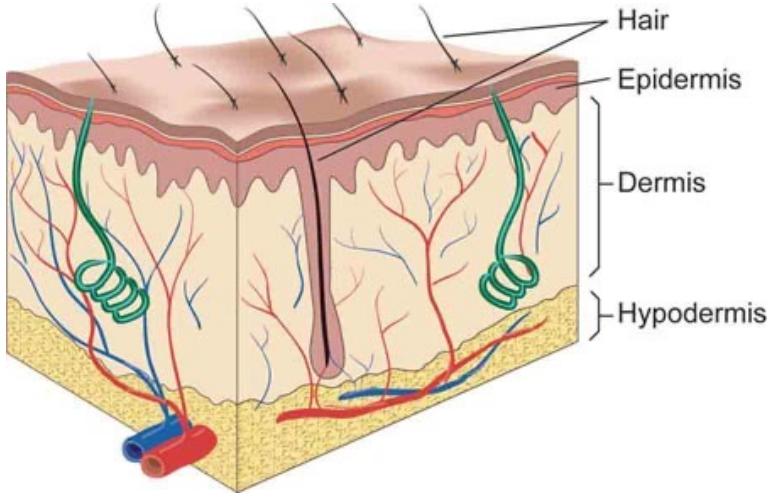
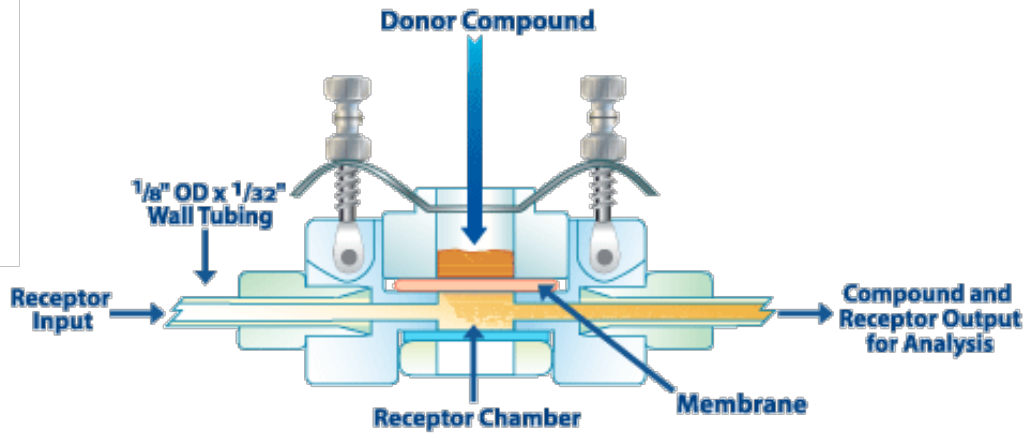
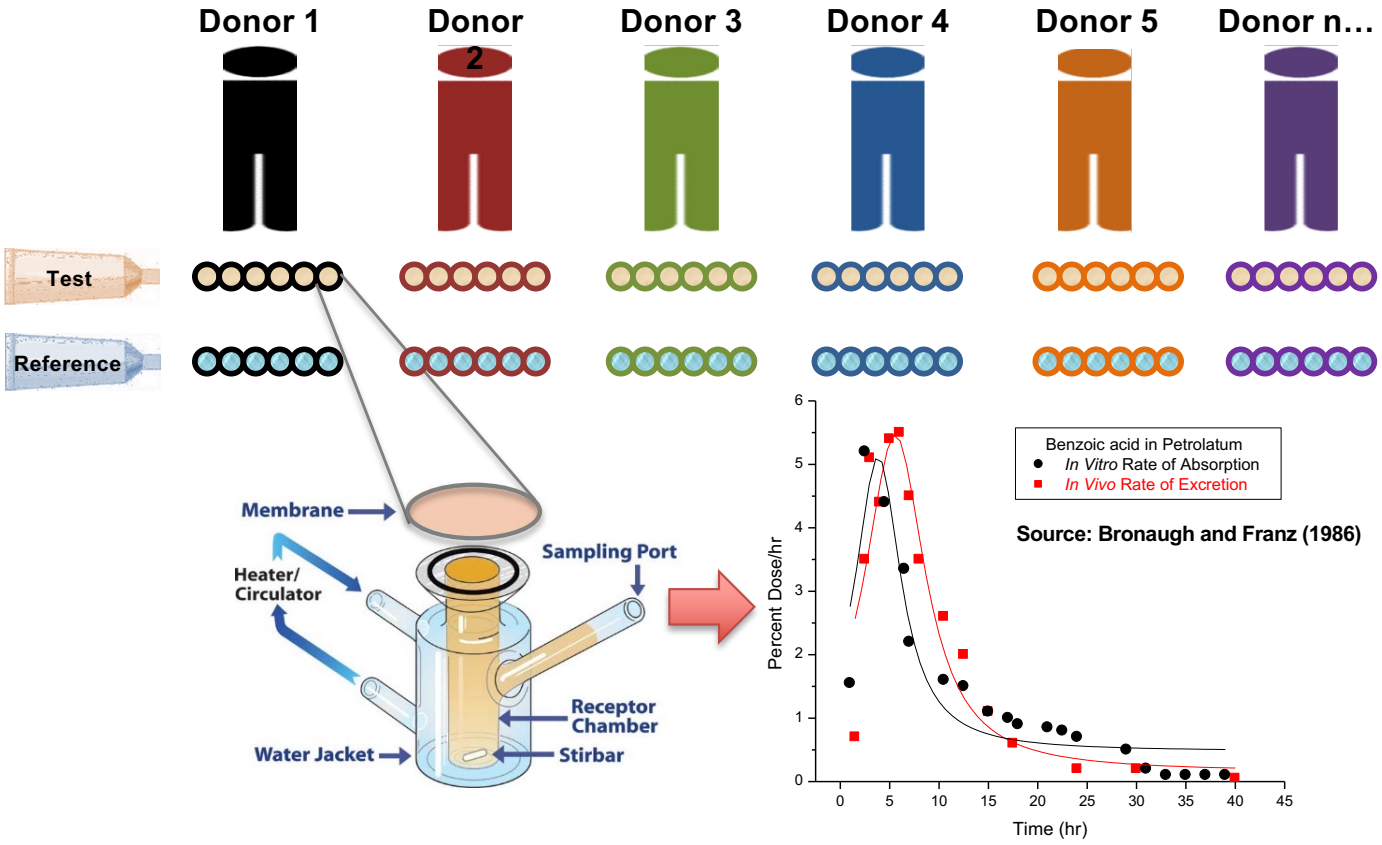


Image courtesy of PermeGear

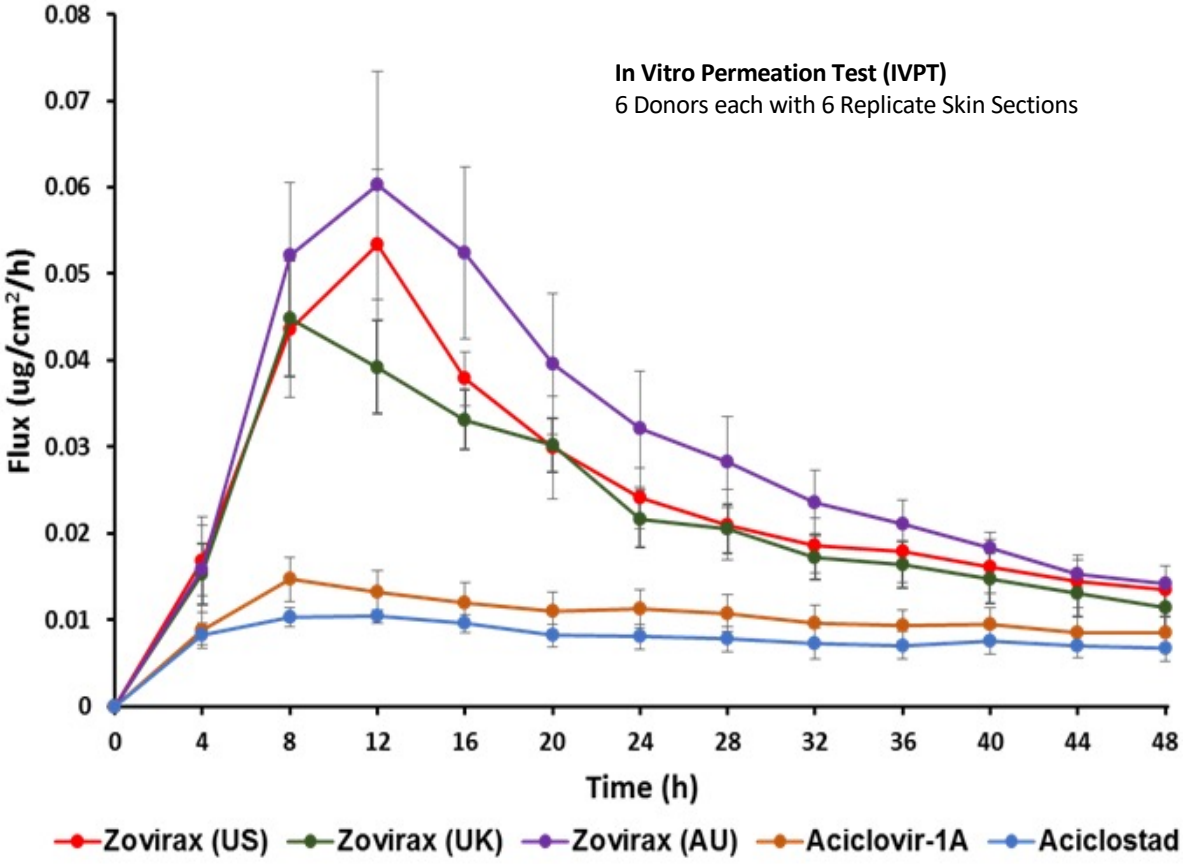




IVPT Study Design



IVPT Study Results



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

IVPT vs. IVRT Studies

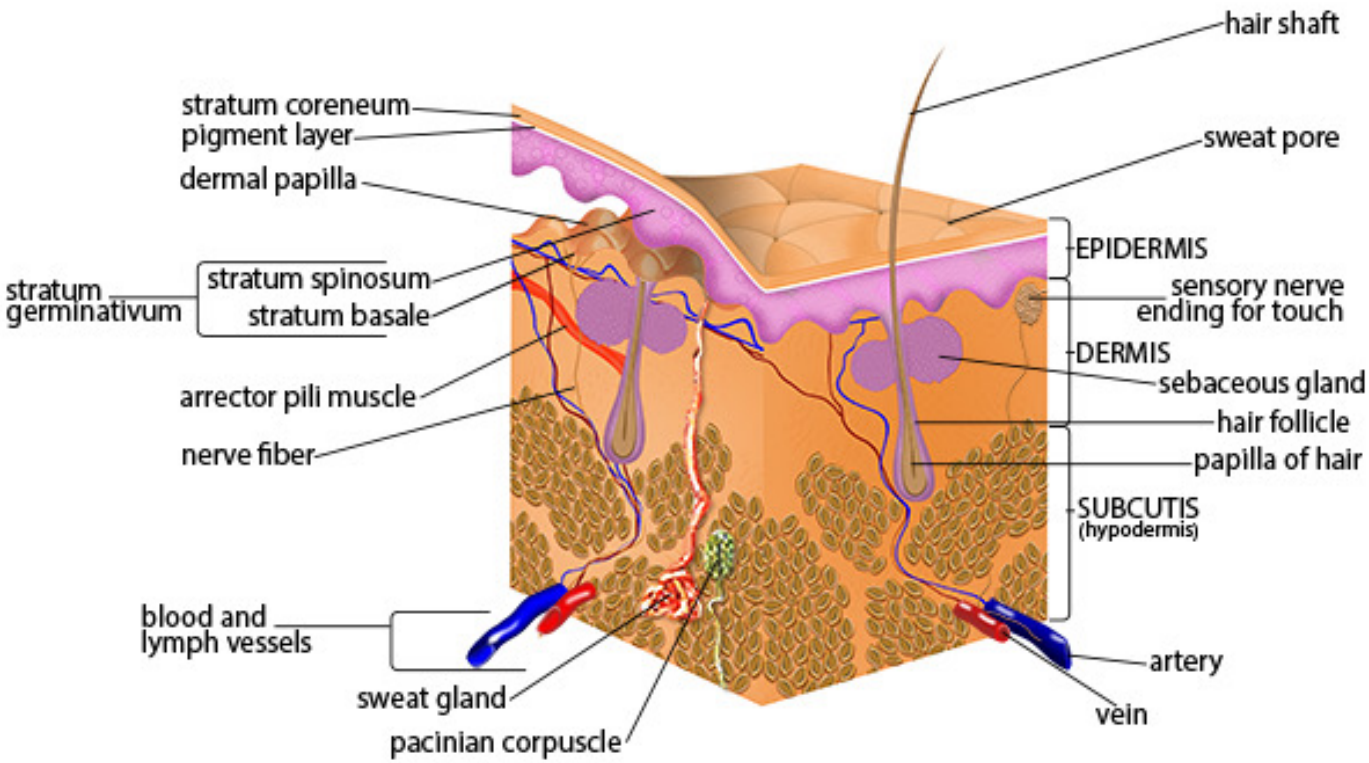
IVPT (Permeation)

- **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

From Anatomy to Pharmacology

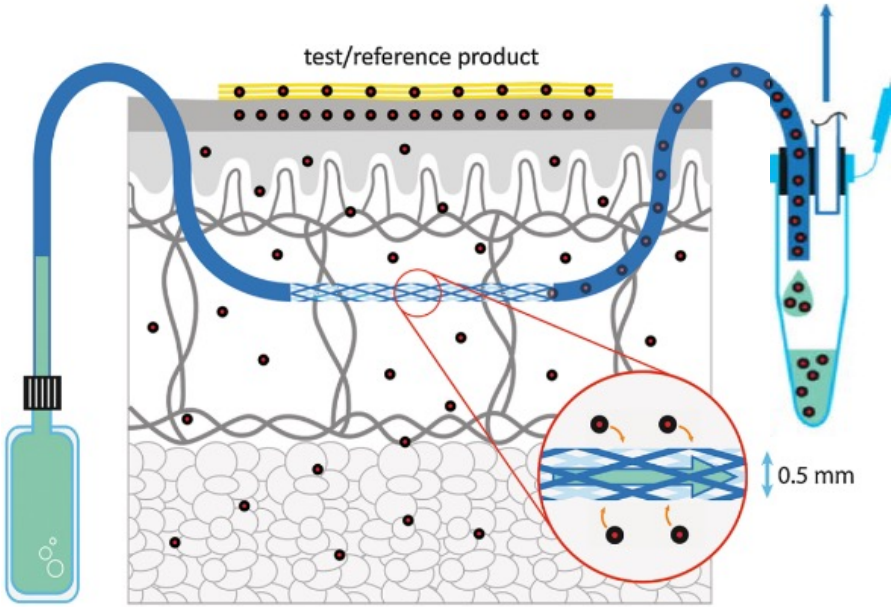


Cutaneous Raman Spectroscopy

- We can utilize unique molecular signatures when excited by laser light to detect changing concentrations and gradients of drug across the stratum corneum.
- This promises to allow non-invasive measurement of drug concentration into the skin.
- When combined with confocal microscopy techniques, we may be able to co-localize drug flux to skin micro-anatomy.

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.



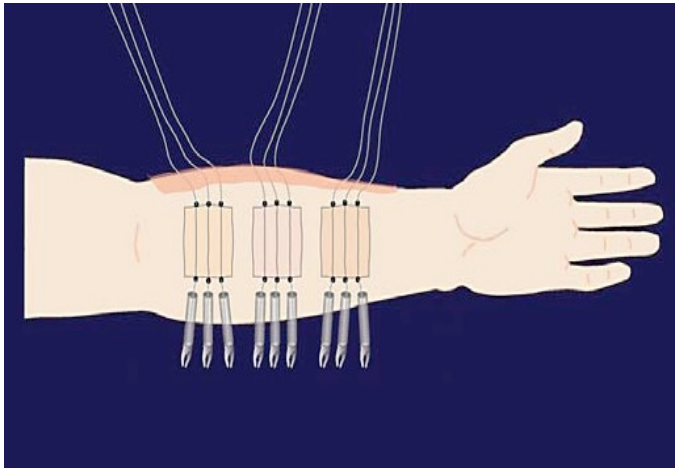
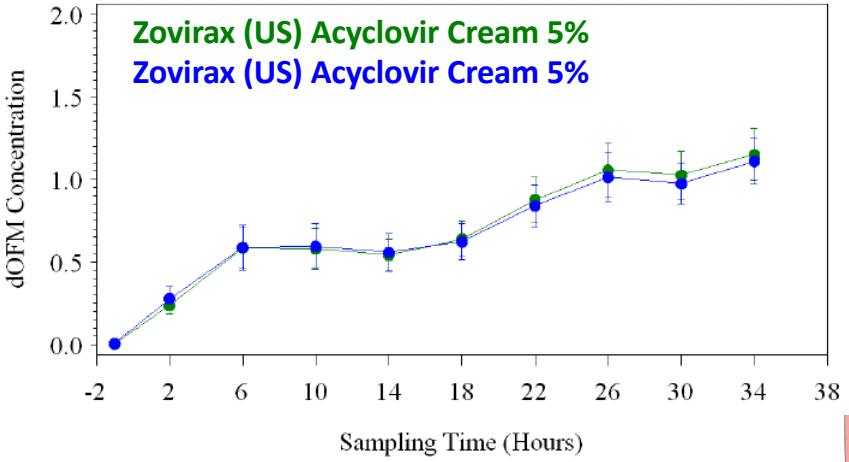


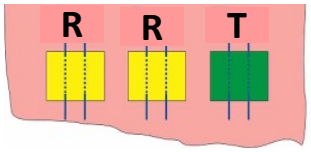
Image provided courtesy of Dr. Frank Sinner, Joanneum Research

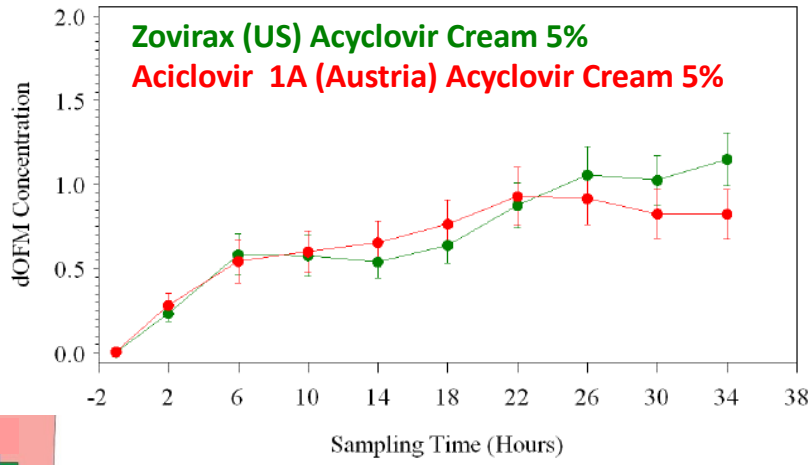
Skin Pharmacol Physiol 2011;24:44–53

Pivotal BE Study for Acyclovir Cream



Outcome variable	$CI_{90\%}$	BE-limits	BE
$log(AUC_{0\text{-}36h})$	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]	[-0.223 ; 0.223] or [80% ; 125%]	passed
$log(C_{max})$	[-0.155 ; 0.190] or [85.7 % ; 120.9%]		passed





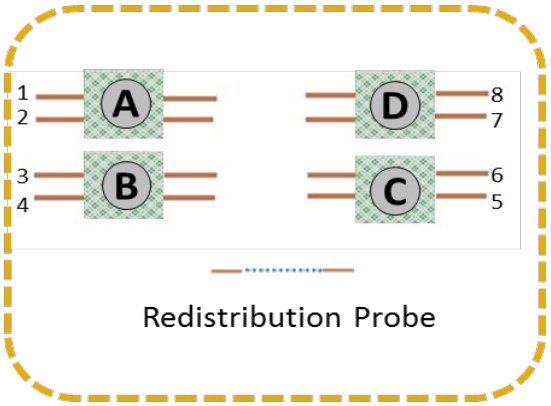
Outcome variable	$CI_{90\%}$	BE-limits	BE
$log(AUC_{0\text{-}36h})$	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]	[-0.223 ; 0.223] or [80% ; 125%]	x Failed
$log(C_{max})$	[-0.498 ; 0.022] or [60.8 % ; 102.2%]		x Failed

Clinical pharmacokinetics vol. 56,1 (2017): 91-98

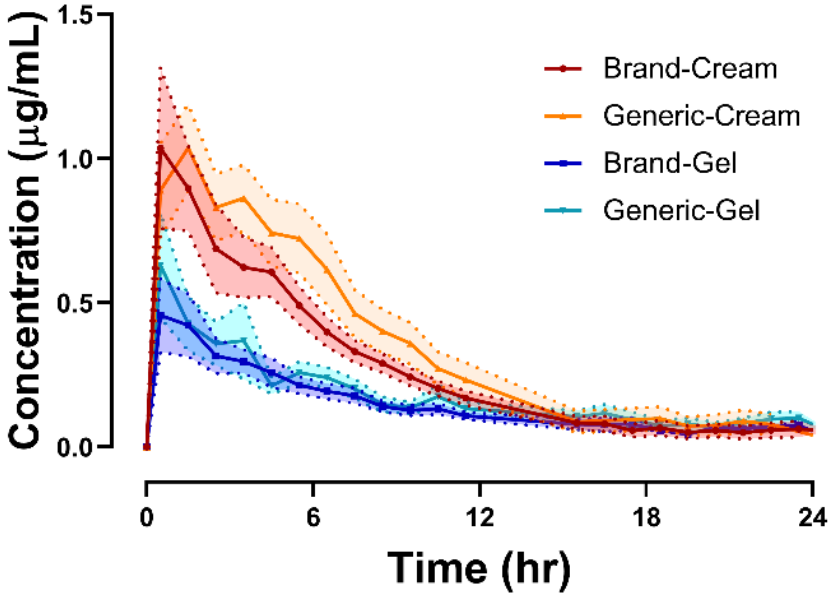
Formulations Can Alter Bioavailability

- 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

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 ± SEM, n=7), in rabbits*

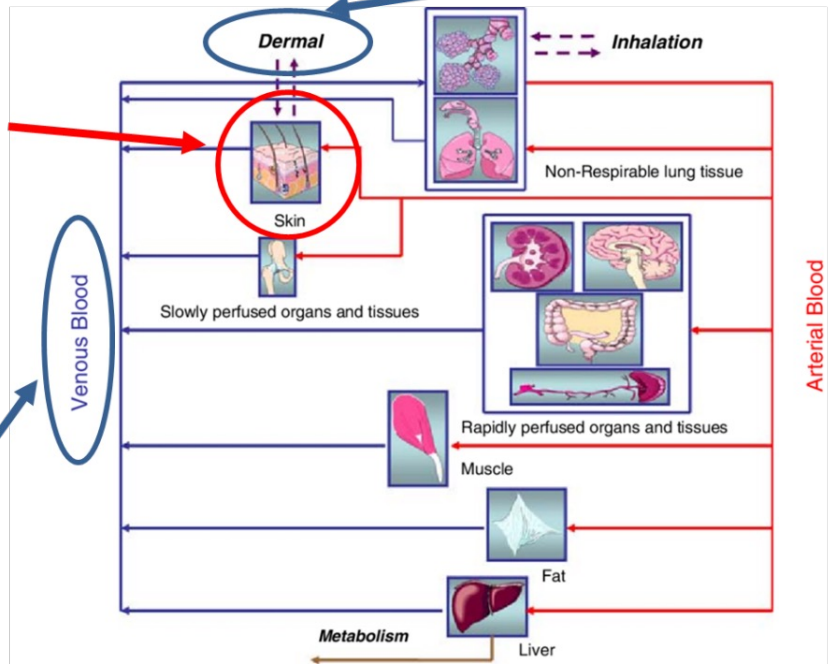
Data/images provided courtesy of Dr. Grazia Stagni, Long Island University

Dermal Physiology-Based(PB) PK models

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

What we can measure:
-Formulation in vitro performance

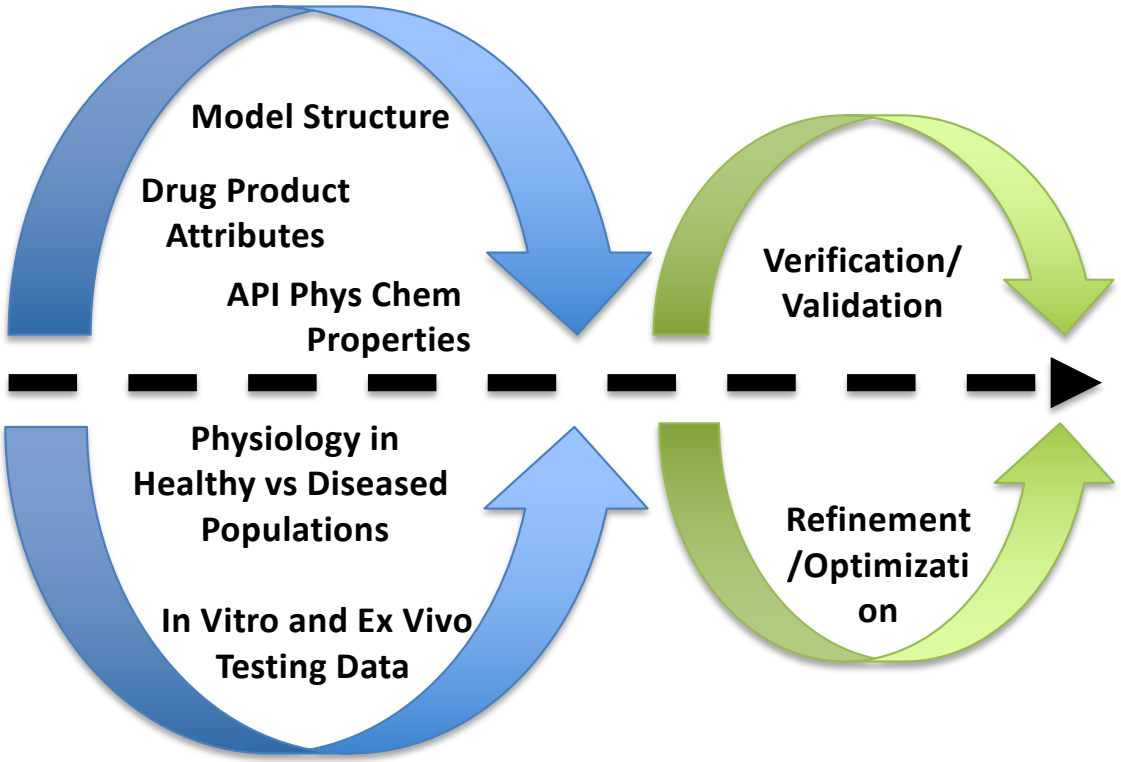
What we would like to know:
-local drug concentrations

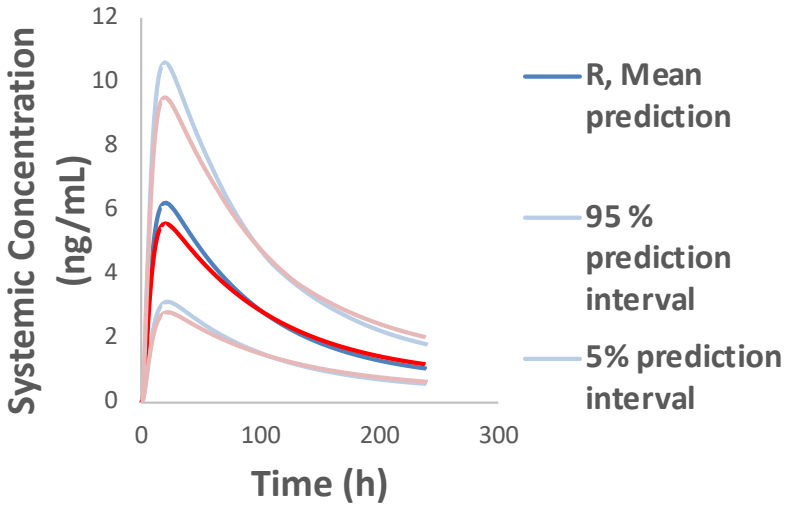


What we can measure:
-Systemic drug exposure

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

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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