U.S. FOOD & DRUG ADMINISTRATION

A Generic Perspective on the Use of In Vitro Assessment Methods

Bridging Results from Maximum Use Trials with Sunscreen Reformulations

Topical Drug Development
Evolution of Science and Regulatory Policy

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Disclaimer

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

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.
- 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

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** pharmacokinetic (PK) studies may be appropriate
  - **In Silico** computational modeling may be useful

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

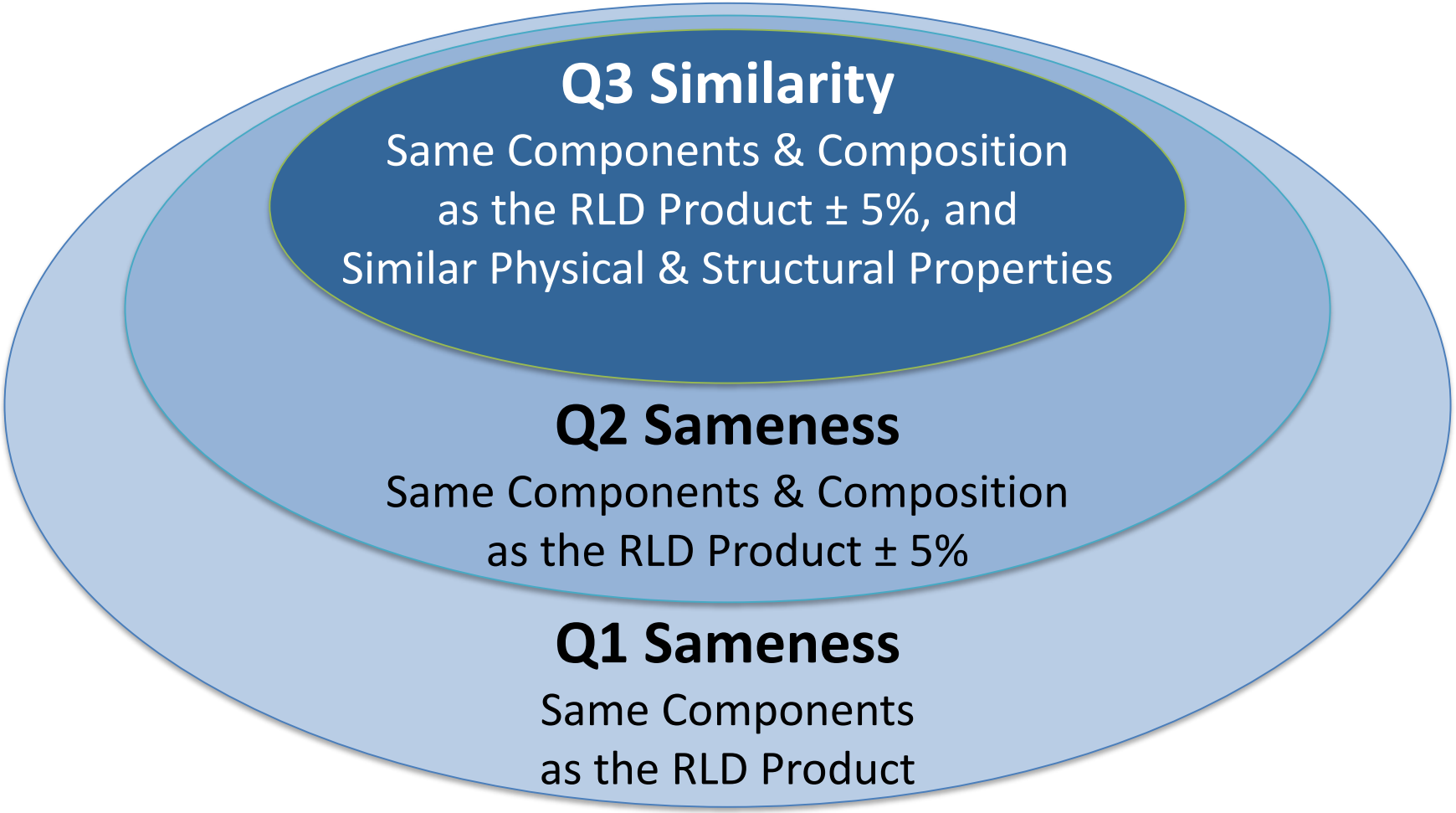
Formulations Can Alter Bioavailability

- 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

Developing In Vitro BE Standards

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

  An evolving regulatory concept:



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 into the stratum corneum (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
  - Thermodynamic activity profile of the drug
    - Thermodynamic effects and heat effects are areas of active research for topical semisolid products and transdermal delivery systems

Developing In Vitro BE Standards

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

  Mitigates the risk of potential failure modes related to:

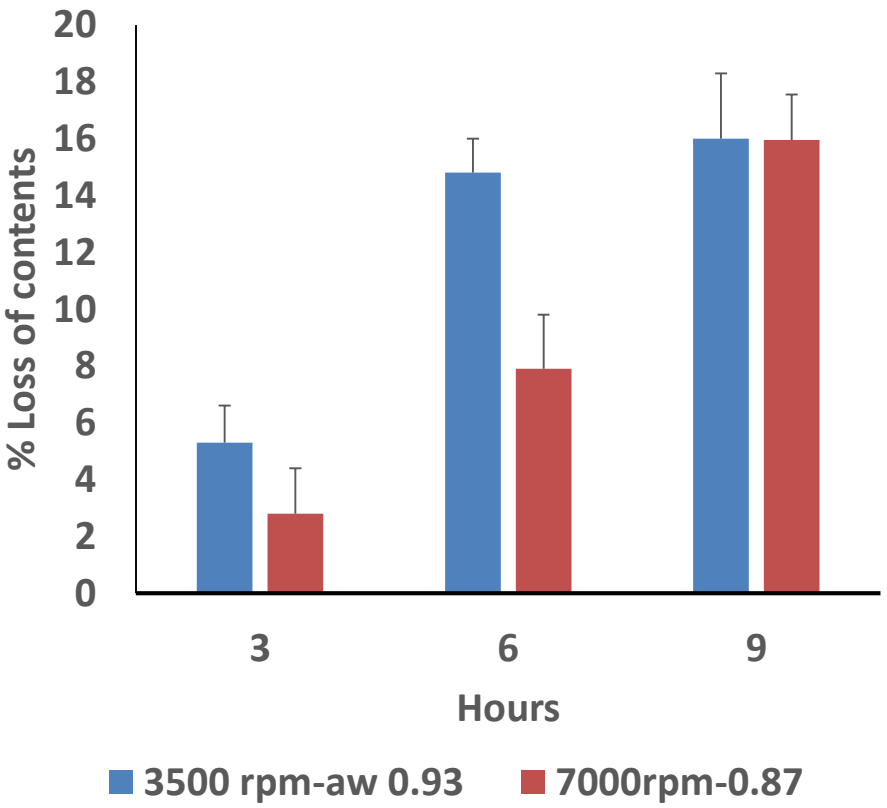
  - Differences in Q1/Q2 sameness (± 5% tolerances)
  - Differences in pH that may sting or irritate diseased skin
  - Differences in the polymorphic form of the drug
  - Differences in rheology that alter the spreadability, retention, or surface area of contact with the diseased skin
  - Differences in entrapped air and drug amount per dose
  - Differences in phase states and diffusion, partitioning, etc.
  - Differences in metamorphosis and drying rates

Dosage Form Metamorphosis

- Solvent Activity of Q1/Q2 Identical Creams

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

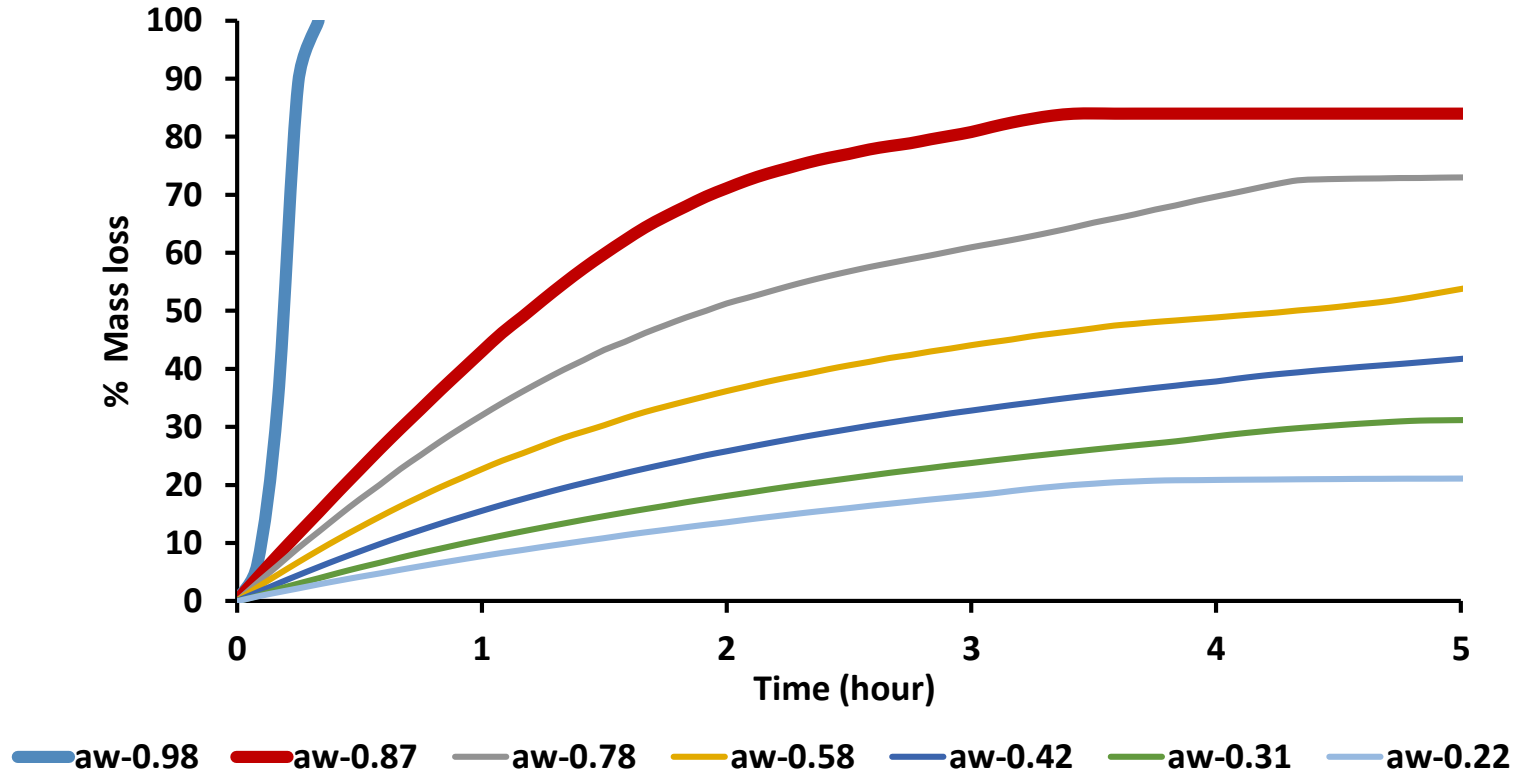
Manufacturing Conditions	Solvent Activity (a_w)
3500 RPM (15 min)	**0.931 ± 0.002**
7000 RPM (45 min)	**0.875 ± 0.006**



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

Dosage Form Metamorphosis

- Solvent Activity (a_s) = ρ/ρ_0
  - ρ = partial vapor pressure of Solvents in the product
  - ρ_0 = vapor pressure of pure Solvent system



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

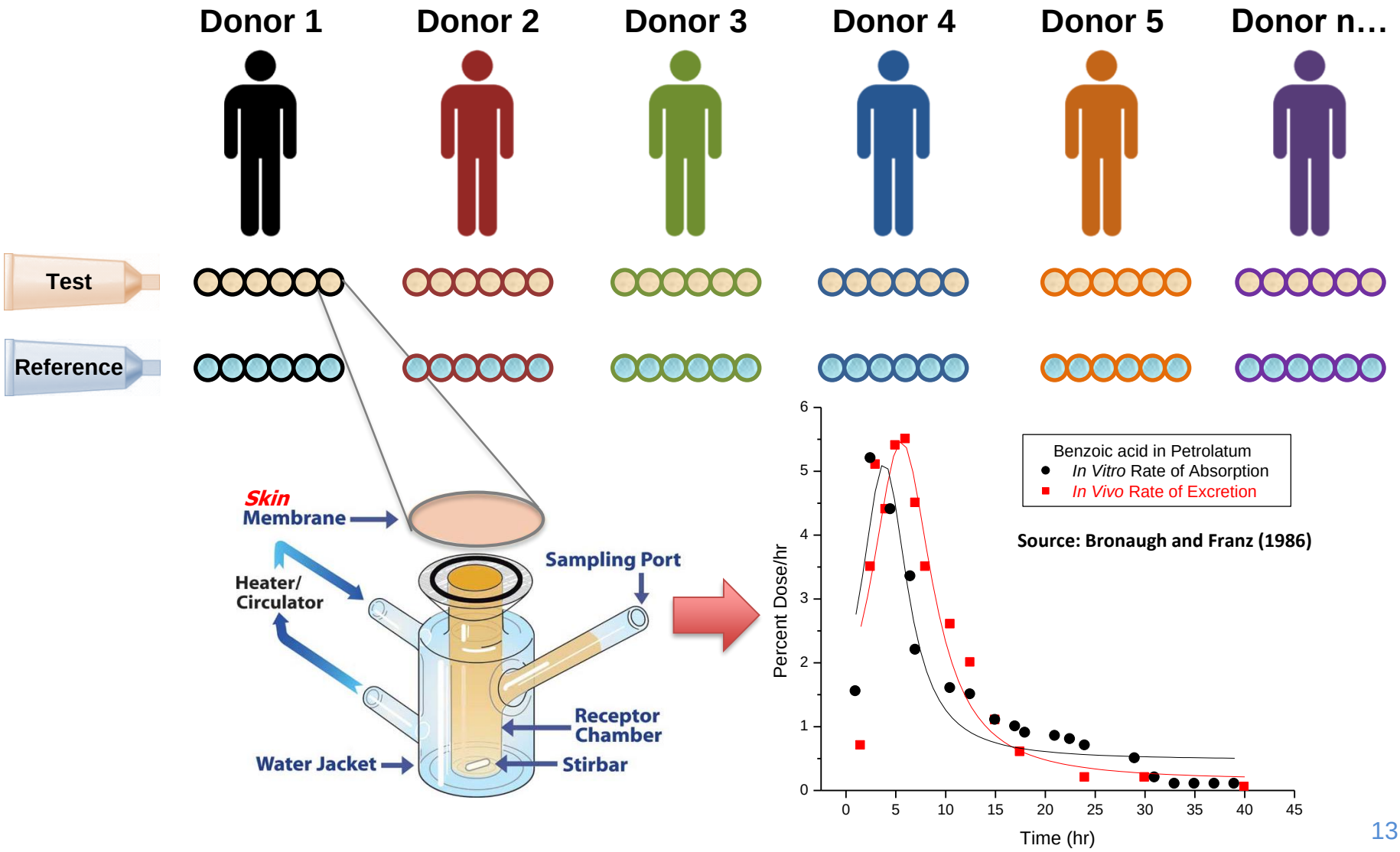
Developing In Vitro BE Standards

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

  Mitigates the risk of other unknown failure modes related to:

  - Differences in Q1 and/or Q2
  - 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 in vitro in vivo correlation (IVIVC)
- IVPT studies can compare the relative bioavailability of sunscreen actives (or other components of interest) between a test and reference formulation

IVPT Study Design



IVPT: *In Vitro In Vivo* Correlation

- Lehman et al., 2011 (92 IVIVC Data Sets)

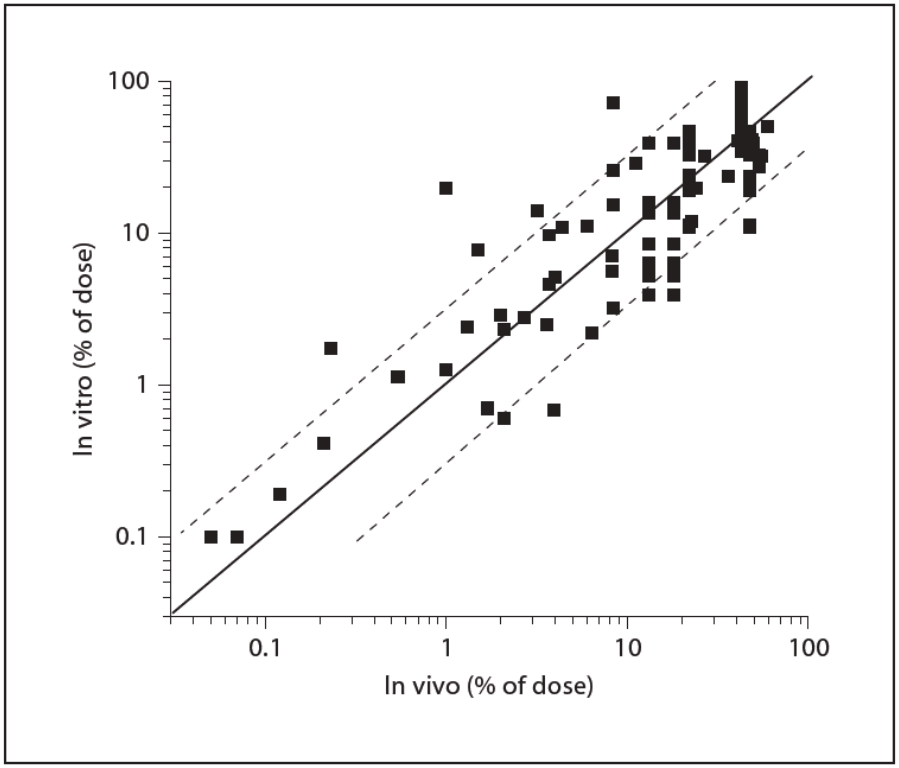


Fig. 1. IVIV ratios of total absorption for all 92 data sets plotted on log-log scale. The IVIV ratios ranged from 0.18 to 19.7, with an overall mean of 1.6. Solid line: ideal 1:1 correlation. Dashed lines: ±3-fold difference from ideal.

IVPT: *In Vitro In Vivo* Correlation

- Lehman et al., 2011 (92 IVIVC Data Sets)

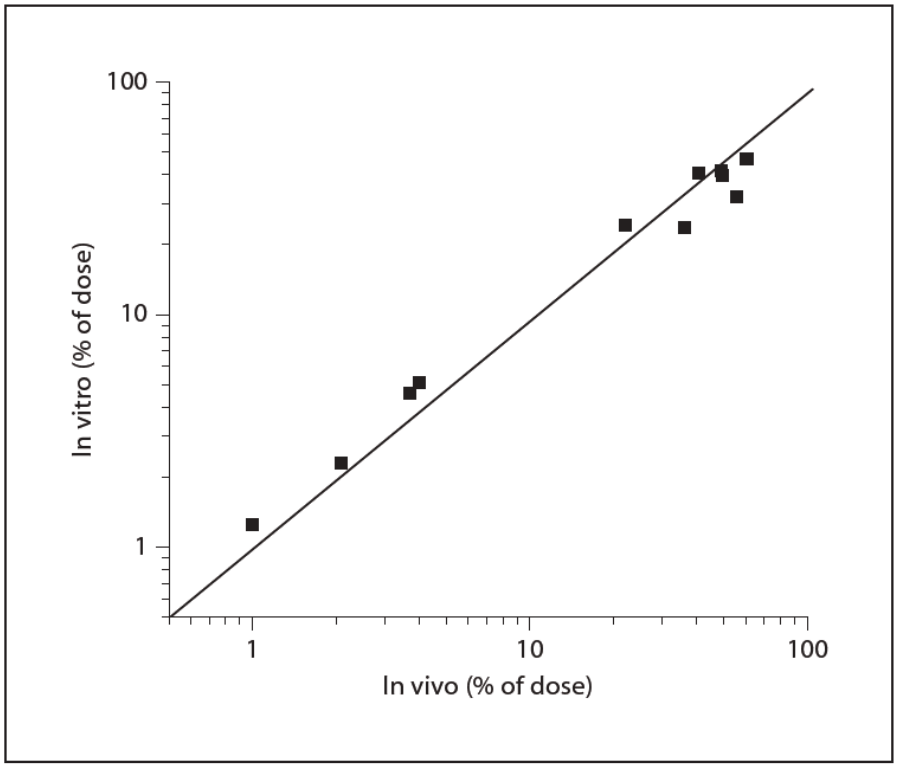
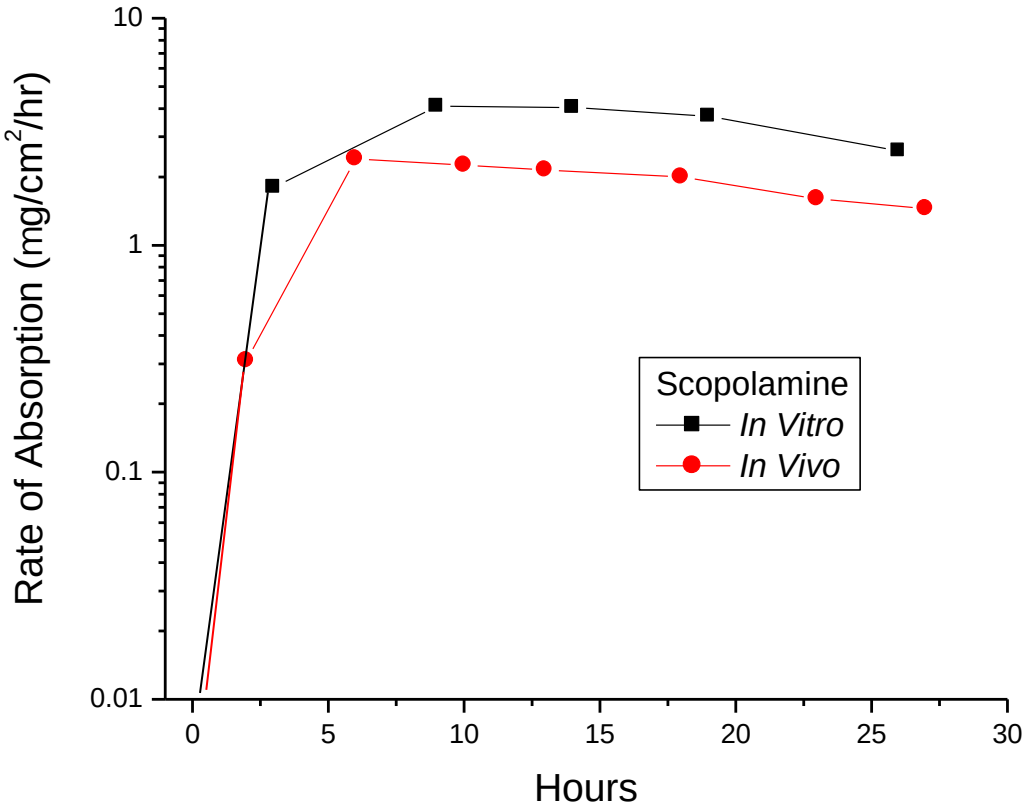


Fig. 2. IVIV ratios of total absorption for 11 fully harmonized data sets plotted on log-log scale. The IVIV ratios ranged from 0.58 to 1.28, with an overall mean of 0.96. Line: ideal 1:1 correlation.

IVPT: *In Vitro In Vivo* Correlation

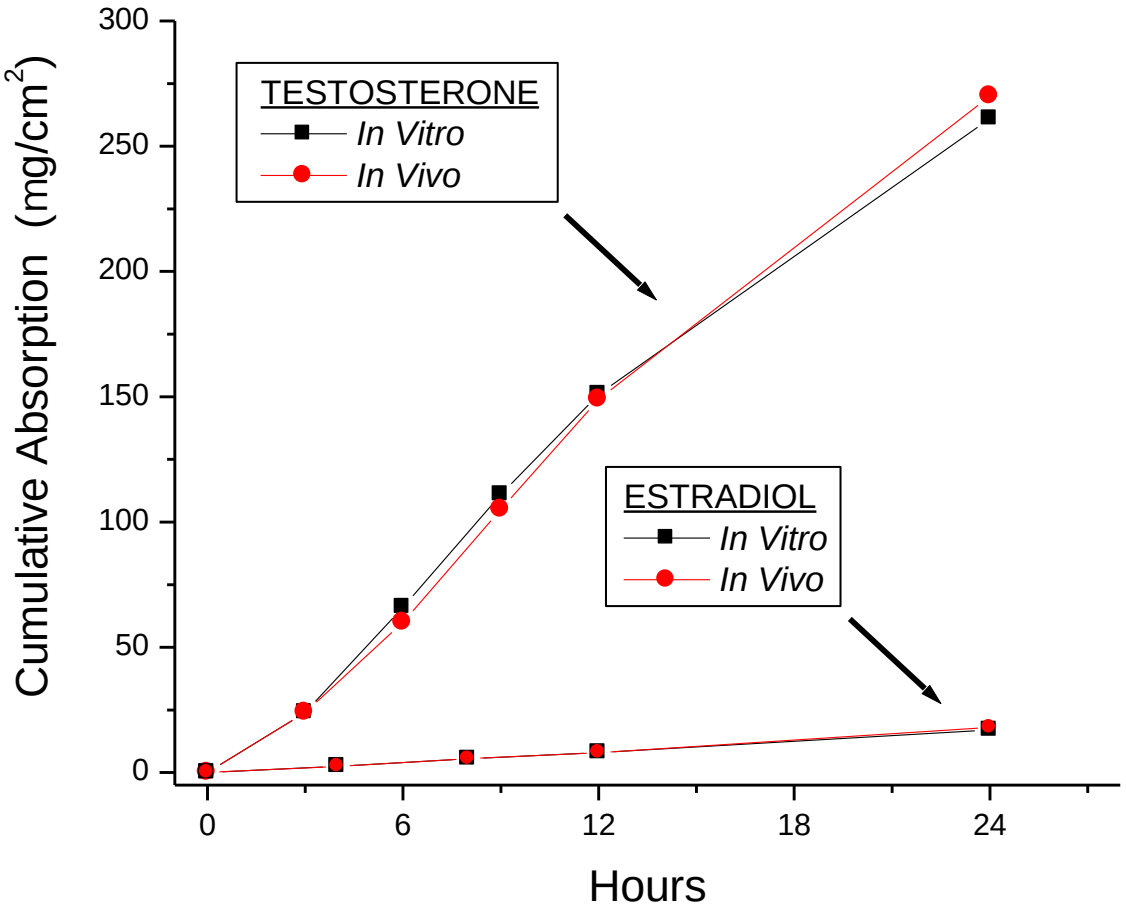
- Shaw et al., 1975

"… *in vitro* accurately predicted the situation which pertains *in vivo*."



IVPT: *In Vitro In Vivo* Correlation

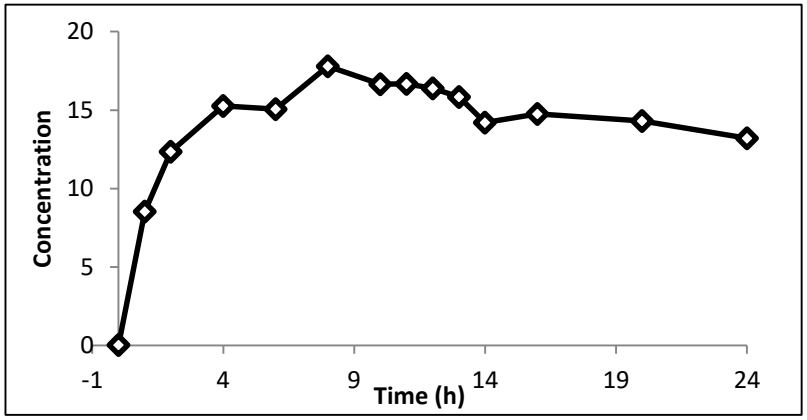
- Venkateshwaran S, 1997

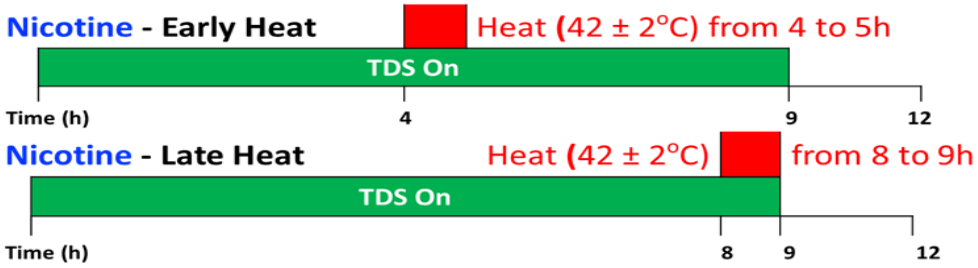


Nicotine TDS* Heat Effects Studies

*TDS = Transdermal Delivery System

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

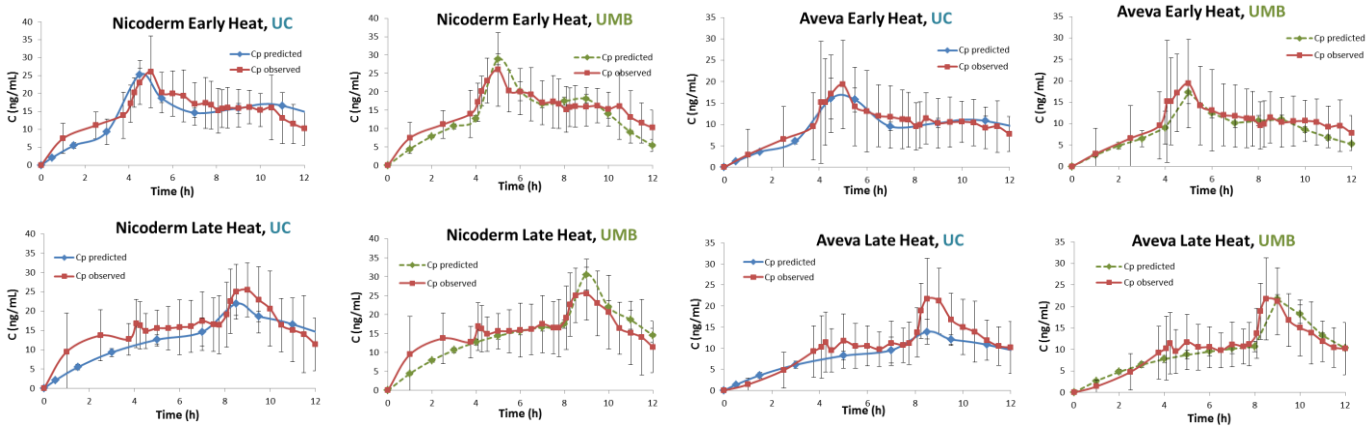




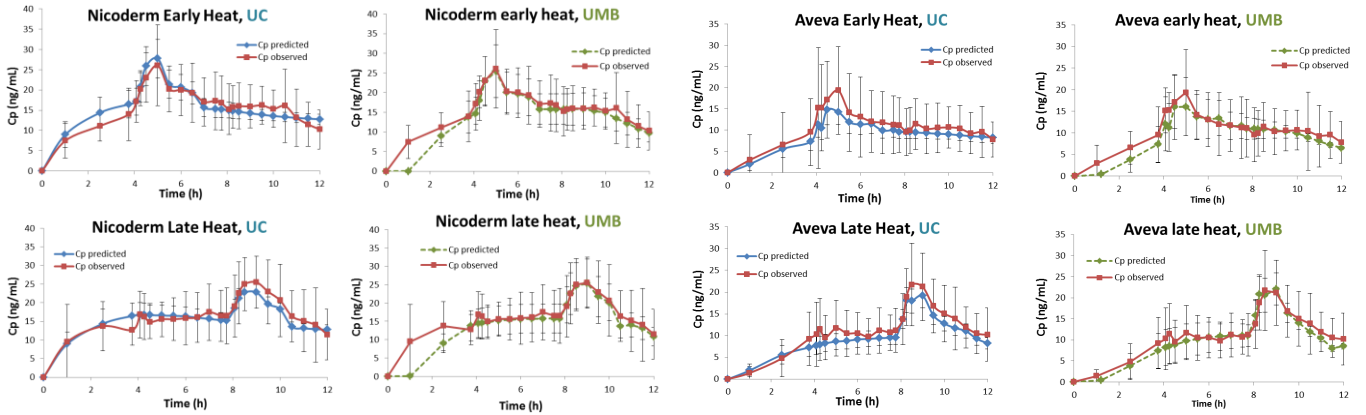
Data provided courtesy of Prof. Audra Stinchcomb (University of Maryland) ***FDA Award U01-FD004955***

Level A IVIVC/IVIVR for Nicotine TDS

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

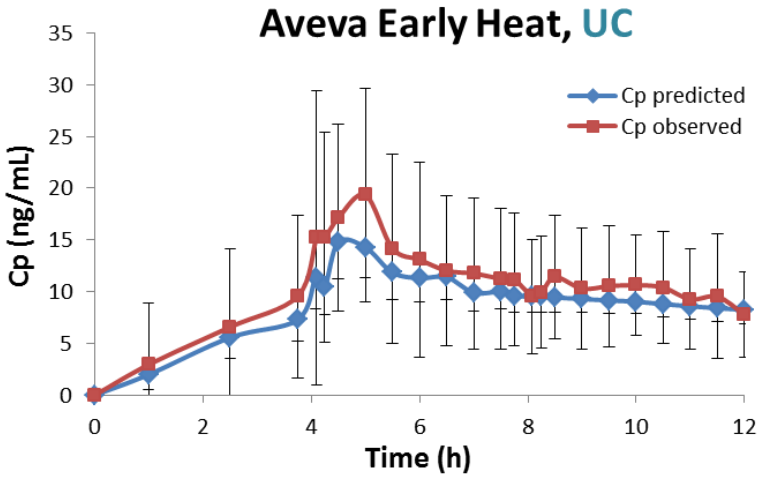


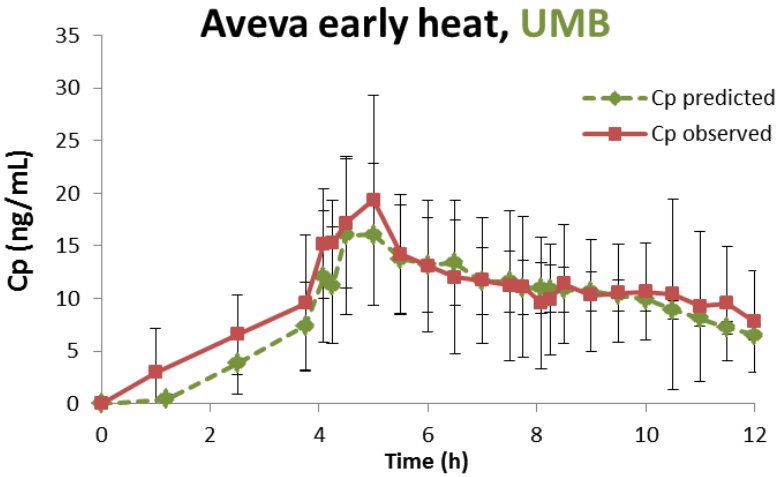
- Approach II (including an in vivo-derived heat factor)

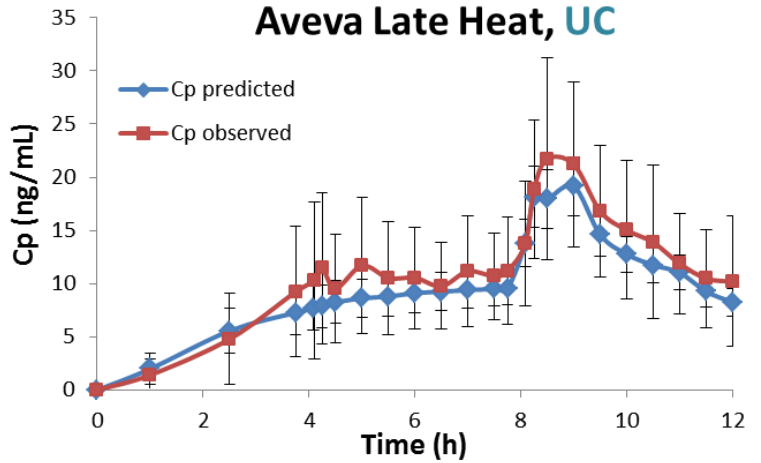


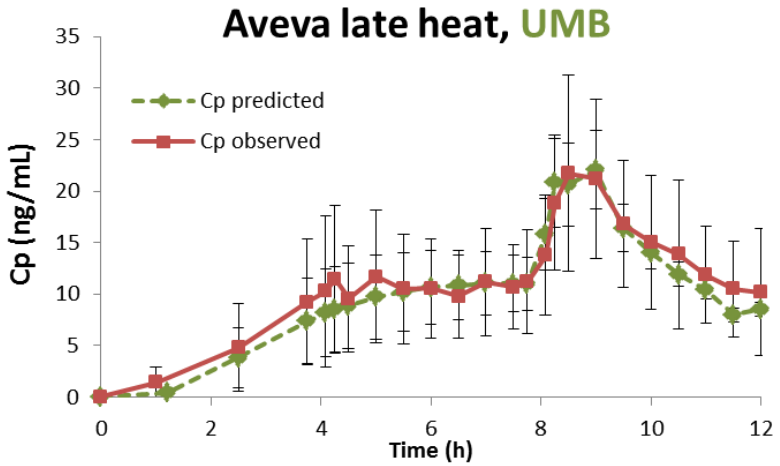
*Refer to Shin et al. (2018) In vitro-in vivo correlations for nicotine transdermal delivery systems evaluated by both in vitro skin permeation (IVPT) and in vivo serum pharmacokinetics under the influence of transient heat application. J Control Release. 270: 76-88. (Funded, in part, through **FDA award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

Level A IVIVC/IVIVR for Nicotine TDS









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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)
  - University of Maryland/Bath (USA/UK) — Tape Stripping

Coordinated Research Strategy

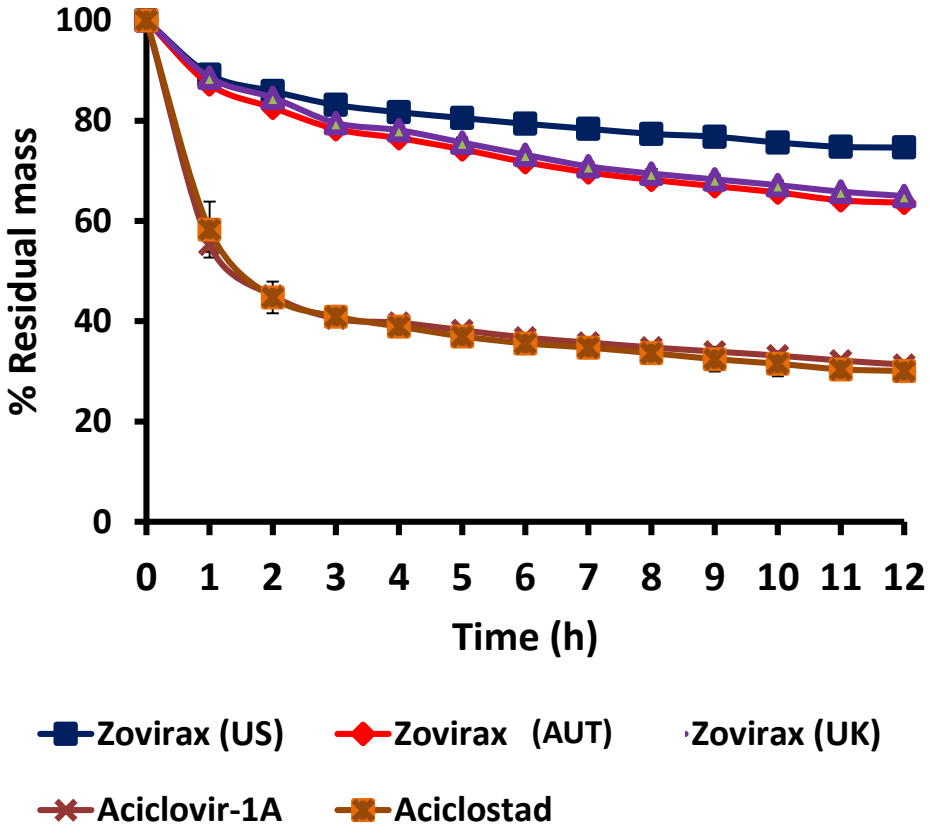
- Pharmaceutically Equivalent Acyclovir 5% Creams
  - **Positive** and **Negative** Controls for BE

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	[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

Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

  Prof. Narasimha Murthy FDA Award U01-FD005223



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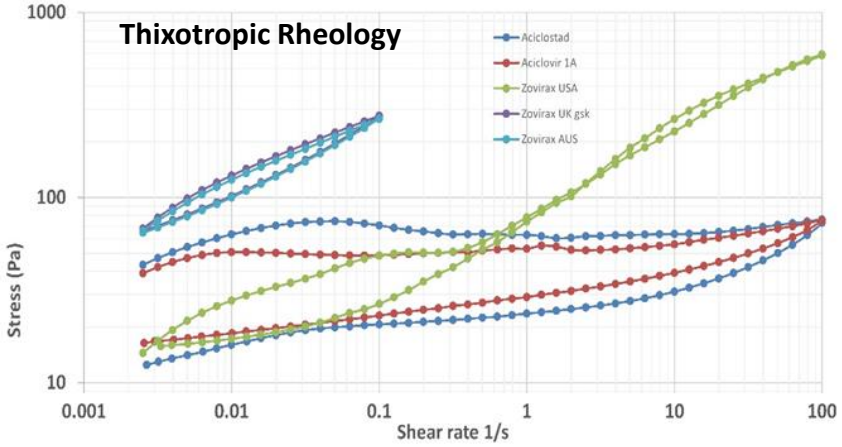
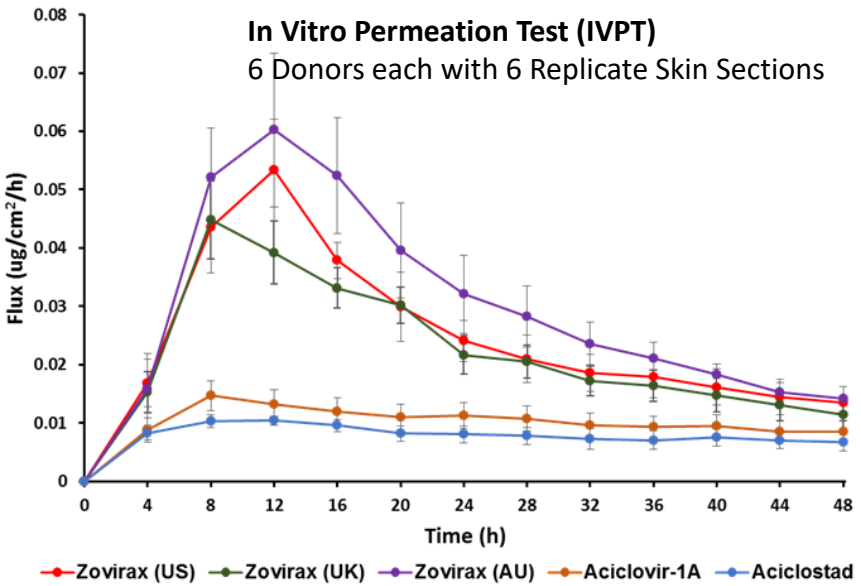
Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732± 0.002
Aciclovir 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

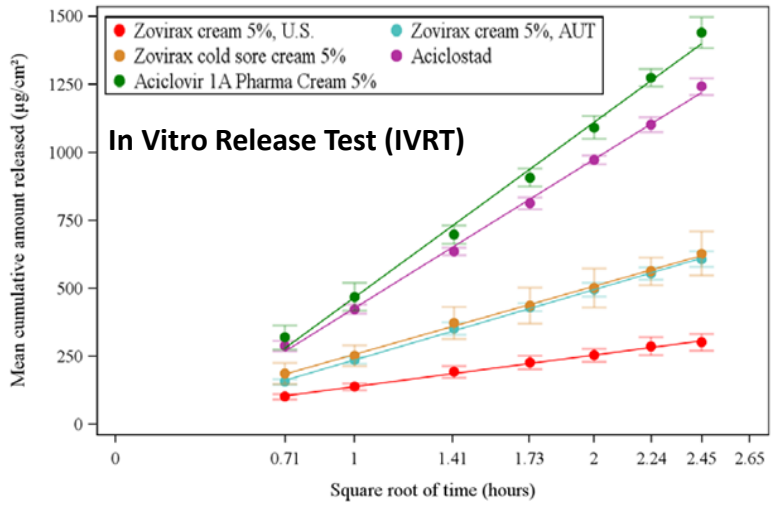
Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

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



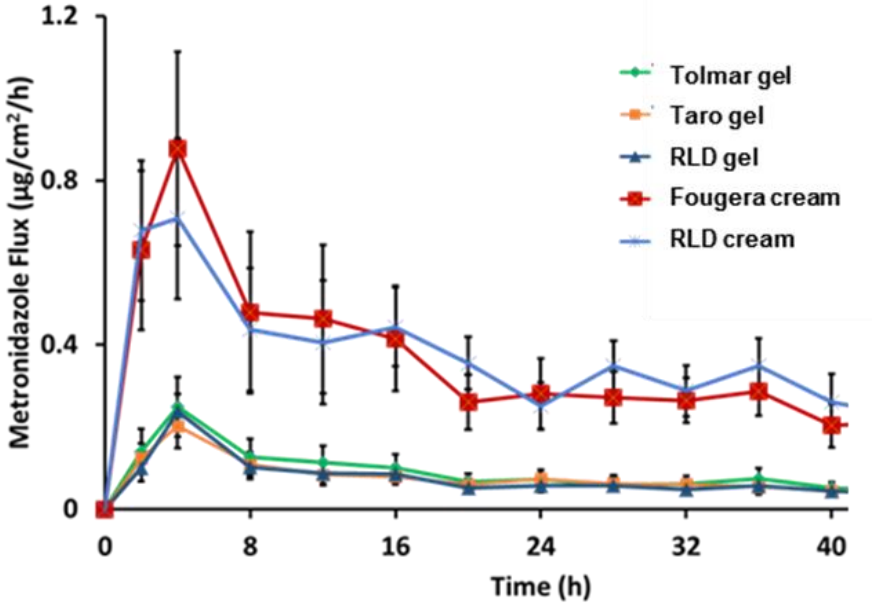


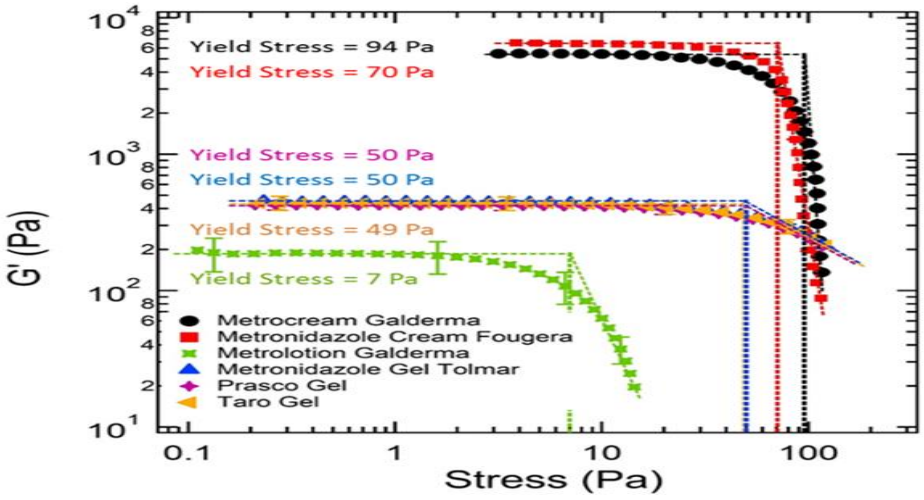


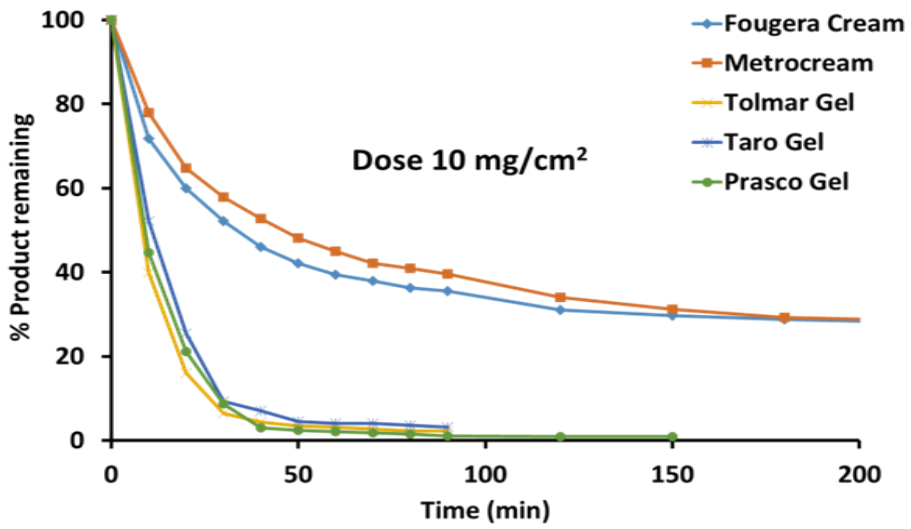
Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223*** *and Dr. Frank Sinner (Joanneum Research* ***FDA Award U01-FD004946***

Product Quality and Performance

Quality Attribute	Metrocream®	Generic Cream (Fougera)	Metrogel®	Generic Gel (Tolmar)	Generic Gel (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingredient is completely dissolved				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
Drug in Oil (mg/g)	2.58	3.94	---	---	---
Solvent Activity	0.977	0.974	0.992	0.994	1.002
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drying, T_{30}(min)	17	11.4	5.5	4.7	6.5







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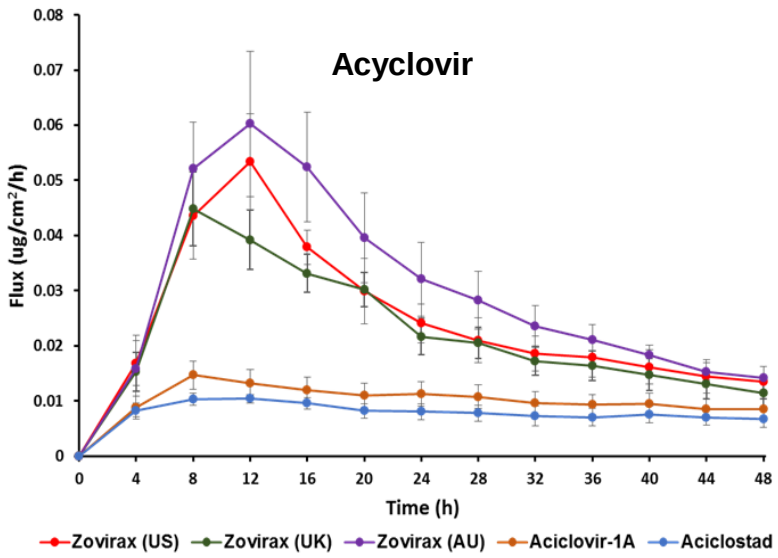
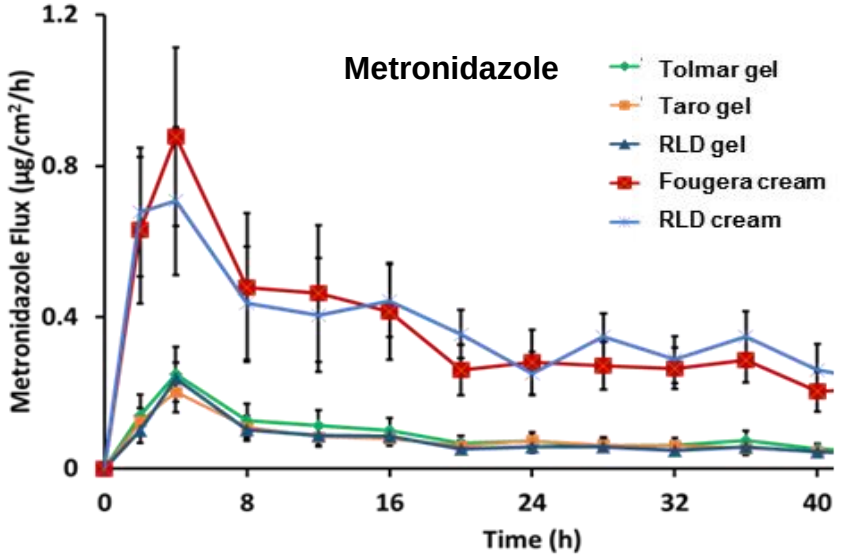
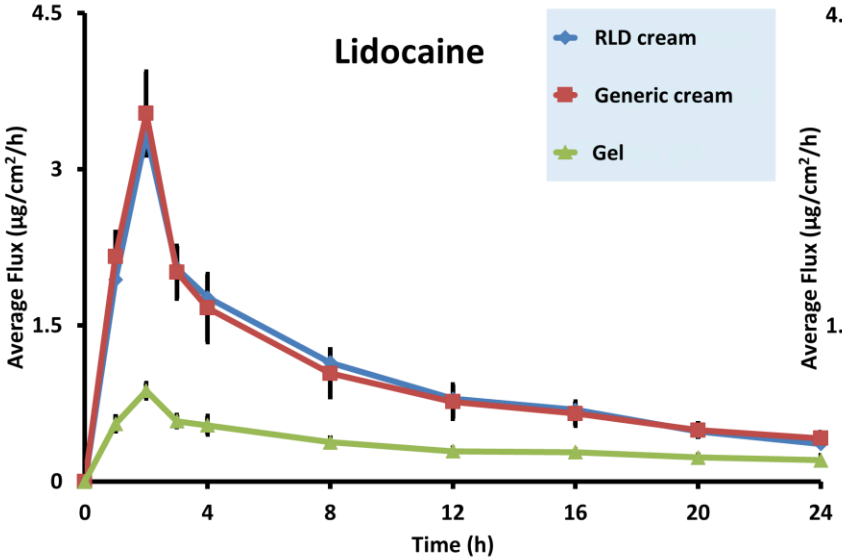
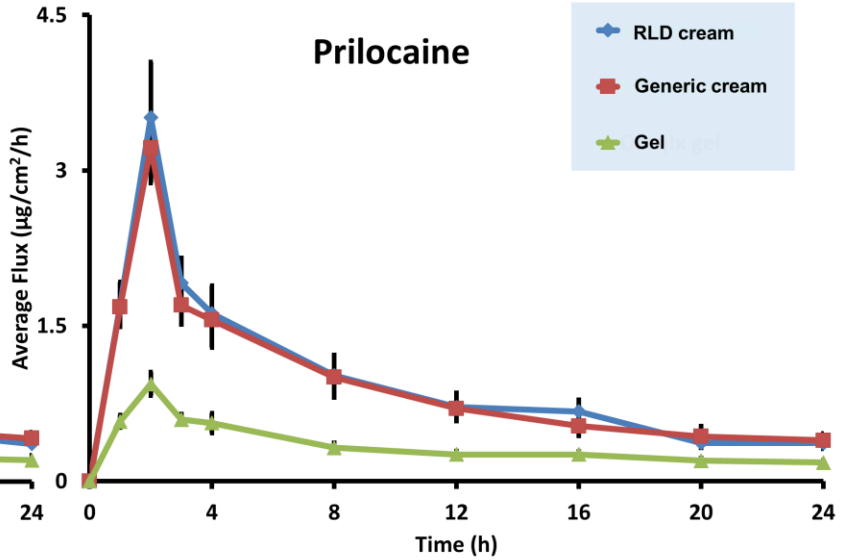
IVPT Results for Different Products









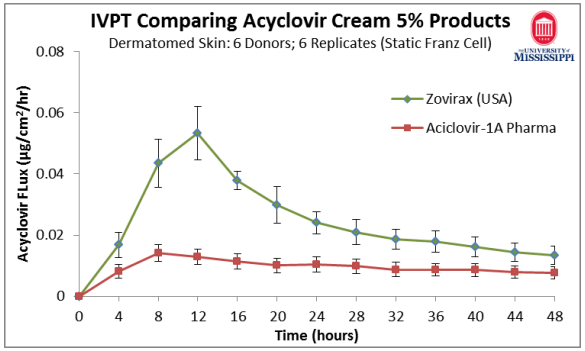
Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

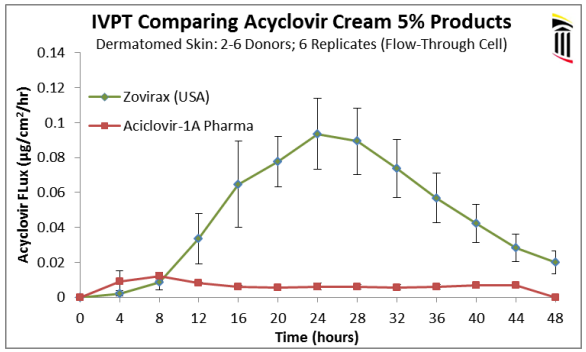
IVPT Results: Acyclovir Cream, 5%

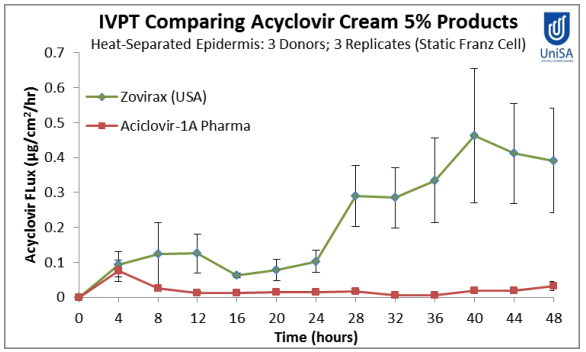
- Cutaneous Pharmacokinetics by IVPT

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







Data provided courtesy of
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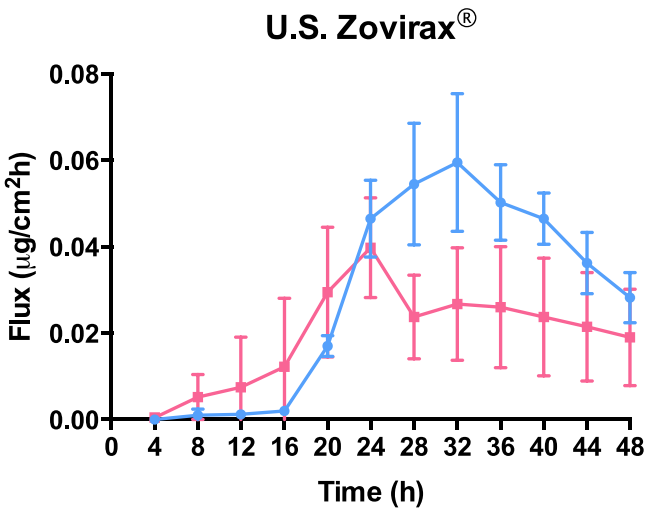
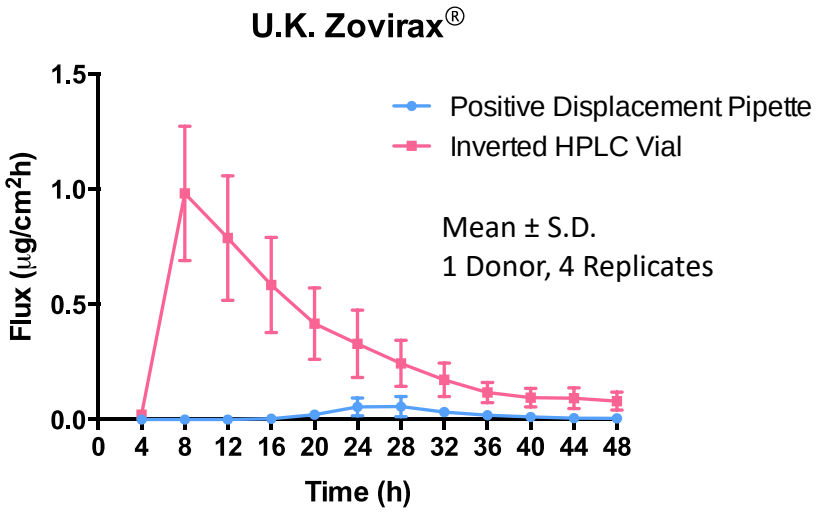
Prof. Audra Stinchcomb (University of Maryland) ***FDA Award U01-FD004947****, and*
Prof. Michael Roberts (University of South Australia) ***FDA Award U01-FD005226***

Influence of Quality on Performance

- Influence of Dose **Application** on Bioavailability

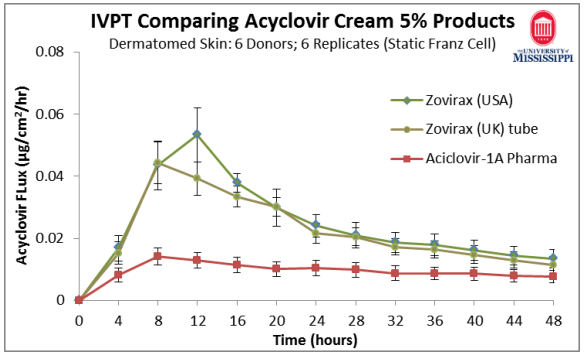


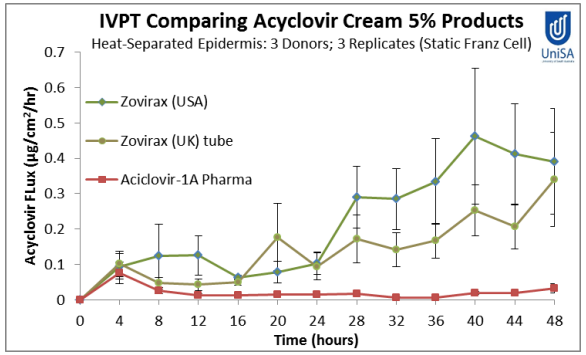


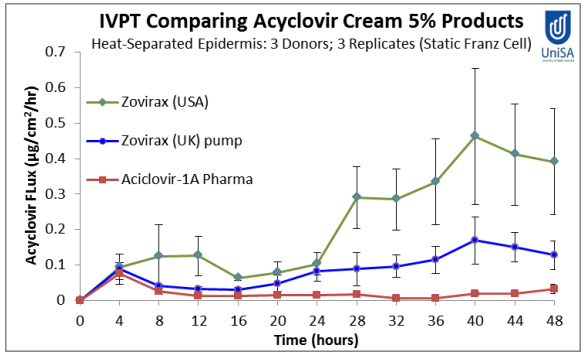
Data provided courtesy of Prof. Audra Stinchcomb (University of Maryland) ***FDA Award U01-FD004947***

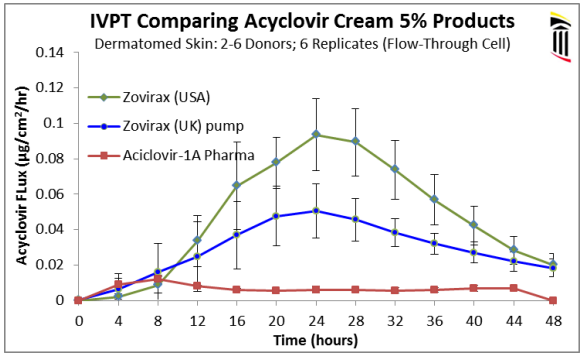
Influence of Quality on Performance

- Influence of Dose **Dispensing** on Bioavailability









Data provided courtesy of
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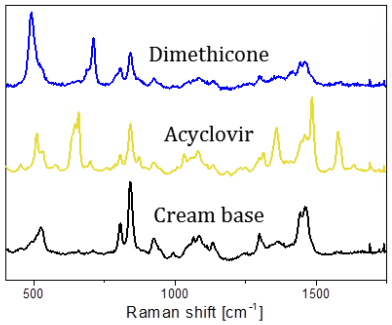
Prof. Michael Roberts (University of South Australia) ***FDA Award U01-FD005226***

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

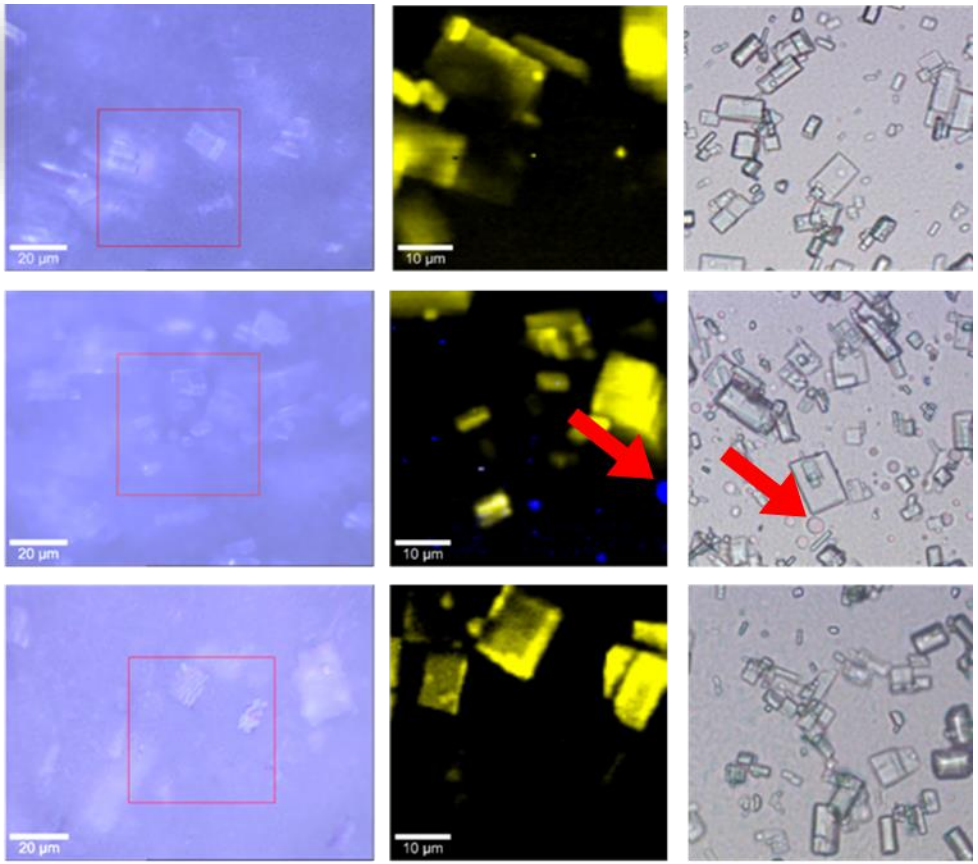
  Prof. Michael Roberts FDA Award U01-FD005226



Zovirax® UK
Tube

Zovirax® UK
Pump

Zovirax® UK
Pump
(from inside container)

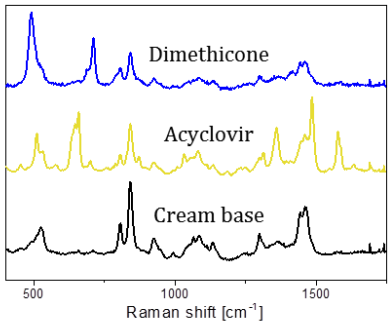


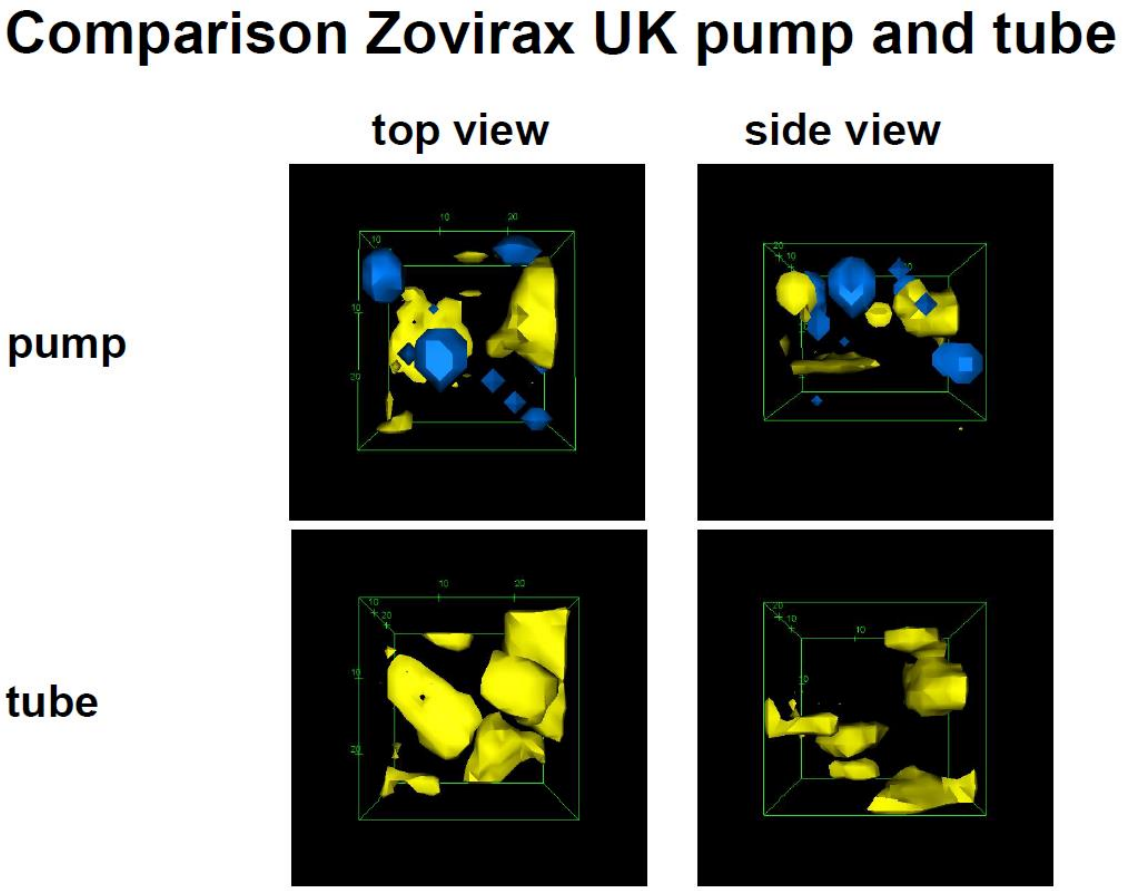
Data provided courtesy of Prof. Michael Roberts (University of South Australia) ***FDA Award U01-FD005226***

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

  Prof. Michael Roberts FDA Award U01-FD005226

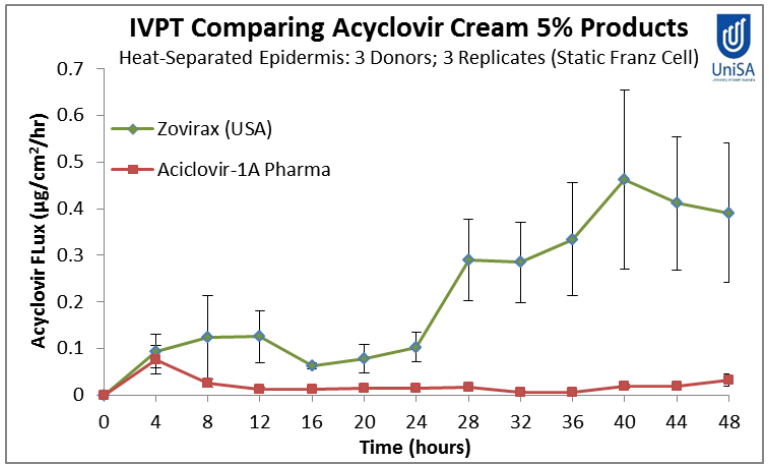


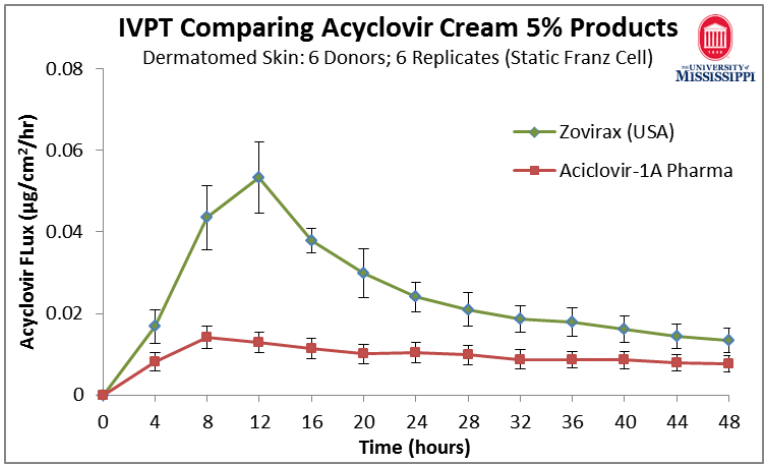


Data provided courtesy of Prof. Michael Roberts (University of South Australia) ***FDA Award U01-FD005226***

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)**

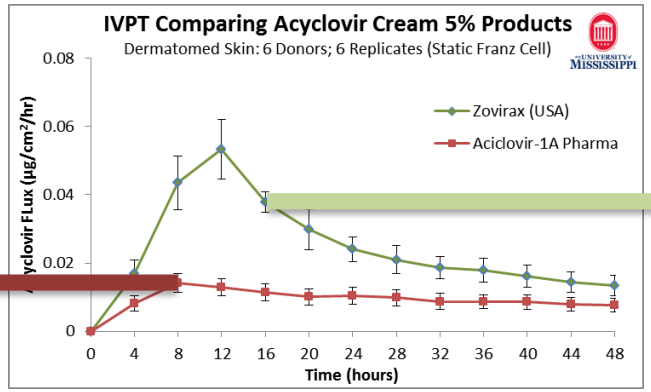
IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.290	0.366
$S_{Within\ Reference}$	0.575	0.419
SABE [0.80, 1.25]	2.383 (**Non-BE**)	1.884 (**Non-BE**)
N for [0.80, 1.25] with 6 Replicates	8	20

Data provided courtesy of
Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223****, and*
Prof. Michael Roberts (University of South Australia) ***FDA Award U01-FD005226***

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+

Data provided courtesy of Prof. Audra Stinchcomb (University of Maryland) ***FDA Award U01-FD004947***

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