U.S. FOOD & DRUG ADMINISTRATION

Regulatory Research on the Effect of Excipients on Drug Absorption

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ASCPT Membrane Transporter (MT) Community Meeting

Disclaimer

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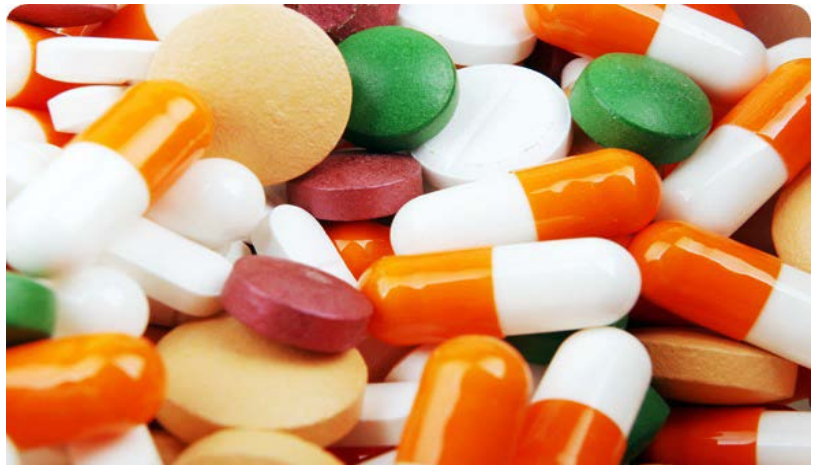
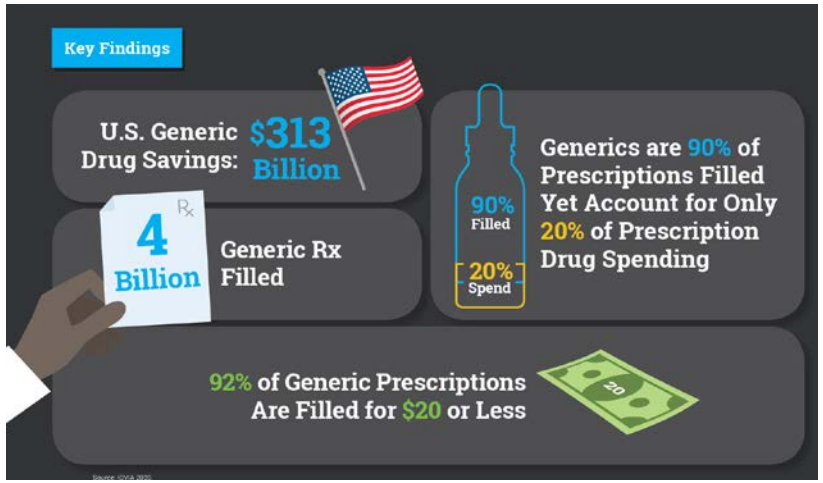
Drug Products





https://accessiblemeds.org/sites/default/files/2020-09/AAM-2020-Generics-Biosimilars-Access-Savings-Report-US-Web.pd

- **Drug Product**
  =Drug Substance (Active Ingredient)
  + Excipients (Inactive Ingredients)

- **An Active Ingredient** (per 21 CFR 210.3(b)(7))
  - Any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body

- **An Inactive Ingredient** (per 21 CFR 210.3(b)(8))
  - Any component of a drug product other than the active ingredient

Excipients and Oral Products

- Differences in excipients between brand and generic products are allowed by regulations
- Excipients in generic products generally must be used at levels that are the same or below those of approved products for that route of administration
  - See FDA's Inactive Ingredient Database (IID)
- Excipients have activity, function, and side-effects that affect safety, efficacy, and equivalence
- Excipients can impact the in vivo performance of generic products

FDA IID: https://www.fda.gov/media/128687/download

Biopharmaceutics Classification System (BCS)-Based Biowaivers

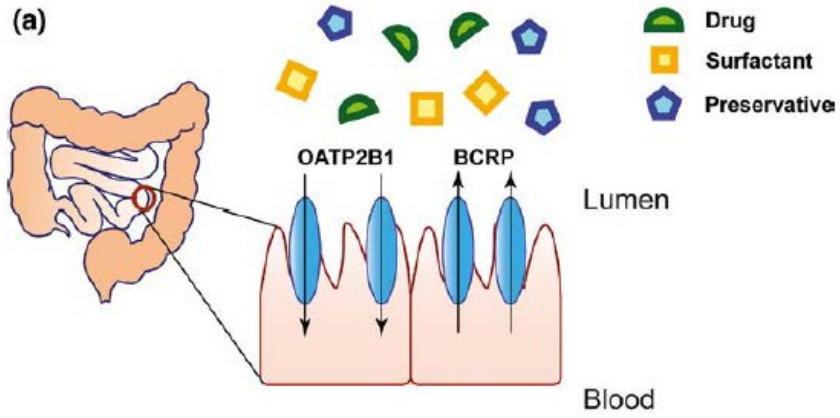
- BCS Class I (high solubility , high permeability)
  - Waivers when the drug product (test and reference) is rapidly dissolving
- BCS Class III (high solubility , low permeability)
  - Waivers when the drug product (test and reference) is **very** rapidly dissolving
  - **The product formulations are qualitatively the same and quantitatively very similar**
    - Based on a concern that **excipient** might affect bioequivalence

Regulatory Questions

- How may excipients affect oral drug absorption?
- Can we expand BCS Class III waivers for generic drugs to non-Q1/Q2 products?
  - In vitro models to predict excipients effect on drug absorption/permeation

Effect of Excipients on Transporters

- FDA-UCSF/Stanford CERSI project (Grants: U01FD004979/U01FD005978)
- 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
- Transporters in the intestine: P-gp, BCRP and OATP2B1



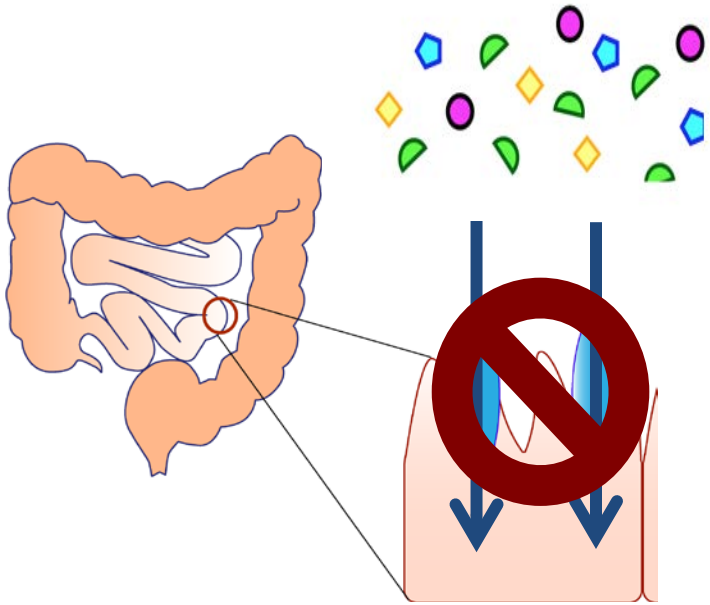
Zou L, et al., *Clin Pharm Ther*. 105 (2),323-325, 2019;
Irwin JJ, et al., *Clin Pharm Ther*. 101 (3), 320-323, 2017

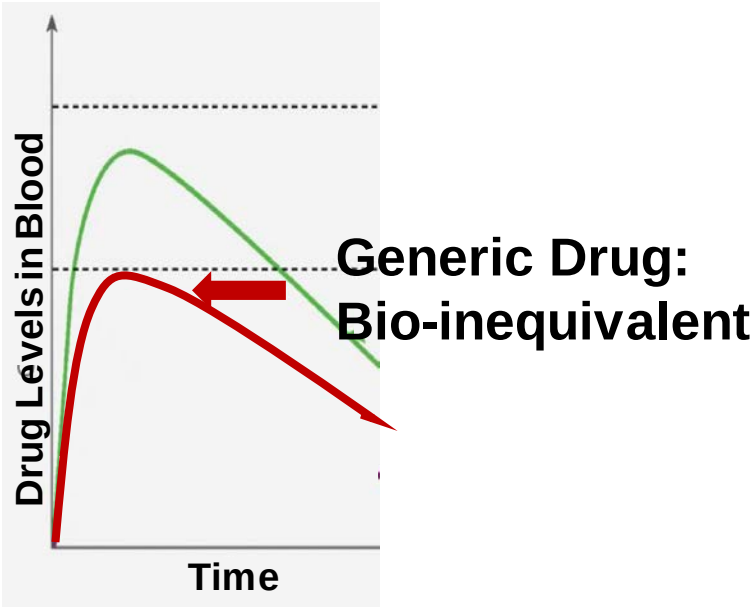
https://www.fda.gov/drugs/generic-drugs/science-research

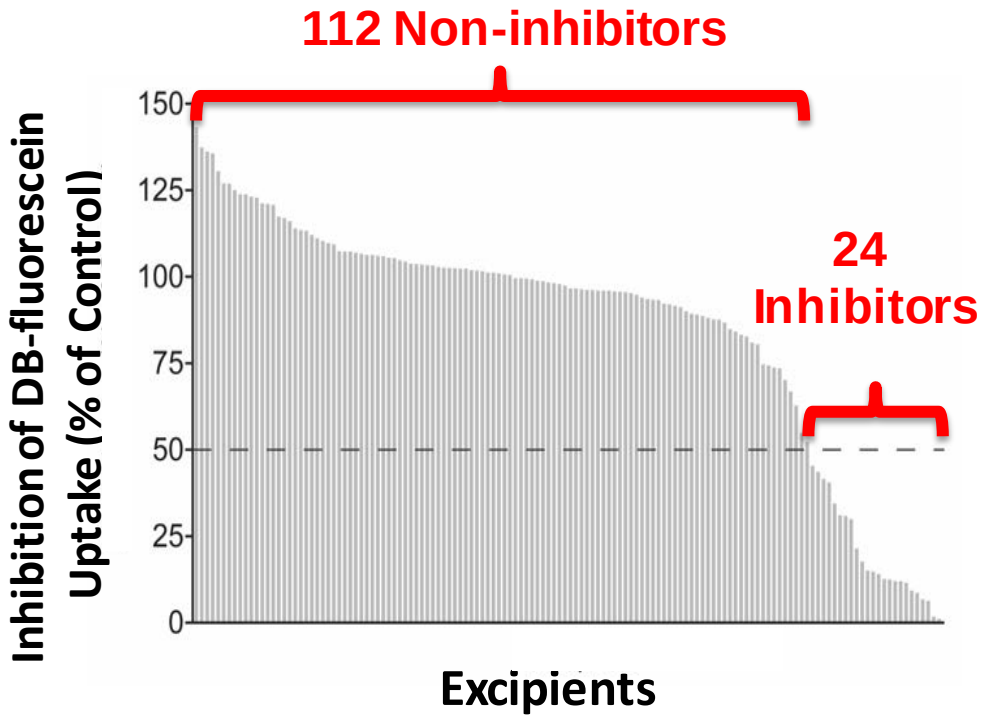
Zou L, et al., *Mol Pharmaceutics*. 17, 748-756, 2020;
Bajaj, R, et al., *AAPS J.* 23, 106, 2021
Zou L, et al., *PNAS*. 117(27),16009-16018, 2020

Screen of Oral Excipients for OATP2B1 Inhibitors

If excipient inhibits OATP2B1, the result is lower bioavailability







Zou L, et al., *PNAS*. 117(27),16009-16018, 2020

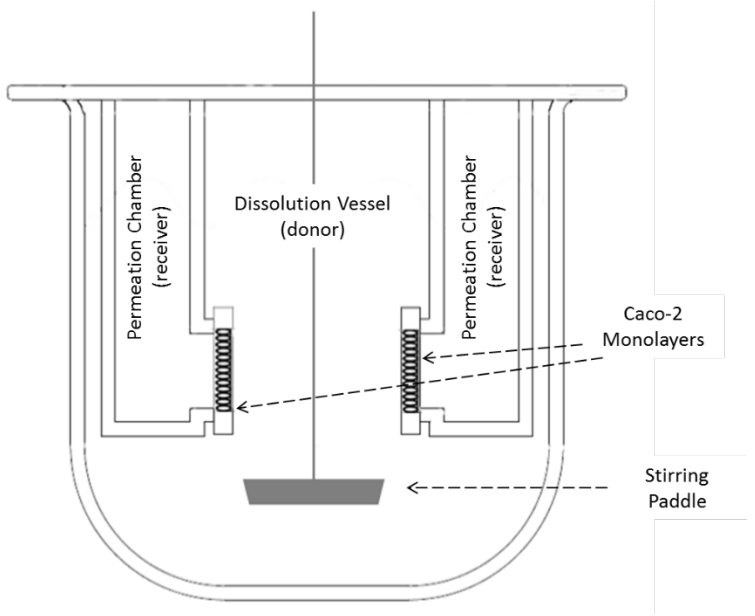
Courtesy: Kathy Giacomini

Investigate the Effect of Excipients on the Oral Absorption of Fexofenadine in Humans

- Excipient: Sodium lauryl sulfate (SLS), inhibitor of OATP2B1
- Drug: Fexofenadine
  - OATP2B1 substrate and a BCS Class III drug
- Research outcomes will support guidance on what range of SLS may be used without likely inhibition of OATP2B1-mediated absorption of BCS class 3 drugs.
- Ongoing: NCT04534153

Effect of Excipients on Permeation

- Absorption Systems (Contract: 75F40119C10127)
- Research was conducted to explore a in vitro model to evaluate the effects of excipients on drug absorption
  - Expanding BCS Class III waivers for generic drugs to non-Q1/Q2 products
  - Four BCS Class III drug products, one BCS Class I drug product
    - Acyclovir (Class III, clinical data on excipient effects)
    - Atenolol (Class III, cell monolayer integrity marker)
    - Cimetidine (Class III, clinical data on excipient effects)
    - Ranitidine (Class III, clinical data on excipient effects)
    - Minoxidil (Class I)
  - 15 common excipients representing all major functional classes (3 concentrations)



In-Vitro Dissolution Absorption System (IDAS) model

Chris Bode, et al, FDA-CRCG PBPK Workshop, Oct 2021
http://www.complexgenerics.org/media/SOP/complexgenerics/pdf/Conference-Slides/D2-05%20Chris%20Bode_2021CRCG-PBPK-workshop_Impact%20of%20Excipients_FINAL.pdf

Effect of Excipients on Permeation

Effect	Excipients	Change in Permeation
None	HPMC Microcrystalline cellulose Croscarmellose sodium Talc Mannitol Silicon dioxide	no effects on all model drugs
Spotty	Povidone K30	decrease in permeation of acyclovir and ranitidine
	Magnesium stearate	decrease in permeation of acyclovir
	Lactose, Calcium phosphate, Pregelatinized starch, PEG-400	increase in permeation of cimetidine and ranitidine
Inconsistent	Sorbitol	effects on all drugs but different directions in two tests
Consistent	SLS	dose-dependent increase in permeation of all model drugs

- SLS increased permeation of all model drugs.
- Most of the excipients tested had little or no effect on the permeation of BCS Class III drugs, suggesting that expanding biowaivers to non-Q1/Q2 formulations within a certain range for a BCS Class III drug biowaiver may be possible.

PBPK: physiologically-based pharmacokinetic

HPMC: hydroxypropyl methylcellulose

Chris Bode, et al, FDA-CRCG PBPK Workshop, Oct 2021

Summary and Future Directions

- Excipients can affect drug absorption by modulating transporters and permeation
- In vitro models and physiologically-based pharmacokinetic (PBPK) models of absorption could help predict effect of excipients on drug absorption on a mechanistic basis
  - Help formulation design
  - Help expansion of BCS Class III waivers to non-Q1/Q2 formulations
- GDUFA research has made an impact on key generic drug decisions by both industry and FDA

GDUFA Science and Research Report

- The FY2020 GDUFA Science and Research Report is available at: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-related-guidances-reports

- It highlights the scope and impact of **all** GDUFA-supported research across FDA

- High transparency to the generic industry on what we use GDUFA resources for

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Thank you!

Any Questions?

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