Development of FDA's Guidance for Industry on IVPT Studies for Topical Drug Products Submitted in ANDAs

FDA-CRCG Workshop on Implementing FDA's IVPT Guidance Recommendations: A Step-By-Step Illustration

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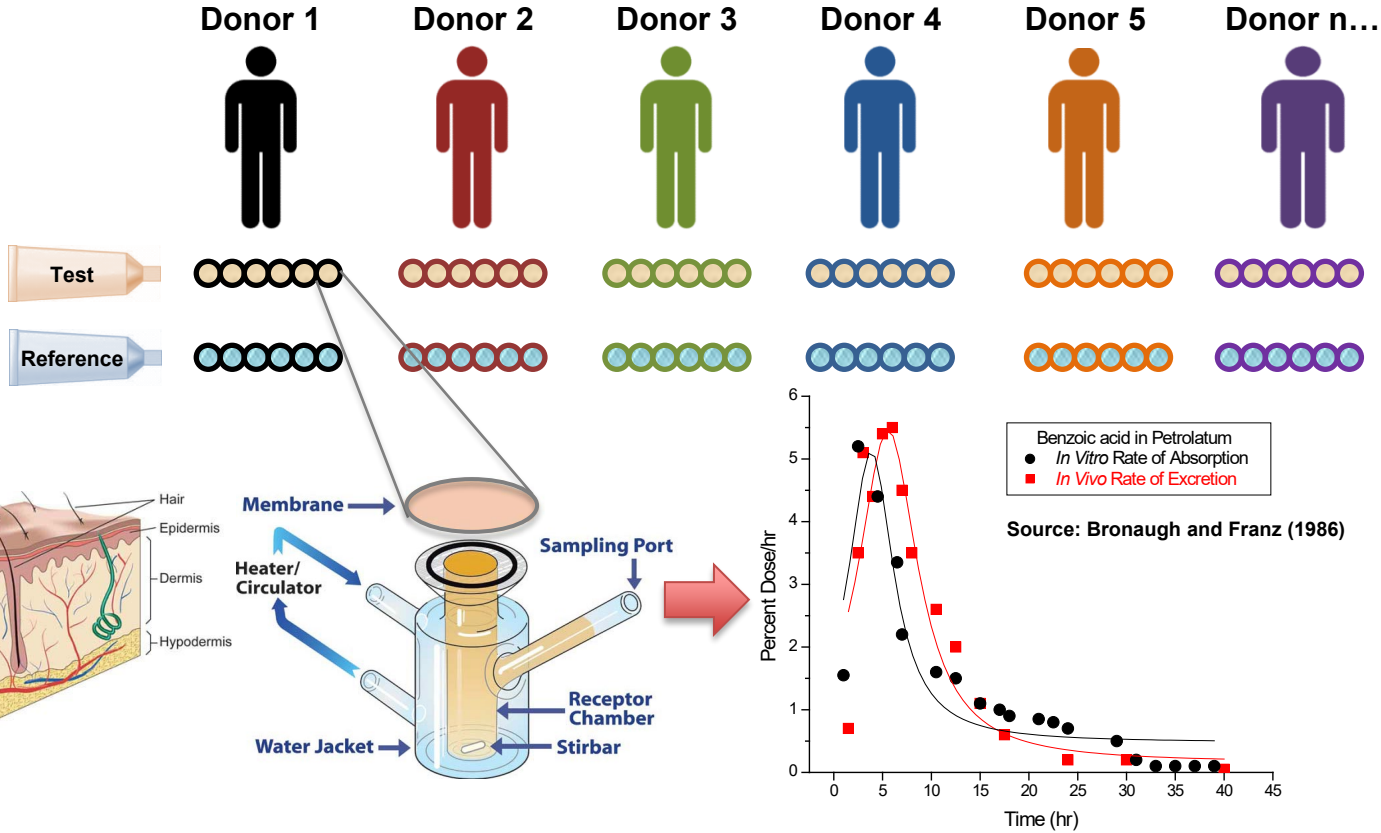
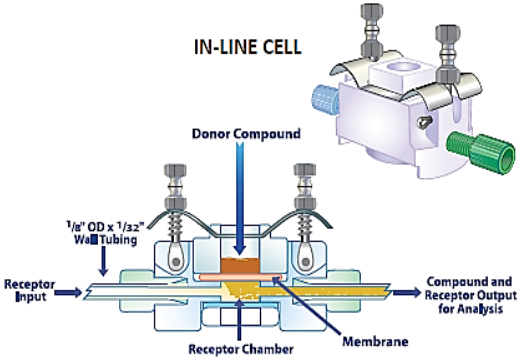
Disclaimer

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

IVPT Study Design

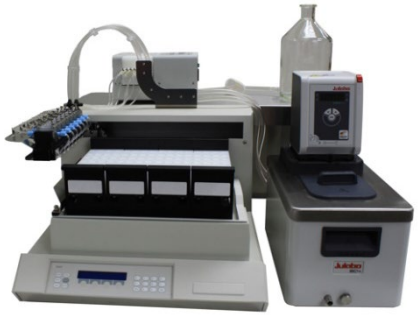


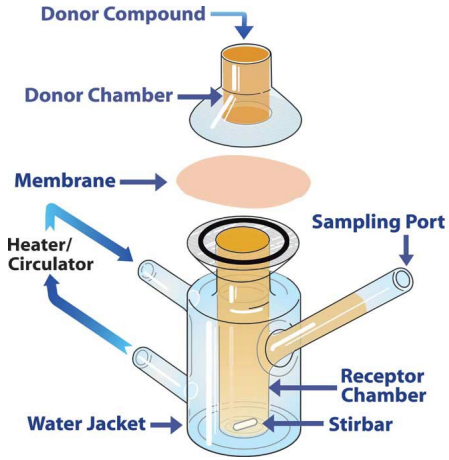
IVPT Diffusion Cell Equipment



https://permegear.com/

https://www.loganinstruments.com/

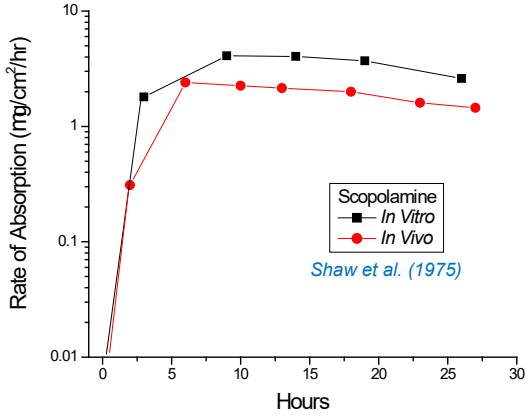


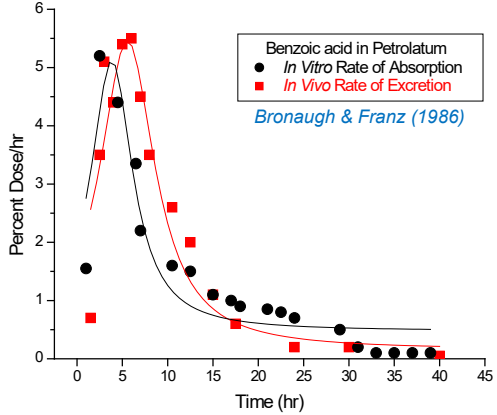


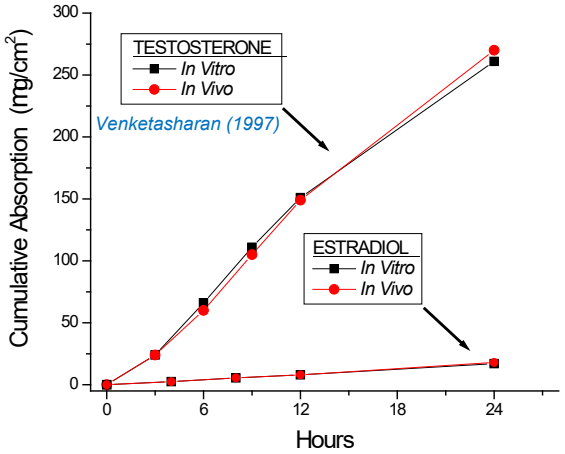
https://permegear.com/

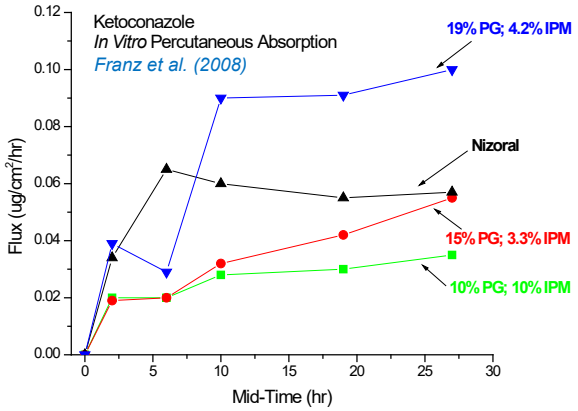
https://www.teledynelabs.com/products/diffusion/phoenix-db-6

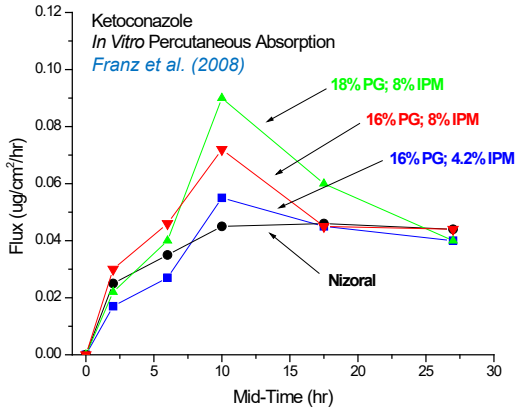
IVPT Studies: A Brief History



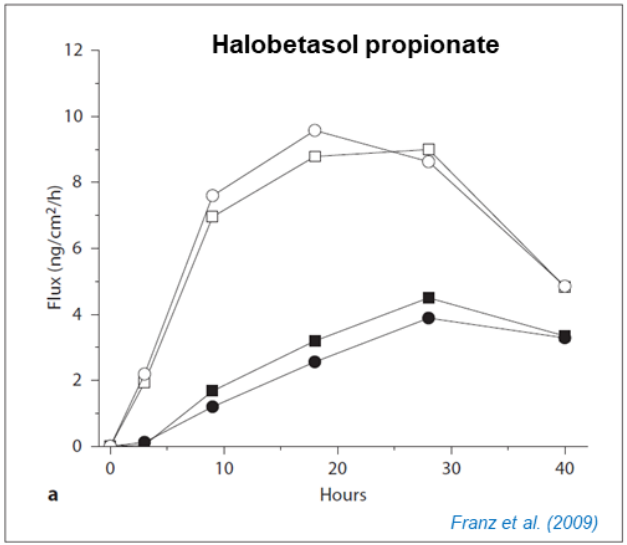


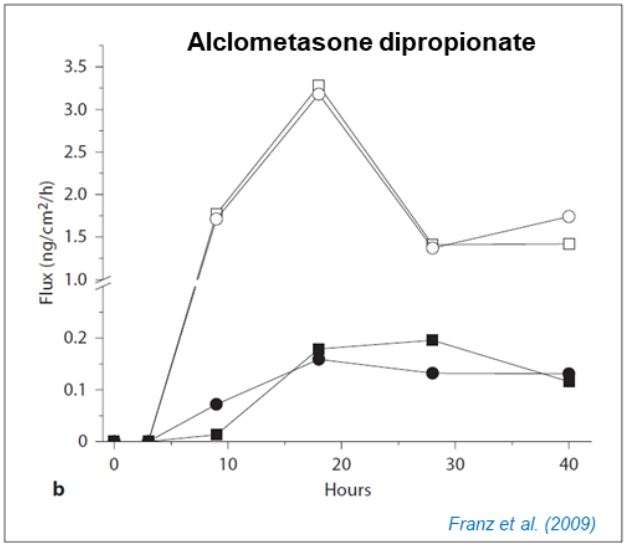






IVPT Studies: A Brief History





■ = Test cream, ● = reference cream; □ = test ointment, ○ = reference ointment.

From: Franz et al. (2009)	In Vitro Absorption (ng/cm²/ 48 h)			In Vivo VC Assay (Negative $AUEC_{0\text{-}24\ h}$)		
	Test	Ref	Test/Ref	Test	Ref	Test/Ref
Alclometasone cream	4.52	4.39	1.03	18.5	16.8	1.10
Alclometasone ointment	66.95	70.0	0.96	16.0	17.4	0.92
Halobetasol cream	110.4	96.9	1.14	33.1	30.7	1.08
Halobetasol ointment	246.7	256.3	0.96	28.6	28.5	1.00

Topical Bioequivalence (BE) Standards

Q1: Components in a topical product

- Q1 characterization of a topical product provides a profile of the qualitative components (ingredients) in that product

Q2: Composition of a topical product

- Q2 characterization of a topical product provides a profile of the quantitative formulation composition of that product

Q3: Arrangement of matter in a topical product

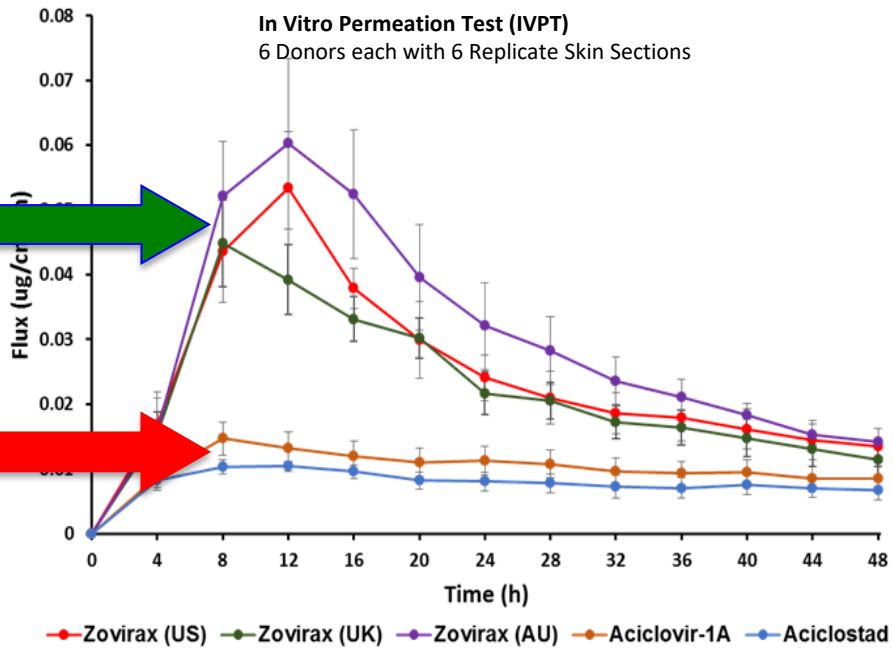
- Q3 characterization of a topical product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that product

Topical Bioequivalence (BE) Standards

- IVPT is a biorelevant test method that can
  - Sensitively discriminate the rate and extent of topical bioavailability between formulations across a wide range of drugs and dosage forms
  - Provide biorelevant results that correlated with in vivo bioavailability and successfully predicted the bioequivalence of topical generic products
  - Support a demonstration of bioequivalence for prospective topical generic products that were closely Q1/Q2/Q3 matched to the RLD
- Had no established procedures for validation, BE study design, or statistical analysis, and no systematic assessment of inter-lab reproducibility with positive and negative controls for BE

IVPT Studies (Acyclovir Cream)

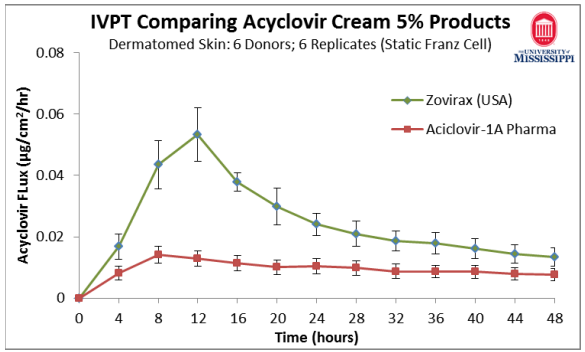
	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol Stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	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

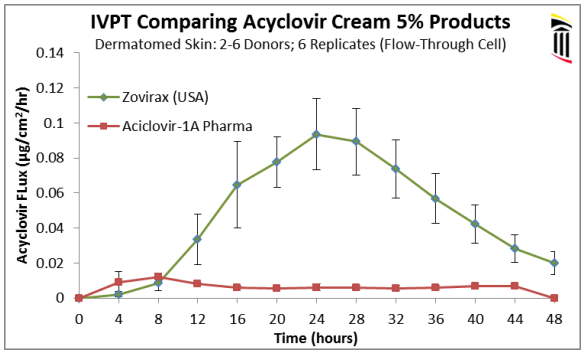


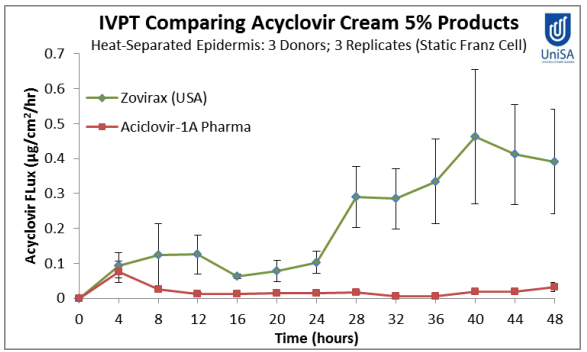
Data from Prof. Narasimha Murthy (University of Mississippi) FDA Award U01FD005223

IVPT Studies (Acyclovir Cream)

	University of Mississippi	University of Maryland	University of South Australia
Dose	15 mg/cm^2 Acyclovir Cream, 5%		
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

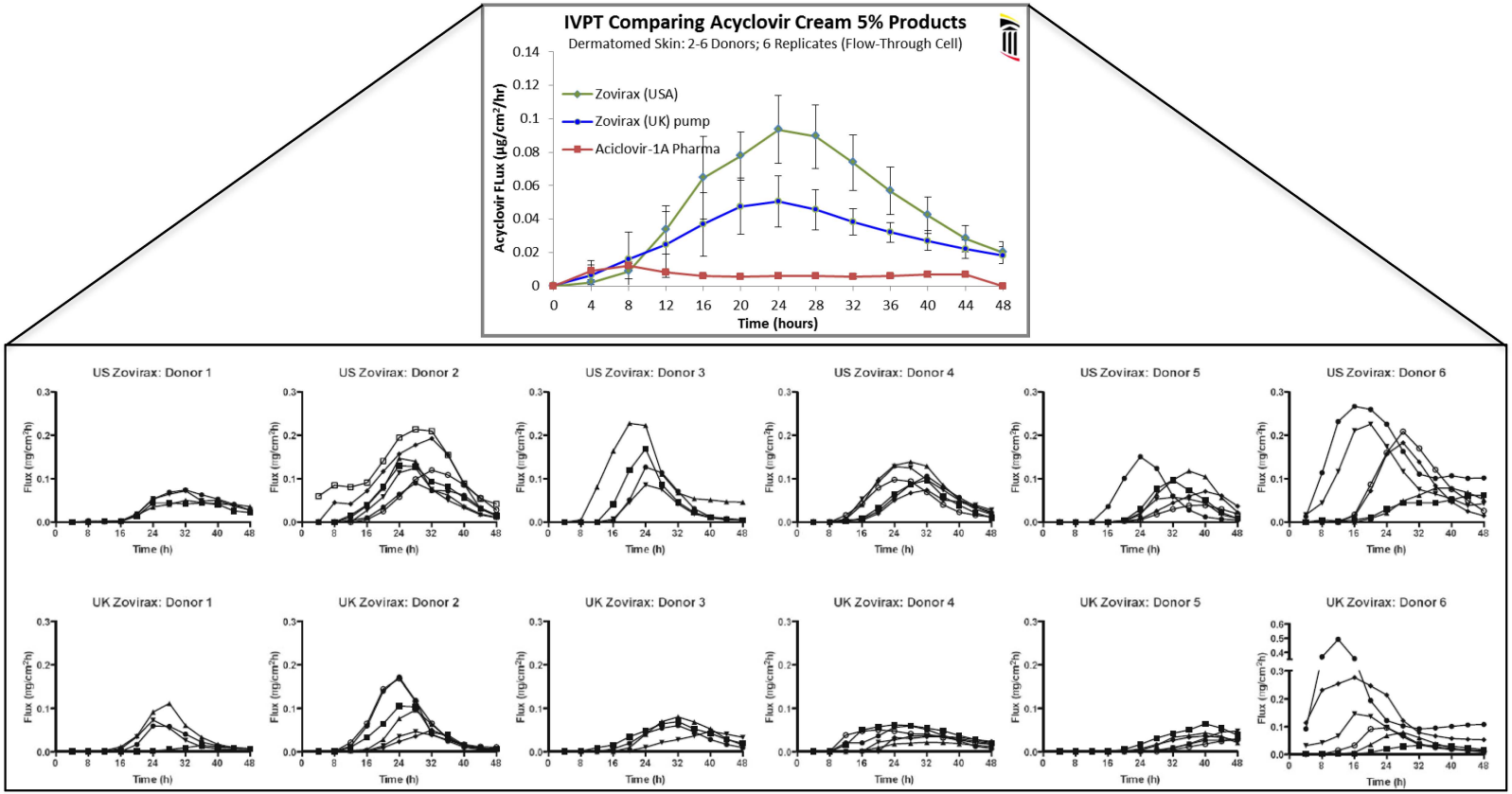






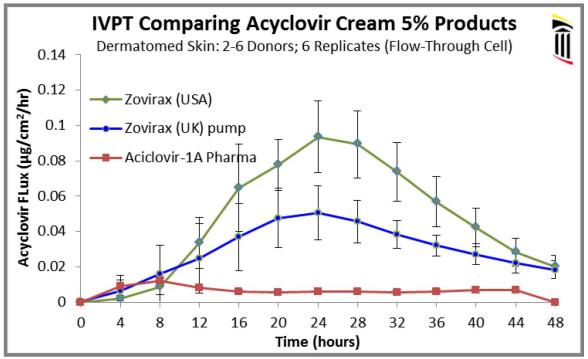
Data from Prof. Narasimha Murthy (University of Mississippi) Grant U01FD005223, Prof. Audra Stinchcomb (University of Maryland) Grant U01FD004947, and Prof. Michael Roberts (University of South Australia) Grant U01FD005226

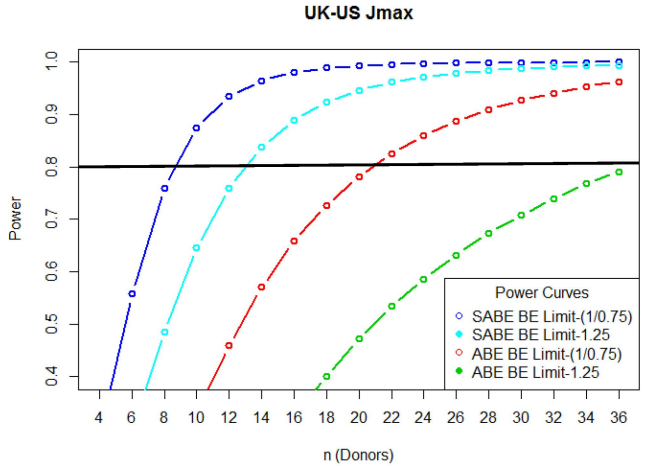
IVPT Studies (Acyclovir Cream)

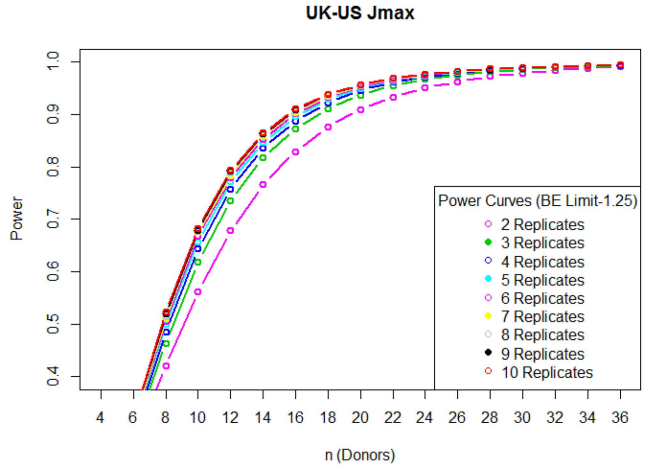


Data from Prof. Audra Stinchcomb (University of Maryland) Grant U01FD004947, including Shin et al. (2020)

IVPT Studies (Acyclovir Cream)



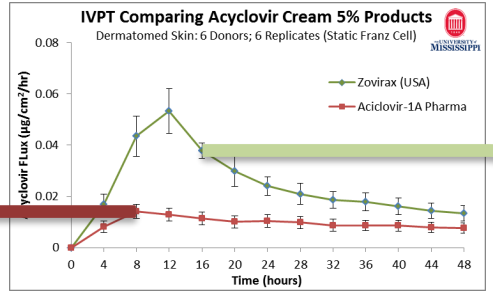




Data from Prof. Audra Stinchcomb (University of Maryland) Grant U01FD004947; Statistical analyses by Dr. Elena Rantou, FDA

IVPT Studies (Acyclovir Cream)

- **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 from Prof. Narasimha Murthy (University of Mississippi) Grant U01FD005223; Statistical analyses by Dr. Elena Rantou, FDA

IVPT Studies (Acyclovir Cream)

- **Positive Controls** for BE: 5 Acyclovir Creams vs. Self

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

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	1.0557	1.1072
Σ Within Reference	0.5605	0.4047
SABE [0.80, 1.25]	-0.0805 (**BE**)	-0.0268 (**BE**)
SABE [0.75, 1.33]	-0.1989 (**BE**)	-0.0437 (**BE**)

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

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.934	0.9632
Σ Within Reference	0.4254	0.407
SABE [0.80, 1.25]	-0.0535 (**BE**)	-0.0303 (**BE**)
SABE [0.75, 1.33]	-0.0247 (**BE**)	-0.0955 (**BE**)

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

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.9465	0.9197
Σ Within Reference	0.4477	0.4477
SABE [0.80, 1.25]	-0.0407 (**BE**)	-0.0085 (**BE**)
SABE [0.75, 1.33]	-0.0479 (**BE**)	-0.0671 (**BE**)

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

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.8339	0.9439
Σ Within Reference	0.7618	0.5032
SABE [0.80, 1.25]	-0.0326 (**BE**)	-0.0864 (**BE**)
SABE [0.75, 1.33]	-0.2459 (**BE**)	-0.1629 (**BE**)

Aciclostad® (T) vs. **Aciclostad® (R)**

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.9273	0.9276
Σ Within Reference	**0.2798**	0.3009
ABE or SABE [0.80, 1.25]	[0.8049,1.0684] (**BE**)	-0.0278 (**BE**)
ABE or SABE [0.75, 1.33]	[0.8049,1.0684] (**BE**)	-0.0585 (**BE**)

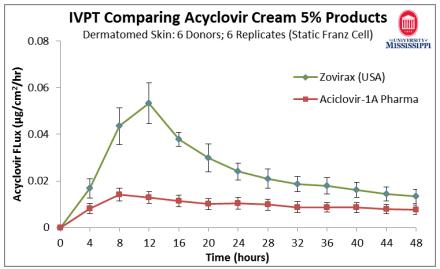
Aciclovir-1A® (T) vs. **Aciclovir-1A® (R)**

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.9783	0.9864
Σ Within Reference	**0.229**	0.301
ABE or SABE [0.80, 1.25]	[0.8177,1.1704] (**BE**)	-0.0409 (**BE**)
ABE or SABE [0.75, 1.33]	[0.8177,1.1704] (**BE**)	-0.0689 (**BE**)

Data from Prof. Audra Stinchcomb (University of Maryland) Grant U01FD004947 and Prof. Narasimha Murthy (University of Mississippi) Grant U01FD005223; Statistical analyses by Dr. Elena Rantou, FDA

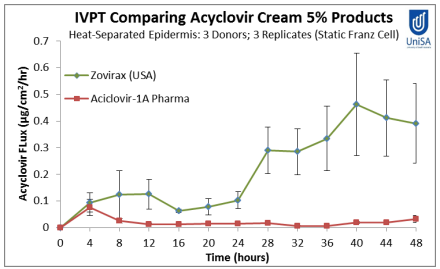
IVPT Studies (Acyclovir Cream)

- **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	0.2902	0.3661
Σ Within Reference	0.5747	0.4193
SABE [0.80, 1.25]	2.3828 (Non-BE)	1.8843 (Non-BE)
SABE [0.75, 1.33]	2.2138 (Non-BE)	1.7932 (Non-BE)
N for [0.80, 1.25]	8	20
N for [0.75, 1.33]	6	12



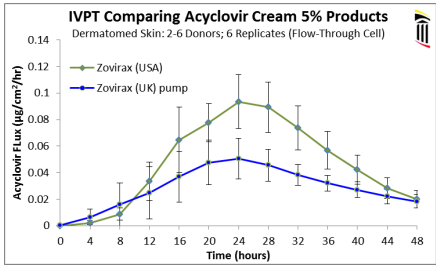
Aciclovir-1A® (T) vs. **Zovirax® US (R)**

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.1722	0.1042
Σ Within Reference	0.5214	0.5512
SABE [0.80, 1.25]	4.4326 (Non-BE)	7.2356 (Non-BE)
SABE [0.75, 1.33]	4.2964 (Non-BE)	7.0832 (Non-BE)
N for [0.80, 1.25]	6	8
N for [0.75, 1.33]	4	6

Data from Prof. Narasimha Murthy (University of Mississippi) Grant U01FD005223 and Prof. Michael Roberts (University of South Australia) Grant U01FD005226 ; Statistical analyses by Dr. Elena Rantou, FDA

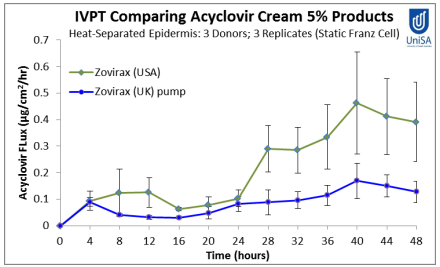
IVPT Studies (Acyclovir Cream)

- **Selectivity Test** for BE: Zovirax® UK Pump vs. Zovirax® US



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

IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.6537	0.6470
Σ Within Reference	0.5535	0.7396
SABE [0.80, 1.25]	0.5819 (**Non-BE**)	0.5952 (**Non-BE**)
SABE [0.75, 1.33]	0.7346 (**Non-BE**)	0.7033 (**Non-BE**)
N for [0.80, 1.25]	16	8
N for [0.75, 1.33]	10	6



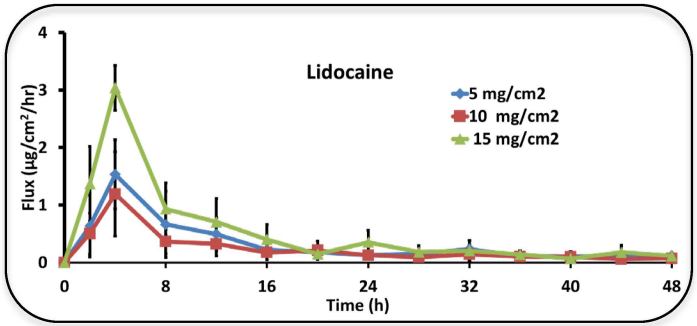
Zovirax ® UK Pump (T) vs. **Zovirax® US (R)**

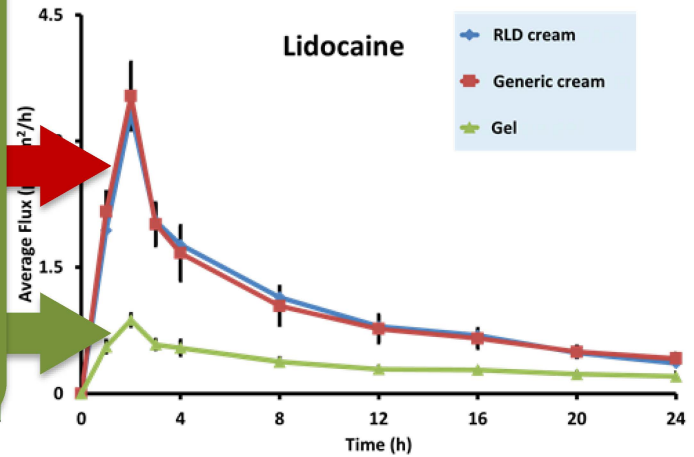
IVPT PK Endpoint	Maximum Flux **(Jmax)**	Total Bioavailability **(AUC)**
Point Estimate	0.6537	0.6470
Σ Within Reference	0.5535	0.7396
SABE [0.80, 1.25]	0.5819 (**Non-BE**)	0.5952 (**Non-BE**)
SABE [0.75, 1.33]	0.7346 (**Non-BE**)	0.7033 (**Non-BE**)
N for [0.80, 1.25]	38	40+
N for [0.75, 1.33]	24	30

Data from Prof. Audra Stinchcomb (University of Maryland) Grant U01FD004947 and Prof. Michael Roberts (University of South Australia) Grant U01FD005226 ; Statistical analyses by Dr. Elena Rantou, FDA

IVPT Studies (Lidocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved				the formulation
Globule Size, d50 (µm)	3.30		3.00		---
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.2	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3

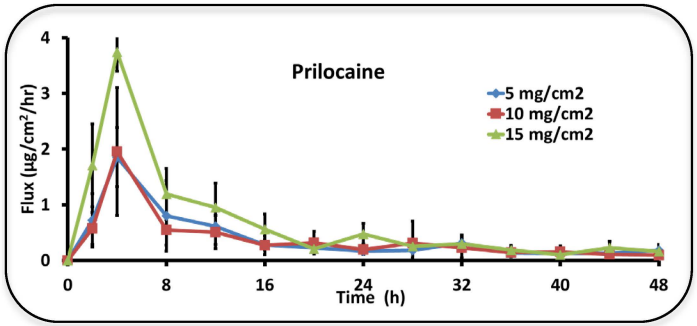


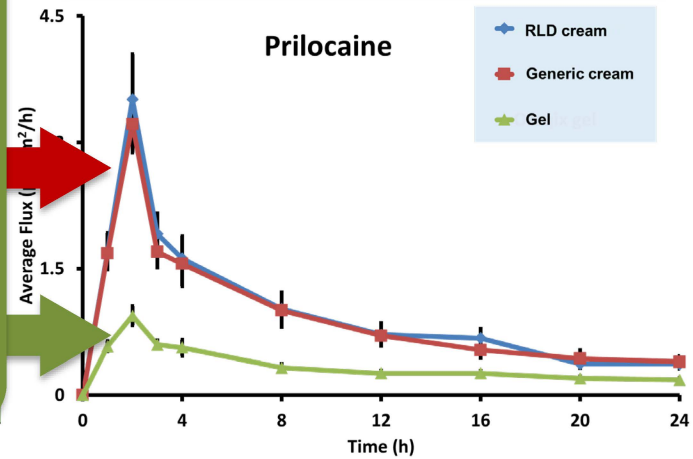


Data provided courtesy of Prof. Narasimha Murthy associated with FDA funding for award U01FD0005233
RLD = Reference Listed Drug

IVPT Studies (Prilocaine)

Q3 Attribute	Lidocaine2.5%, Prilocaine2.5% RLD Cream		Lidocaine-2.5%, Prilocaine-2.5% Generic Cream		Lidocaine-2.5%, Prilocaine-2.5% Gel
pH	9.22 ± 0.08		8.92 ± 0.03		7.76 ± 0.05
Density (g/cc)	1.0142 ± 0.0002		1.0148 ± 0.0002		1.0374 ± 0.0001
WOA (g.sec)	59.427 ± 0.338		65.893 ± 0.614		3.186 ± 0.207
Particle Size of API (µm)	Lidocaine and Prilocaine completely dissolved				the formulation
Globule Size, d50 (µm)	3.30		3.00		---
Drug in Aqueous Phase (µg/g)	Lidocaine	1.64 ± 0.06	Lidocaine	1.74 ± 0.12	---
	Prilocaine	1.99 ± 0.06	Prilocaine	2.11 ± 0.15	
Drug in Oil Phase (µg/g)	Lidocaine	23.45 ± 0.36	Lidocaine	23.21 ± 0.18	---
	Prilocaine	23.47 ± 0.18	Prilocaine	23.12 ± 0.2	
Water Activity	1.003 ± 0.002		1.004 ± 0.007		1.002 ± 0.005
Drying,T50 (min)	3.37 ± 0.15		3.82 ± 0.73		7.9 ± 0.46
Rheology Yield Stress(Pa)	36.7 ± 1.2		35.7 ± 0.6		15.7 ± 2.3

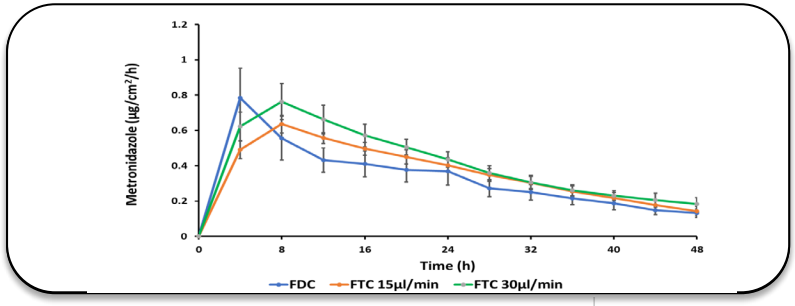


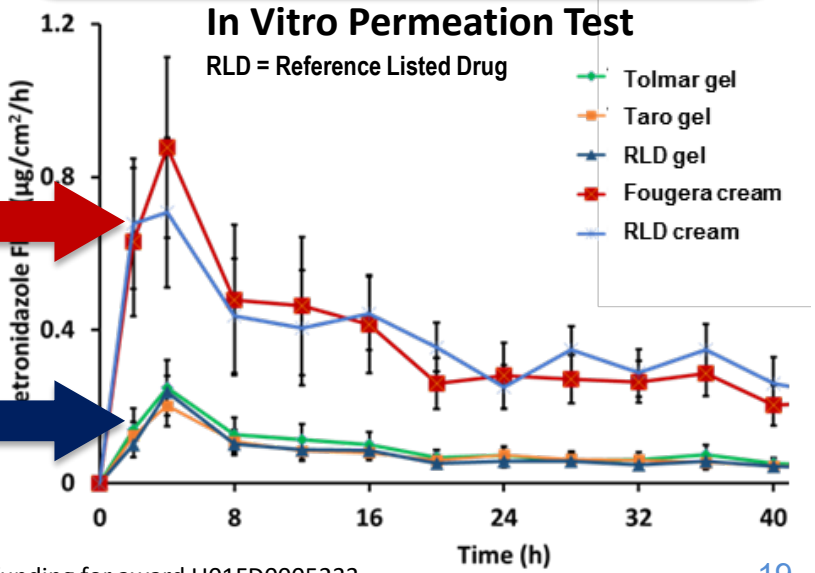


Data provided courtesy of Prof. Narasimha Murthy associated with FDA funding for award U01FD0005233
RLD = Reference Listed Drug

IVPT Studies (Metronidazole)

Quality Attribute	MetroCream® (RLD Cream)	Generic Crear (Fougera)	Metrogel® (RLD Gel)	Generic Gel (Tolmar)	Generic Ge (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 ingre		nt 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

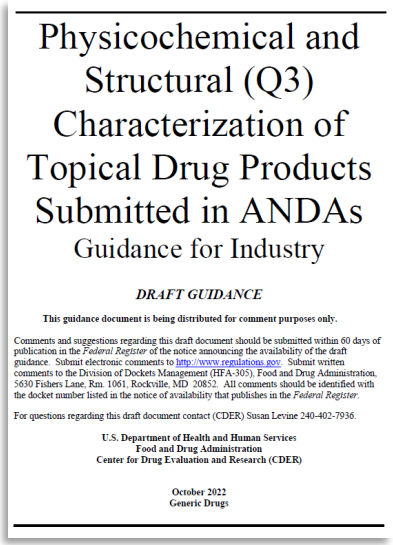




Data provided courtesy of Prof. Narasimha Murthy associated with FDA funding for award U01FD0005233

State of Topical BE Standards

- In addition to publishing and presenting results from IVPT studies extensively, FDA has utilized new insights to establish novel and efficient BE pathways and modern regulatory standards



Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs

Guidance for Industry

DRAFT GUIDANCE

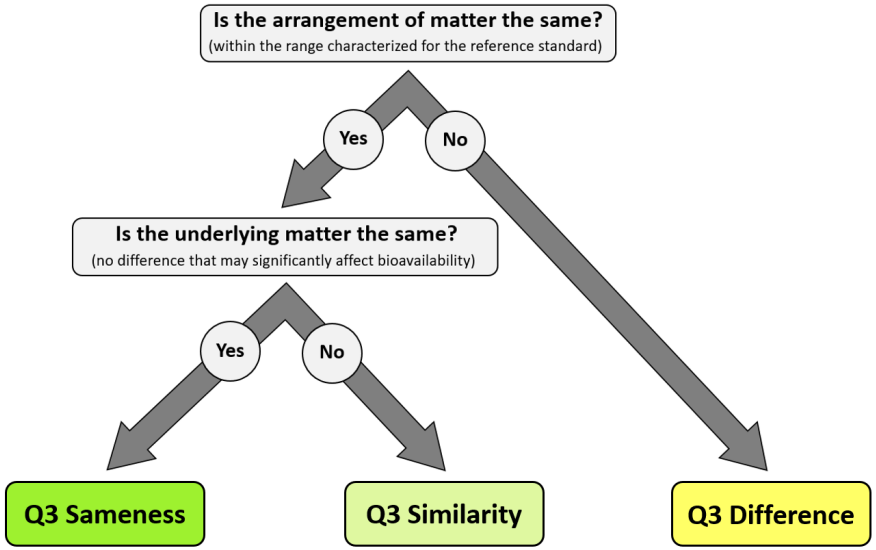
This guidance document is being distributed for comment purposes only.

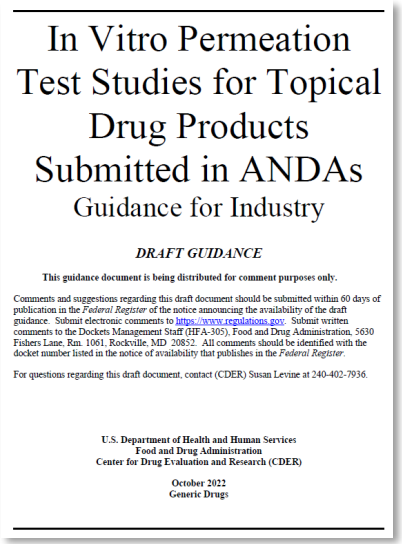
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets 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
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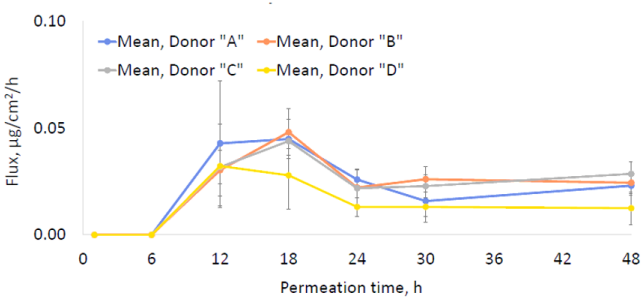
Generic Drugs

State of Topical BE Standards

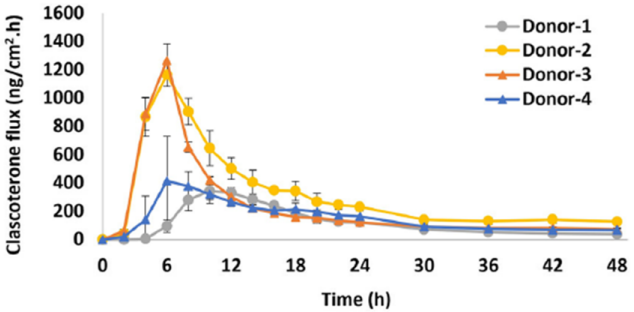
- FDA's Guidances for Industry and PSGs describe BE approaches for almost all topical drugs, many for which a characterization-based (in vitro) BE option is made possible because of an IVPT study

Roflumilast Cream



Kamal et al. (2024) Development of In Vitro Skin Permeation Testing Method to Assess Bioequivalence of Topical Roflumilast Cream Formulations. Poster presentation at AAPS PharmSci 360.

Clascoterone Cream



Yang et al. (2024) Evaluation of *in vitro* Skin Permeation of Clascoterone From Clascoterone Topical Cream, 1% (w/w) AAPS PharmSciTech (2024) 25:186 https://doi.org/10.1208/s12249-024-02887-7

PSGs: Product-Specific Guidances

State of Topical BE Standards

- Efficient in vitro characterization-based BE options are now the dominant approach for topical ANDAs submitted to FDA
- More topical generic drugs have been approved in the last decade alone than in all previous decades combined, and several of these approved applications were supported by IVPT studies
- Yet, topical products are complex, and IVPT studies can be challenging to develop, validate, and analyze
- This workshop will illustrate and discuss practical ways to address these challenges, with multiple diffusion cell systems

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