U.S. FOOD & DRUG ADMINISTRATION

Advanced Analytical Methods in Generic Drug Development and Approval

Darby Kozak, Ph.D.
Darby.Kozak@fda.hhs.gov
Deputy Director
Division of Therapeutic Performance 1,
Office of Research and Standards
OGD | CDER | U.S. FDA

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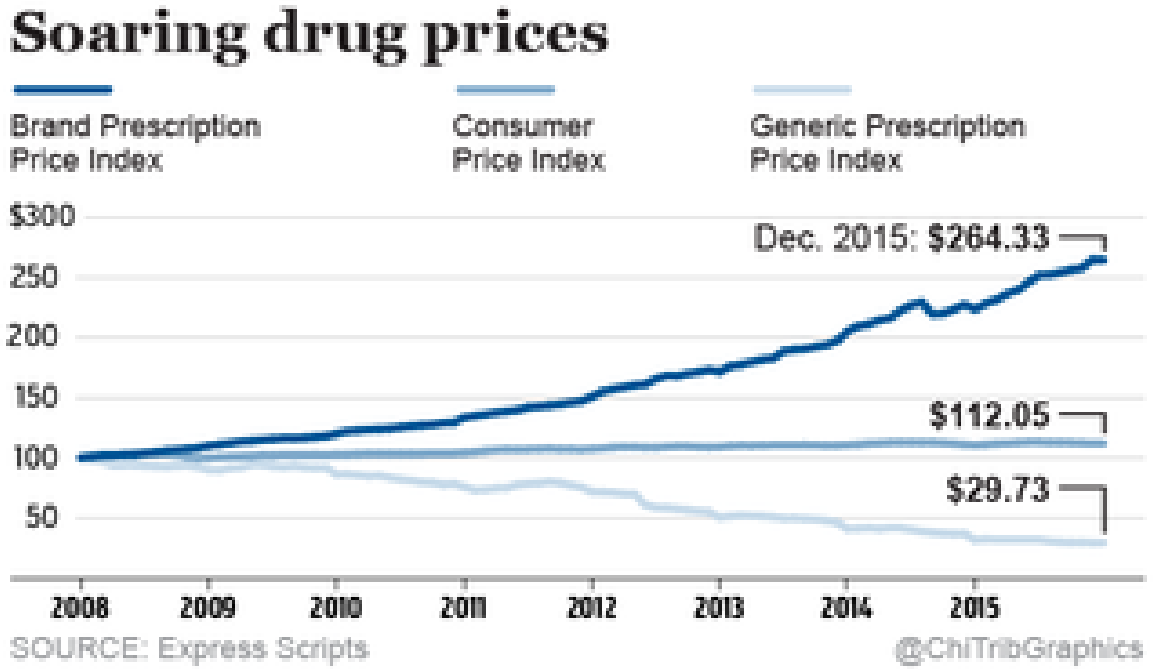
Analytical Methods for Generic Drug Development

- What is a generic drug and the importance of advanced analytical methods for generic drug development and approval
- Facilitating generic drug development via the Generic Drug User Fee Amendments (GDUFA) research program
- Examples of GDUFA research on advanced analytical methods for characterizing:
  - Complex heterogenous and polymeric macromolecules
  - Physicochemical properties and drug distribution in complex particulate and non-Newtonian formulations
  - In vitro product performance to support product equivalence

Impact of Generic Drugs

- Generics create competition that can reduce drug prices, saving the U.S. health care system $2.2 trillion dollars in the past decade and improving patient access and adherence to a therapy.[1]
- Generics can reduce drug shortages by diversifying the supply chain.
- Ninety percent of prescriptions filled in the United States are for a generic, but many complex[2] drug products still do not have a generic available.



Chicago Tribune, 2016

1. Association for Accessible Medicines' 2020 Report: https://accessiblemeds.org/2020-Access-Savings-Report ; and Ophthalmology 122.4 (2015): 738-747
2. Complex product as per FDA's 2016 GDUFA II Commitment Letter https://www.fda.gov/media/101052/download

Regulatory Pathways of Drug Applications

New Drug Application (NDA) Name Brand Drug	Abbreviated NDA (ANDA) Generic Drug
A drug product that may have a New Molecular Entity (NME), new formulation, and/or new indication and includes information/investigations to demonstrate its safety and effectiveness	Must ***reference a listed drug***, contain information to establish ***therapeutic equivalence***, and may not be submitted if studies are necessary to establish safety or effectiveness
Labeling Pharm/Tox Chemistry Manufacturing	Controls Microbiology Inspection Testing
*Labeling** Pharm/Tox Chemistry Manufacturing	Controls Microbiology Inspection Testing
Animal Studies Clinical Studies Bio availability	Bioequivalence

*ANDA labeling is the same as the labeling for the listed drug (with limited exceptions)

Generic Drugs

- FDA approved generic drugs are **Therapeutically Equivalent (TE)** to a Reference Listed Drug (RLD)
- They can be substituted for the RLD (brand product)
- Generic and RLD have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

Generic Drugs: Therapeutic Equivalence

A generic product that is TE to the RLD product must be:

- Pharmaceutical Equivalent (PE)
  - Contain identical amount of the identical active ingredient(s)
  - Identical dosage form
  - Identical route of administration
  - Does not necessarily contain the same inactive ingredients *
  - Meet compendial or other applicable standards
- Bioequivalent (BE)
  - The absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when administered under similar conditions

** If required under 21 CFR 314.94(a)(9) or recommended by a product specific guidance*

Common Challenges in Generic Development

Advanced analytical methods can help address generic product development and assessment challenges, such as demonstrating:

- Active ingredient sameness
  - Characterizing and comparing heterogenous mixtures and polymers
- Pharmaceutical equivalence
  - Characterizing complex formulations
  - Comparing inactive ingredients if needed*
  - Comparing impurities if needed
- Bioequivalence
  - Locally acting …

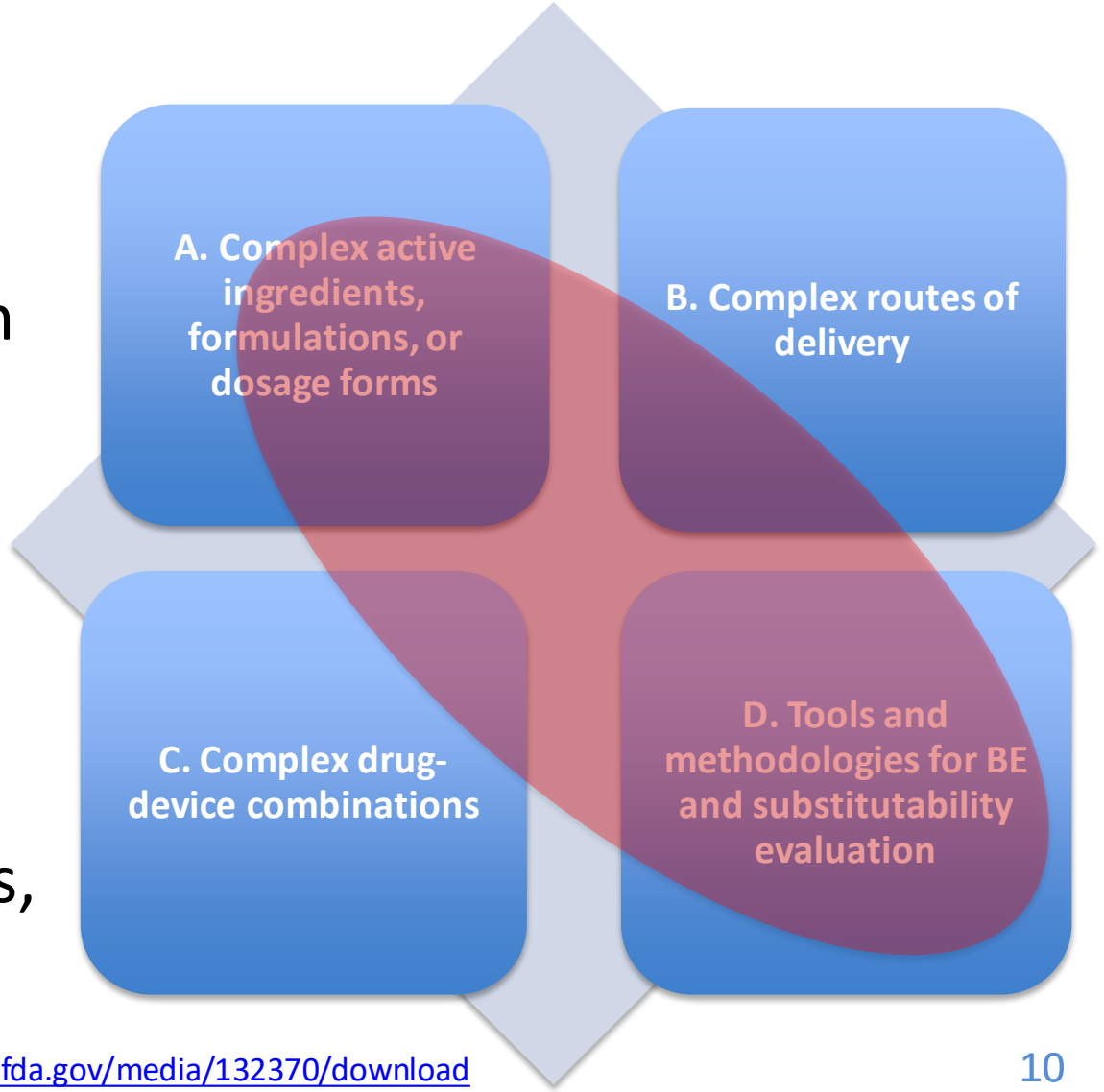
** If required under 21 CFR 314.94(a)(9) or recommended by a product specific guidance*

Generic Drug User Fee Amendments (GDUFA) Research

- FDA's research on complex generics helps the development of more generic competition in areas where bioequivalence evaluation is scientifically challenging
- FDA's research helps to make generic drug development and review more efficient
- In 2020, FDA's GDUFA Science and Research Program funded approximately $20 million in research.

GDUFA Research Priority Areas

- In 2020 there were 15 priority areas under 4 broad categories
- New analytical methods have focused on improving:
  - A. Complex active ingredient and formulation characterization
  - D. Tools for bioequivalence evaluation
- External and internal research have explored developing new testing methods, optimizing analytical protocols, and improving analytical sensitivity



https://www.fda.gov/media/132370/download

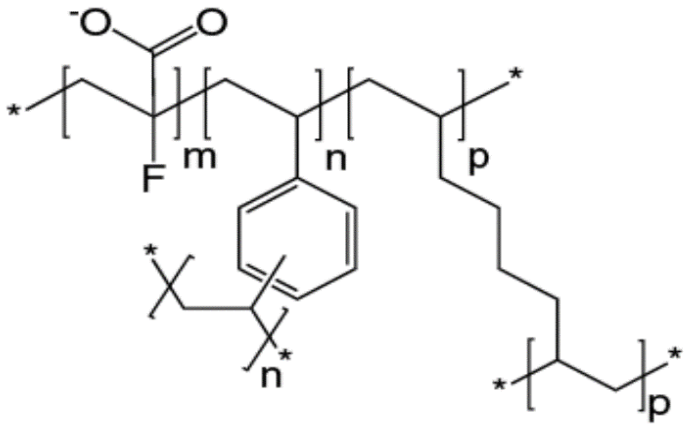
Complex Active and Inactive Ingredient Characterization

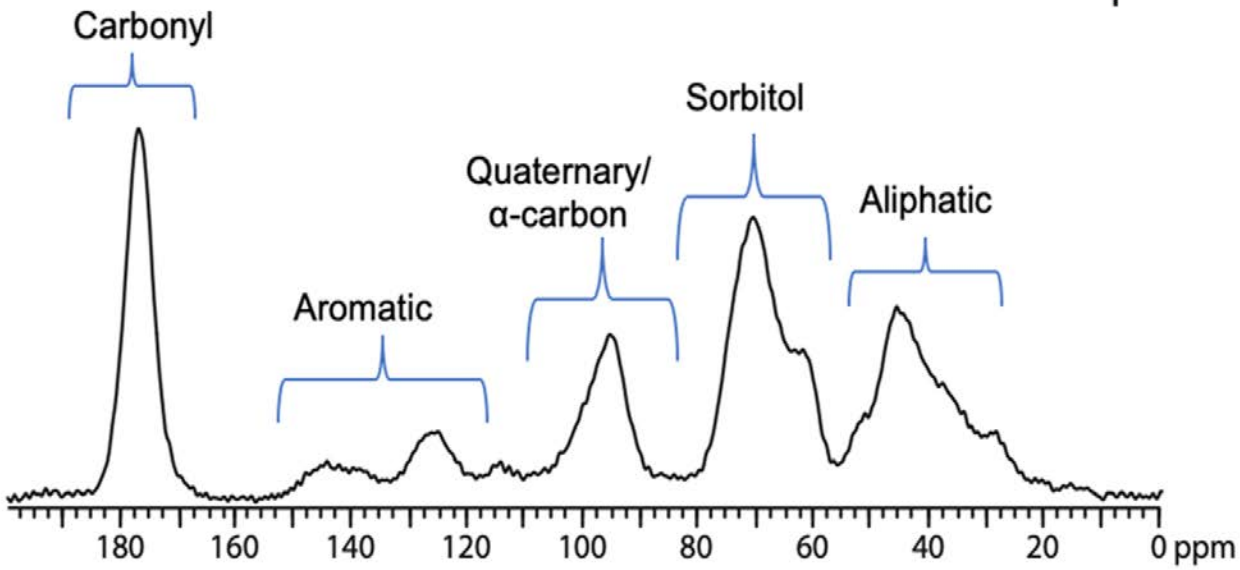
- A generic drug applicant provides analytical information to demonstrate active sameness to the RLD and inactive ingredient identity, which is typically straightforward analysis for highly purified small molecules.
- There remains a need for sensitive analytical methods to characterize the chemical structure, and in some instances the impurity profile, of heterogenous macromolecules.
- Recent GDUFA research has focused on the feasibility of solid-state and 2D NMR, LC-MS/MS, and GPC-4D to characterize complex polymer structures and mixtures used in drug products.

Solid-State Nuclear Magnetic Resonance (ssNMR)

- VELTASSA (patiromer sorbitex calcium) oral powder is a cross-linked copolymer composed of three monomers that binds potassium in the GI tract and is insoluble in most solvents.
- To better understand RLD variability and provide industry with methods to support API sameness, ^{13}C ssNMR was used to characterize the monomer (m), (n) and (p) composition including lot-to-lot variability:

(m) = 90.8%; (n) = 7.7%; (p) = 1.5%

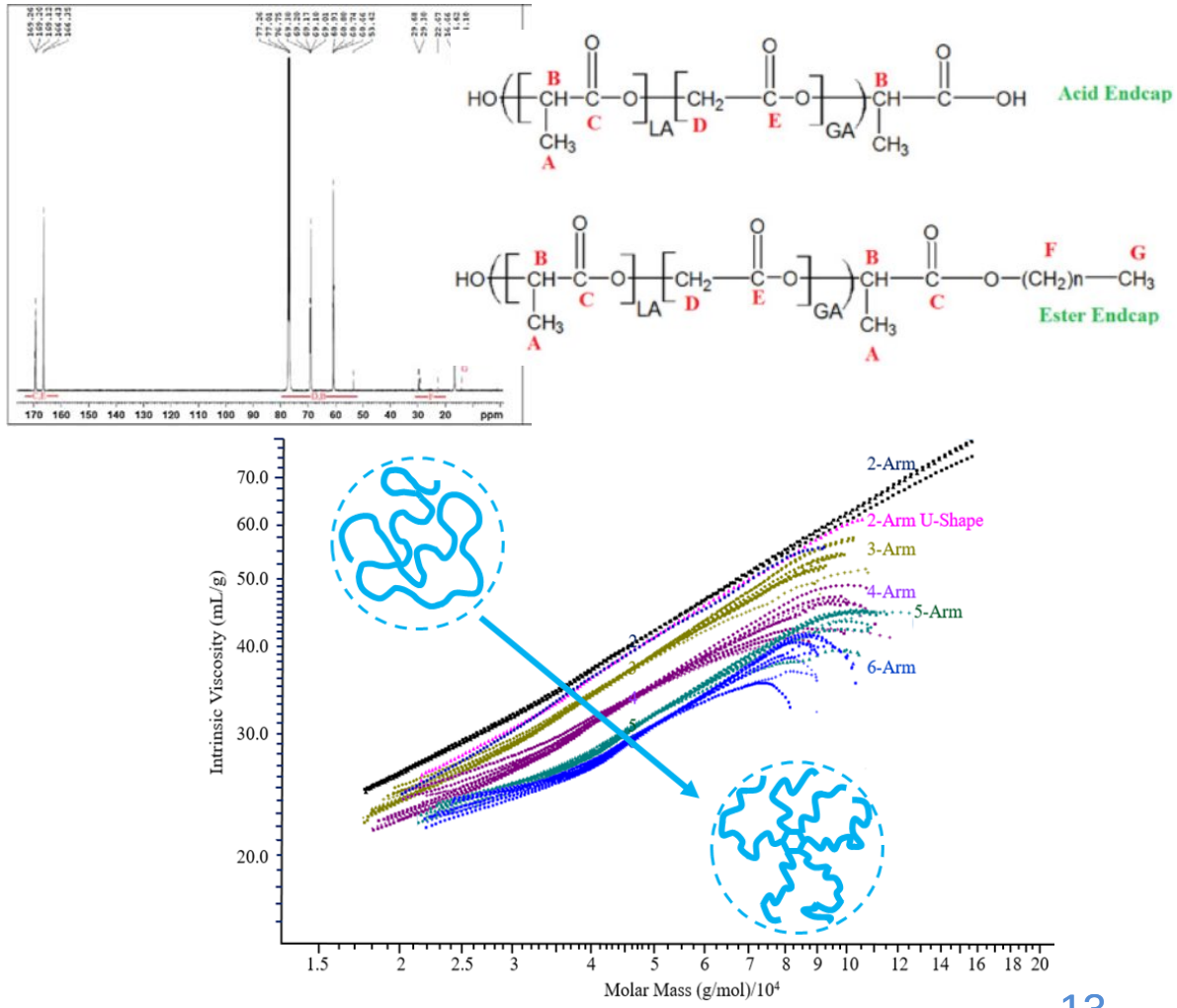




GDUFA grant 5U01FD004275-07 to Eric Munson via National Institute for Pharmaceutical Technology and Education (NIPTE).

NMR and 4 Detector Gel Permeation Chromatography

- Poly(lactide-co-glycolide) is a biodegradable copolymer excipient used to enhance drug release.
- L:G ratio, polymer molecular weight, linear and branching structure, and end group chemistry can affect polymer degradation and drug release rates.
- To facilitate reverse engineering and demonstrating comparable ingredient identity, ^{13}C and ^{1}H NMR along with Gel permeation chromatography with refractive index, viscosity, multi-angle light scattering, and infrared detectors (GPC-4D) enables complex polymer characterization.



GDUFA contract HHSF223201610091C & HHSF223201710123C to Akina Inc

Inter J Pharma 495 (2015) 87–92; J Control Release (2019), 304: 75-89

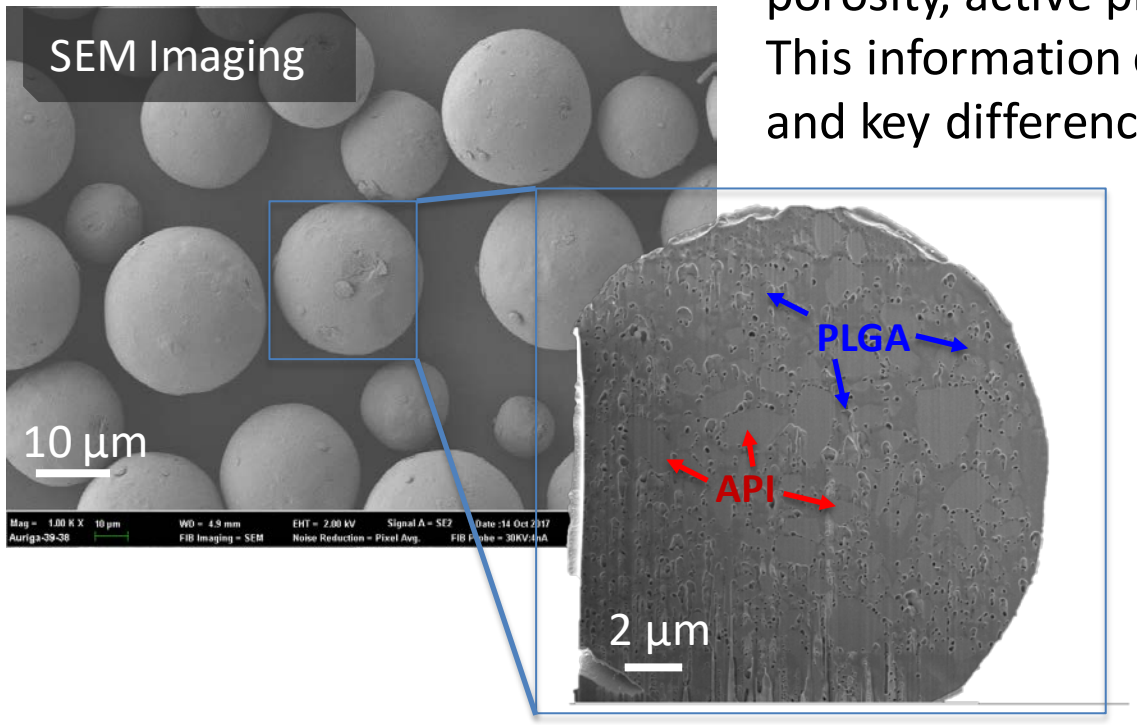
Complex Formulation Characterization

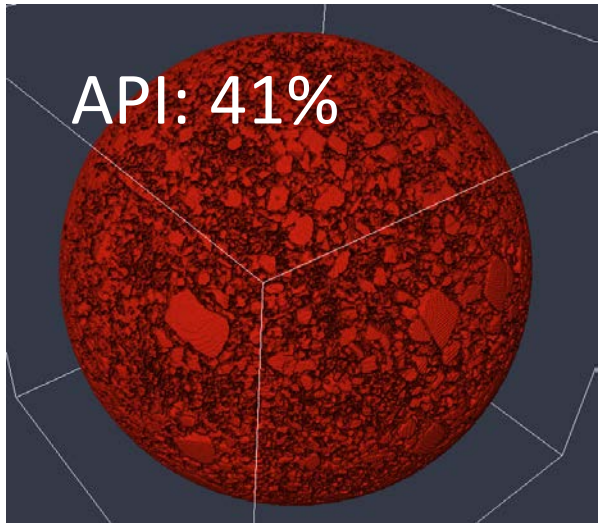
- Improved methods to characterize and compare the critical quality attributes of complex formulations would enhance generic drug development by reducing potential modes for a non-bioequivalent product.
- Recent GDUFA research has focused on spectroscopic imaging methods to differentiate chemical regions within the formulation and local distribution post administration.

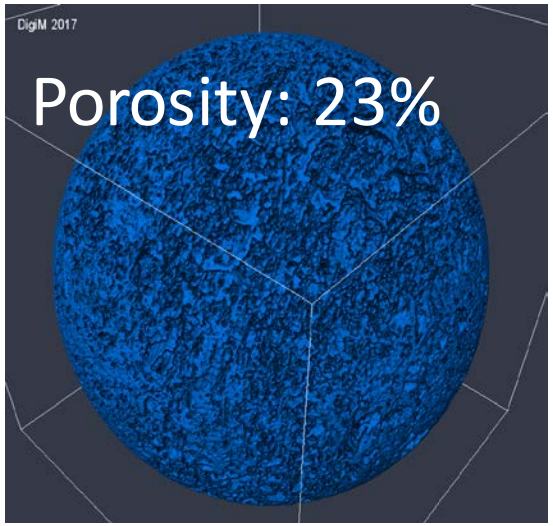
Focused Ion Beam Scanning Electron Microscopy (FIB-SEM)

FIB-SEM Cross Section of PLGA Controlled Release Microspheres

Artificial intelligence (AI)-based analyses of the imaging data can reconstruct porosity, active pharmaceutical ingredients (API), and PLGA polymer domains. This information could be helpful to better understand drug release behaviors and key differences in these domains that can impact BE.



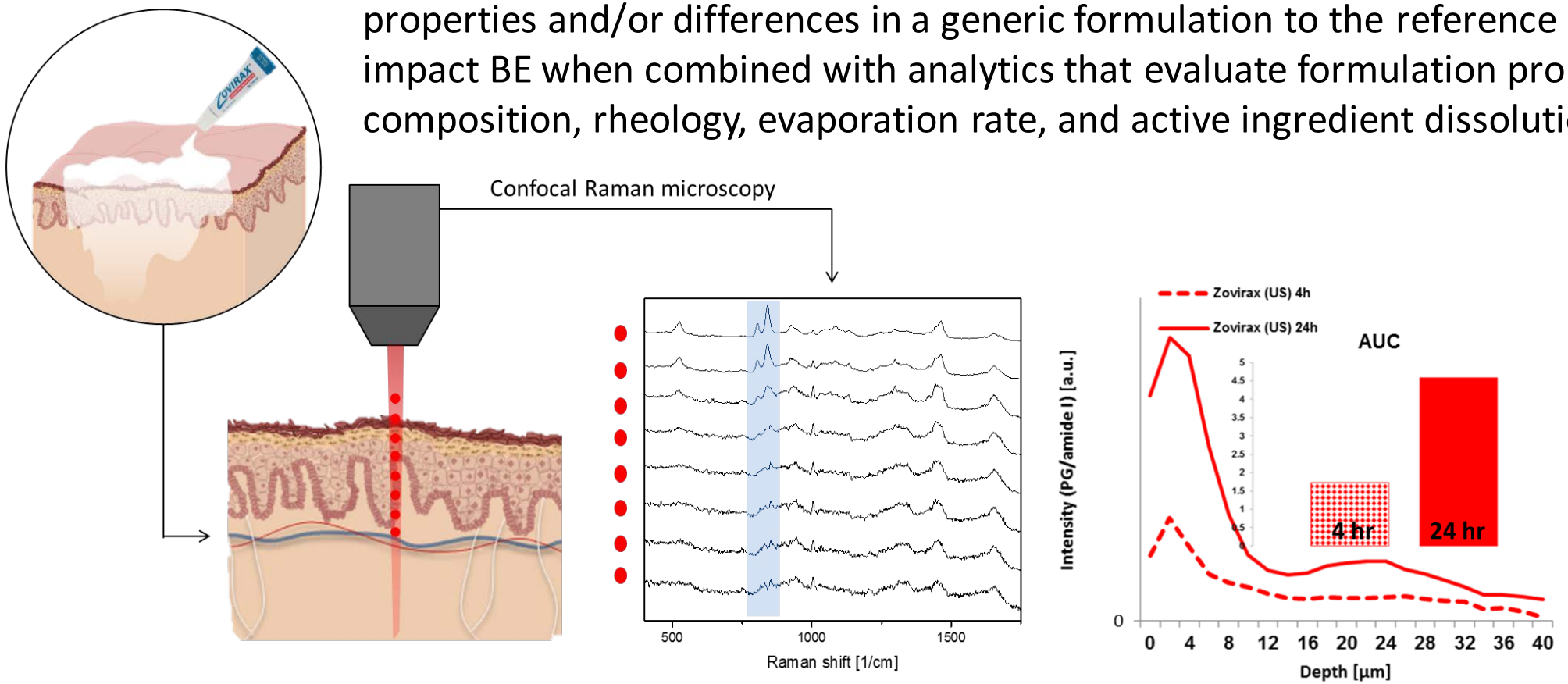




GDUFA Contract # 75F40119C10157 to DigiM Soluton LLC

Confocal Raman Microscopy

Depth profile analysis (penetration) of specific chemical moieties can enable local (e.g., cutaneous) pharmacokinetic measurements. This will help inform how formulation properties and/or differences in a generic formulation to the reference product can impact BE when combined with analytics that evaluate formulation properties, such as composition, rheology, evaporation rate, and active ingredient dissolution.



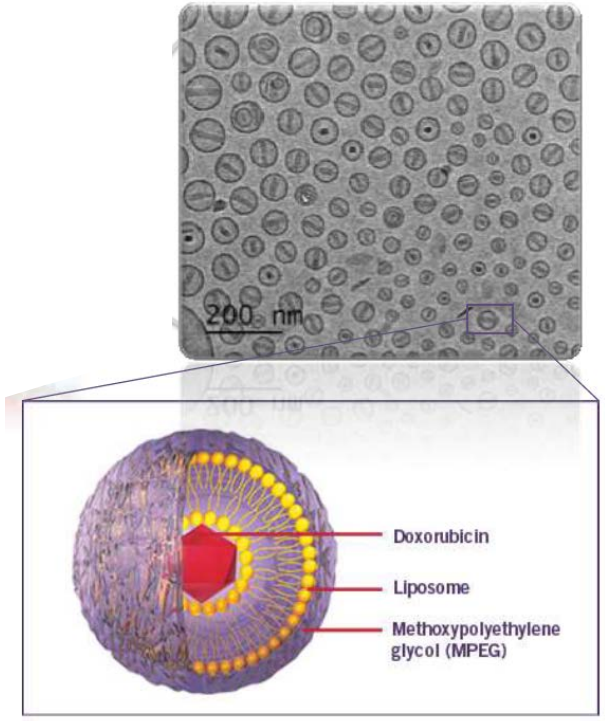
1U01FD006533 Bioequivalence of Topical Products to Prof. Richard Guy at University of Bath
1U01FD006698 Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence, PI Prof. Conor Evans, Massachusetts General Hospital/ Harvard Medical School

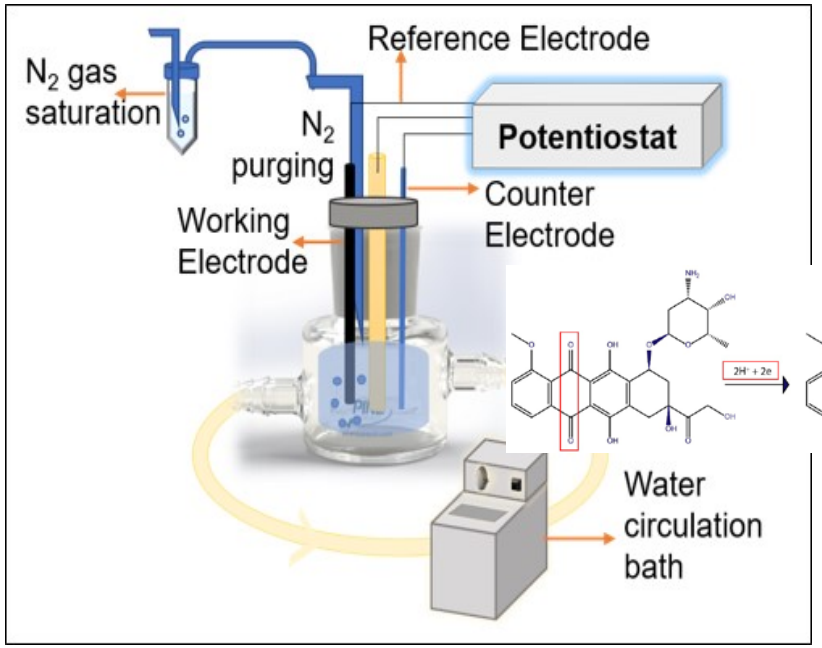
Tools for Product Performance and BE Evaluation

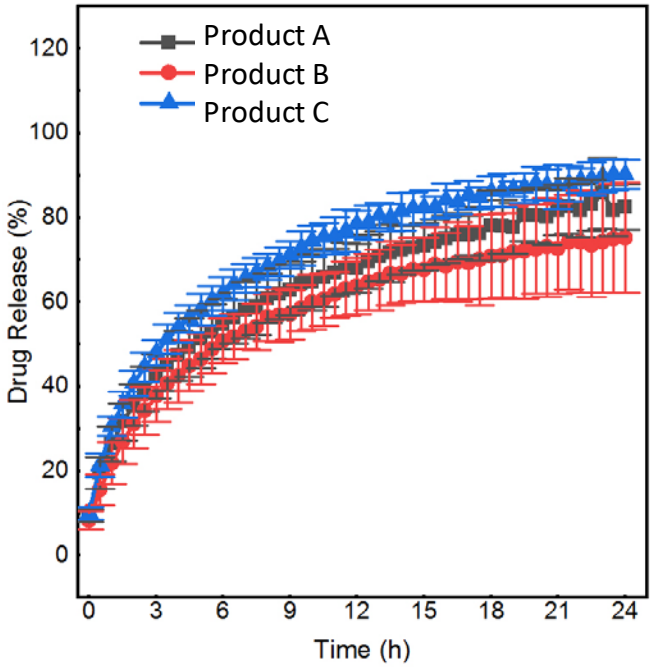
- Need for methods that can better and more efficiently discriminate non-BE products from those that are BE to the reference listed drugs. In addition, to support alternative BE approaches, specialized tools and tests that can bridge to the expected in vivo performance are sought after.
- Recent GDUFA research has focused on development of:
  - In vitro release testing (IVRT) methods that are more sensitive to formulation properties
  - Tools that may better mimic the variability of human physiology and product use conditions

New Tools for Measuring In Vitro Drug Release of Complex Products

- An electroanalytical method was developed for the continuous and direct quantitation of drug released from liposomes that overcomes the limitations and inaccuracies of conventional separation analysis methods.



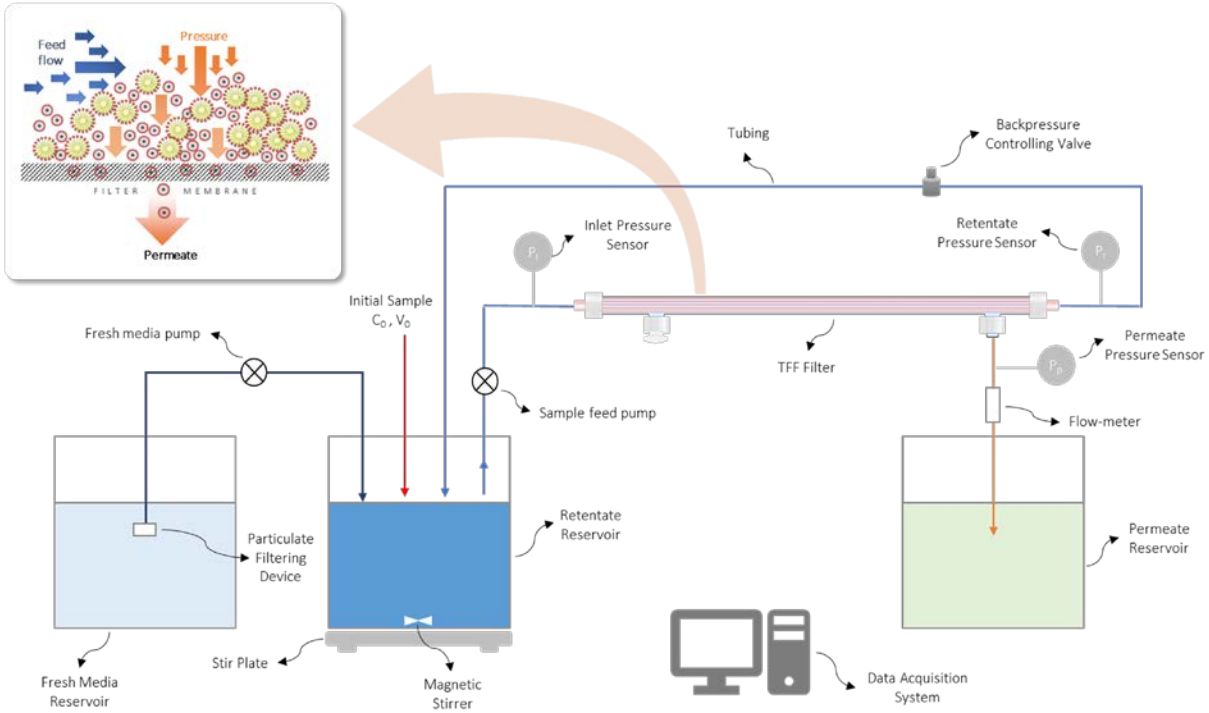


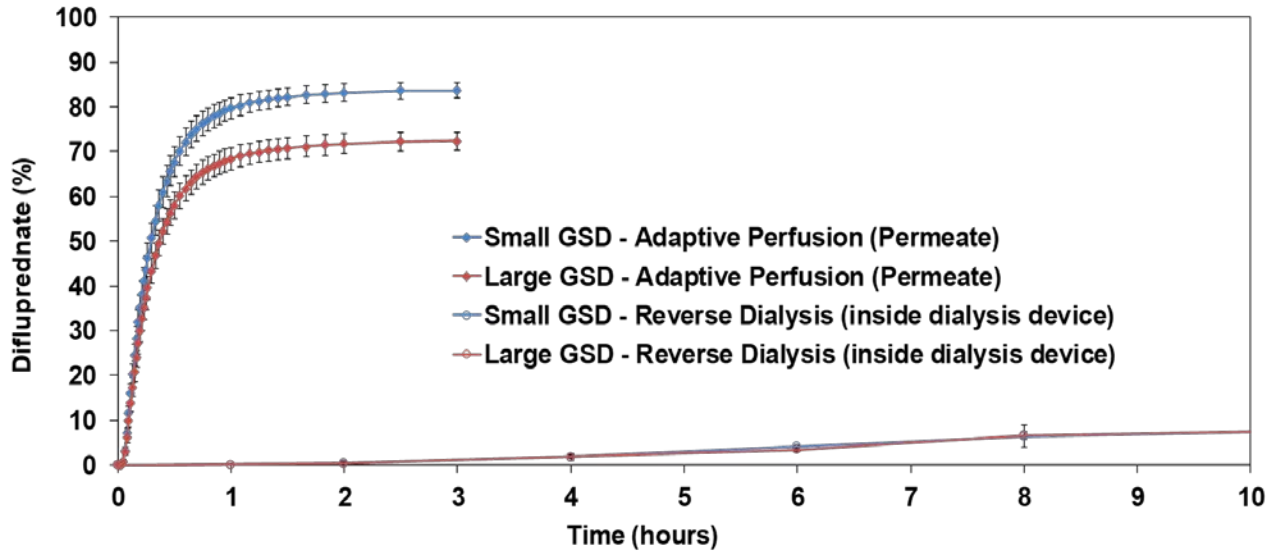


FDA GDUFA research project by Fatma M. Yurtsever, Dumindika A. Siriwardane, Wenlei Jiang, and Thilak Mudalige done at the Nanotechnology Core Facility (NanoCore) located on the U.S. Food and Drug Administration's Jefferson Laboratories campus (Jefferson, AR)

New Tools for Measuring In Vitro Drug Release of Complex Products

- A tangential flow filtration method was developed that uses size-based particulate separation to simultaneous measure the amount of drug released from and amount remaining in complex formulation particulates, such as emulsions.

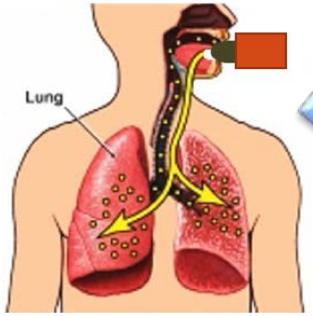




Comparison of extent of drug release (from small and large difluprednate emulsions) between the adaptive perfusion and the reverse dialysis(n=3, mean ± sd).

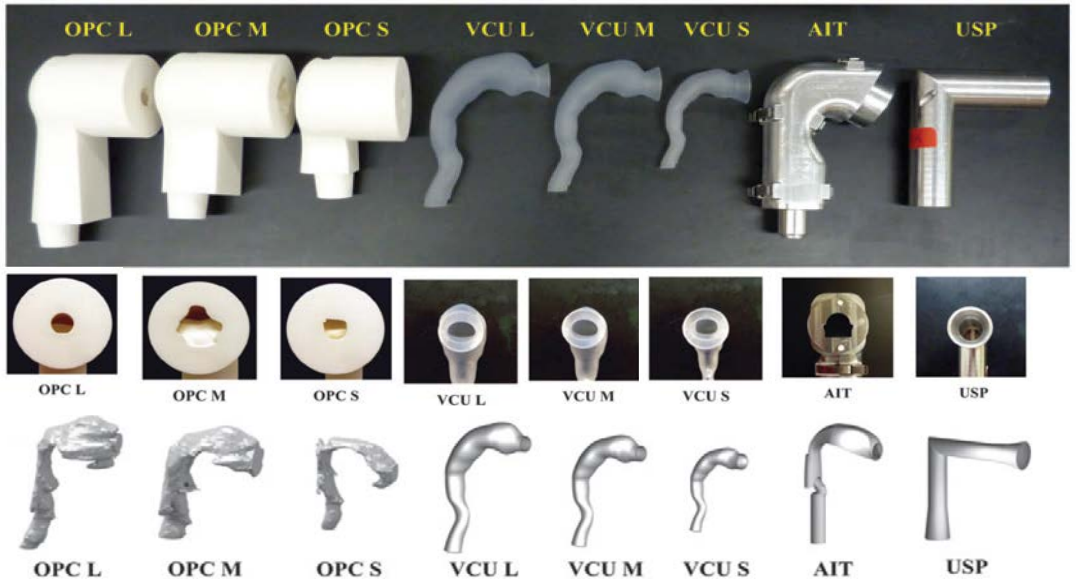
J Control Release 333 (2021): 65-75.

More Realistic Aerodynamic Particle Size Distribution (APSD) Testing

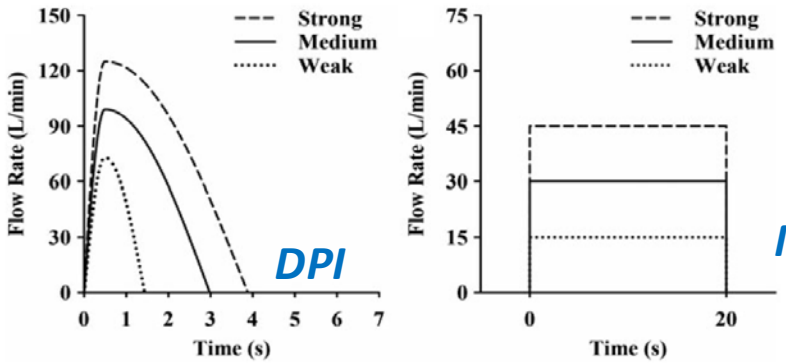


http://images.lifescript.com/images/ebsco/images/inhaled_poison.jpg

Realistic mouth-throat (MT) models

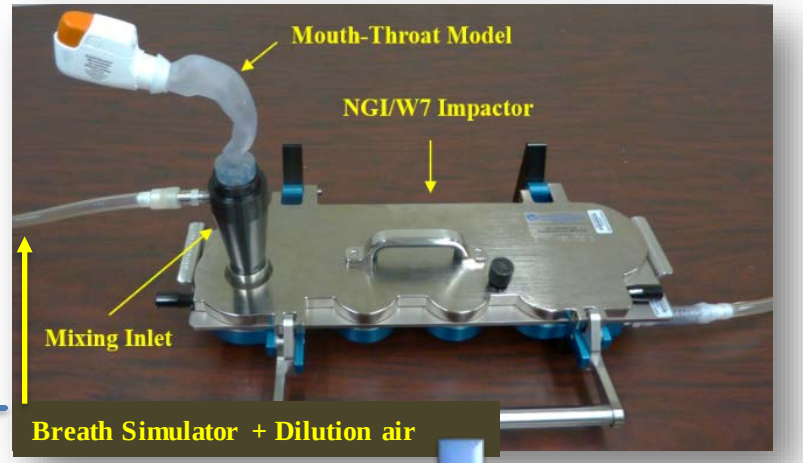


Inhalation profiles (IPs)



VCU: Virginia Commonwealth University
OPC: Oropharyngeal Consortium
AIT: Alberta Idealized Throat
USP: United States Pharmacopeia

NGI: next generation impactor



In vitro APSD method more predictive of in vivo deposition

Wei, Xiangyin, et al. *Journal of aerosol medicine and pulmonary drug delivery* 31.6 (2018): 358-371. https://collaboration.fda.gov/p1qe3izohvy/

Engaging FDA When Proposing to Use a New Analytical Method

FDA is committed to supporting the latest scientific methods and tools to evaluate generic drug equivalence and for industry to efficiently develop new generic products.

Utilizing a New Method in an ANDA

Discuss new method with FDA via:

- **Pre-ANDA product development meeting**
  - Discuss technical aspects of the method and study design proposed/preliminary data to support generic product development
- **Pre-ANDA pre-submission meeting**
  - Discuss technical aspects of data generated on ANDA batches and rationale/justification how the data supports ANDA approval.
  - Guidance for Industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*

Engaging FDA on Developing a New Analytical Method

Developing a New Method

Propose research initiative or project on a new analytical method and/or approach to solve a complex generic drug issue:

- **Annual GDUFA Public Workshop**
  - Public can propose GDUFA research initiatives for FDA to undertake in FY22
  - Regulations.gov, Open Docket FDA-2017-N-6644
- **Broad Agency Agreement (BAA) applications**
  - Propose a research project to undertake that you believe will provide FDA with new tools / understanding to of generic drug development and/or approval.
  - FedBizOpps.gov, Solicitation FDABAA-19-00123
- **Grant Opportunities**
  - Respond to FDA's request for application (RFA) to develop and conduct a specific research project.
  - RFAs posted on NIH Grants & Funding and Generic Drugs Collaboration Opportunities websites

Conclusions

- FDA is committed to supporting the latest scientific methods and tools to develop and evaluate new generic products.
- GDUFA research on new analytical methods have focused on improved characterization of complex active and inactive ingredients, complex formulation evaluation, and creating new performance and assessment tools.
  - This research aims to aid both generic drug industry and FDA Reviewers in the development and assessment of complex drug products.
- Public, industry, and prospective ANDA applicant using a new analytical method can engage with FDA via research project proposals and pre-ANDA meetings.

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- Akina Inc
- DigiM Solutions and University of Connecticut
- University of Bath and Massachusetts General Hospital/ Harvard Medical School
- Virginia Commonwealth University


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