U.S. FOOD & DRUG ADMINISTRATION

Drug-Drug Interactions and Generic Drugs

Lei Zhang, Ph.D.
Deputy Director, Office of Research and Standards
Office of Generic Drugs, CDER, FDA

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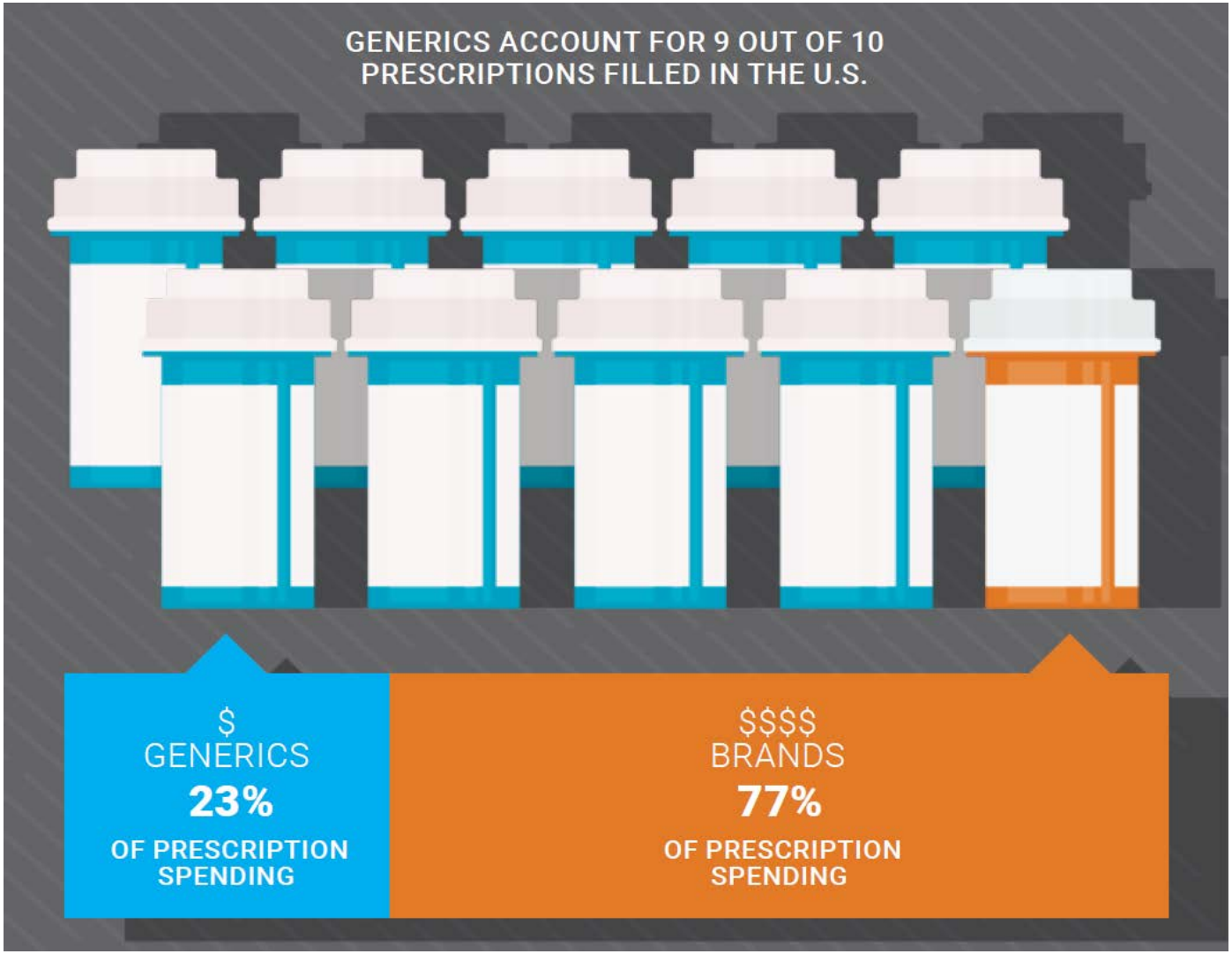
Disclaimer: The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views or policy of the U.S. Food and Drug Administration.

Generic Drugs in the United States

Generic Drugs:

- 90% of prescription
- 23% of spending



https://accessiblemeds.org/sites/default/files/2018_aam_generic_drug_access_and_savings_report.pdf

Generic Drugs

- A generic drug is a medication created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use
- These similarities help to demonstrate bioequivalence, which means that **a generic medicine works in the same way and provides the same clinical benefit as its brand-name version**

(Feb 2019, Clinical Pharmacology and Therapeutics Themed Issue)

From FDA website – "Generic Drugs: Questions & Answers"
https://www.fda.gov/drugs/questions-answers/generic-drugs-questions-answers

Allowed Difference in Generics

A generic product cannot have *significant differences* that would change the safety or efficacy profile as compared to the brand-name drugs (or reference listed drugs, RLDs)

- Generics may vary in the following, depending on the drug product:
    - Shape
    - Scoring configuration
    - Release mechanism
    - Packaging
    - **Excipients**
    - 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)

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

Basic Generic Drug Requirements

No Significant Differences from the RLD

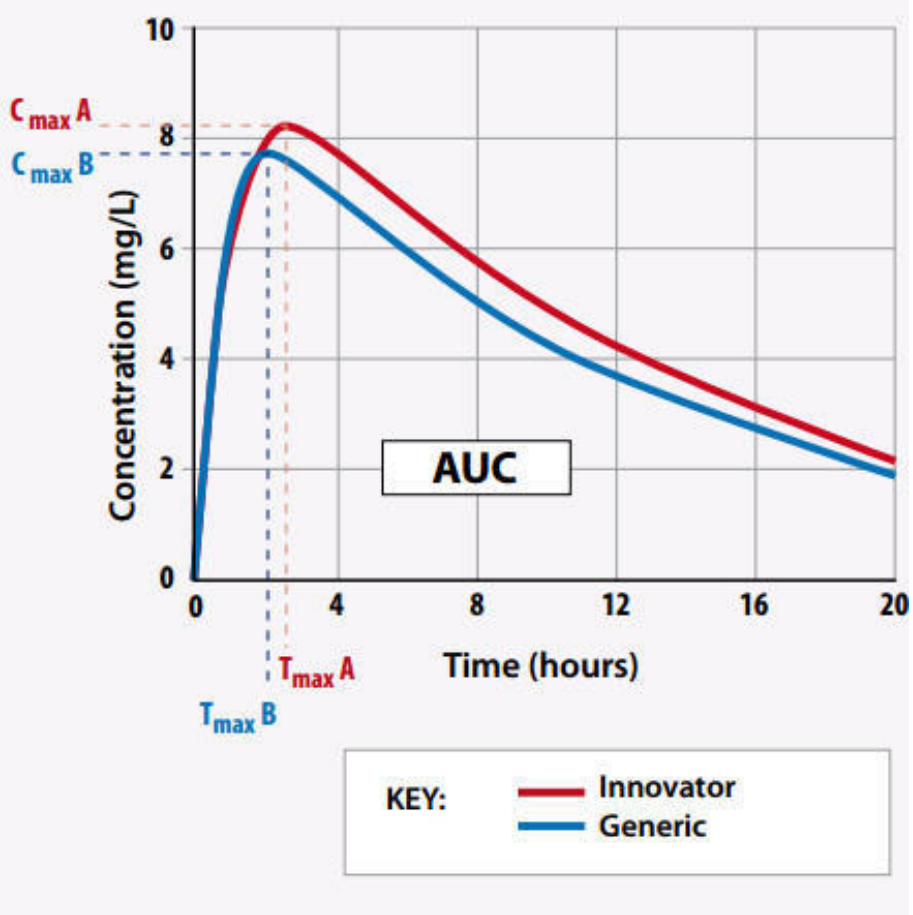
- **PHARMACEUTICAL EQUIVALENCE:** the foundation of equivalence
  - Same active ingredient(s)
  - Same strength
  - Same dosage form
  - Same route of administration
- **Bioequivalence:** supports true pharmaceutical equivalence
  - absence of a significant difference in the **rate** and **extent** of absorption after administration
  - **available at the site of drug action** when administrated at the same molar dose under similar conditions

Infer
TE

Limited confirmatory clinical studies may be acceptable in an ANDA if the purpose is not to establish safety and effectiveness.

TE: Therapeutic Equivalence

Bioequivalence (BE) Determinations



- For products with systemic site of action, BE via systemic pharmacokinetic (PK) endpoints (e.g., C_{max} and AUC) helps infer comparable safety and efficacy

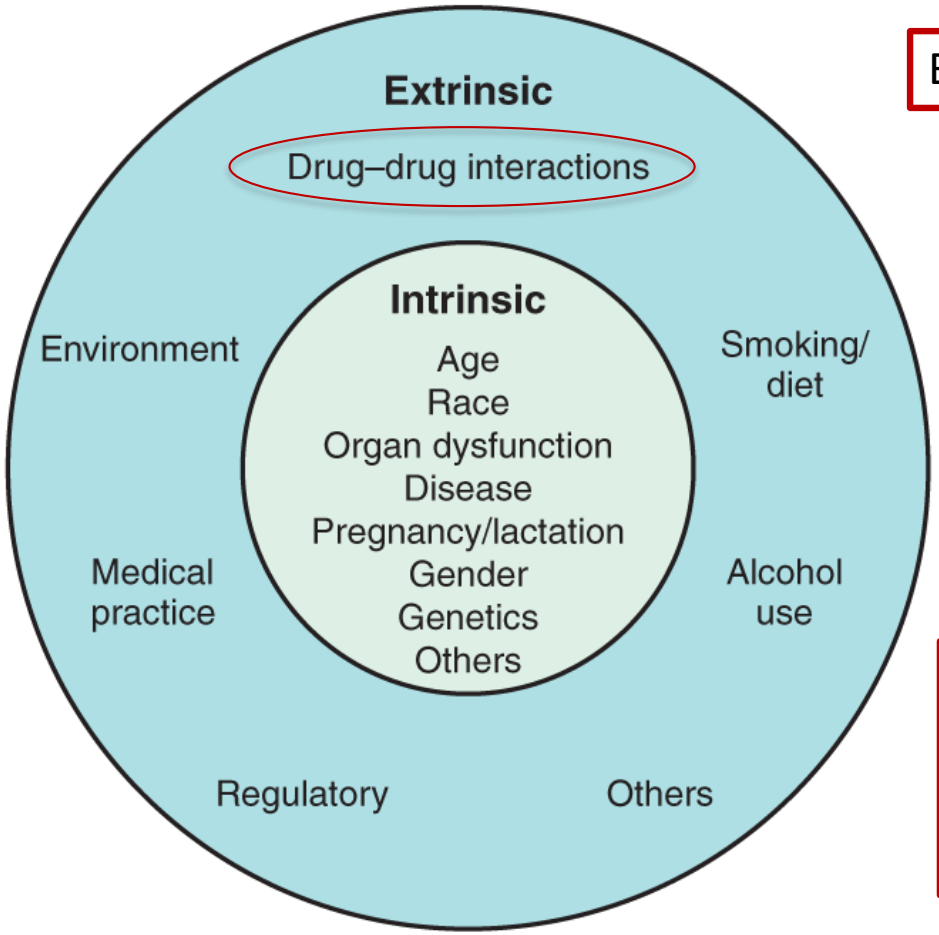
- For products that are locally acting, it is more difficult to assess local exposure
  - The site of action may not be directly correlated with systemic PK
  - Alternative methods

Therapeutic Equivalence (TE)

Generic drug has the same clinical efficacy and safety profiles **(e.g., same therapeutic effect)** as the brand-name drug (or RLD) when administered to patients under conditions specified in the labeling

- The generic drug product has no significant differences from the RLD
- Can be substituted for each other without any adjustment in dose or other additional monitoring or training
- Substitution occurs at the pharmacy level

Multiple Factors Can Impact Drug Exposure



BE established in healthy subjects

Generally BE studies in healthy subjects tell us that products can be substituted in patients because the BE results allow us to conclude that brand-name and generic drug products perform the same.

Therapeutic Equivalence in patients under conditions specified in the labeling are inferred

Huang S-M and Temple R, Clin Pharmacol Ther 84: 287-294, 2008

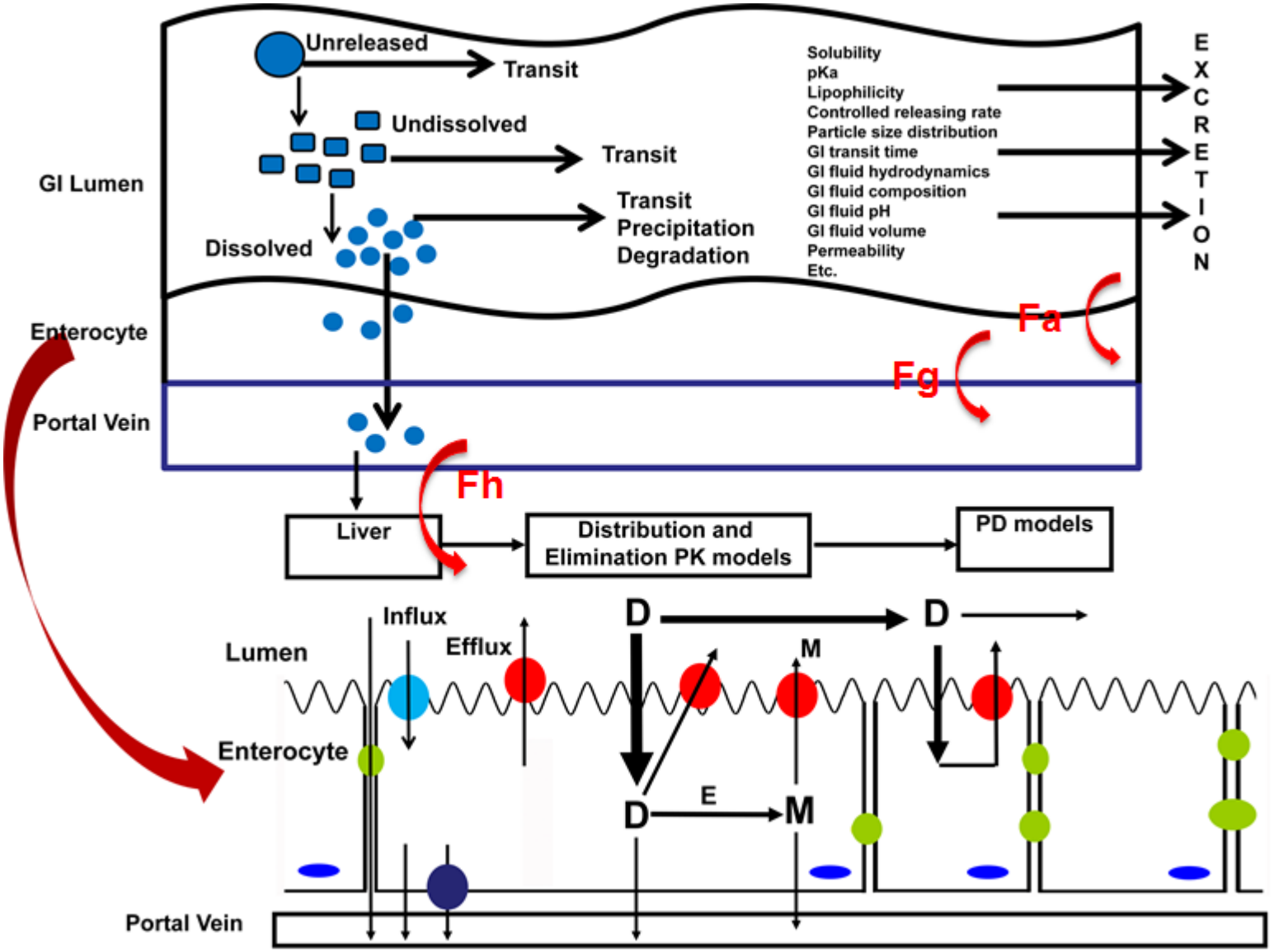
Mechanisms of Pharmacokinetic DDI

The main differences between oral dosage forms for new and generic drugs are in the formulation (excipients, etc.)

- **Absorption**
  - Altered gastric pH or GI motility
  - Inhibiting/inducting intestinal cytochrome P450s or transporters

- Distribution
  - Altered Plasma protein binding
- Metabolism
  - Inhibiting/inducing hepatic cytochrome P450s, glucuronidation, etc.
- Excretion
  - Inhibiting transporters

Understanding of Oral Absorption



Source: Xinyuan (Susie) Zhang

How May a Co-Administered Drug Affect the Absorption of the Substrate Drug Product?

- pH-Modulation (patients who have achlorhydria or take acid reducing agents, e.g., proton pump inhibitors)
  - Weak base drug products
  - Extended-release drug products
- Enzyme/Transporter Inhibitor
  - Effect of excipients on transporters
- Microbiome?
  - Drugs designed to be metabolized by gut bacteria

pH-Modulation May Alter Drug Systemic Exposure Significantly

- Caused by perpetrator drugs that can alter the gastric pH
  - Acid reducing agent (ARA): Antacid, histamine H_2-receptor antagonists, proton pump inhibitors (PPIs)
- Generally observed for victim drugs with pH-dependent solubility
  - Weak acid: solubility increases with increased (elevated) pH → increased absorption in the presence of ARA
  - Weak base: solubility decreases with increased (elevated) pH → decreased absorption in the presence of ARA
- Affect drug release from a drug product and drug absorption consequently
  - Raltegravir (weak acid): ~1.5 fold increased in C_{max} and AUC by omeprazole
  - Atazanavir (weak base): ~95% decreased in C_{max} and AUC by omeprazole

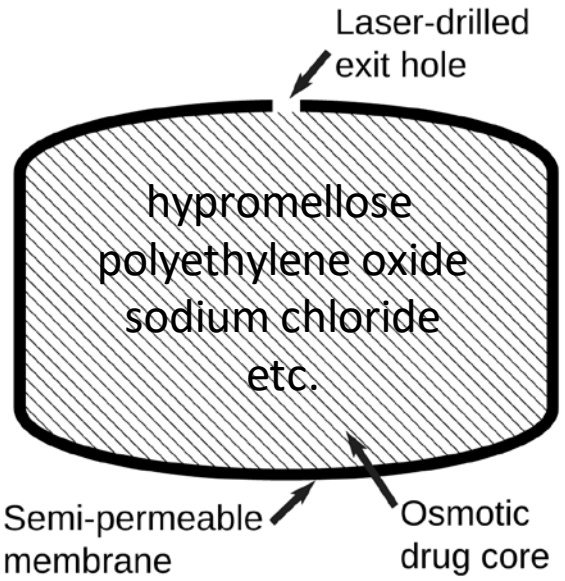
Example: Immediate-Release Weak Base Drugs

- Addition of acidic excipients may lead to improved dissolution and absorption of a free base formulation and minimize DDI with pH-modulators
- Will BE be affected by the presence of an ARA (e.g., PPIs)?
- Will BE study conducted under fed conditions mimic the pH-elevation condition?
- Can in vitro dissolution and modeling help determine the need for additional BE studies?
  - pH-dependent dissolution?
  - Mechanistic PBPK modeling?
- Additional BE with a gastric pH modulator?
  - Free base vs. salt
    - Not allowable for generics but maybe relevant for new drug applications
    - Zhu, et. al., CTS, 2019

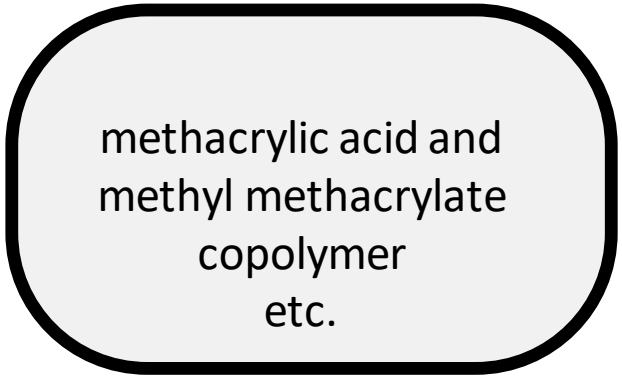
Example: Extended-Release (ER) Product Nifedipine ER Tablets

Evaluation of Potential Formulation Dependence of Drug-Drug Interaction (DDI) with a Proton Pump Inhibitors (PPI)

Product A
osmotic pump



Product B
matrix

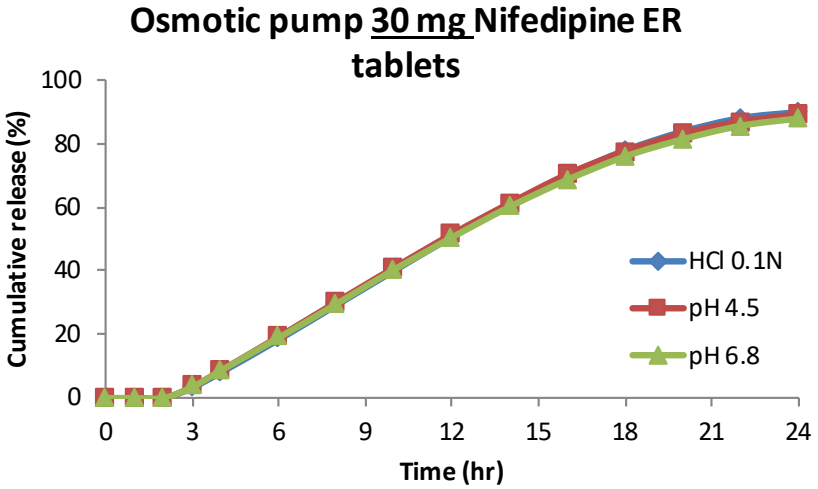


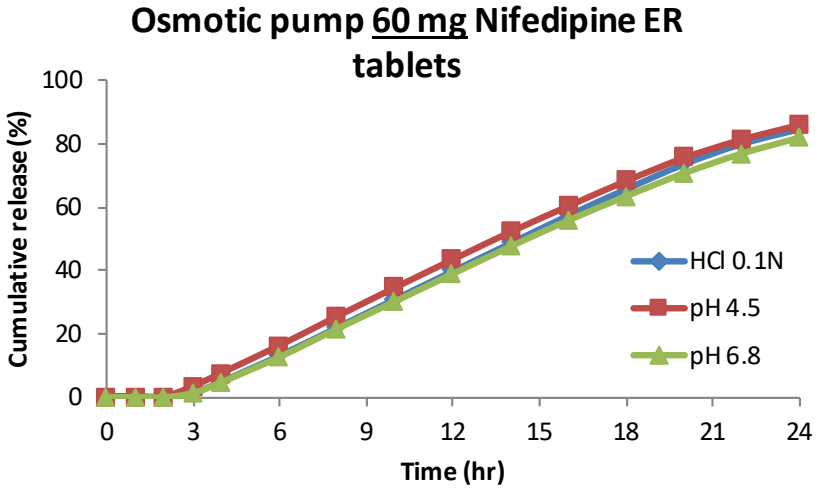
Nifedipine ER Tablets

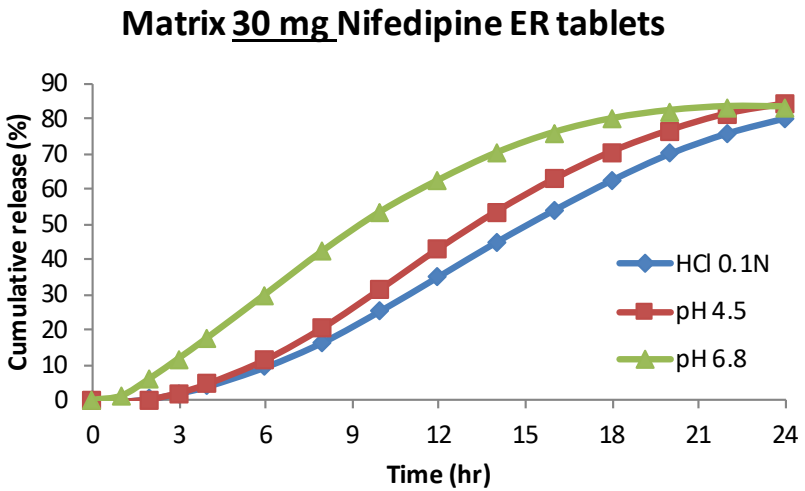
- Nifedipine is a weak acid
- Drug release from matrix is more vulnerable to change of gastric pH than that from osmotic pump

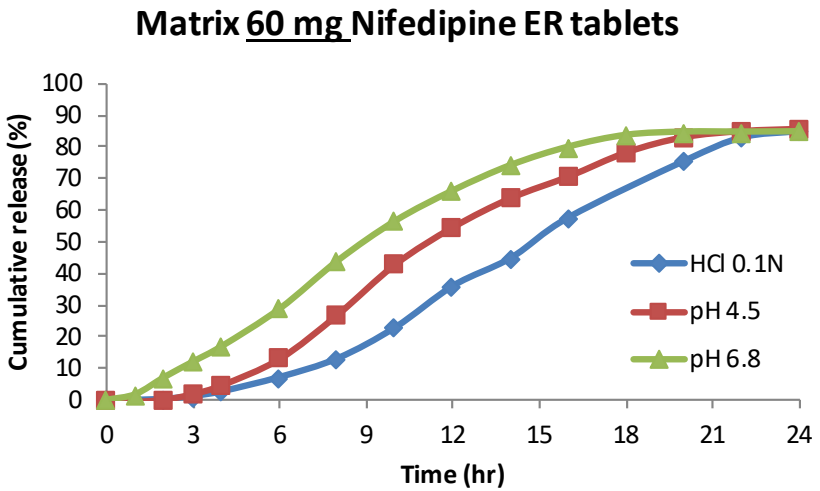
Will gastric pH condition/change in the presence of PPI affect BE differently for nifedipine osmotic pump and matrix ER formulations?

In Vitro Dissolution Testing









Dissolution conditions:

USP II, 50 rpm, 37°C, 900mL at different pH with 1% sodium lauryl sulfate

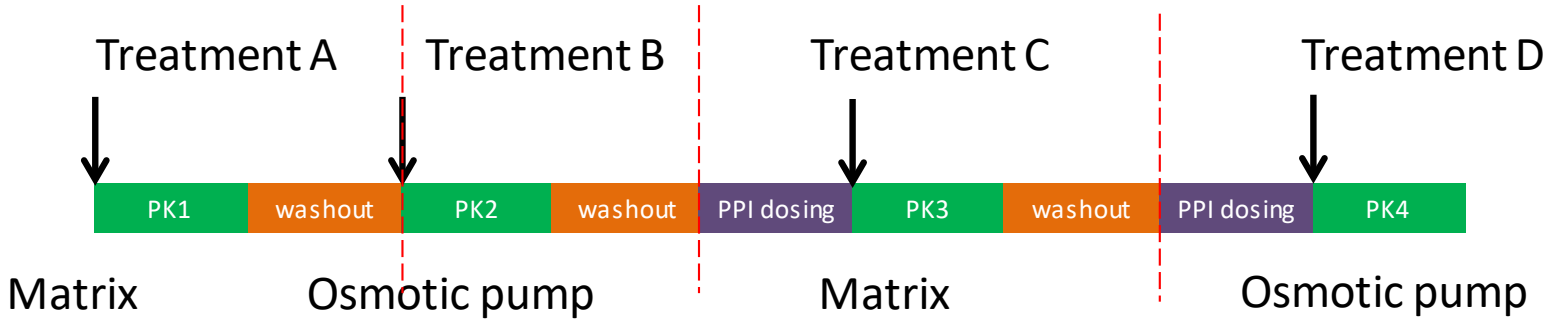
Gao et, al., J Pharm Sci, 108 (3), 1189-1194, 2019

f_2	pH 1.2/4.5	pH 4.5/6.8	pH 6.8/1.2
O 30 mg	97	93	90
O 60 mg	81	71	85
M 30 mg	67	47	41
M 60 mg	55	52	40

Clinical Study with a PPI

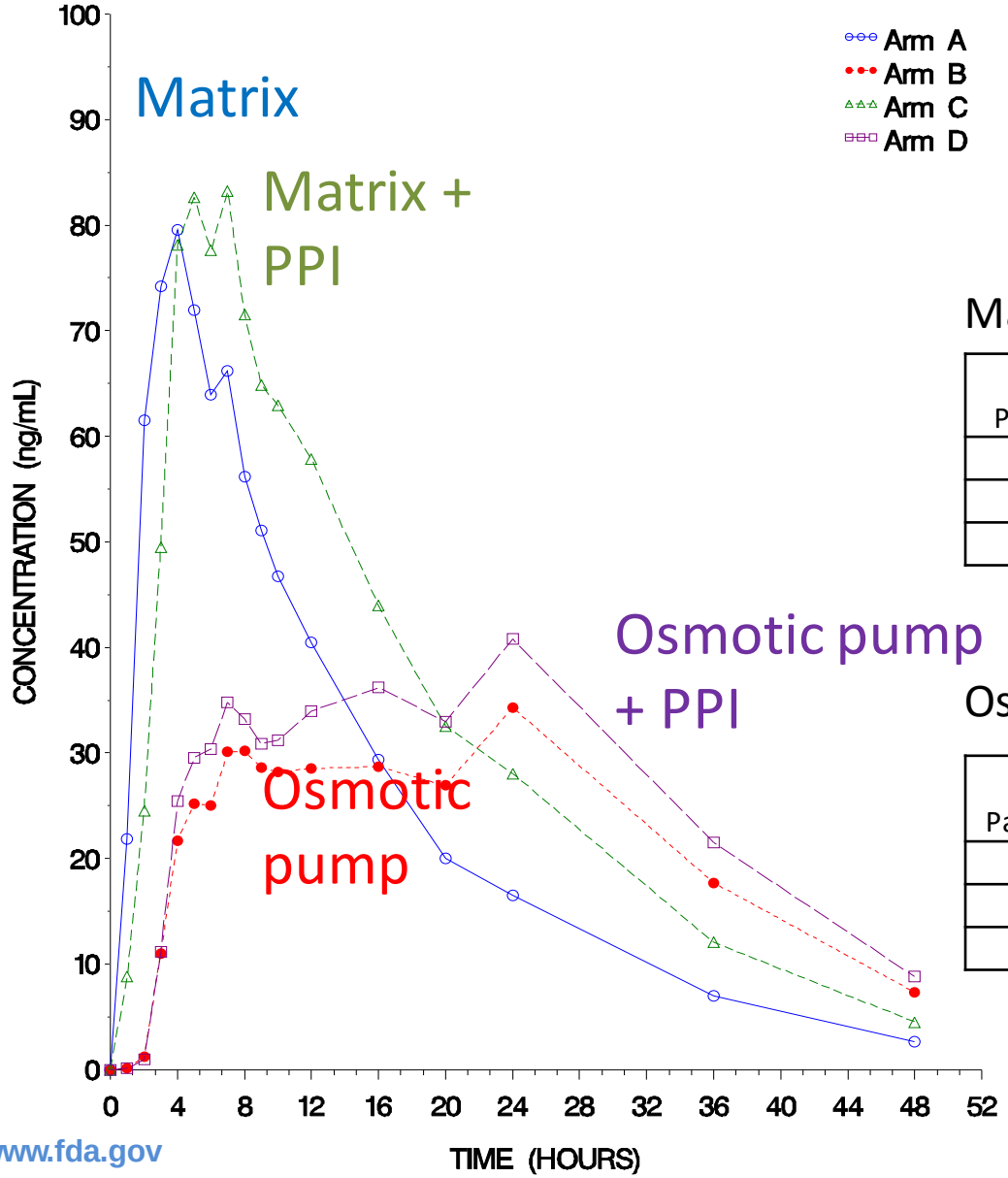
- Single center, randomized, open-label, single-dose, 4-sequence, 4-period, 4-treatment crossover design under fasting conditions in healthy subjects

- Treatment arms:
  - **A. Matrix –** Matrix-based Nifedipine ER Tablet (60 mg)
  - **B. Osmotic pump –** Osmotic pump-based Nifedipine ER Tablet (60 mg)
  - **C. Matrix + PPI –** Test Nifedipine ER Tablet (60 mg) + 7 days of omeprazole/sodium bicarbonate (40/1100 mg)
  - **D. Osmotic pump + PPI –** Osmotic pump Nifedipine ER Tablet (60 mg) + 7 days of omeprazole/sodium bicarbonate (40/1100 mg**)**



https://clinicaltrials.gov/ct2/show/NCT03100838

PPI Study Results



A. **Matrix**
B. **Osmotic pump**
C. **Matrix + PPI**
D. **Osmotic pump + PPI**

Matrix + PPI vs Matrix

PK Parameter	Geometric Mean Ratio (%)
AUC_t	137.72 (128.11 – 148.05)
AUC_{inf}	139.01 (126.77 – 152.45)
C_{max}	112.59 (102.10 – 124.17)

Osmic pump + PPI vs Osmic pump

PK Parameter	Geometric Mean Ratio (%)
AUC_t	124.38 (115.59 – 133.84)
AUC_{inf}	131.22 (114.35 – 150.57)
C_{max}	121.67 (110.26 – 134.27)

Sun et al, 2019 (unpublished)

Results

- In vitro testing shows that matrix nifedipine is more vulnerable to change of gastric pH than osmotic pump
- In vivo testing shows that the extent of PPI effect (change of gastric pH) on PK metrics of nifedipine ER tablets is similar between matrix and osmotic pump
- Omeprazole inhibits CYP3A4 that metabolizes nifedipine → may increase nifedipine AUC (in addition to pH-change)
  - PBPK modeling on nifedipine immediate-release product showed that the main interaction mechanism between omeprazole and nifedipine was via enzyme inhibition

Manuscript under preparation

Effect of Excipients on Drug Product Absorption

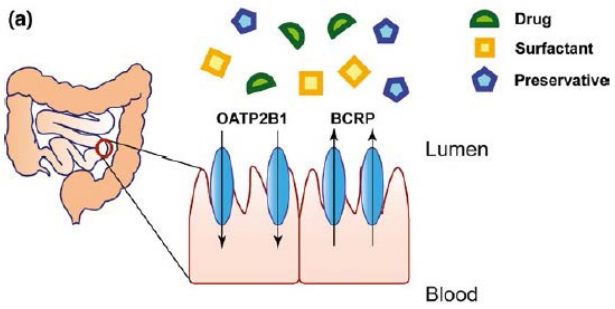
- Research was conducted to comprehensively determine the effects of excipients on oral drug absorption to support mechanistic understanding-based formulation strategy for developing generic oral drug products

- 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)
  - UCSF

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

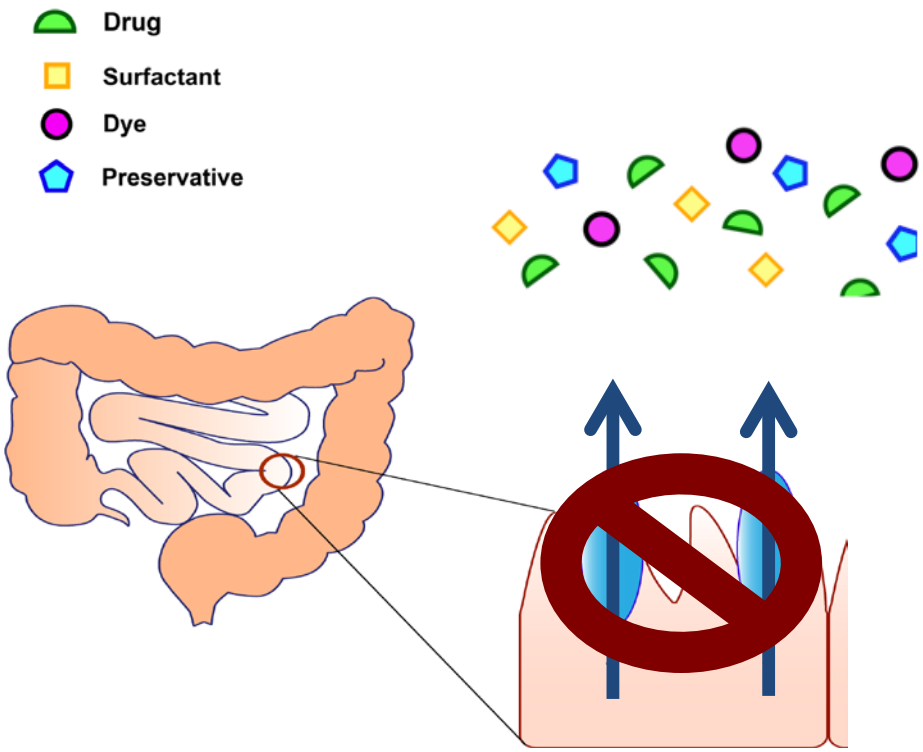
14 excipients were selected from a list of 20 most common excipients in oral products; **12** common excipients were found not impact cimetidine and acyclovir absorption in humans.

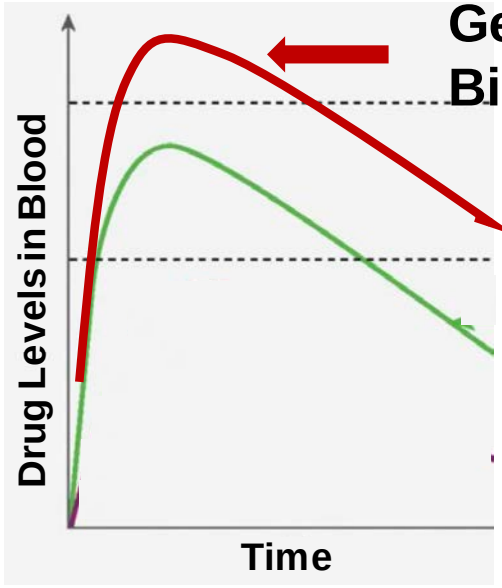
Excipient	Recommended maximum allowable amount for a class 3 biowaiver (mg)	Maximum excipient amount studied here (mg)	Typical excipient amount (when present) in an IR tablet or capsule with a total weight of 300mg	Maximum amount (mg) in Inactive Ingredient Database
Microcrystalline Cellulose	Qualitatively 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.

BCRP Reduces Transporter Mediated Drug Absorption

If excipient inhibits BCRP, the result is higher bioavailability



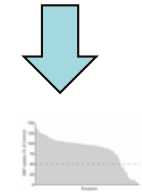


Generic Drug:
Bio-inequivalent

Courtesy: Kathy Giacomini

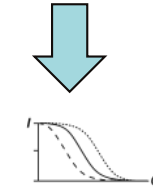
Screen of Oral Excipients for BCRP Inhibitors

Establish Vesicle Assay For 136 Oral Molecular Excipients



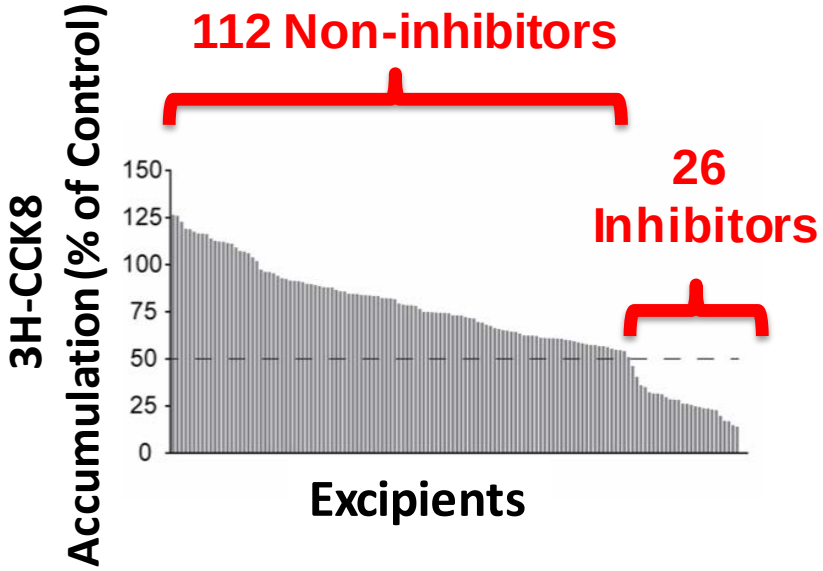
Identified 26 Inhibitors (> 50%)

Conduct Aggregation Tests



Conduct IC_{50} Studies

Potential Clinical Relevance

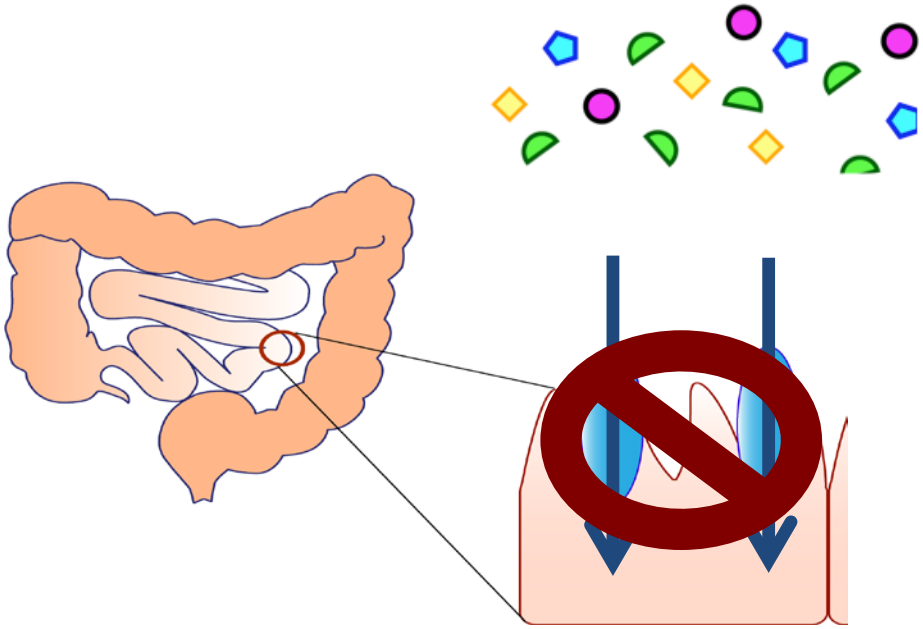


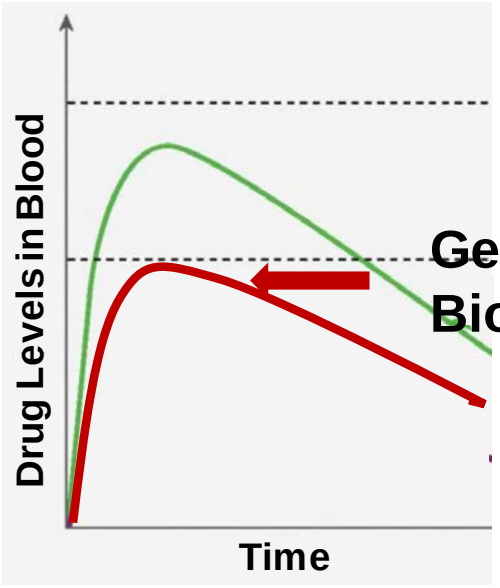
Only rhodamine B inhibited BCRP in cellular assays

Courtesy: Kathy Giacomini

OATP2B1 Mediates Drug Absorption

If excipient inhibits OATP2B1, the result is lower bioavailability





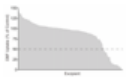
Generic Drug:
Bio-inequivalent

Courtesy: Kathy Giacomini

Screen of Oral Excipients for OATP2B1 Inhibitors

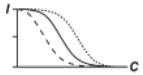
Establish Fluorescence Assay
Screen 136 Oral Molecular Excipients

Identified 24 Inhibitors (> 50%)

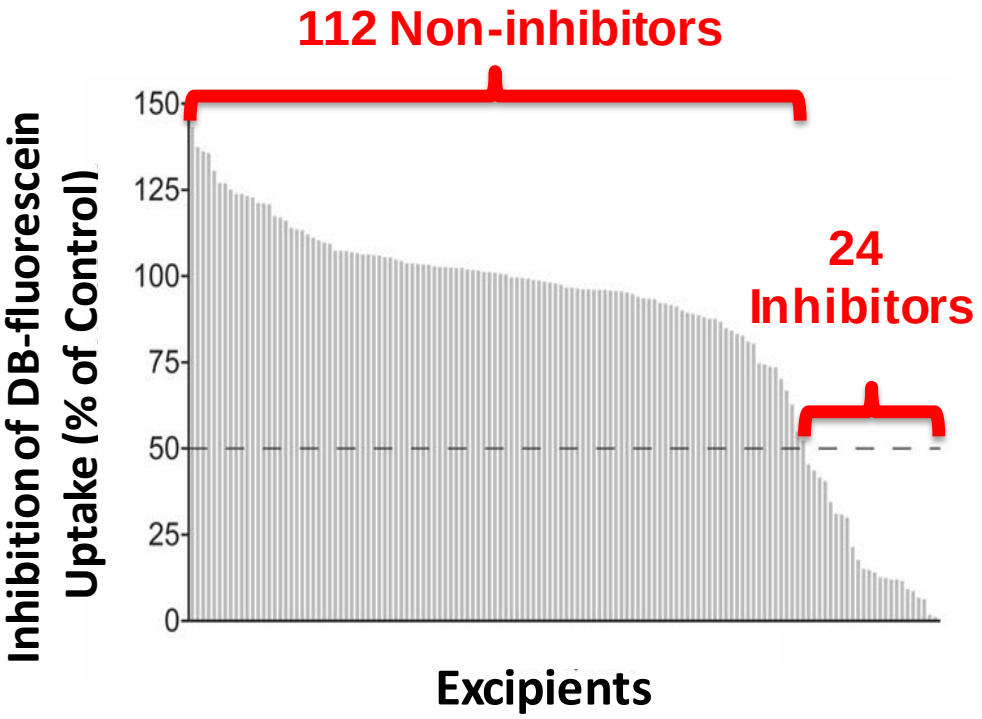


Conduct Aggregation Tests

Conduct IC_{50} Studies

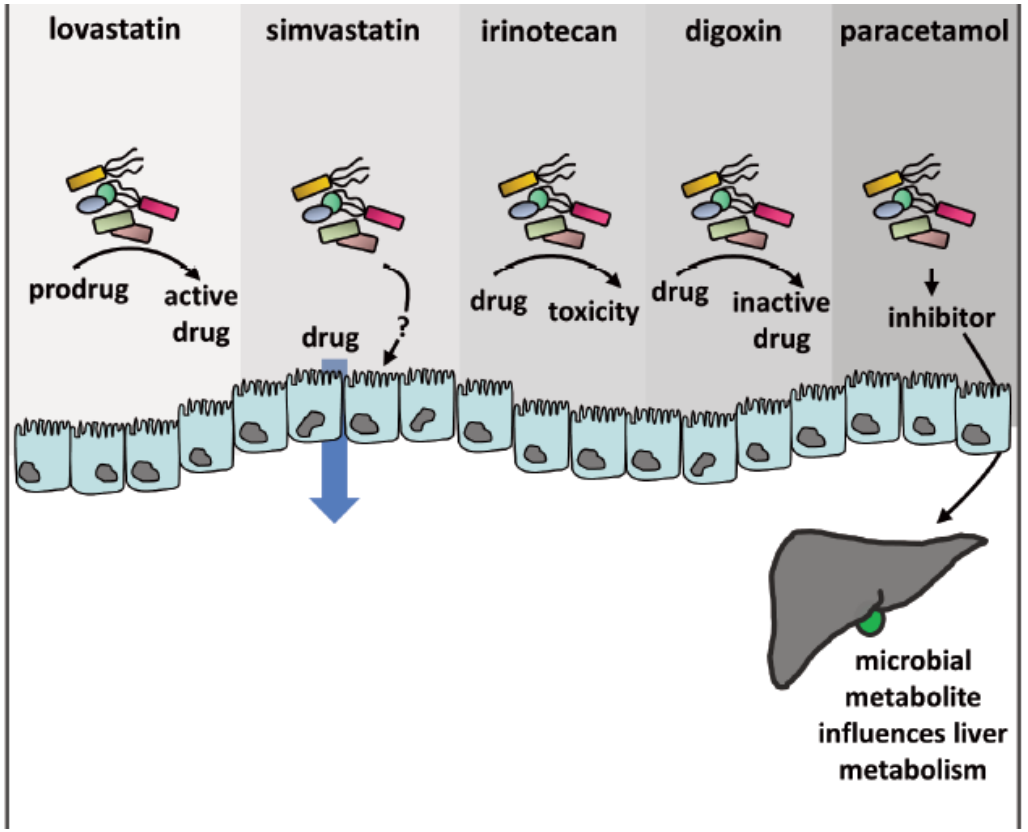


Potential Clinical Relevance



Courtesy: Kathy Giacomini

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

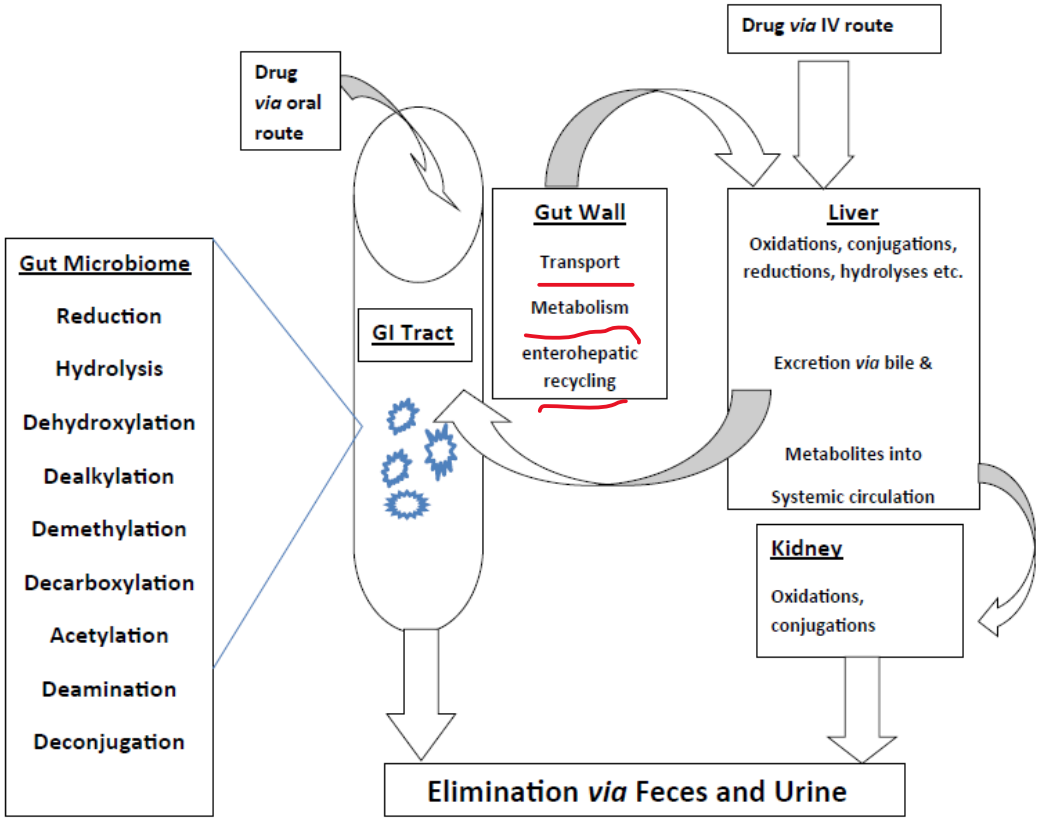
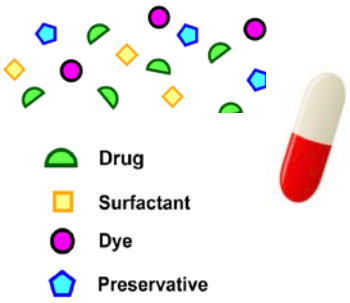


Fig 1. Sites and types of metabolism for drugs after oral or intravenous administration. IV, intravenous.

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



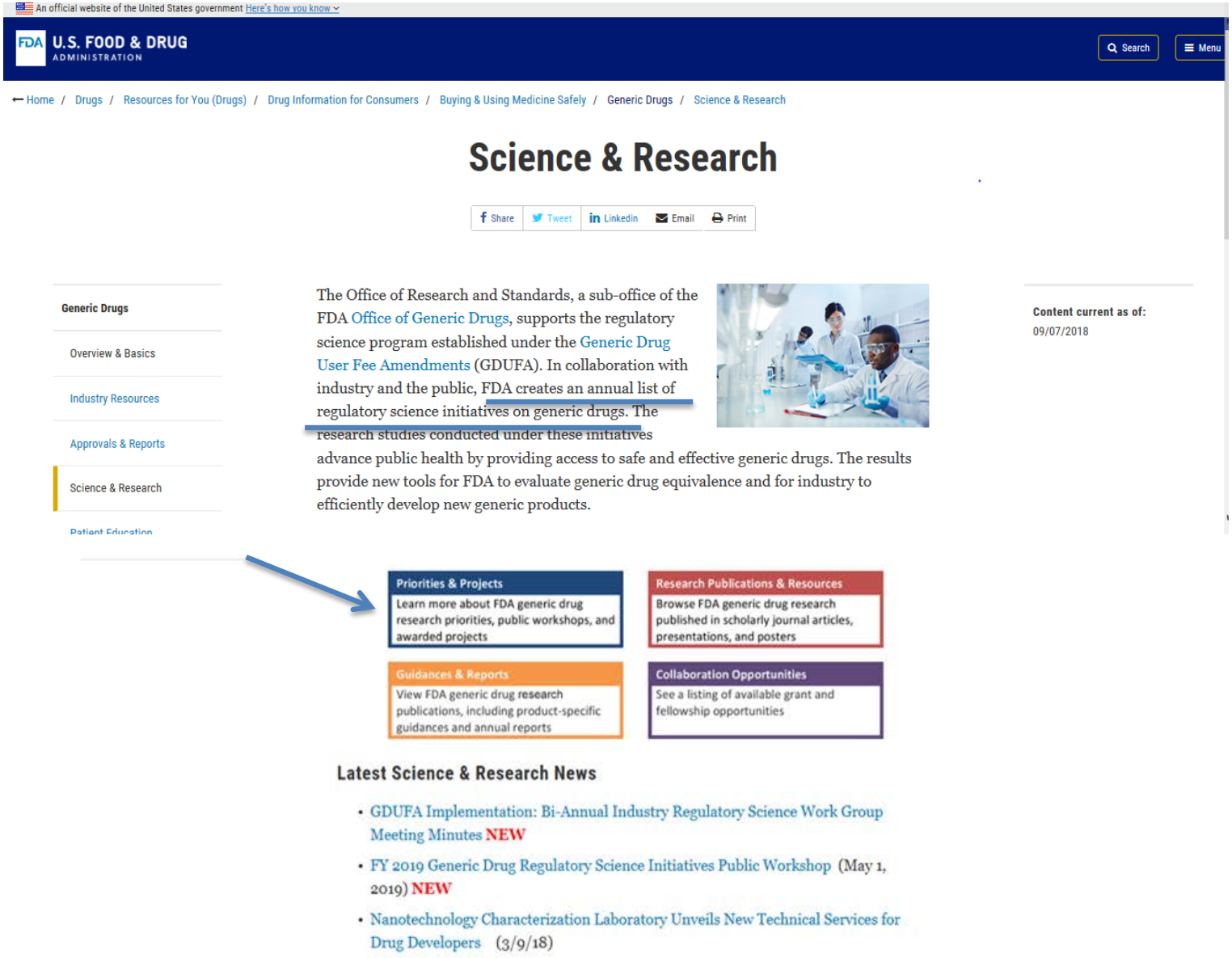
How May Microbiota Affect Drug Product Absorption and BE?

- 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

Summary

- Drug interaction considerations for oral generic drugs focus on absorption and formulation effect
- Recent research has utilized mechanistic physiologically-based pharmacokinetic models coupled with in vitro dissolution data to understand possible interactions due to pH-modulation in the GI tract or excipient effect

GDUFA Science and Research Website



https://www.fda.gov/drugs/generic-drugs/science-research

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Thank you!

Any Questions?

Contact: leik.zhang@fda.hhs.gov


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