FROM MOLECULE TO PATIENT

Regulatory Science Issues in the Effect of Microbiomes on Bioequivalence Determination for Generic Drug Products

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The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views or policy of the U.S. Food and Drug Administration.

Generic Drugs

- Are duplicates of brand-name drugs (or “innovator” or reference listed drug, RLD)
- Are the same as those brand name drugs in active ingredients, dosage form, strength, route of administration, quality, performance characteristics, safety, efficacy, and intended use

From FDA website – Understanding Generic Drugs
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm

Allowed Difference in Generics

- A generic product cannot have *significant differences* that would impact the safety or efficacy profile of the brand name drugs
- Generics may vary in the following, depending on the drug product:
    - Shape
    - Scoring configuration
    - Release mechanism
    - Packaging
    - **Excipients**
    - Buffers, Preservatives, Thickening Agents, Tonicity Adjusters (for Ophthalmic Products)
    - Expiration dating
    - Minor labeling differences
    - Storage requirements

https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/default.htm

New Drug Application (NDA) vs. Abbreviated New Drug Application (ANDA)

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NDA

1. Chemistry, Manufacturing & Controls (CMC)
2. Testing
3. Labeling
4. Inspection
5. Animal Studies
6. Bioavailability
7. Clinical Studies

ANDA

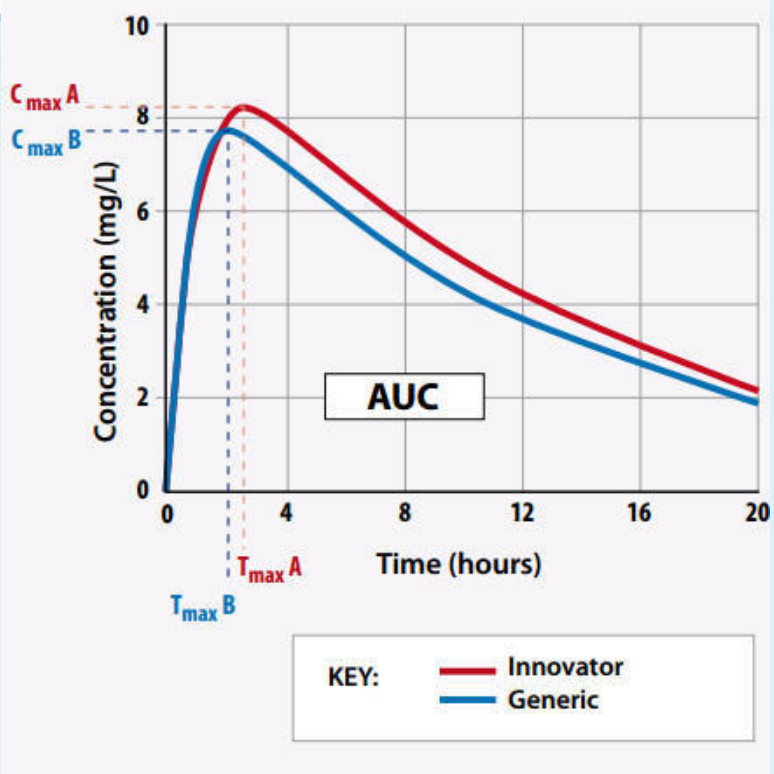
1. Chemistry, Manufacturing & Controls (CMC)
2. Testing
3. Labeling
4. Inspection
5. Bioequivalence

Equivalence Concepts

- **Pharmaceutical Equivalence (PE)**
  - Same active ingredient(s) and
  - Same dosage form and
  - Same route of administration and
  - Same strength and more …
- **Bioequivalence (BE)**
  - No significant difference in rate and extent of drug at site of action
- **Therapeutic Equivalence (TE) of Generic Products**
  - Generics must demonstrate PE and BE to the RLD
  - Generics rely on the safety and efficacy of the RLD
  - TE products can be substituted freely

(Feb 2019, CPT)

Bioequivalence (BE) Determinations



- For products with systemic site of action, BE via systemic PK endpoints (e.g. C_{max} and AUC) helps infer comparable safety and efficacy
- For products that are locally acting, it is more difficult to assess local exposure
  - The site of action may not be directly correlated with systemic PK
  - Alternative methods

Bioequivalence Approaches

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Maybe demonstrated by in vivo or in vitro data or both:

- In vivo PK study
  - Endpoints: blood, plasma, etc.
- In vivo PD study
- In vivo comparative clinical endpoint BE study
- In vitro studies
  - Waiver of in vivo studies for certain immediate-release (IR) oral dosage forms
    - Biopharmaceutics Classification System (BCS)-based
    - Additional strength
  - In vitro tests predictive of human in vivo bioavailability (IVIVC) (for extended-release oral dosage forms)
- Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence

21 CFR 320.22 and 320.24(b)

“Biowaiver”

- For highly soluble and rapidly dissolving, orally administered immediate-release drug products, in vitro data may be acceptable to demonstrate BE based on the biopharmaceutics classification system (BCS1 and BCS3 drugs)
  - Guidance for Industry: *“Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System”*
    - **Class 1: High Solubility – High Permeability**
    - Class 2: Low Solubility – High Permeability
    - **Class 3: High Solubility – Low Permeability**
    - Class 4: Low Solubility – Low Permeability

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf (Dec 2017)

“Biowaiver”

- BCS Class 1:
  - High solubility and high permeability
  - Rapidly or very rapidly dissolving
  - Does not contain any excipients that will affect the rate or extent of absorption of the drug
- BCS Class 3:
  - High solubility and low permeability
  - Very rapidly dissolving
    - At least 85% dissolution in 15 min or less in all three BCS media
  - Must contain qualitatively the same excipients as the reference product, and quantitatively very similar to the reference product (Q1/Q2)

Excipients

- Excipients, or inactive ingredients, are generally defined as substances contained in a drug product other than the active ingredients
- Play crucial roles in drug products
  - Improving solubility
  - Increasing stability
  - Facilitating manufacturing and other important functions
- FDA has an inactive ingredient database (IID) that aids in the selection of inactive ingredients for new and generic drug development

Common Excipients and Their Function

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Sweetener	• Sugar alcohols (sorbitol, maltitol) • Sodium saccharin • Sucralose • Fructose
Solvent	• Water • Glycerin • Propylene glycol
Preservative/ antimicrobial	• Methylparaben • Propylparaben • Sodium benzoate
Antioxidant	• Dl-alpha-tocopherol • Butylated hydroxyanisole
Flavor	• Cherry • Peppermint • Bubble gum
Taste modifier	• Malic acid • Sodium chloride
Colorant	• FD&C red • FD&C yellow
Buffer	• Sodium hydroxide • DL-lactic acid • Citric acid • Sodium citrate dihydrate
Stabilizer	• Disodium edetate
Solubilizing agent	• Beta cyclodextrin • Glycerin • Propylene glycol

Courtesy: S. Hakeem and W Jiang

Generic Drug User Fee Amendment (GDUFA) Regulatory Science

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- FDA has been playing a more active role in performing and funding research to advance drug science
- This provides new tools for FDA and industry to evaluate generic drug equivalence, to enable more efficient development of generic drugs and thus improve access
- ~$30 million per year for stakeholder-driven generic drug regulatory science
  - Goal: Access to generics in all product categories
  - 75 ongoing external research collaborations in 2018
  - Recent focus on complex drug products

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

FY18 GDUFA Research Priority
(#14) Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System of Class 3 bio-waivers to non-Q2 (quantitatively inequivalent) formulations

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- **FDA Internal Research**
  - Bi-phasic dissolution systems
  - Impact of excipients on drug solubility, passive permeability, and intestinal metabolism and transport
  - A database on commonly observed excipients in IR products for BCS Class III drug substances

- **Ongoing Grants and Contracts Funded in FY2017**
  - Effect of excipients on intestinal drug transporters (PI: Kathy Giacomini)

Zhang L, FY2018 Generic Drug Regulatory Science Initiatives Public Workshop, May 24, 2018
https://www.fda.gov/downloads/Drugs/NewsEvents/UCM608740.pdf

Effect of Excipients on Drug Product Absorption

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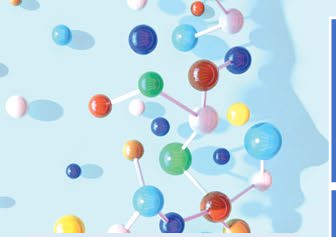
- Research was conducted to comprehensively determine the effects of excipients on oral drug absorption to support mechanistic understanding-based formulation strategy for developing generic oral drug products

- Excipients' impact on bioavailability of BCS Class 3 drugs (Contracts: HHSF223200910020C and HHSF223200810041C)
  - Univ. of Maryland

Vaithianathan S, et al., J Pharm Sci. 105(2):996-1005, 2016; Vaithianathan S, et al., J Pharm Sci. 105(4):1355-1357, 2016.

- FDA-UCSF/Stanford CERSI project (Grants: U01FD004979/U01FD005978)
  - Kathy Giacomini's presentation

Zou L, et al., *Clin Pharm Ther*. 105 (2)323-325, 2019; Irwin JJ, et al., *Clin Pharm Ther*. 101 (3) 320-323, 2017



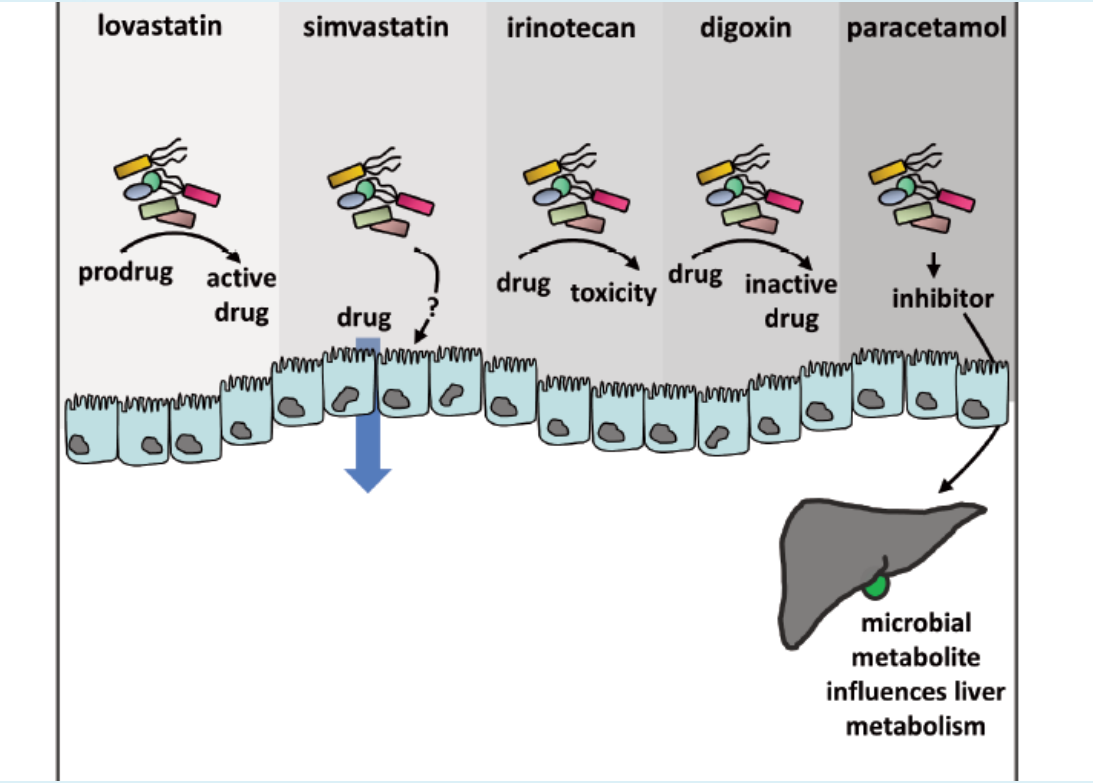
BCS3 drugs: Cimetidine and Acyclovir

14 excipients were selected from a list of 20 most common excipients in oral products; **12** common excipients were found not impact cimetidine and acyclovir absorption in humans.

Excipient	Recommended maximum allowable amount for a class 3 biowaiver (mg)	Maximum excipient amount studied here (mg)	Typical excipient amount (when present) in an IR tablet or capsule with a total weight of 300mg	Maximum amount (mg) in Inactive Ingredient Database
Microcrystalline Cellulose	Qualitatively same and quantitatively v similar	600	100mg (20%-90%)	1385.3
Hydroxypropyl Methyl Cellulose	Qualitatively same and quantitatively v similar	40	10mg (2%-5%)	444.4
Sodium Lauryl Sulfate	50	50	4.5mg (0.5%-2.5%)	51.69
Corn Starch	900	900	150mg (25%-75%)	1135
Sodium Starch Glycolate	200	200	12mg (4%)	876
Colloidal Silicon Dioxide	40	40	1.5mg (0.1%-1%)	100
Dibasic Calcium Phosphate	600	600	150mg (25%-75%)	635.5
Crospovidone	100	100	10mg (2%-5%)	340
Lactose	900	900	240mg (80%)	1020
Povidone	70	70	7.5mg (0.5%-5%)	240
Stearic Acid	80	80	6mg (1%-3%)	72
Pregelatinized Starch	200	200	150mg (5%-75%)	435.8
Croscarmellose Sodium	120	120	37.5mg (0.5%-25%)	180
Magnesium Stearate	40	40	7.5mg (0.25% to 5%)	400.74

Vaithianathan S, et al., J Pharm Sci. 105(2):996-1005, 2016; Vaithianathan S, et al., J Pharm Sci. 105(4):1355-1357, 2016.

Microbiota/Microbiome May Influence Drug Metabolism or Pharmacokinetics by Multiple Mechanisms (Direct/Indirect)



Microbiota: The entire population of microorganisms that colonizes a particular location or organism

Microbiome: Genetic make-up of respective microbiota

Enright E, et al., *YALE JOURNAL OF BIOLOGY AND MEDICINE* 89, 375-382, 2016.

Gut Microbiome Interactions with Drugs

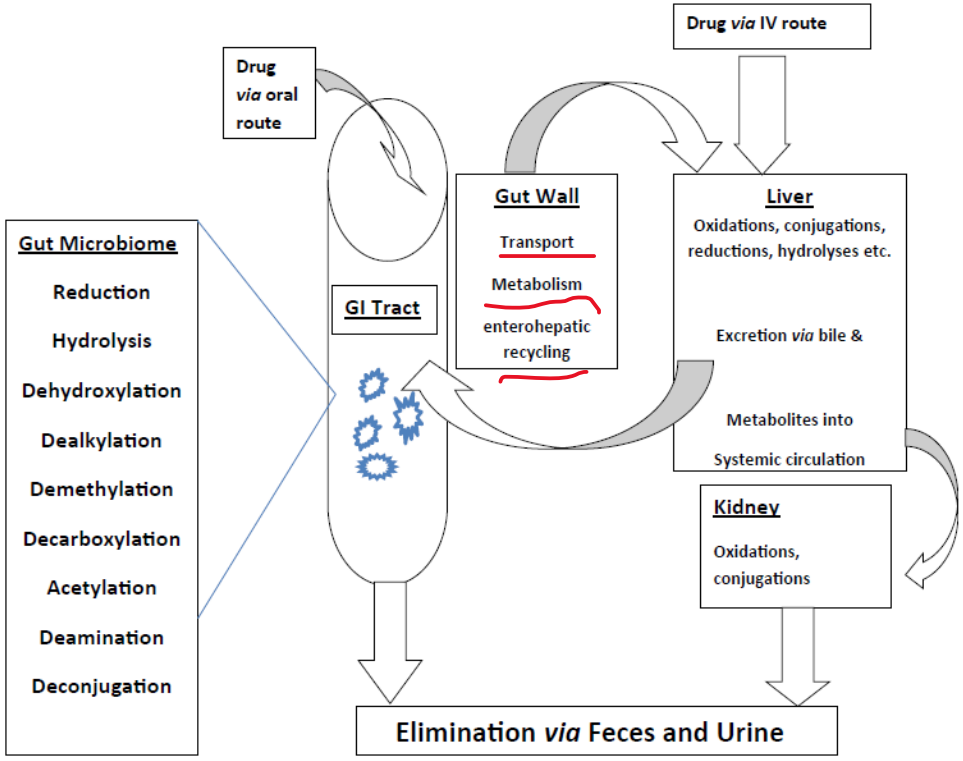
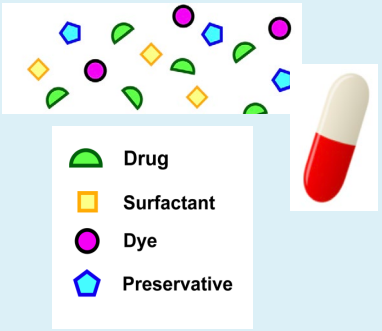


Fig 1. Sites and types of metabolism for drugs after oral or intravenous administration. IV, intravenous.

Wilson and Nicholson, *Translational Res.*, 179, 204-222, 2017

How May Microbiota Affect Drug Product Absorption and BE?

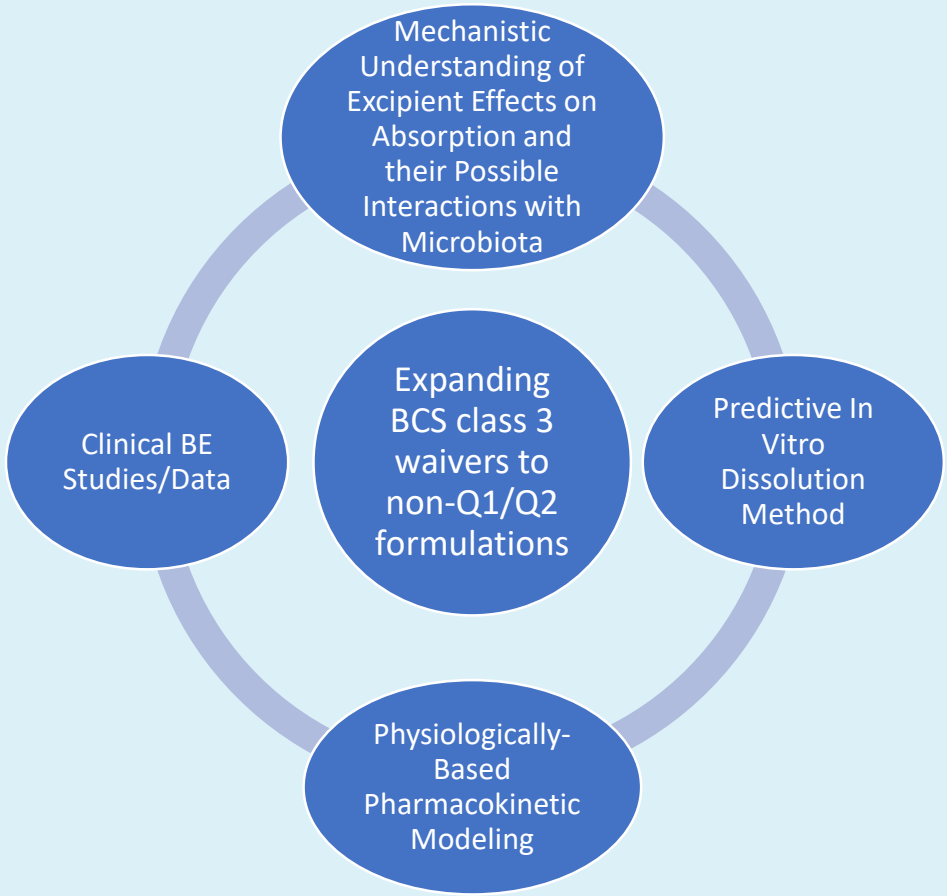
- Biotransformation of drugs can occur in the gut by microbiota
  - Differences in microbiome in subjects → Sources of variation in drug PK and clinical outcome
  - Metabolites formed by microbiota can affect enzymes or transporters
  - Drugs can affect microbiota → drug interactions
- Excipients may be metabolized by microbiota
  - Generic drugs can differ in excipients from RLD
- Contribute to inter-individual and/or intra-individual variabilities
  - Could microbiome potentially impact BE determination?
    - Need to be understood further



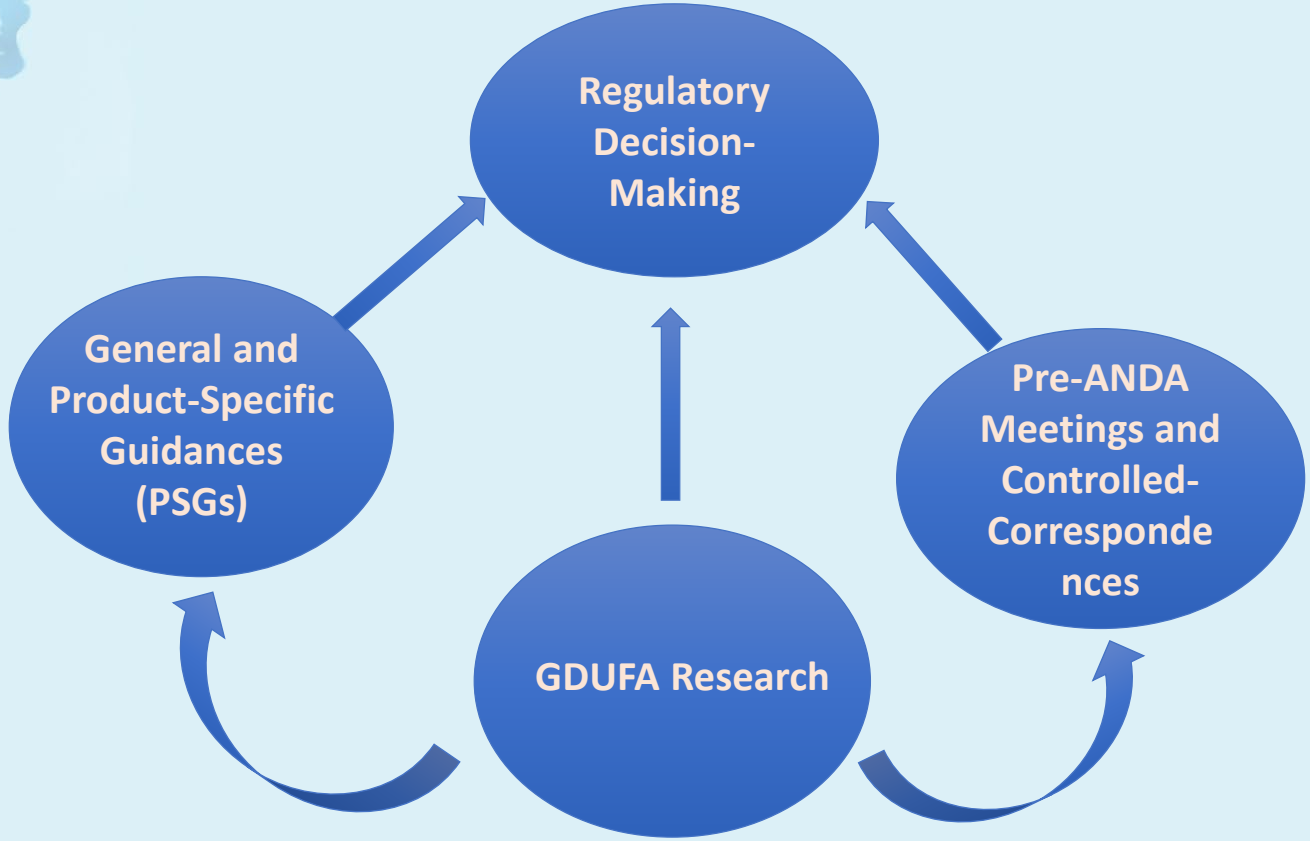
How May Microbiota Affect Drug Product Absorption and BE?

- There is no known BE study failure that has been attributed to excipients interactions with the microbiome
- The current BE standards will likely detect any significant impact of excipient differences include their interactions with the microbiome
- There may be some drugs where generic drug developers need to understand this interaction to ensure their products will pass a BE study
  - For example, pro-drugs like balsalazide, that are designed to be metabolized by gut bacteria

An Integrated Approach



Science Informs Regulatory Decisions



Surveillance of Generic Drug Products

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- Post-market surveillance of generic drug products is critical to providing assurance to the public and to physicians that they are fully substitutable for their brand-name counterparts
- Surveillance also expands our knowledge of what are *"significant differences"* by identifying minor formulation or pharmacokinetic changes that lead to unanticipated inequivalence
- Surveillance can discover significant issues for specific patient subpopulations
- Surveillance serves to quickly identify counterfeit or poor quality products
- Surveillance ensures that marketed generic drug products maintain the high quality that earned them approval

Save the Date!

One of topics for Discussion: The value to the generic industry in expanding BCS class 3 waivers to non-Q1/Q2 formulations

https://www.fda.gov/Drugs/NewsEvents/ucm624723.htm

FY 2019 Generic Drug Regulatory Science Initiatives Public Workshop

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Meeting Information

Date:

Wednesday, May 1, 2019, from 8:30 - 4:30pm

Location:

FDA White Oak Campus, 10903 New Hampshire Ave. Bldg. 31, Rm. 1503 Sections B&C Silver Spring, MD 20993

Background:

FDA will hold a public workshop that will provide an overview of the current status of the regulatory science initiatives for generic drugs and will provide an opportunity for public input on research priorities in these topic areas. FDA is seeking input from a variety of stakeholders—industry, academia, patient advocates, professional societies, and other interested parties—as it fulfills its commitment under the reauthorization of the Generic Drug User Fee Amendments (GDUFA) to develop an annual list of regulatory science initiatives specific to generic drugs. FDA will take the information it obtains from the public workshop into account in developing the fiscal year (FY) 2020 Regulatory Science Plan. The workshop will be held on May 1, 2019, at the FDA White Oak Campus, 10903 New Hampshire Avenue Building 31, Great Room Sections B & C, Silver Spring, MD 20993.FDA wants your input. You may submit ideas on generic drug research topics to be included on the FY 2020 Regulatory Science Plan by emailing GDUFARegulatoryScience@fda.hhs.gov.

Additional details are available in the Federal Register Notice.

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ASCPT 2019 ANNUAL MEETING