U.S. FOOD & DRUG ADMINISTRATION

CUTANEOUS PHARMACOKINETICS AND PHARMACODYNAMICS FOR THE 21ST CENTURY

7th AGAH Dermatology Product Development Workshop
May 12th, 2017

Sam Raney, Ph.D.
Scientific Lead for Topical and Transdermal Drug Products
Division of Therapeutic Performance, Office of Research and Standards
Office of Generic Drugs, U.S. Food and Drug Administration

Disclaimer

- The views expressed in this presentation do not reflect the official policies of the FDA, or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

Establishing Bioequivalence

- **Foundations of Bioequivalence in the 20th Century**
  - Hatch-Waxman generic drug legislation enacted in 1984
  - Regulatory concepts of bioequivalence and Q1/Q2 sameness
    - Qualitative (Q1) Sameness of formulations
      - Q1 = the **same inactive ingredients**
    - Quantitative (Q2) Sameness of formulations
      - Q2 = the **same amount** (± 5%) of each of the **same inactive ingredients**
  - Acceptable types of bioequivalence evidence established (*please see 21 CFR 320.24 for precise descriptions*)
    - Pharmacokinetic bioequivalence approaches considered to be among the most accurate, sensitive, and reproducible types of evidence with which to demonstrate bioequivalence
    - Pharmacodynamic bioequivalence approaches considered to be relatively less accurate, sensitive, and reproducible

Advancing Bioequivalence

- **Foundations of Bioequivalence in the 21st Century**
  - Generic Drug User Fee Amendments (GDUFA) of 2012
  - Office of Generic Drugs regulatory science research infrastructure developed
  - Simultaneous scientific advances in:
    - Cutaneous pharmacokinetic methods
    - Semisolid drug product characterization
    - Concept of Q3 similarity (the same amount (± 5%) of each of the same inactive ingredients, with the same arrangement of matter)
  - Exploration of local/regional pharmacokinetics and physiologically-based pharmacokinetic (PBPK) models
  - Exploration of in vitro bioequivalence approaches and the concept of "Bioequivalence-by-Design"

U.S. FDA Office of Generic Drugs

- **Mission** of the Office of Generic Drugs is to make **high quality**, **affordable** medicines **available** to the public.

- **GDUFA** Regulatory Research Priorities include:
  - Equivalence of complex products (e.g. topical products)
  - Equivalence of locally-acting products (e.g. topical products)

- **Vision** to support our commitments:
  - Product Quality Characterization (**high quality medicines**)
  - Efficient Bioequivalence(BE) Standards (**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" bioequivalence standards

Overall Drug Products [1]

89% of prescriptions dispensed in 2015 were for generics

- Efficient **Pharmacokinetics (PK)-based** methods are available

Topical Drug Products [2]

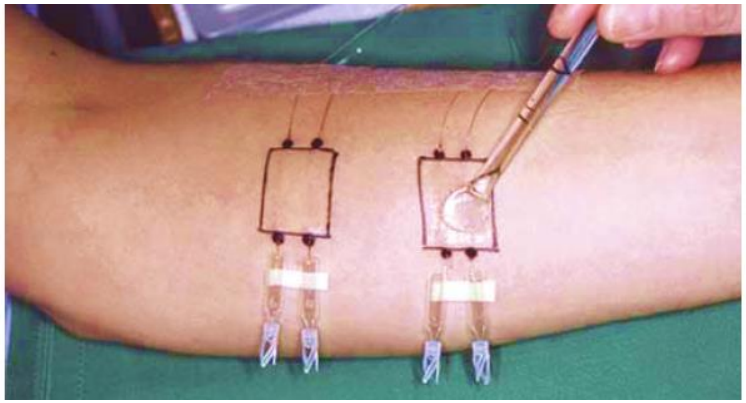
Relatively fewer topical products have generics

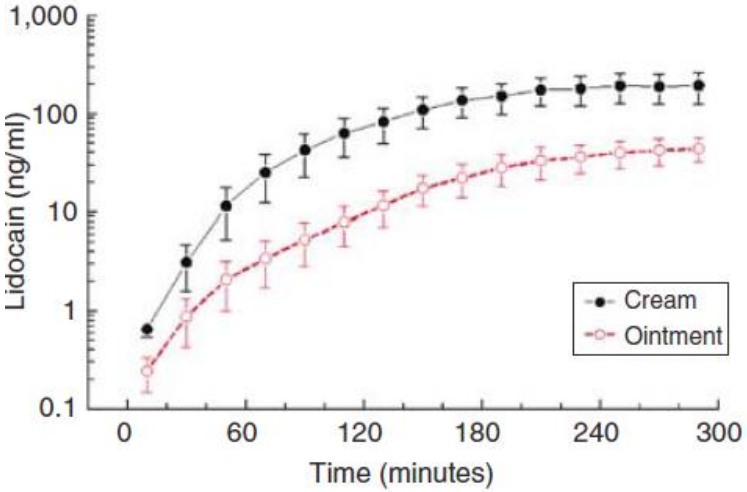
- Efficient **In Vitro Bioequivalence** methods may be useful
  - Particularly for generic products that are compositionally, physically and structurally similar to a Reference Listed Drug (RLD) product
- Efficient **Pharmacokinetics (PK)-based** methods may be useful
  - Particularly for generic products that may not be compositionally, physically and structurally similar to a RLD product

[1] GPhA 2016 Generic Drug Savings & Access in the United States Report

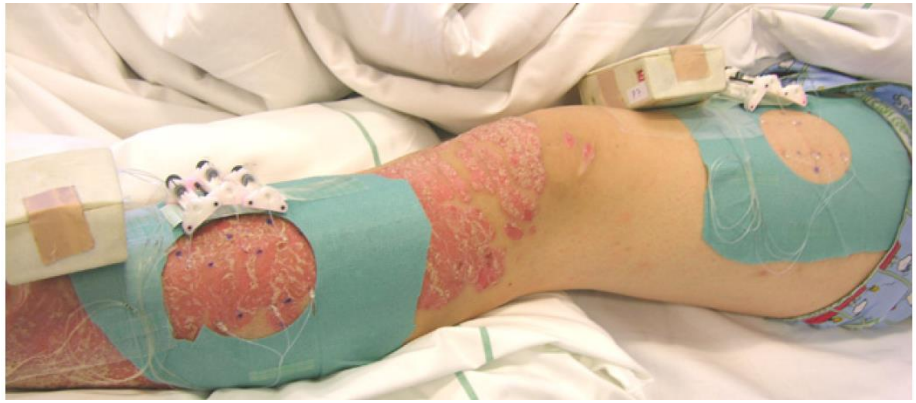
[2] FDA Office of Generic Drugs Topical & Transdermal Products Database

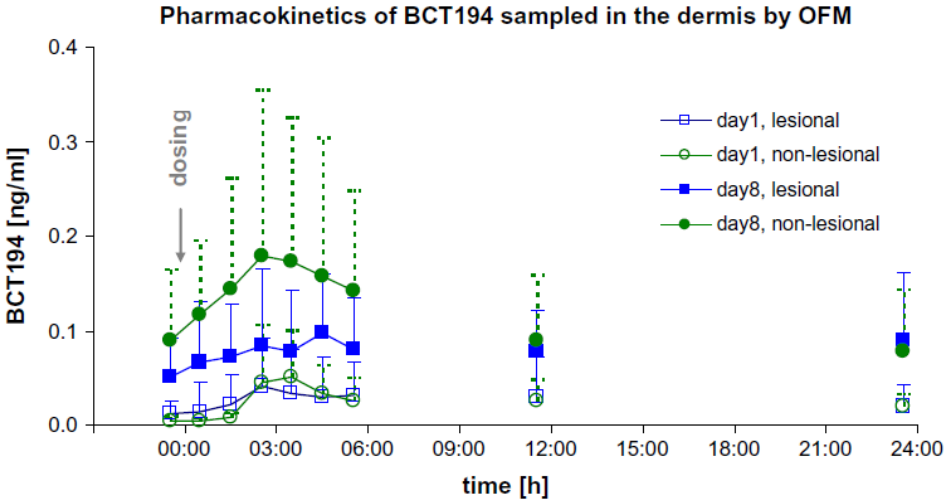
In Vivo Cutaneous Pharmacokinetics





Source: Benfeldt et al. (2007) **Bioequivalence of Topical Formulations in Humans: Evaluation by Dermal Microdialysis Sampling and the Dermatopharmacokinetic Method**. Journal of Investigative Dermatology (2007) 127, 170–178. doi:10.1038/sj.jid.5700495

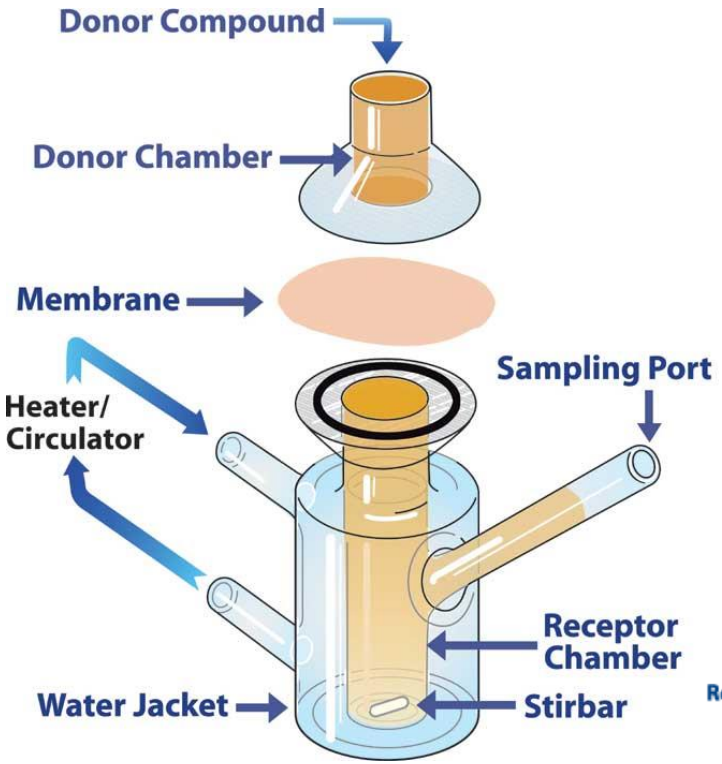


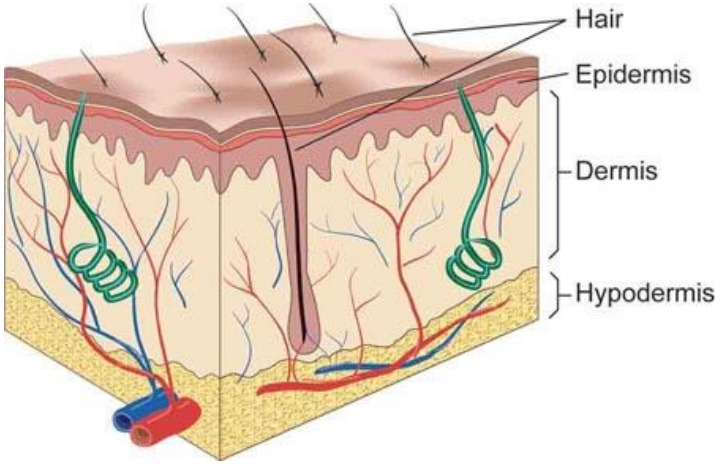


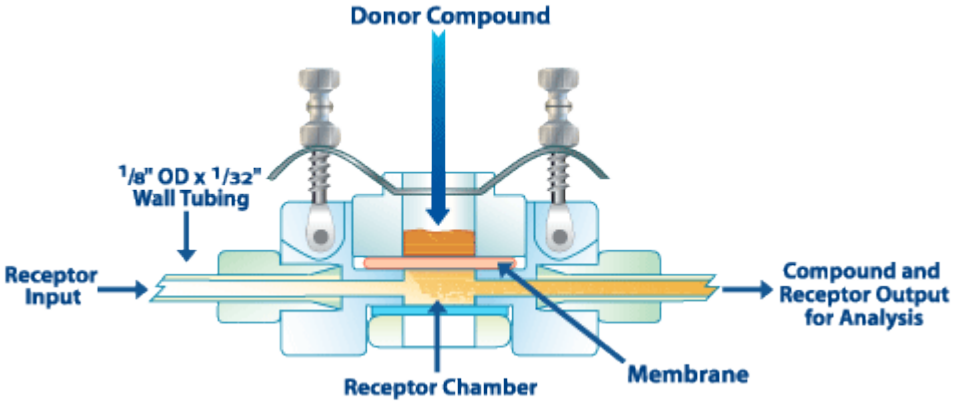
Source: Bodenlenz et al. (2012) **Dermal PK/PD of a lipophilic topical drug in psoriatic patients by continuous intradermal membrane-free sampling**. European Journal of Pharmaceutics and Biopharmaceutics 81 (2012) 635–641. doi:10.1016/j.ejpb.2012.04.009

In Vitro Cutaneous Pharmacokinetics

- IVPT (In Vitro Permeation Test)

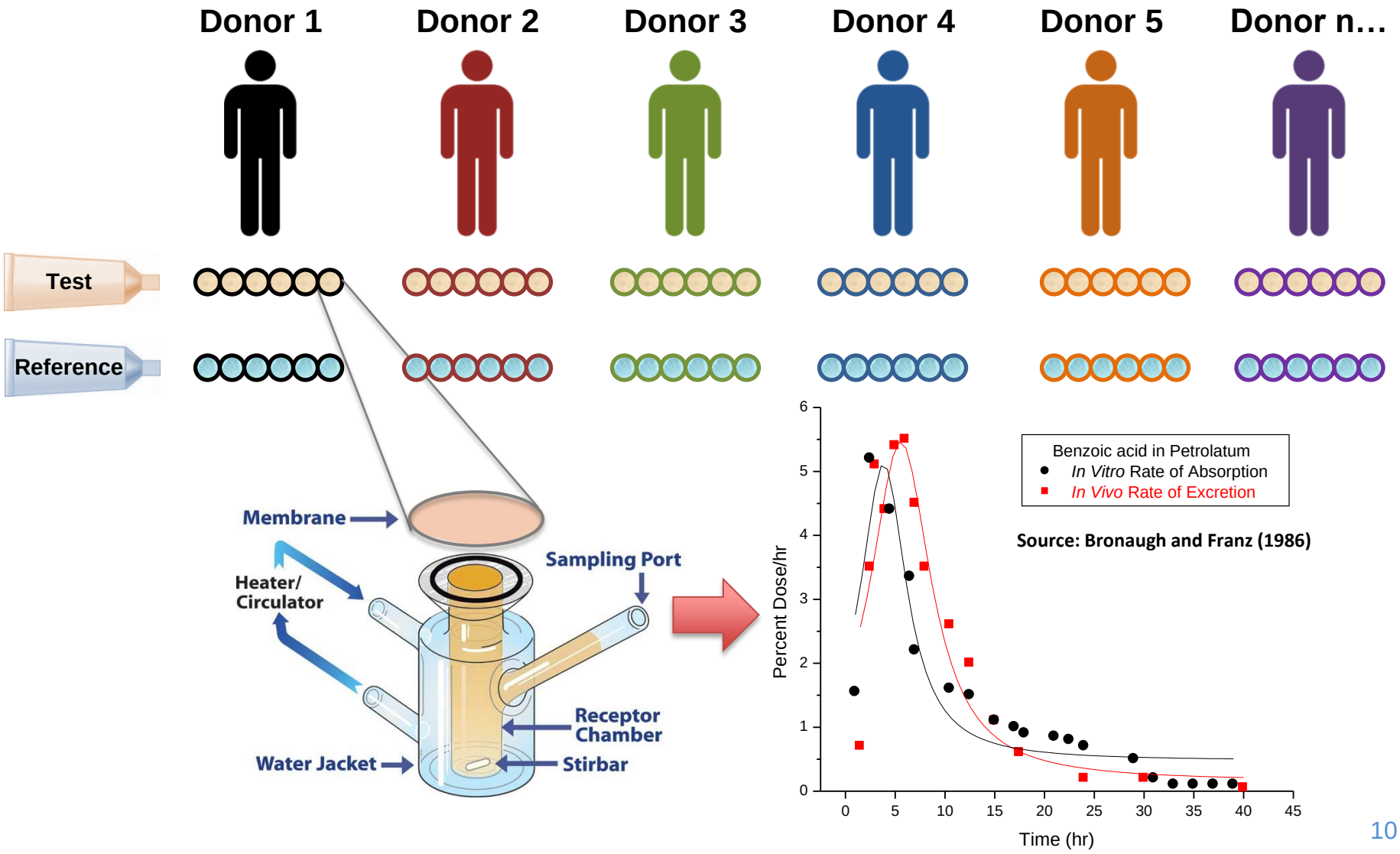






Cell images courtesy of PermeGear

IVPT Study Design



IVPT: *In Vitro In Vivo* Correlation

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

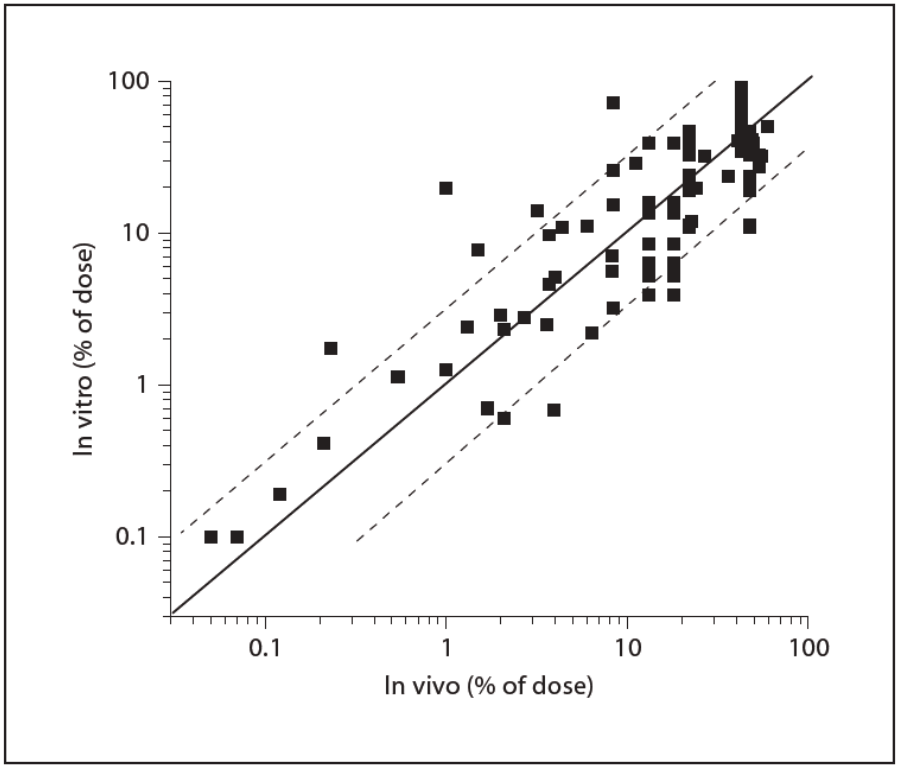


Fig. 1. IVIV ratios of total absorption for all 92 data sets plotted on log-log scale. The IVIV ratios ranged from 0.18 to 19.7, with an overall mean of 1.6. Solid line: ideal 1:1 correlation. Dashed lines: ±3-fold difference from ideal.

IVPT: *In Vitro In Vivo* Correlation

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

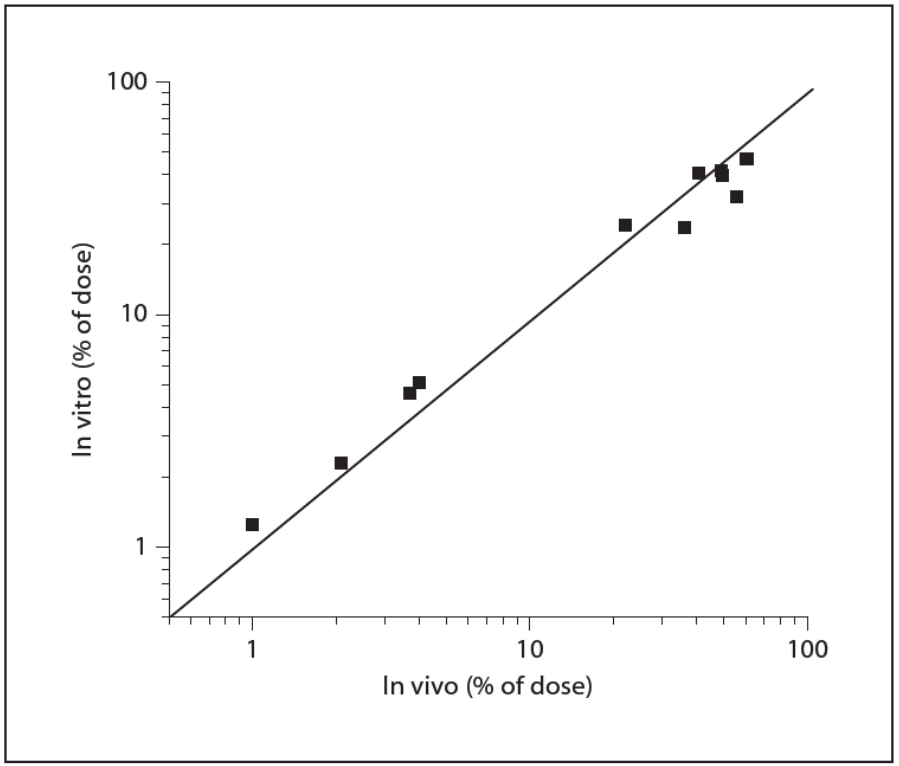


Fig. 2. IVIV ratios of total absorption for 11 fully harmonized data sets plotted on log-log scale. The IVIV ratios ranged from 0.58 to 1.28, with an overall mean of 0.96. Line: ideal 1:1 correlation.

Developing In Vitro BE Standards

- **A Rational Framework for In Vitro Topical BE**
  - **Q1/Q2** sameness (of inactive ingredient composition)
  - **Q3** tests included as relevant to the nature of the product
  - **IVRT** (In Vitro Release Test) also included for moderately complex products
  - **IVPT** (In Vitro Permeation Test) or another bio-relevant assay included for the more complex drug products

- **May be appropriate for certain topical products**

In Vitro Topical BE

- **Q1/Q2 Sameness** (of inactive ingredient composition)

  Can mitigate the risk of known failure modes related to:

  - Irritation and sensitization
  - Formulation interaction with diseased skin
  - Drug stability, solubility, etc.
  - Vehicle (placebo) contribution to efficacy

In Vitro Topical BE

- **Q3 Similarity** (physical, chemical & structural similarity)

  Can mitigate the risk of potential failure modes related to:

  - Slight differences among Q1/Q2 formulations
  - Differences in pH that may sting or irritate (broken) skin
  - Differences in the polymorphic form of the drug
  - Differences in rheology that may 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

In Vitro Topical BE

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

  Can mitigate the risk of unknown failure modes related to:

  - Differences in Q1/Q2 sameness (± 5% tolerances)
  - Differences in Q3 similarity
  - Differences that may not be identified by Q3

- IVRT is a compendial method with established statistical analyses which can be sensitive and discriminating (but no IVIVC is expected)

In Vitro Topical BE

- **IVPT (In Vitro Permeation Test)**

  Can mitigate the risk of unknown failure modes related to:

  - Differences in Q1/Q2 sameness (± 5% tolerances)
  - Differences in Q3 similarity
  - Differences that may not be identified by IVRT or Q3 tests

- IVPT can be a sensitive, discriminating indicator of relative bioavailability, and it can exhibit IVIVC

Statistical Analysis of Topical BE

- **Statistical Analysis of BE based upon PK endpoints**
  - The approach for Scaled Average Bio-Equivalence (SABE) analysis of highly variable drugs may be adapted for the replicate design of the study comparing the topical products
  - A mixed criterion, accompanied by a point estimate constraint, may use the within-reference variability (σ_{WR}) as a cutoff point for BE analysis:
    - When $\sigma_{WR} \leq 0.294$, Average Bio-Equivalence (ABE) may be used
    - When $\sigma_{WR} > 0.294$, Scaled ABE (SABE) may be used
  - Potentially applicable to cutaneous PK endpoints
    - In vitro (J_{max} and AUC) for IVPT studies
    - In vivo (C_{max} and AUC) for dermal microdialysis/microperfusion studies

Research on Acyclovir Cream, 5%

- Positive and Negative Controls for Bioequivalence

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

Comprehensive Research Strategy

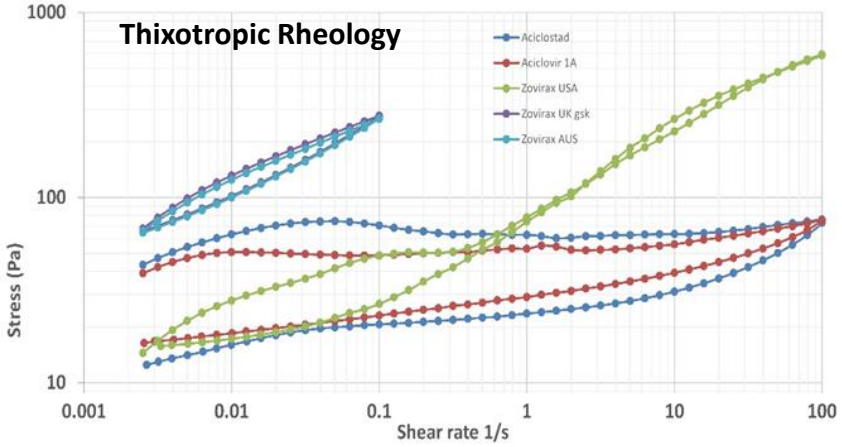
- **Q3 Product Quality Characterization**
  - FDA/CDER/OTS/DPQR (USA) — Q3 Tests
  - University of Mississippi (USA) — Q3 Tests
  - University of South Australia (and Germany) — Q3 Tests
- **In Vitro Release Test (IVRT)**
  - FDA/CDER/OTS/DPQR (USA) — IVRT
  - Joanneum Research (Austria) — IVRT
- **Cutaneous 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 (U.K.) — Tape Stripping

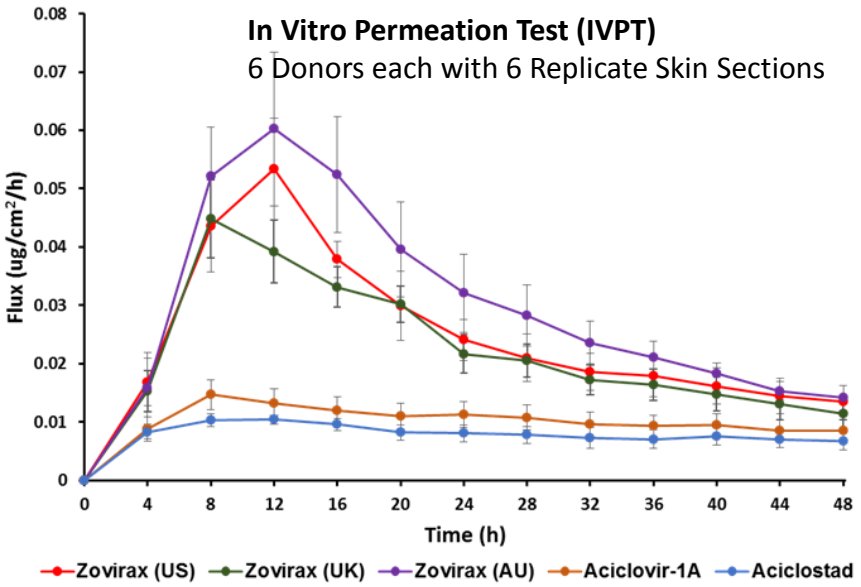
Q3 Characterization

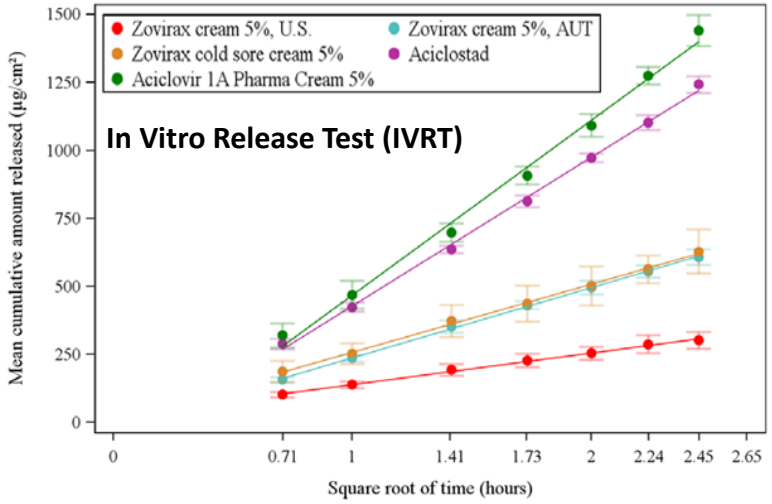
- Characterizing Complexity & Critical Quality Attributes
  - Phase States and the Arrangement of Matter (globules/lamella)
  - Drug Amounts in Dissolved/Undissolved States in Drug Product
  - Drug Amount in Aqueous Phase
  - Drug Particle Size Distribution
  - Drug Polymorphic State
  - Drug Crystalline Habit
  - Texture Analysis
  - Water Activity
  - Drying Rate
  - Rheology
  - Density
  - pH
  - Etc.

Orthogonal In Vitro Testing Approach

	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



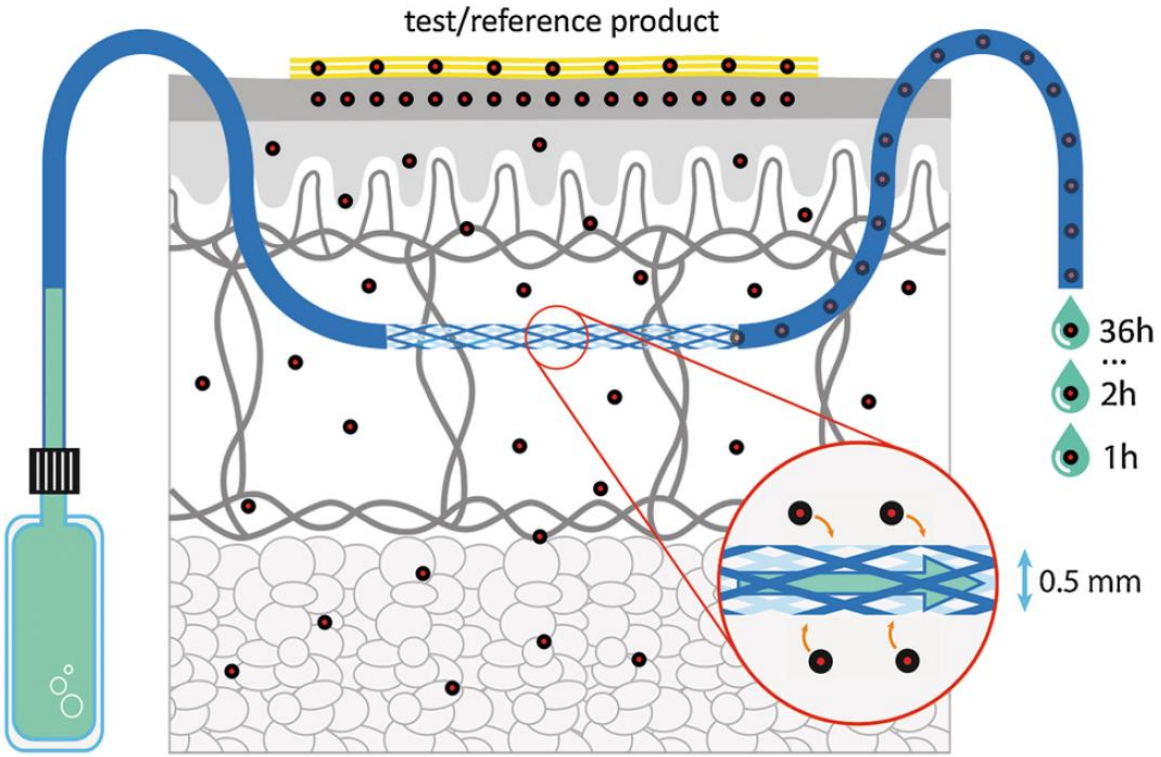


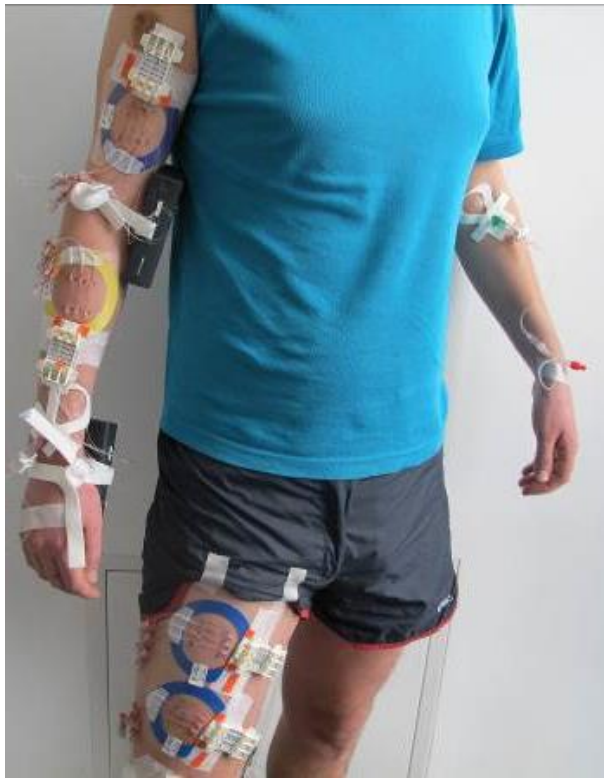


Data provided courtesy of Prof. Narasimha Murthy & Dr. Frank Sinner

In Vivo Cutaneous Pharmacokinetics

- Dermal Open Flow Microperfusion (dOFM)

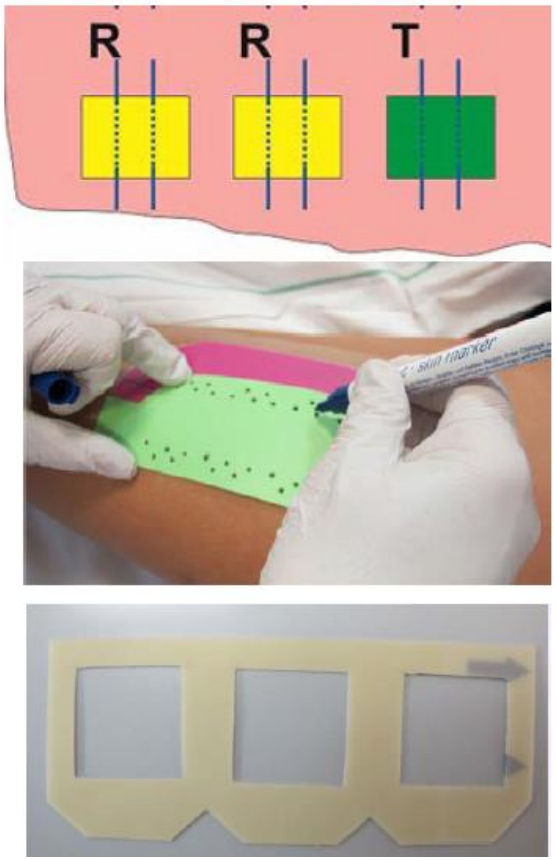


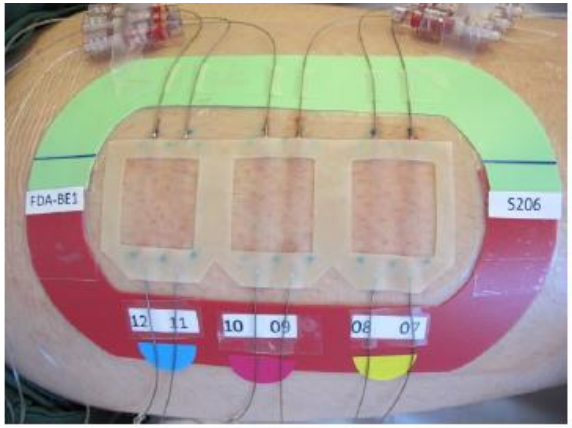


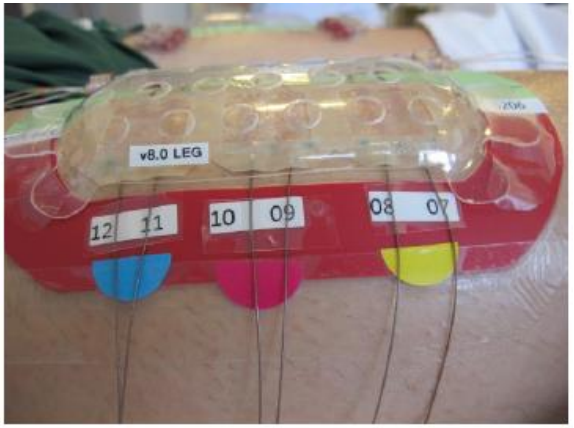
Images courtesy of Joanneum Research

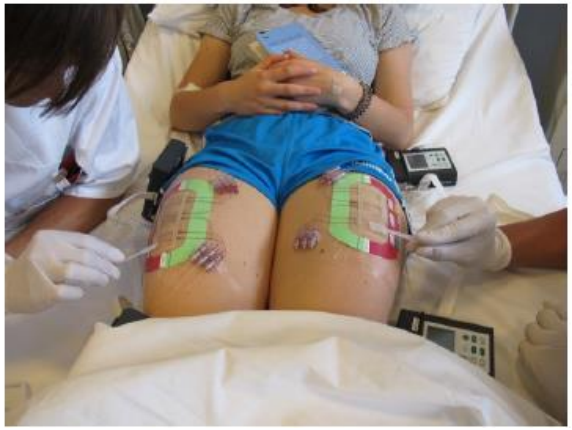
In Vivo Cutaneous Pharmacokinetics

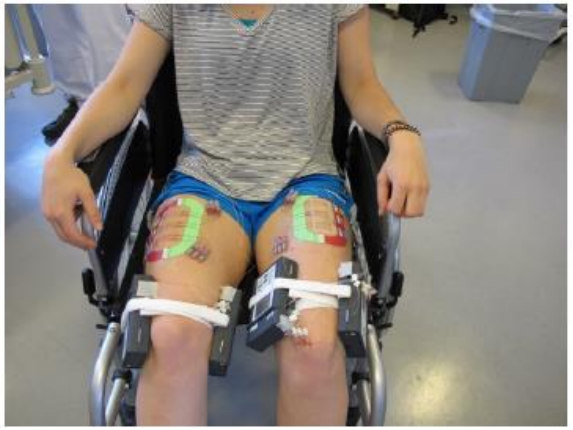
- Dermal Open Flow Microperfusion (dOFM)







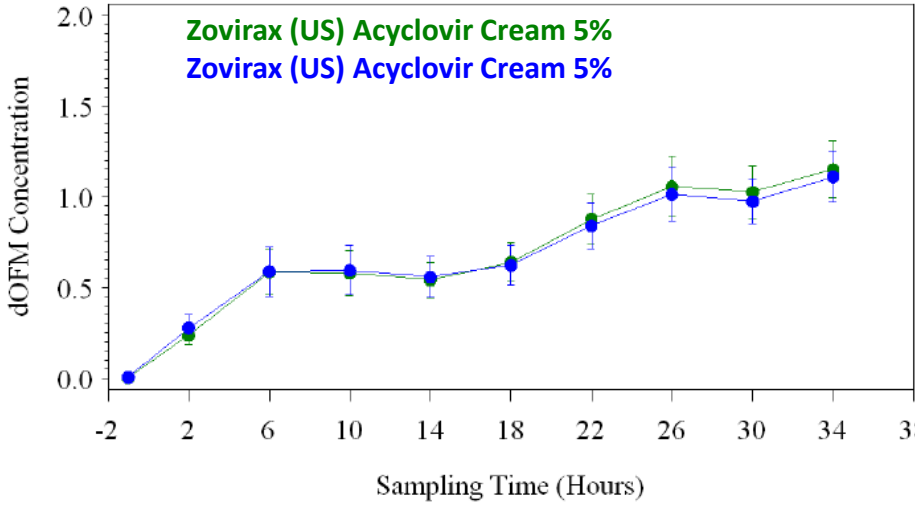


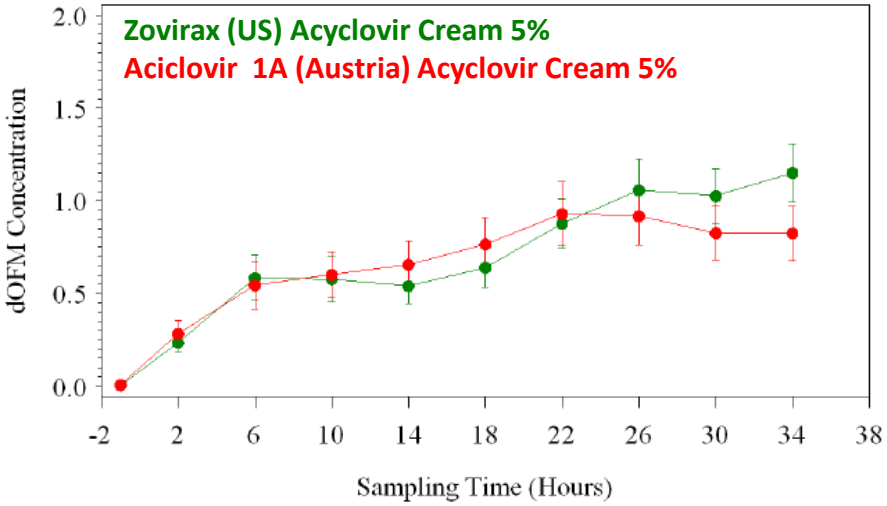


Images courtesy of Joanneum Research

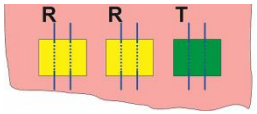
In Vivo Bioavailability/Bioequivalence

- Dermal Pharmacokinetics by dOFM (20 subjects)





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%]

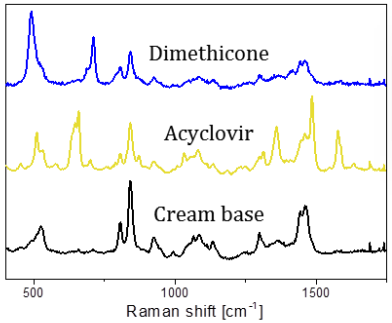
JOANNEUM RESEARCH HEALTH

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

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

  Prof. Michael Roberts FDA Award U01-FD005226



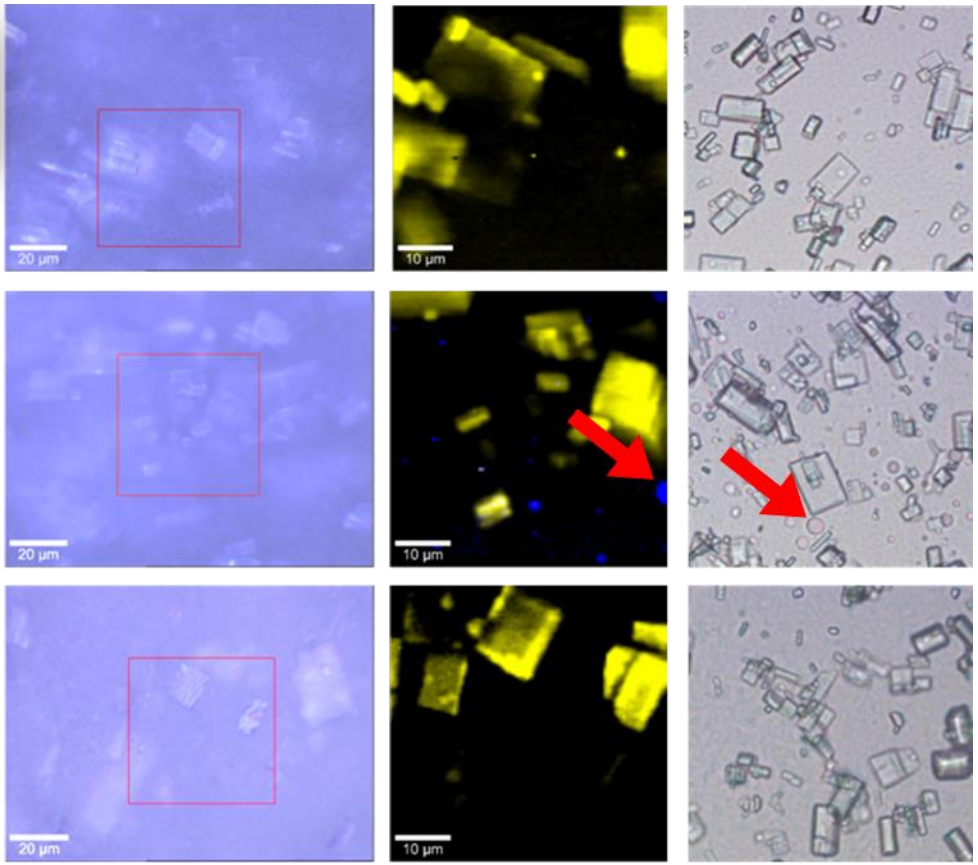
Zovirax® UK
Tube

University of South Australia

UNIVERSITÄT DES SAARLANDES

Zovirax® UK
Pump

Zovirax® UK
Pump
(from inside container)

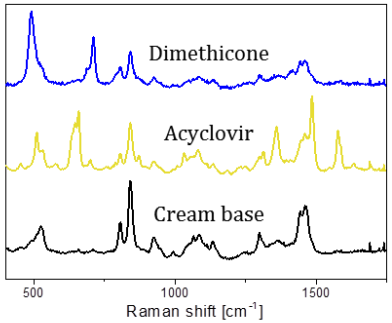


Data provided courtesy of Prof. Michael Roberts & Prof. Maike Windbergs

Influence of Dispensing Stress on Q3

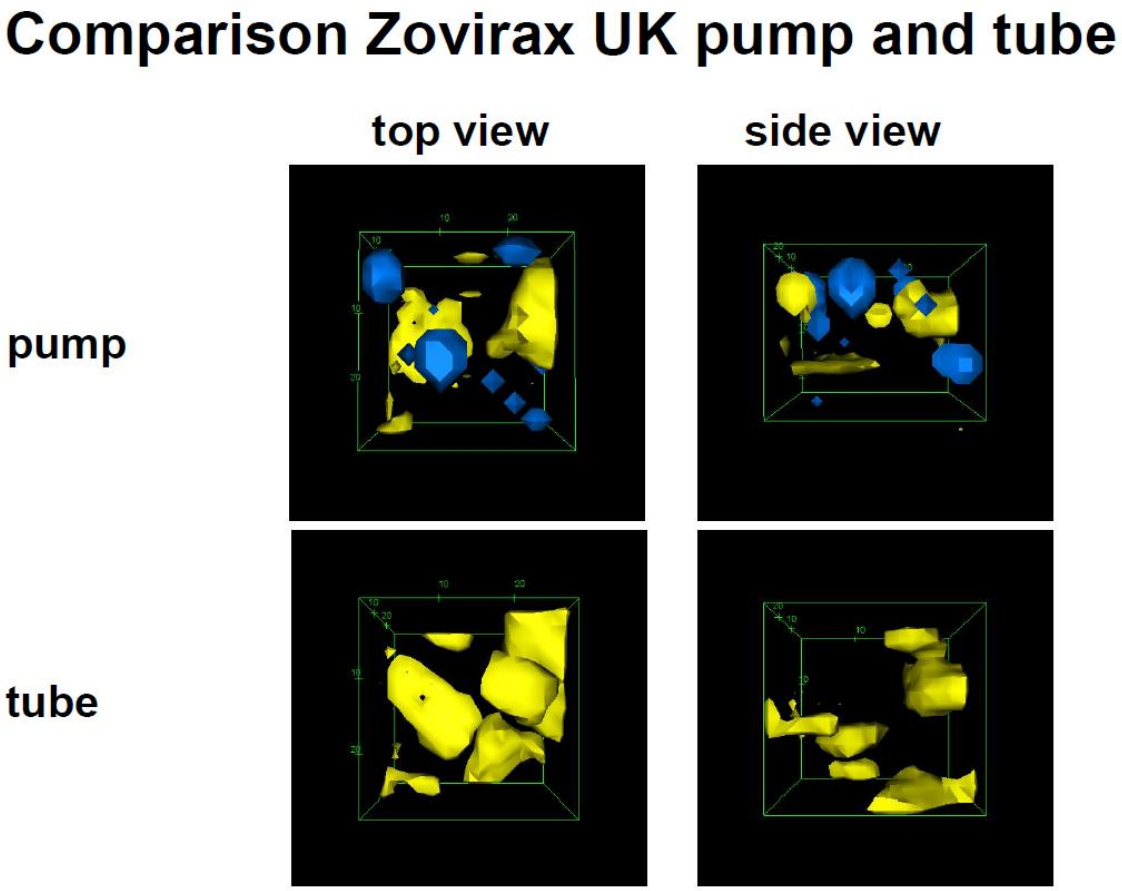
- Influence of Dose Dispensing on Product Quality

  Prof. Michael Roberts FDA Award U01-FD005226



University of South Australia

UNIVERSITÄT DES SAARLANDES



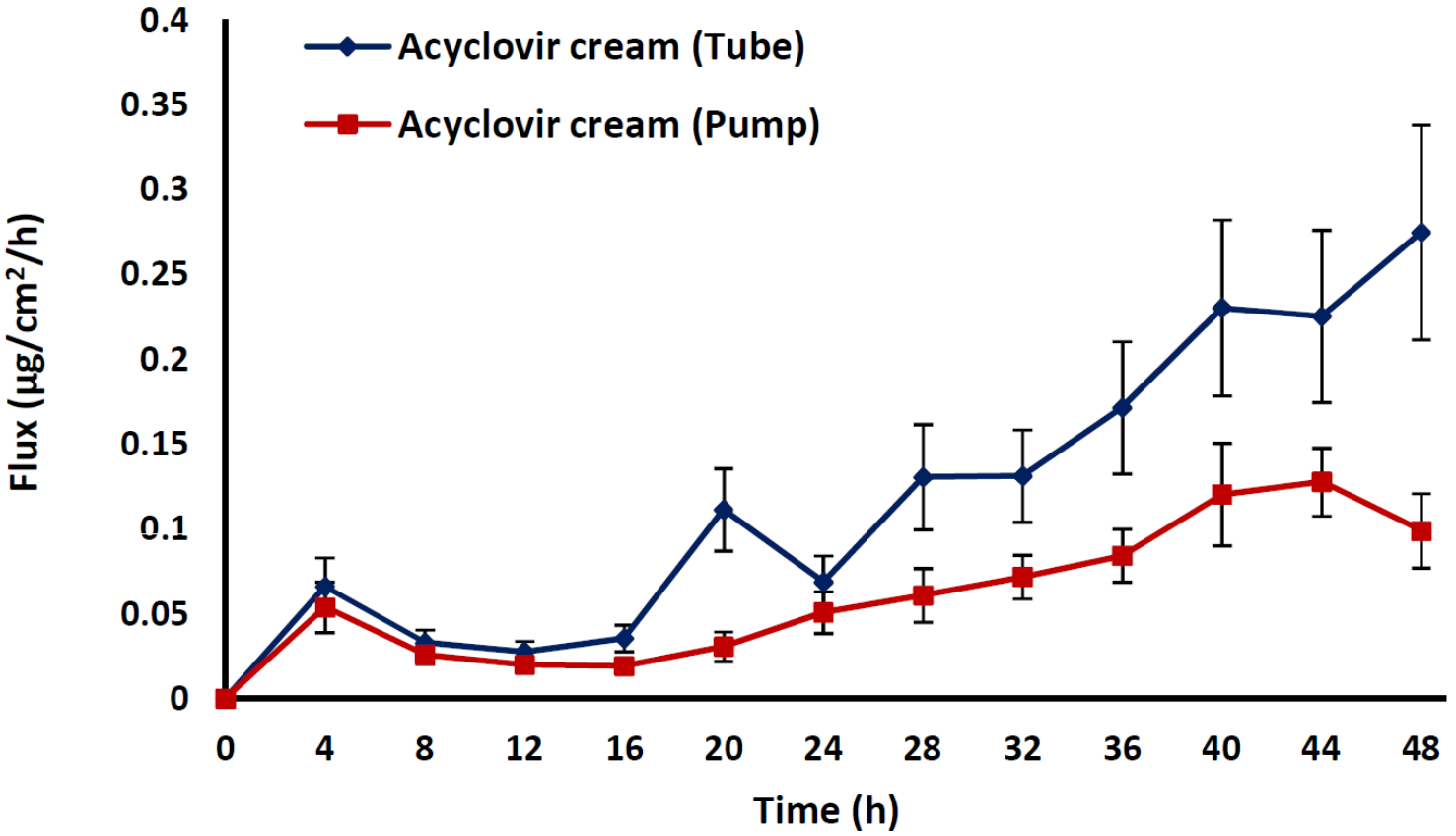
Data provided courtesy of Prof. Michael Roberts & Prof. Maike Windbergs

Influence of Dispensing Stress on Q3

- Influence of Dose Dispensing on Product Quality

  Prof. Michael Roberts FDA Award U01-FD005226

University of South Australia



Data provided courtesy of Prof. Michael Roberts

Summary: Acyclovir Cream Research

- Developed several orthogonal Q3 tests
- Characterized the complexity of Acyclovir cream
- Identified potential CQAs for Acyclovir cream
- Correlated Q3 attributes with IVPT (In Vitro BE)
- Correlated Q3 attributes with dOFM (In Vivo BE)
- Corroborated Q3 test results (at multiple labs)
- Corroborated IVPT results (at multiple labs)
- Developed insights that may be applicable to other topical semisolid dosage forms

The Future

- Ongoing research with other dermatological products
  - Different active and inactive ingredients
  - Different dosage forms
  - Different routes of administration
    - Topical
    - Transdermal
- Further exploration of Q3 attributes and patient/caregiver perceptions of product quality
- Further exploration of dermal pharmacokinetics in vivo by independent research groups
  - Continuous dermal Open Flow Microperfusion
  - Continuous and intermittent dermal microdialysis

Acknowledgements

FDA Office of Generic Drugs (ORS)

- Priyanka Ghosh, PhD
- Bryan Newman, PhD
- Yi Zhang, PhD
- Kimberly Witzmann, MD
- Xiaohui (Jeff) Jiang, PhD
- Markham Luke, MD, PhD
- Robert Lionberger, PhD

Research Collaborators

Funding for four projects was made possible, in part, by the FDA through:

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

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

GDUFA Award U01FD00**4947**
- Audra Stinchcomb, PhD

GDUFA Award U01FD00**4946**
- Frank Sinner, PhD

FDA Center for Drug Evaluation & Research

- 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)

FDA CDER OGD (Other Offices)

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION