INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

STREAMLING FOOD EFFECT ASSESSMENT VIA PBPK MODELING

ARE REPEAT FOOD EFFECT STUDIES NEEDED?

Sponsored by the IQ Translational and ADME Sciences Leadership Group (TALG)

Presented by the PBPK Food Effect Working Group

15 March 2023

Arian Emami Riedmaier, PhD (Certara)

Filippos Kesisoglou, PhD, FAAPS (MSD)

ACKNOWLEDGEMENT

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IQ PBPK Food Effect Working Group Members

- Christian Wagner (Merck Healthcare KGaA*)
- John Chung (Amgen)
- Priyanka Kulkarni (Takeda)
- Neil Parrott (Roche)
- Tejashree Belubbi (Roche)
- Phil Bransford (Vertex)
- Stephanie Dodd (Novartis)
- Sumit Basu (Novartis)
- Xiaojun Ren (Novartis)
- Andrea Moir (AstraZeneca)
- Pradeep Sharma (Astrazeneca)
- Michael Dolton (Genentech)
- Christophe Tistaert (Janssen)
- Tycho Heimbach (MSD)
- Shruthi Vaidhyanathan (BMS)
- Konstantinos Stamatopoulos (GSK)
- Mirko Koziolek (Abbvie)
- Wen Lin (Sanofi)
- Co-chair: Arian Emami Riedmaier (Certara)
- Chair: Filippos Kesisoglou (MSD)
- TALG sponsor: Christine Xu (Sanofi)

* The healthcare business of Merck KGaA, Darmstadt, Germany

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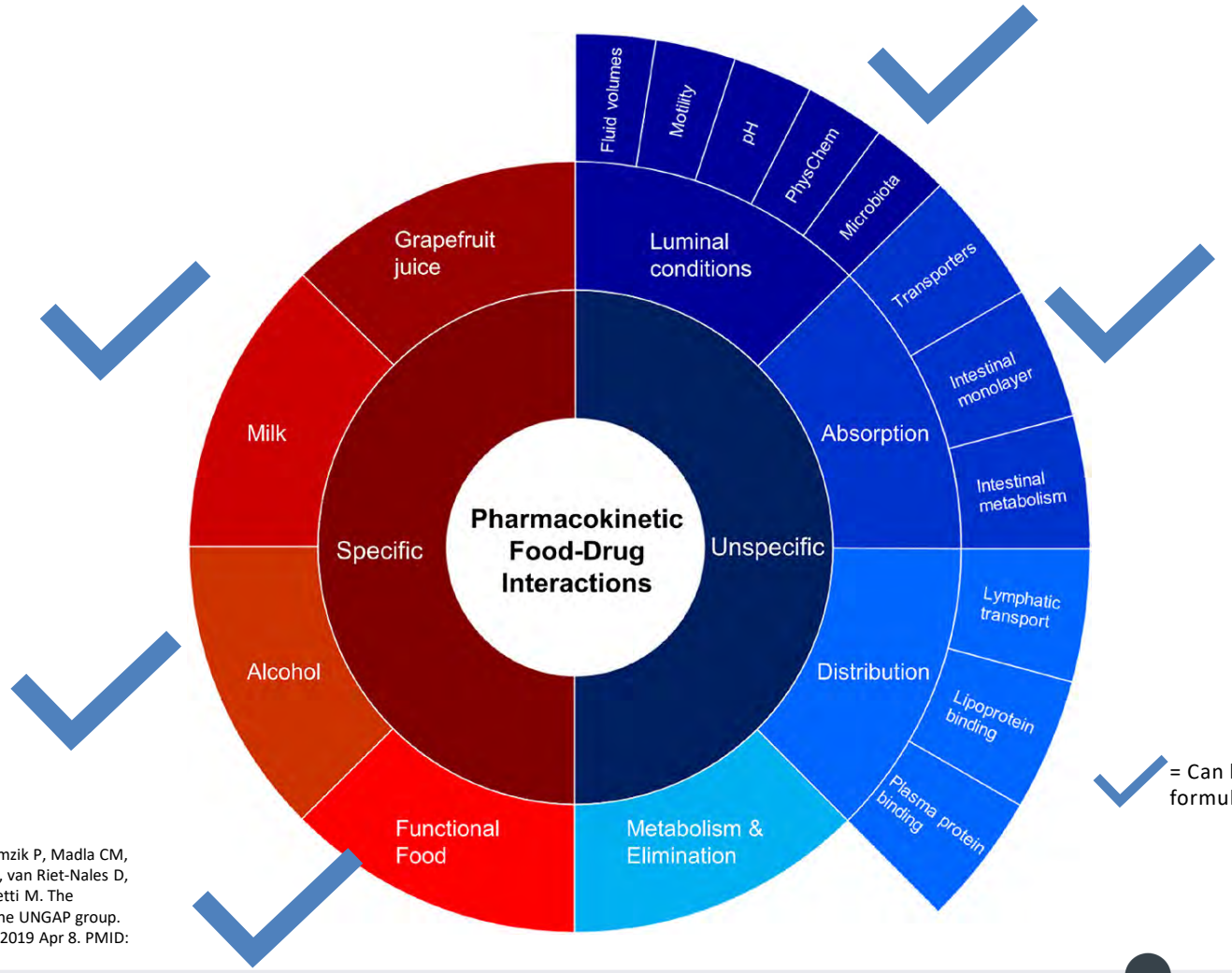
Part 1. Bottom-up or Middle-out Food Effect Prediction via PBPK Models

What Causes a Drug-Food Effect Interaction?

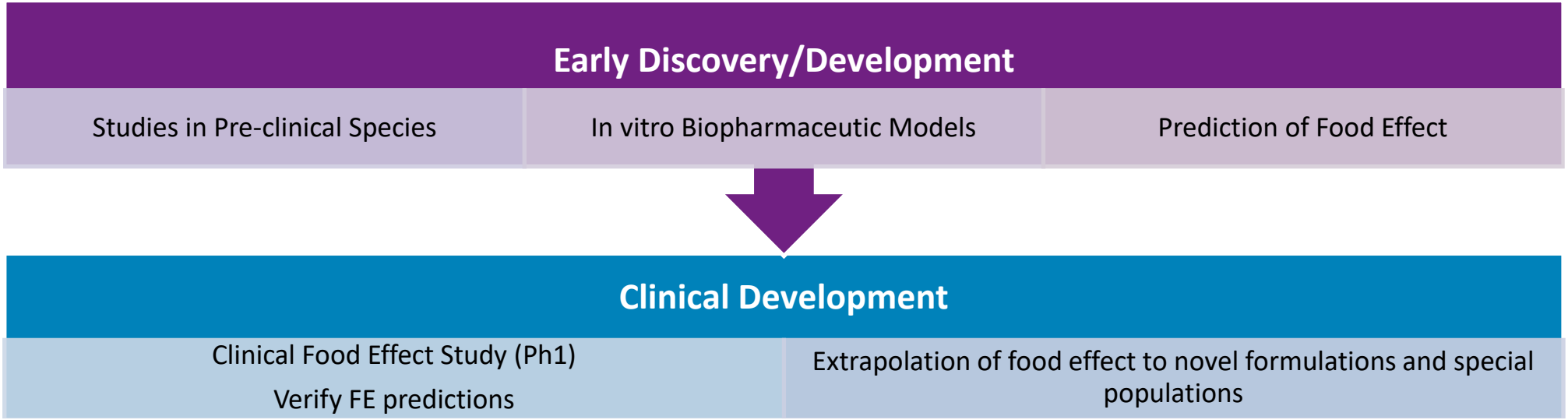


= Can be related to CMC aspects and impacted by formulation changes

Koziolek M, Alcaro S, Augustijns P, Basit AW, Grimm M, Hens B, Hoad CL, Jedamzik P, Madla CM, Maliepaard M, Marciani L, Maruca A, Parrott N, Pávek P, Porter CJH, Reppas C, van Riet-Nales D, Rubbens J, Statelova M, Trevaskis NL, Valentová K, Vertzoni M, Čepo DV, Corsetti M. The mechanisms of pharmacokinetic food-drug interactions - A perspective from the UNGAP group. Eur J Pharm Sci. 2019 Jun 15;134:31-59. doi: 10.1016/j.ejps.2019.04.003. Epub 2019 Apr 8. PMID: 30974173.

Impact of Food Effect on Drug Development

- Food effect and bioavailability studies usually conducted to support NDAs and label recommendations



Given the complex nature of food effect, an integrated approach is required: physiologically-based absorption models have emerged as a key platform for the support of food effect predictions

Manuscripts Published by Food Effect PBPK WG

Springer Link

Research Article | Open Access | Published: 27 September 2020

Use of Physiologically Based Pharmacokinetic (PBPK) Modeling for Predicting Drug-Food Interactions: an Industry Perspective

Arian Emami Riedmaier, Kevin DeMent, James Huckle, Phil Bransford, Cordula Stillhart, Richard Lloyd, Ravindra Alluri, Sumit Basu, Yuan Chen, Varsha Dhamankar, Stephanie Dodd, Priyanka Kulkarni, Andrés Olivares-Morales, Chi-Chi Peng, Xavier Pepin, Xiaojun Ren, Thuy Tran, Christophe Tistaert, Tycho Heimbach, Filippos Kesisoglou, Christian Wagner & Neil Parrott

The AAPS Journal **22**, Article number: 123 (2020) | Cite this article

Springer Link

Research Article | Published: 04 January 2021

Understanding Mechanisms of Food Effect and Developing Reliable PBPK Models Using a Middle-out Approach

Xavier J. H. Pepin, James E. Huckle, Ravindra V. Alluri, Sumit Basu, Stephanie Dodd, Neil Parrott & Arian Emami Riedmaier

The AAPS Journal **23**, Article number: 12 (2021) | Cite this article

609 Accesses | **1** Citations | **2** Altmetric | Metrics

The AAPS Journal (2021) 23:85
DOI: 10.1208/s12248-021-00601-0

Research Article

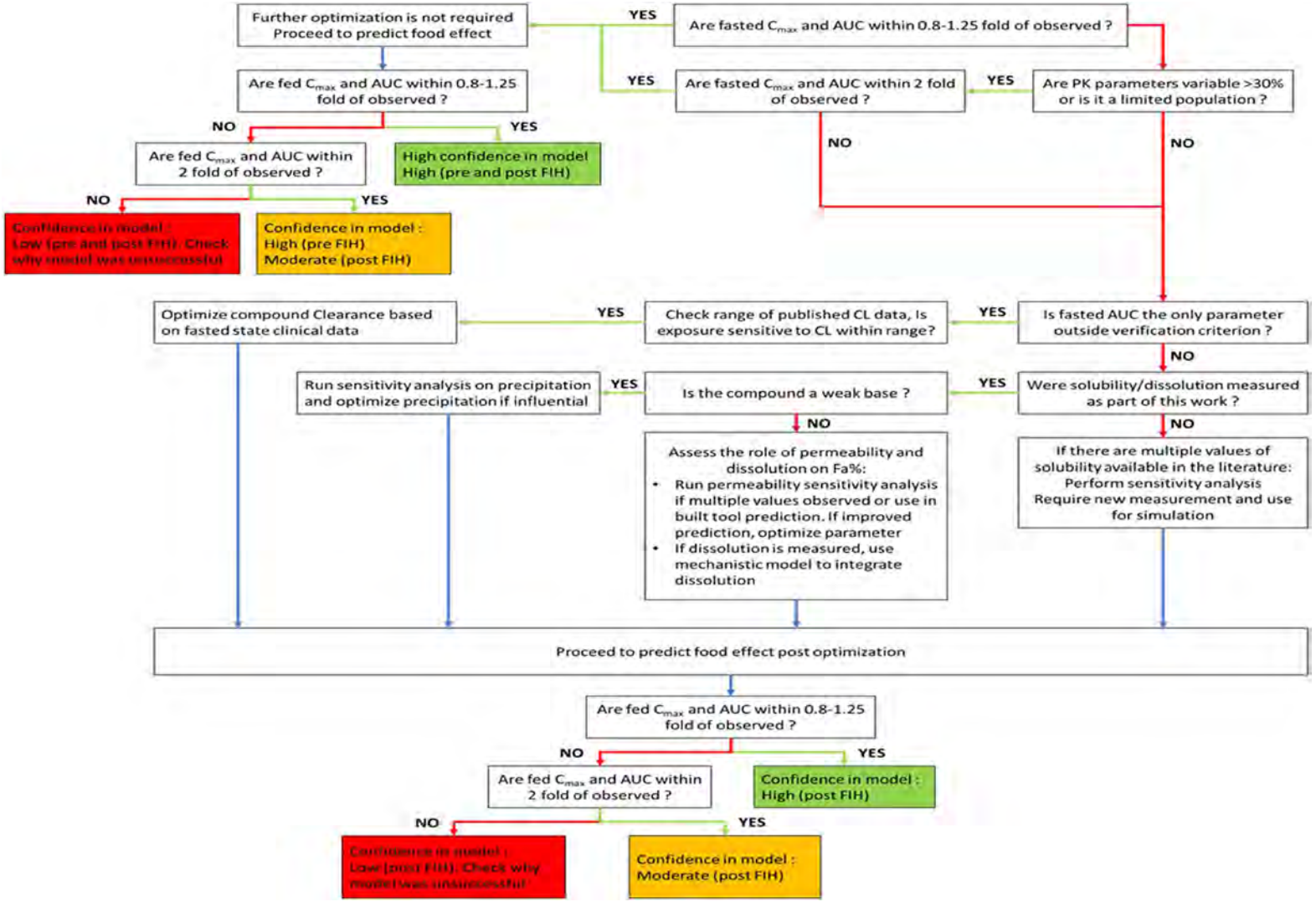
Theme: Use of PBPK Modeling to Inform Clinical Decisions: Current Status of Prediction of Drug-Food Interactions
Guest Editor: Filippos Kesisoglou

Use of Physiologically Based Pharmacokinetic Modeling for Predicting Drug–Food Interactions: Recommendations for Improving Predictive Performance of Low Confidence Food Effect Models

Christian Wagner,[1,6] Filippos Kesisoglou,[2] Xavier J. H. Pepin,[3] Neil Parrott,[4] and Arian Emami Riedmaier[5]

IQ Food Effect Working Group

Decision Tree

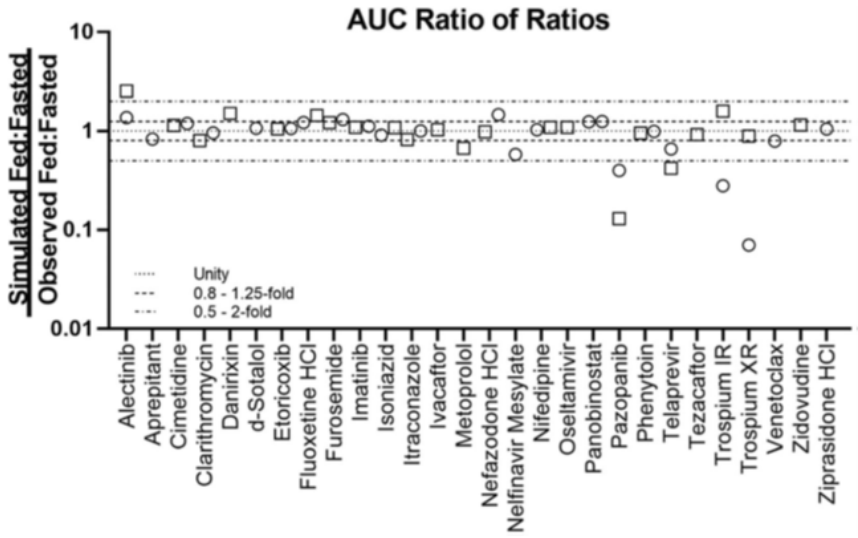


Study Outline for Evaluating Model Success

- The 30 compounds tested covered a range of BCS classifications and food effect types, including:
  - 13 compounds with positive food effect
  - 8 compounds with negative food effect
  - 9 compounds with no food effect
- Simcyp and GastroPlus used for modeling.
- Model performance and confidence was evaluated in the context of the stage of drug development; i.e. purely bottom-up (discovery only) or middle-out (discovery + development)
- The direction and magnitude of food effect was evaluated using a purely bottom-up vs. middle-out approach

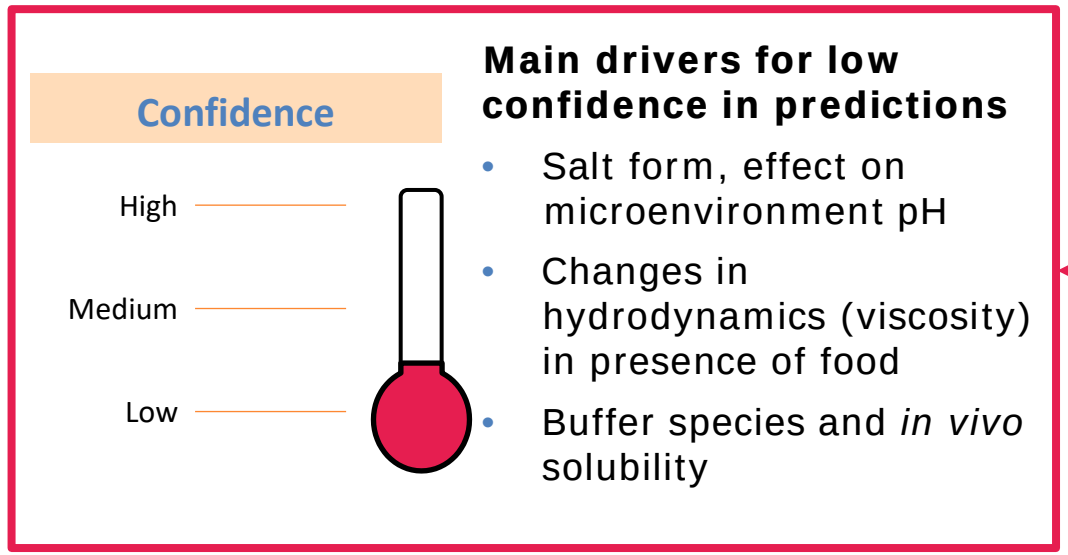
Overview of the Predicted Food Effect (Standard High Fat Meal) for 30 Compounds

- The rate of correctly identifying the “risk” for food effect was very high, with **only 2 examples of false negative**
- The **direction of food effect** was accurately predicted for approximately 90% of the compounds, without the need for optimization with clinical data
- The **magnitude of food effect** was predicted with high (1.25-fold) or moderate (2-fold) confidence for 80% of the compounds
- While assigning confidence based on BCS classification may be an over-simplification, it was deemed that the **driving mechanism of food effect** can provide a novel perspective on the prediction confidence
- Where the mechanism of food effect is well-understood, but the ***in vitro to in vivo correlation*** is weak (e.g., compounds that undergo precipitation), a middle-out approach can be utilized with higher confidence using a clinical anchor study



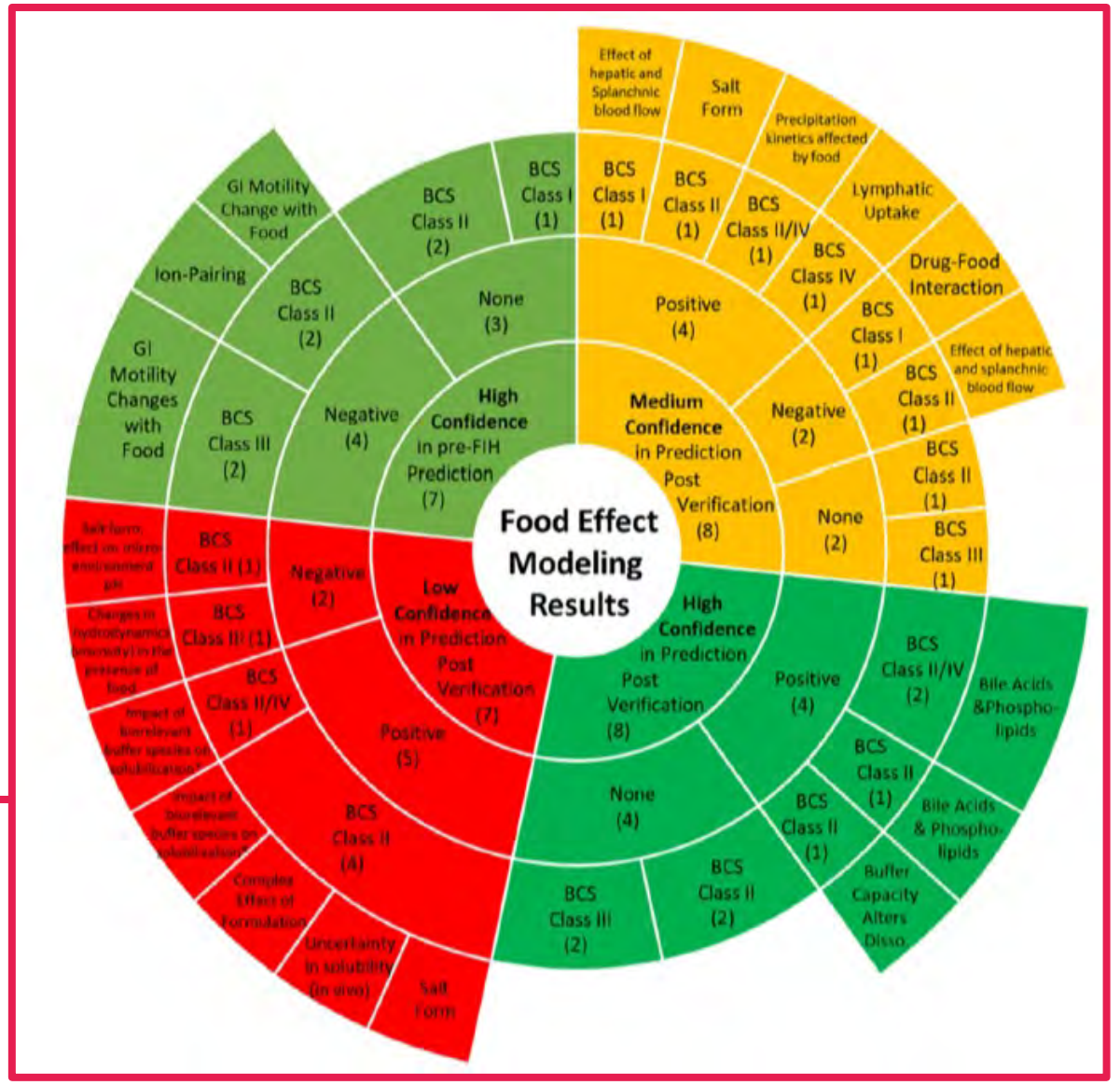
Prediction Success was Correlated to the Driving Mechanism of Food Effect

- Areas of high to moderate confidence were mainly associated with changes in GI luminal fluid and physiology
- Low confidence cases were commonly associated with complex mechanisms and/or interplay between multiple mechanism for which standardized in vitro assays and model inputs were not available to characterize food effect



Main drivers for low confidence in predictions

- Salt form, effect on microenvironment pH
- Changes in hydrodynamics (viscosity) in presence of food
- Buffer species and *in vivo* solubility



Areas of Improvement: Easy Wins to Increase Confidence

Category 1 – Improvements to *in vitro* Methodologies

- Consider the use of more bio-predictive media as PBPK input parameters (e.g., bicarbonate-buffered media) to capture the fed-state solubility; Pazopanib case study

Category 2 – Improvements to PBPK Models

- Enable the use of solubility data from media simulating the fed stomach
- Enable the use of full salt solubility profile in the PBPK software to capture the common ion effect
- Enable the ability to capture changes in GI physiology over time (e.g., simulation of gastric re-acidification)

Improvements that may require more research…

- More bio-predictive tools and correlations to capture precipitation kinetics
- Improved mechanistic hydrodynamic models that allow users to calculate the luminal drug dissolution
- More realistic simulation of gastric residence times of formulations/drug
- Better understanding of the food-transporter and food-enzyme interactions (*in vitro* tools, *in vitro to in vivo* correlations and implementation in PBPK software)

Riedmaier, A.E., et al., AAPS J, 2020. 22(6)
*Wagner, C., et al., AAPS J, 2021. **23**(4)*

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Part 2. Repeat Food Effect Studies – Can We Streamline Food Effect Assessment?

When Do We Repeat Food Effect Studies?

- During NCE developed, food effect is often explored early in the clinical program (as early as SAD studies)
- Food effect may be repeated
  - If formulation changes from that used in the early food effect prior to larger patient studies (e.g., Phase 2B or 3) (most common scenario)
    - Changes may be specifically intended to impact food effect or may be simply part of scaling up formulation.
  - Formulation changes between pivotal studies and commercial formulation or post-approval
  - Changes from co-administration to fixed-dose combination
- Food effect also explored for pediatric formulations
- For generic drug products, food effect bioequivalence studies may be required depending on label.

IQ WG Q: For development/scale up changes, how often do these repeat food effect studies add value?

Most Agencies Expect Reassessing Food Effect for New Formulations

The sponsor should conduct a definitive FE study using the final to-be-marketed oral formulation. In cases where the clinical trial formulation had no significant effect of food, and the to-be-marketed formulation is not significantly different from the clinical trial formulation, …. an FE study with the to-be-marketed formulation might not be necessary. Further, a FE study with the to-be-marketed formulation might not be necessary in a situation where a biowaiver is accepted for a formulation change … In cases where the clinical trial formulation is significantly different from the final to-be-marketed formulation, **the sponsor should conduct a relative bioavailability study to compare the systemic exposures and an FE assessment using the to-be-marketed formulation, if appropriate**

Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry, FDA CDER, June 2022.
https://www.fda.gov/media/121313/download

Different Formulations - What Could Be the Clinical/Regulatory Implications of Food Effect?

Formulation	Food Effect	Prescribing Information
Posaconazole Oral Suspension	~3x AUC/Cmax with nonfat meal ~4x AUC/Cmax with high fat	In order to assure attainment of adequate plasma concentrations, it is recommended to administer Noxafil oral suspension during or immediately following a full meal. In patients who cannot eat a full meal, Noxafil oral suspension should be taken with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale).
Posaconazole HME Tablets	~16% increase in Cmax and ~51% in AUC with high fat meal	US: In order to enhance the oral absorption of posaconazole and optimize plasma concentrations, posaconazole delayed-release tablets should be administered with food EU: Each tablet dose may be taken without regard to food intake.

Information obtained from product insert

Scope of IQ WG work

A) How often do repeat food effect studies result in different food effect?
   - Focus on “routine” scale up/development changes (i.e., not changes that are specifically intended to alter the food effect).

B) What is the role of PBPK modeling to provide confidence and replace repeat food effect studies?

Methodology

- Step 1: Collect case studies from member companies with repeat food effect (53 studies collected)
  - Focus on BCS 2/4 and primarily IR dosage forms
  - Ideally meal was consistent between initial and repeat study
  - Collect AUC and Cmax GMR (and confidence intervals if possible) and Tmax shift
  - Description at high level of formulation change so it can be assigned to a SUPAC level change

Step 2: Analyze case studies for agreement in outcome between initial and repat study

Step 3: When a PBPK model was available, assess how PBPK modeling predicted initial and repeat study outcome

Example 1: No food effect with minor formulation change Suvorexant Early HME Tablet → Final Market Image

BCS Class 2, Level 1 change (compositionally proportional formulations)

	Phase 2 tablet (30 mg)	Phase 3 tablet (40 mg)	Fold Change Between Studies (ratio of GMRs)
High Fat/High Calories Meal			
AUC GMR (90% CI)	1.06 (0.86-1.32)	0.98 (0.91 -1.07)	0.92
Cmax GMR (90% CI)	1.23 (1.13-1.34)	1.09 (0.88-1.34)	0.89
Tmax (hrs)	Fasted 2.0, Fed 2.0	Fasted 1.5, Fed 3.0	

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204569Orig1s000ClinPharmR.pdf

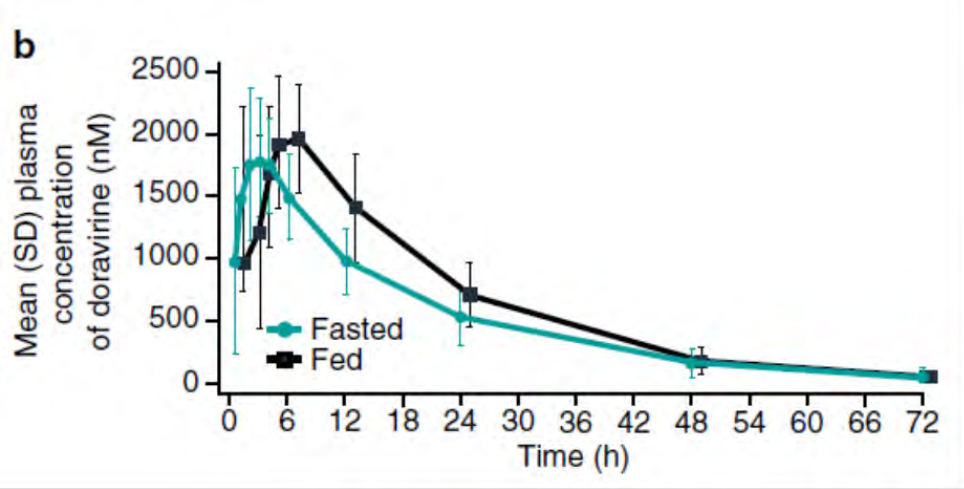
Example 2: Significantly positive food effect Anacetrapib Early HME Tablet -> Scale-Up Tablet

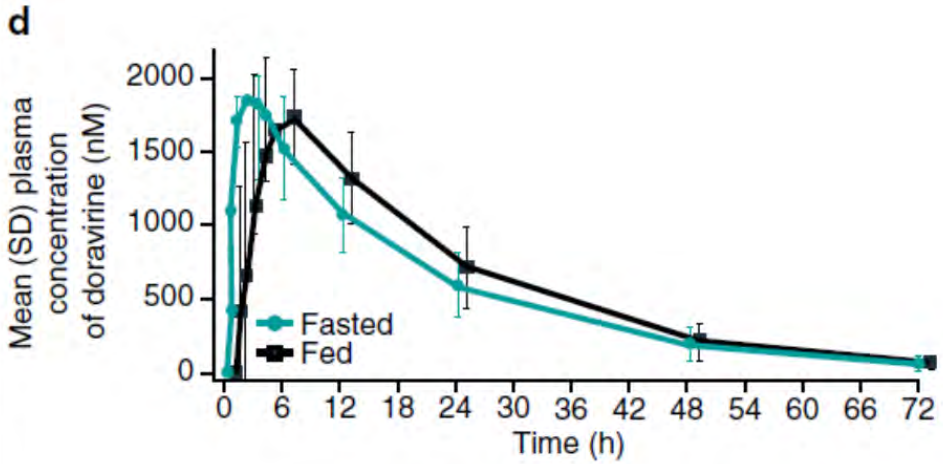
BCS Class 4, Level 2 change (scale up)

	Early HME Tablet (150 mg)	Scale-up HME Tablet (100 mg)	Fold Change Between Studies (ratio of GMRs)
High Fat/High Calories Meal			
AUC GMR (90% CI)	7.15 (4.51-11.33)	8.27 (6.25-10.96)	1.16
Cmax GMR (90% CI)	17.58 (10.23-30.21)	12.39 (9.47-16.20)	0.70
Tmax (hrs)	Fasted 3.0, Fed 5.0	Fasted 5.0, Fed 4.5	
Low Fat/Low Calories Meal			
AUC GMR (90% CI)	2.02 (1.28-3.20)	4.53 (3.44-5.95)	2.24
Cmax GMR (90% CI)	3.97 (2.33-6.76)	5.52 (4.29-7.10	1.39
Tmax (hrs)	Fasted 6.0, Fed 4.0	Fasted 5.0, Fed 5.0	

- Krishna R, et al. Clin Pharmacol Ther. 2008 Dec;84(6):679-83.
- Krishna R, et al.. AAPS J. 2011 Jun;13(2):179-90.

Example 3: FDC with No Food Effect Change Doravirine Single Entity→Doravirine FDC





	Doravirine single entity	Doravirine in FDC	Fold Change Between Studies (ratio of GMRs)
High Fat/High Calories Meal			
AUC GMR (90% CI)	1.16 (1.06-1.26)	1.10 (1.01 -1.20)	0.95
Cmax GMR (90% CI)	1.18 (1.08-1.19)	0.95 (0.80-1.12)	0.81
C24hr (90% CI)	1.36 (1.19-1.55)	1.26 (1.13-1.41)	0.93

Behm MO, et al, Clin Drug Investig. 2017 Jun;37(6):571-579

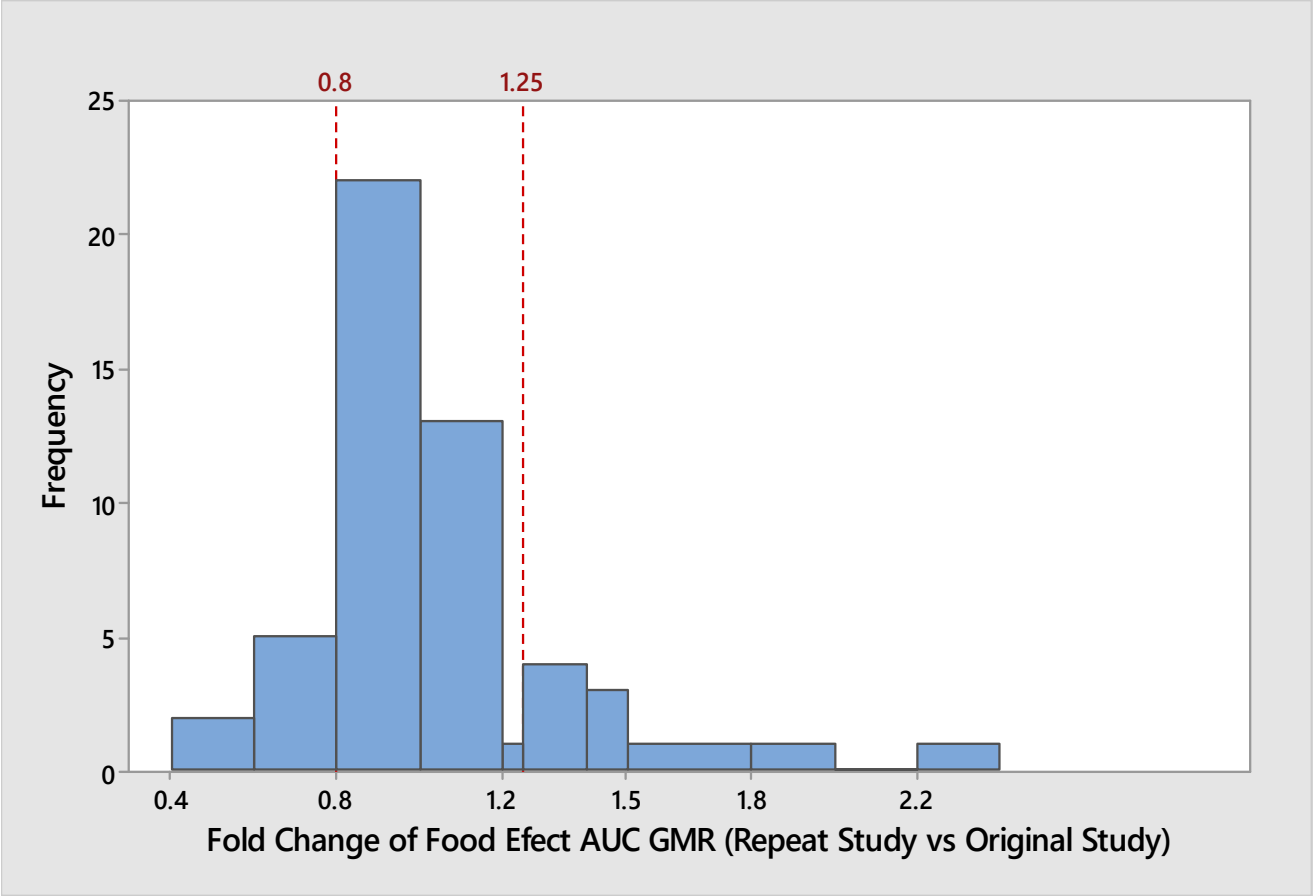
Example 4: FDC with Food Effect Change
HCV NS5A Inhibitors – Early (single entity) vs Late (FDC) Formulation Food Effect

Compound	Dose (mg)	AUCinf	Cmax	Label Recommendation
Elbasvir (early formulation)	50	0.67 (0.38-1.07)	0.56 (0.28-1.16)	N/A
Elbasvir (FDC)	50	0.891 (0.81, 0.96)	0.85 (0.77, 0.94)	Can be taken with or without food
Ledipasvir (early formulation)	30	0.56 (0.37, 0.84)	0.55 (0.39, 0.77)	N/A
Ledipasvir (FDC)	90	1.03 (0.89-1.19)	0.88 (0.76-1.03)	Can be taken with or without food
Velpatasvir (early formulation)	100	0.86 (0.73-1.01)	0.75 (0.63-0.90)	N/A
Velpatasvir (EPCLUSA FDC)	100	1.21 (0.99-1.48)	1.05 (0.87-1.27)	Can be taken with or without food
Velpatasvir (VOSEVI FDC)	100	1.40 (1.13-1.75)	1.37 (1.11-1.70)	Taken orally once daily with food[a]

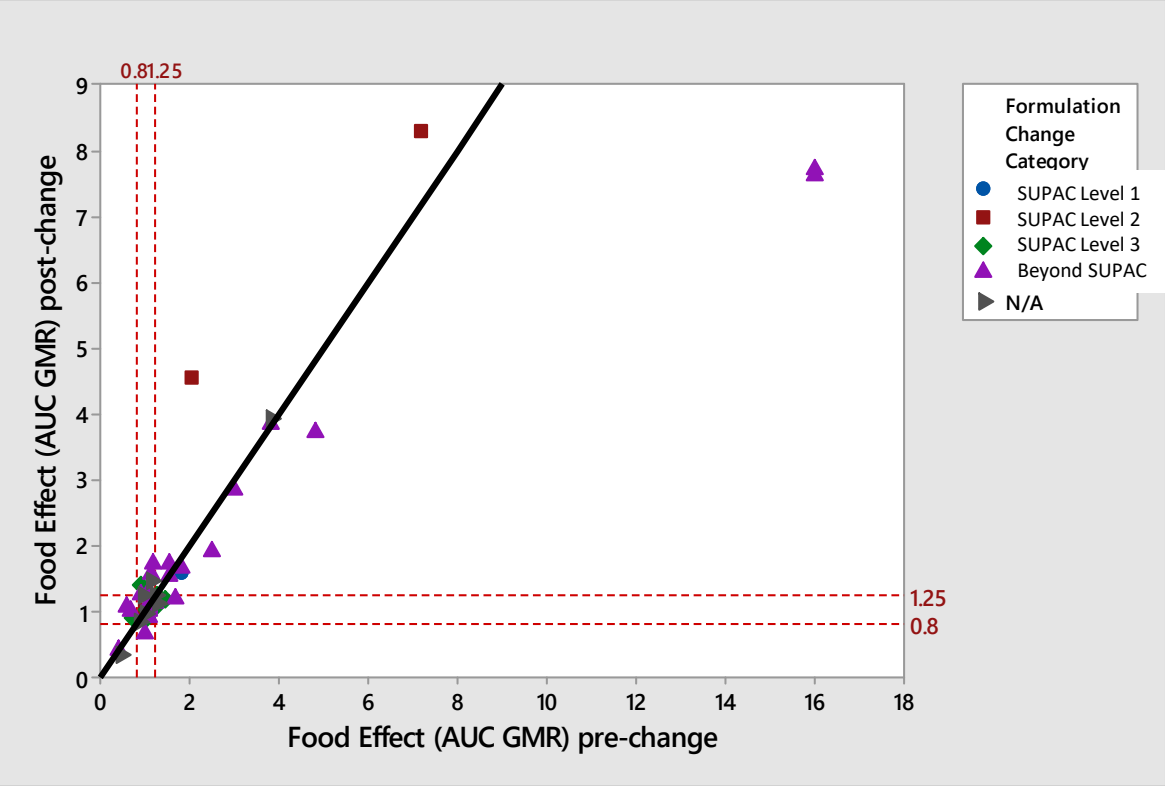
McKelvey CA, Kesisoglou F. Enabling an HCV Treatment Revolution and the Frontiers of Solid Solution Formulation. J Pharm Sci. 2019 Jan;108(1):50-57. doi: 10.1016/j.xphs.2018.11.003.

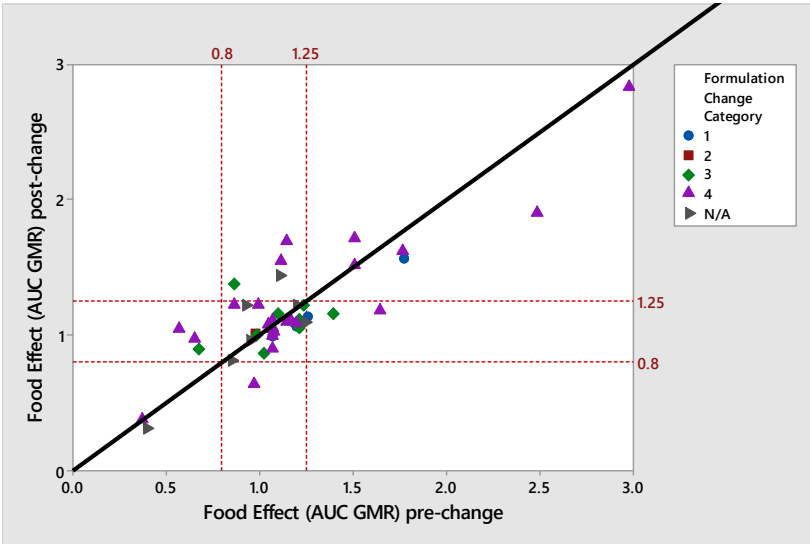
Analysis Outcome - AUC

- Majority of repeat studies did not result in clinically meaningful food effect change
  - Only 3/53 studies the AUC food effect changed more than 50%
  - 68% of the studies AUC fold-change within 0.8-1.25



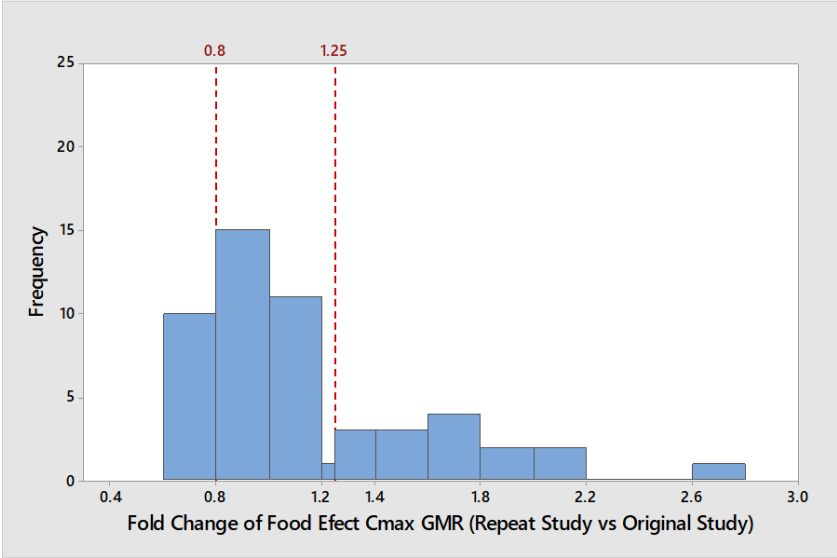
Analysis Outcome - AUC

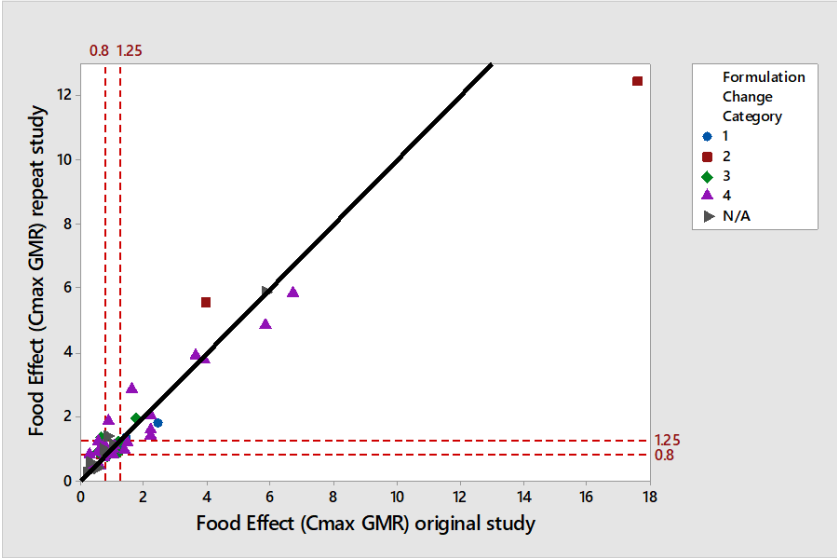




Analysis Outcome - Cmax

- Majority of repeat studies did not result in clinically meaningful food effect change
  - Only 3/53 studies the AUC food effect changed more than 2-fold
  - 52% of the studies AUC fold-change within 0.8-1.25
  - Relative to AUC, higher proportion of Cmax changes above 50%
  - No clear differentiation of level of formulation change

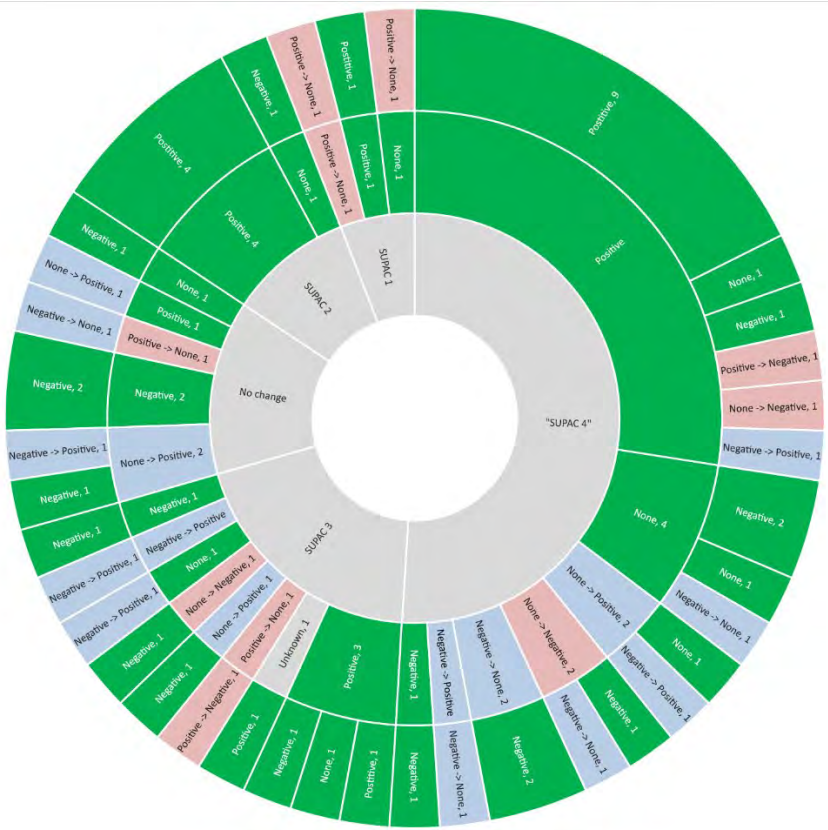




Categorical Food Effect Assessment

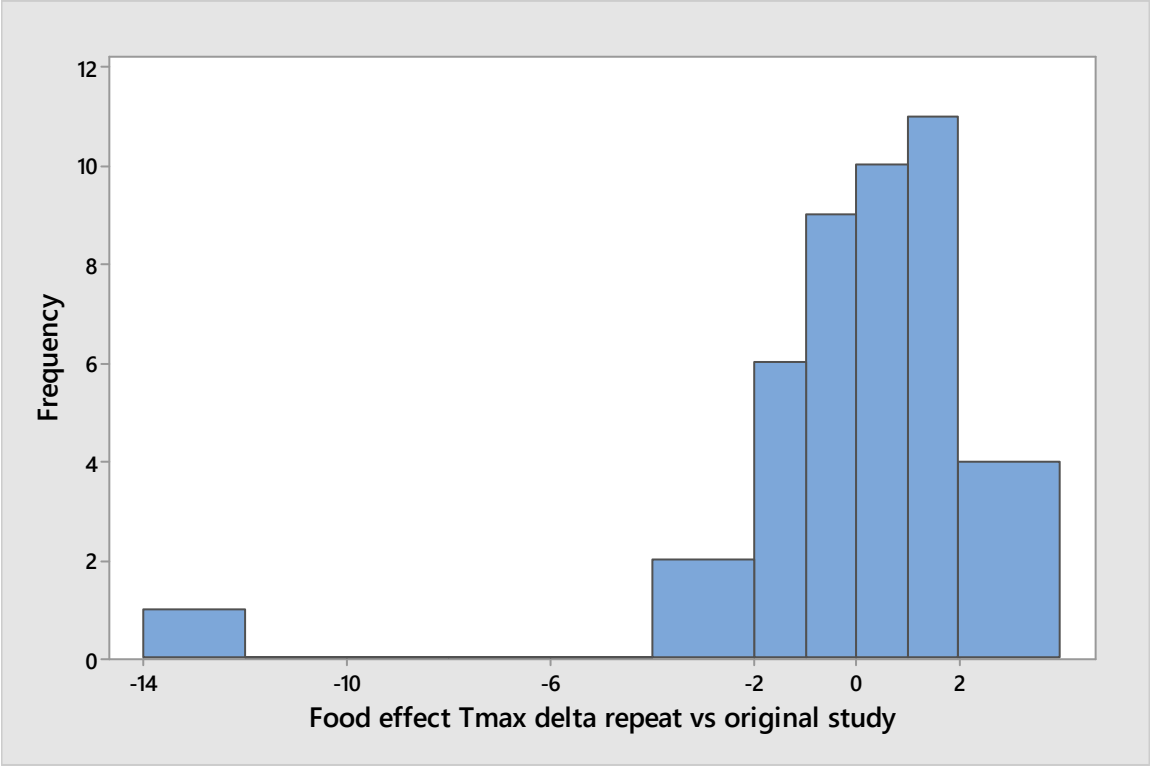
- Categorical Change in AUC or C_{max} food effect were assigned from the lower $L90$ and upper $U90$ 90% confidence interval of the GMRs

$L90 > 1$	Positive FE
$U90 < 1$	Negative FE
$L90 \geq 0.8 \wedge U90 \leq 1.25$	No FE
Otherwise	Inconclusive



- Categorical FE outcomes were largely consistent between studies in ~72% of case
- There was no clear differentiation of behavior based on formulation changes, even for formulation changes that would be considered SUPAC Level 3 or beyond.

Analysis Outcome - Tmax



Tmax changes between studies was generally in line with the range of Tmax values seen within a study.

Analysis Outcome

- Majority of typical scale up formulation changes did not result in different food effect
  - Most of the shifts were less than 20% (i.e. if the initial study fed/fasted GMR was 1, it was 1.2 in the second study)
- Perhaps surprisingly, formulation change (SUPAC category) didn't seem to correlate with the outcome of the 2nd food effect study
  - Exception would be cases where formulation change was intentionally made to alter food effect (typically reduce positive food effect, only 2 case studies included in the dataset)
- May indicate that food effect for compounds, once formulated appropriately within a specific formulation technology, may be seen more as a compound property rather than a formulation-dependent behavior.
  - The modest shifts observed in the majority of cases would be unlikely to result in change in labeling recommendations

Recommendations

- A case-by-case approach considering the totality of evidence appears appropriate for assessing the impact of routine formulation changes on food effect.
- Our analysis supports the recently updated FDA guidance that states repeated food effect may not be required for compounds with no food effect, to begin with, that undergo not-significant formulation changes.
- Our research further suggests that this could possibly be extended to changes beyond SUPAC guidelines for scenarios where the formulation change is not specifically intended to alter food effect

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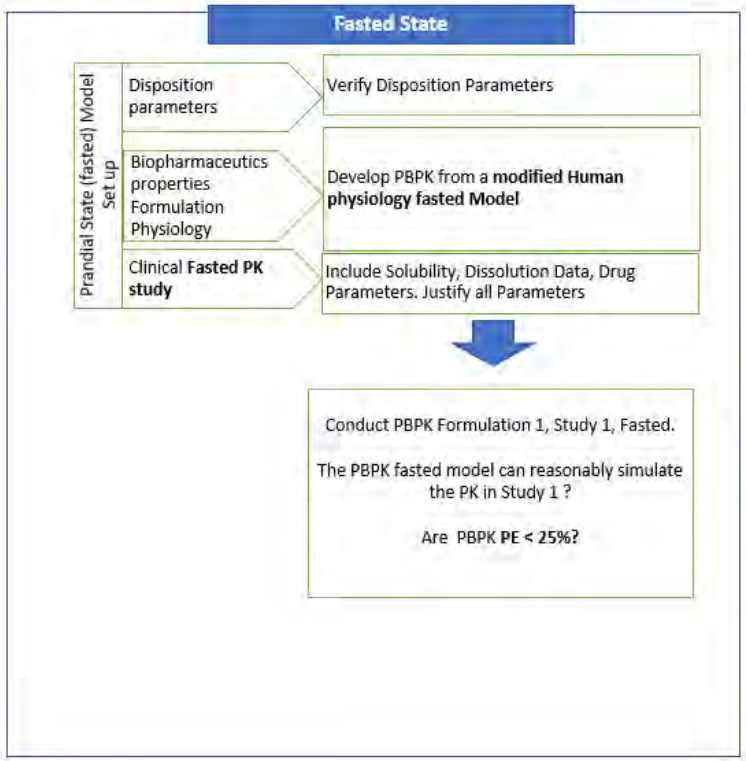
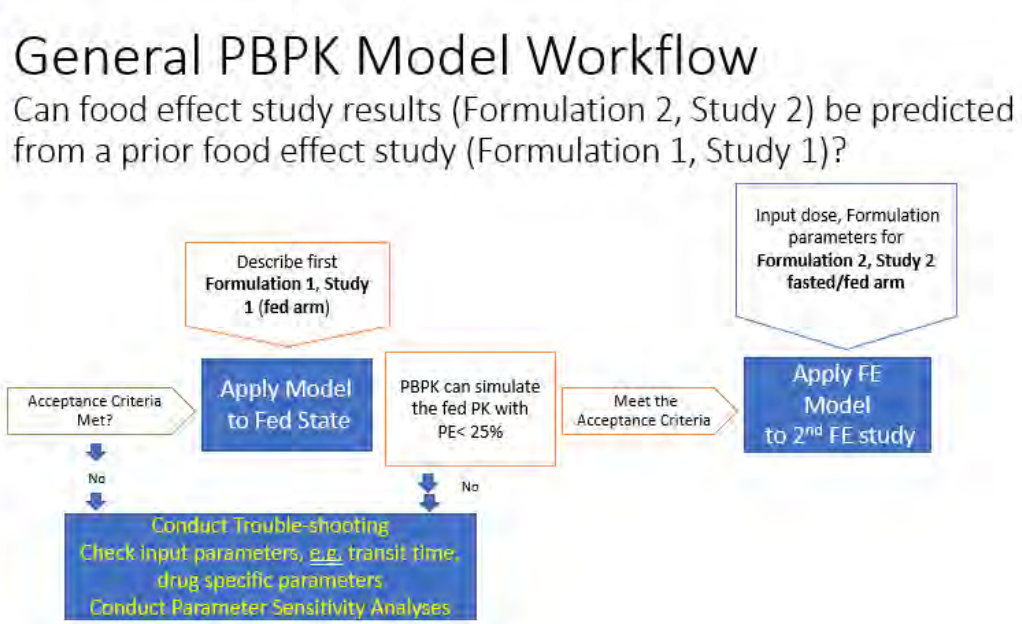
Part 3. PBPK Applications to Repeat Food Effect Studies

More Focused PBPK Model Application to Increase Confidence?





PBPK Case Example Alpelisib (Middle-Out)

Physicochemical Properties	
BCS Class	BCS class 2
pKa(s) / $LogD_{6.8}$	3.3 weak base and 9.4 (weak acid) / logD 2.8
Solubility in buffers	pH-dependent solubility; Soluble at pH 1.0 (3.64 mg/mL), pH 2.0 (0.37 mg/mL), low solubility pH ≥ 3.0 (~0.03 mg/mL)
Solubility in bio-relevant media	~10-fold increase in solubility in FeSSIF (pH 5.0; 0.32 mg/mL)
Permeability	High passive permeability in absence of efflux (LE-MDCK); moderate permeability in Caco-2
PK Characteristics	
Dose / Formulation	300 mg oral once daily; **tablet**
Pharmacokinetics	**Linear PK across wide dose range**; available population PK model (estimates of CL/F and Vd/F) and preclinical IV data in mouse, rat and dog
Metabolism and Excretion	Negligible first-pass metabolism and preclinical species and human No known interaction of food with intestinal enzymes and/or disposition transporters
Clinical Pharmacology – Available biopharmaceutic studies	
Food Effect (300 mg)	**Positive Food Effect** (AUC ↑70-80%) independent of type of meal (LFLC and HFHC)
Acid reducing agent DDI	Reduction in exposure in presence of food (LFLC) not clinically significant with ranitidine (H2RA); in the fasted state decrease more pronounced
Absolute / rel. bioavailability study	No absolute BA conducted (no iv data); relative BA not required
Bioequivalence (200 mg)	Originally not thought to be required; requested by HA

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212526Orig1s000MultidisciplineR.pdf

Tycho Heimbach, Food-Effect Prediction – Considerations from the IQ WG and Fasted/Fed Case Studies, AAPS 2021

PBPK Case Example: Alpelisib – Dissolution of Pivotal (PCF) and Commercial (CF) Formulations

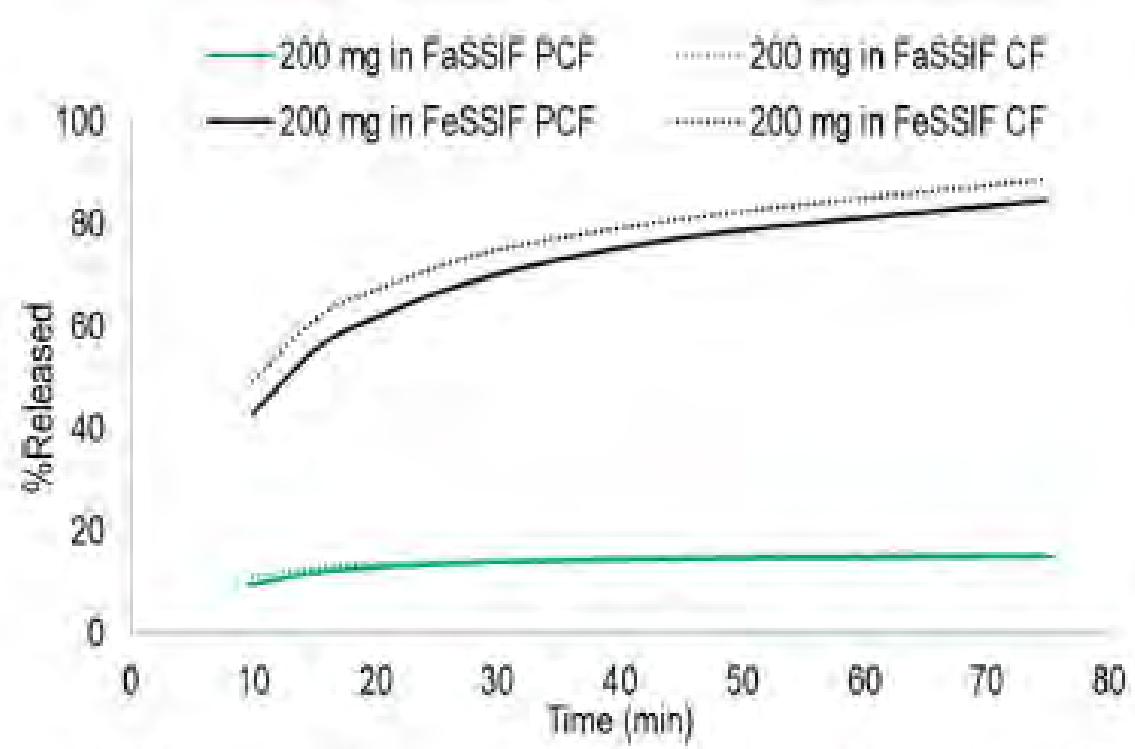
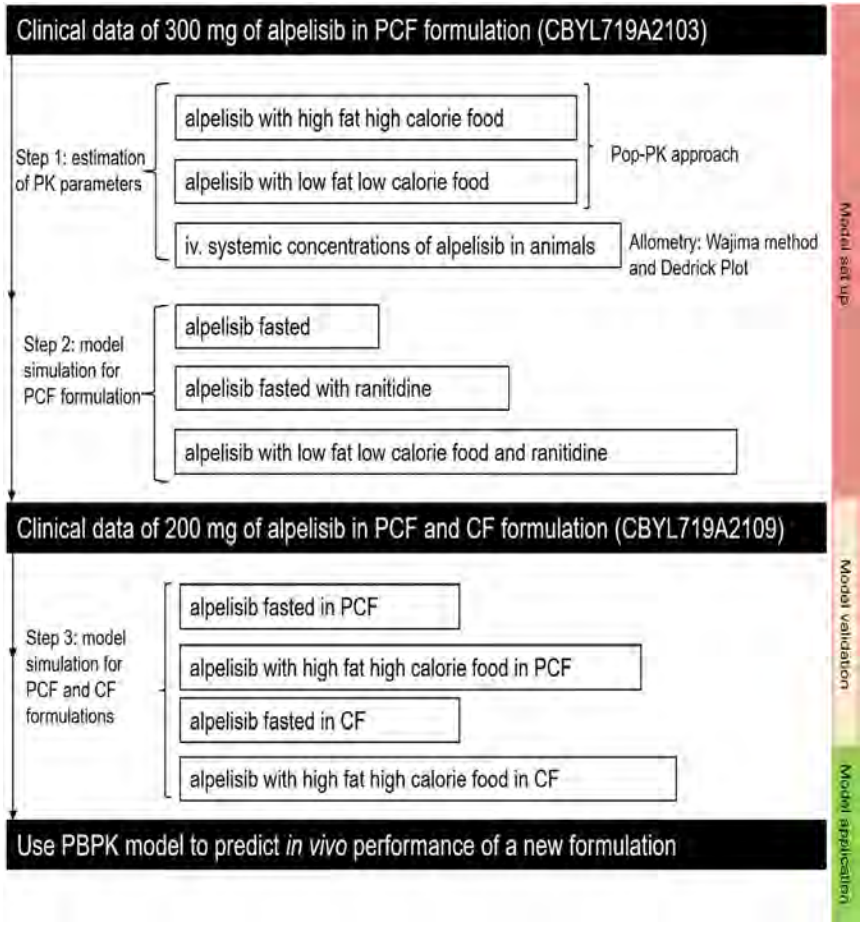


Fig. 1. *In vitro* dissolution results for 200 mg alpelisib in PCF and CF

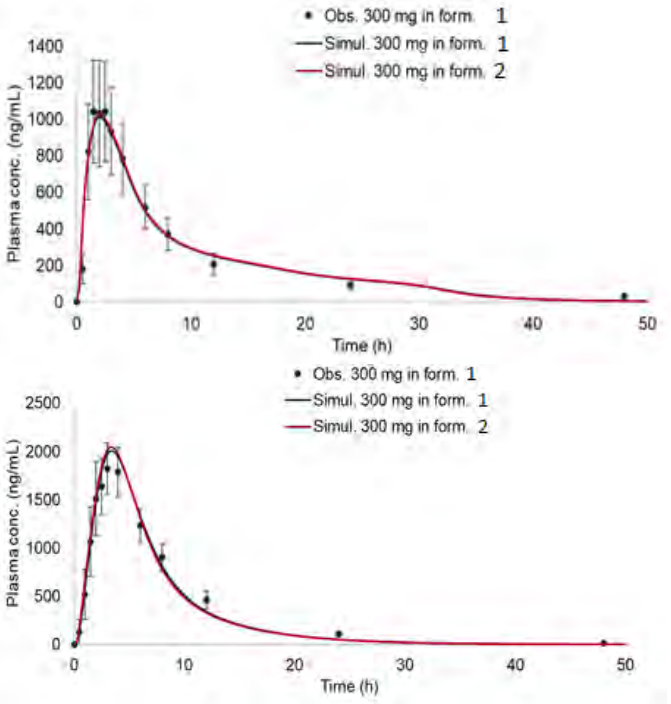
PCF = original formulation
CF = new formulation

Gajewska M, Blumenstein L, Kourentas A, Mueller-Zsigmondy M, Lorenzo S, Sinn A, Velinova M, Heimbach T. Physiologically Based Pharmacokinetic Modeling of Oral Absorption, pH, and Food Effect in Healthy Volunteers to Drive Alpelisib Formulation Selection. AAPS J. 2020 Oct 18;22(6):134.

PBPK Case Example – Model Initial Alpelisib Formulation



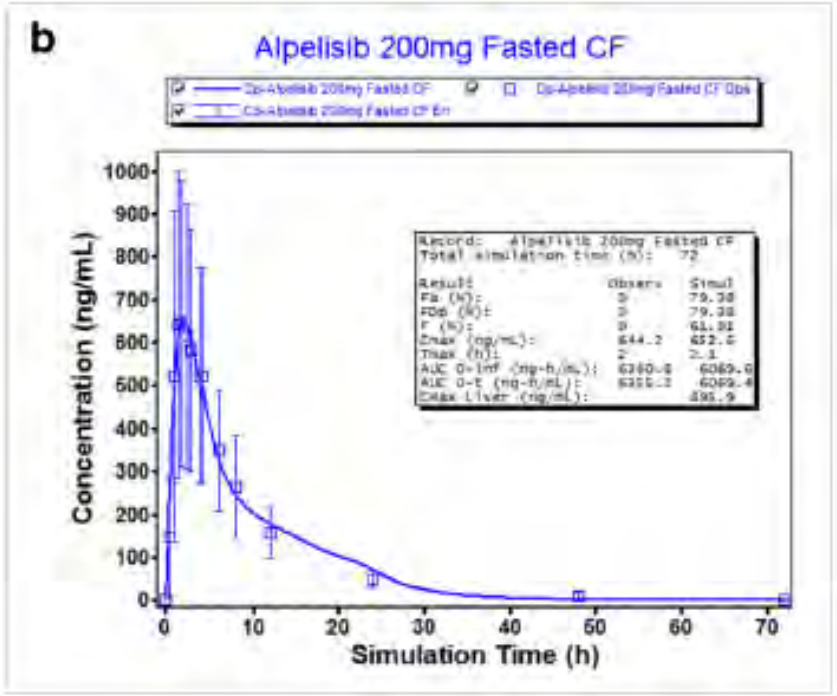
Assess model prediction of fasted state and food effect for original formulation (PCF)

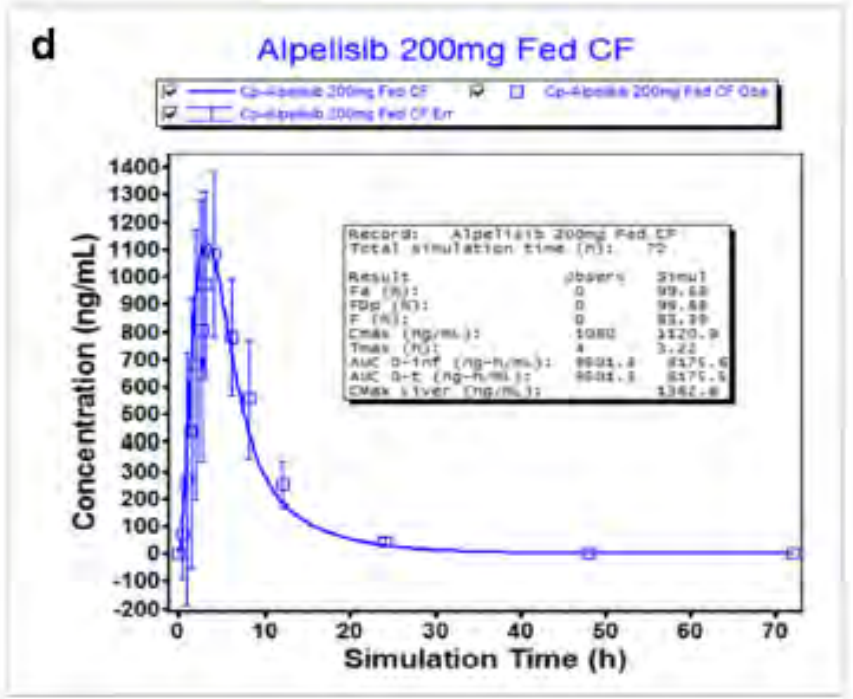


Gajewska M, Blumenstein L, Kourentas A, Mueller-Zsigmondy M, Lorenzo S, Sinn A, Velinova M, Heimbach T. Physiologically Based Pharmacokinetic Modeling of Oral Absorption, pH, and Food Effect in Healthy Volunteers to Drive Alpelisib Formulation Selection. AAPS J. 2020 Oct 18;22(6):134.

Tycho Heimbach, Food-Effect Prediction – Considerations from the IQ WG and Fasted/Fed Case Studies, AAPS 2021

PBPK Case Example – Model Accurately Predicts Food Effect of Follow-up Formulation





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PBPK Case Example Basmisanil

pharmaceutics

MDPI

Article

Physiologically Based Biopharmaceutics Modeling of Food Effect for Basmisanil: A Retrospective Case Study of the Utility for Formulation Bridging

Tejashree Belubbi [1], Davide Bassani [1], Cordula Stillhart [2] and Neil Parrott [1,*]

Basmisanil is a lipophilic BCS class 2 drug

It shows less than dose proportional increases in exposure
- **Dissolution rate-limited below 200 mg, solubility limited for higher doses**

Food effect was explored in Ph1 with uncoated tablet at 600 mg

Granules formulation developed during Ph2 and food effect study performed at 120 mg

PBBM was used retrospectively to compare PBBM prediction to observations

Table 1. Physicochemical characteristics and kinetics of disposition of Basmisanil.

Parameter *	Value
Molecular weight	445.5 g/mol
pK_a	2.07 (base)
logD (pH 7.4)	1.86
Melting point	148.3 °C
Blood/plasma concentration ratio	0.59
Fraction of drug unbound in plasma	5.6%
Solubility at 25 °C	
Aqueous buffer pH 1–9 Solubility at 37 °C	0.001 mg/mL
SGF pH 1.6	0.008 mg/mL
FaSSIF pH 6.5	0.010 mg/mL
FeSSIF pH 5	0.032 mg/mL
Particle size distribution	
D10	1.4 µm
D50	4.7 µm
D90	10.1 µm
Effective human jejunal permeability	3.75×10^{-4} cm/s

PBPK Case Example Basmisanil

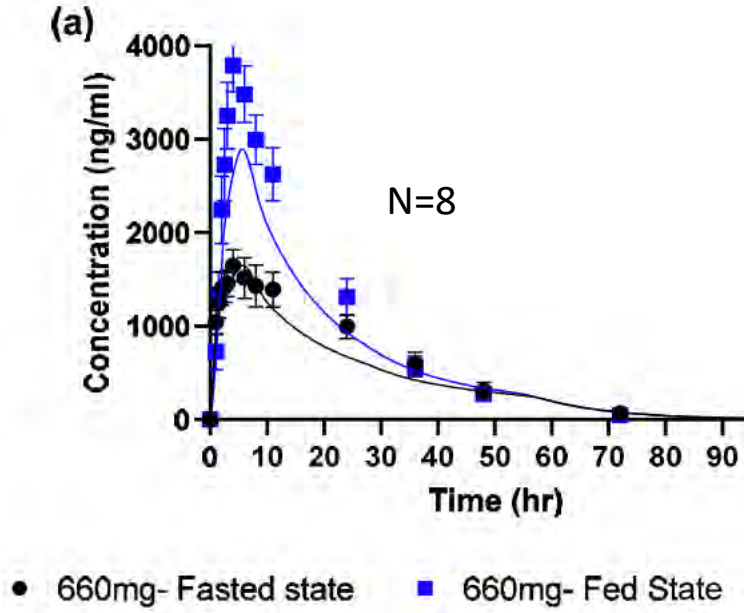
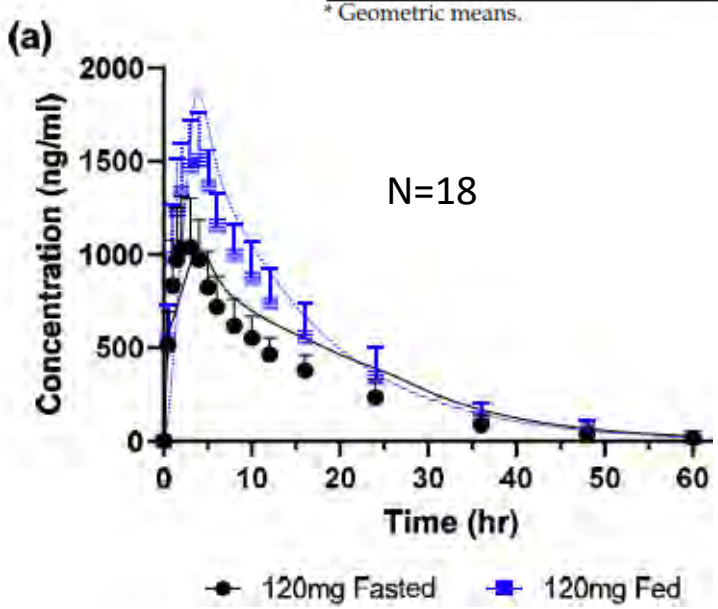


Table 5. Fed/Fasted ratios for simulated and observed profiles.

Formulation	Simulated		Observed *		Ratio of Simulated/Observed Food Effect	
	Cmax	AUC	Cmax	AUC	Cmax	AUC
660 mg uncoated tablets	1.75	1.42	2.31	1.52	0.76	0.93
120 mg granules	1.86	1.25	1.38	1.5	1.35	0.83

* Geometric means.



Standard PBBM model building approach according to IQ FE paper
IV data were available (microdose arm in ph1)
Biorelevant solubility inputs; API particle size dissolution model
Standard GastroPlus fasted and fed physiological ACAT with adjustments for calorie and fat content of meals

PBPK Case Example Basmisanil

- Bottom-up PBBM was used pre-clinically to anticipate a positive food effect (~1.5-fold)
  - Clinical Ph1 was conducted in fed state. Food effect of tablet explored in 1 arm
- Clinical data confirmed the predicted food effect and could be used to refine the model (including IV microdose data)
- PBBM anticipated a similar positive significant difference for the granules & this was confirmed in a food effect study
- NB: tablet and granules used the same micronized API & were the same in qualitative composition and manufacturing technology

Webinar Summary

- Many repeat food effect studies don’t result in clinically meaningful food effect differences
- A case-by-case approach considering totality of evidence appears more appropriate on deciding to repeat food effect assessment for modest formulation and scale-up changes
  - Doesn’t appear that strict formulation change criteria (e.g. SUPAC) exclude repeat food effect studies with little added value
- PBPK/PBBM models following appropriate validation against clinical data can further increase confidence on anticipating food effect for formulation changes.