FDA Initiatives to Stimulate Innovation and Improve Patient Access to Generic Topical & Transdermal Products Part I

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CDER | US FDA

Disclaimer

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

Equivalence of Complex Generics

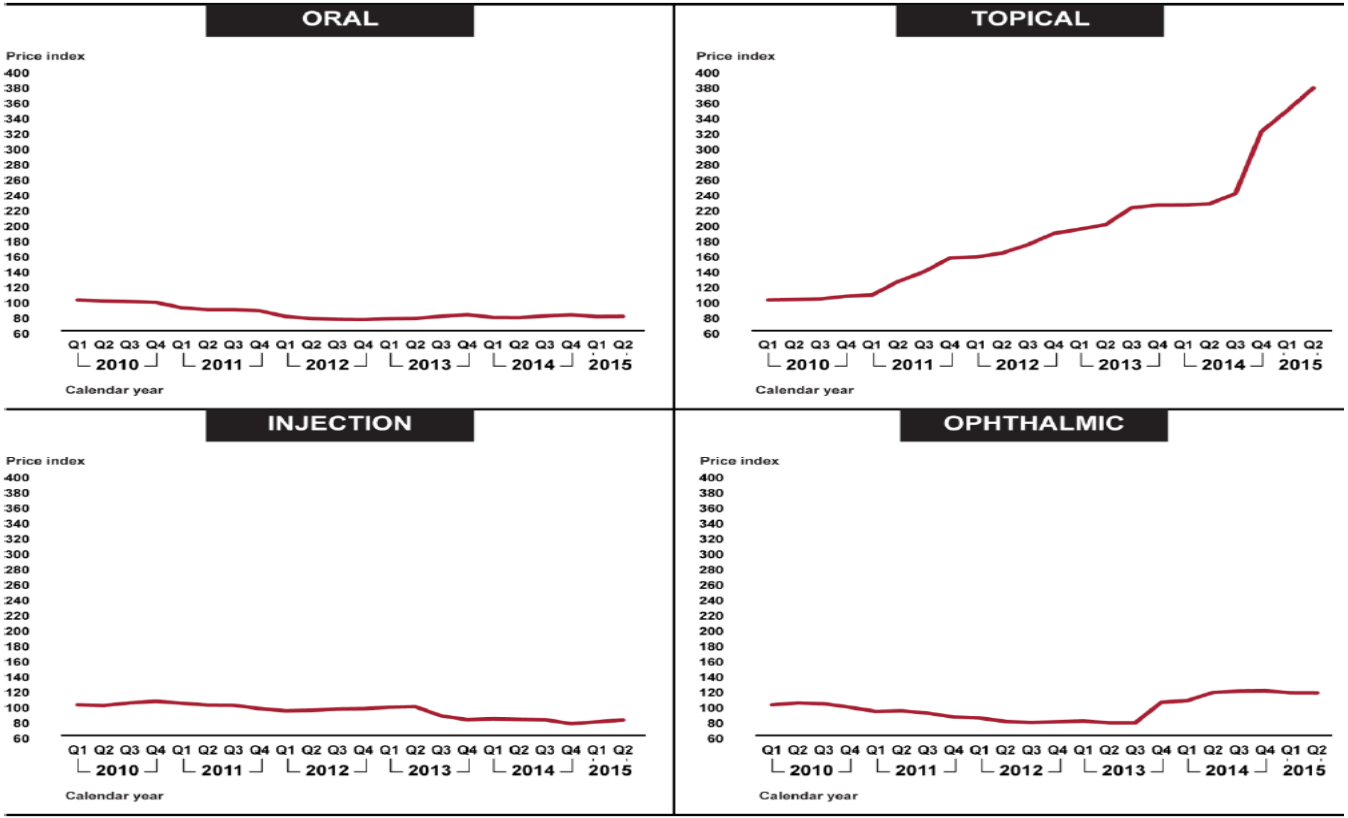
- Topical and transdermal reference listed drug (RLD) products are typically complex, often in multiple ways
- There are unique considerations impacting equivalence for complex generic topical and transdermal products
- Let us discuss these considerations independently for:
  - **Topical products**
  - **Transdermal Delivery System (TDS) products**

Topical Dermatological 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 $ 2009	2011	2014	2015	Absolute Change, 2009-2015	% Change, 2009-2015
Altabax, 15 g	I	92.50	106.18	168.75	196.86	104.36	112.82
Benzaclin, 50 g	A	166.79	205.80	451.29	503.85	337.06	202.08
Carac cream, 30 g	N	159.40	227.16	2939.68	2864.70	2705.30	1697.18
Clobex spray, 4 oz	S	389.57	500.29	827.11	958.01	568.44	145.91
Cloderm cream, 30 g	S	96.47	132.92	220.75	360.02	263.55	273.19
Cutivate lotion 120 mL	S	305.00	493.92	918.63	1067.25	762.25	249.91
Derma-Smoothe FS oil, 4 oz	S	45.70	47.23	247.84	322.67	276.97	606.06
Finacea, 50 g	A	124.42	185.42	288.92	284.30	159.88	128.51
Olux-E foam, 100 g	S	307.58	382.79	750.79	841.76	534.18	173.67
Oracea, 40 mg (30 tablets)	A	439.01	416.09	632.80	702.46	263.45	60.01
Oxistat cream, 30 g	I	76.50	119.25	399.00	544.66	468.16	611.97
Oxsoralen-Ultra, 10 mg (50 capsules)	P	1227.32	2150.49	4568.54	5204.31	3976.99	324.04
Retin-A Micro, 0.1%, 50 g	A	178.05	335.73	791.47	914.52	736.47	413.64
Solaraze gel, 100 g	N	442.89	618.56	1738.91	1883.98	1441.09	325.38
Soriatane, 25 mg (30 capsules)	P	757.75	958.50	1452.50	1595.27	837.52	110.53
Taclonex, 60 g	P	465.99	522.58	848.21	962.90	496.91	106.64
Targretin gel, one 60-g tube	N	1686.78	1787.97	15 708.40	30 320.12	28 633.34	1697.51
Tazorac cream, 0.1%, 60 g	A	266.18	464.96	656.20	722.27	456.09	171.34
Xolegel, 30 g	I	212.50	278.00	389.25	641.96	429.46	202.10

Abbreviations: A, acne and rosacea; I, antiinfective; N, antineoplastic; P, psoriasis; S, corticosteroid.

Source: Miranda E. Rosenberg, BA and Steven P. Rosenberg, MD (2016) *Changes in Retail Prices of Prescription Dermatologic Drugs From 2009 to 2015*. JAMA Dermatology. 152(2):158-163. doi:10.1001/jamadermatol.2015.3897

Patient Access to Topical Products

- Approximately 80% of topical dermatological drug products have fewer than three generic competitors; for many products no generics are available at all.
- This may have been attributable to the historical barriers to the development of topical dermatological drug products, possibly including
  - Difficulty/issues with comparative clinical endpoint bioequivalence (BE) studies
  - The complex nature of topical formulations

Topical Dermatological Formulations

- The formulation of a topical product matters greatly
- The components and composition modulate the physical and structural arrangement of matter
- The resulting topical product characteristics can influence metamorphosis and bioavailability

Topical Dermatological Formulations

- Components, composition, physical and structural properties of a topical product can influence:
  - The drug state(s) and phase(s) of the dosage form
  - The distribution of the drug in the dosage form
  - Drug diffusion within the dosage form
  - Drug partitioning from the dosage form into the skin barrier
  - The structure and chemistry of the skin barrier
  - Drug diffusion within the skin itself
  - Drug delivery & bioavailability at the target site
  - Skin (de)hydration, irritation or damage
  - The metamorphosis of the dosage form on the skin

Failure Modes (BE) – Drug Substance

Is the Drug Substance **Dissolved** in the Formulation?

- Isomers of the drug
- pKa(s) of the drug
- pH of the formulation

Is the Drug Substance **Suspended** in the Formulation?

In addition to the potential failure modes identified on the left….

- Polymorphic forms of the drug
- Particle size distribution of the drug (and crystalline habit)

Failure Modes (BE) – Dosage Form

Is the Formulation a **Single Phase** System? *e.g., solution, gel*

- Excipient differences
- Viscosity/Rheology
- pH

Is the Formulation a **Multi Phase** System? *e.g., lotion, cream*

In addition to the potential failure modes identified on the left….

- Phases and arrangement of matter
- Distribution/localization of drug

Note: The packaging configuration itself may impact bioavailability

Mechanism and/or Site of Action

Is the Mechanism/Site of Action **Well Understood?**

- Acyclovir Topical Cream
- Benzyl Alcohol Topical Solution

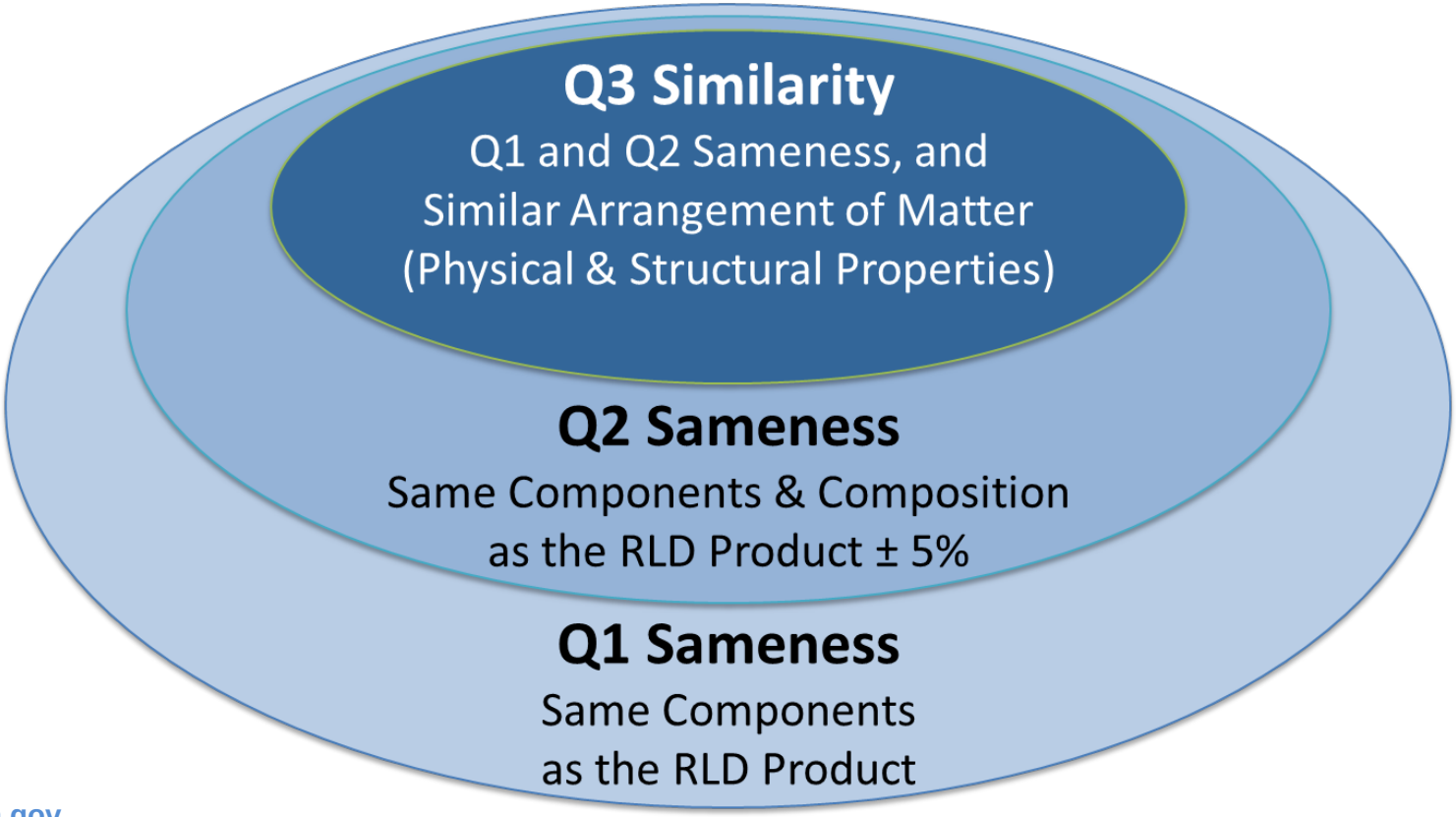
An in vitro characterization based approach may be recommended

Is the Mechanism/Site of Action **Not Well Understood?**

- Dapsone Topical Gel
- Ivermectin Topical Cream

If the mechanism and/or site of action may be (partially) systemic, an in vivo PK study may also be recommended

Topical Dermatological Formulations



Q1/Q2 Sameness of Topical Generics

- Q1/Q2 Sameness (Components and Composition)

  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

Q3 Similarity of Topical Generics

- Q3 Similarity (Arrangement of Matter)

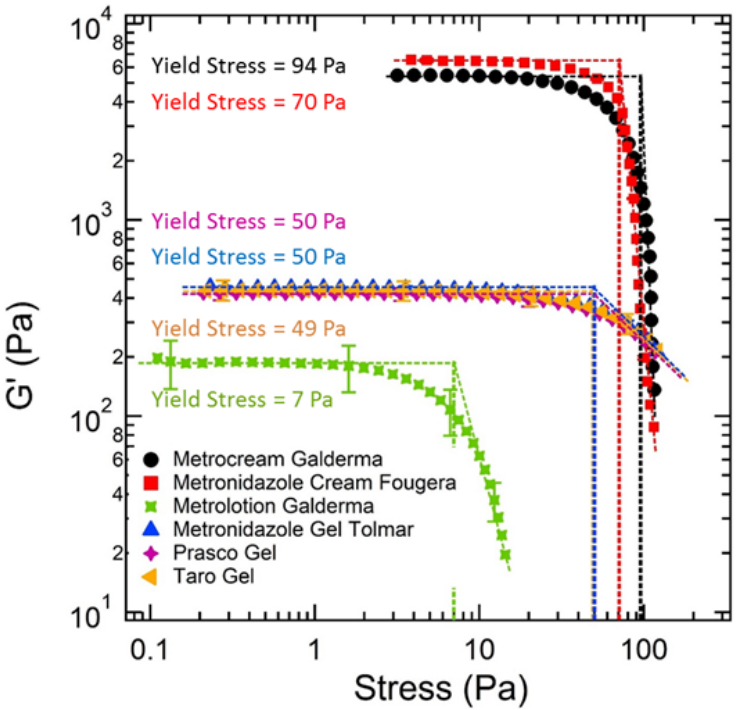
  Mitigates the risk of potential failure modes related to:

  - 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, etc.
  - Differences in entrapped air and drug amount per dose
  - Differences in phase states and diffusion, partitioning, etc.
  - Differences in metamorphosis and drying rates

Metronidazole, 0.75% **In Vitro** Data

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

Rheology



Data provided courtesy of Prof. Narasimha Murthy

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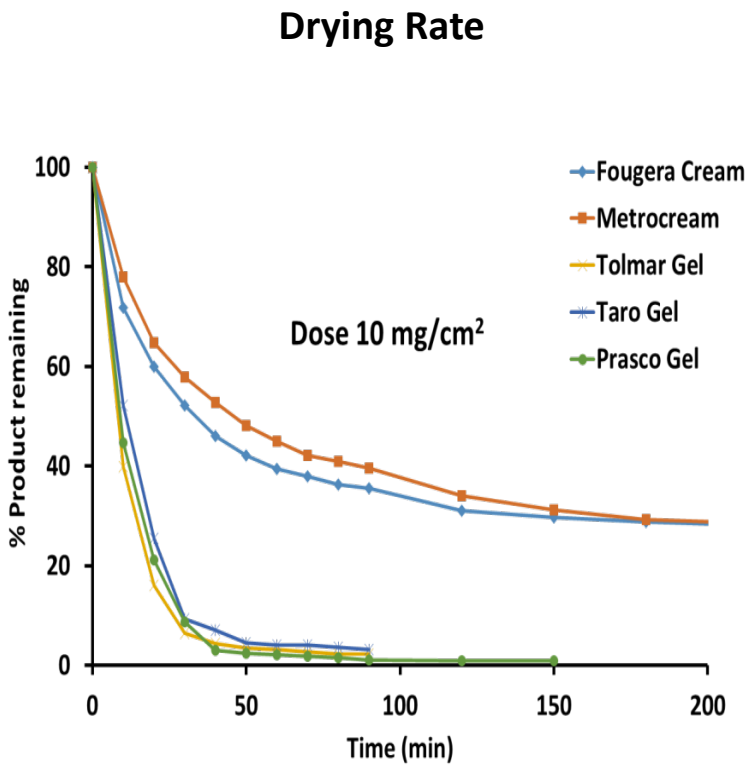

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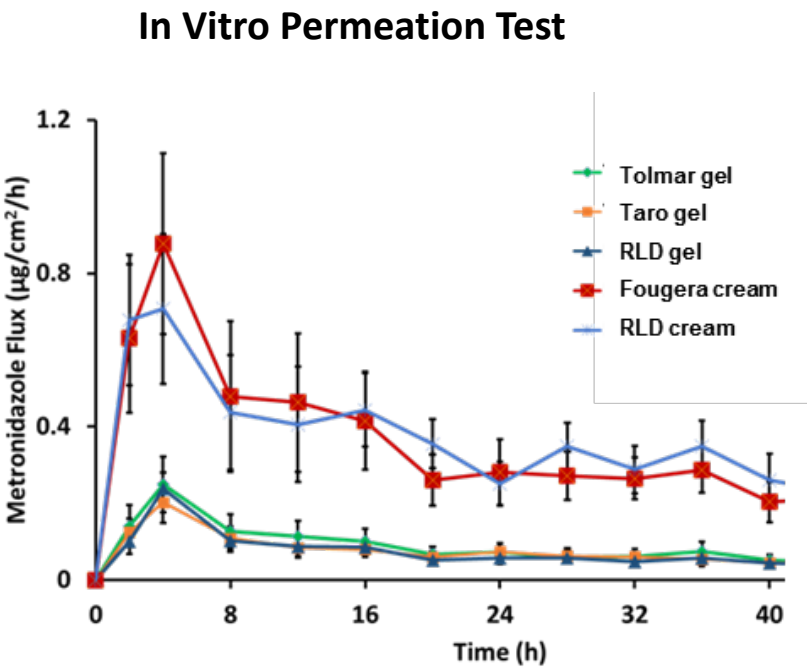

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Metronidazole, 0.75% **In Vivo** Data

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	---	---	---
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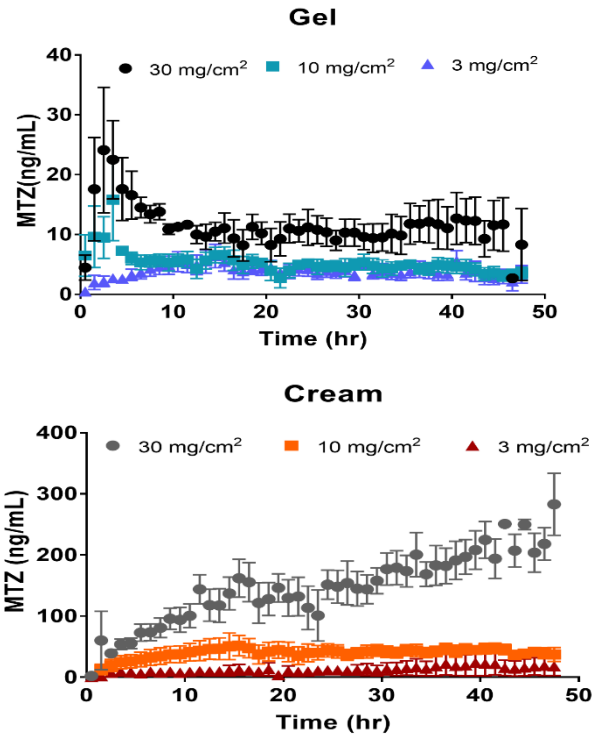
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drying, T_{30} (min)	17	11.4	5.5	4.7	6.5

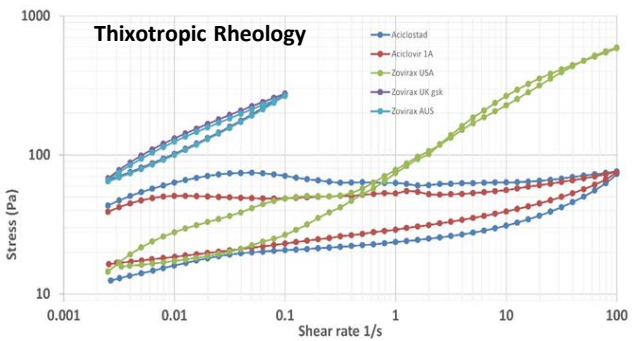
In Vivo Dermal Microdialysis (Porcine)

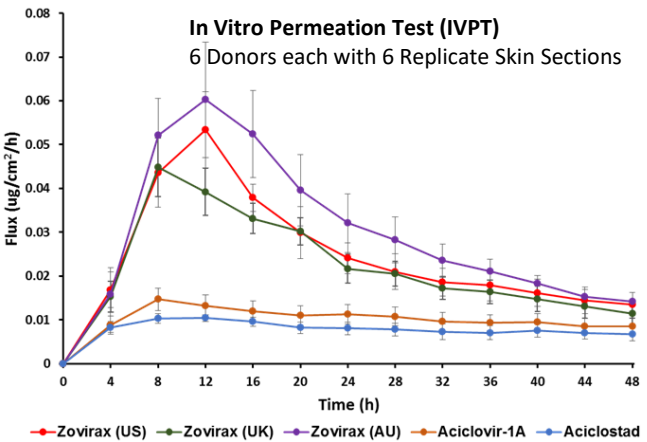


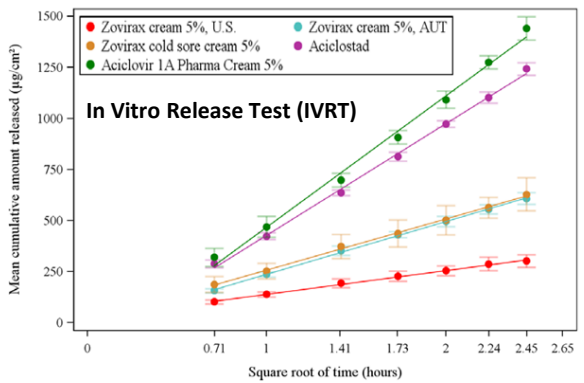
Data provided courtesy of Prof. Grazia Stagni

Acyclovir Cream, 5% **In Vitro** Data

	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



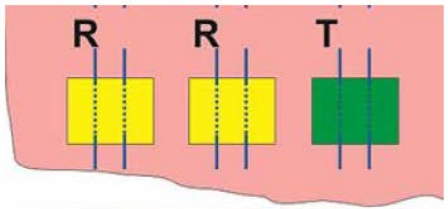


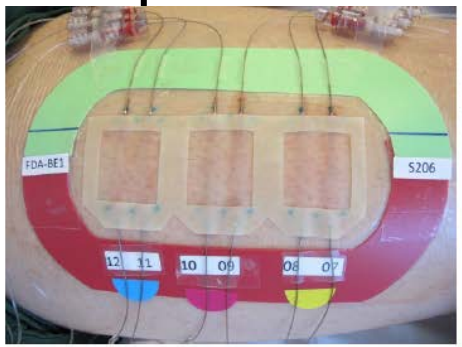


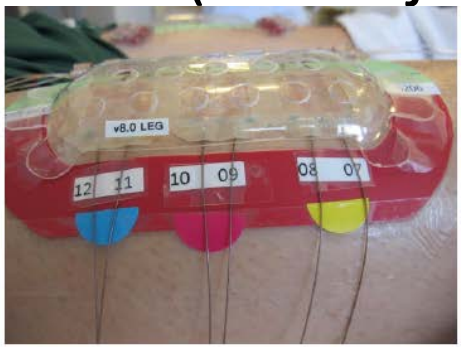
Data provided courtesy of Prof. Narasimha Murthy & Dr. Frank Sinner

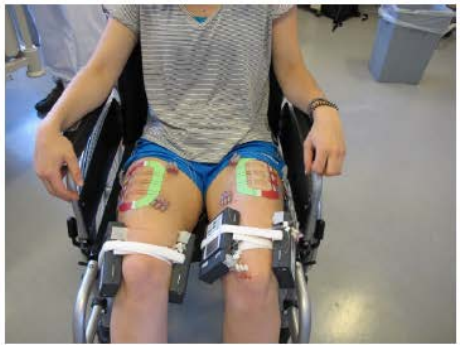
Acyclovir Cream, 5% **In Vivo** Data

- Dermal Open Flow Microperfusion dOFM (20 subjects)









Refer to Bodenlenz et al. (2017) Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence. Clin Pharmacokinet. 2017 Jan;56(1):91-98. doi: 10.1007/s40262-016-0442-z (FREE Full Text Article)

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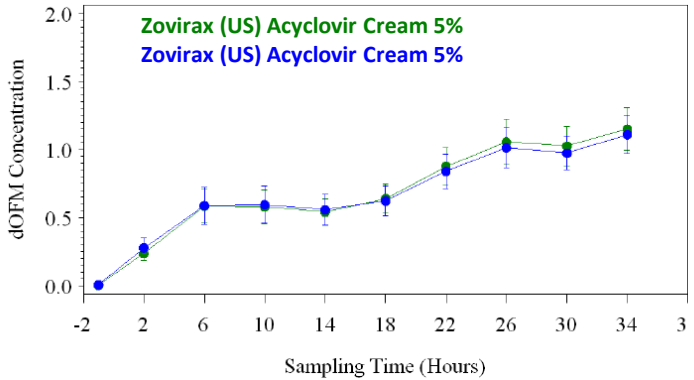
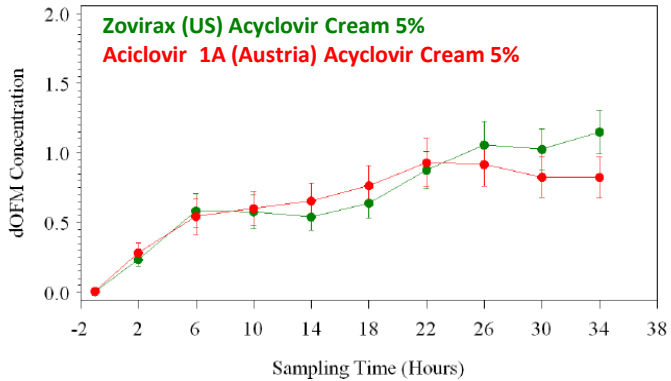
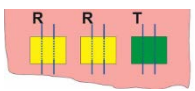




Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]
$log(C_{max})$	[-0.155 ; 0.190] or [85.7 % ; 120.9%]



Outcome variable	$CI_{90\%}$
log(AUC0-36h)	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]
$log(C_{max})$	[-0.498 ; 0.022] or [60.8 % ; 102.2%]

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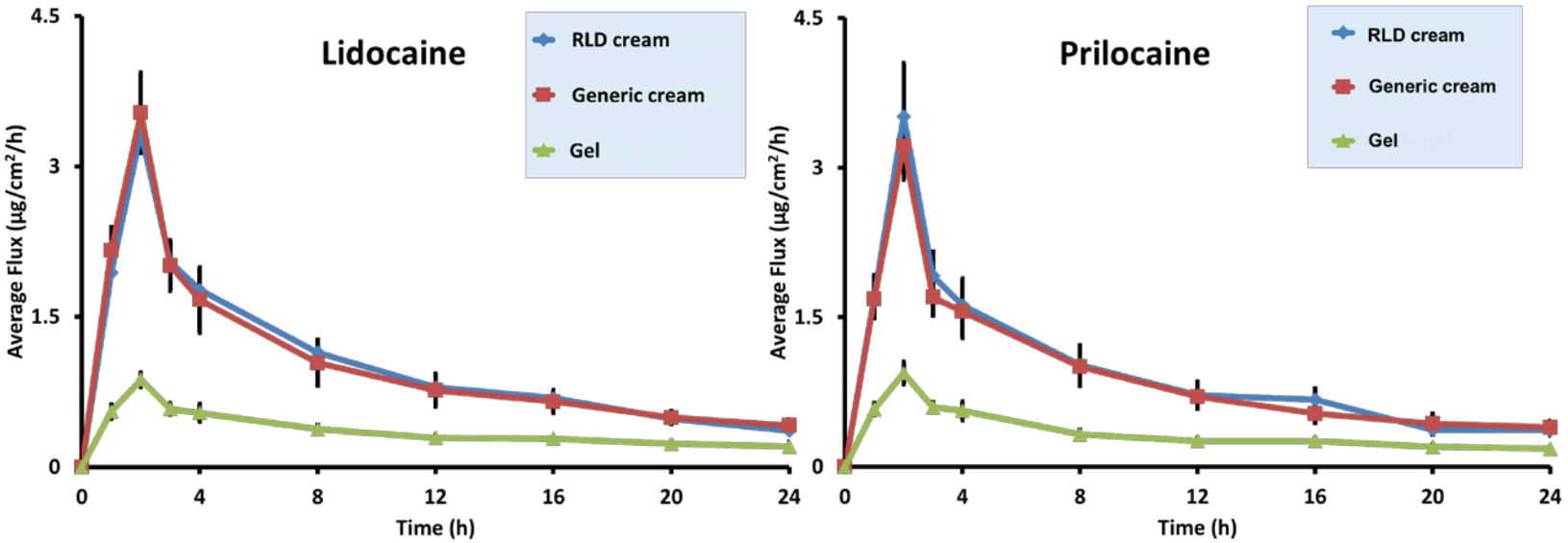
Data provided courtesy of Dr. Frank Sinner

Lidocaine/Prilocaine, 2.5%/2.5% **In Vitro** Data

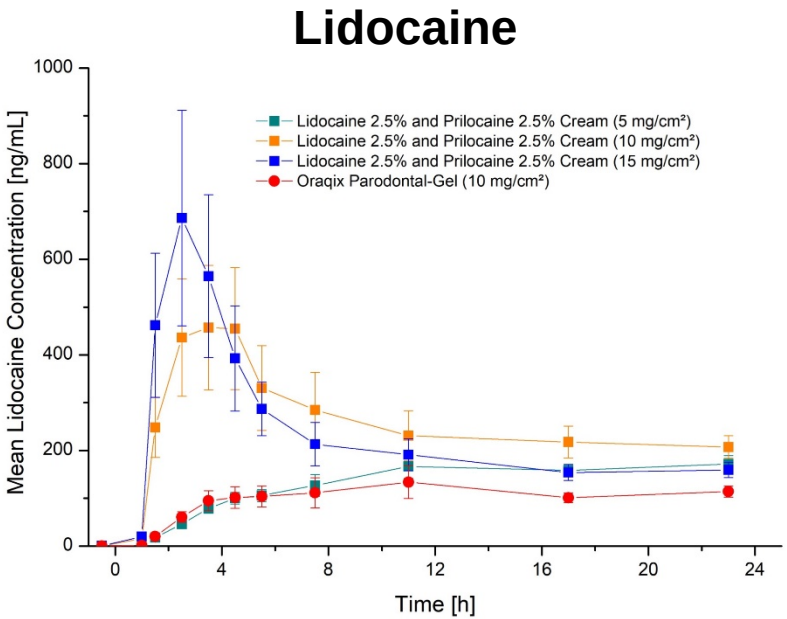
- In Vitro Permeation Test (IVPT)

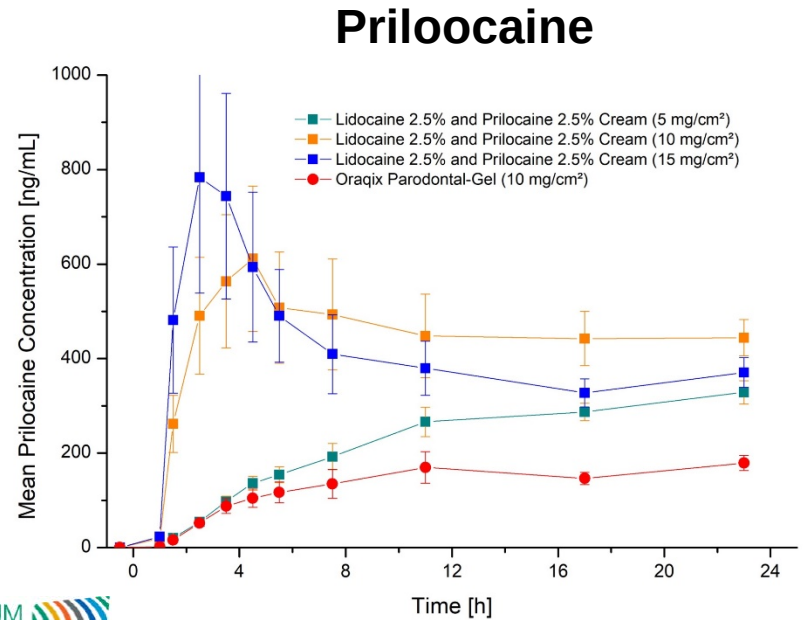


Data provided courtesy of Prof. Narasimha Murthy

Lidocaine/Prilocaine, 2.5%/2.5% **In Vivo** Data

- Dermal Open Flow Microperfusion dOFM (6 subjects)

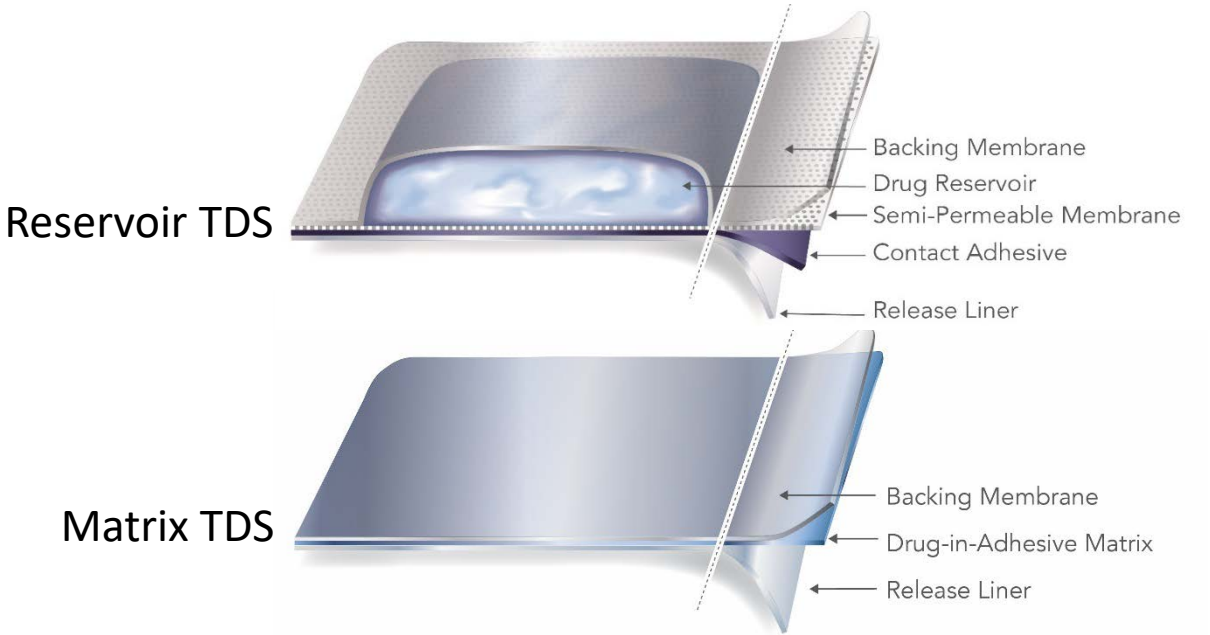




Data provided courtesy of Dr. Frank Sinner

Evaluation of BE for Topical Products

- A Modular Framework for In Vitro BE Evaluation
  - **Q1/Q2** sameness
  - **Q3** similarity
  - **IVRT** (In Vitro Release Test)
  - **IVPT** (In Vitro Permeation Test)
- Multiple Approaches for BE Evaluation
  - **In Vivo Pharmacokinetic** studies
  - **In Vivo Pharmacodynamic** (Vasoconstrictor) studies
  - **In Vivo Comparative Clinical Endpoint BE** studies
  - **In Silico** Quantitative Methods, Modeling and Simulation



Transdermal Delivery System Products

Generic TDS products

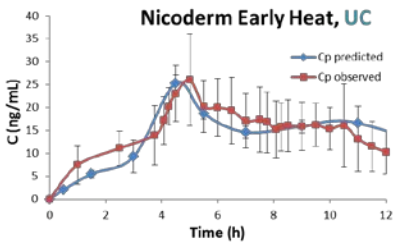
- Compared to the RLD product, a generic TDS may have
  - Different product design
    - Reservoir or Matrix TDS designs
  - Differentiated failure modes related to the product design
    - Leakage (bursting) or cold flow
    - Release liner removal issues
    - Abuse potential
    - Crystallization
    - Heat effects
    - Adhesion
    - Etc.

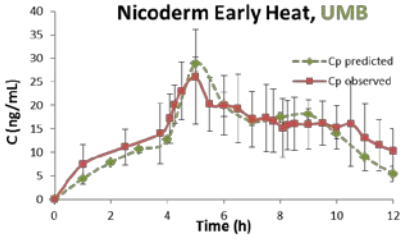
Evaluation of BE and Quality for TDS

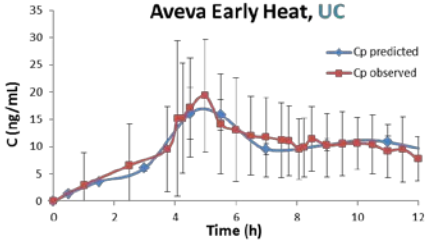
- In Vivo Studies With Which to Demonstrate BE for TDS
  - A comparative BE study with pharmacokinetic endpoints
  - A comparative study of the adhesion performance of the TDS
  - A comparative study of the irritation/sensitization potential of the TDS
- An In Vitro Study to Compare the Effects of Heat on TDS
  - A study evaluating the quality of prospective generic TDS, comparing how heat alters the rate and extent of transdermal drug delivery

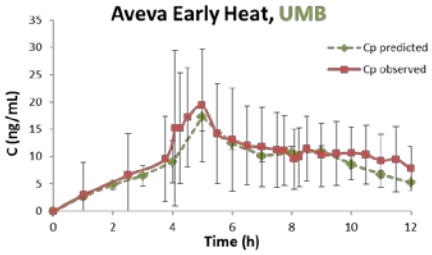
Level A IVIVC/IVIVR for Nicotine TDS

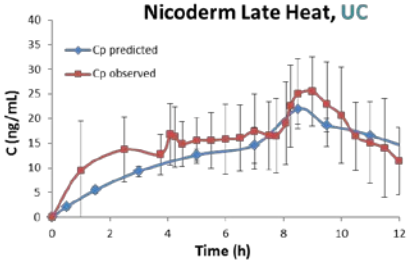
- Predicted In Vivo PK based upon IVPT results

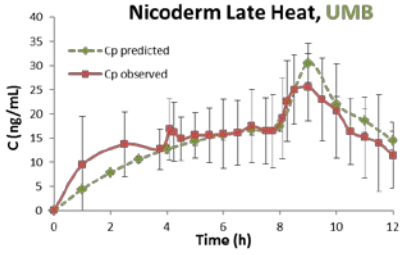


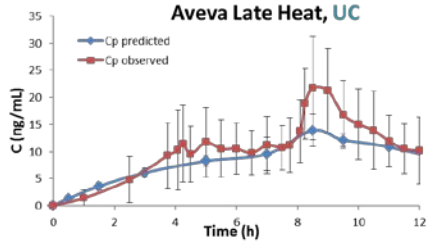


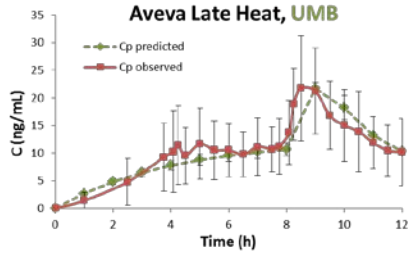












Refer to Shin et al. (2018) In vitro-in vivo correlations for nicotine transdermal delivery systems evaluated by both in vitro skin permeation (IVPT) and in vivo serum pharmacokinetics under the influence of transient heat application. J Control Release. 270: 76-88. (Funded, in part, by FDA through awards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

Ongoing & Future Research Interests

- **In Vitro** Characterization and Prediction of Product Behavior
  - Elucidating the Thermodynamic and Functional/Sensorial Characteristics of Variously Complex and Compositionally Different Topical & Transdermal Products
- **In Vivo** Characterization of Cutaneous Pharmacokinetics
  - Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products by Pharmacokinetic Tomography and/or Dermal Microperfusion/Microdialysis
- **In Vivo** Characterization of Adhesion, Irritation and Sensitization
  - Improving Methodologies for Assessing the Adhesion, Irritation, or Sensitization of Topical and Transdermal Products (Novel Tools, Techniques & Data Analyses)
- **In Silico** Modeling and Simulation to Support Bioequivalence Assessments
  - Developing & Verifying Models Integrate the Product, the Skin & Local Tissues, and the Systemic Circulation to Predict Drug Concentrations at a Site of Action

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