Considerations for Medical Scientists: Product Development, Career Development and Regulatory Science

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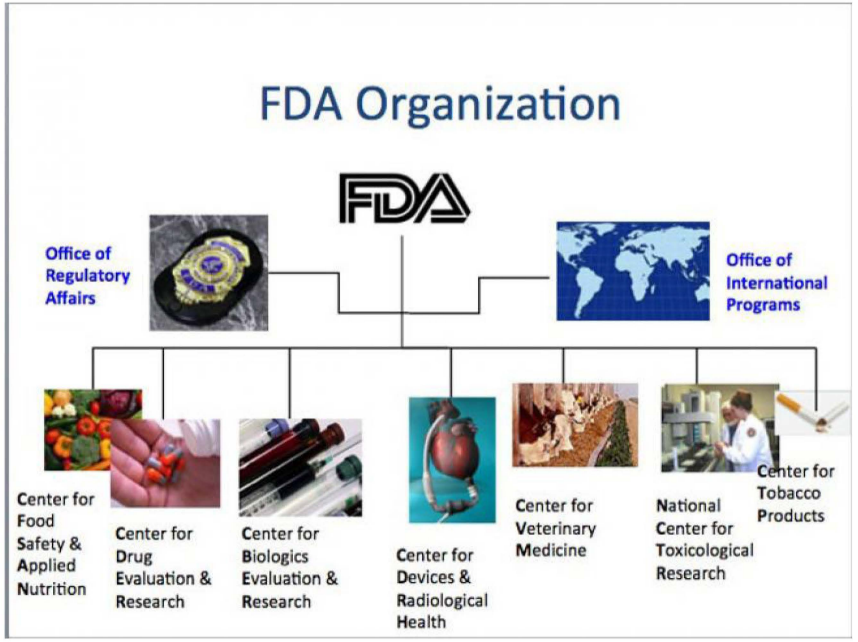
Johns Hopkins University SOM, Baltimore, MD

FDA Campus


FDA
U.S. Department of Health and Human Services
Food and Drug Administration


FDA Organization
FDA
Office of Regulatory Affairs
Office of International Programs
Center for Food Safety & Applied Nutrition
Center for Drug Evaluation & Research
Center for Biologics Evaluation & Research
Center for Devices & Radiological Health
Center for Veterinary Medicine
National Center for Toxicological Research
Center for Tobacco Products

FDA Centers

Most Relevant to Dermatology:

- **Center for Drug Evaluation and Research (CDER)**
  - Office of New Drugs (OND)
    - Division of Dermatology and Dental Drug Products
  - Office of Generic Drugs (OGD)
- **Center for Devices and Radiological Health (CDRH)**
- **Center for Biologics Evaluation and Research (CBER)**

  - Office of Cosmetics and Colors (now in Office of Chief Scientist) – 2023 reorganization of Foods

Developing and Enabling Therapies for Dermatologic Use - My FDA Journey

- 1998 to 2008 - Office of New Drugs
  - Corticosteroids, Retinoids, Biologics, Photodermatology, Fixed Combination Drugs, Sunscreens
- 2008 to 2016 - Office of Device Evaluation
  - Advisory Committees, Dermal fillers, Lasers, Radio-Frequency
  - Device Safety, Clinical Efficacy Determinations, UV Lamps
  - 2012 – Detail to Office of Cosmetics and Colors
- 2016 to Now - Office of Generic Drugs
  - Research and Regulation, Drug Formulation, Q1/Q2/Q3, Product Specific Guidance, Drug-Device Combination Products, Drug Access

What I strive for - Leading Public Health

- Working with others/Breaking down silos/Building bridges
- Understanding risks and benefits
- Leading response/Leading change
- Good public health leadership is position agnostic
- Science-based decision-making/Asking the right questions
- Hiring the right people for the job and supporting them
- Positioning to make a difference in the right direction
- Training others/Leaving a legacy

Stages of Medical Product Clinical Study

1) Exploratory Stage – first in human and feasibility/pilot studies, iterative learning and product development, dose ranging
2) Pivotal Stage – definitive study(ies) to support the safety and effectiveness evaluation of the medical product for its intended use
3) Regulatory Evaluation – product impact on public health ecosystem
4) Post-approval Stage – includes studies intended to better understand the long-term effectiveness and safety, including rarer adverse events, use of real-world evidence

10th Anniversary for Indoor Tanning Bed Reclassification

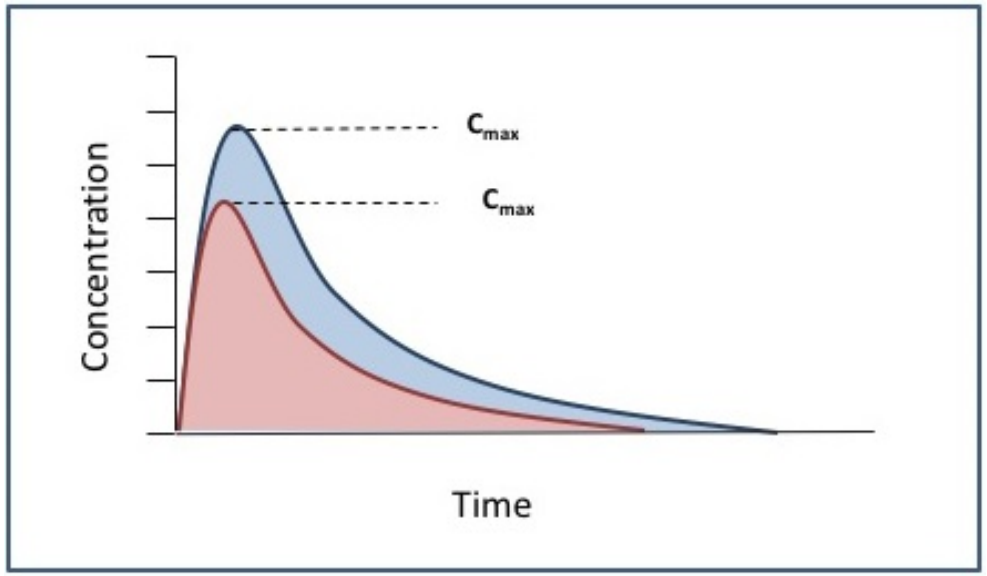
- FDA/CDRH regulates indoor tanning beds/booths.
- Regulated as Class 1 – low risk - devices until June 2014, when they were reclassified to Class 2 – higher risk.
- As part of the reclassification, indoor tanning beds have a boxed warning regarding safety and recommendations not to used by children.
- Notable reduction in the use of UV indoor tanning, in favor of spray tanning booths.

The Promise of Generic Drugs

- Generic drug products use the same active ingredient(s) and can be expected to have the same clinical effect and safety profile when administered under conditions specified in the labeling, as the brand-name (reference) listed drug products
- Generic drug products can be substituted for the reference listed drug product
- ….And they can cost less money

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

How are Most Generic Drugs Approved?



Bioavailability (BA) is assessed, and bioequivalence (BE) is typically established by showing that a generic drug product and the reference standard are similar in terms of their concentrations over time at the site of action (e.g., in the blood – pharmacokinetics or PK)

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

What are Complex Generic Products?

- **Complex active ingredients**
  - –Complex mixtures of APIs, polymeric compounds, peptides
- **Complex formulations**
  - –Liposomes, suspensions, emulsions, gels
- **Complex routes of delivery**
  - –Locally acting such as dermatological and inhalational drugs
- **Complex dosage forms**
  - –Long acting injectables, implantable drugs
- **Complex drug-device combination products**
  - –Transdermals, metered dose inhalers (MDIs)
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

GDUFA Regulatory Science and Product-Specific Guidances (PSGs)

- GDUFA provides resources to allow FDA to perform and fund research to advance generic drug regulatory science and decision-making
  - Goal: Access to generics in all product categories
  - 90+ on-going projects
  - Recent focus on complex drug products
- Research provides new tools for FDA and industry to evaluate generic drug equivalence, to enable more efficient development of generic drugs and thus improve access
- Results from GDUFA research manifest in our PSGs as recommendations for new alternative approaches to demonstrate bioequivalence

Generic Drug Science & Research Website:
https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

PSGs for Complex Drug Products

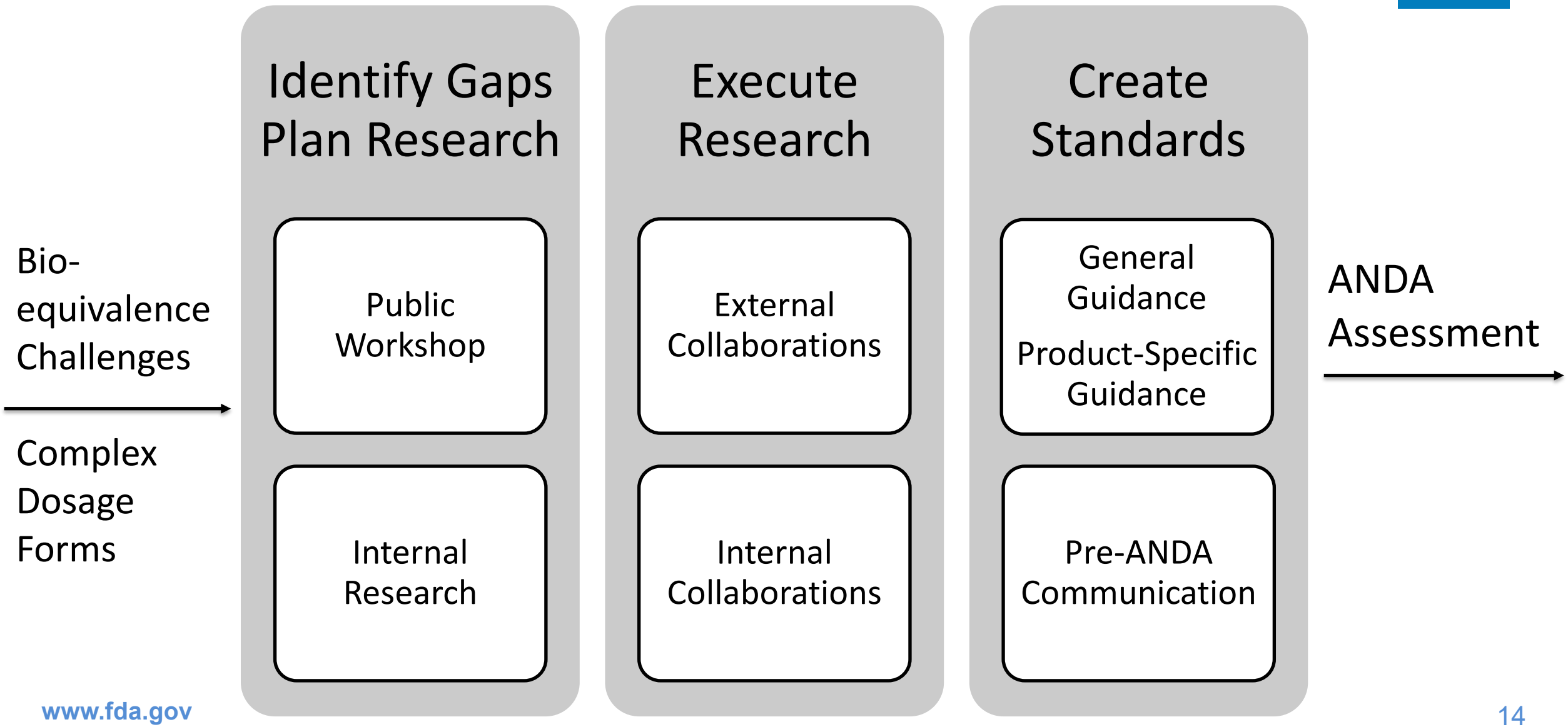
- **There are over 2,000 published PSGs.**
- **These guidance documents have helped provide public access to current thinking on bioequivalence (BE) approaches for our regulated drugs.**
- **The PSGs helped industry in reducing the need for submitting controlled correspondence requests to FDA, allowing better utilization of FDA and industry generic drug development resources.**
- **In recent years, approximately 40% of published PSGs have been for complex products.**
    - BE for some complex products have historically utilized comparative clinical endpoint BE studies. PSGs would provide outlines of the recommended study protocols.
    - As science evolves, PSGs become the conduit for alternative approaches.
    - These approaches are outlined for new PSGs, and as revisions to currently published PSGs.

Over 10 years with GDUFA

- The Generic Drug User Fee Amendments (GDUFA) was signed into law in July 2012, as part of the Food and Drug Administration Safety and Innovation Act (FDASIA)
- One out of numerous User Fee Programs that help the FDA to fulfill its mission of protecting the public health and accelerating innovation in the industry
- GDUFA is designed to speed the delivery of safe and effective generic drugs to the public and improve upon the predictability of the review process
- One unique feature of GDUFA is the Regulatory Science and Research Program ~ $20 million annually
- GDUFA must be reauthorized every 5 years (currently in GDUFA III)

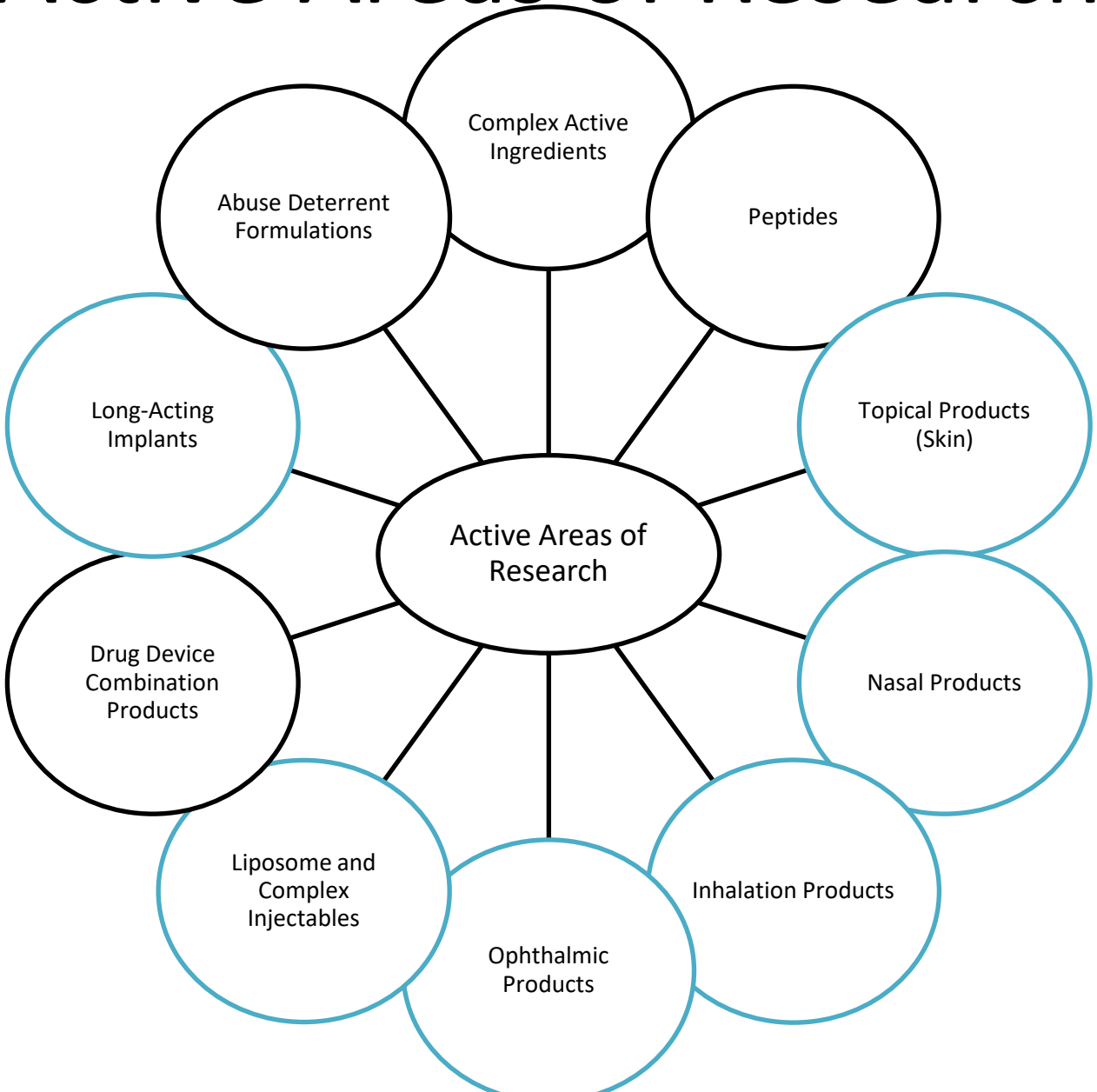
https://www.fda.gov/industry/fda-user-fee-programs
https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments

GDUFA Science and Research Program



BE: bioequivalence

Active Areas of Research



Cutaneous Pharmacokinetics (PK)

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

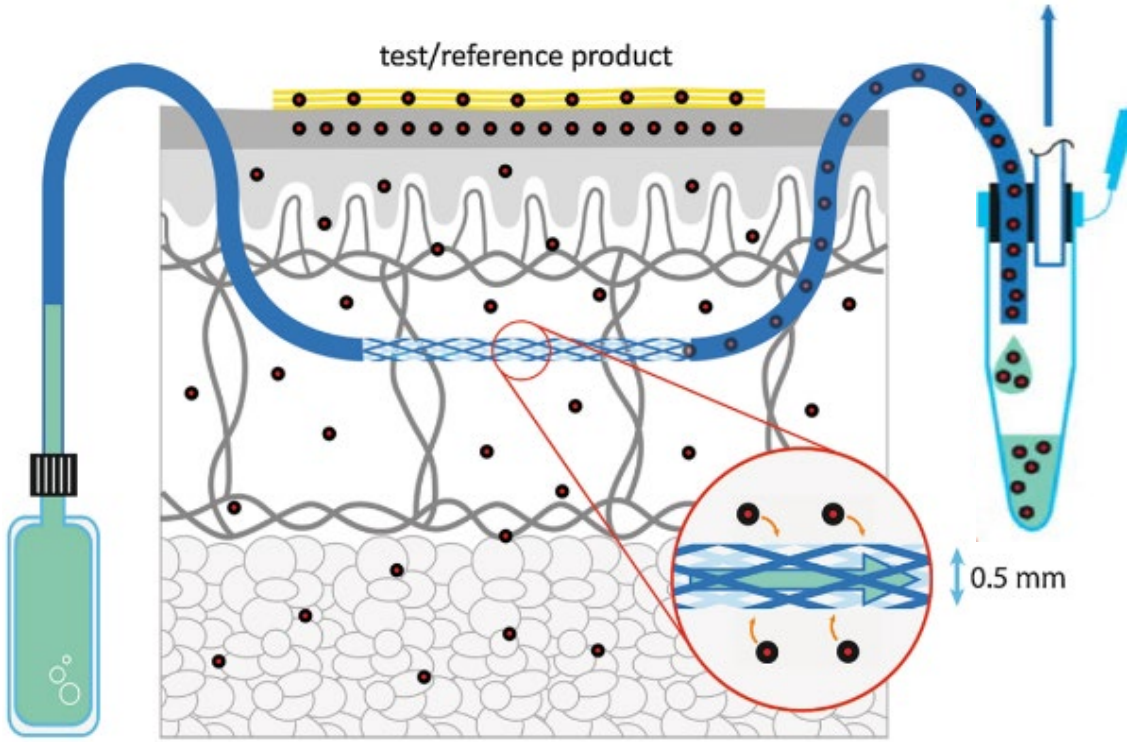
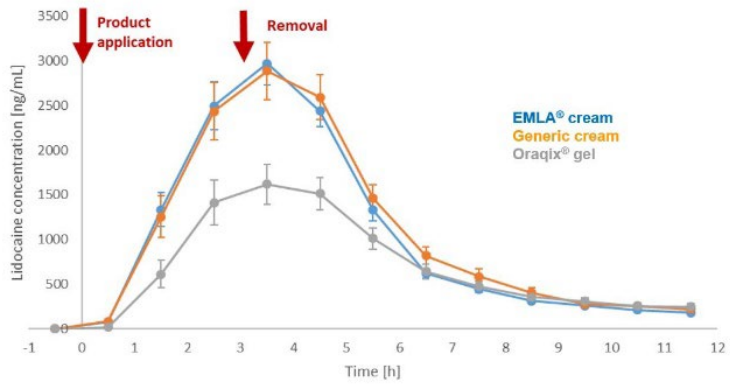
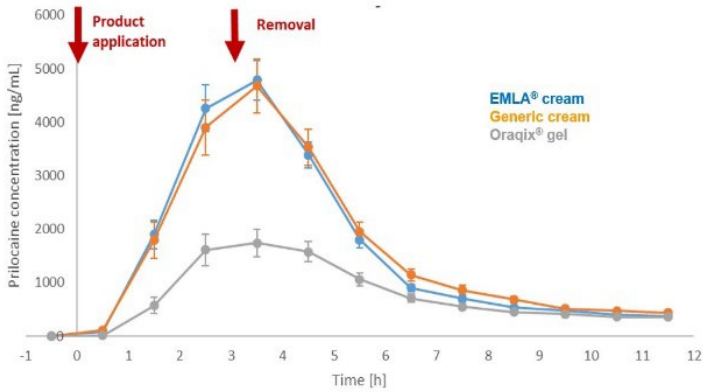


Image provided courtesy of Dr. Frank Sinner, Joanneum Research



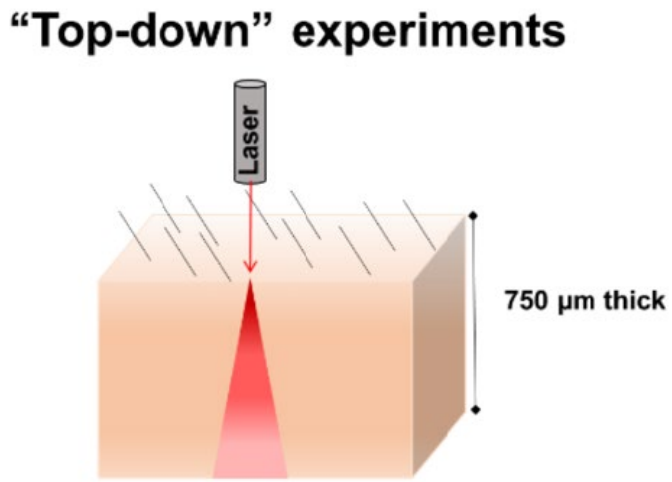


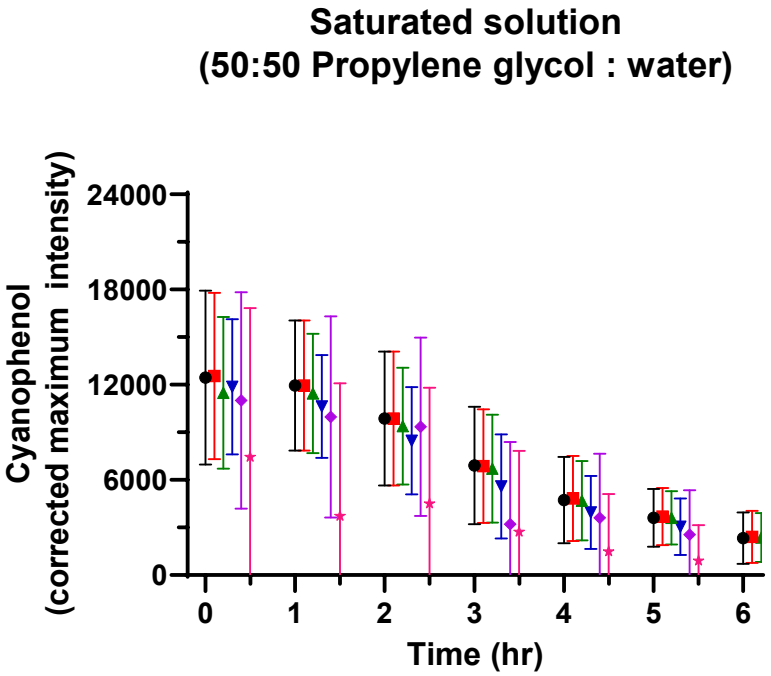
Dr. Frank Sinner provided with FDA funding for award U01-FD005861

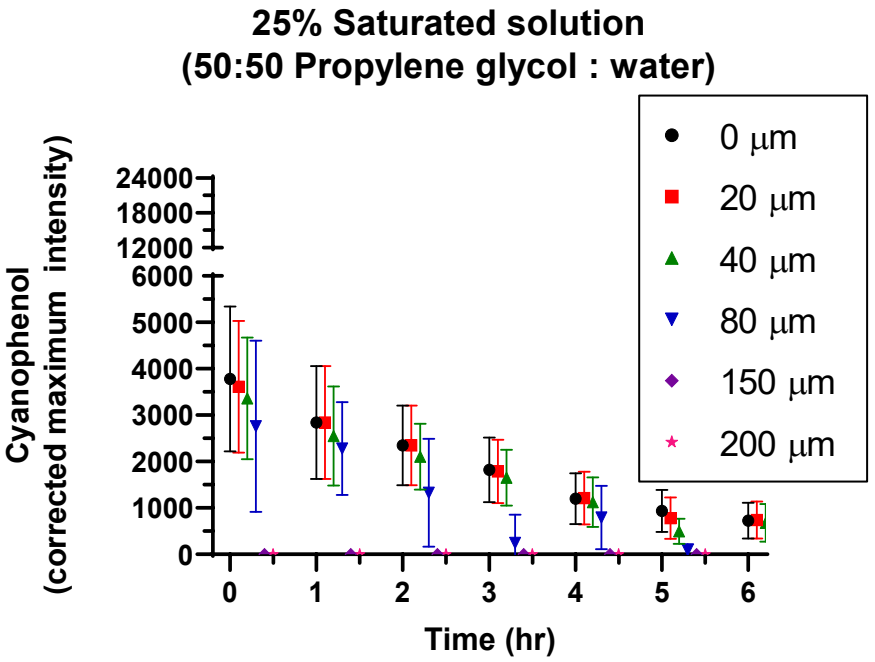
BA: bioavailability

Cutaneous PK

Confocal and Simulated Raman Spectroscopy can directly measure the rate and extent of drug bioavailability at/near the site of action in the skin.



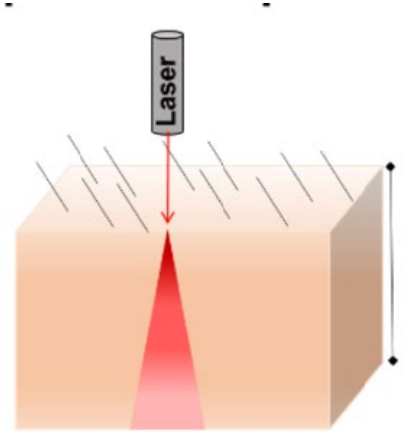


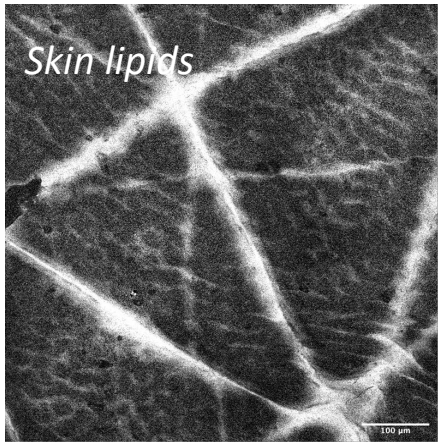


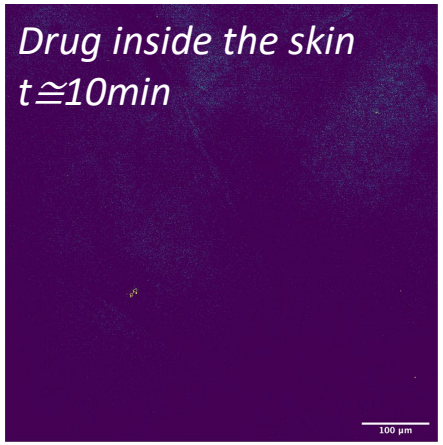
Dr. Richard Guy provided with FDA funding for award U01FD0006533

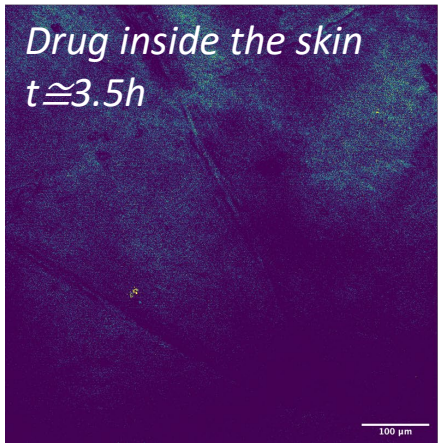
Cutaneous PK

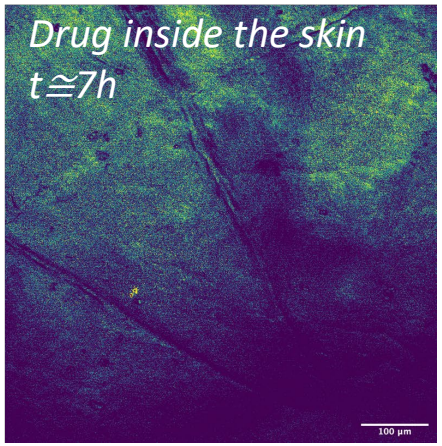
Confocal and Simulated Raman Spectroscopy can directly measure the rate and extent of drug BA at/near the site of action in the skin.

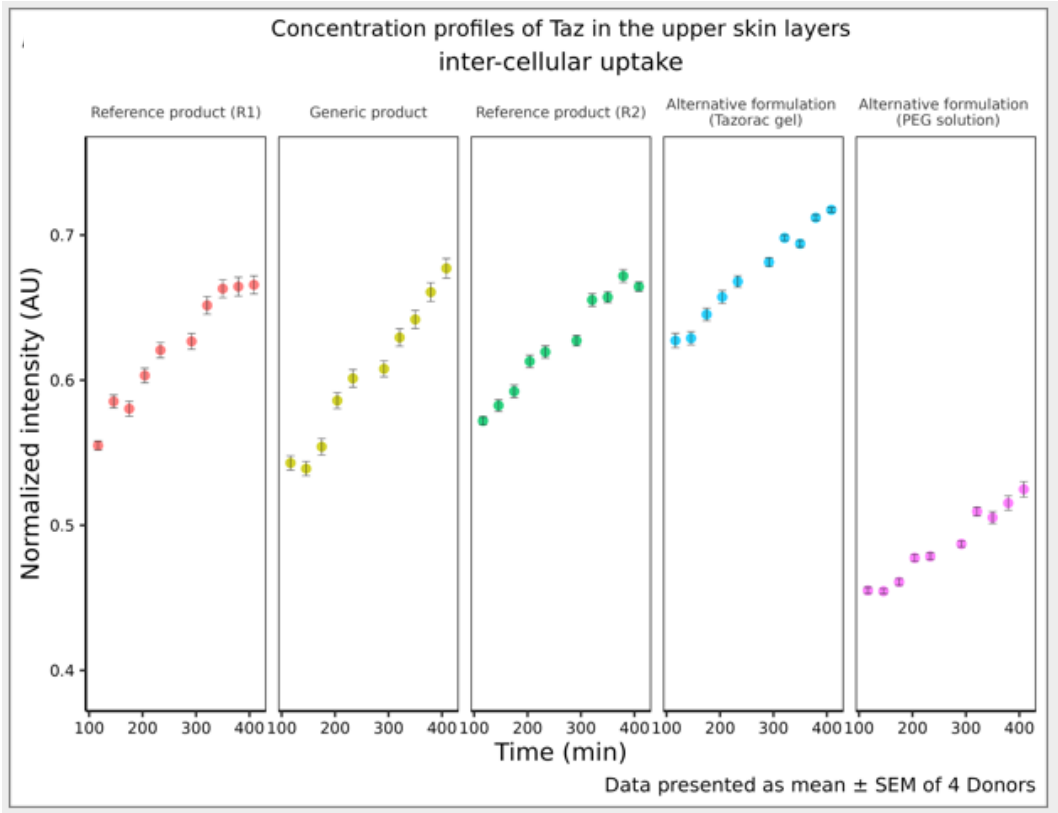






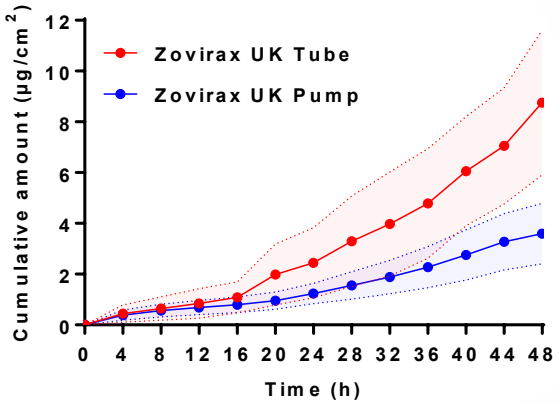






Dr. Conor Evans provided with FDA funding for award U01FD0006698

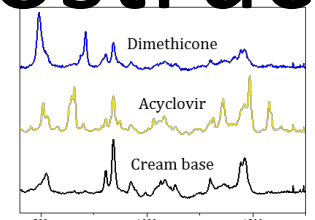
Understanding Product Microstructure

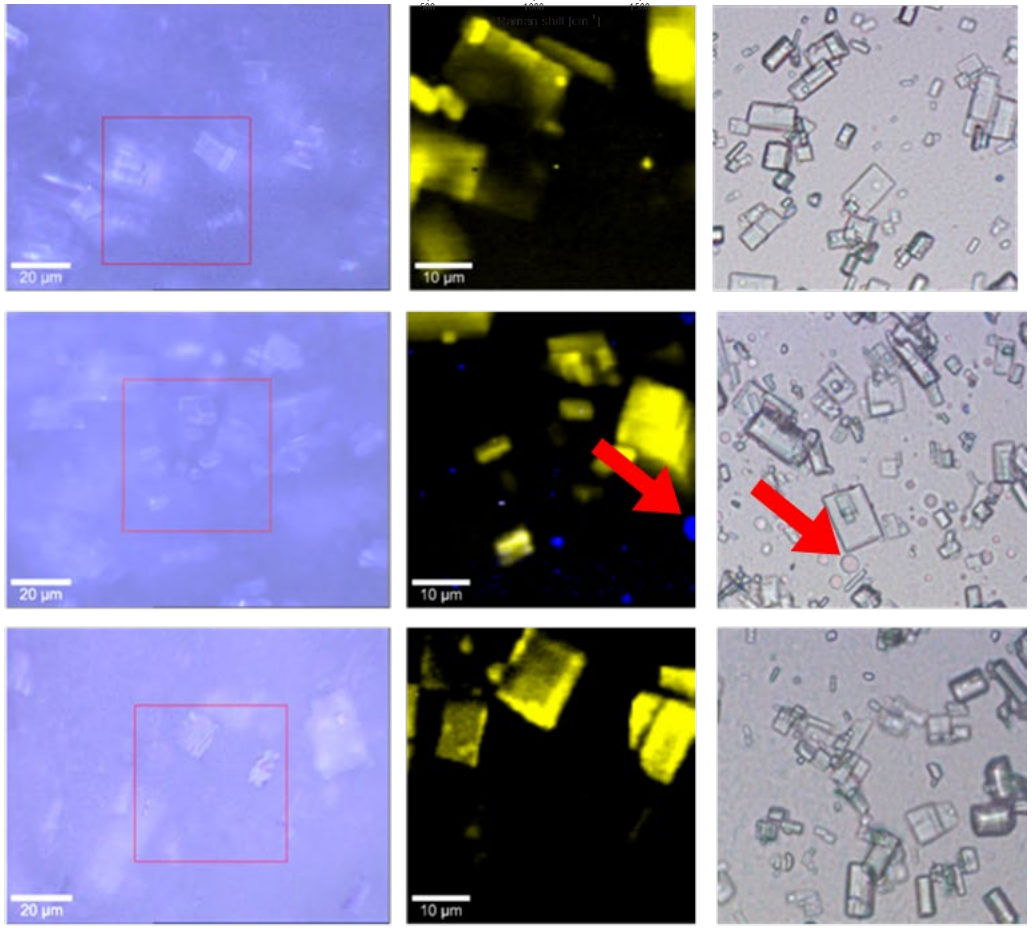


Zovirax® UK
Tube

Zovirax® UK
Pump

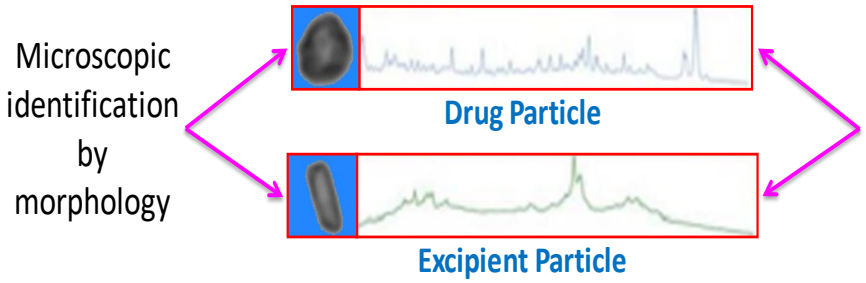
Zovirax® UK
Pump
(from inside container)

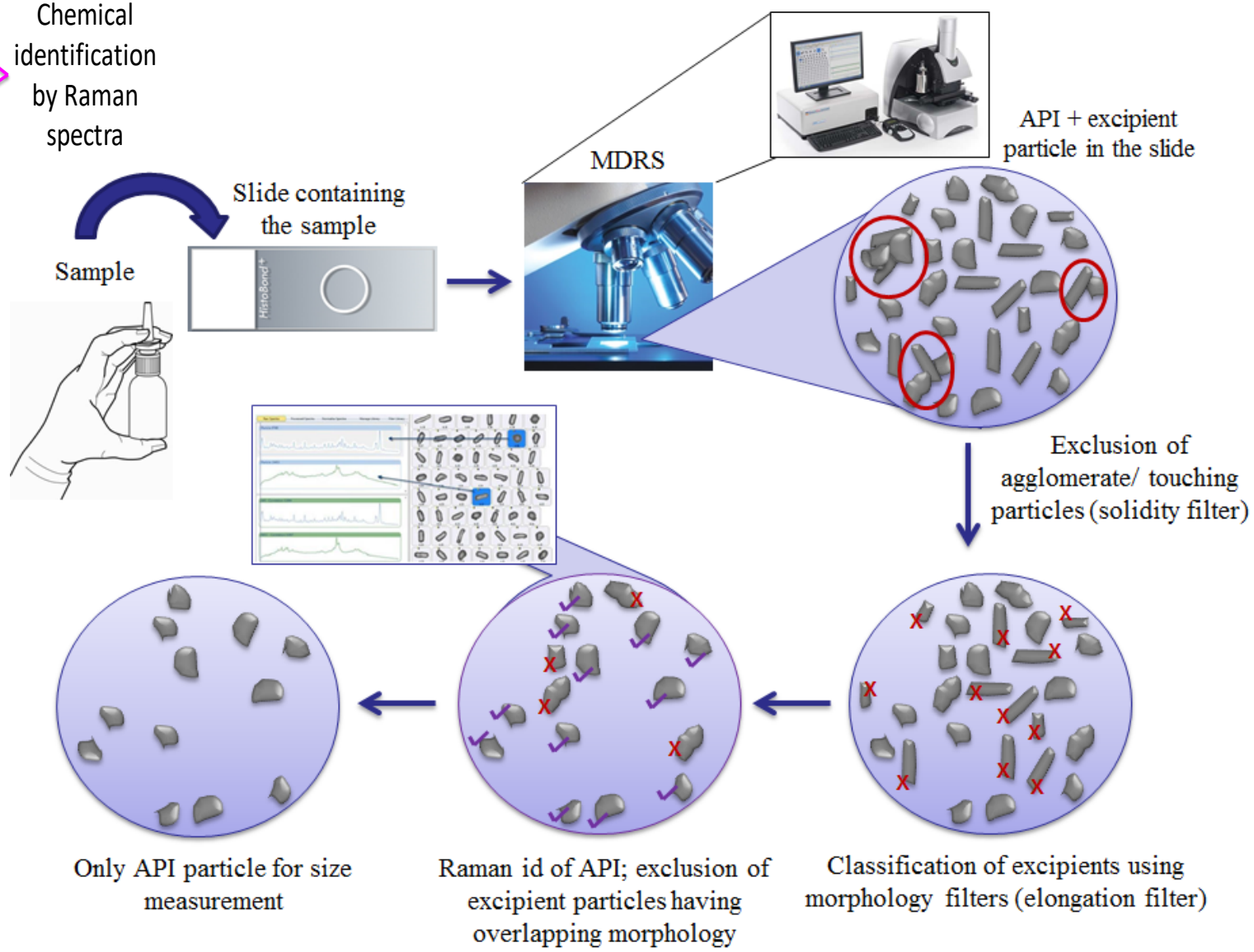




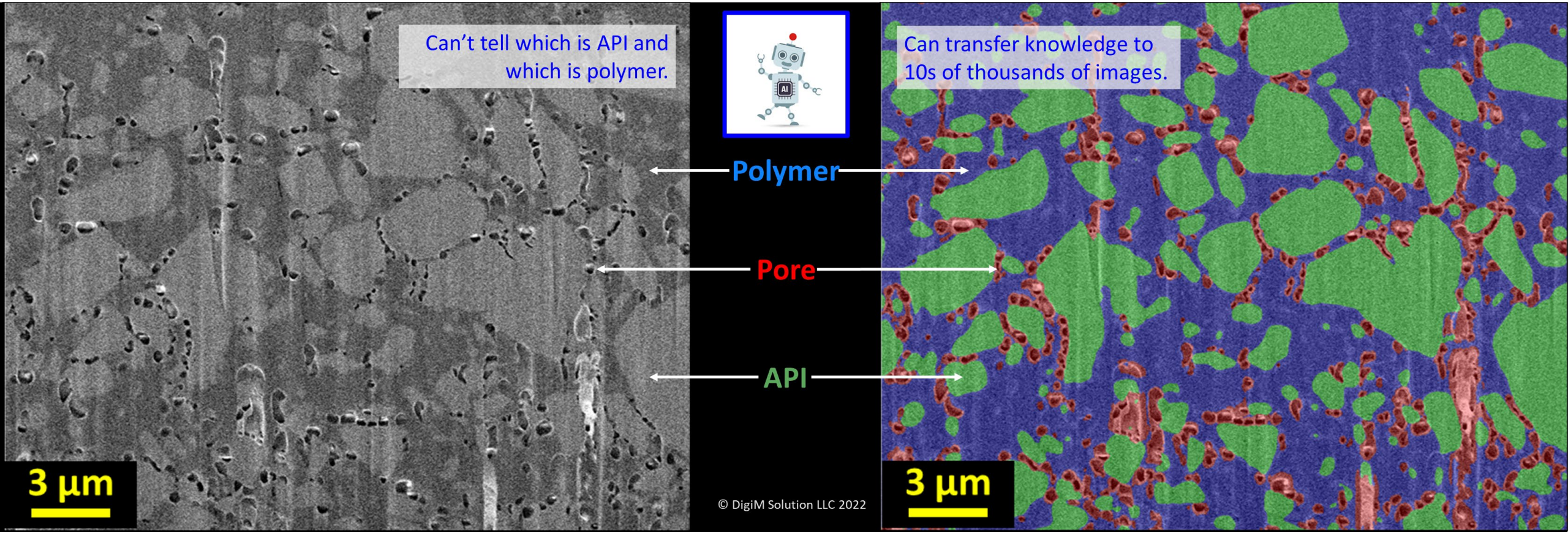
Prof. Michael Roberts provided with FDA funding for award U01-FD005226

Morphologically-Directed Raman Spectroscopy





Imaging and Artificial Intelligence



Dr. Shawn Zhang (DigiM) provided with FDA funding for award Contract # 75F40119C10157

Oct 1, 2023

Division of Therapeutic Performance I (DTP I)

Markham C Luke, MD, PhD
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Darby Kozak, PhD
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Complex API, Injectable, Ophthalmic, and Otic Products Team

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Team Leader

Eric Pang, PhD

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Deyi Zhang, PhD

Yuan Zou, PhD

Qi (Ellen) Li, PhD

Qiangnan Zhang, PhD

Andre O'Reilly Beringhs, PhD

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Bryan Newman, PhD
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Susan Boc, PhD

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Megan Kelchen, PhD

Ying Jiang, PhD

Drug-Device Combination Products Team

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Team Leader

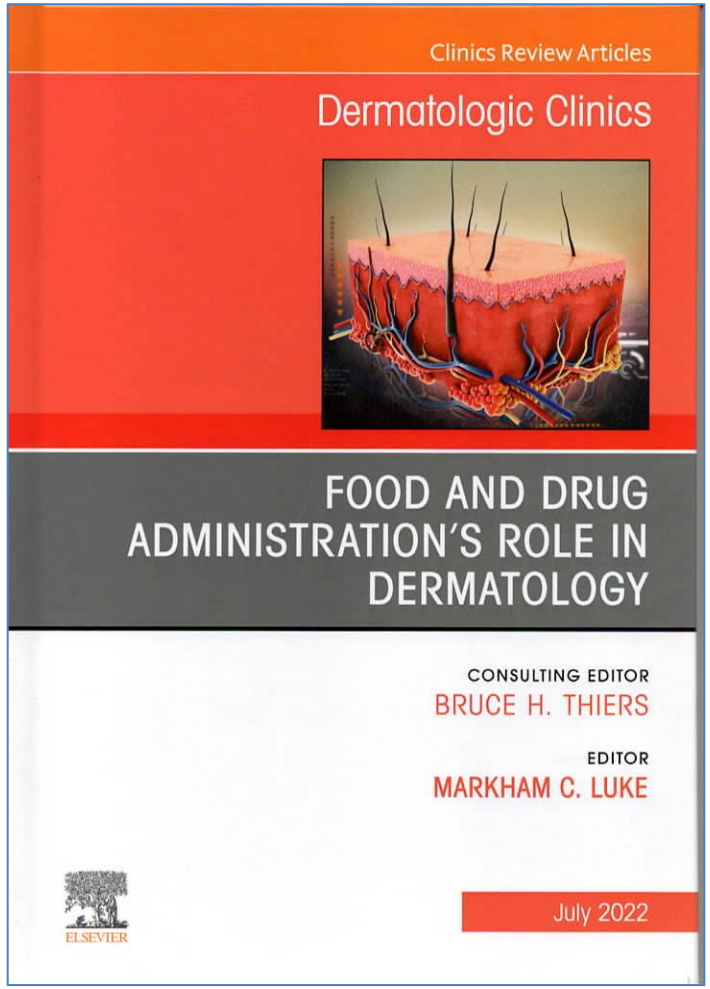
Kathryn (Katie) Hartka, PhD

Betsy Ballard, MD

Karthika Natarajan, PhD

www.fda.gov

July 2022 Dermatologic Clinics



Insightful articles on:

- The History of Dermatology at FDA
- FDA and Dermatologic Drug Development
- Postmarket Assessment for Dermatology Drugs and Cutaneous Adverse Reactions
- How does FDA Approve Generic Drugs
- Dermatology Drugs for Children
- Regulation of Medical Devices for Dermatology
- Regulation of Cosmetics in the United States
- Cutaneous Pharmacokinetic Approaches
- Measuring What Matters to Patients in Dermatology Drugs

FDA HQ Building, White Oak

Reserved Slides

What is a Medical Device?

Defined by the Food Drug & Cosmetic Act as an **instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent**, or other similar or related article, including a component part, or accessory which is:

- intended for use in the **diagnosis of disease** or other conditions, or in the **cure, mitigation, treatment, or prevention of disease**
- intended to **affect the structure or any function** of the body of man

21 U.S.C. 321(h)

What is a Medical Device?

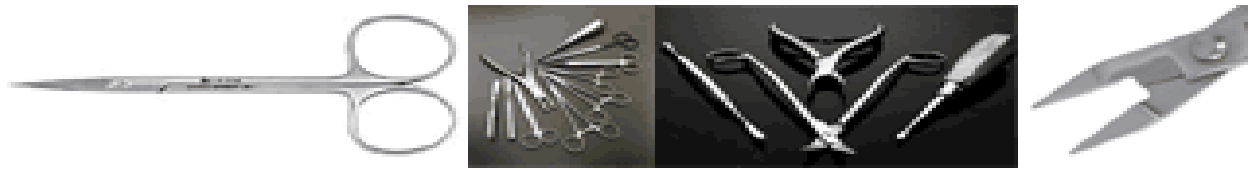
Unlike a drug, a medical device to achieve its primary purpose:

- **does not rely on chemical action** within or on the body of man
- is **not dependent upon being metabolized**

Combination products can be device/drug or device/biologics that are either physically linked or used together and raise unique regulatory issues.

Risk-Based Classification of Medical Devices

- Class I: simple, lower risk devices
  - Subject to “General Controls”
    - Registration and Listing, Quality System, Adverse Event Reporting, Prohibitions against misbranding and adulteration
  - Most exempt from premarket review



Risk-Based Classification of Medical Devices

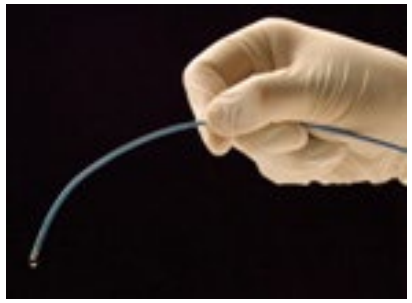
- Class II: more complex, higher risk
  - Subject to General Controls PLUS Special Controls
  - Most require Premarket Notification [510(k)]
  - Regulatory standard is “Substantial Equivalence”
  - Most cleared based on preclinical and animal testing (10% require clinical)

Substantial Equivalence (SE)

- 510(k) submissions compare new devices to “predicate” marketed devices
- A decision flowsheet results in a binary determination of SE vs. NSE
  - Indication and Intended Clinical Effect/Use
  - Technological Characteristics (Design/Material)
  - New types of Safety/Effectiveness Concerns
  - Performance Data (including clinical)

Risk-Based Classification of Medical Devices

- Class III: most complex, highest risk
  - Bench – Animal - Clinical
  - Premarket Application [PMA]
  - Regulatory standard is “reasonable assurance of safety and effectiveness”
  - May include post-approval study requirements



De Novo Applications

- Added in 1997 under FDAMA as an alternate pathway to classify novel devices of low to moderate risk that had automatically been placed in Class III after receiving an NSE determination for a 510(k).
- Under FDASIA, two pathways for de novo classification: (1) NSE first – then request risk-based classification, or (2) to submit a de novo classification request to FDA directly without first being required to submit a 510(k) for a low to moderate risk device.
- Devices that are classified through the de novo process may be marketed and used as predicates for future 510(k) submissions.

Combination Products

- Include device/drug and device/biologic products that are:
  - physically linked; or
  - separately packaged together (e.g., drug and device products); or
  - packaged separately but required to be used together.
- Raise unique regulatory and scientific issues