FDA Regulatory Initiatives Related to Generic Dermatological and Transdermal Drug Products

30th Anniversary

Perspectives in Percutaneous Penetration Conference

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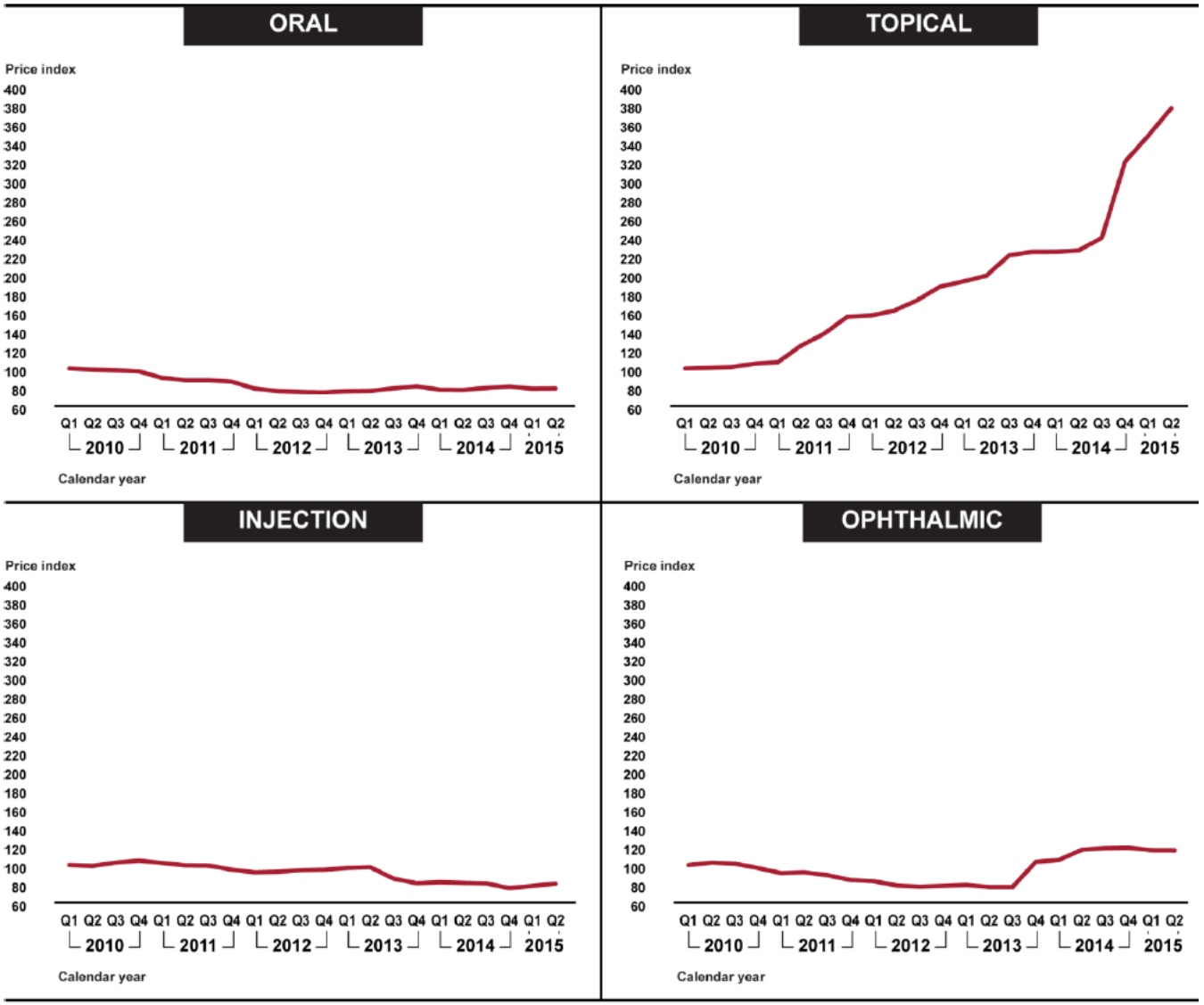
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Part I: Topical Drug Products

The GAO Report (GAO-16-706)

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

The GAO Report (GAO-16-706)



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

Retail Prices for Dermatologic Drugs

Drug	Type	Price, US $				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
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

- The vast majority (approximately 80%) of topical dermatological drug products have fewer than three generic competitors, and in many cases, have no approved generics at all.[1]
- This may have been attributable to the historical barriers to the development of topical dermatological drug products, possibly including
  - Comparative clinical endpoint bioequivalence (BE) studies
  - The complex nature of topical formulations
  - The relatively small market capitalization for some products

[1] FDA Office of Generic Drugs Topical & Transdermal Products Database

Patient Access to Topical Generics

- **Mission** of the Office of Generic Drugs (OGD)
  - To make **high quality**, affordable medicines **available** to the public.

Patient Access to Topical Generics

- Availability of Topical Generic Drug Products can
  - Help to make medicines affordable for patients
  - Increase the likelihood that patients will actually purchase the medicine prescribed for them and receive therapeutic benefit
  - Stabilize the drug supply against shortages
- High Quality Topical Generic Drug Products can
  - Ensure that there are no differences in quality or performance between the generic drug product and the RLD product
  - Help satisfy perceptions of quality by patients and prescribers
  - Help eliminate “dispense as written” substitution concerns
  - Help establish or maintain confidence in generic substitution

Patient Access to Topical Generics

- **Mission** of the Office of Generic Drugs (OGD)
  - To make **high quality**, affordable medicines **available** to the public.
- **Vision** to support OGD's commitments:
  - Product Quality Characterization
    - ➔ Supports **high quality** medicines
  - Efficient BE Standards
    - ➔ Helps make medicines **available**

High Quality Drug Products

- What does "quality" mean for a drug product?

Fitness for Purpose

*"The totality of **features and characteristics of a product…** that bear on its ability to satisfy stated or implied needs"*

- International Organization for Standardization (ISO)

Control of Failure Modes

*"Good pharmaceutical quality represents **an acceptably low risk of failing** to achieve the desired clinical attributes."*

- Dr. Janet Woodcock, Director, FDA CDER

Woodcock, J. (2004) *The concept of pharmaceutical quality*. Am Pharm Review 7(6):10-15

Available (and Affordable) Products

- Power of "efficient" BE standards

  Overall Drug Products [2]

  - **89%** of prescriptions dispensed in 2016 were for generics
  - Efficient **Pharmacokinetics (PK)-based** methods available

  Topical Drug Products [3]

  - Most topical products have few or no generics available
  - Efficient **Local and Systemic PK-based** methods may be useful
  - Efficient **In Vitro BE** standards may be useful
  - Efficient BE approaches supported by a collective weight of evidence from in silico, in vitro and/or in vivo studies?

[2] AAM 2017 Generic Drug Access & Savings in the United States Report

[3] FDA Office of Generic Drugs Topical & Transdermal Products Database

Developing Rational BE Standards

- **A <u>Modular</u> Framework for In Vitro BE Evaluation**
  - **Q1/Q2** sameness of inactive ingredient components and quantitative composition
  - **Q3 (Physical & Structural Characterization)** as relevant to the nature of the product
  - **IVRT** (In Vitro Release Test) for moderately complex products
  - **IVPT** (In Vitro Permeation Test) or another bio-relevant assay for more complex drug products
- **A <u>Scalable</u> Framework for BE Evaluation**
  - **In Vivo** systemic PK studies may be appropriate
  - **In Silico** computational modeling may be useful

Comprehensive Research Strategy

- **Q3 Product Quality Characterization**
  - FDA/CDER/OTS/DPQR (USA) — Q3 Tests
  - University of Mississippi (USA) — Q3 Tests
  - University of South Australia (and Germany) — Q3 Tests
- **In Vitro Release Test (IVRT)**
  - FDA/CDER/OTS/DPQR (USA) — IVRT
  - Joanneum Research (Austria) — IVRT
- **Cutaneous PK: In Vitro Permeation Test (IVPT)**
  - University of Mississippi (USA) — IVPT
  - University of Maryland (USA) — IVPT
  - University of South Australia — IVPT
- **Cutaneous PK: In Vivo Methods**
  - Joanneum Research (Austria) — dermal Open Flow Microperfusion (dOFM)
  - Univ of Maryland/Bath (USA/UK) — Tape Stripping

Coordinated Research Strategy

- Pharmaceutically Equivalent Acyclovir 5% Creams
  - **Positive** and **Negative** Controls for BE

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

Developing In Vitro BE Standards

- **Q1/Q2 Sameness** (components and composition of excipients)

  Mitigates the risk of known failure modes related to:

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

Developing In Vitro BE Standards

- **Q3 (Physical and Structural) Similarity**

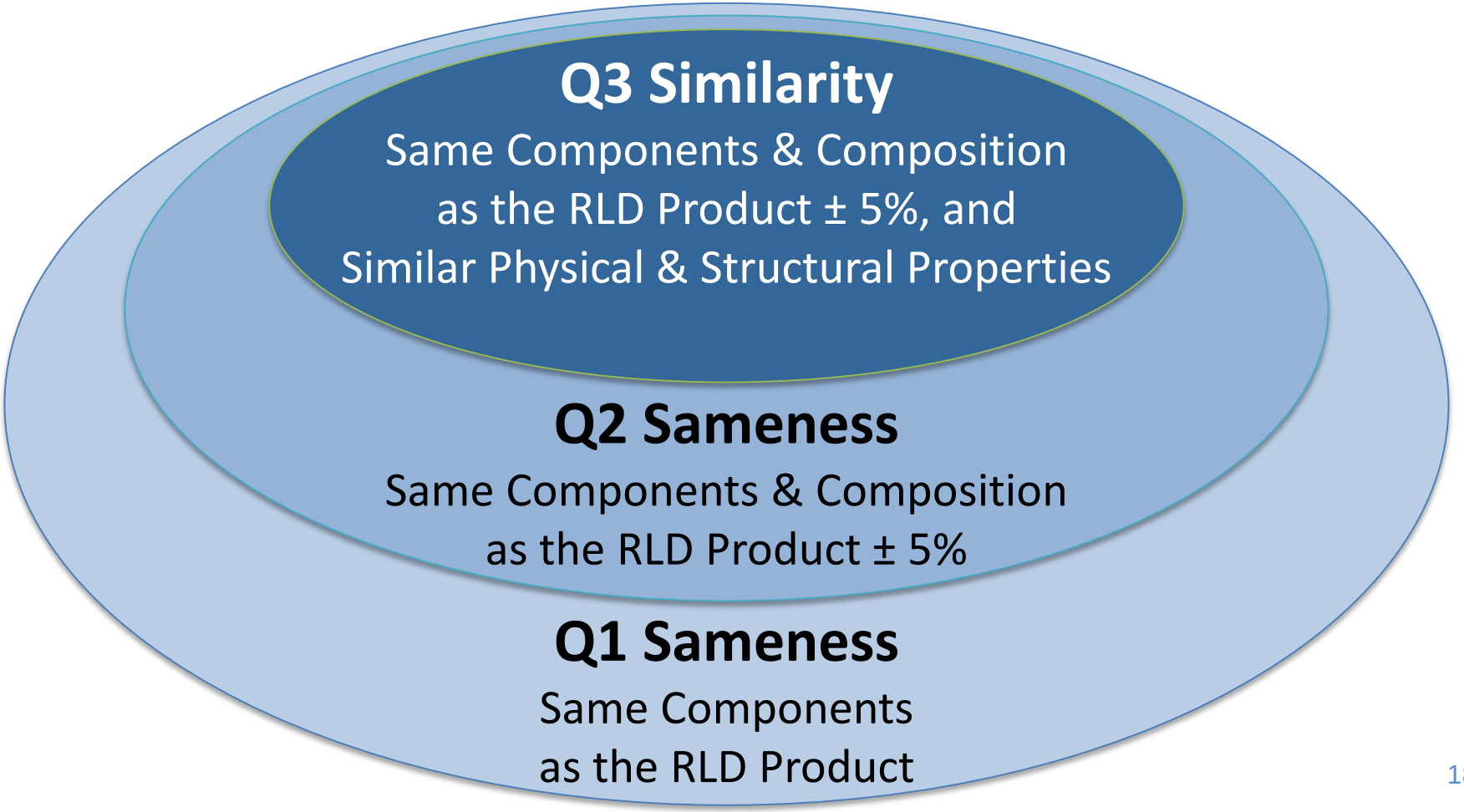
  Mitigates the risk of potential failure modes related to:

  - Differences in Q1/Q2 sameness (± 5% tolerances)
  - Differences in pH that may sting or irritate diseased skin
  - Differences in the polymorphic form of the drug
  - Differences in rheology that alter the spreadability, retention, surface area of contact with the diseased skin
  - Differences in entrapped air and drug amount per dose
  - Differences in phase states and diffusion, partitioning, etc.
  - Differences in metamorphosis and drying rates
  - *Many of these Q3 concepts and the associated test methods had not been developed or standardized*

Developing In Vitro BE Standards

- **Q3 (Physical and Structural) Similarity**

  An evolving regulatory concept:



Effects of Formulation on Bioavailability

- It is widely understood that the formulation of a topical semisolid dosage form matters greatly
- It is now increasingly clear how excipients 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

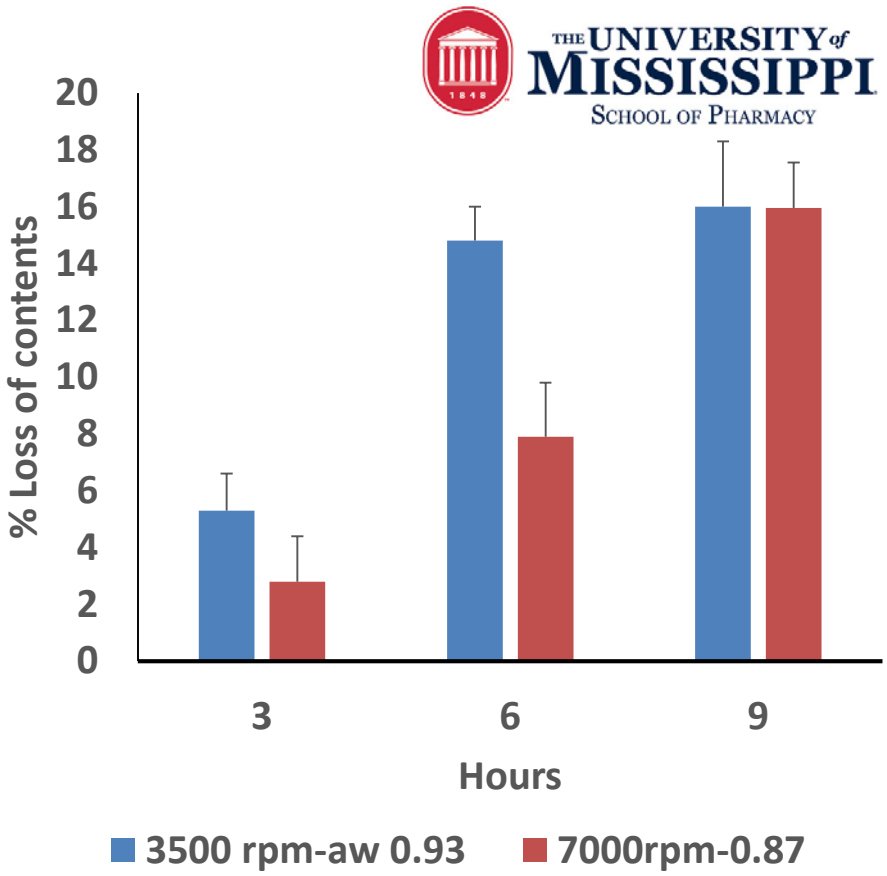
Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

Prof. Narasimha Murthy FDA Award U01-FD005223

Ingredients	Quantity (%w/w)
Cetostearyl Alcohol	12.5
White Wax	12
Mineral Oil	56
Sodium Borate	0.5
Water	19
Total	100

Manufacturing Conditions	Solvent Activity (a_w)
3500 RPM (15 min)	**0.931 ± 0.002**
7000 RPM (45 min)	**0.875 ± 0.006**



Data provided courtesy of Prof. Narasimha Murthy

Dosage Form Metamorphosis

- Solvent Activity (a_s) = ρ/ρ_0

  Prof. Narasimha Murthy FDA Award U01-FD005223

  - ρ = partial vapor pressure of Solvents in the product
  - ρ_0 = vapor pressure of pure Solvent system

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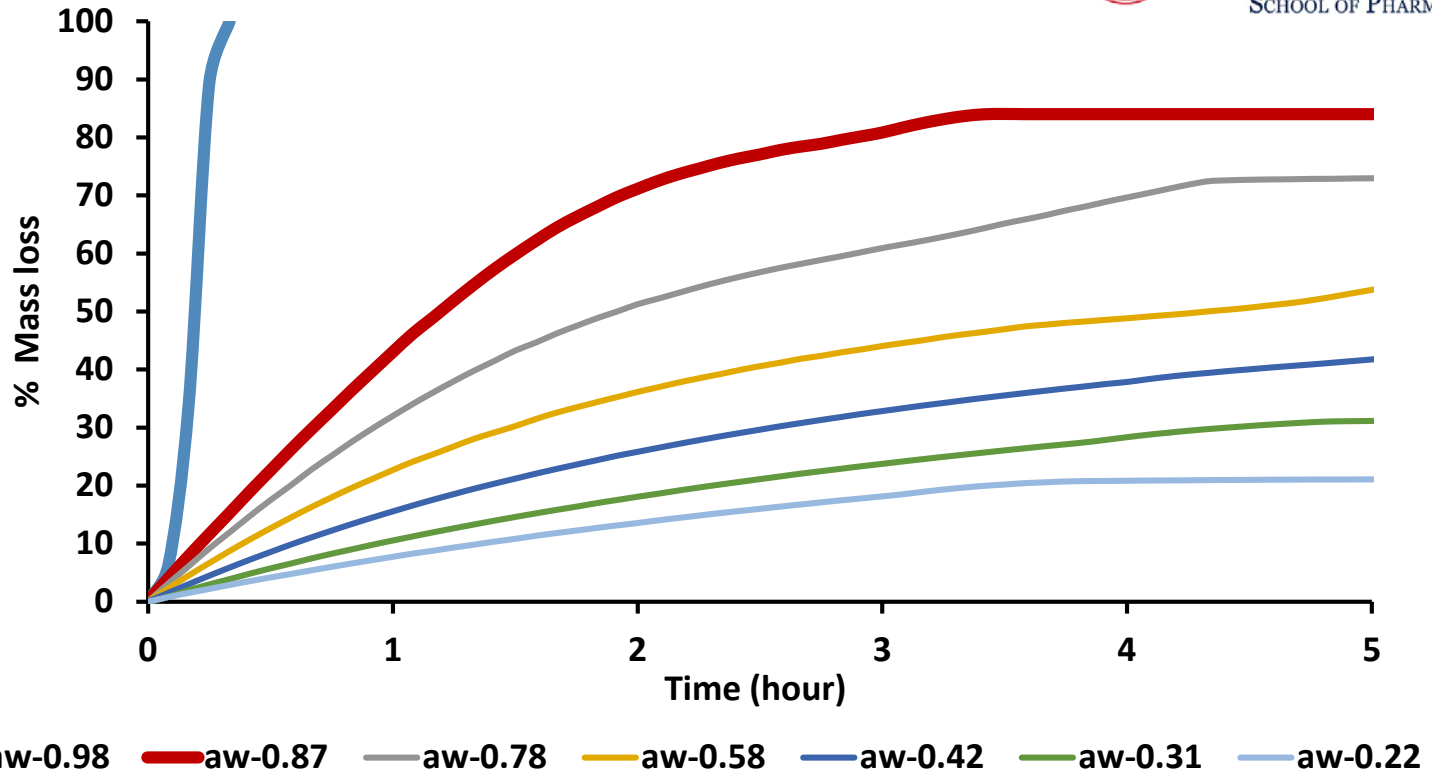

Data provided courtesy of Prof. Narasimha Murthy

Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

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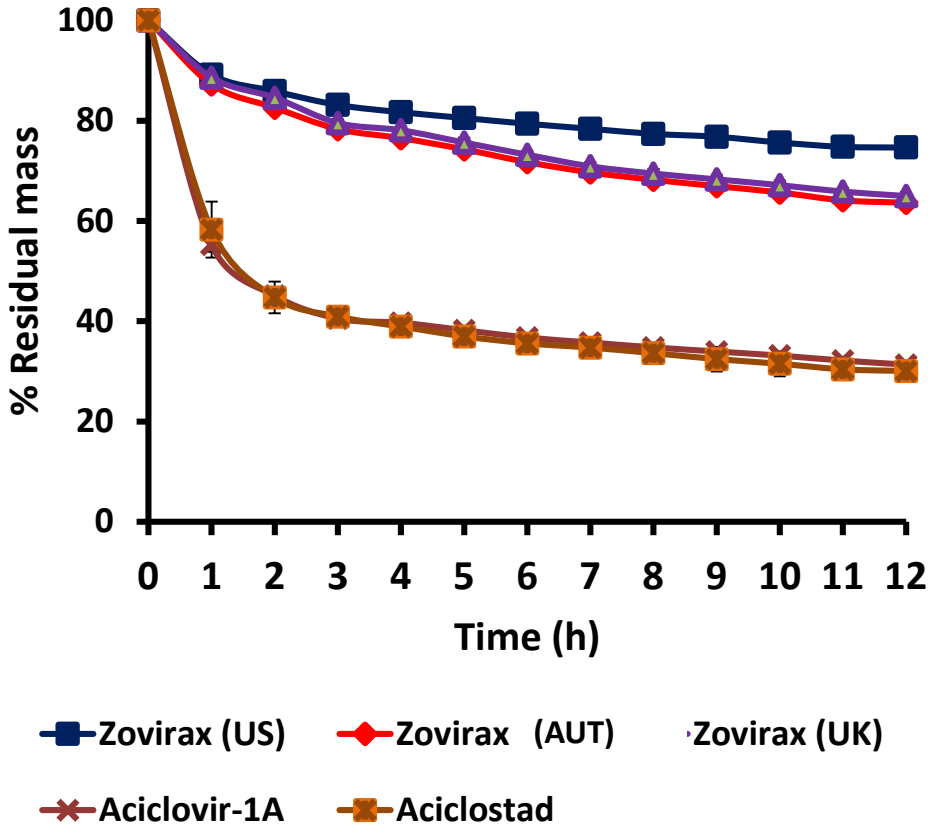

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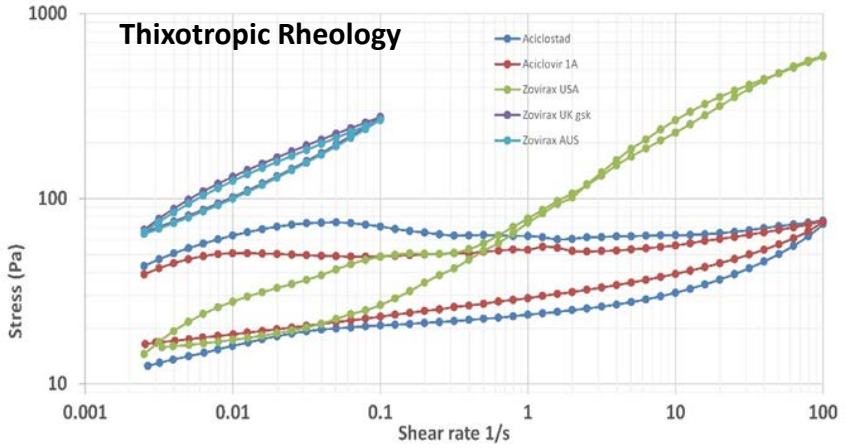
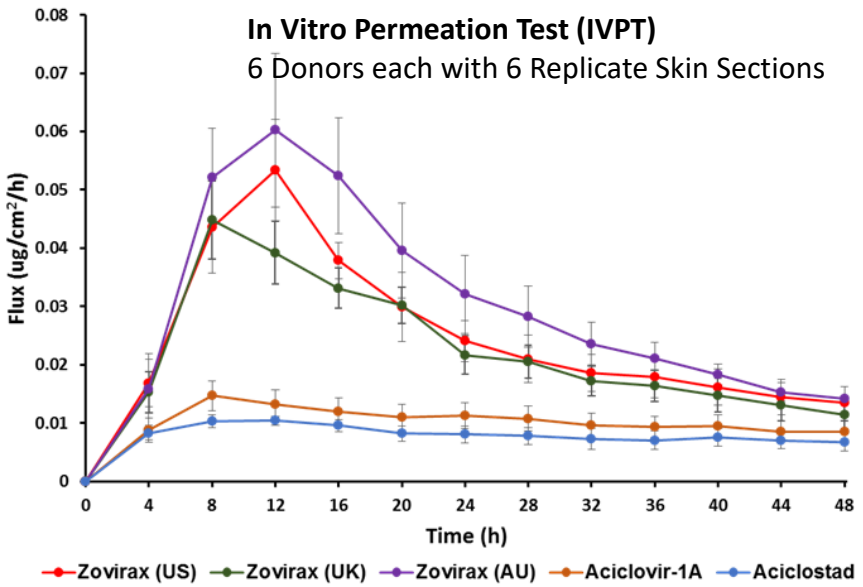
Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732± 0.002
Aciclovir 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

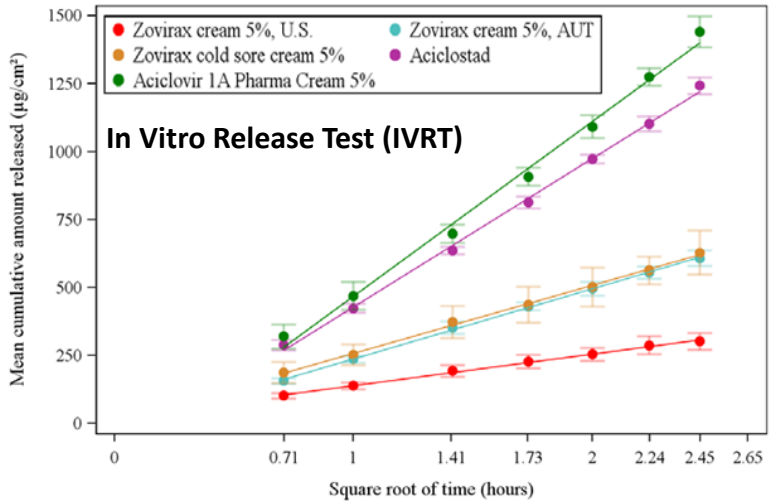
Data provided courtesy of Prof. Narasimha Murthy

Product Quality and Performance

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS	[redacted]	[redacted]
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
	[redacted]	Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95







Data provided courtesy of Prof. Narasimha Murthy & Dr. Frank Sinner

Effects of Q1/Q2/Q3 on Bioavailability

- Q1, Q2 or Q3 Differences can affect:
  - The phase states and the arrangement of matter
  - Drug diffusion within the dosage form
  - Drug partitioning from the dosage form into the SC
  - Alteration of skin structure and chemistry
  - Drug diffusion within the skin itself
  - Drug delivery & bioavailability at the target site
  - Skin (de)hydration, irritation or damage
  - Metamorphosis of the dosage form on the skin

Developing In Vitro BE Standards

- **IVRT (In Vitro Release Test)**

  Mitigates the risk of unknown failure modes related to:

  - Differences in Q1/Q2 sameness (± 5% tolerances)
  - Differences in physical and structural similarity
  - Differences that may not be identified by quality tests
- IVRT is a sensitive, discriminating compendial method with established statistical analyses
- However, no In Vitro – In Vivo Correlation (IVIVC) is expected
- *Standard procedures for IVRT method development and validation had not been established*

IVRT Method

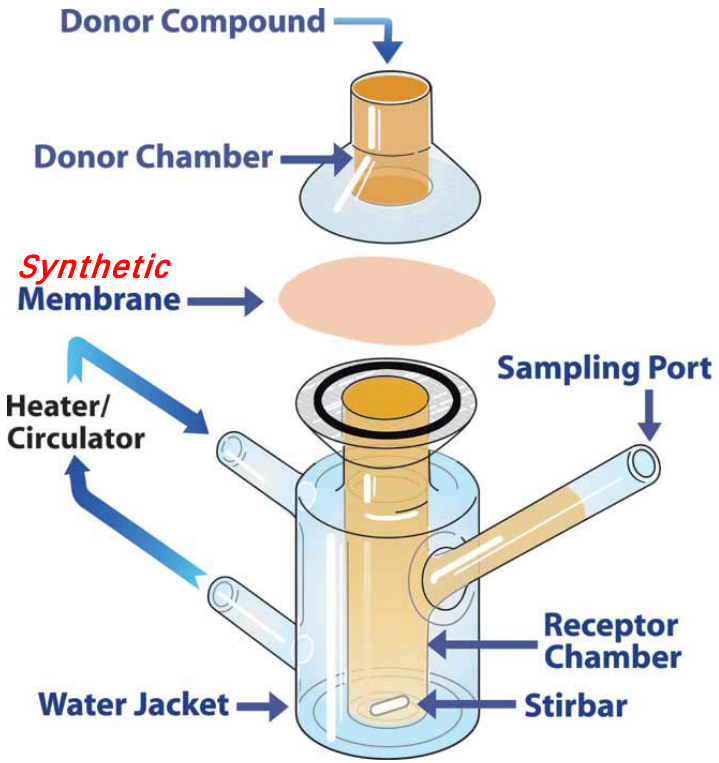
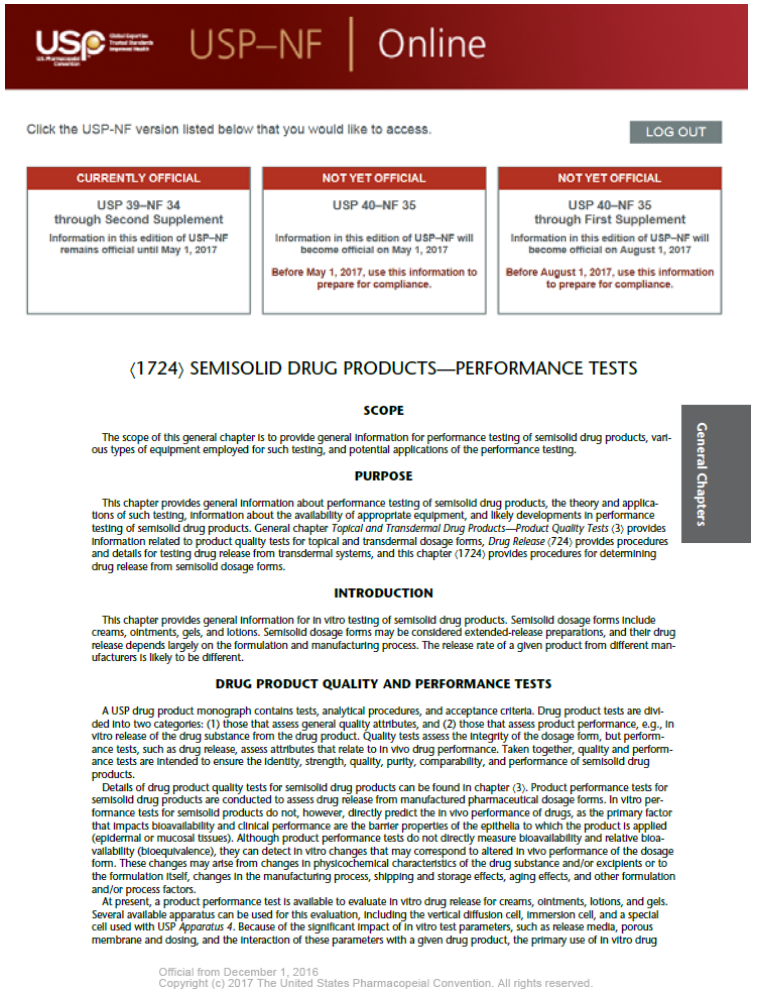


Image courtesy of PermeGear



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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

Official from December 1, 2016

IVRT Qualifications & Validations

1. IVRT Apparatus Qualification

- Cell Capacity
- Cell Orifice Diameter
- Receptor Medium & Membrane Temp.
- Stirring Speed
- Dispensed Sampling Volume
- Environmental Conditions

2. IVRT Laboratory Qualification

- Inter-run Variability
- Intra-run Variability
- Product Sameness Test

3. IVRT Sample HPLC Method Validation

- Selectivity and Specificity
- Linearity
- Accuracy, Precision and Robustness
- Stability

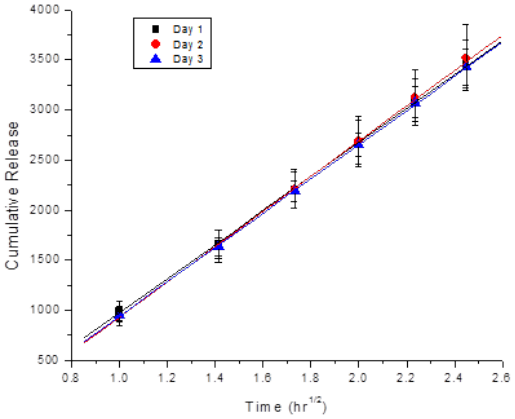
4. IVRT Method Validation

- Linearity and Range
- Precision and Reproducibility
- Recovery Mass Balance, and Dose Depletion
- Sensitivity, Specificity, and Selectivity
- Apparatus Qualification
- Membrane Inertness
- Receptor Solution Solubility
- Robustness

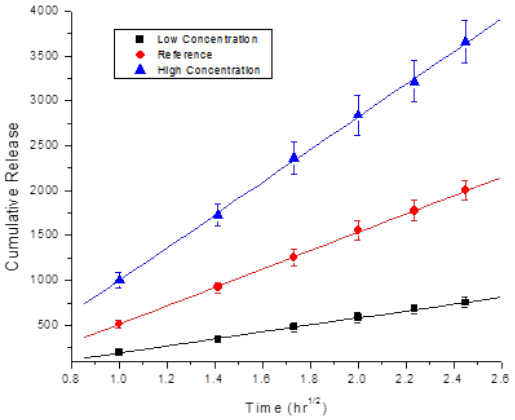
Refer to Tiffner et al. (2017) *A Comprehensive Approach to Qualify and Validate the Essential Parameters of an In Vitro Release Test (IVRT) Method for Acyclovir Cream, 5%*. International Journal of Pharmaceutics. (Funded, in part, by FDA through award U01FD004946)

IVRT Method Validation

- **Validation Components**
  - Linearity and Range
  - Precision and Reproducibility
  - Recovery, Mass Balance & Dose Depletion



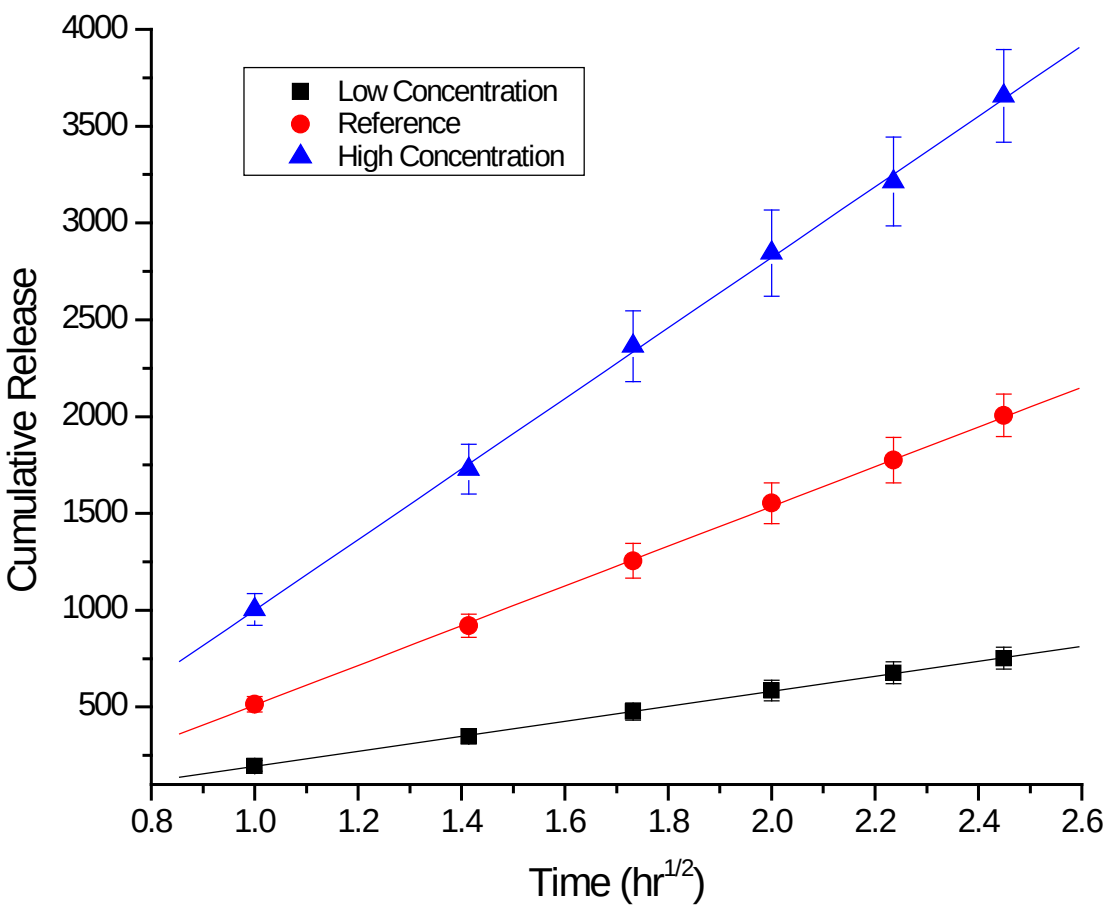
  - Sensitivity
  - Specificity
  - Selectivity



  - Apparatus Qualification
  - Membrane Inertness
  - Receptor Solution Solubility
  - Robustness

IVRT Method Validation

Sensitivity (to an increase or decrease in release)



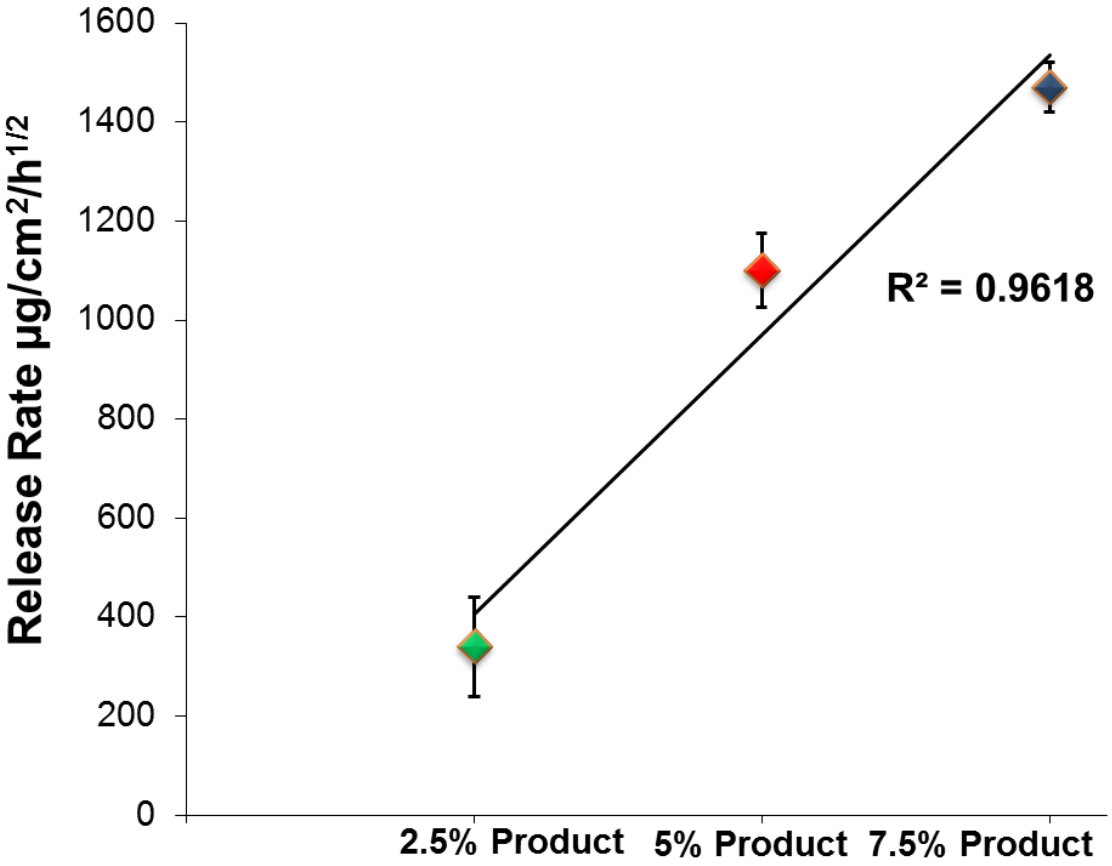
7.5% Product **Slope = 1470**

5% Product **Slope = 1100**

2.5% Product **Slope = 340**

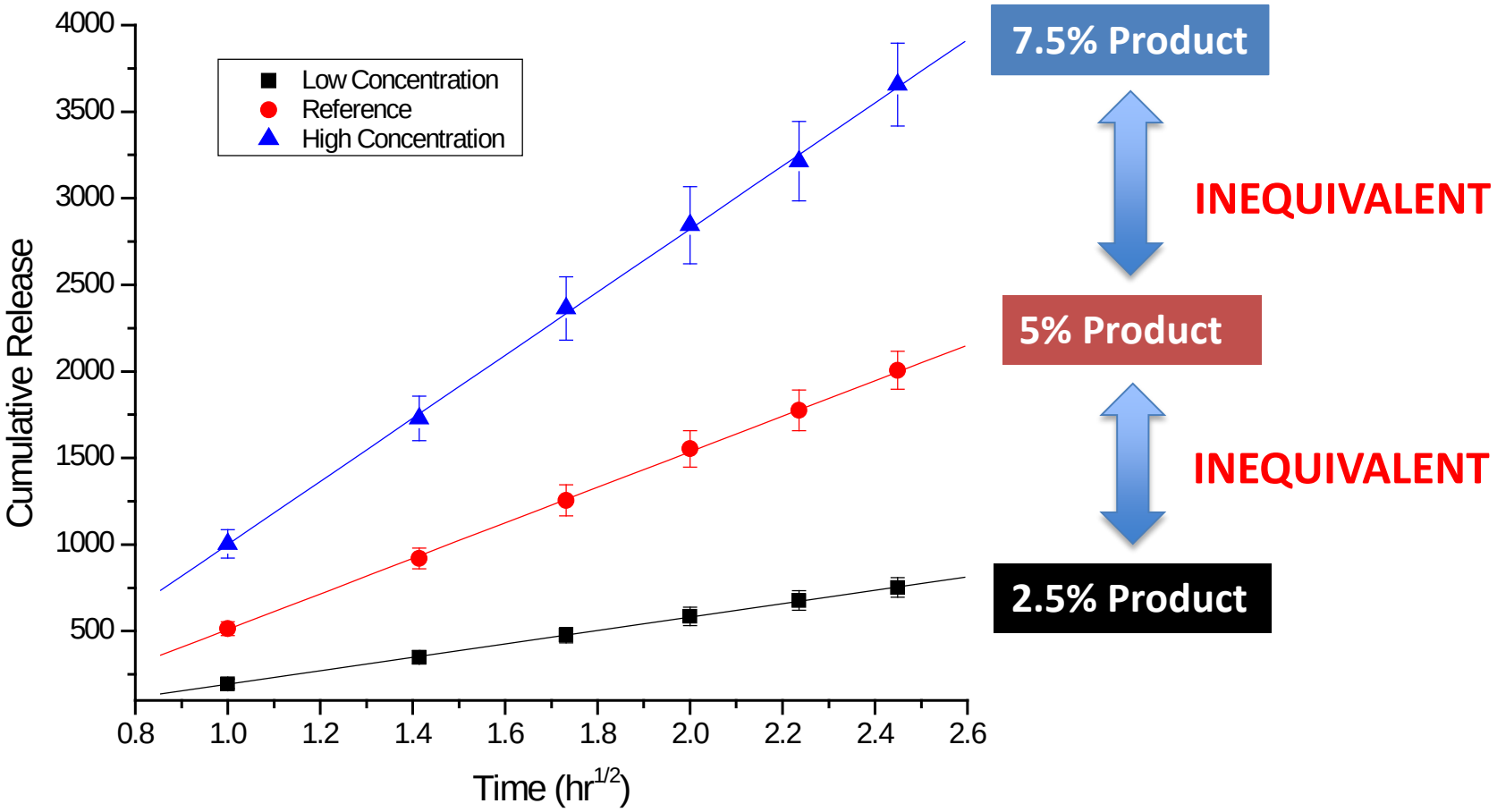
IVRT Method Validation

Specificity (proportional response to a change in release)



IVRT Method Validation

Selectivity (to discriminate inequivalent release rates)



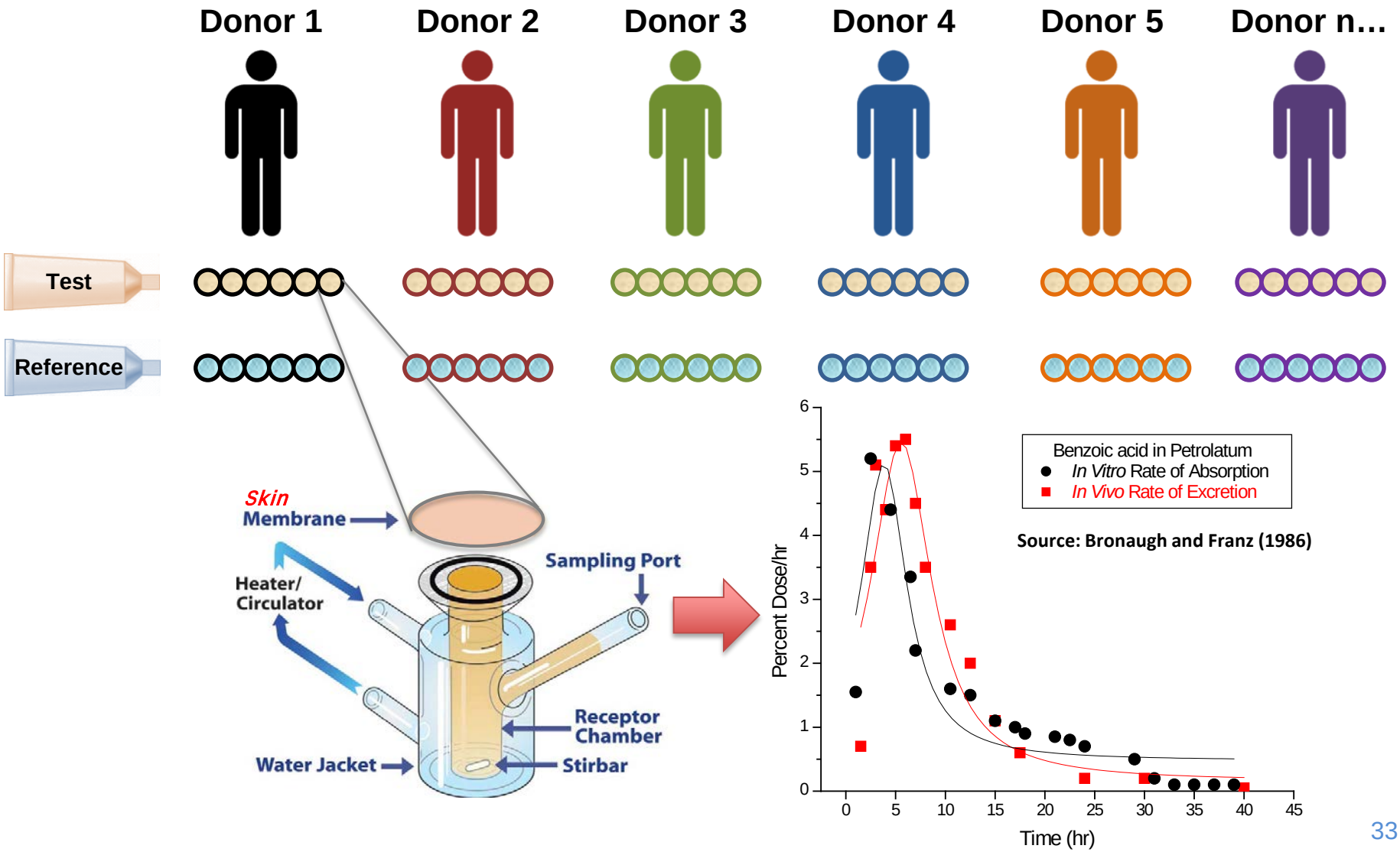
Developing In Vitro BE Standards

- **IVPT (In Vitro Permeation Test): Cutaneous PK Study**

  Mitigates the risk of other unknown failure modes related to:

  - Differences in Q1/Q2 sameness (± 5% tolerances)
  - Differences in physical and structural similarity
  - Differences that may not be identified by other tests
- IVPT is a sensitive, discriminating indicator of relative BA
- IVPT results can exhibit IVIVC
- *Standard procedures for IVPT method development and validation had not been established*

IVPT Study Design



IVPT Method Development

- Suitability of IVPT apparatus, flow rate, etc.
- Selection of dose amount and IVPT sensitivity
- Evaluation of sample concentrations
- Evaluation of sampling schedule
- Evaluation of flux profile and study duration
- Development of sample analysis method

IVPT Method Validation

- Apparatus qualification
- Membrane (skin) qualification
- Receptor solution qualification
- Receptor solution sampling qualification
- Receptor solution HPLC/MS method validation
- Environmental control
- Permeation profile and range
- Precision and reproducibility
- Recovery, dose depletion, etc.
- Discrimination sensitivity and selectivity

IVPT Pilot Study

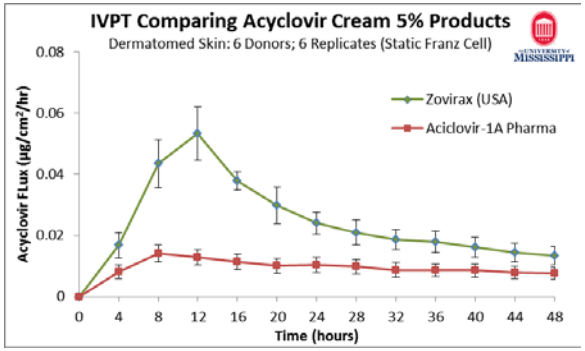
- Multiple donors
- Multiple replicates per donor per treatment
- Treatments
  - Reference product
  - Test product
  - Other product with a differentiated flux profile

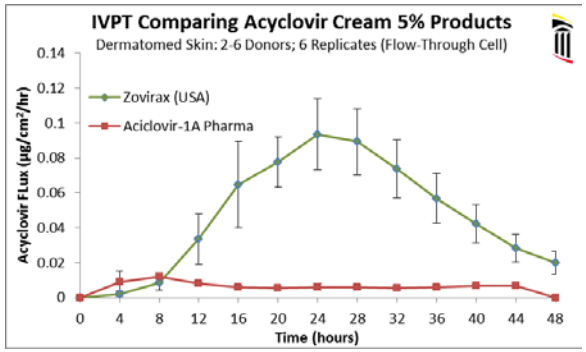
IVPT Results: Acyclovir Cream, 5%

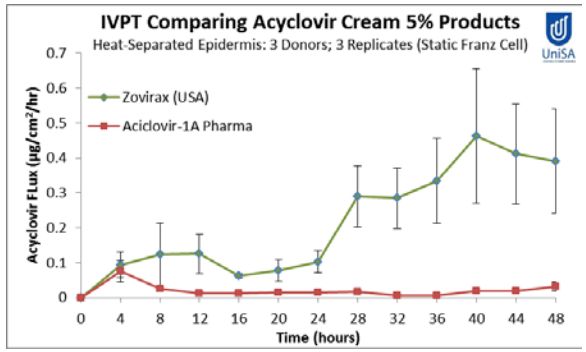
- Cutaneous Pharmacokinetics by IVPT (15 Donors)

Negative Controls for Bioequivalence

	University of Mississippi	University of Maryland	University of South Australia
Dose	15 mg/cm^2		
Dosing technique	Dispensed-Spatula Dispersed-glass rod	Dispensed and dispersed- Positive displacement pipette	Dispensed- Pipette Dispersed- Syringe plunger
Skin type	Torso	Abdomen	Abdomen
Thickness	Dermatomed	Dermatomed	Heat separated epidermis
Instrument	Franz diffusion cell (2 cm^2)	In-Line Flow through cell (0.95 cm^2)	Franz diffusion cell (1.3 cm^2)
Skin Integrity	Electrical Resistance	Trans Epidermal Water Loss	Electrical resistance

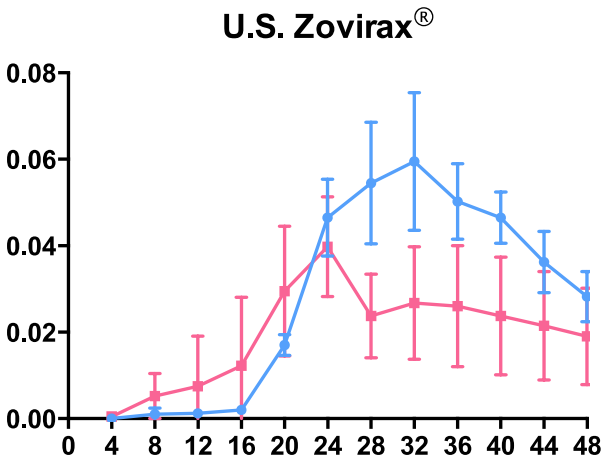


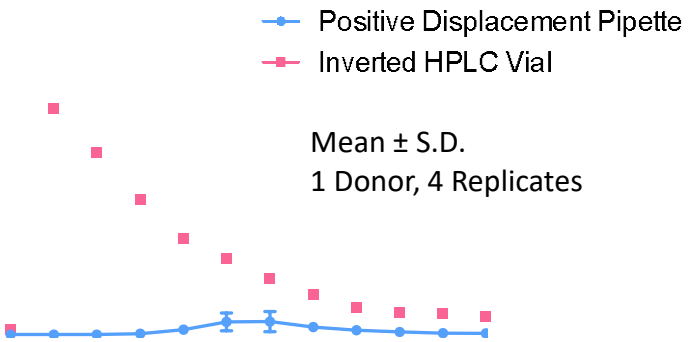




Influence of Quality on Performance

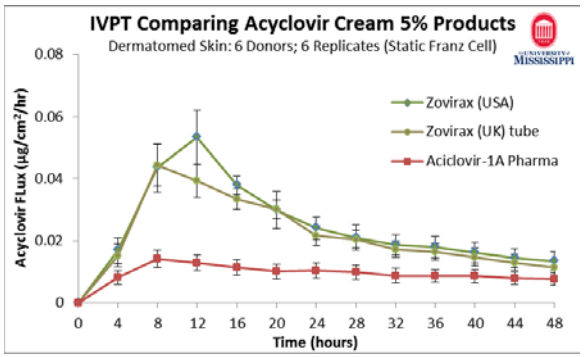
- Influence of Dose **Application** on Bioavailability

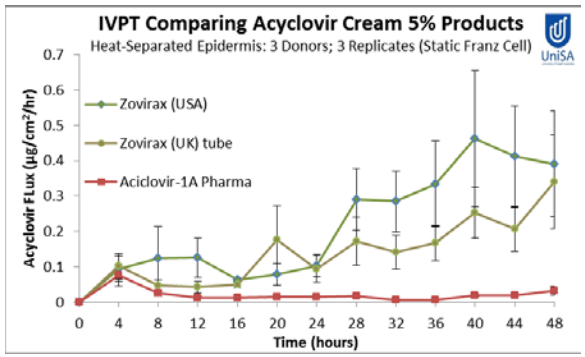


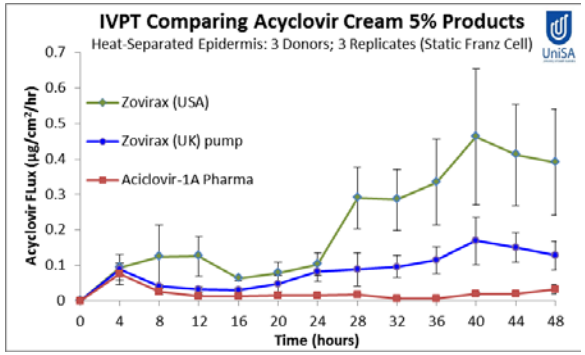


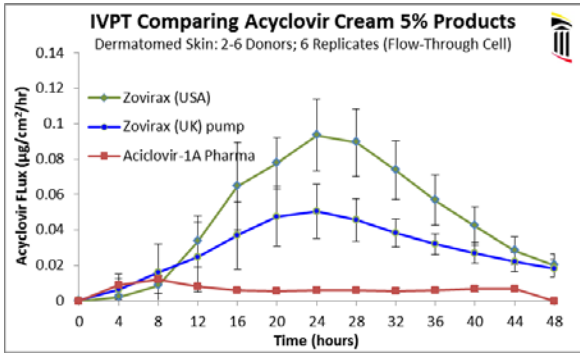
Influence of Quality on Performance

- Influence of Dose **Dispensing** on Bioavailability





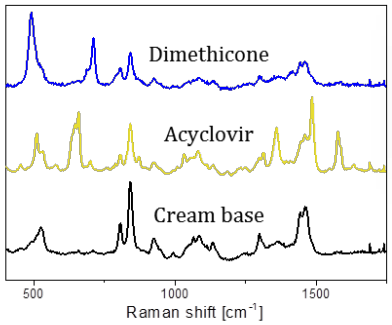




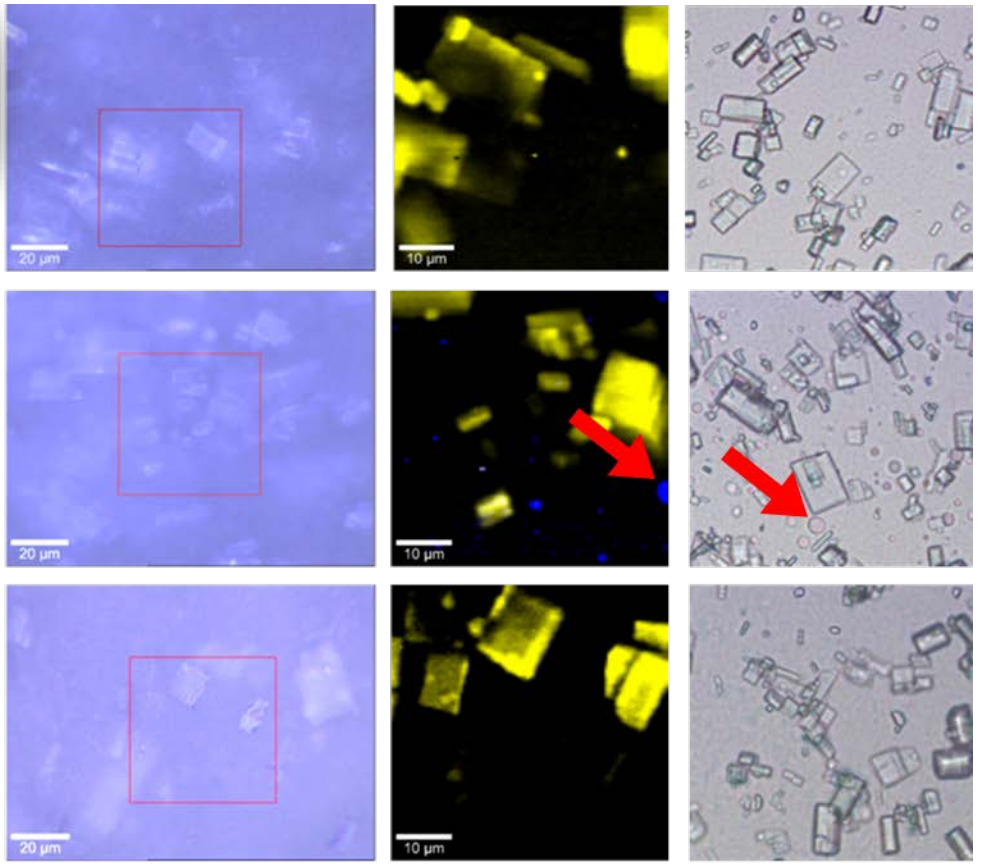
Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

  Prof. Michael Roberts FDA Award U01-FD005226



Zovirax® UK
Tube



University of South Australia

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Zovirax® UK
Pump

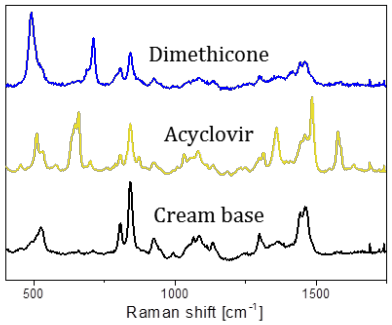
Zovirax® UK
Pump
(from inside container)

Data provided courtesy of Prof. Michael Roberts & Prof. Maike Windbergs

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

  Prof. Michael Roberts FDA Award U01-FD005226



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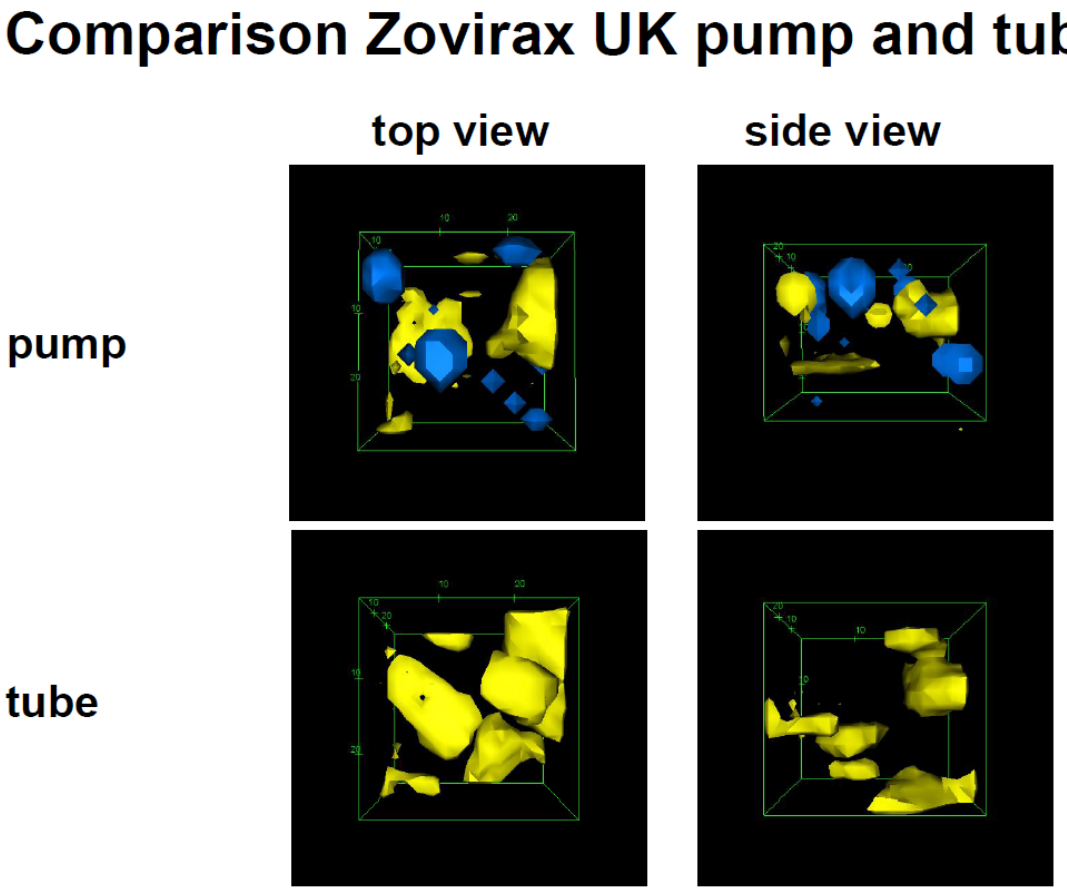
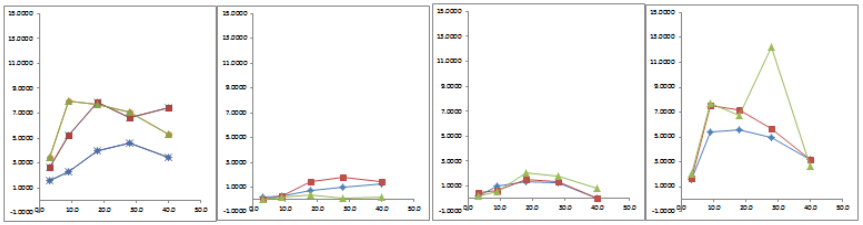


Data provided courtesy of Prof. Michael Roberts & Prof. Maike Windbergs

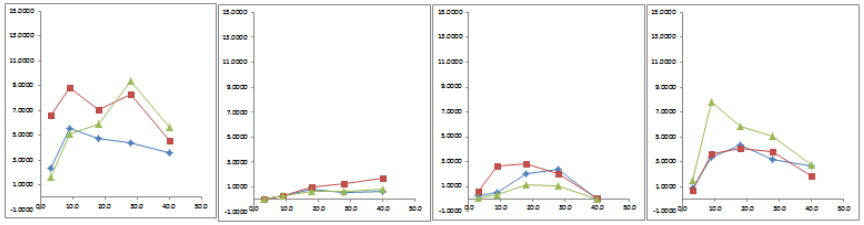
Developing In Vitro BE Standards

- **IVPT Statistical Analysis of Bioequivalence**

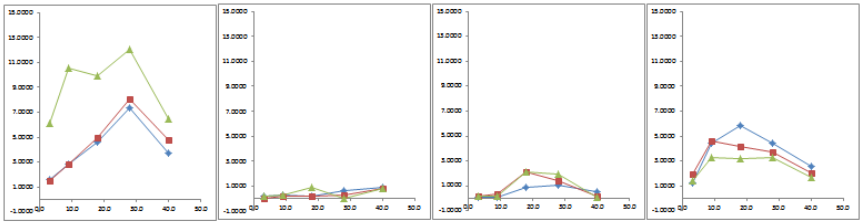
RLD Product Lot# "**1**" (redacted)



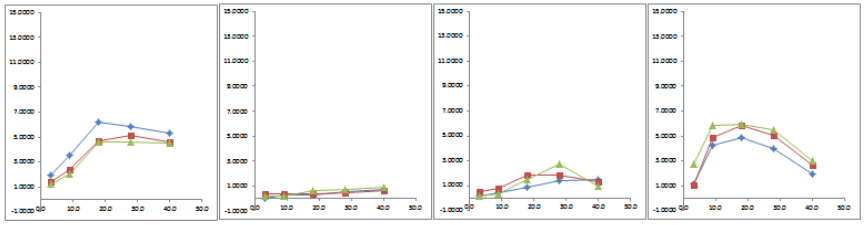
RLD Product Lot# "**2**" (redacted)



RLD Product Lot# "**3**" (redacted)



Test Product

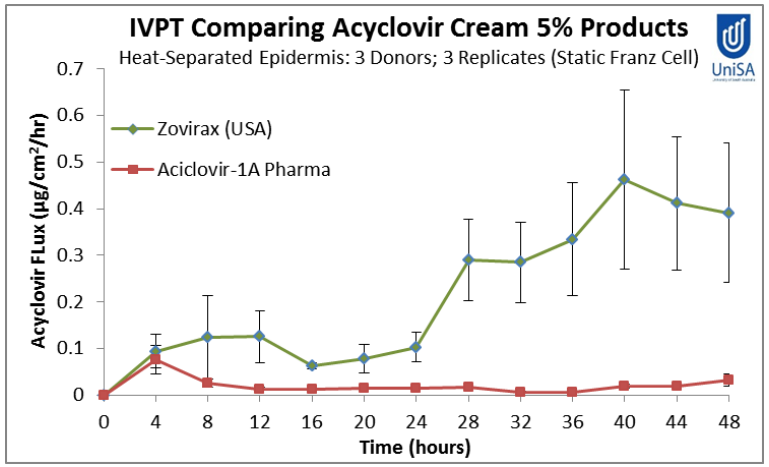


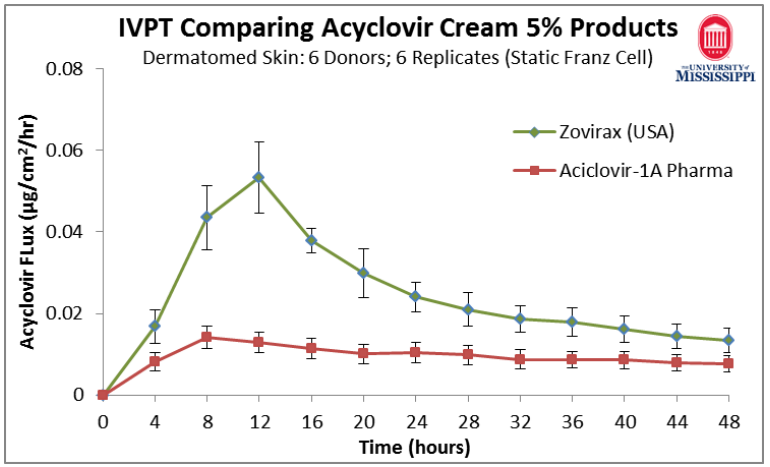
Developing In Vitro BE Standards

- **IVPT Statistical Analysis of Bioequivalence**
  - The approach for Scaled Average Bio-Equivalence (SABE) analysis of highly variable drugs was modified for the IVPT study design
  - The mixed criterion uses the within-reference variability (σ_{WR}) as a cutoff point for bioequivalence analysis
  - When $\sigma_{WR} \leq 0.294$, Average Bio-Equivalence (ABE) is used
  - When $\sigma_{WR} > 0.294$, Scaled ABE (SABE) is used
- *Standard procedures for IVPT study statistical analysis of BE had not been established*

IVPT Statistical Analysis

- **Negative Controls** for BE: Aciclovir-1A® vs. Zovirax® US





Aciclovir-1A® (T) vs. **Zovirax® US (R)**

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.172	0.104
$S_{Within\ Reference}$	0.521	0.551
SABE [0.80, 1.25]	4.433 (**Non-BE**)	7.236 (**Non-BE**)
N for [0.80, 1.25] with 3 Replicates	6	8

Aciclovir-1A® (T) vs. **Zovirax® US (R)**

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.290	0.366
$S_{Within\ Reference}$	0.575	0.419
SABE [0.80, 1.25]	2.383 (**Non-BE**)	1.884 (**Non-BE**)
N for [0.80, 1.25] with 6 Replicates	8	20

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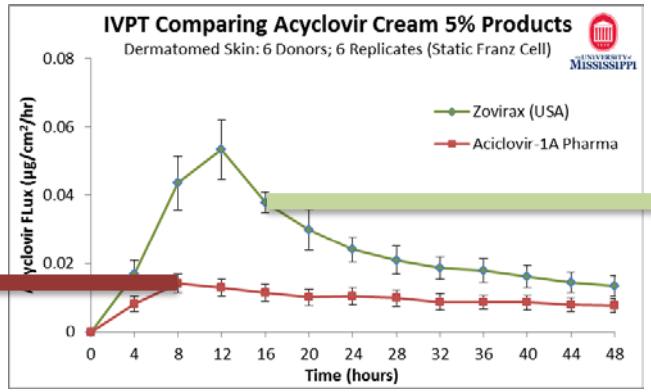
IVPT Statistical Analysis

- **Positive Controls** for BE: Aciclovir-1A® and Zovirax® US



Comparison to Self by dividing up 6 replicates

Comparison to Self by dividing up 6 replicates

Aciclovir-1A® (T) vs. **Aciclovir-1A® (R)**

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.983	0.958
$S_{Within\ Reference}$	0.303	0.318
SABE [0.80, 1.25]	-0.026 (**BE**)	-0.041 (**BE**)
N for [0.80, 1.25] with 4 Replicates	26+	15
N for [0.80, 1.25] with 3 Replicates	26+	15

Zovirax® US (T) vs. **Zovirax® US (R)**

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.962	1.101
$S_{Within\ Reference}$	0.697	0.469
SABE [0.80, 1.25]	-0.214 (**BE**)	-0.020 (**BE**)
N for [0.80, 1.25] with 4 Replicates	12+	14
N for [0.80, 1.25] with 3 Replicates	14	15+

Detailed In Vitro BE Standard

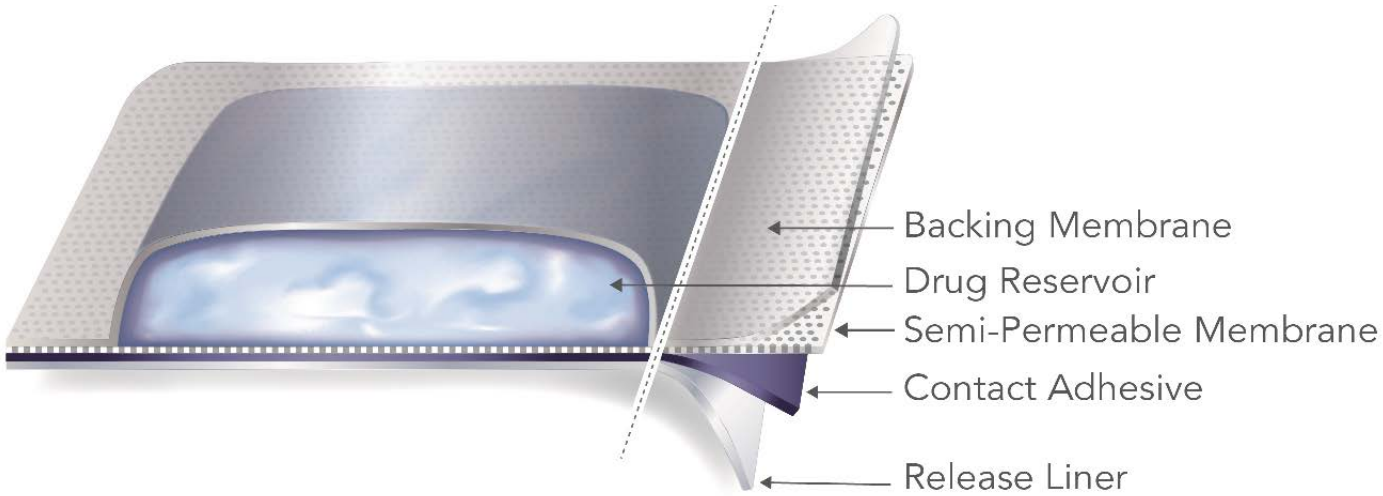
- **FDA Draft Guidance on Acyclovir Cream, 5%** *(Dec 2016)*

Ongoing Challenges with Topical BE…

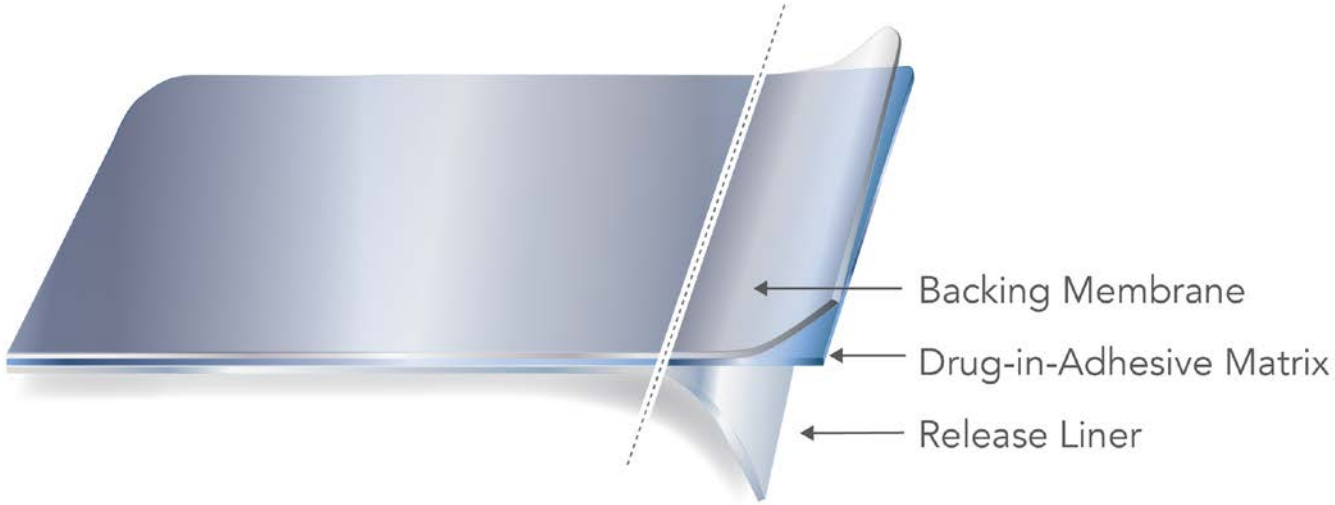
- How might **in silico computational models** and simulations supplement in vitro and/or in vivo evidence, particularly for topical drug products with complex mechanisms or sites of action?
- How might **in vivo cutaneous PK studies** (involving patients) supplement in vitro and in silico evidence?
- How can we evaluate whether the **non-Q1/Q2** prospective generics would provide the same therapeutic efficacy, when the vehicle (placebo) contribution to efficacy may be significant.

Part II: Transdermal Delivery Systems

Reservoir TDS



Matrix TDS



TDS Heat Effects

FIGURE SOURCES: © http://www.clinicaladvisor.com/termsandconditions/ (Authorized non-commercial use)
Inset image from the Ortho Evra® Prescribing Information (package insert)

TDS Heat Effects

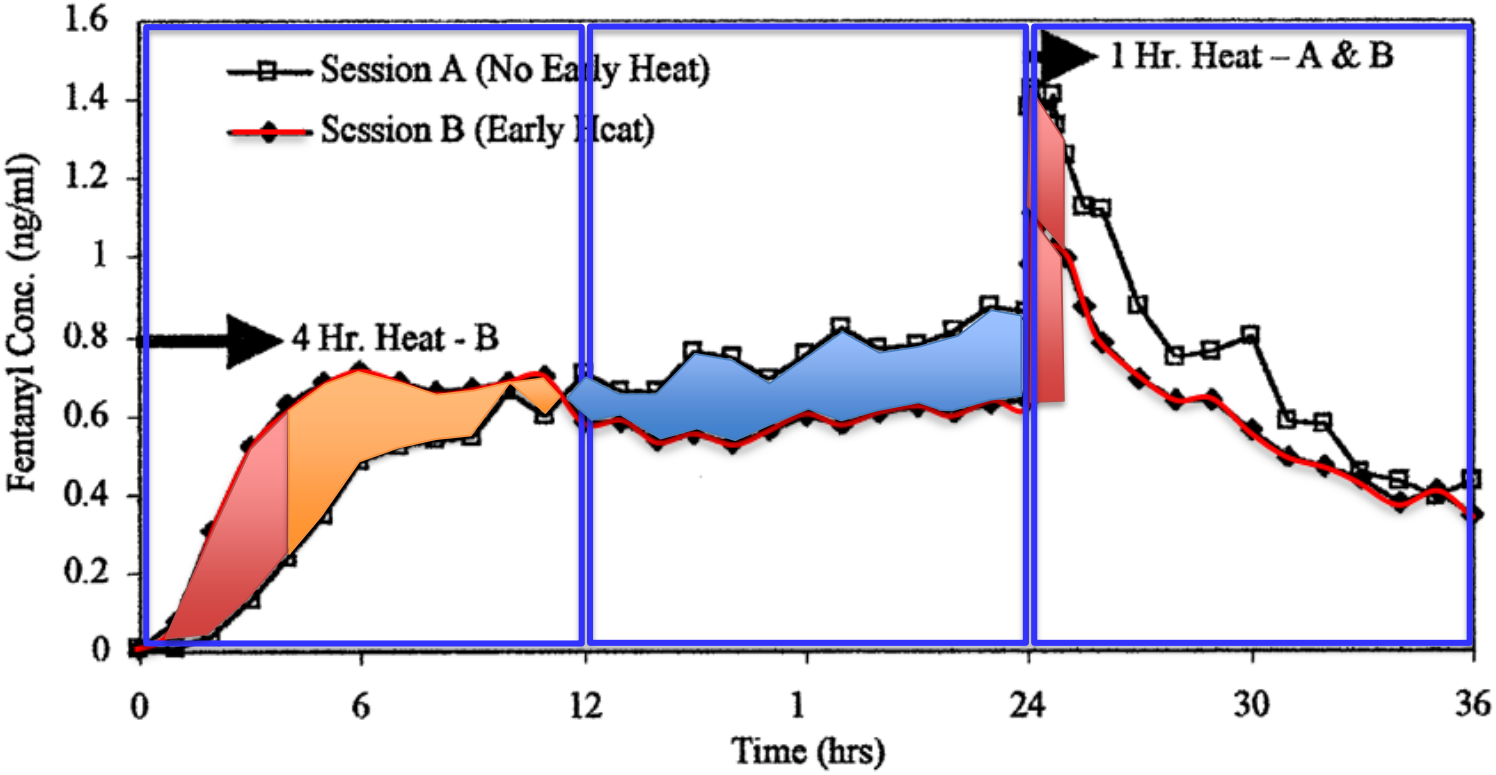
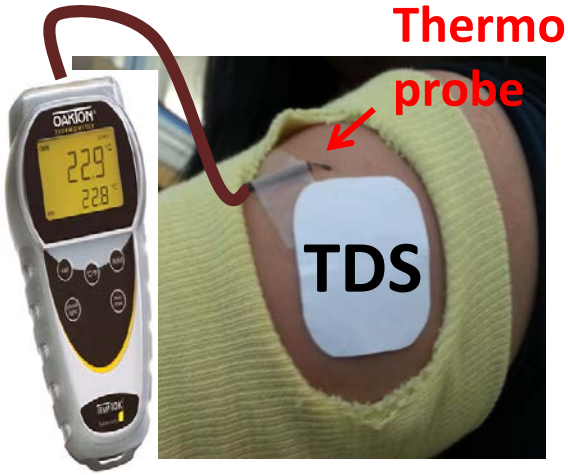


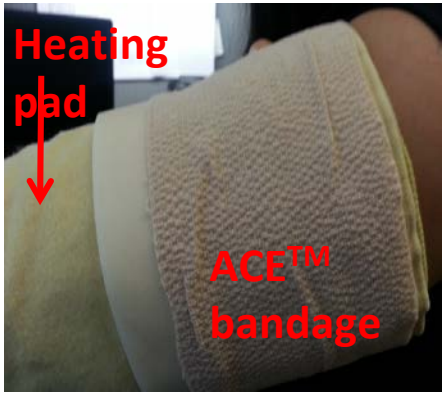
Figure 1. Mean serum fentanyl concentrations after transdermal fentanyl delivery with and without heat (n = 10).

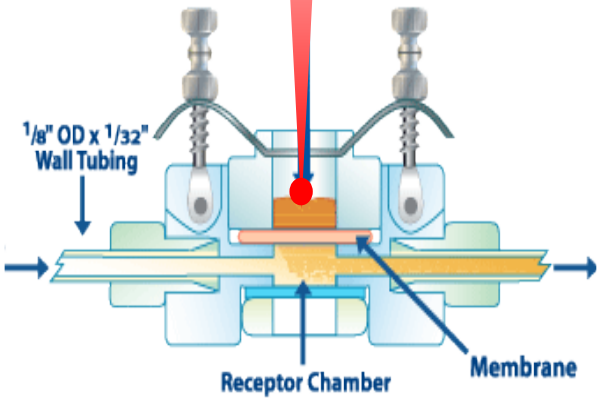
FIGURE SOURCE: Ashburn et al. (2003) The Pharmacokinetics of Transdermal Fentanyl Delivered With and Without Controlled Heat. Journal of Pain Vol. 4, No 6: 291-297

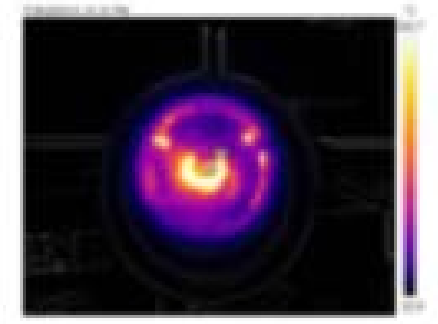
TDS Heat Effects Studies

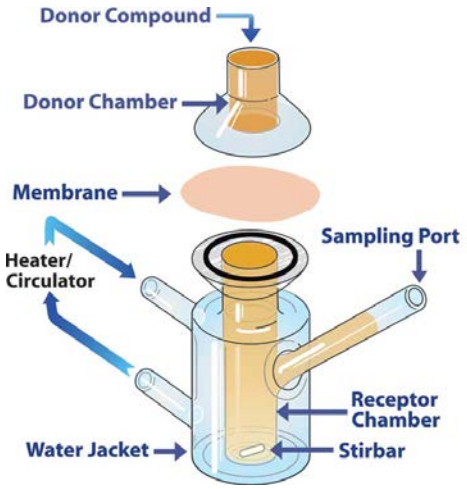
University of Maryland (in vivo)	University of Maryland (in vitro)	University of Cincinnati (in vitro)





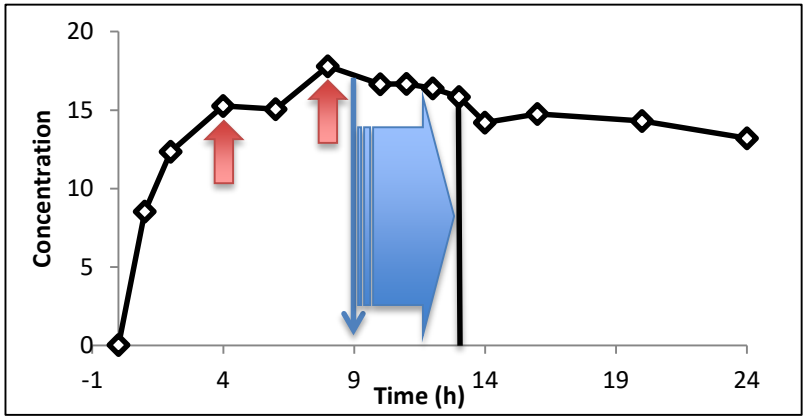


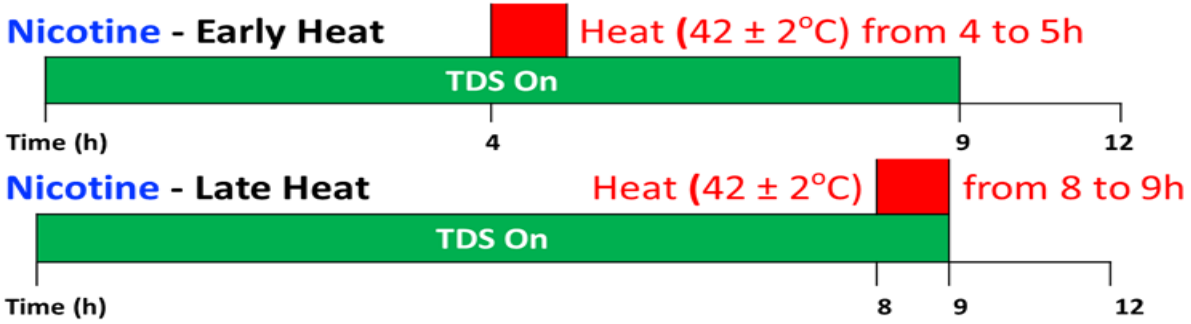




Nicotine TDS Heat Effects Studies

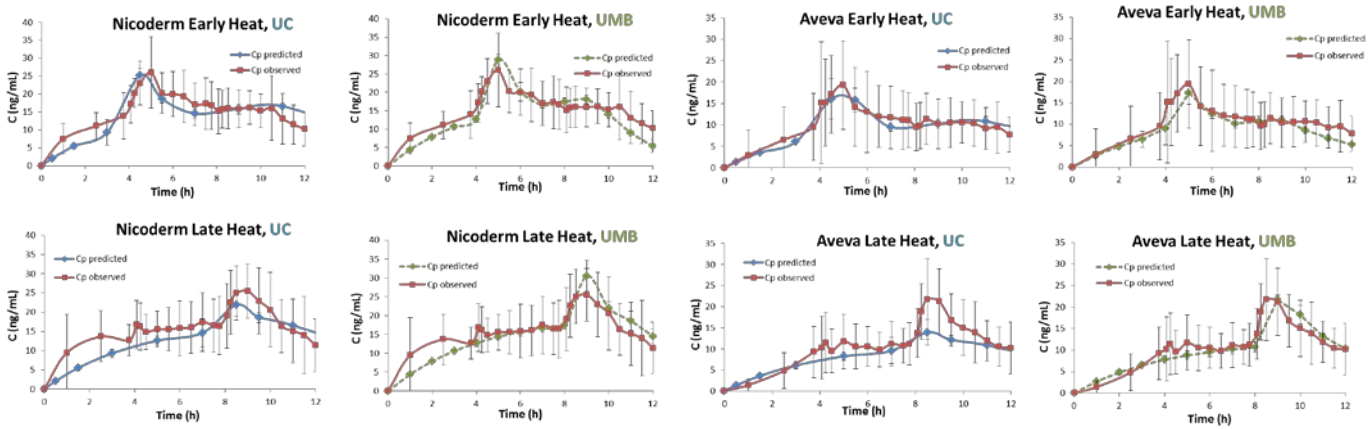
Nicotine TDDS 14 mg/24h	Patch size (cm^2)	Rate/Area ($\mu g/h/cm^2$)	Adhesive type	Other inactive ingredients
Nicoderm CQ®	15.75	37	Polyisobutylene	Ethylene vinyl acetate-copolymer, polyethylene between pigmented and clear polyester backing
Aveva	20	29	Polyacrylate/Silicone	Polyester backing



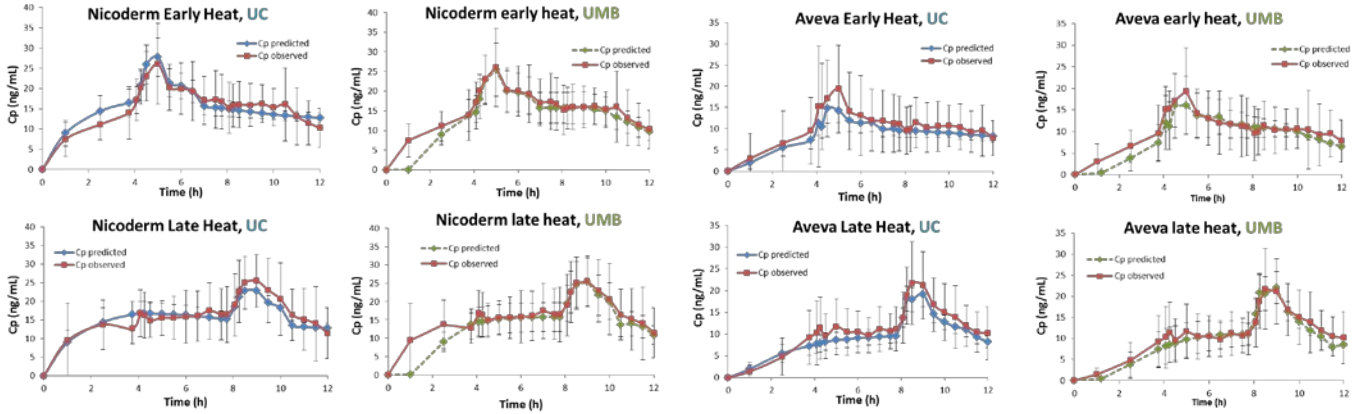


Level A IVIVC/IVIVR for Nicotine TDS

- Approach I (prediction based upon in vitro data only)

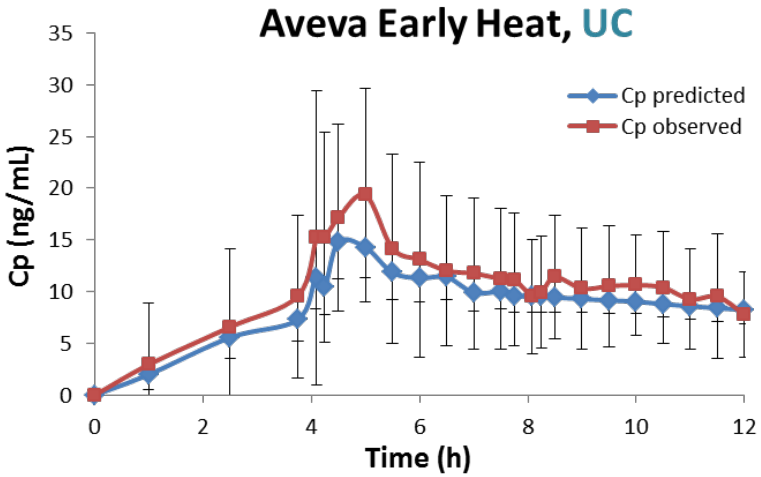


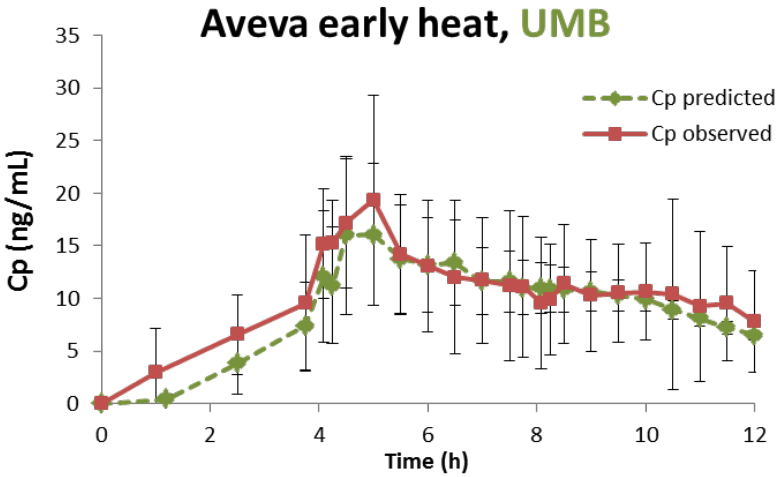
- Approach II (including an in vivo-derived heat factor)

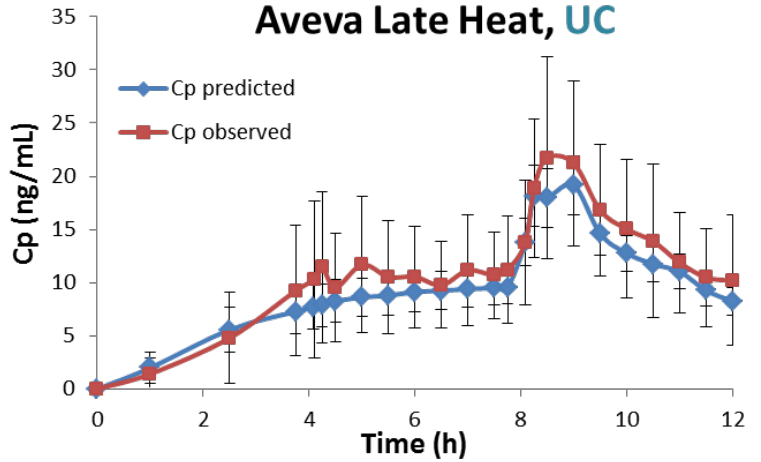


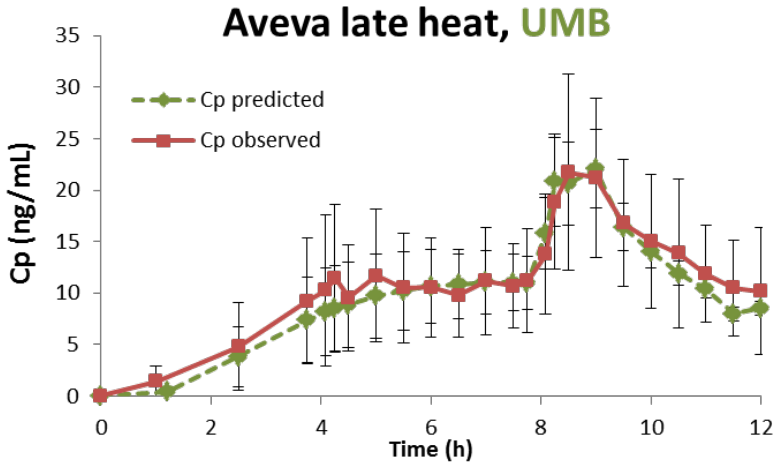
Refer to Shin et al. (2018) In vitro-in vivo correlations for nicotine transdermal delivery systems evaluated by both in vitro skin permeation (IVPT) and in vivo serum pharmacokinetics under the influence of transient heat application. J Control Release. 270: 76-88. (Funded, in part, by FDA through awards U01FD004955 (Dr. Audra Stinchcomb; University of Maryland, Baltimore) and U01FD004942 (Dr. Kevin Li; University of Cincinnati))

Level A IVIVC/IVIVR for Nicotine TDS









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Part II: Conclusions

IVIVCs/IVIVRs were successfully developed for

- Different nicotine TDS
- Under normal skin surface temperature
- Under elevated temperature conditions
- At different periods in the duration of product wear
- By independent research groups at different study sites
- Using different IVPT apparatus, skin preps & heat application methods
- Using different IVIVC approaches

The results suggest that the IVPT model is able to correlate with and be predictive of in vivo bioavailability for nicotine TDS products exposed to transient heat, when in vitro and in vivo study designs are harmonized.

Acknowledgements

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- Yi Zhang, PhD
- Kimberly Witzmann, MD
- Robert Lionberger, PhD

Research Collaborators

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GDUFA Awards U01FD00**4947/4955**
- Audra Stinchcomb, PhD

GDUFA Award U01FD00**5223**
- Narasimha Murthy, PhD

GDUFA Award U01FD00**5226**
- Michael Roberts, PhD

GDUFA Award U01FD00**4942**
- Kevin Li, PhD

OGD (Other Offices)

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- Ravi Juluru, PhD
- Ethan Stier, PhD
- Bing Li, PhD
- Nilufer Tampal, PhD
- Utpal Munshi, PhD
- Dale Conner, PharmD
- Andrew LeBoeuf, JD

CDER

- Pahala Simamora, PhD (OPQ)
- Richard Chang, PhD (OPQ)
- Bing Cai, PhD (OPQ)
- Andre Raw, PhD (OPQ)
- Katherine Tyner, PhD (OPQ)
- Elena Rantou, PhD (OTS)
- Stella Grosser, PhD (OTS)
- Jill Brown, BSN (OTS)
- E. Dennis Bashaw, PharmD (OCP)


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New Research Funding Opportunities

Funding Opportunity Title:

Bioequivalence of Topical Products:

Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations (U01)

Application Due Date: **May 19, 2018**, by 11:59 PM Eastern U.S. Time

Award Budget: **USD $1,250,000** ($250.000/year over 5 years)

Website: https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-**18-010**.html

New Research Funding Opportunities

Funding Opportunity Title:

Bioequivalence of Topical Products:

Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques (U01)

Application Due Date: **June 4, 2018**, by 11:59 PM Eastern U.S. Time

Award Budget: **USD $1,250,000** ($250.000/year over 5 years)

Website: https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-**18-012**.html

New Research Funding Opportunities

Funding Opportunity Title:

Characterize skin physiology parameters utilized in dermal physiologically-based pharmacokinetic model development across different skin disease states (U01)

Application Due Date: **May 29, 2018**, by 11:59 PM Eastern U.S. Time

Award Budget: **USD $500,000** ($250.000/year over 2 years)

Website: https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-**18-017**.html

New Research Funding Opportunities

Funding Opportunity Title:

Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems (U01)

Application Due Date: **May 28, 2018**, by 11:59 PM Eastern U.S. Time

Award Budget: **USD $500,000** ($250.000/year over 2 years)

Website: https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-**18-019**.html