

# Non-Invasive Raman Spectroscopy-Based Bioequivalence Approaches

**SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop**

**Session 3: Future Directions, Emerging Technology, and Current Thinking on Alternative BE Approaches**

Topic 2: Topical Dermatologic Products

**Priyanka Ghosh, PhD**

Senior Staff Fellow (Pharmacologist)

Division of Therapeutic Performance, Office of Research And Standards

Office of Generic Drugs | CDER | U.S. FDA

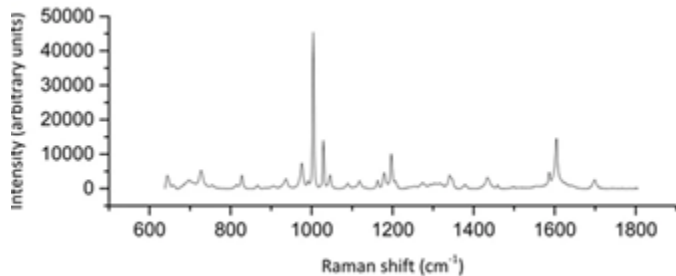
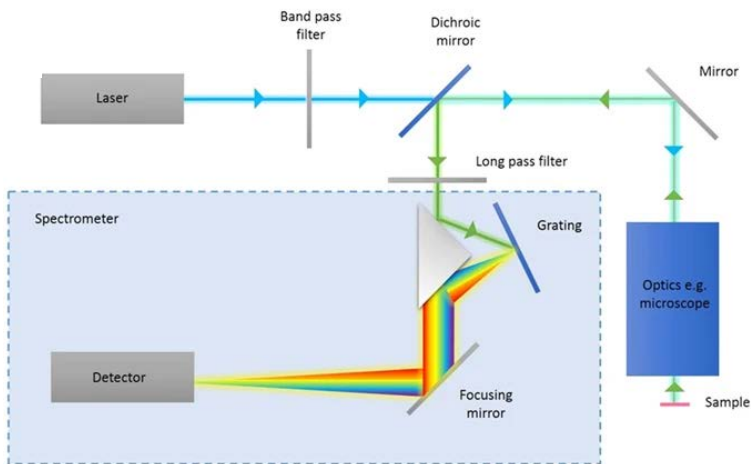
September 30, 2020



# Learning Objectives

- Understand non-invasive imaging-based techniques
- Utilize imaging-based techniques in generic drug development
  - to understand product microstructure
  - to understand the metamorphosis and drug release
  - for evaluation of (cutaneous) pharmacokinetics

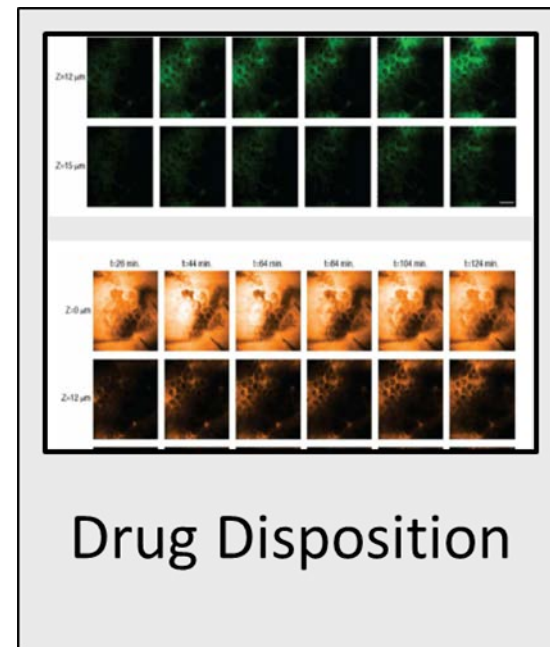
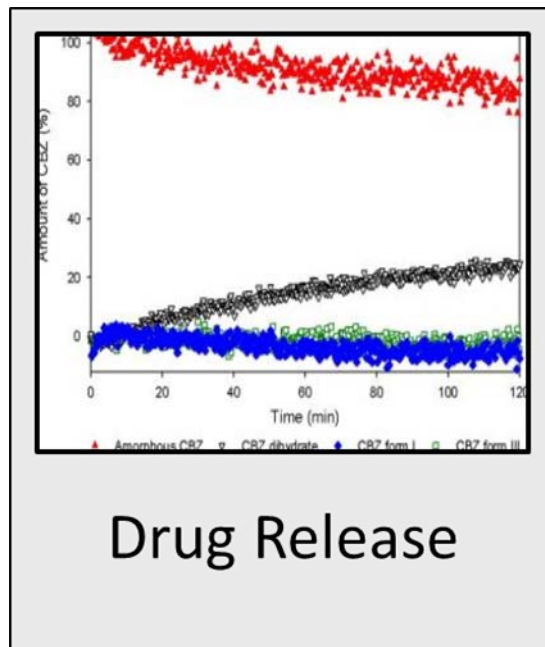
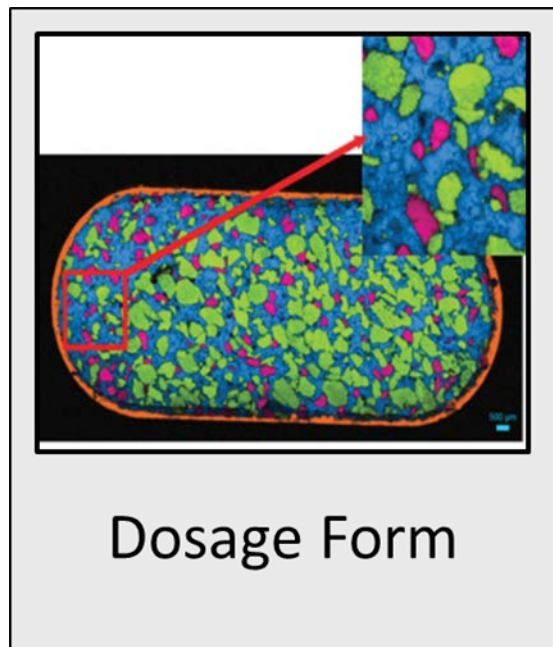
# Current Utility of Raman Spectroscopy



***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

# Potential Utility in Dermal Drug Development

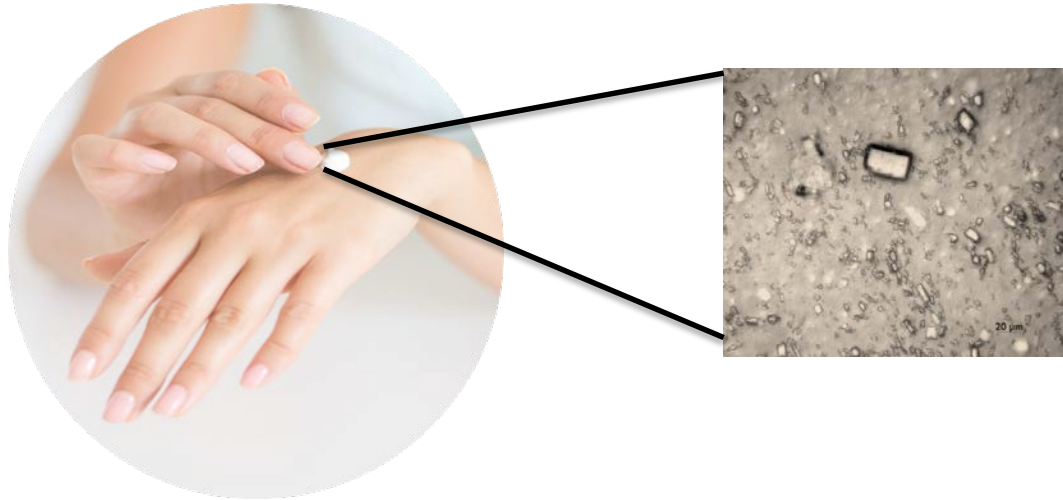


[https://www.horiba.com/en\\_en/raman-imaging-and-spectroscopy-recording-spectral-images-profiles/](https://www.horiba.com/en_en/raman-imaging-and-spectroscopy-recording-spectral-images-profiles/)

Savolainen M, Kogermann K, Heinz A, et al. **Better understanding of dissolution behaviour of amorphous drugs by in situ solid-state analysis using Raman spectroscopy.** Eur J Pharm Biopharm. 2009;71(1):71-79.

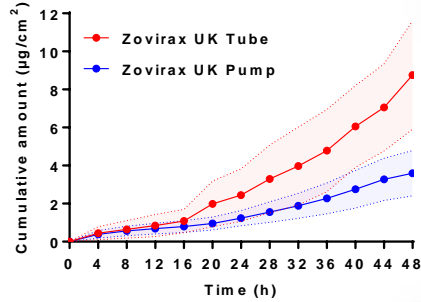
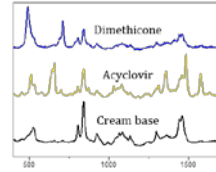
[www.fda.gov](http://www.fda.gov) Saar Brian G. , Contreras-Rojas L. Rodrigo , Xie X. Sunney , and Guy Richard H. **Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy** Molecular Pharmaceutics 2011 8 (3), 969-975





# Understanding the Product Microstructure

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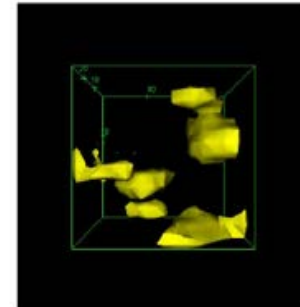
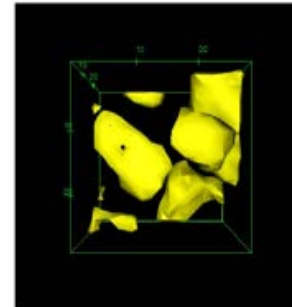
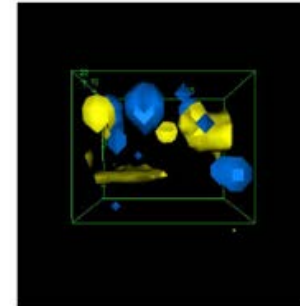
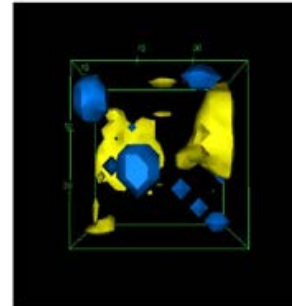
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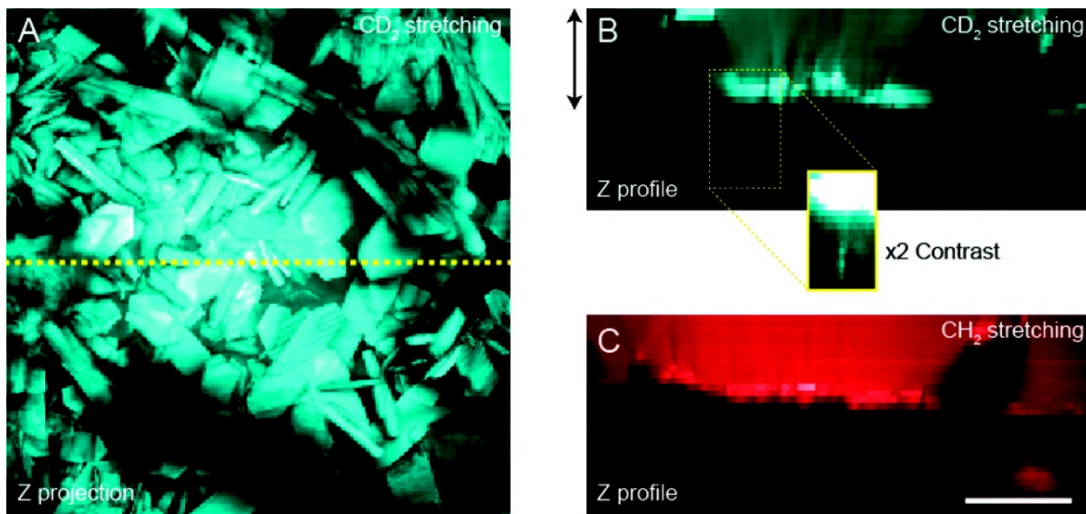
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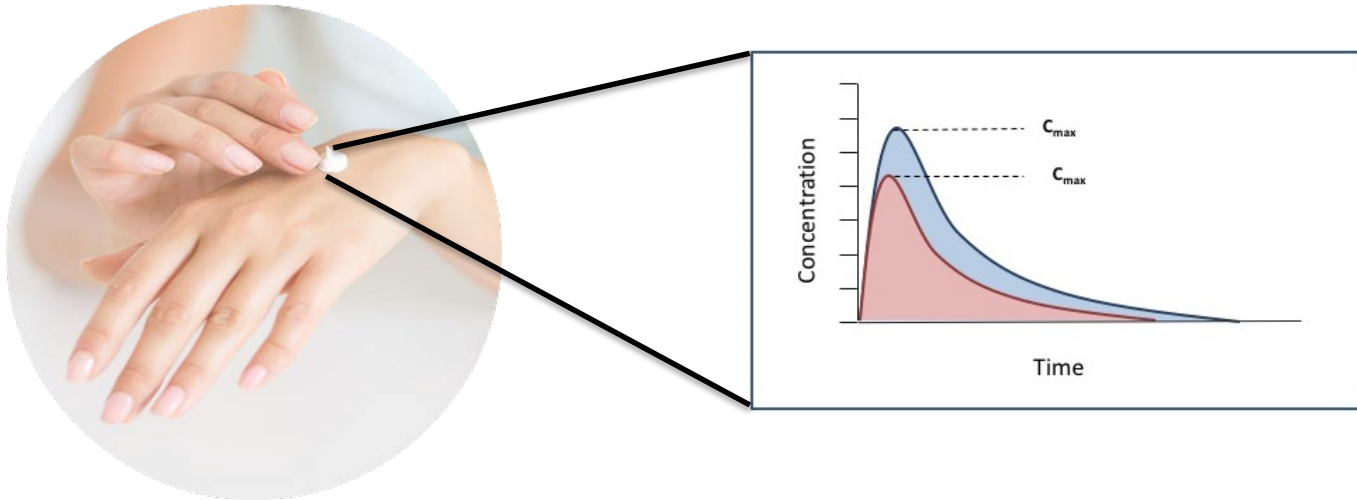
top view

side view



# Understanding the Product Metamorphosis



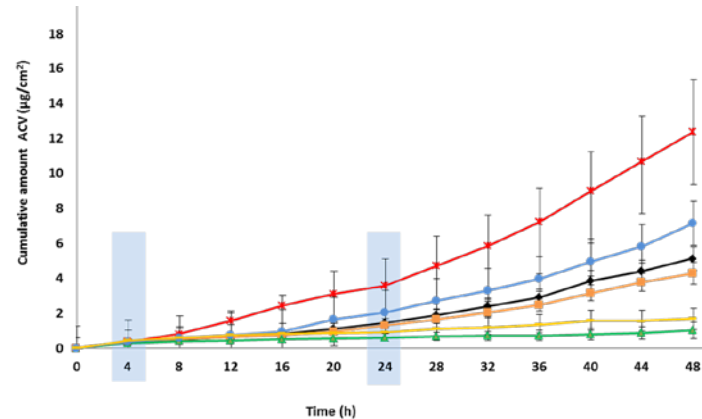
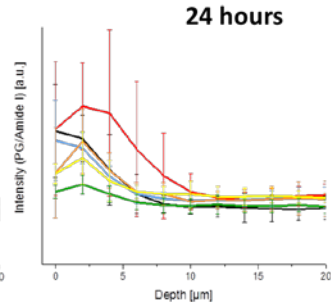
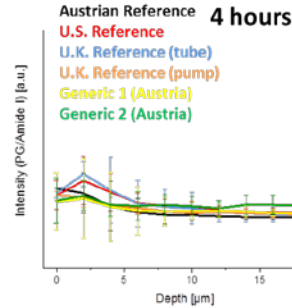
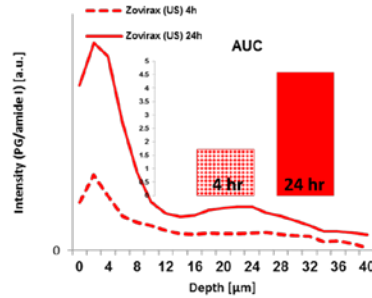
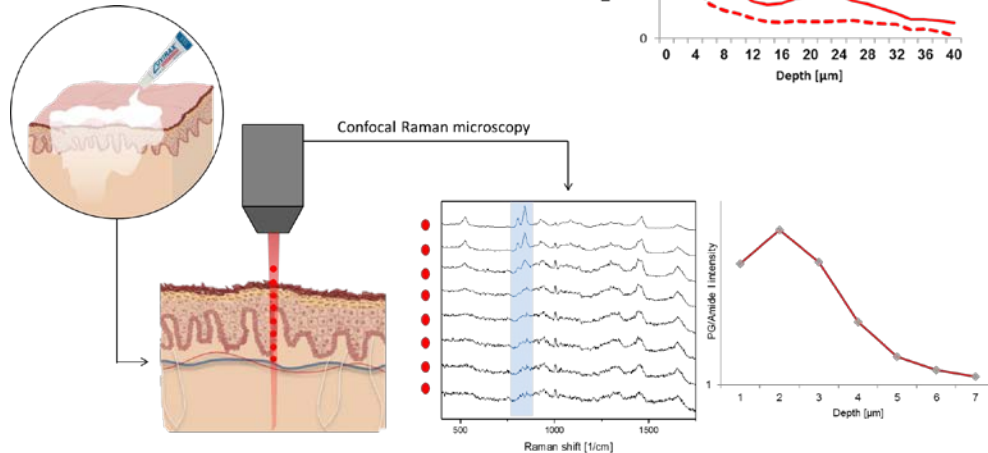


# Evaluation of Cutaneous Pharmacokinetics





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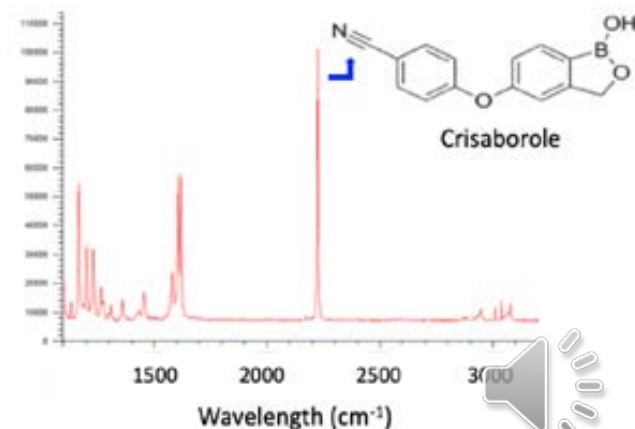
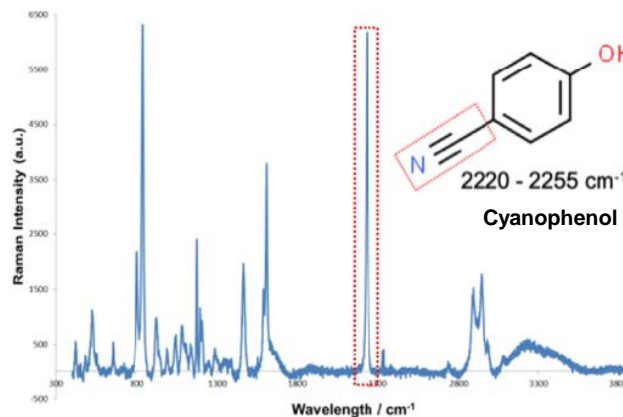
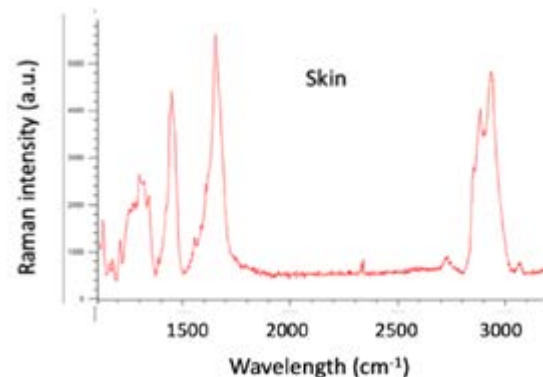
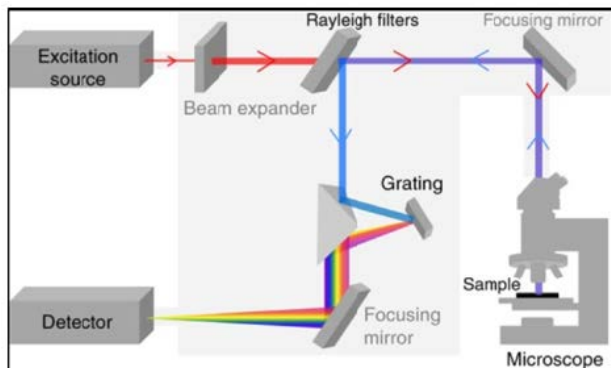
## Current Limitations

- *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 strong 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

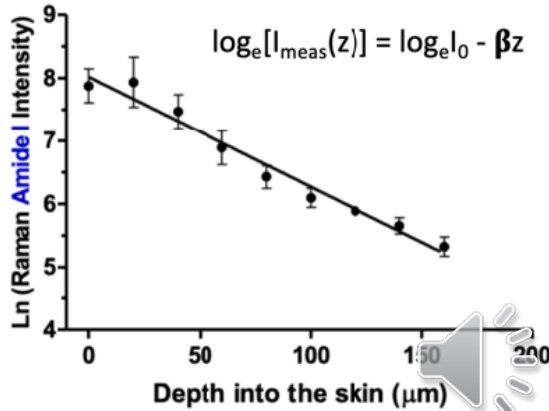
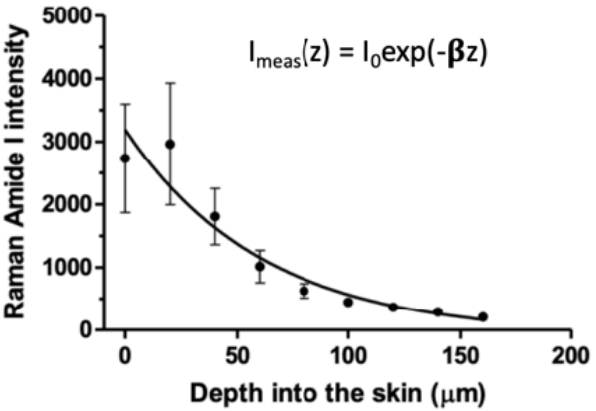
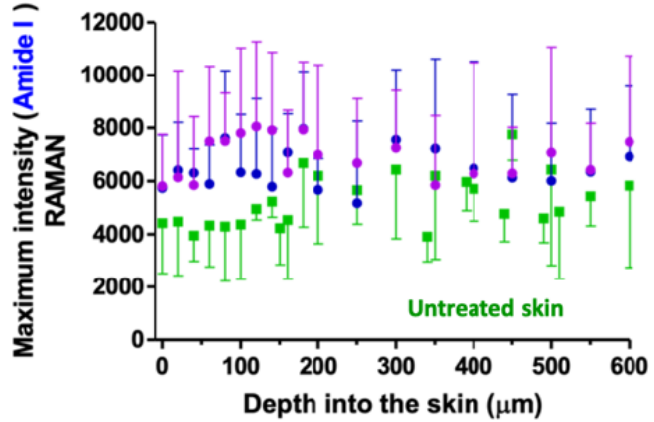
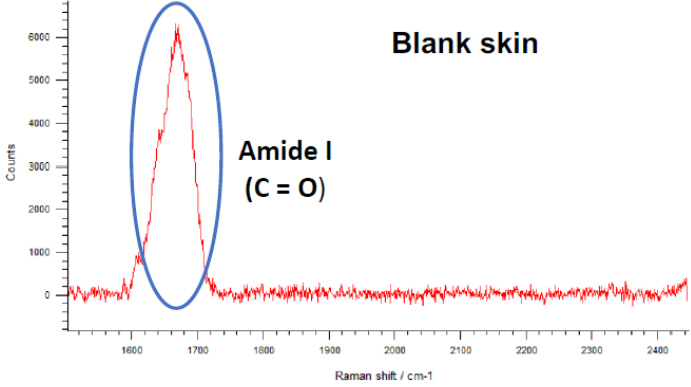
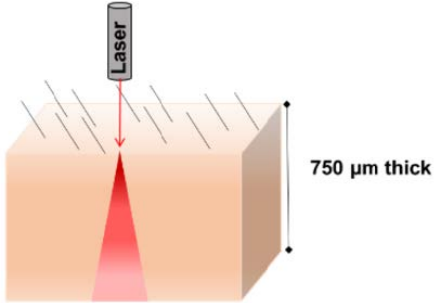
- *1U01FD006533 Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques, PI Prof. Richard Guy, University of Bath*
- *1U01FD006698 Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence, PI Prof.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

# Detection of a Molecule Within the Skin



# Strategies to Correct for Signal Attenuation

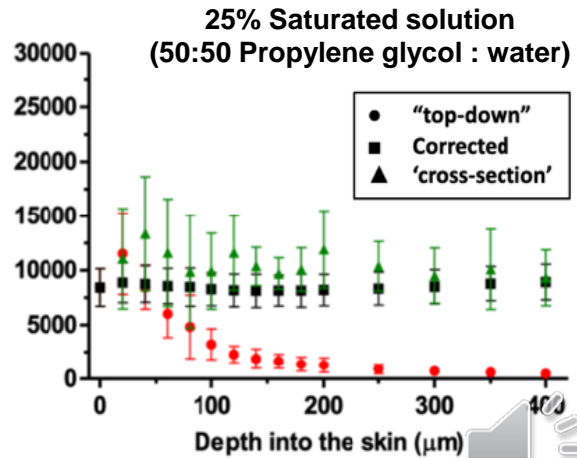
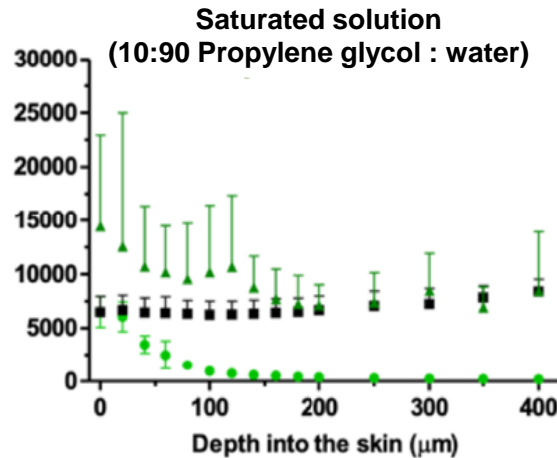
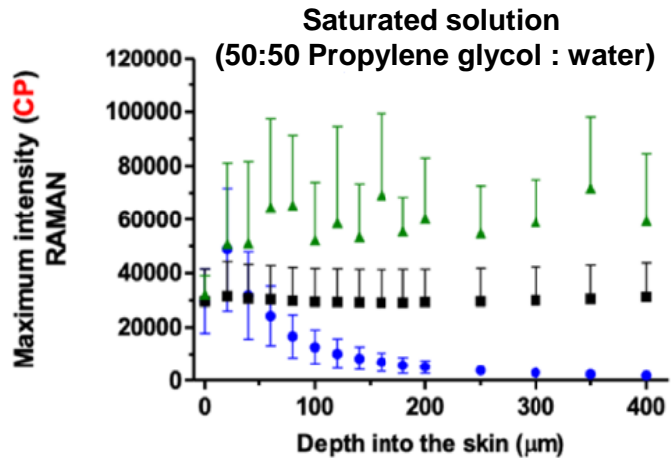
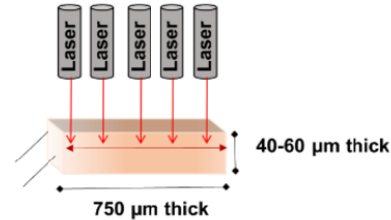
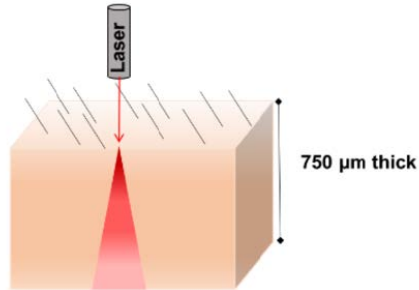
“Top-down” experiments



# Development of a “Semi-Quantitative” Tool

“Top-down” experiments

Cross-section experiments

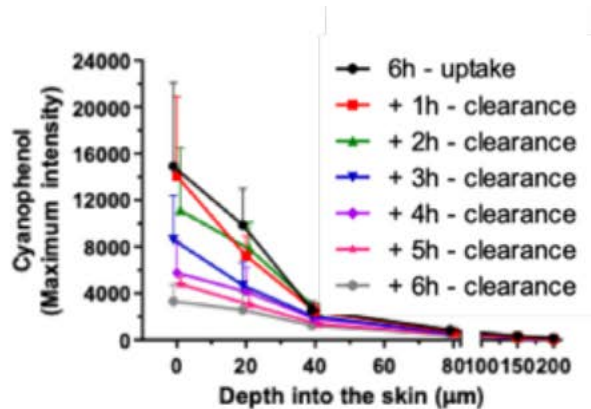


# Evaluation of Cutaneous Pharmacokinetics

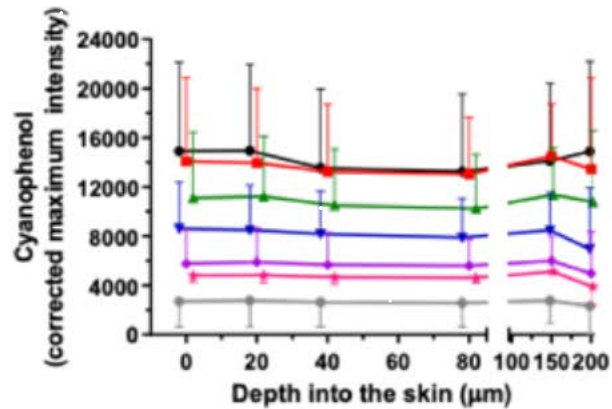


Saturated solution  
(50:50 Propylene glycol : water)

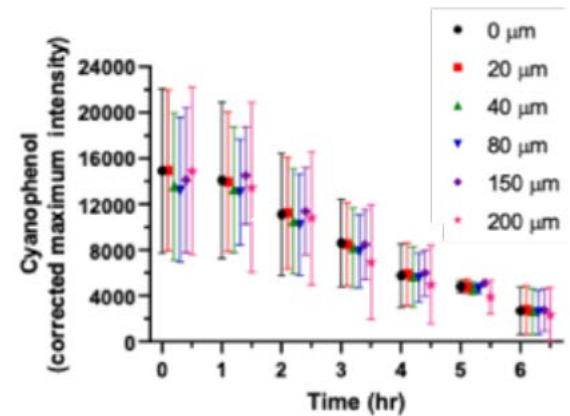
Uncorrected data as function of depth



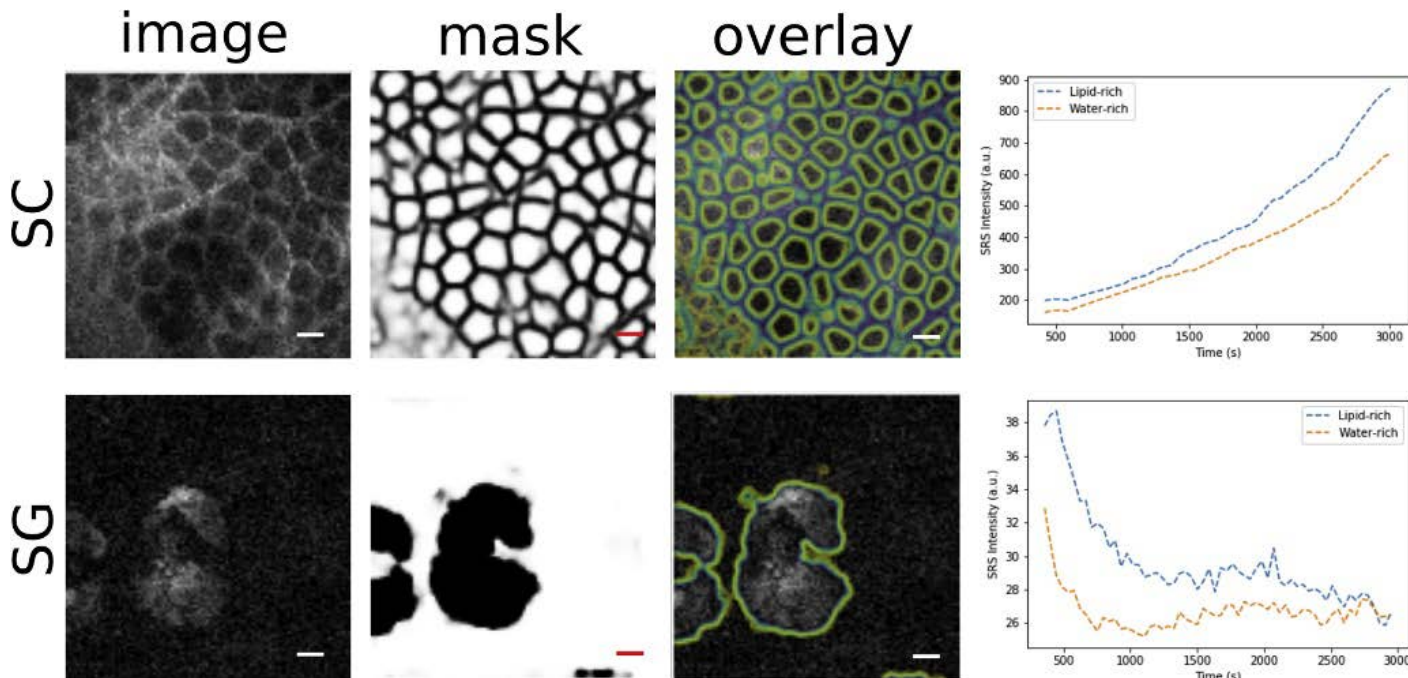
Corrected data as function of depth



Pharmacokinetic profile



# Data Collection and Analysis Tools



# Summary

- Imaging-based techniques are prevalent within the pharmaceutical industry
- Current literature/data illustrates that it is feasible to use Raman-based techniques for evaluation of drug product microstructure (including metamorphosis), drug release, and cutaneous pharmacokinetics
- Goal of the GDUFA-funded research studies is to develop Raman-based techniques as a “regulatory tool”
  - Identify strategies to enhance the applicability of Raman to a wide range of active ingredients
  - Develop hand-held tools that can be utilized for the evaluation of pharmacokinetics
  - Automate data collection and data analysis tools
  - Develop method validation strategies



# Challenge Question

**Raman-based imaging techniques can be utilized to monitor :**

- A. The changes in the color of the skin
- B. The indication of the drug product
- C. A molecule that generates a Raman signal
- D. The mechanism of action of a drug

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# Acknowledgements



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- ***GDUFA Award U01FD005226***  
*(PI Prof. Michael Roberts, University of South Australia)*
- ***GDUFA Award U01FD006533***  
*(PI Prof. Richard Guy, University of Bath)*
- ***GDUFA Award U01FD006698***  
*(PI Prof. Conor Evans, Massachusetts General Hospital, Harvard Medical School)*

# Closing Thought



*“Ask the right questions, and nature will open the doors to her secrets”...*

Dr. C.V. Raman

The goal over the next few years is to be able to develop and utilize imaging-based strategies to facilitate generic drug development

# Thank You

**Priyanka Ghosh, PhD**

Senior Staff Fellow (Pharmacologist)

Division of Therapeutic Performance, Office of Research And Standards

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