

# Demonstrating Complex Generic Product Equivalence: Benefits and Considerations When Using New Analytical Methods

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# Generic Drug User Fee Amendments (GDUFA)

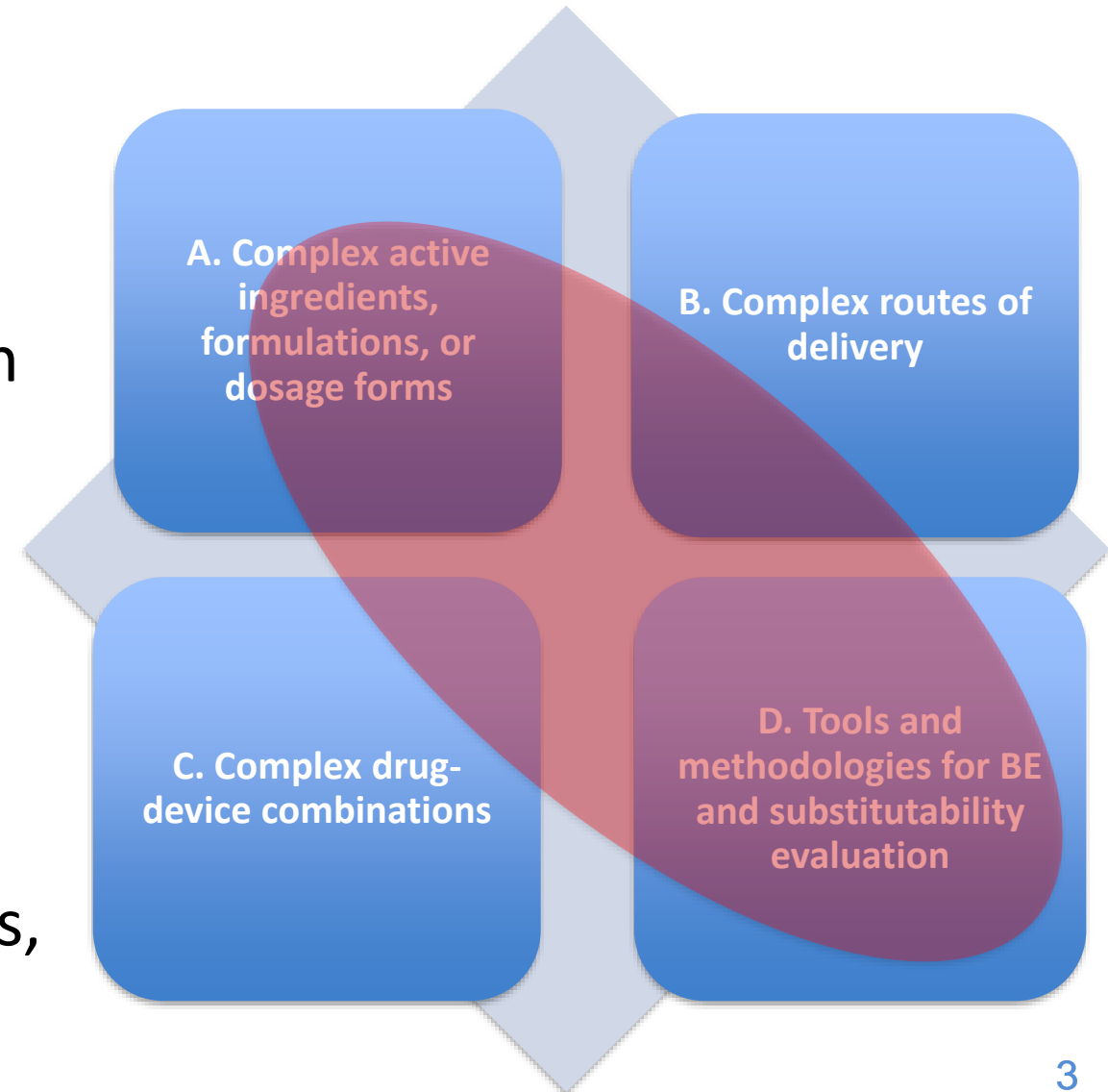


## Research on New Analytical Methods

- Characterization of complex active and inactive ingredients
  - Analytical needs, recent research, and new complex active pharmaceutical ingredient (API) products
- Characterization of complex formulations
  - Analytical needs, recent research, and new complex formulations
- New tools for product performance and bioequivalence (BE) evaluation
  - Analytical needs and recent research

# GDUFA Research Priority Areas

- In FY2020 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



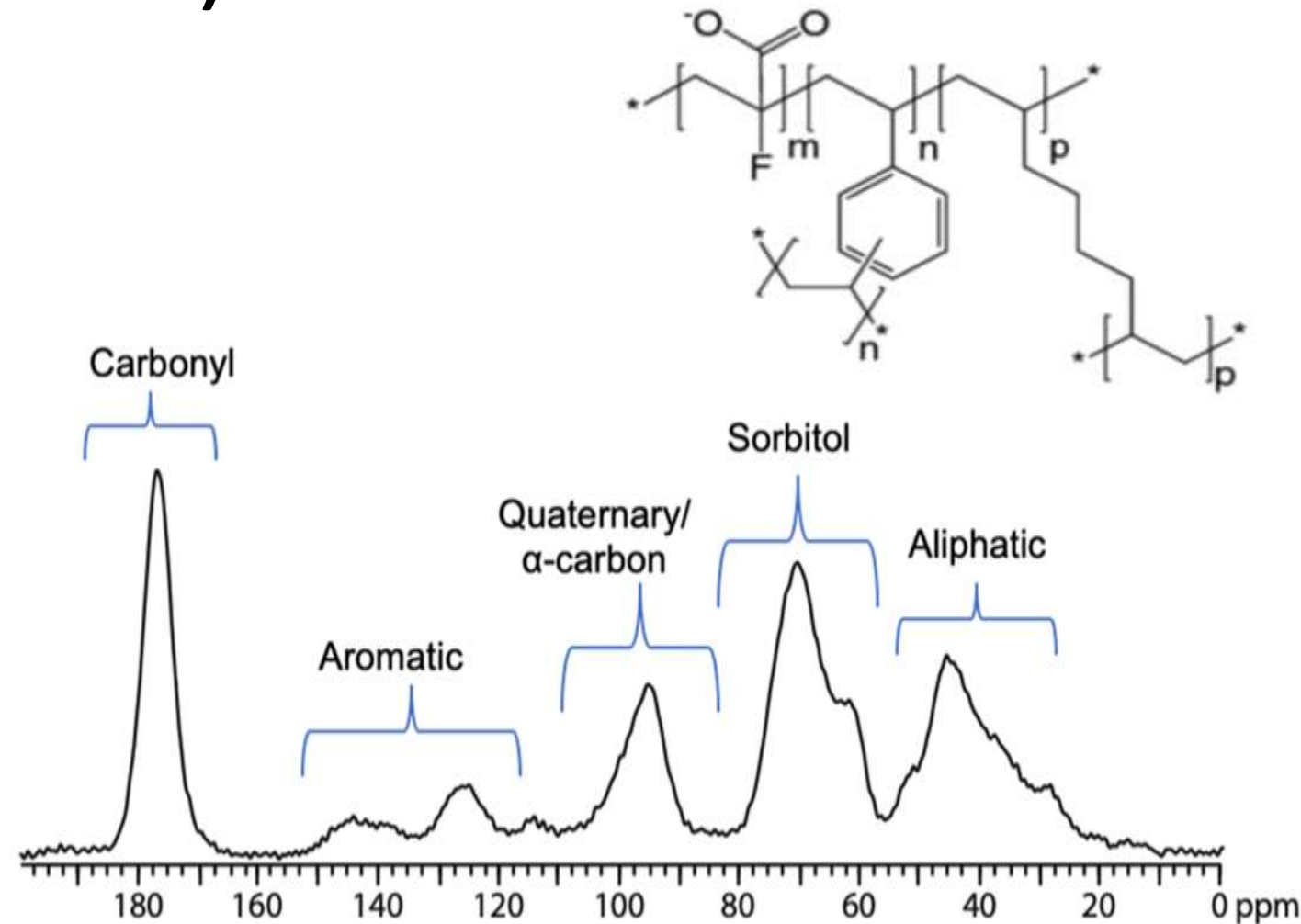
# Complex Active and Inactive Ingredient Characterization

- 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 solid-state NMR, LC-MS/MS, and GPC-4D to characterize complex polymer structures and mixtures.

# Solid-State Nuclear Magnetic Resonance (ssNMR)



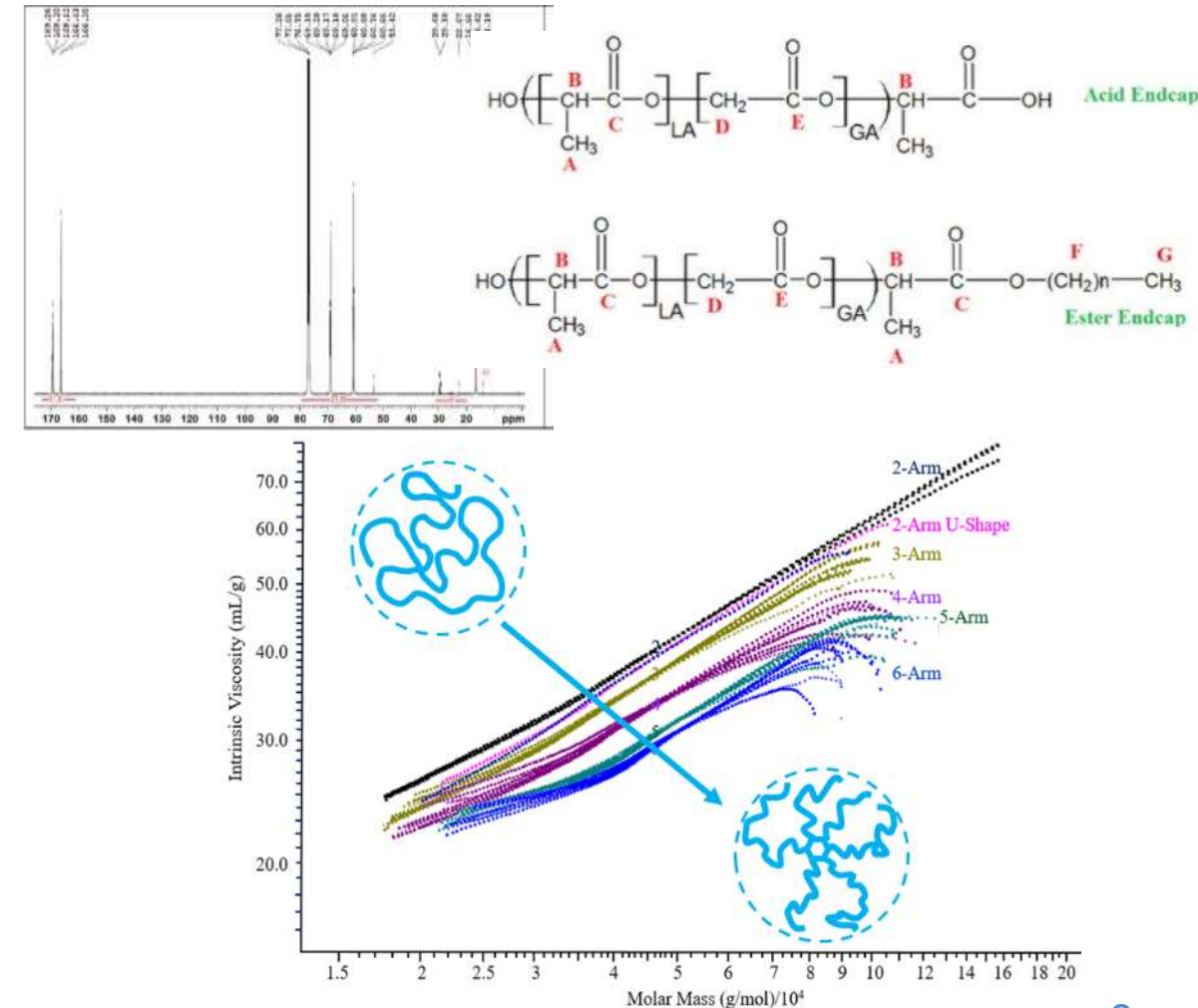
- VELTASSA (patiomer sorbitex calcium) oral powder is a complex API cross-linked polymer composed of three monomers.
- $^{13}\text{C}$  ssNMR was used to characterize the monomer (m), (n) and (p) composition including lot-to-lot variability: (m) = 90.8%; (n) = 7.7%; (p) = 1.5%



# Characterizing Polymer Excipients: Poly(lactide-co-glycolide) (PLGA)



- PLGA 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.
- $^{13}\text{C}$  and  $^1\text{H}$  NMR along with Gel permeation chromatography with refractive index, viscosity, multi-angle light scattering, and infrared detectors (GPC-4D) enables complex polymer characterization.



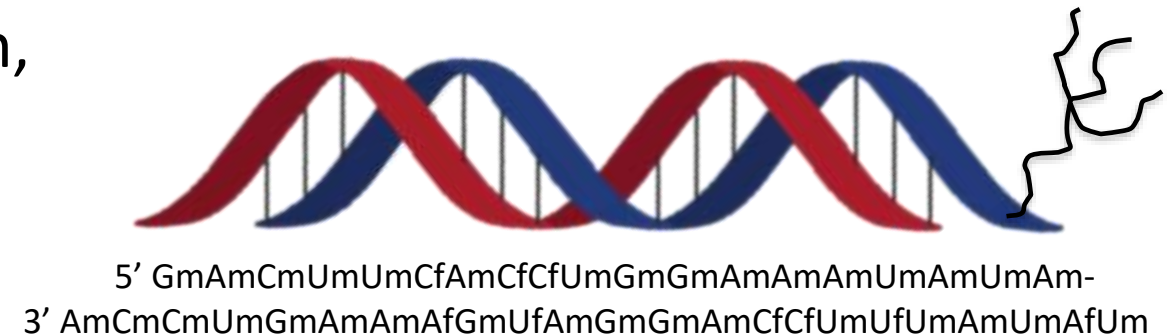
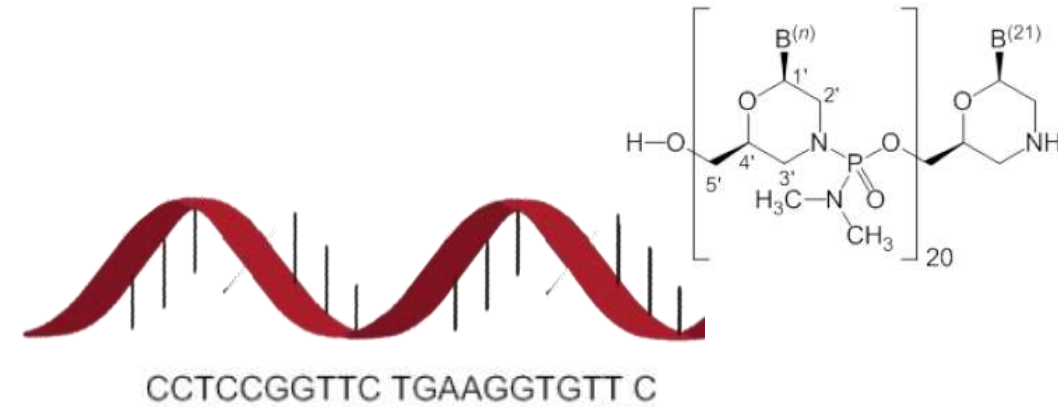
GDUFA contract HHSF223201610091C &  
HHSF223201710123C to Akina Inc

# Recently Approved Complex Active Ingredient Products



- Oligonucleotides are complex APIs that present unique analytical needs to characterize the sequence, structural chemistry (e.g., modifications to the phosphate, sugar, and base), and impurities.

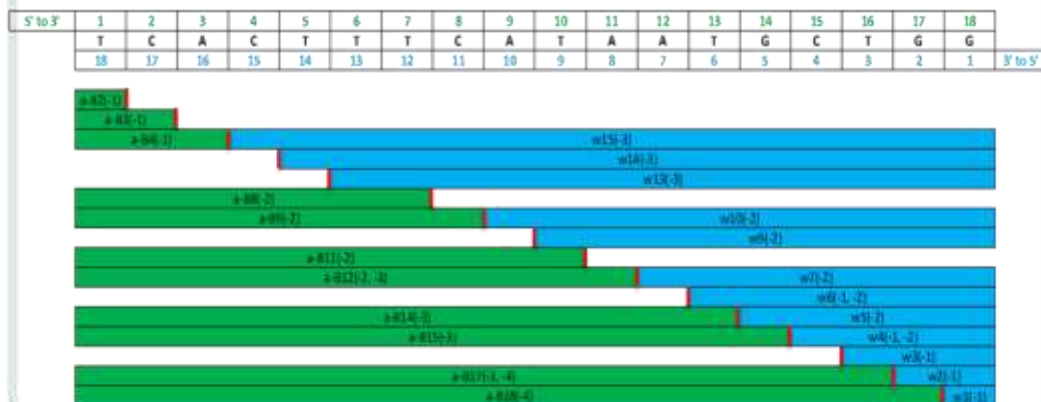
- VILTEPSO, viltolarsen, injectable solution, approved Aug 12, 2020
- OXLUMO, lumasiran sodium, injectable solution, approved Nov 23, 2020



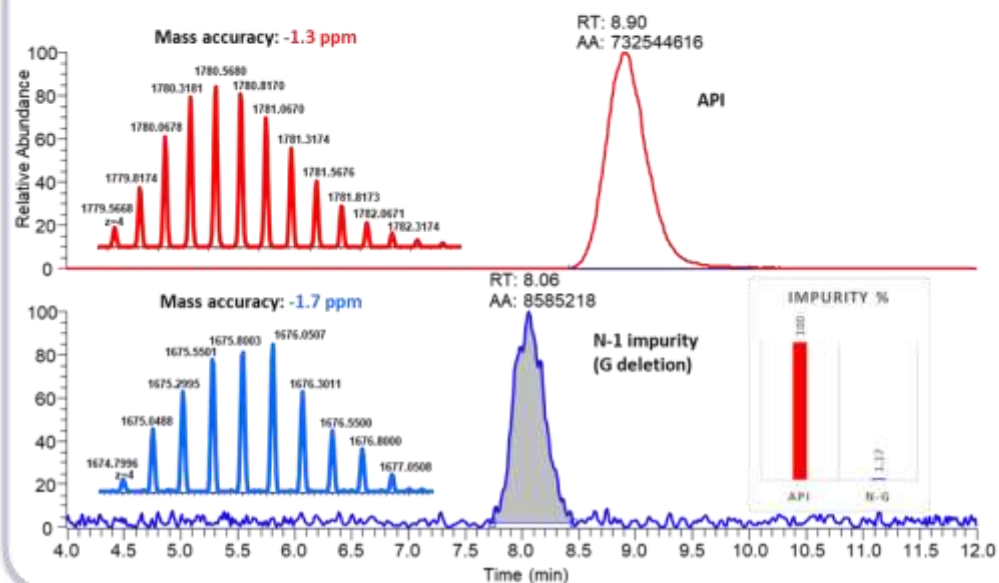


# Oligonucleotide Characterization

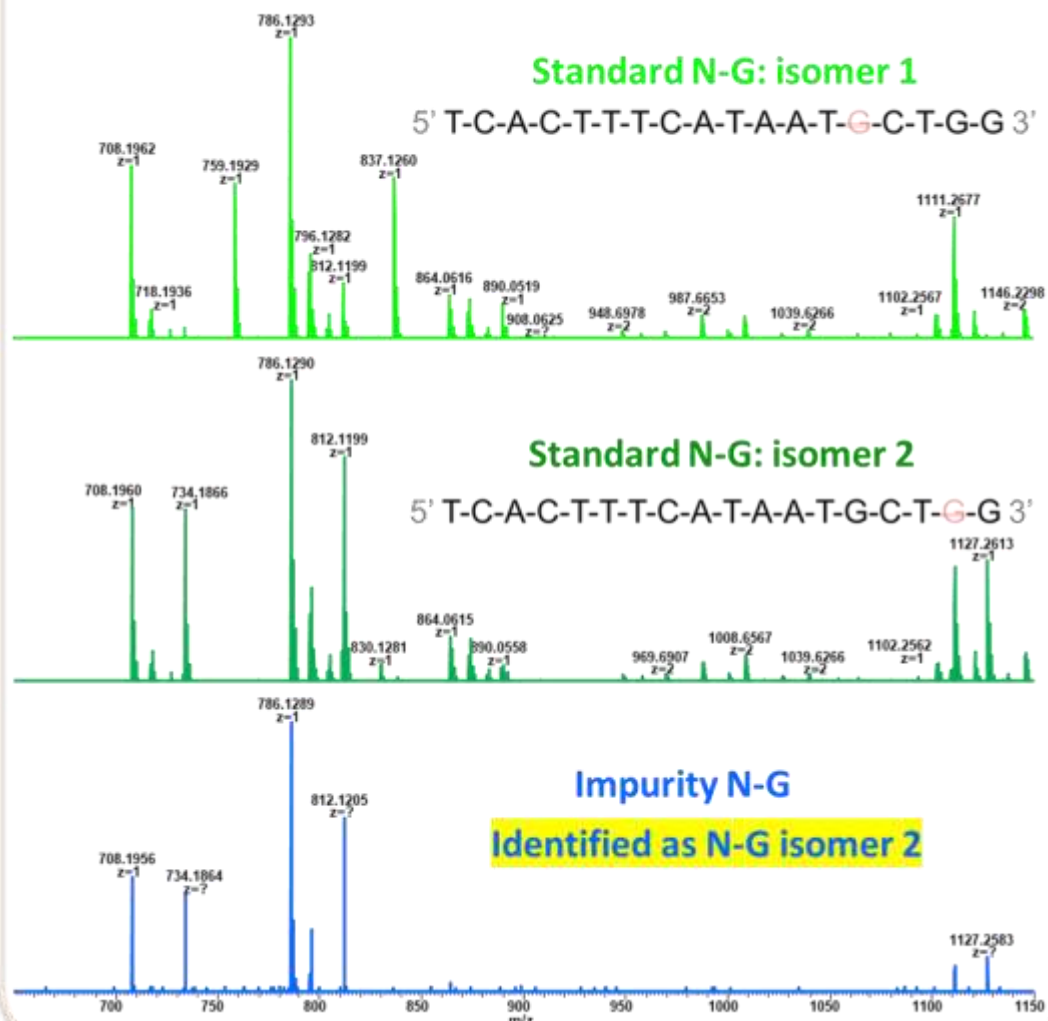
## Sequence Mapping



## Impurity Profiling



## Impurity Identification





# Complex Formulation Characterization



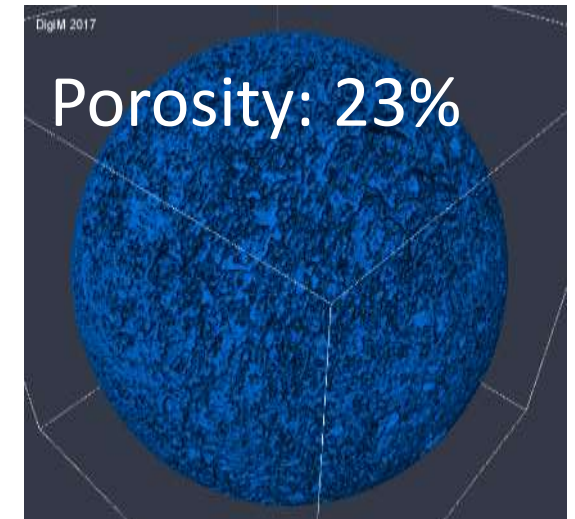
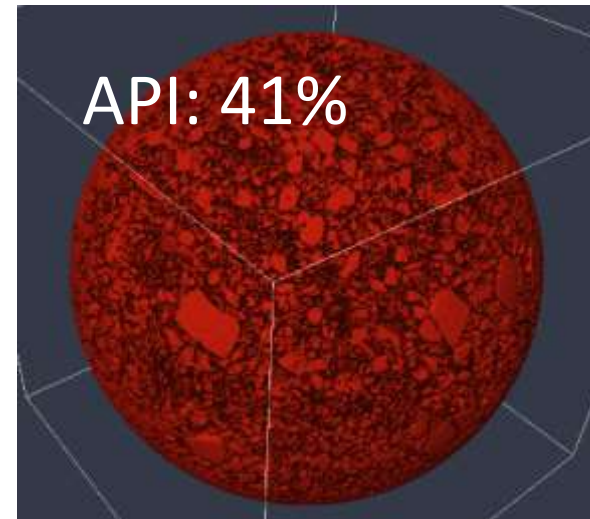
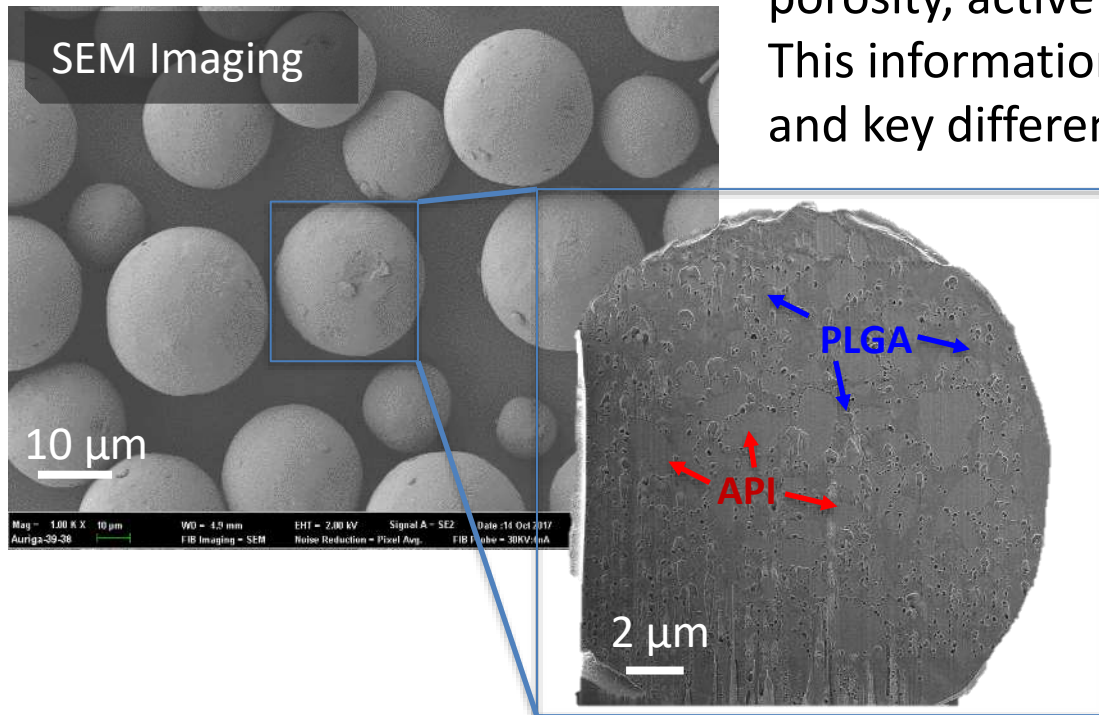
- Improved methods to characterize and compare the critical quality attributes of complex formulations would enhance generic drug development by reducing potential modes for a non-bioequivalent product.
- Recent GDUFA research has focused on spectroscopic imaging methods to differentiate chemical regions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

# Focused Ion Beam Scanning Electron Microscopy (FIB-SEM)



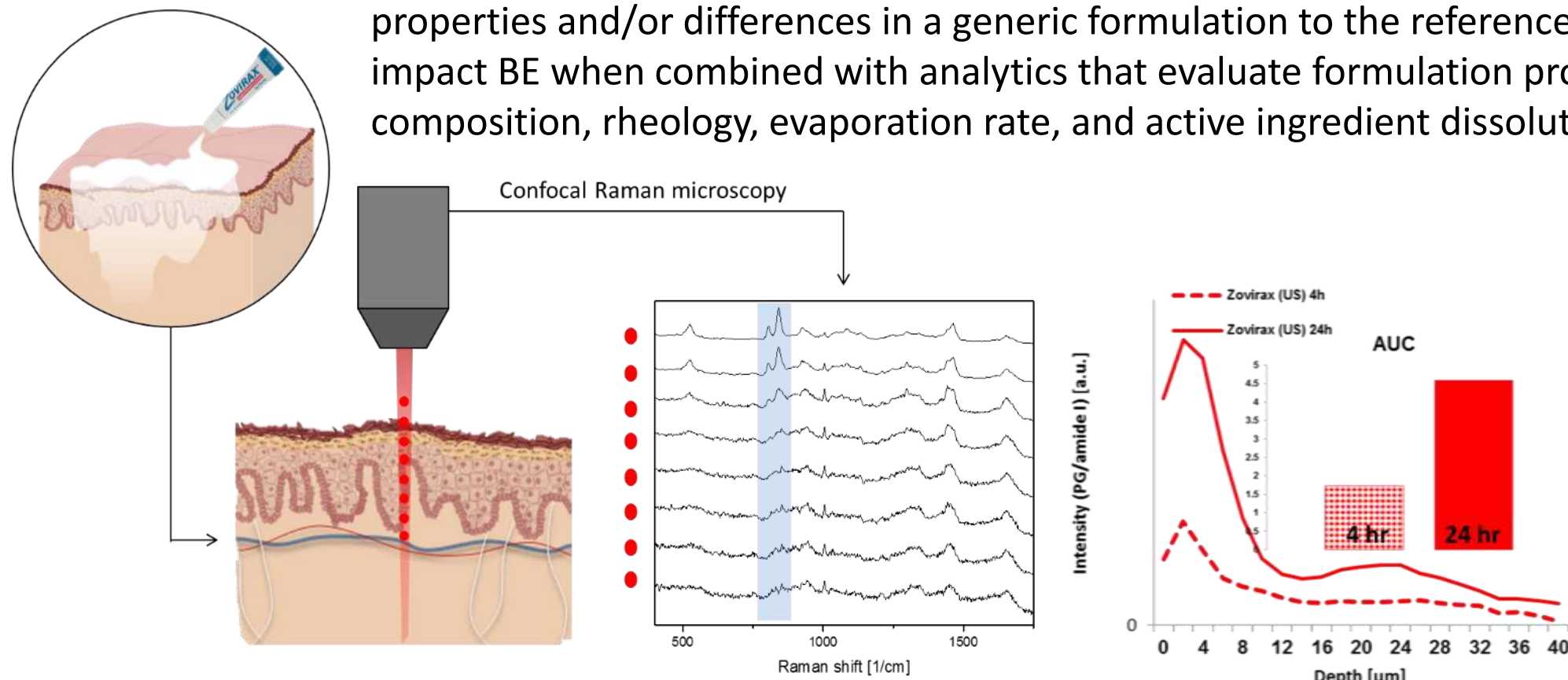
## FIB-SEM Cross Section of PLGA Controlled Release Microspheres

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.



# 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

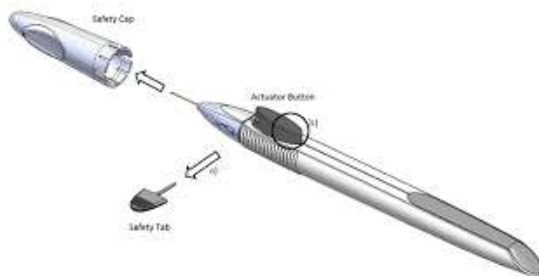
1U01FD006698 Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence, PI Prof. Conor Evans, Massachusetts General Hospital/ Harvard Medical School

# Newly Approved Complex Formulation Products



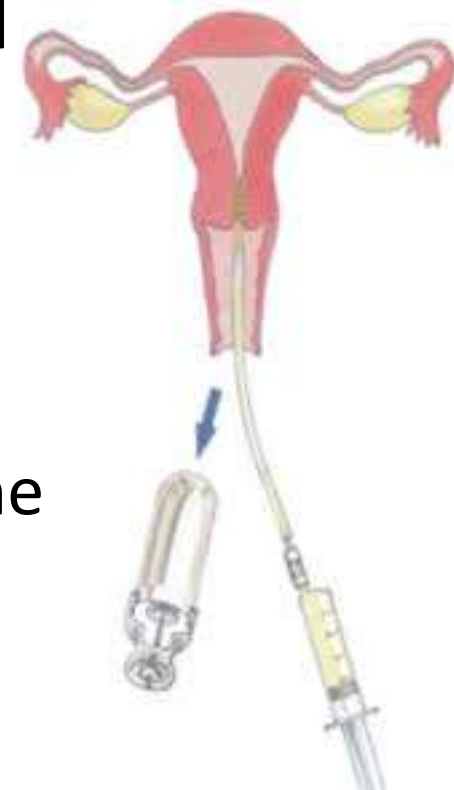
## Durysta

- NDA211911, approved Mar 2020, is a biodegradable PLGA intracameral bimatoprost implant to reduce intraocular pressure
- Drug release rate and PLGA degradation impact performance



## ExEm Foam Kit

- NDA 212279, approved Nov 2019, is a complex ultrasound contrast agent foam to assess fallopian tube patency
- Structure and size of the foam component gives rise to the contrast signal performance



# Tools for Product Performance and BE Evaluation



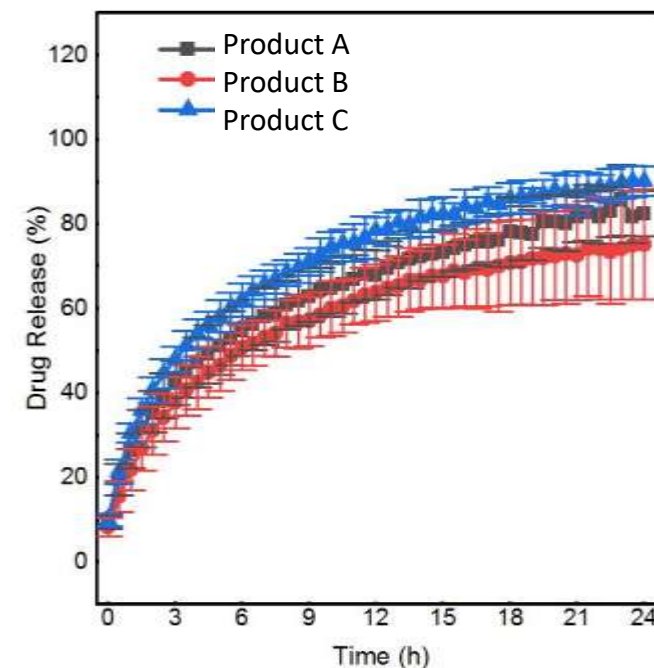
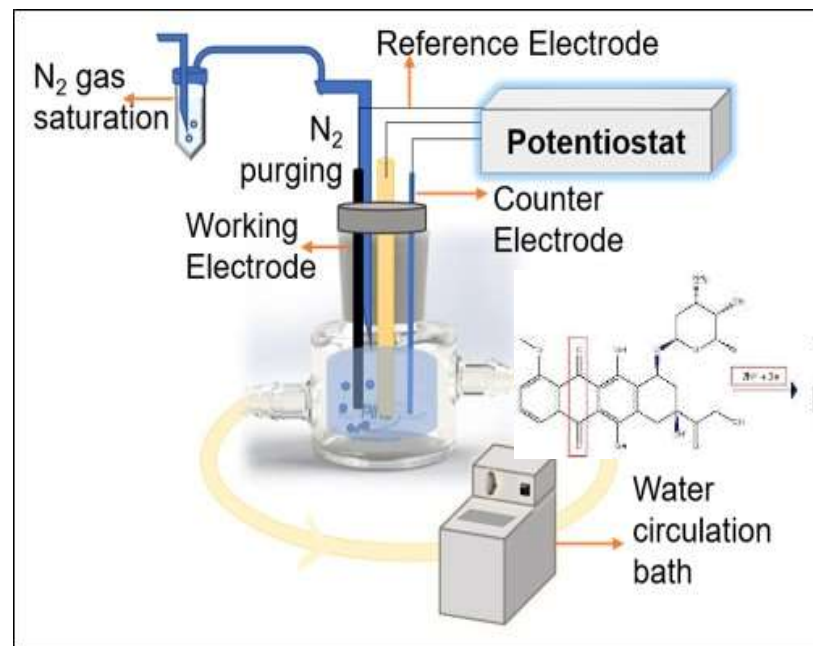
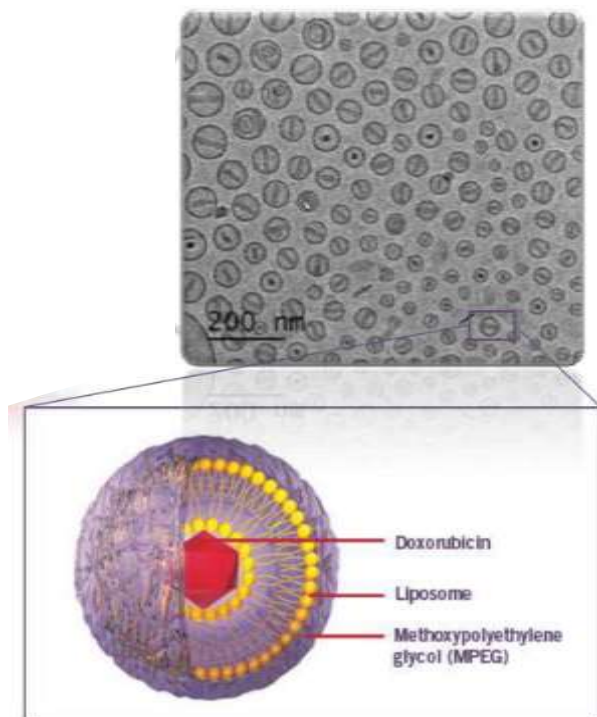
- Need for methods that can better and more efficiently discriminate non-BE products from those that are BE to the reference listed drugs. In addition, to support alternative BE approaches, specialized tools and tests that can bridge to the expected in vivo performance are sought after.
- Recent GDUFA 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



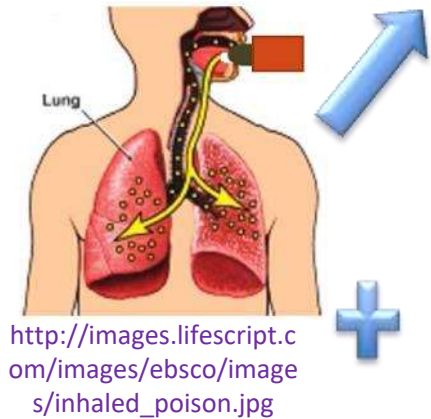
# New Tools for Measuring In Vitro Drug Release of Complex Products



- 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.



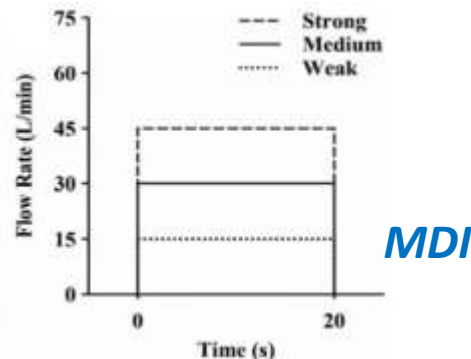
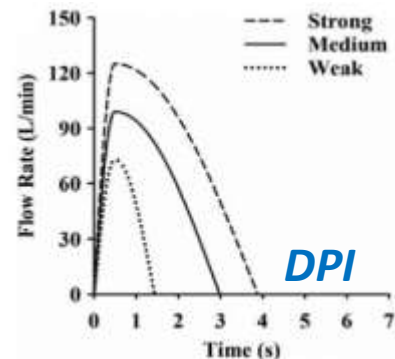
# More Realistic Aerodynamic Particle Size Distribution (APSD) Testing



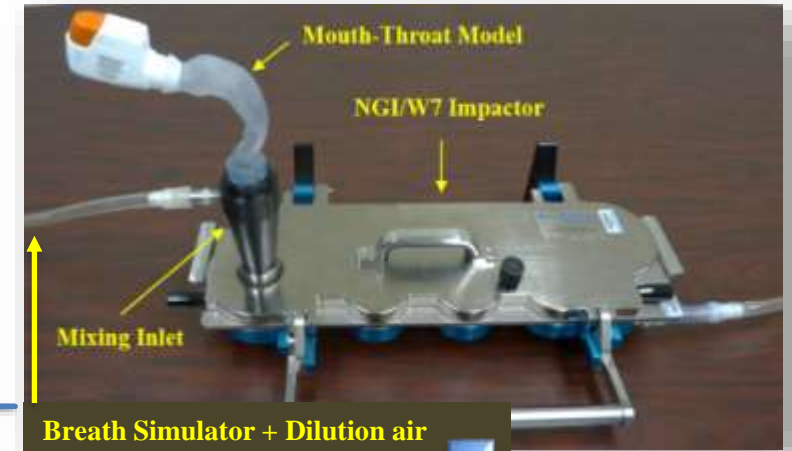
## Realistic mouth-throat (MT) models



## Inhalation profiles (IPs)



## 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/>



# Summary

- 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 BE assessment tools.
- This research aims to aid both generic drug industry and FDA Assessors in the development and assessment of complex drug products.
- Research is continually needed as new analytical methods and complex products are developed.



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- Virginia Commonwealth University



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