Leveraging Modeling to Understand the Effects of Food on Dosage Selection

Optimizing Dosages for Oncology Drug Products:
Using Modeling and Simulation to Evaluate Effects of Intrinsic and Extrinsic Factors

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- The case examples presented are for illustrative purpose only.

Outline

- Mechanistic modeling of oral absorption
- Food effect mechansims
- Mechanistic modeling for food effect case study
  - Ceritinib and Sonidegib
  - Trospium – importance of identifying relevant mechanism(s)
- Summary

Scope of today's 'food effect' discussion

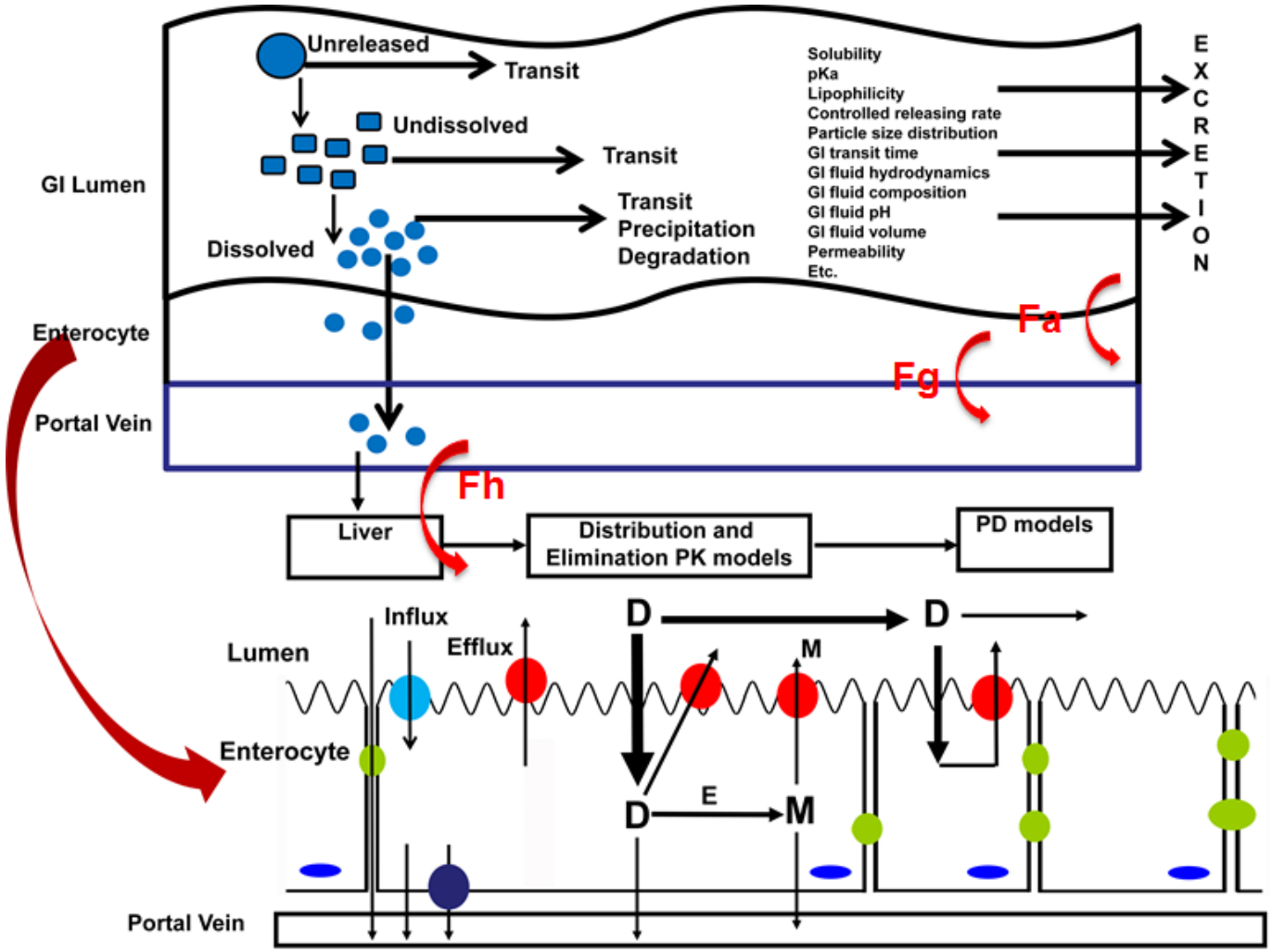
In Scope

- 'Standard meal' or 'regular / general meal'
- Immediate release formulations

Out of Scope

- Special food or drinks (such as grapefruit juice, alcohol, etc.)
- Modified release formulations

Factors affecting oral absorption



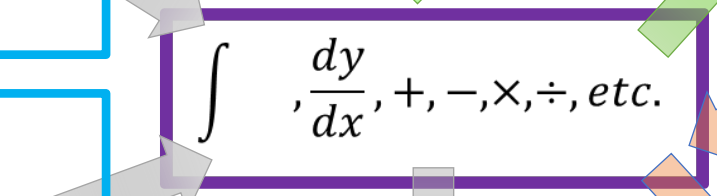
Zhang X. et al. PMID: 24747237

PBPK modeling of oral absorption

Drug substance and product information:
- Dose and dose volume
- Solubility vs. pH profiles
- logP, pKa
- Dissolution: MR: dissolution profiles; IR: particle size and density
- Diffusion coefficient
- Permeability
- Metabolic kinetics

Physiological parameters
- GI transit time
- GI geometry
- GI fluid properties
- Enzymes/transporters distribution
- Blood flow

PK parameters
- Clearance, Vd
- Tissue/organ parameters for physiologically based distribution and elimination models



- Fh, BA
- PK profiles

Metabolite Info

Parent and metabolite PK

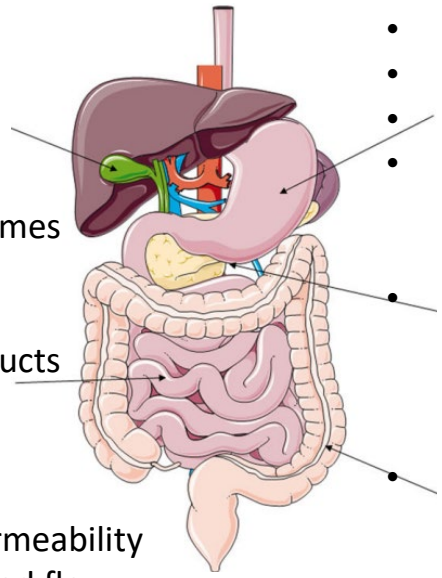
- Fa, Fg
- In vivo dissolution
- Drug in each GI compartment

Factors affecting oral absorption due to the intake of food

Physiology Factors

<u>Gall bladder</u>
- Release of bile salts

<u>Small intestine</u>
- Increased intestinal enzymes
- Increased bile salts
- Increased motility
- Increased digestion products
- Increased osmolality
- Potential inhibition of transporters and CYP
- Potential decrease in permeability
- Increased splanchnic blood flow
- Others



<u>Stomach</u>
- Increased pH
- Delayed gastric emptying
- Increased fluid volume
- Increased pepsin
- Increased acid secretion

<u>Pancreas</u>
- Enzyme secretion induced when food is in duodenum
  - Lipases, proteases, nucleases and amyloytic enzymes
- Insulin secretion

<u>Large intestine</u>
- Increased buffer capacity
- Increased fatty acid content
- Increased bile salts
- Decreased surface tension

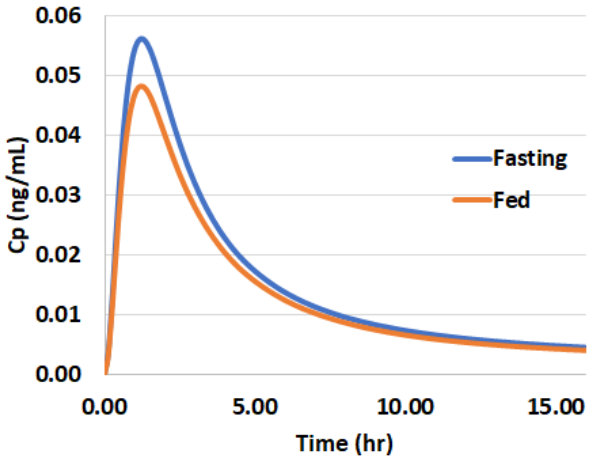
Partial translation

Drug Product Factors
- Drug solubilization / precipitation
- Drug in vivo dissolution profile
- Saturation of liver enzyme and first pass metabolism

Modified from O'Shea, J.P. et al. PMID: 29956330. https://doi.org/10.1111/jphp.12957

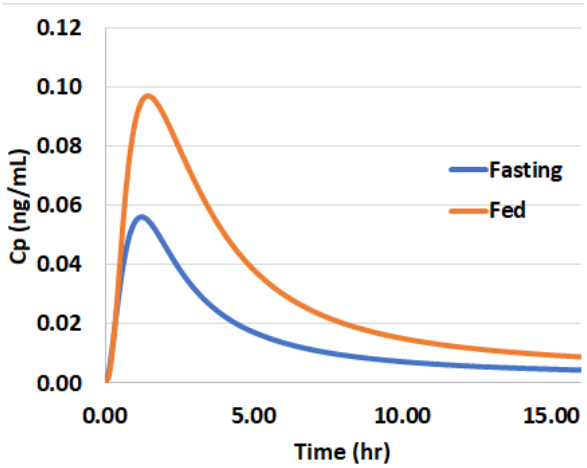
Observed food effect and associated mechanisms

No Food Effect



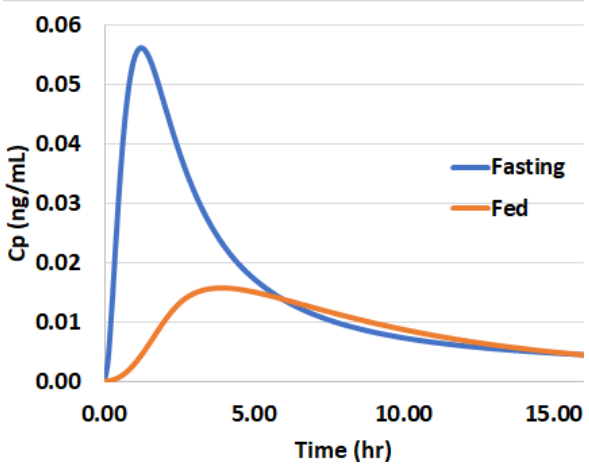
- Delayed gastric emptying time
- Physiological changes (due to the intake of food) does not impact absorption and PK

Positive Food Effect



- Increased bile salt concentration
- Increased pH
- Increased splanchnic blood flow
- Inhibition of efflux transporters
- Others

Negative Food Effect



- Decrease in permeability
- Food-drug binding
- Food caused increase in drug degradation
- Increase in viscosity of GI fluid
- Increased pH
- Others

Food effect may not be directly translated into dosage recommendation

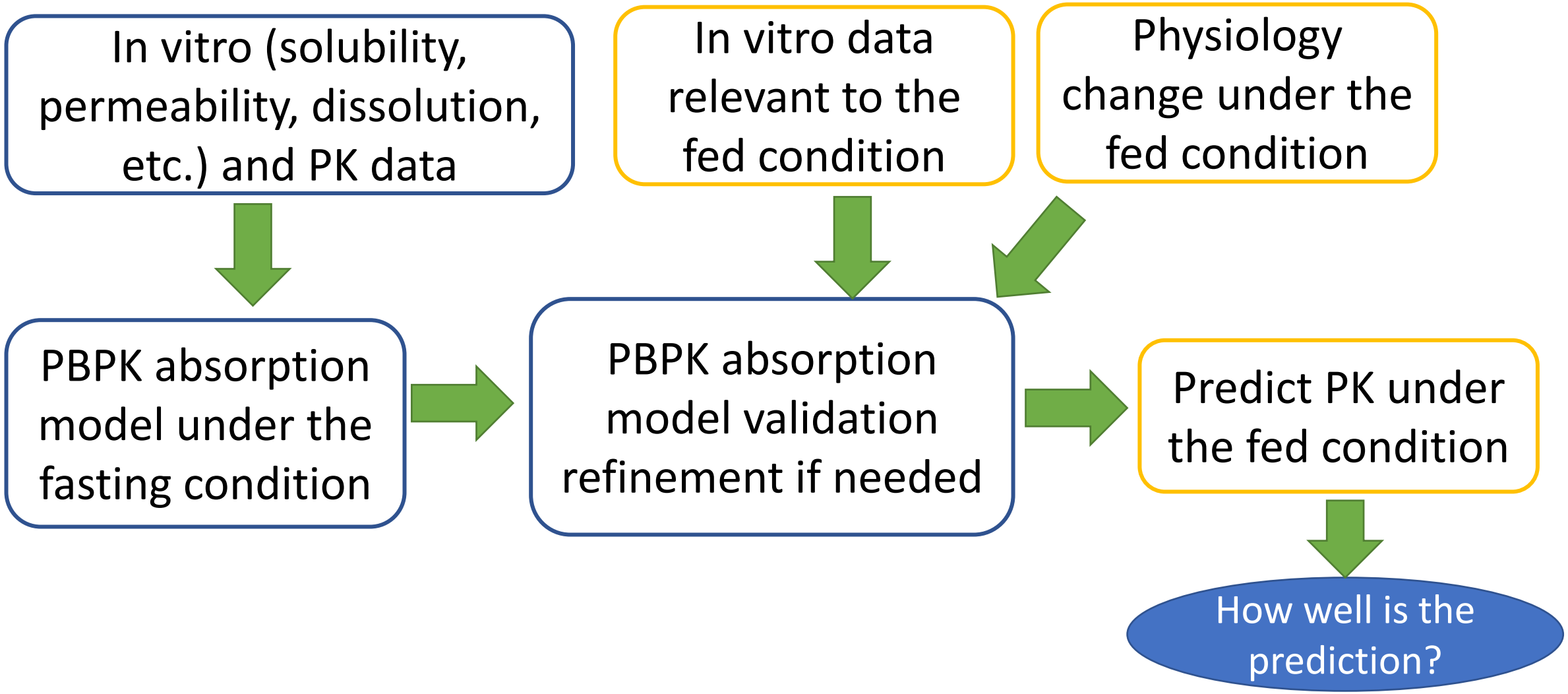
Food effect	Drug	AUCR (fed/fasting)	CmaxR (fed/fasting)	Dosage Recommendation
Positive	Venetoclax	5.1-5.3 (HF); 3.4 (LF)	---	with food
	Sonidegib	7.4-7.8 (HF)	7.4-7.8 (HF)	without food
	Vemurafenib	5 (HF)	2.5 (HF)	regardless of food
Negative	Betrixaban	0.52 (HF); 0.39 (LF)	0.50 (HF); 0.30 (LF)	with food
	Asciminib	0.38 (HF); 0.70 (LF)	0.32 (HF); 0.65 (LF)	without food
	Mirabegron ER	0.83 (HF); 0.49 (LF)	0.55 (HF); 0.25 (LF)	regardless of food for adults (tablet formulation)

HF: high fat; LF: low fat

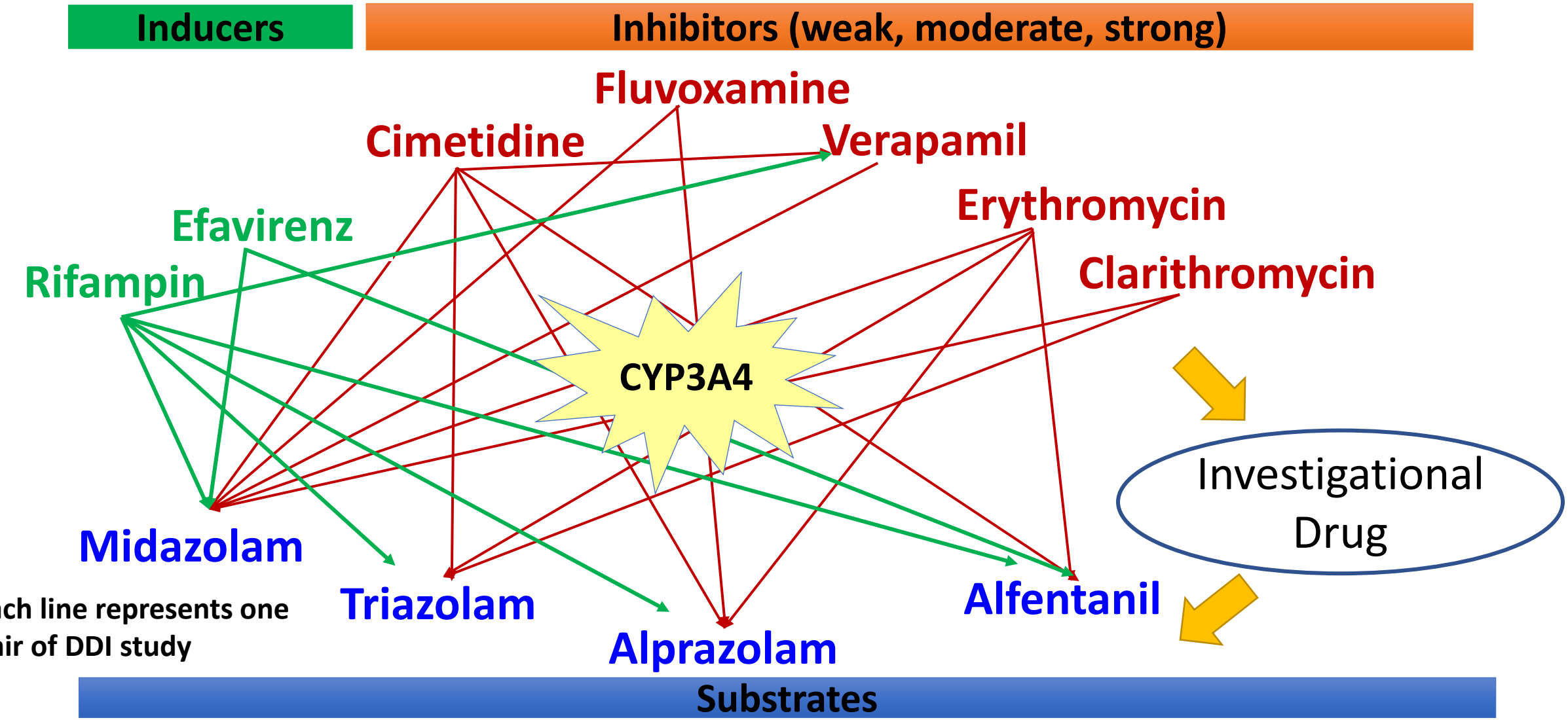
- How was the phase 2/3 study conducted?
- Exposure – response relationships for safety and efficacy
- Therapeutic window

Reference: products labels and reviews

Food-Drug Interaction Model Validation



Drug-Drug Interaction Model Validation



Modified from Frechen S, CPT Pharmacometrics Syst Pharmacol. 2021 Jun;10(6):633-644.

Drug-Drug interaction vs. Food-Drug interaction predictions

Drug-Drug interaction	Food-Drug interaction
• Interaction mechanism is clear and limited for each drug	• Interaction mechanism is multiple
• Validation is generally conducted for each pathway based on previous studies	• Validation is difficult for each mechanism
• In general, there is an anchor study (such as the DDI study with a strong inhibitor)	• The fasting study is generally used for model validation prior to food effect prediction

How are we doing with food effect prediction?

Prospective approach: completely bottom up or model optimized with **fasting** PK data
Middle-out approach: model optimized with **fed** PK data

Reference	Database	Prospective	Middle-out
Li (2018) PMID 29168611	27 compounds, 36 PBPK models, 48 food effect simulations	72% (within 2-fold)	28%
Riedmaier (2020) PMID 32981010	30 compounds, 32 formulations, 50 models	76%	24%
Kesisoglou (2020) PMID: 33205433	27 compounds	56%	44%

Cases may overlap in the three references.
The survey may contain modified-release products.

Case Study: Ceritinib and Sonidegib

Ceritinib and Sonidegib Clinical Pharmacology Highlights

	Ceritinib	Sonidegib
Dosage and indication	ALK positive NSCLC Immediate release capsules / tablets **150 mg** **750 mg QD on an empty stomach (2014), 450 mg QD with food (2017)** PK dose proportionality in the dose range of 50 to 750 mg	hedgehog pathway inhibitor for basal cell carcinoma Immediate release capsules **200 mg** **200 mg QD on an empty stomach (2015)** PK dose proportionality between 100 and 400 mg, and less than dose-proportionality at doses > 400 mg (presumably due to absorption)
Absorption	Tmax: ~1-2 hours High fat meal: ↑AUC 73%, ↑Cmax 41% Low fat meal: ↑AUC 58%, ↑ Cmax 43%	BA < 10%, Tmax ~ 2-4 hours High fat meal: ↑AUC 7.4-fold, ↑Cmax 7.8-fold
Distribution	fup: 3% , Vd/F = 4230 L, B:P = 1.35	Fup < 3%, Vss/F = 9166 L
Metabolism	CYP3A	CYP3A
Excretion	CLss/F = 33.2 L/h, CLsd/F = 88.5 L/h, T1/2 = 41 hours in patients 68% was excreted as unchanged in feces	T1/2 = 28 days
PBPK analysis in the original submission	Applicant's analysis • Assess the effect of CYP3A modulators on ceritinib PK, and propose dosing recommendation for DDI scenarios	Applicant's analysis • Predict the effect of CYP3A modulators on sonidegib PK
	FDA's analysis to explore • Sensitivity of ceritinib exposure to changes in effective permeability • **Food effect** • Sensitivity of ceritinib exposure to changes in gastric pH	FDA's analysis to explore • **Food effect**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205755s000lbl.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755s010lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205266Orig1s000lbl.pdf

PBPK for Food Effect

Model	Ceritinib	Sonidegib
Dosage	750 mg QD on an empty stomach (2014), 450 mg QD with food (2017)	200 mg QD on an empty stomach (2015)
Purpose	Exploratory analysis	Exploratory analysis
Structure	Mechanistic oral absorption	Mechanistic oral absorption
Predictive Performance	Cmax was reasonably predicted, and AUC was under-predicted under fed condition	Under predicted AUC, and Cmax under fed condition
	Observed • High fat meal: ↑AUC 73%, ↑Cmax 41% • Low fat meal: ↑AUC 58%, ↑ Cmax 43%	Observed • High fat meal: ↑AUC 7.4-fold, ↑Cmax 7.8-fold
Considerations	• PMR to evaluate the GI tolerability, efficacy and PK of 450 mg (fed) and 750 mg (fasting)	• Positive exposure-response relationship for safety (Gr 3+ AEs)

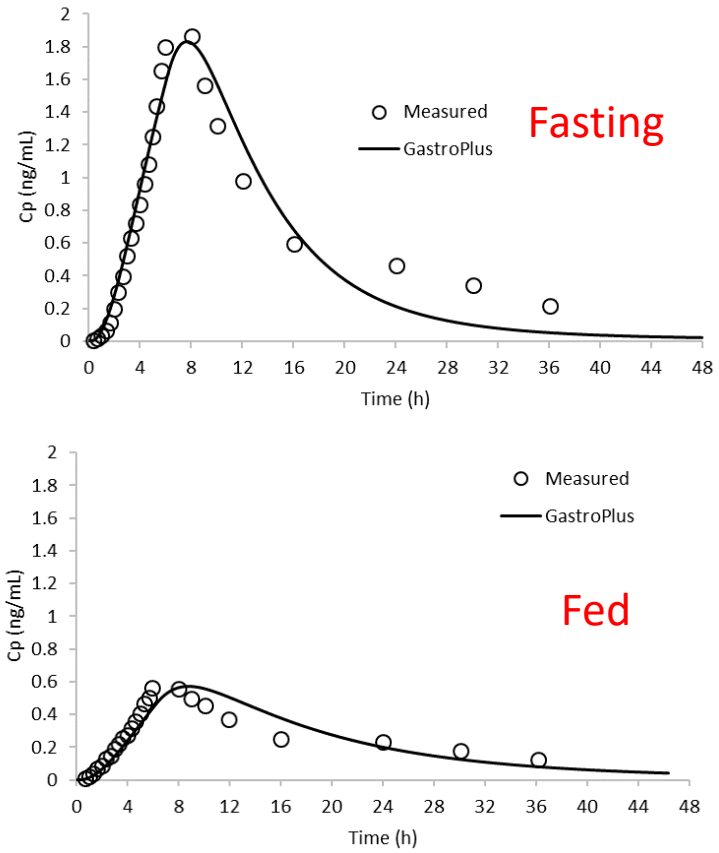
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000ClinPharmR.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205266Orig1s000ClinPharmR.pdf

Case Study: Trospium – importance of identifying relevant mechanism(s)

Trospium biopharmacetics and clinical pharmacology properties

Property	IR tablet
Dosage strength (mg)	20
logP	-1.22
Intrinsic solubility (mg/mL)	0.78
Jejunum Peff (10^{-4} cm/sec)	0.018 (fasted), 0.008 (fed)
Absolution BA	~10%
Tmax	5-6 hrs
Food effect on AUC and Cmax	↓ 70-80%
Excretion	Major pathway: active tubular secretion
$t_{½}$ (hr)	18

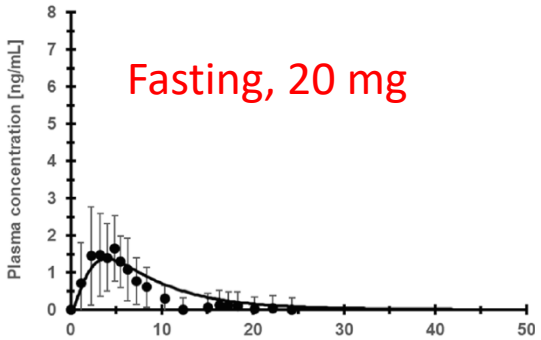
gastric infusion of a trospium-Cl solution over 6 h

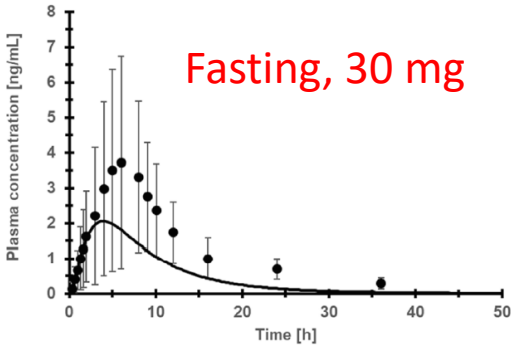


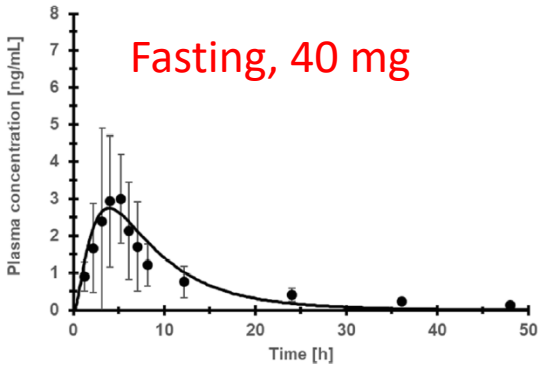
Wagner, C. et al. PMID: 34142242
Tadken, T. et al. PMID: 27765726

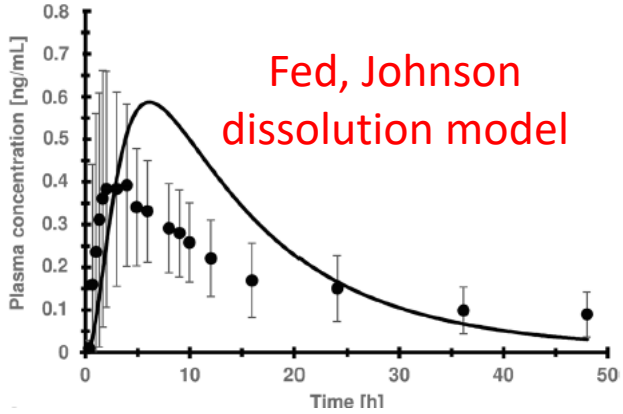
Trospium food effect modeling strategy

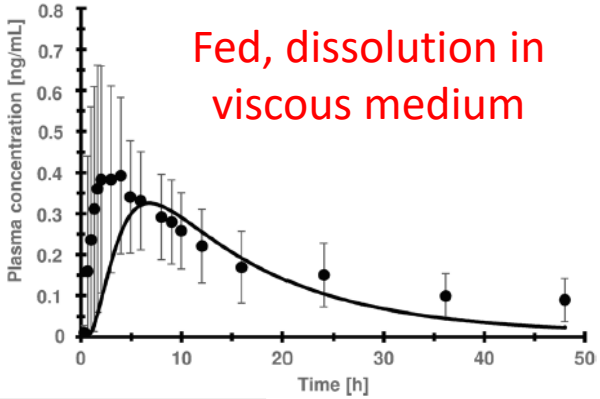
- Disposition model was developed based on IV data
- Permeability derived from gastric infusion data under fasting and fed conditions
- Slower dissolution in the fed state due to higher viscosity of postprandial GI juices







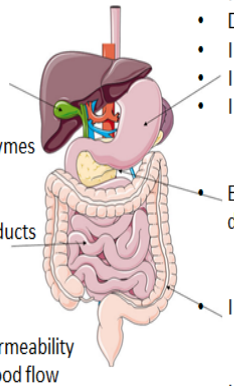




Prandial state	Dose (mg)	AUCinf (µg*h/mL)					Cmax (µg/mL)				
		Pred	Obs	Pre/Obs	Fed/Fasted		Pred	Obs	Pre/Obs	Fed/Fasted	
					Pred	Obs				Pred	Obs
Fasted	20, IR	15.5	11.0	1.41			1.37	1.65	0.83		
Fasted	30, IR	23.2	51.5	0.45			2.06	3.71	0.56		
Fasted	40, IR	29.6	36.2	0.82			2.75	2.99	0.92		
Fed	30, IR, w/o viscosity	11.0	19.0	0.58	0.47	0.37	0.59	0.39	1.51	0.29	0.11
Fed	30, IR, w/ viscosity	6.5	19.0	0.34	0.28	0.37	0.33	0.39	0.85	0.16	0.11

Wagner, C. et al. PMID: 34142242

What are the major gaps?



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Large intestine
- Increased buffer capacity
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Commonly incorporated factors
- Physiological changes
- Drug solubilization / precipitation
- Drug in vivo dissolution profile
- Saturation of liver enzyme and first pass metabolism

Mechanisms that are not captured

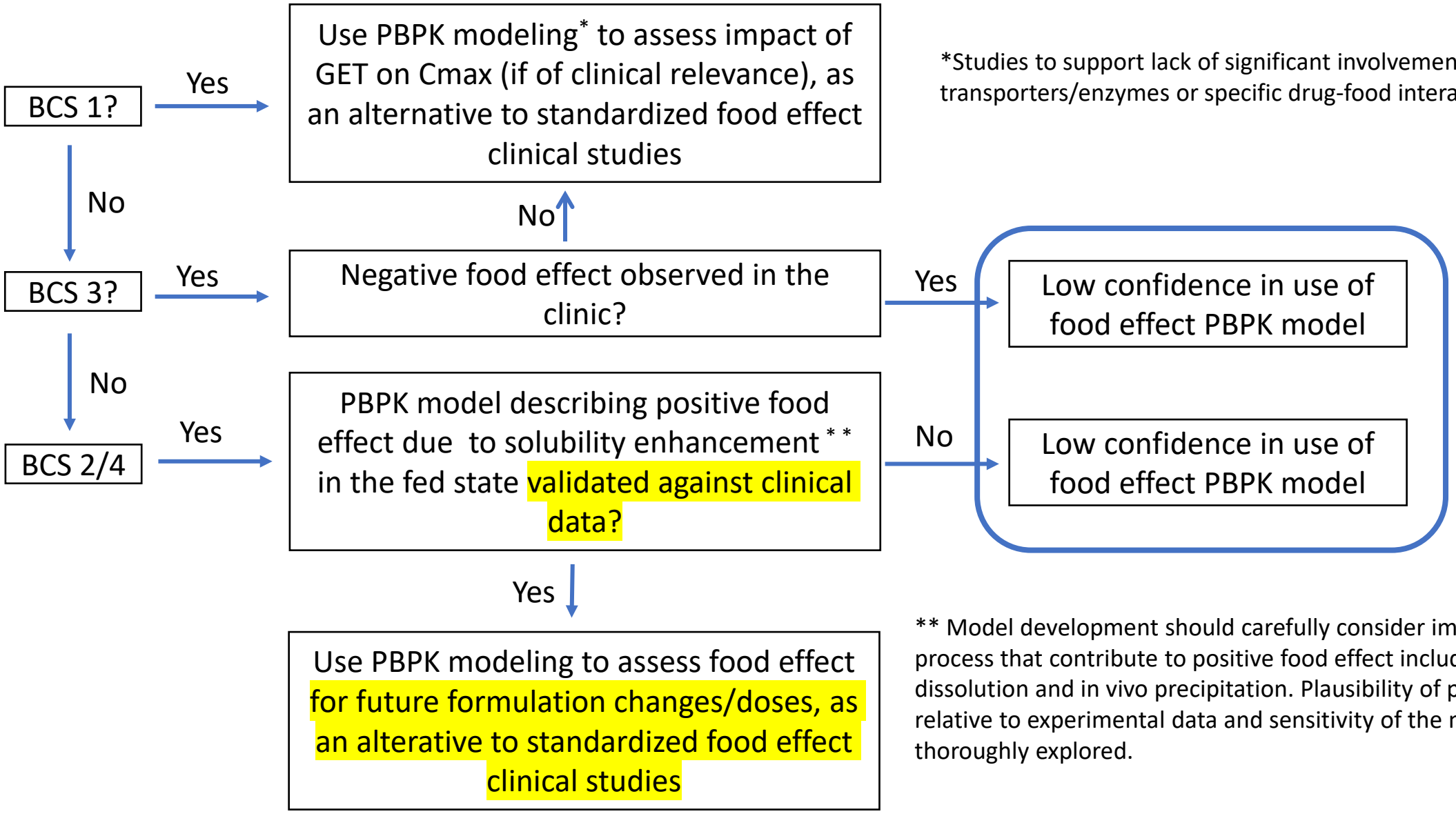
- Decrease in permeability
- Food-drug binding / interaction
- Change in viscosity of GI fluid
- Food impact on drug degradation
- Impact on intestinal enzymes and transporters
- Others

Many of these cause negative food effect, and consequently low confidence in prediction

Best practice (model development, optimization, and validation)

Kesisoglou, F. PMID: 33205433

Proposed Workflow



*Studies to support lack of significant involvement of transporters/enzymes or specific drug-food interactions

** Model development should carefully consider impact of key absorption process that contribute to positive food effect including bile salt solubilization, dissolution and in vivo precipitation. Plausibility of parameter input values relative to experimental data and sensitivity of the model to those should be thoroughly explored.

Kesisoglou, F. PMID: 33205433

Revisit the questions and understand what we can do with PBPK food effect modeling

- Can we use **MIDD** to
  - early to assess different types of meals (high fat, low fat, other types)?
  - better assess food/fasting dosing interval?
  - assess differences in acute FE vs. at steady state?
  - assess patient risks under different fed conditions, and recommend better dosing strategies for testing?

Summary

- Predicting food effect has made great progress in the past decades as shown in the literature.
- There are challenging areas largely due to
  - Multiple mechanisms can be involved
  - Pre-identifying the food effect mechanisms for a specific drug product can be challenging
  - Quantitative in vitro to in vivo correlation can be challenging for certain mechanisms
- In low confidence cases, a fed study could be needed to validate the model
- Model development at early stage could benefit the drug development program, such as selecting the appropriate dose level in consideration of the appropriate prandial condition before taking forward to pivotal studies.

Acknowledgment

- OCP reviewers and colleagues (FDA)
- Yvonne Lau (DSI)