Visualizing and Quantifying Drugs Dermal Drug Development

SPIE Photonics West

Visualizing and Quantifying Drug Distribution in Tissue

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CDER | U.S. FDA

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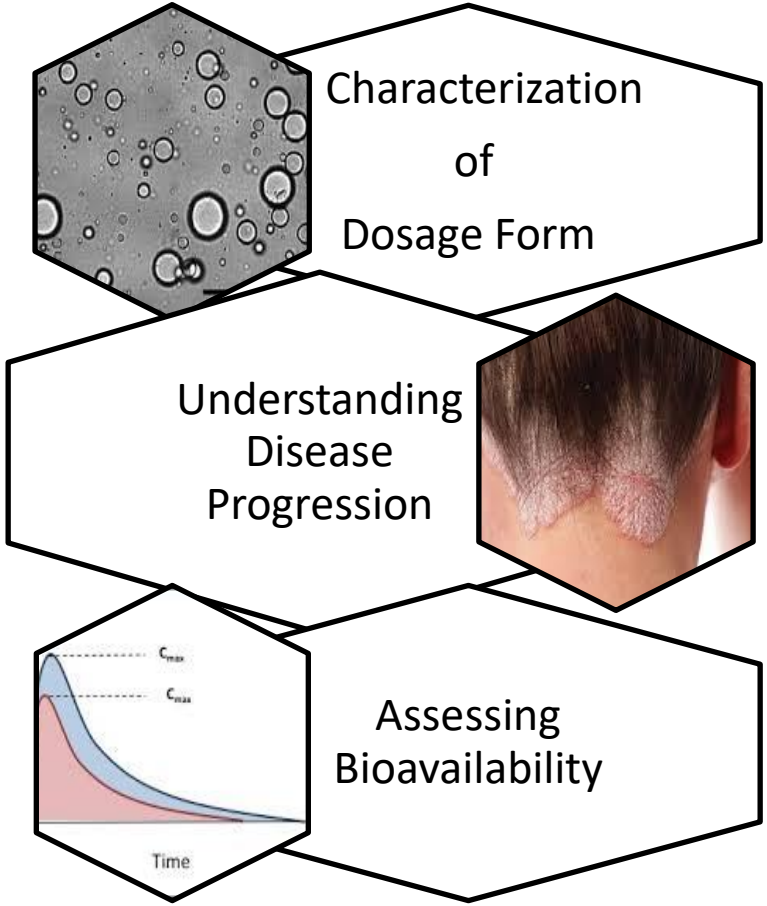
Disclaimer

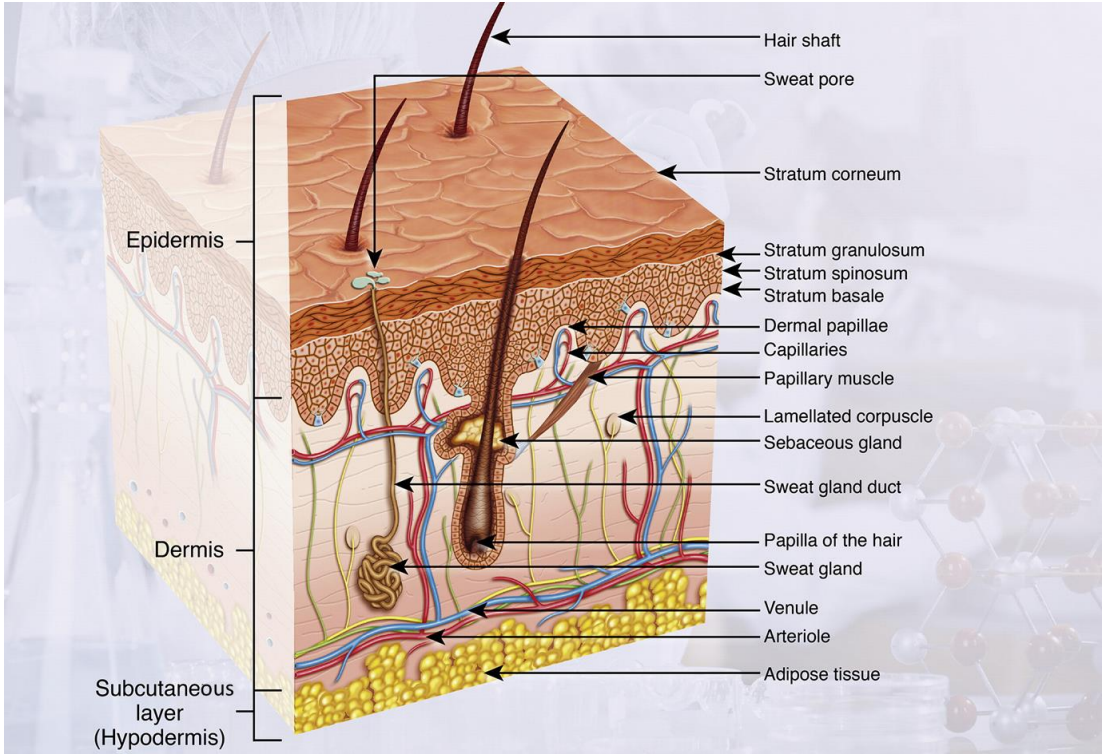
This presentation reflects the views of the author and should not be construed to represent FDA's official views or policies.

Topical (Dermatological) Drug Products

How Can Visualization Help



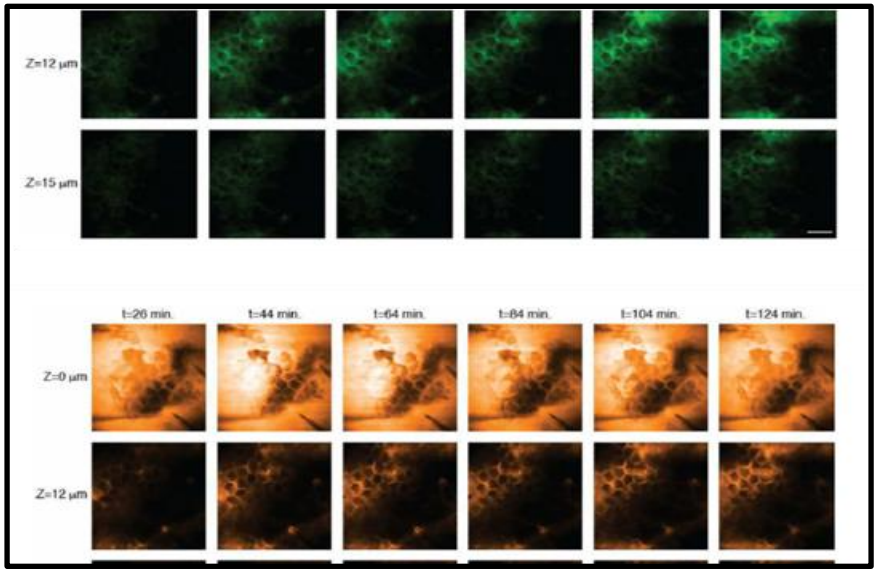
From Anatomy to Pharmacology

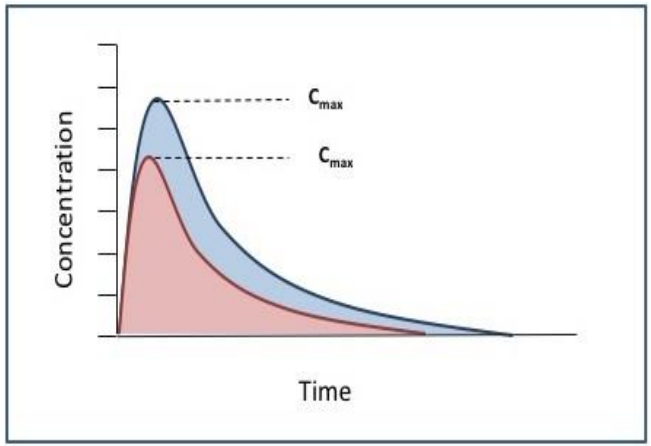


Mathes et al., *Adv Drug Deliv Rev.* **2014**, 69-70, 81-102

Cutaneous Pharmacokinetics (PK)

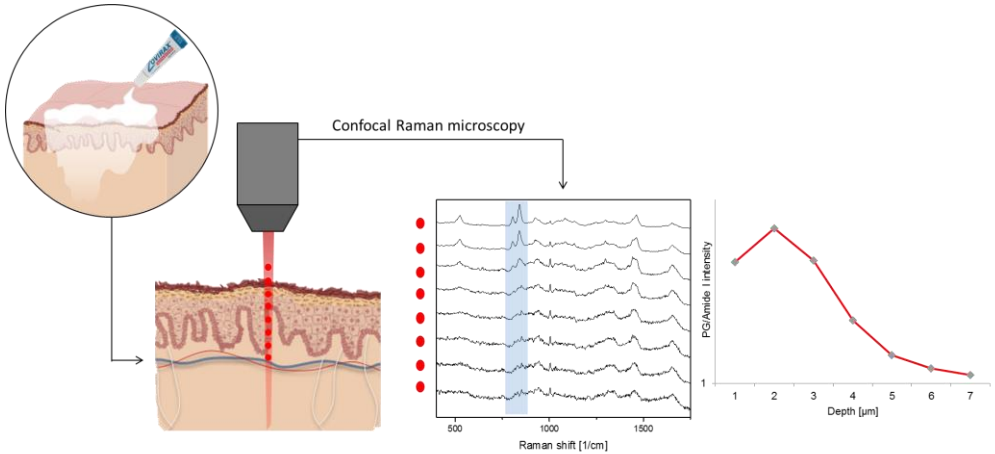
Can we develop **cutaneous PK** based methods to quantify drugs in **“real time”** at or near the **site of action** in the skin?

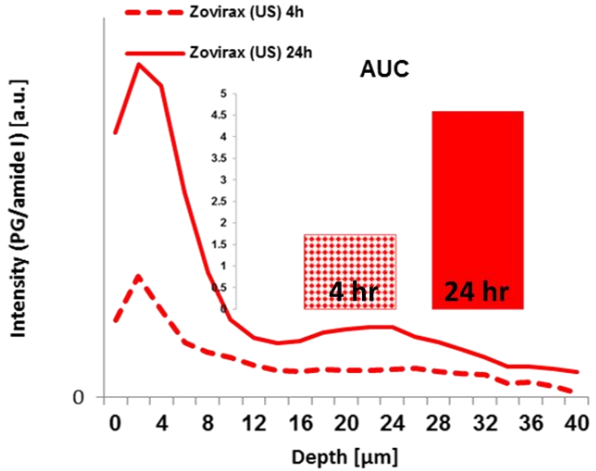




Saar Brian G. , Contreras-Rojas L. Rodrigo , Xie X. Sunney , and Guy Richard H. **Imaging Drug Delivery to Skin with Stimulated Raman Scattering Microscopy** Molecular Pharmaceutics **2011** 8 (3), 969-975

Cutaneous PK





Challenges with Imaging-Based Tools

Examples of historical limitations

- 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

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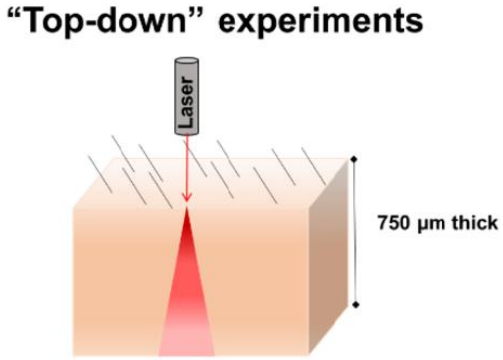
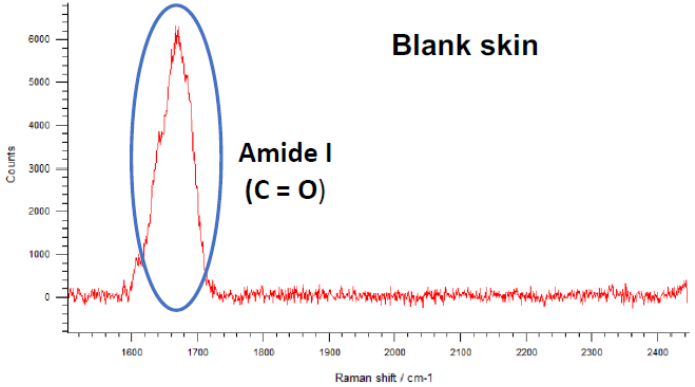
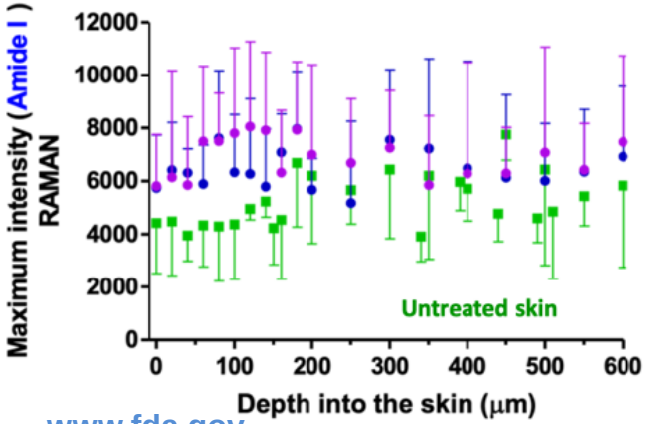
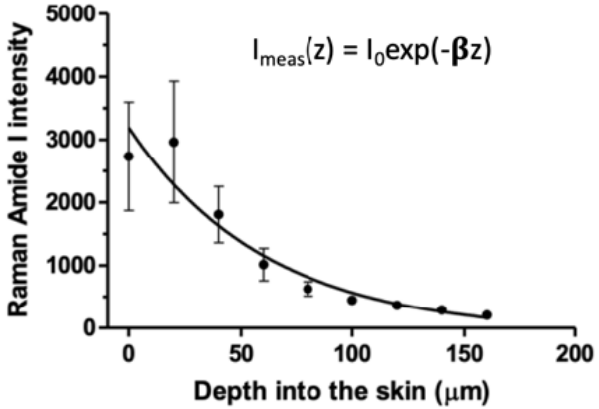
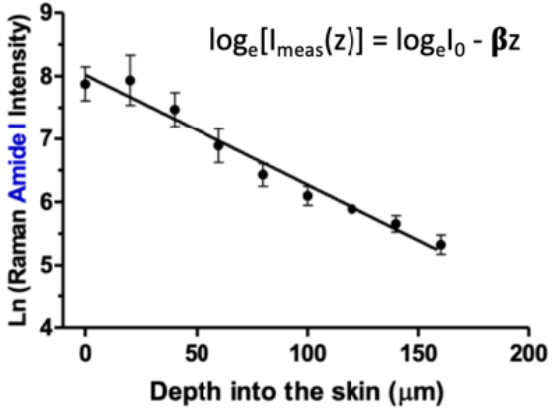
Epidermal PK (Confocal Raman)











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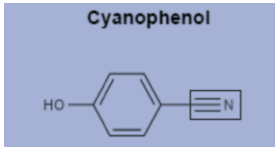
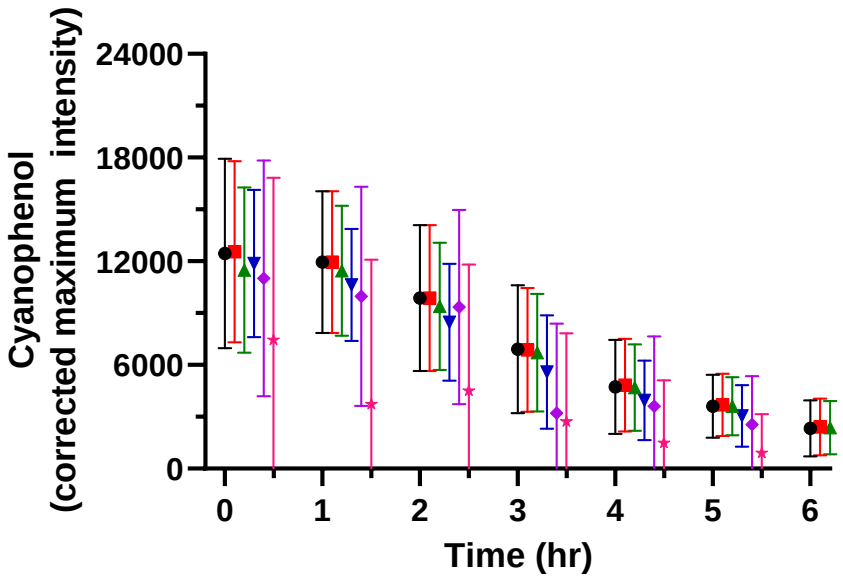
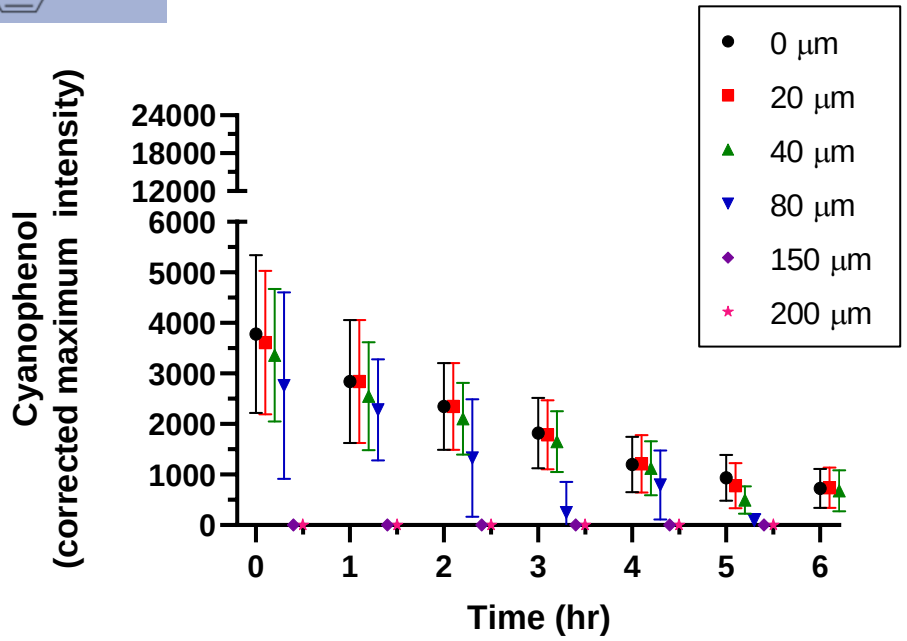
Epidermal PK (Confocal Raman)

Saturated solution
(50:50 Propylene glycol : water)



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





Prof. Richard Guy FDA Award U01-FD006533

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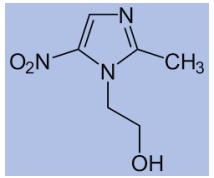
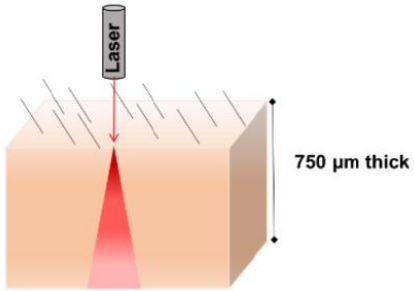
Epidermal PK (Confocal Raman)

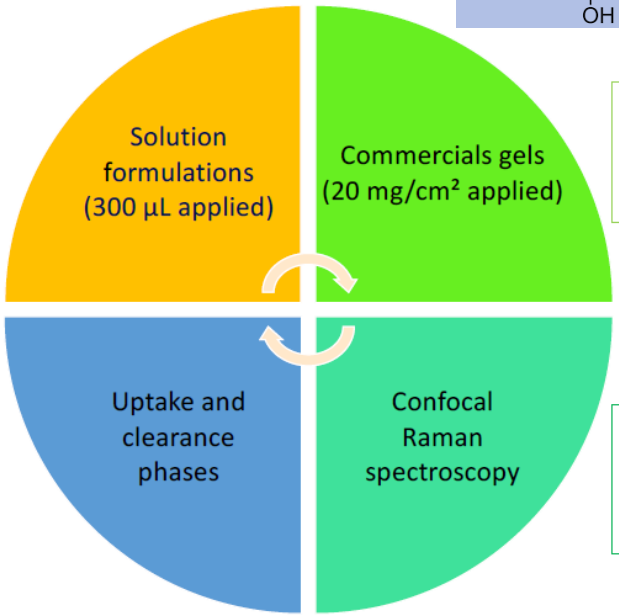
METRONIDAZOLE (MTZ)



"Top-down" experiments



100% saturated MTZ solutions:
- 90:10 water:PG
- 30:70 water:PG



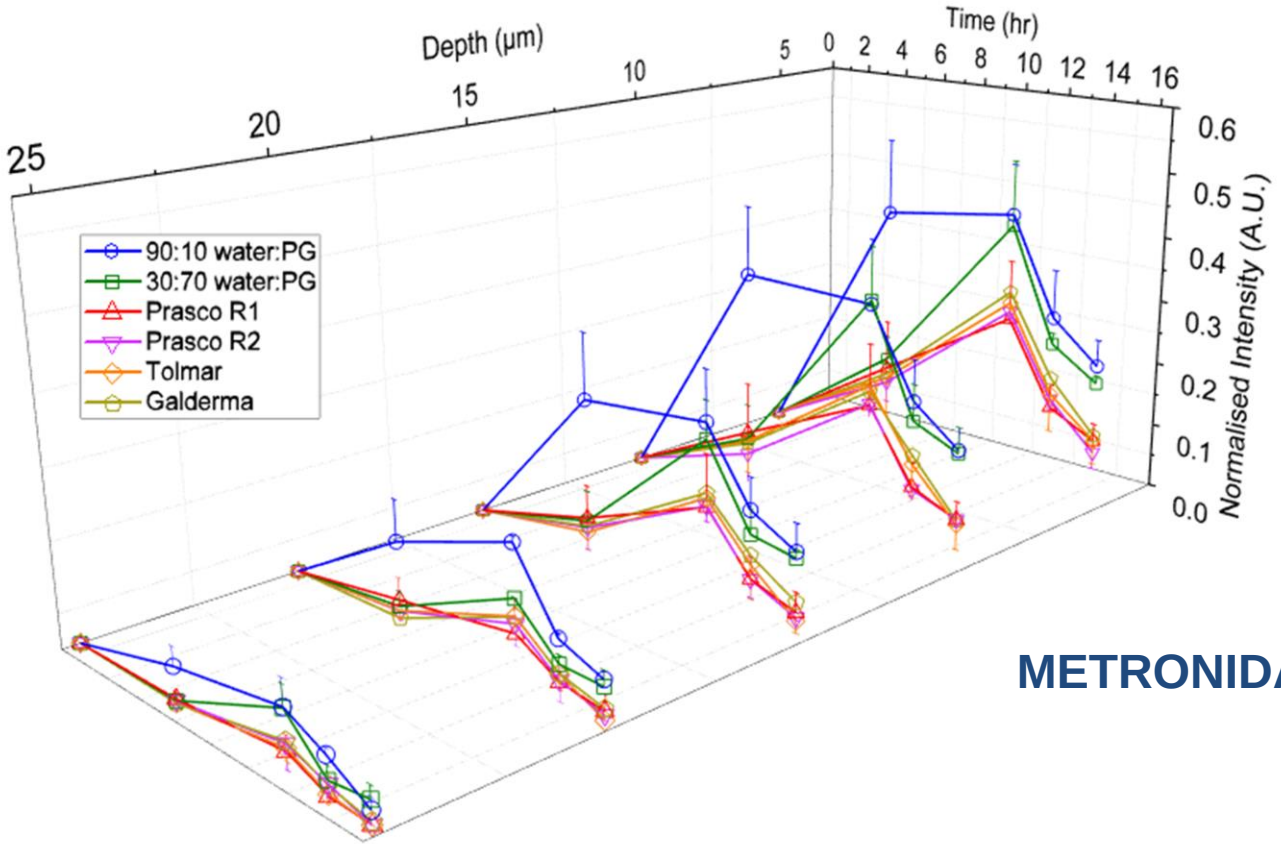
Gels
- Prasco (US) (repeated x2)
- Tolmar (US)
- Rosex (UK)

Uptake
- 6 hr uptake
- 12 hr uptake

Clearance
- 2 hr clearance
- 4 hr clearance

- Depth: 5, 10, 15, 20, 25, 35 µm
- 100% laser power
- 40 accumulations
- 10s per accumulations

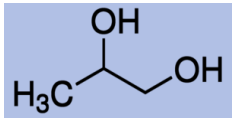
Epidermal PK (Confocal Raman)

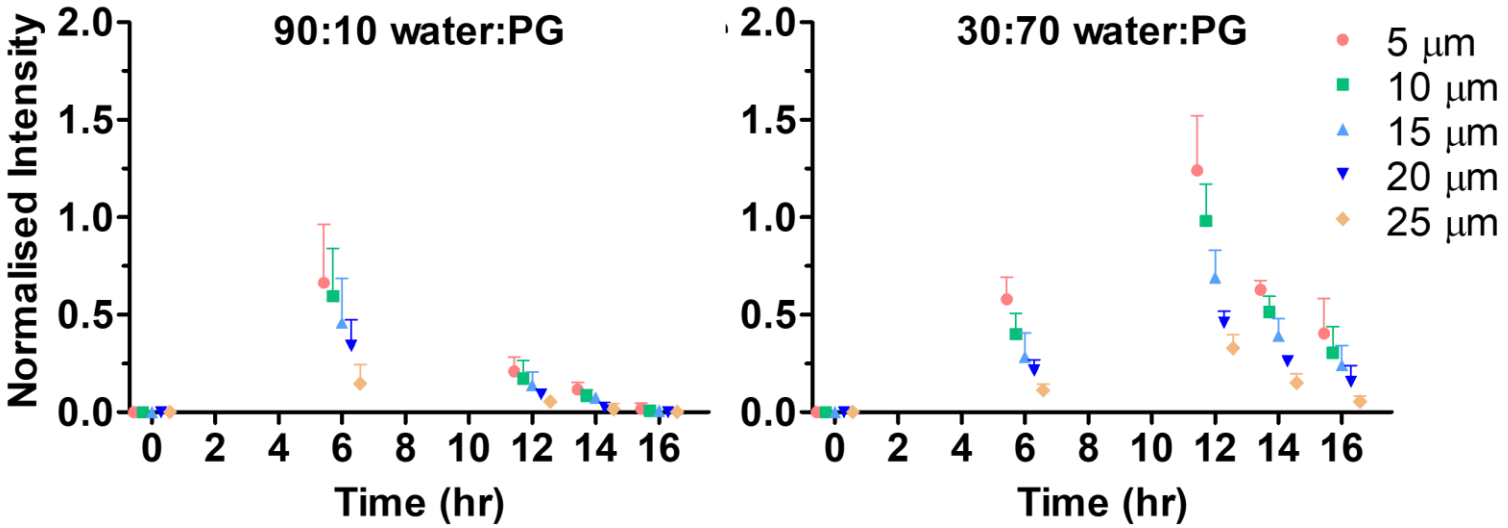


METRONIDAZOLE

Epidermal PK (Confocal Raman)

PROPYLENE GLYCOL (PG)





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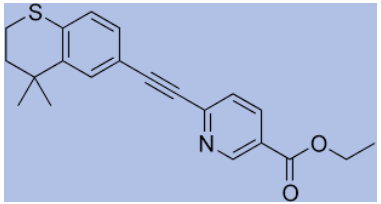
Epidermal PK (Simulated Raman)

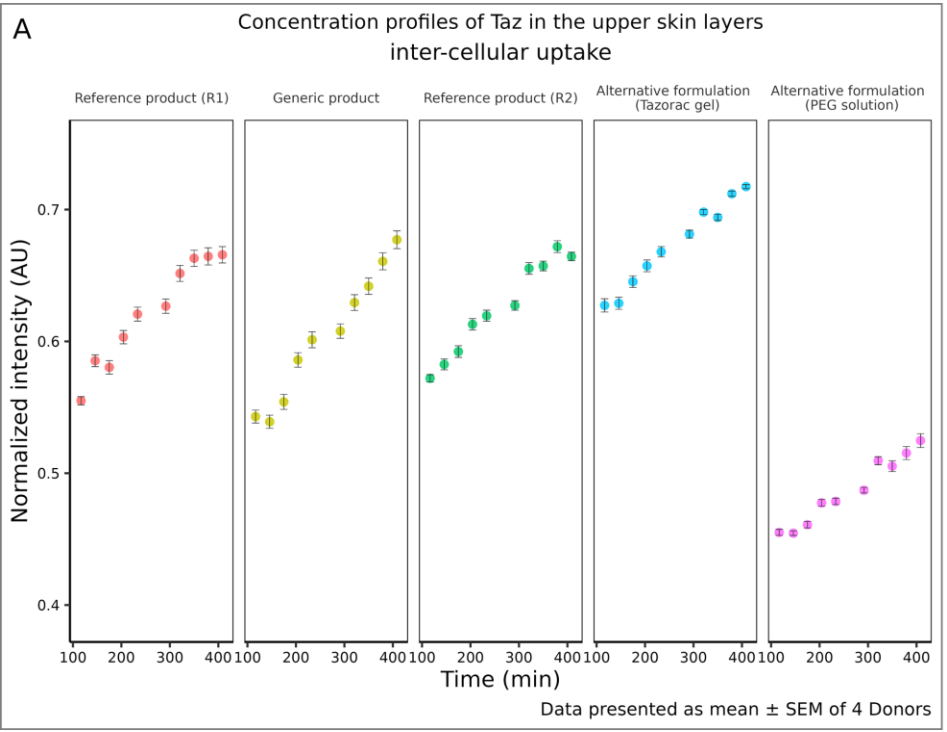
TAZAROTENE (TAZ)

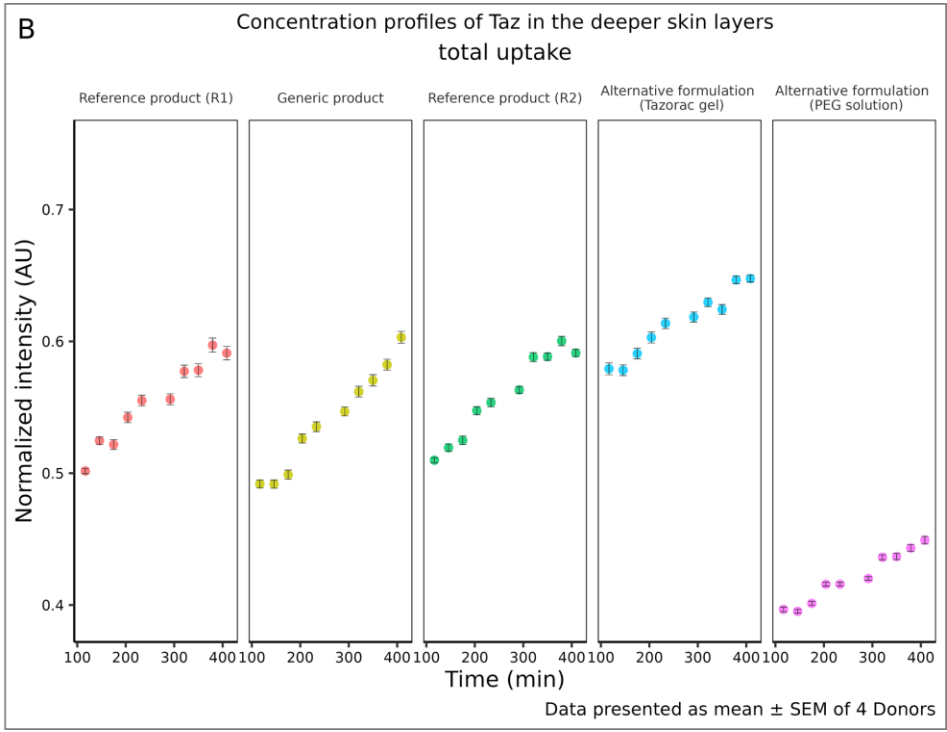


Reference product: Tazorac® cream (x2) **Test product**: Generic tazarotene cream **Alternate formulation**: Tazorac® gel **Alternate formulation**: Lab made tazarotene solution in PEG	
Number of skin samples & regions of interest (ROIs)	4 human donors 4 replicates per formulation; 4 ROIs per skin sample (1024 x 1024 pixel)
Depth stack	Step size: 8 µm; number of slices: 9; final depth at 64 µm
Study duration	~6.5 hours of imaging (15 cycles)
Skin uptake conditions	Finite dose (5 µL); **Occlusive; 32°C**

Epidermal PK (Simulated Raman)

TAZAROTENE





Prof. Conor Evans FDA Award U01-FD006698

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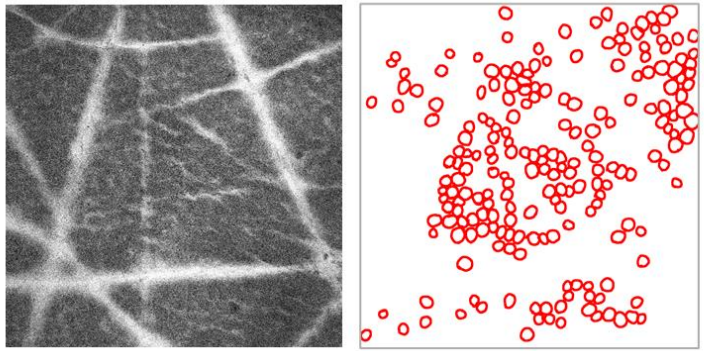
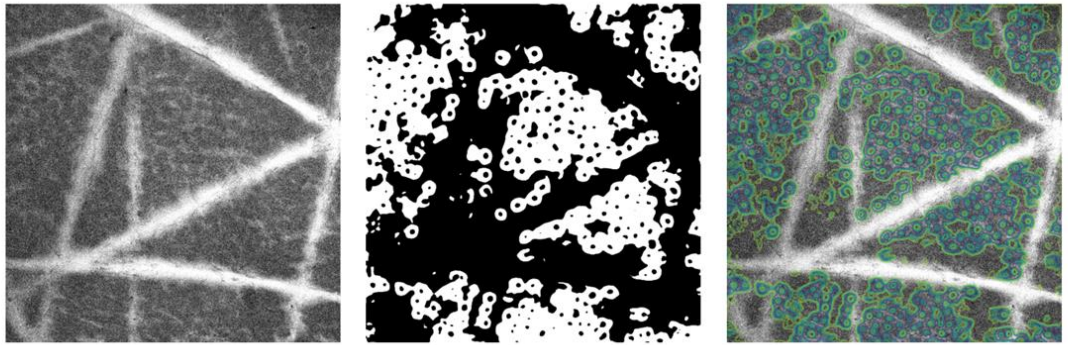
Epidermal PK (Simulated Raman)

A. Original training image set



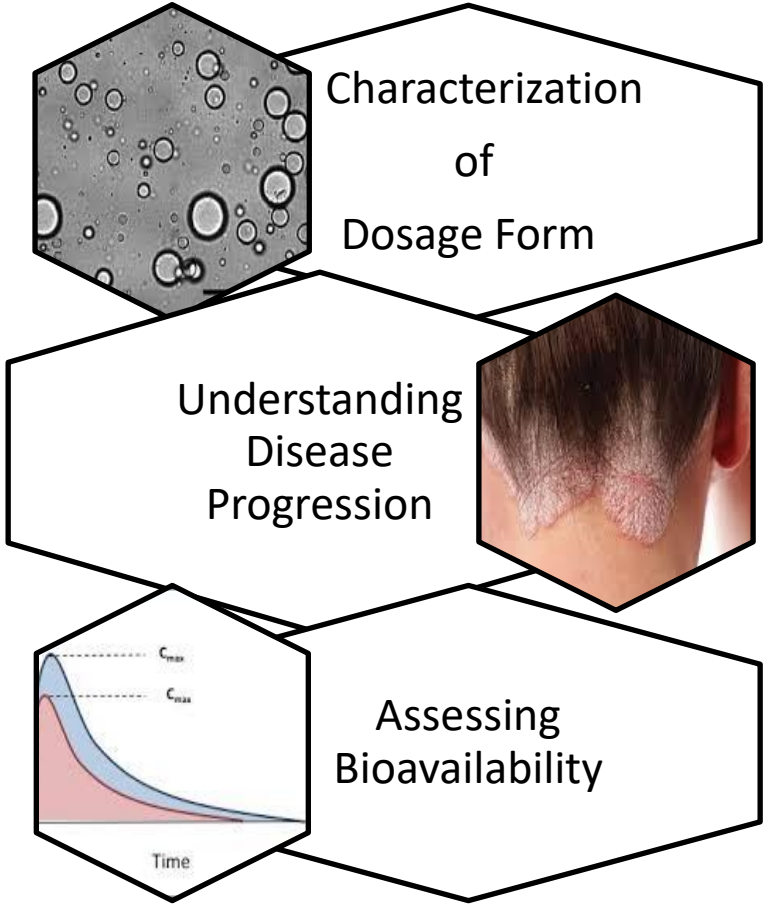
B. Validation of deep learning model on test images



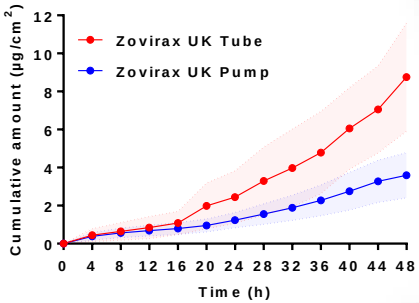
Current State and Next Steps

- *Detection of molecule in the skin*
  - *We can detect certain active ingredients in formulations; however, we are exploring advanced techniques e.g., Sparse Spectral Sampling Stimulated Raman Scattering*
- *Utility of tool as a semi-quantitative evaluation technique*
  - *Preliminary in vitro data with multiple molecules suggests that comparison of cutaneous PK is feasible using the technique*
- *Data collection and data analysis of spectroscopic data*
  - *Multiple approaches including Deep Learning utilized to automate data collection and processing*
- *Development of validation strategies for utilization of method in a regulatory setting*
  - *Currently we are utilizing available data to identify relevant parameters for assessment of cutaneous PK data*
  - *Future scope of work would include development of method validation strategies*

How Can Visualization Help



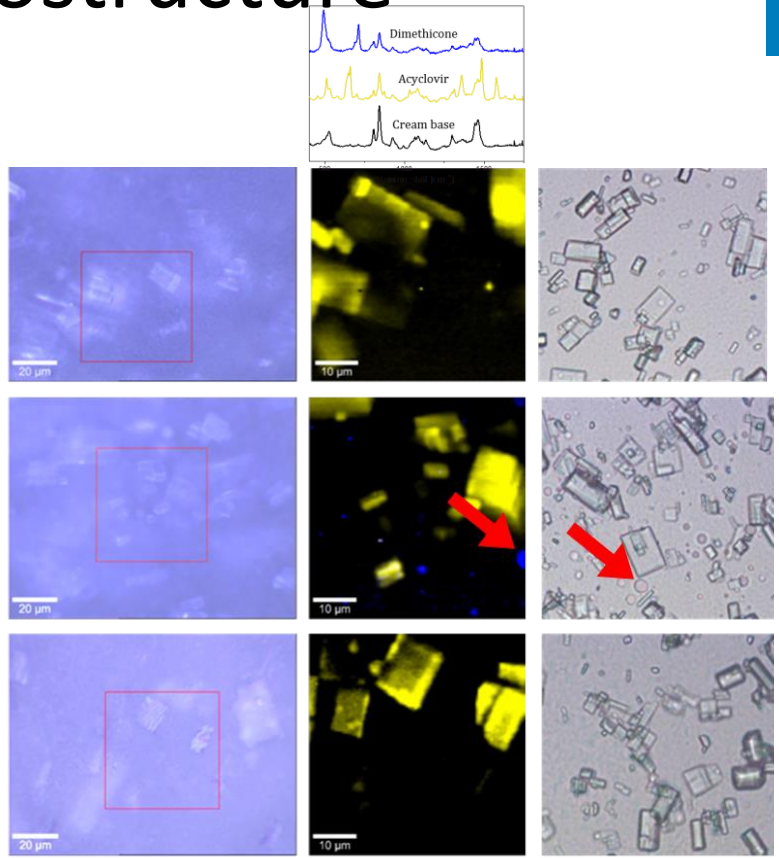
Product Microstructure



Zovirax® UK
Tube

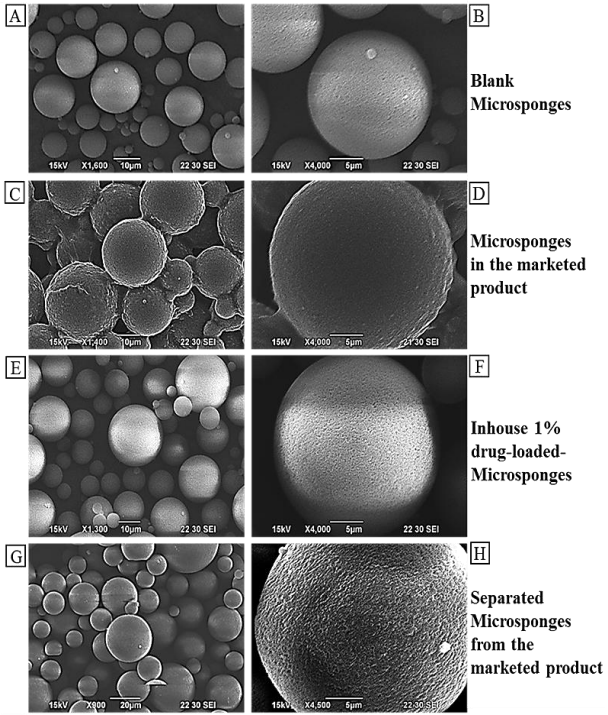
Zovirax® UK
Pump

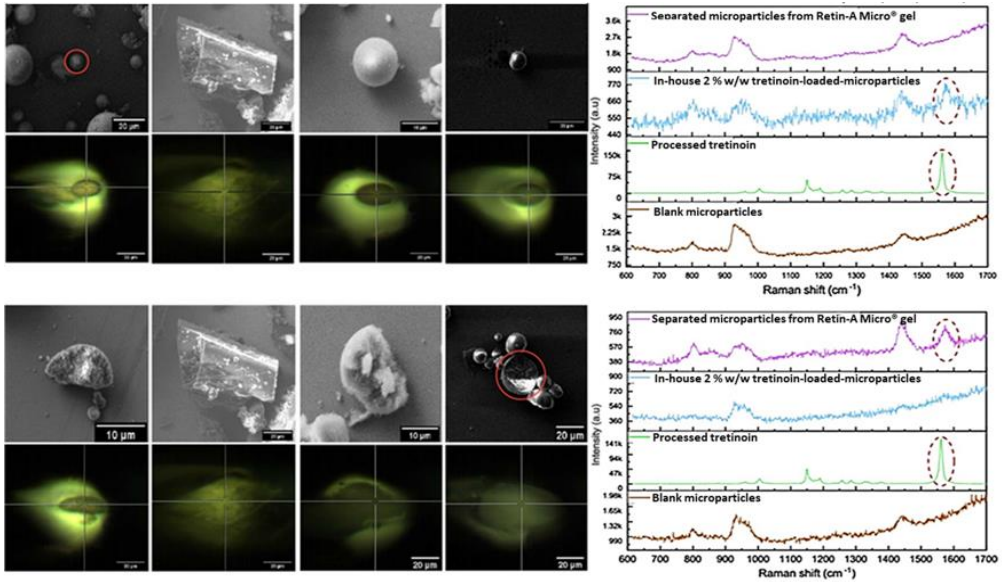
Zovirax® UK
Pump
(from inside container)



Prof. Michael Roberts FDA Award U01-FD005226

Product Microstructure

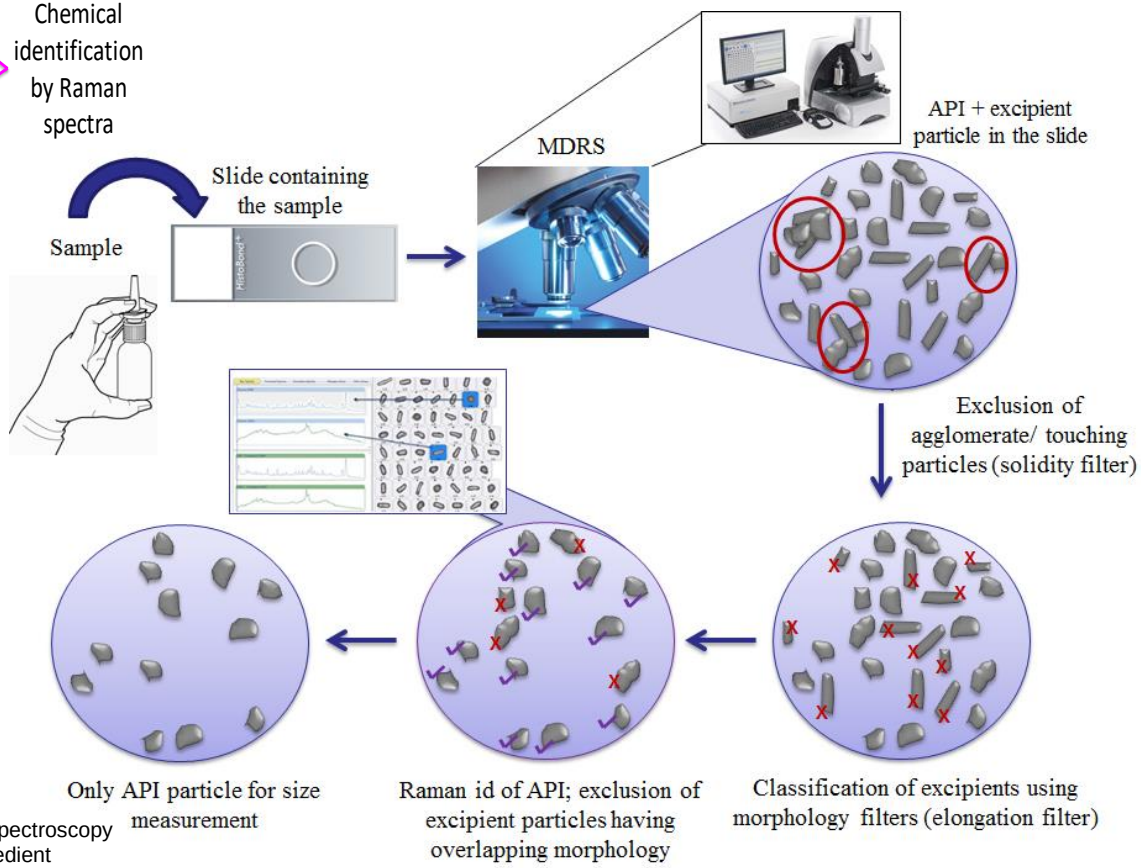




In-SEM SCA Raman analysis of Microsponges® at the surface and inside broken Microsponges®.

Preparation, Characterization and IVRT Study of Tretinoin Loaded Microspheres in Topical Gel Product , AAPS Annual Meeting, 2020
Investigating the Relationship Between Tretinoin Distribution in Microsponges and Release Mechanism Using In-SEM Raman Spectroscopy, CRS Annual Meeting, 2021

Product Microstructure



MDRS – Morphology Directed Raman Spectroscopy
API – Active Pharmaceutical Ingredient

Summary

- Dermal drug products are generally complex dosage forms
- Historically, it has been challenging to assess bioavailability at or near the site of action in the skin
- Spectroscopy can be used as a sensitive and discriminating noninvasive technique for visualization and quantification of drug delivery to the skin. Such understanding of drug bioavailability and localization in the skin can be useful for the evaluation of comparative product performance and formulation optimization.
- Spectroscopy can also be utilized to visualize and quantify where the drug and/or excipient resides within a multiphasic formulation and how the drug diffuses within and is released from the dosage form.
- Goal of the Generic Drug User Fee Amendments (GDUFA)- regulatory science and research program is to facilitate the development of tools that can be utilized to facilitate drug development/ establish bioequivalence and thereby enhance the availability of dermal drug products on the market

Acknowledgements

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- Markham C. Luke, MD, PhD
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- Lei Zhang, PhD
- Robert Lionberger, PhD

Research Collaborators

Collaborations within FDA

All of our collaborators within the GDUFA Regulatory Science Research Program, including

Richard Guy, PhD, ScD

Conor Evans, PhD

U.S. FOOD & DRUG ADMINISTRATION

Thank You

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