Evaluation of Cutaneous Pharmacokinetics The Past, The Present, and The Future

Photonics West 2021 BIOS

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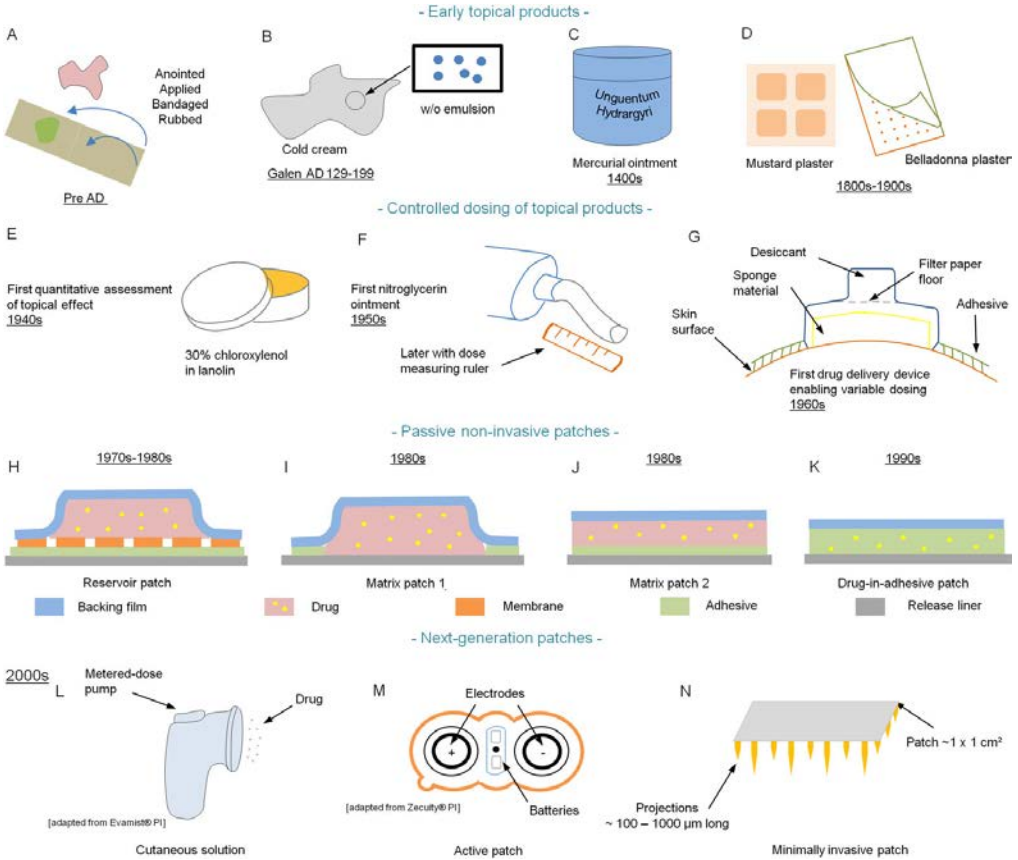
Disclaimer

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

Learning Objectives

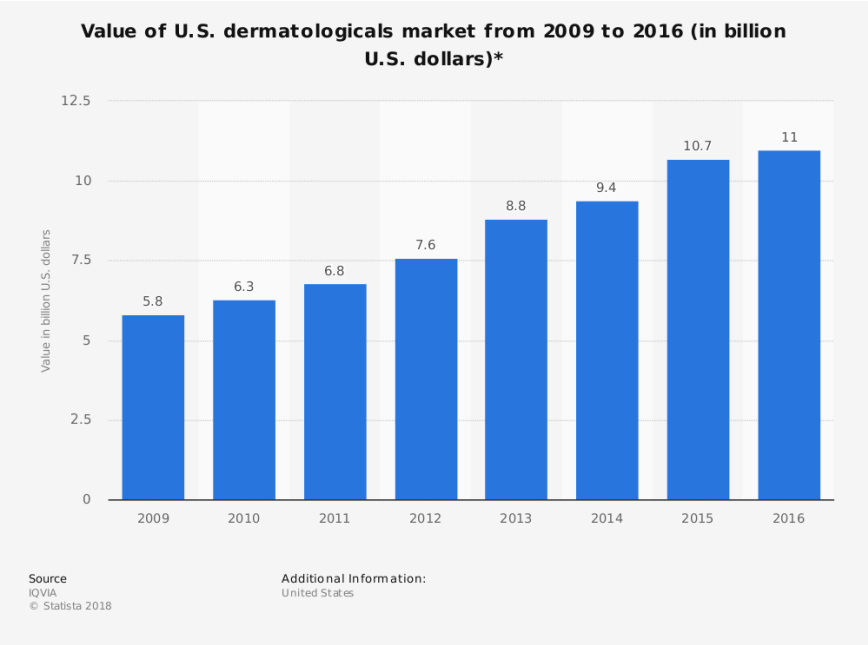
- Understand how cutaneous pharmacokinetic (PK) techniques can support topical drug development
- The landscape of cutaneous pharmacokinetics
- Utilization of imaging-based techniques to facilitate drug development

Dermatological Drug Products



Pastore MN, Kalia YN, Horstmann M, Roberts MS. **Transdermal patches: history, development and pharmacology**. Br J Pharmacol. 2015 May;172(9):2179-209.

Dermatological Drug Products



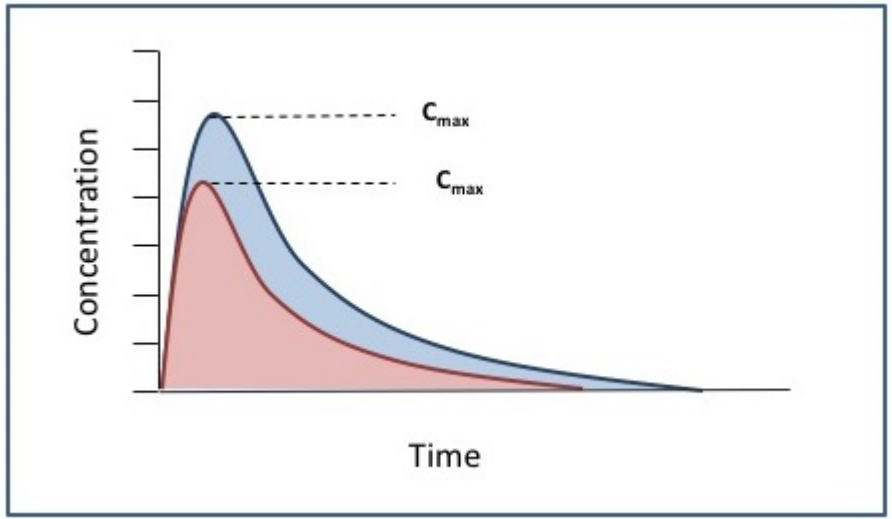
https://brandongaille.com/23-dermatology-industry-statistics-and-trends/
https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

The Promise of Generic Drugs

- Generic medicines use the same active ingredients as reference product and work the same way, so they have the same risks and benefits as the brand-name medicines
- Generic drug products can be substituted for the reference product or for other generics for that reference product
- ….And they can cost a lot less money

https://www.fda.gov/drugs/generic-drugs/generic-drug-facts

Systemically Acting Drug Products



- Reference and generic products can have allowable differences in formulation
- Bioavailability is assessed and bioequivalence is typically established by showing that a generic drug product and the reference product are similar in terms of their concentrations over time at the site of action (e.g., in the blood)

https://www.fda.gov/drugs/regulatory-science-action/impact-story-developing-new-ways-evaluate-bioequivalence-topical-drugs

Locally Acting Drug 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

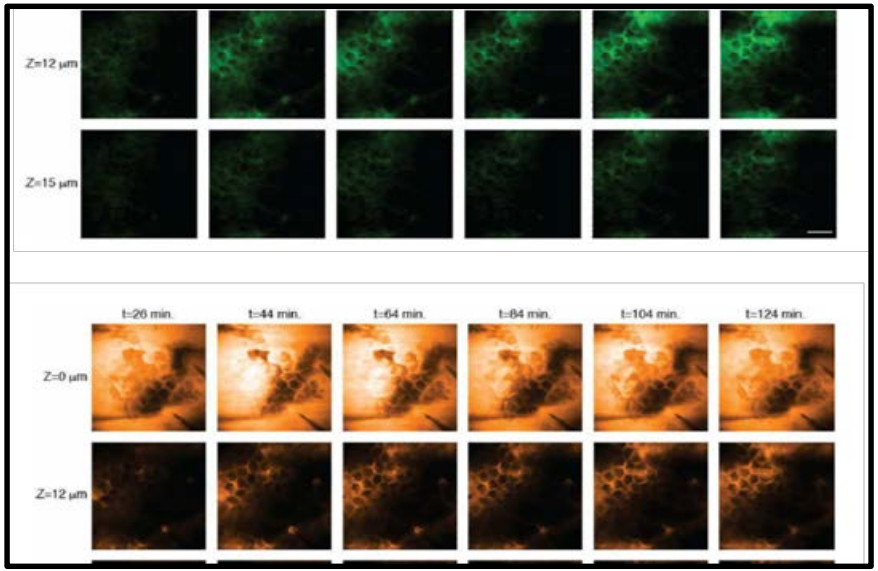
Bioavailability of Locally Acting Product

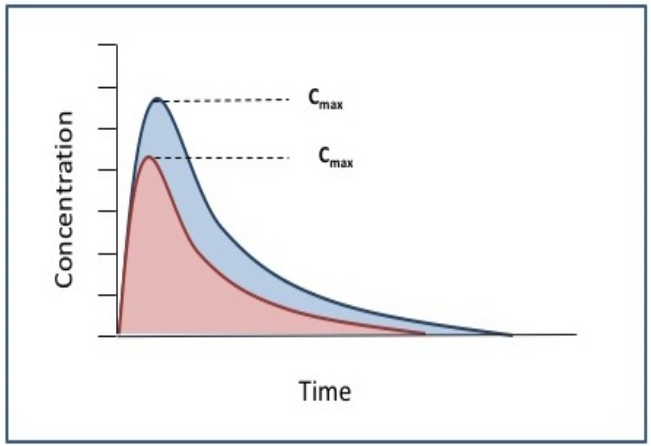
A 2003 addition to the Federal Food, Drug, and Cosmetic Act at Section 505(j)(8)(A)(ii) indicates that–

> "For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action."

Potential of Cutaneous PK

Can we develop **cutaneous PK** based methods to quantify drugs in **“real time”** at or near the **site of action** in the skin?



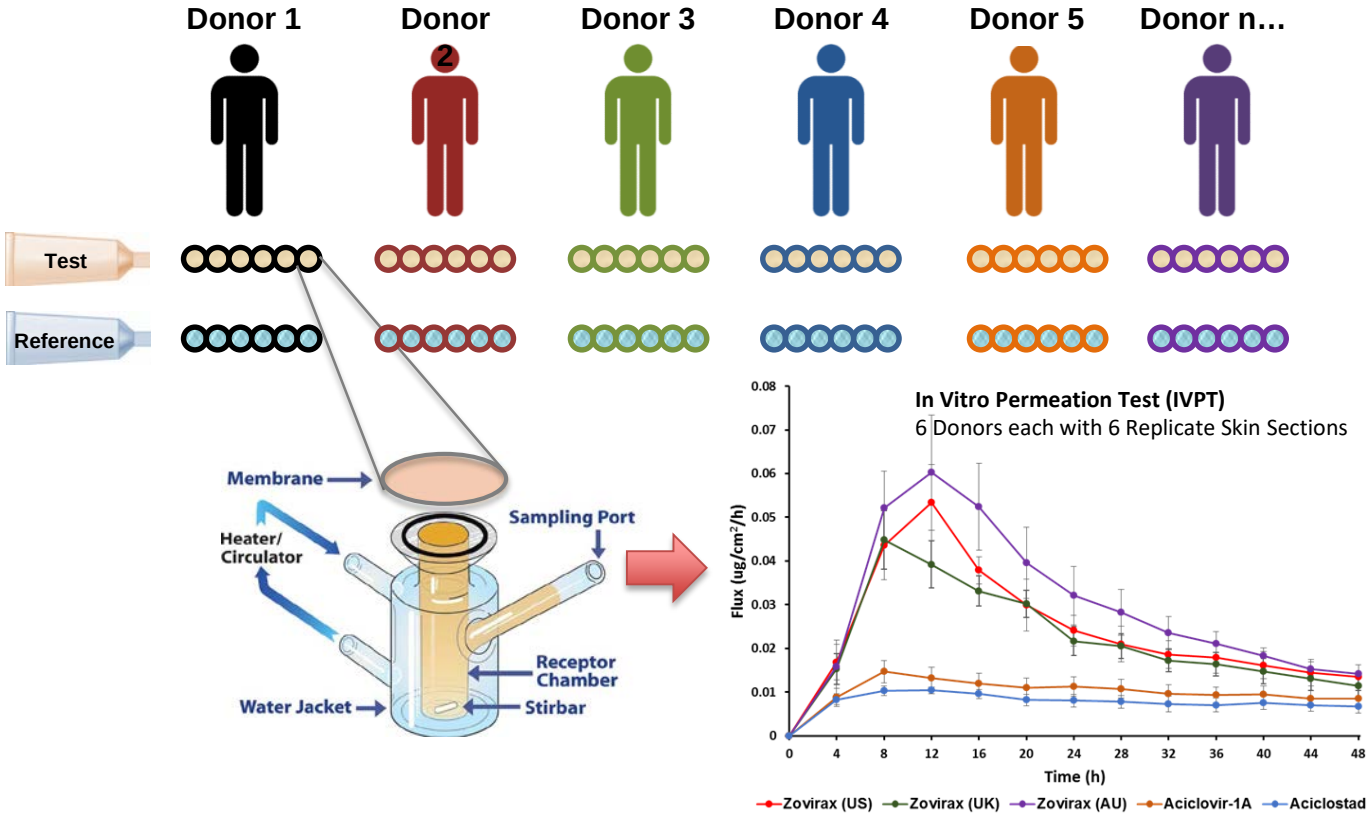


Saar Brian G. , Contreras-Rojas L. Rodrigo , Xie X. Sunney , and Guy Richard H. **Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy** Molecular Pharmaceutics **2011** 8 (3), 969-975

Cutaneous PK Techniques

- Techniques explored in the past
  - **In Vivo** Stratum Corneum Sampling Studies
    - Tapestripping “Dermatopharmacokinetics” (DPK)
- Techniques that are currently being developed/utilized
  - **In Vitro** Cutaneous Pharmacokinetic Studies
    - In vitro Permeation Testing (IVPT)
  - **In Vivo** Cutaneous Pharmacokinetic Studies
    - Dermal Open Flow Microperfusion (dOFM)
    - Dermal Microdialysis (dMD)
    - Systemic Pharmacokinetics (Limited utility)
- Techniques that we hope to develop
  - **In Vivo** Cutaneous Pharmacokinetic Studies
    - Epidermal and/or Dermal Pharmacokinetic Tomography e.g. Raman based methods

In Vitro Cutaneous PK

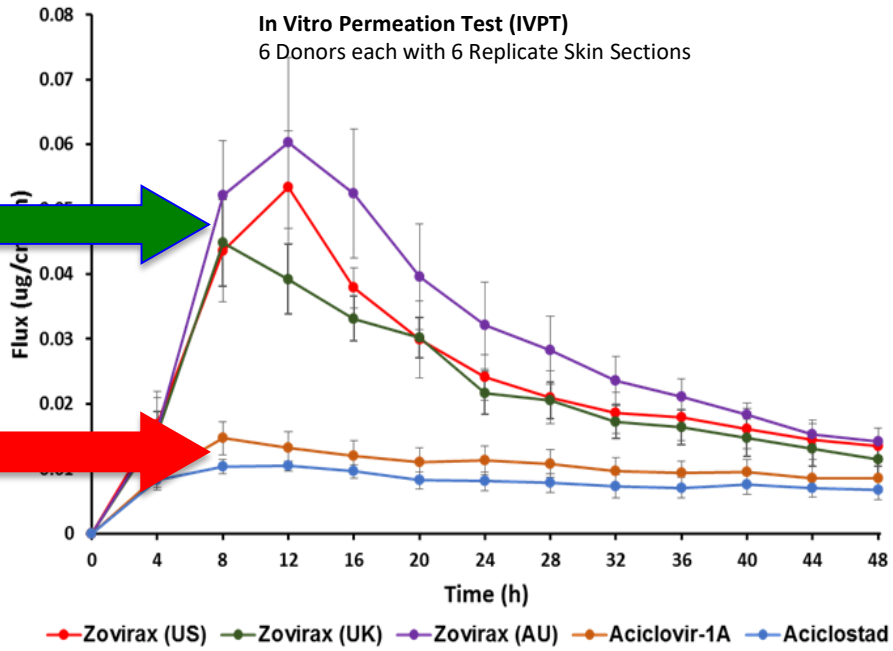


In Vitro Cutaneous PK

In Vitro Cutaneous PK Study

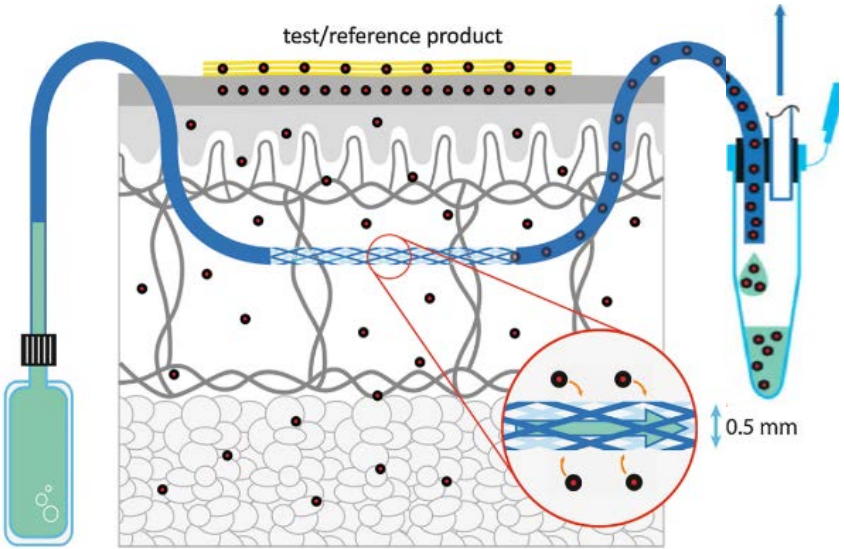
	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	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

In Vitro Permeation Test (IVPT)
6 Donors each with 6 Replicate Skin Sections



In Vivo Cutaneous PK

- Microdialysis (dMD) and Open Flow Microperfusion (dOFM) directly measure the in vivo rate and extent of drug bioavailability at/near the site of action in the skin.



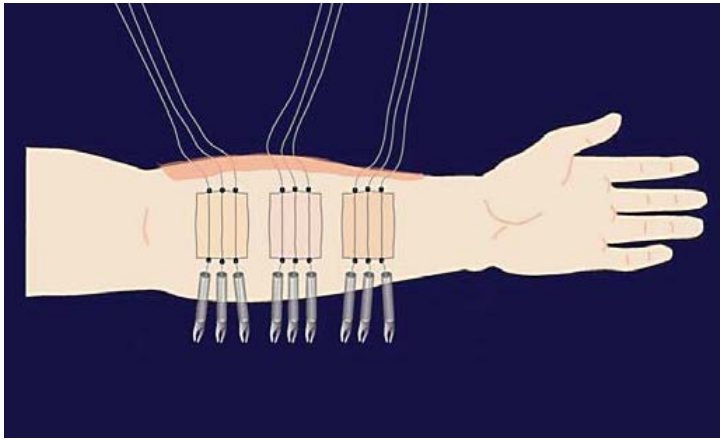


Image provided courtesy of Dr. Frank Sinner, Joanneum Research

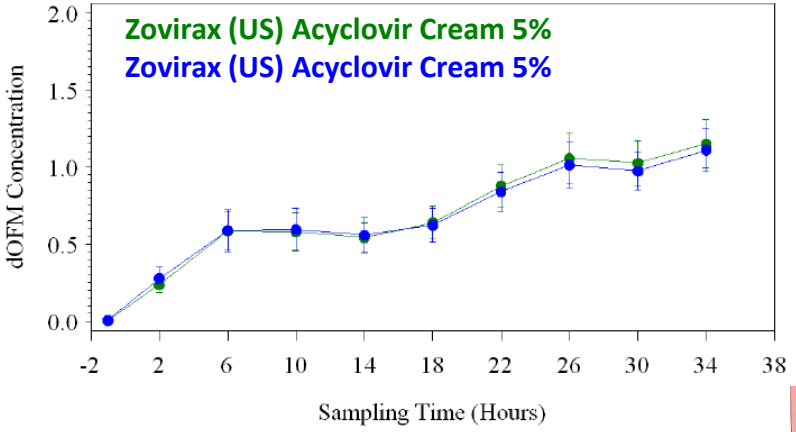
Skin Pharmacol Physiol 2011;24:44–53

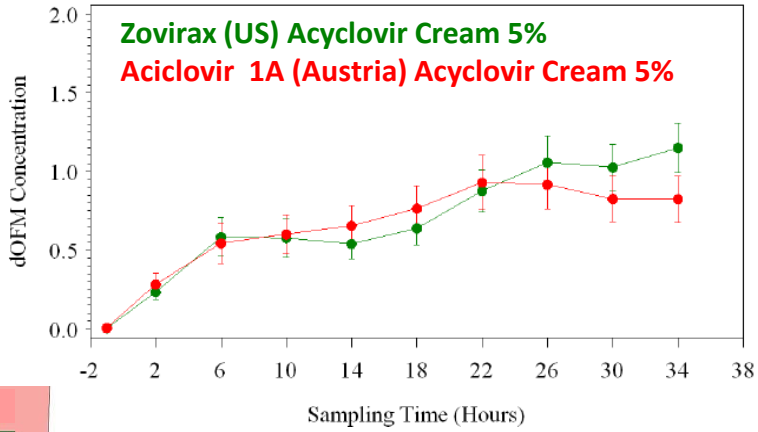
In Vivo Cutaneous PK

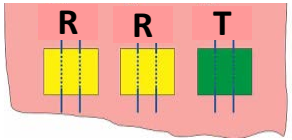
Historical limitations and mitigation strategies

- Analytical limitations/High variability in the data
- Study controls: Application site, dose, application technique, probe depth, barrier integrity, flow rates
- Development of data analysis strategies
- Development method validation strategies

In Vivo Cutaneous PK







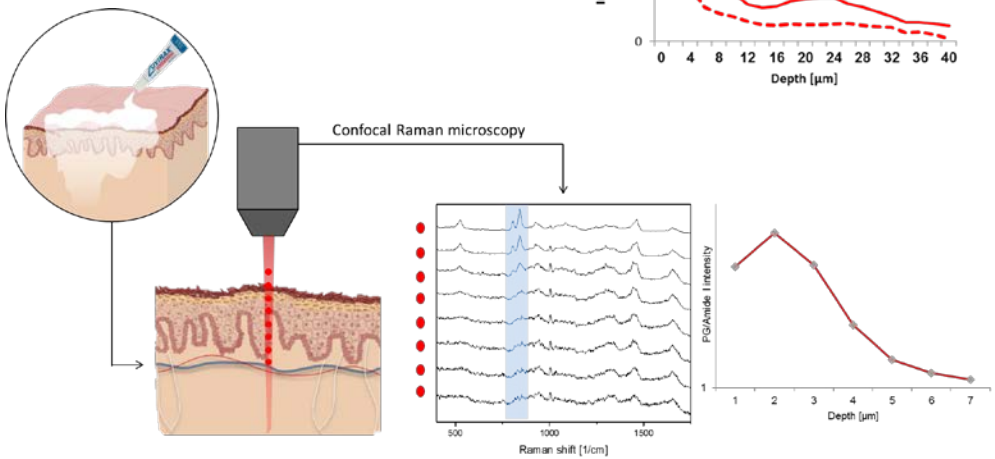
Outcome variable	$CI_{90\%}$	BE-limits	BE
$\log(AUC_{0\text{-}36h})$	[-0.148 ; 0.162] or [86.2 % ; 117.5 %]	[-0.223 ; 0.223] or [80% ; 125%]	passed
$\log(C_{max})$	[-0.155 ; 0.190] or [85.7 % ; 120.9%]		passed

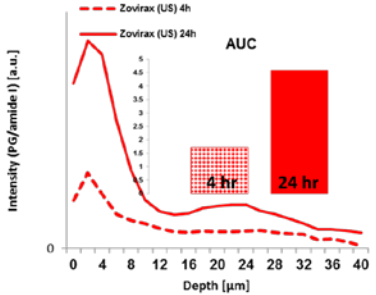
Outcome variable	$CI_{90\%}$	BE-limits	BE
$\log(AUC_{0\text{-}36h})$	[-0.369 ; 0.050] or [69.1 % ; 105.2 %]	[-0.223 ; 0.223] or [80% ; 125%]	x Failed
$\log(C_{max})$	[-0.498 ; 0.022] or [60.8 % ; 102.2%]		x Failed

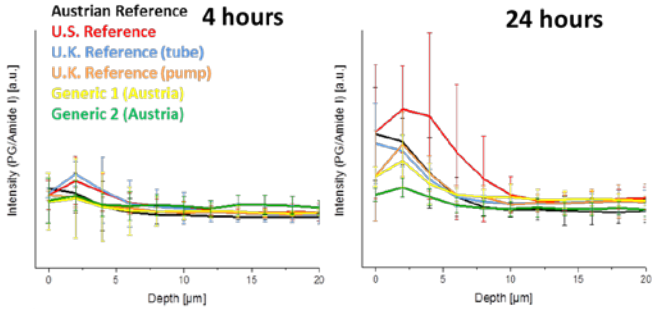
www.fda.gov

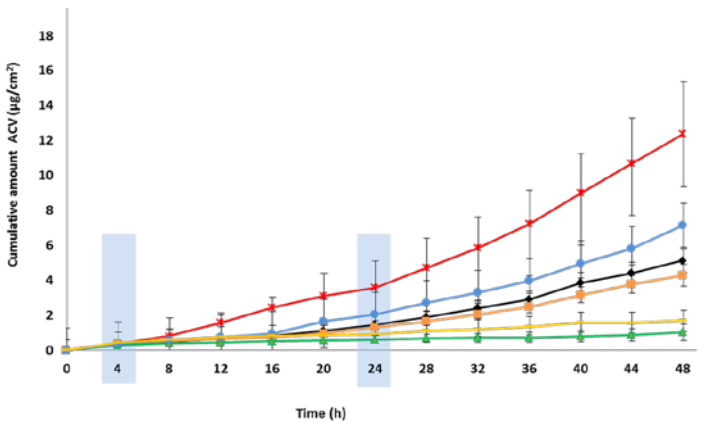
Bodenlenz M, et al. **Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence.** Clin Pharmacokinet. 2017 Jan;56(1):91-98.

Epidermal and/or Dermal PK Tomography









Challenges with imaging based tools

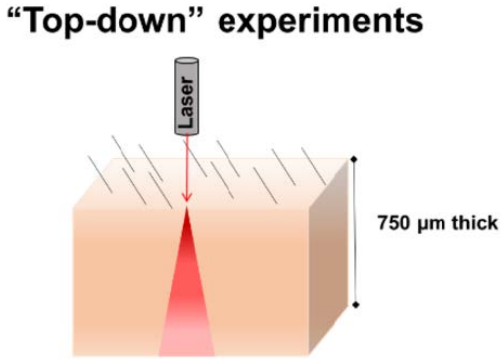
Current Limitations

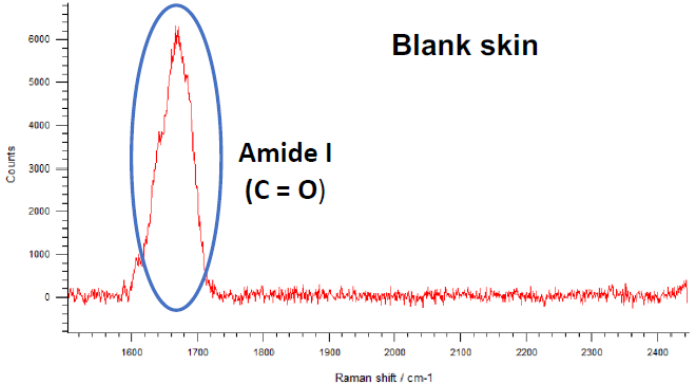
- *Challenges with detection of molecule in the skin*
- *Challenges related to signal attenuation within the skin*
- *Challenges related to utility of tool as a semi-quantitative evaluation technique*
- *Challenges associated with limited utility, applicable for molecules with unique Raman signal*
- *Challenges related to data collection and data analysis of spectroscopic data*
- *Development of validation strategies for utilization of method in a regulatory setting*

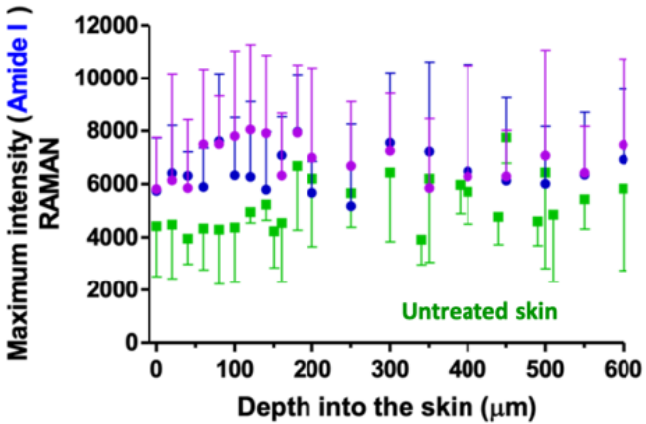
Current Funding

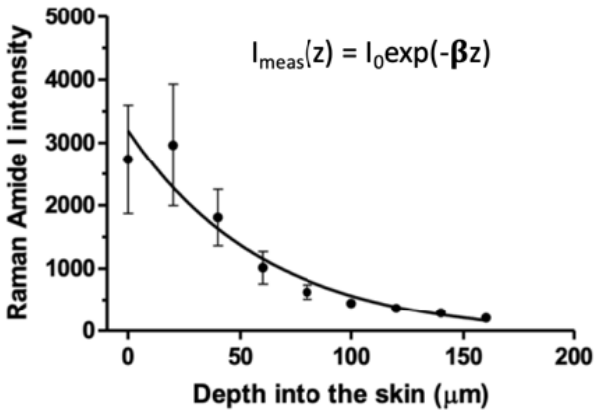
- *1U01FD006533 Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques, PI Prof. Richard Guy, University of Bath*
- *1U01FD006698 Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence, PI Prof. Conor Evans, Massachusetts General Hospital/ Harvard Medical School*

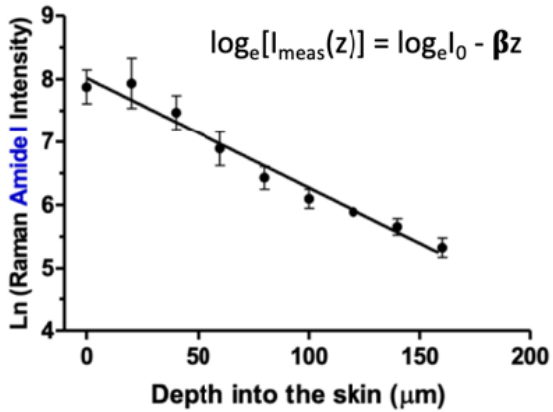
Strategies to Correct for Signal Attenuation



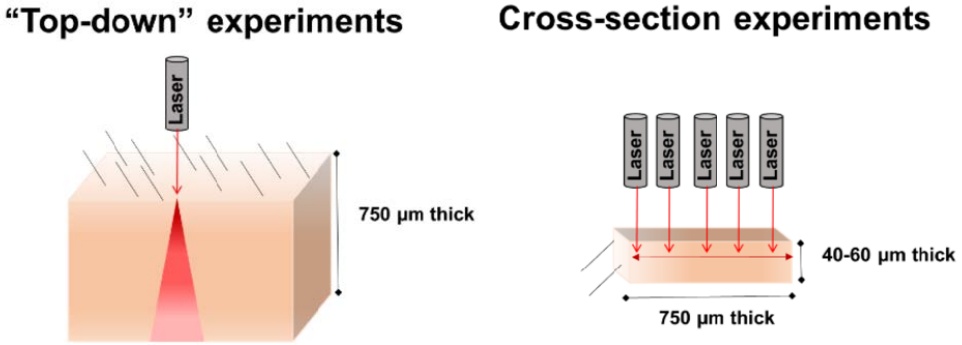


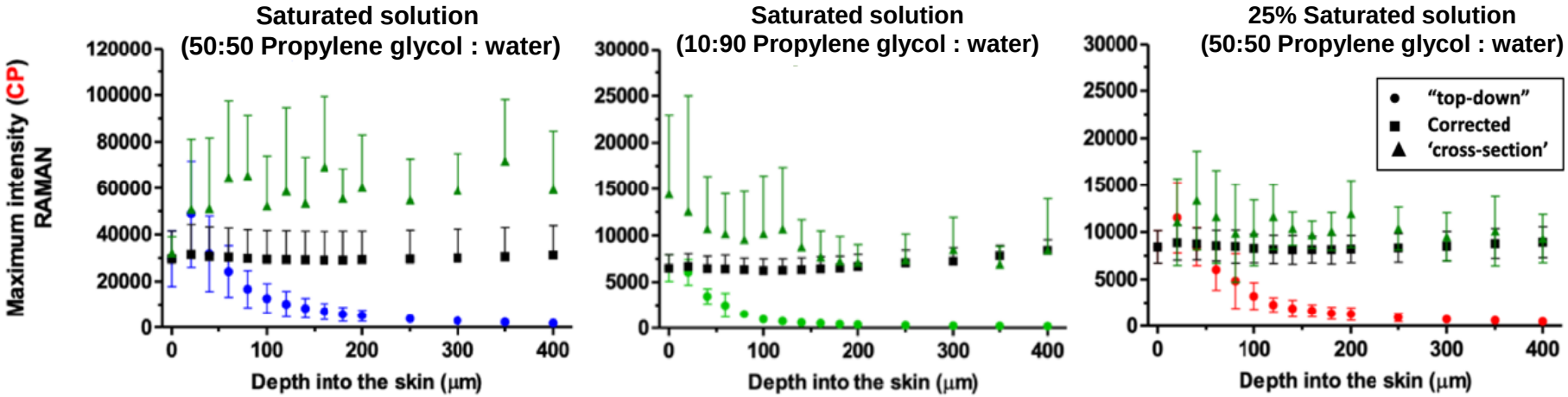






Development of a “Semi-Quantitative” Tool

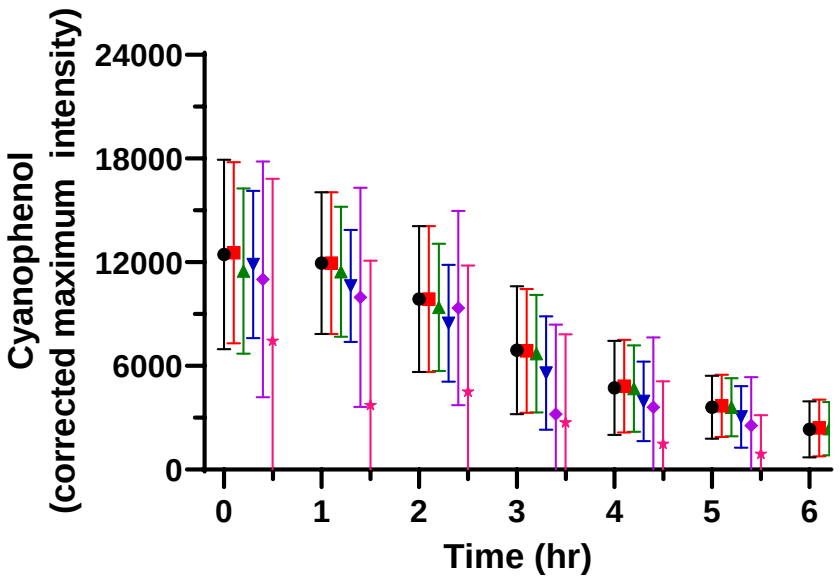




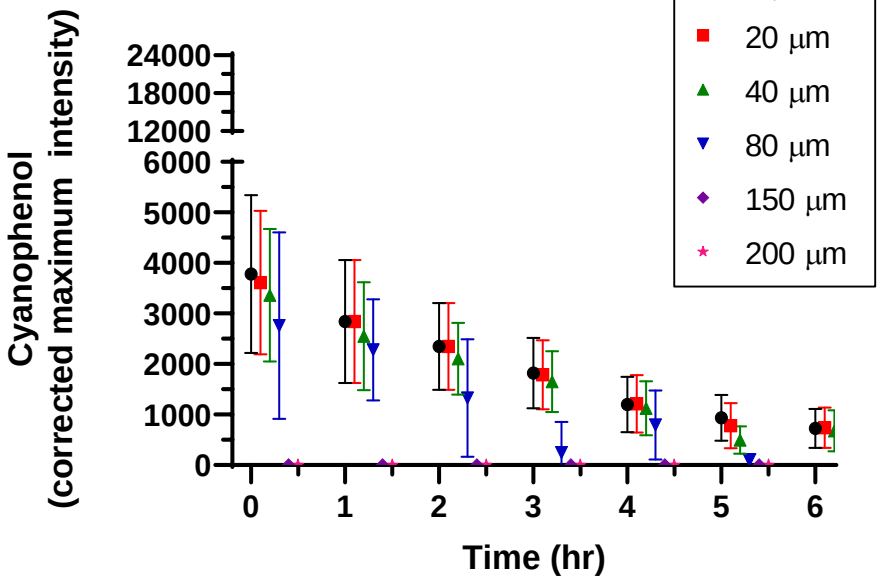
Prof. Richard Guy FDA Award U01-FD006533

Evaluation of Cutaneous PK

Saturated solution
(50:50 Propylene glycol : water)

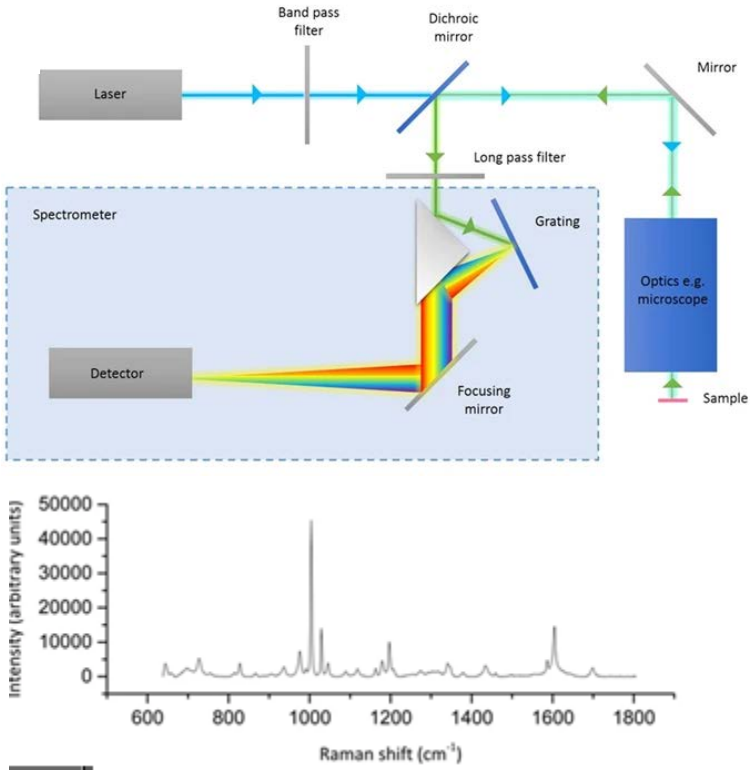


25% Saturated solution
(50:50 Propylene glycol : water)



Prof. Richard Guy FDA Award U01-FD006533

Current Utility of Raman Spectroscopy

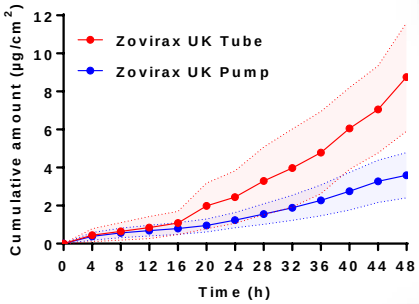


Predominantly used during manufacturing and quality control *for identification of*

- Active ingredient(s)
- Degradation product(s)
- Polymorph/isomorph(s)
- Trace contaminants(s)
- Inactive ingredients including fillers, dyes, coatings

Ember KJI, Hoeve MA, McAughtrie SL, et al. **Raman spectroscopy and regenerative medicine: a review**. NPJ Regen Med. 2017;2:12. Published 2017 May 15.

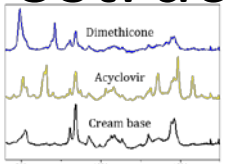
Understanding the Product Microstructure

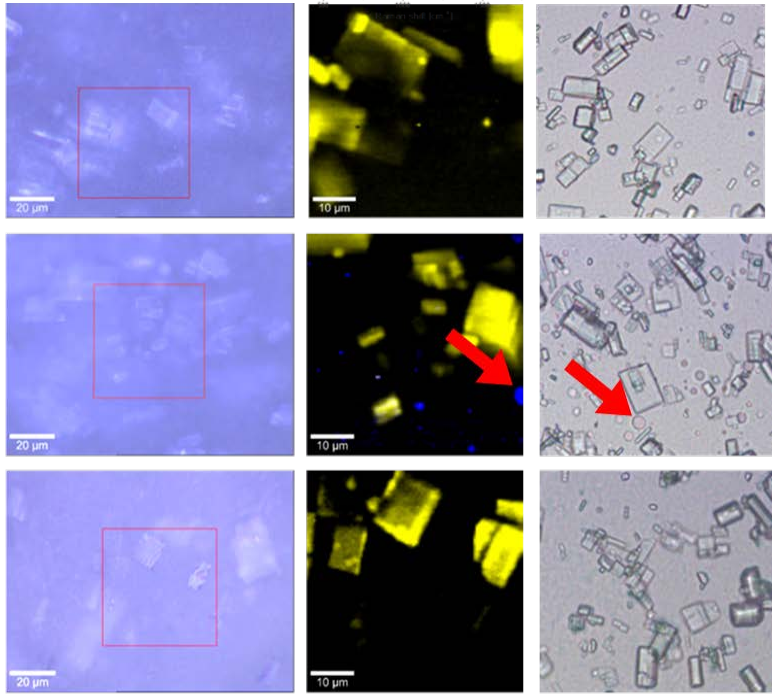


Zovirax® UK
Tube

Zovirax® UK
Pump

Zovirax® UK
Pump
(from inside container)





Prof. Michael Roberts FDA Award U01-FD005226

Goals of GDUFA Research Programs

Enhance patient access to generic drug products

- Overcome barriers limiting generic drug development
- Utilize scientific evidence to establish efficient, modern BE standards
- Continually study, learn, evolve, refine, and harmonize

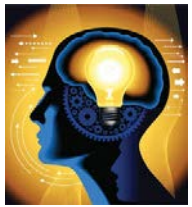
https://www.fda.gov/drugs/generic-drugs/science-research

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** Strategies to Support Bioequivalence Assessments
  - Developing & Verifying Models to Integrate the Product, the Skin & Local Tissues, and the Systemic Circulation Data to Predict Drug Concentrations at a Site of Action

Partnering with the FDA

- Regulatory Science Extramural Research and Development Projects
  - FDA welcomes research proposals for Grants/ Contracts/ Etc.
  - Generic Drug Regulatory Science Initiatives Public Workshop, Summer, 2021
  - Postdoctoral Fellowship Opportunities- https://orise.orau.gov/fda/



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https://www.fda.gov/drugs/generic-drugs/science-research

Summary

- In vitro and in vivo cutaneous PK techniques can be utilized to develop efficient strategies for evaluation of bioavailability of topical dermatological products
- IVPT and dMD/dOFM-based techniques are currently being developed and utilized for evaluation of bioavailability
- Current literature/data illustrates that it is feasible to use Raman-based techniques for evaluation of cutaneous PK, in addition to providing a better understanding of the drug product microstructure
- Goal of the GDUFA-funded research studies is to develop Raman-based techniques as a tool to facilitate drug development

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- Robert Lionberger, PhD

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- *GDUFA Award U01FD005**226***
  (PI Prof. Michael Roberts, University of South Australia)
- *GDUFA Award U01FD006**533***
  (PI Prof. Richard Guy, University of Bath)
- *GDUFA Award U01FD006**698***
  (PI Prof. Conor Evans, Massachusetts General Hospital, Harvard Medical School)

U.S. FOOD & DRUG ADMINISTRATION

Thank You

Priyanka Ghosh, PhD
Senior Staff Fellow (Pharmacologist)
Division of Therapeutic Performance, Office of Research And Standards
Office of Generic Drugs| CDER | U.S. FDA


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