INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Predicting the Power of Food

Using PBPK modeling to predict food effect

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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

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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

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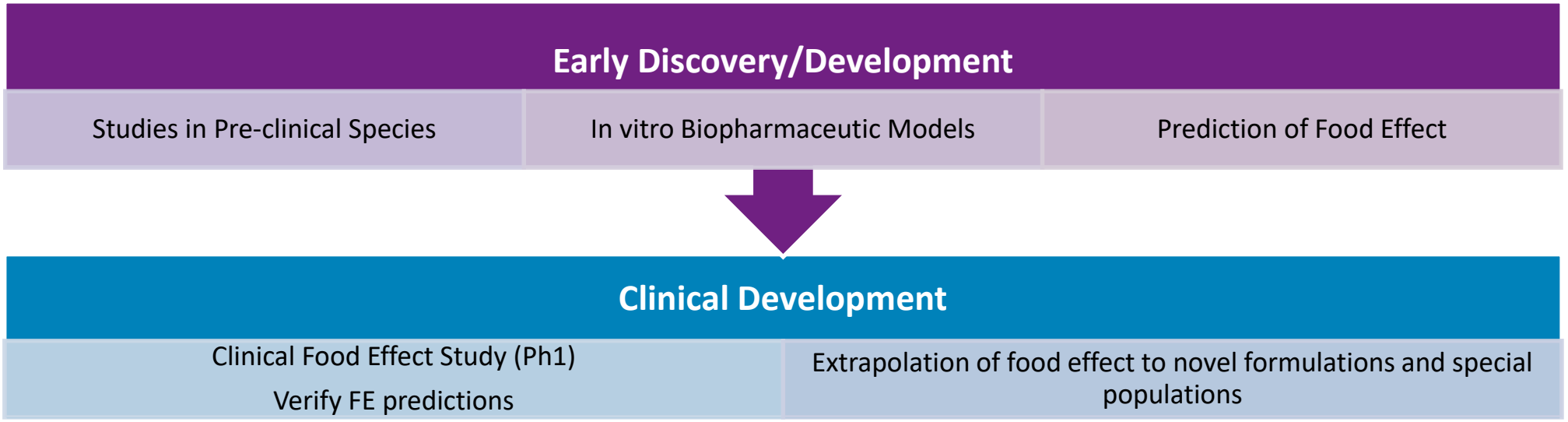
Use of physiologically-based pharmacokinetic modeling for predicting drug-food interactions: Recommendations for improving predictive performance of low confidence food effect models

Christian Wagner, Filippos Kesisoglou, Xavier J. H. Pepin, Neil Parrott, Arian Emami Riedmaier

Impact of Food Effect on Drug Development

- Due to changes in GI physiology in the presence of food, absorption of orally administered drugs can be affected when taken with a meal
- 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

Prediction of Food Effect
An Industry Perspective

- Various publications from industry, including an IQ paper published in 2015 have demonstrated high to moderate confidence for predicting food effect using PBPK for compounds where intestinal transporters do not play a key role

- Retrospective analysis published in 2018 concluded we are not there yet for several compound classes and more in-depth analysis is lacking

- While BCS classification may serve as a generalization of drug property, appropriately verified, physiologically-relevant models can provide a more powerful assessment of drug properties in combination with pharmacokinetics and physiological considerations

IQ Food Effect Working Group
Scope and Rationale

Background

At the start of this initiative, there were no publications available, which assessed the ability of PBPK models to predict absorption and food effect **using a consistent, prospective approach**

Scope

- Cross-functional team of formulation scientists and modelers from 12 pharmaceutical companies
- Establish a consistent workflow for modeling with standardized input data
- Agreed-upon principles, decision trees and data generation methodology
- Appropriate verification of models prior to a food effect prediction and/or recommendation

Vision

- A well-conducted and published verification study of food effect prediction using PBPK will aid in understanding of modeling applications
- Highlight cases where high and moderate vs. low confidence is expected in predicting food effect
- Provide an aligned industry perspective on cases where modeling may be used in lieu of clinical studies

IQ Food Effect Working Group
Workflow

Software: SimCYP V 17.1; GastroPlus V 9.5

Population: Healthy Volunteer Population (all system parameters were left as default during model development)

Phys Chem and Blood Binding: Literature values were used for all parameters

Model Development:

- Absorption was developed mechanistically based on an aligned workflow and decision tree
  - All in vitro input data was generated within the working group unless literature data was available that was generated using the working group-aligned methodology
- Distribution and elimination was informed using IV PK data to remove any model uncertainty around drug disposition and isolate the verification step to the absorption component of the model
- Clinical studies were clearly defined as training vs. verification/test set to avoid bias

Exclusion Criteria

- Compounds where IV clinical data was not available for informing disposition
- Compounds expected to have high hepatic extraction
- Compounds where absorption is expected to be limited by active intestinal transport and prodrugs

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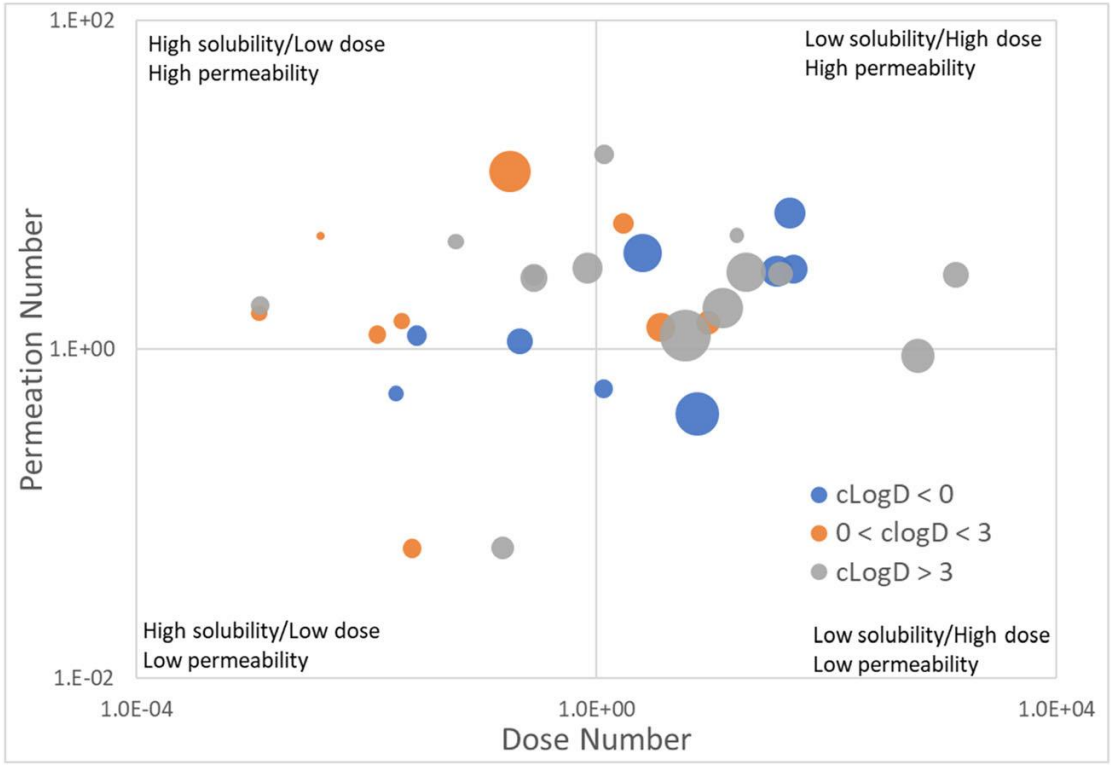
Compound Selection

- Physchem data for more than 200 compounds was collected and used to create a final dataset of 30 compounds after applying all exclusion criteria
- Selected compounds for the final dataset covered a range of solubility, permeability, molecular weight and lipophilicity properties



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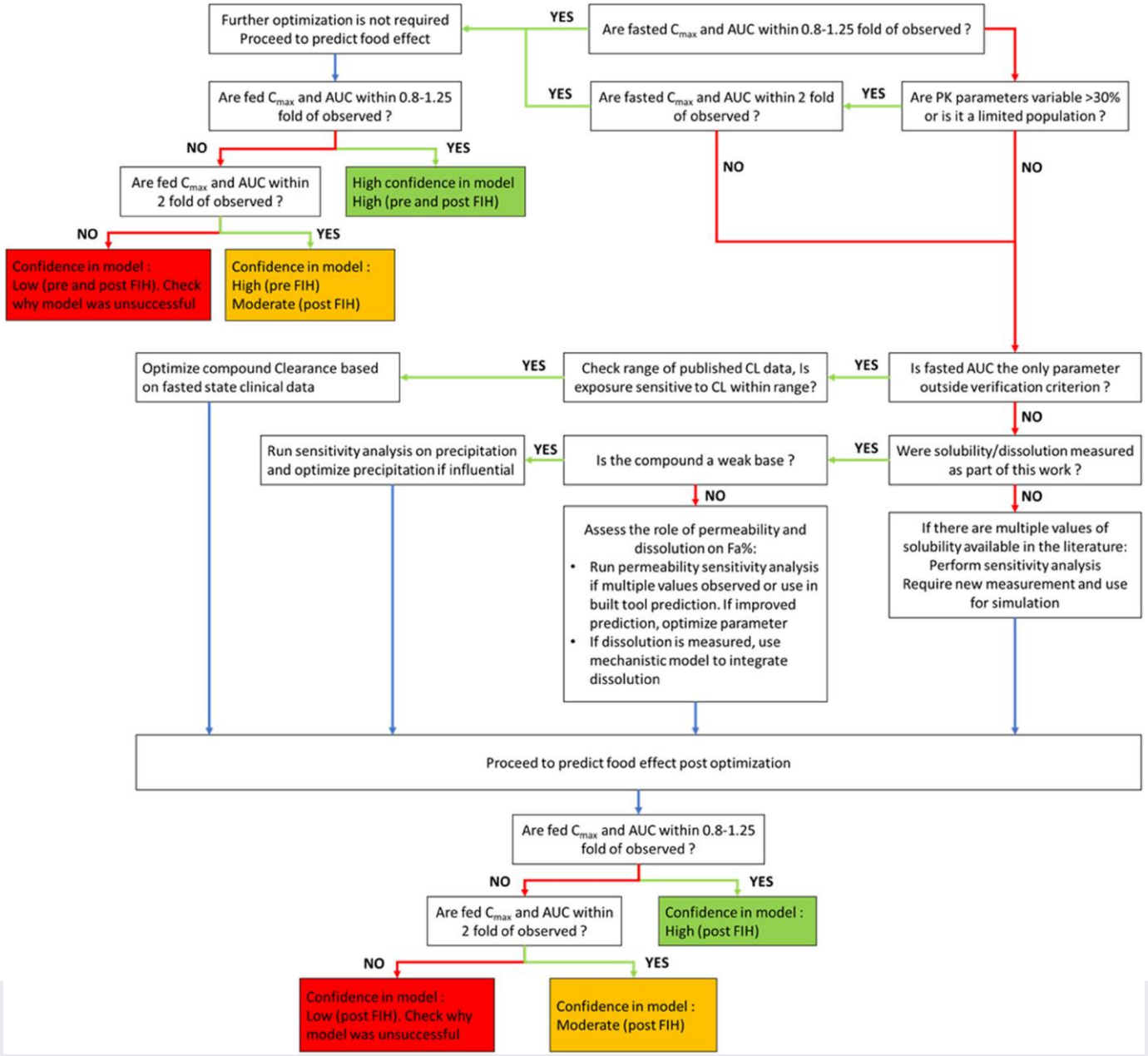
Decision Tree



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
- 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 for 30 Compounds

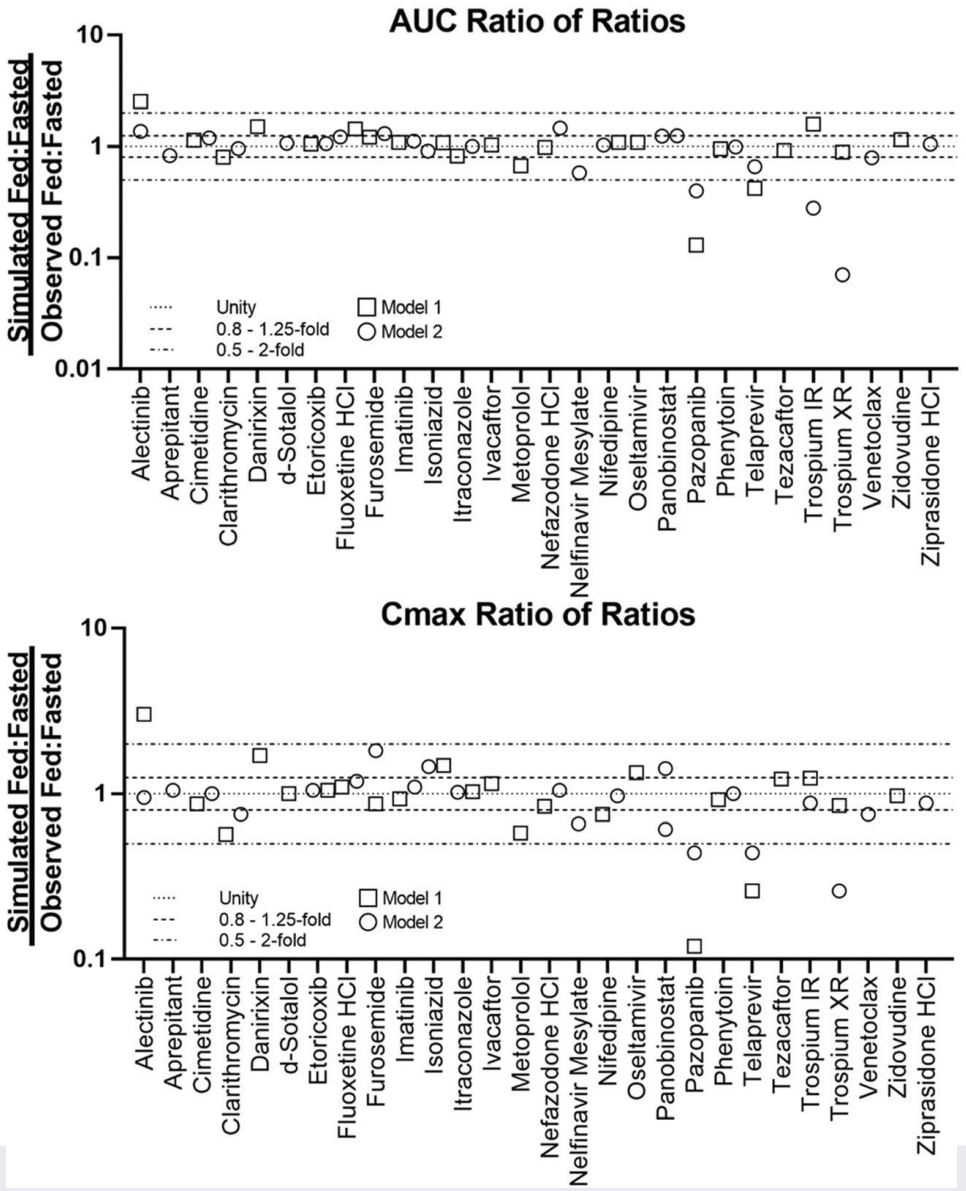
- The rate of correctly identifying the “risk” for food effect was very high, with **only 2 examples of false negative**
- The **direction of food effect** was accurately predicted for approximately 90% of the compounds, without the need for optimization with clinical data
- The **magnitude of food effect** 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
- High confidence in PBPK food effect models can be extended to:
  - All BCS 1 and 3 compounds, where a significant contribution of transporter-mediated food effects can be ruled out
  - A subset of BCS 2 and 4 compounds where the driving mechanism of food effect can be attributed to changes in solubility in the fed state related to changes in GI luminal physiology
- 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

Impact and magnitude of Food Effect

Evaluating success through predicted vs. observed C_{max} and AUC ratios

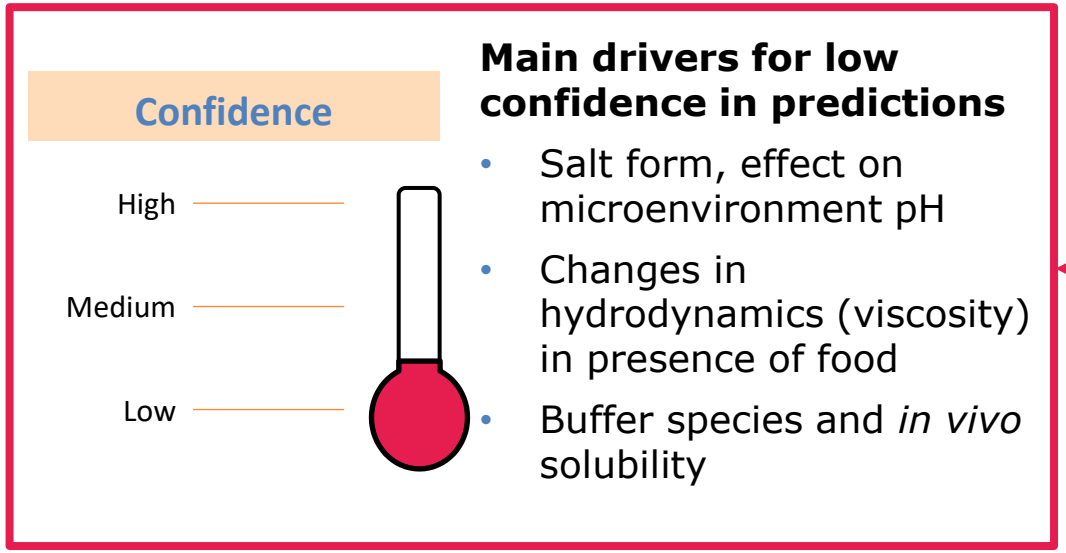
- **High confidence (15 compounds)** was defined as models that:
  - Accurately captured fasted and fed PK parameters and profile within 2-fold of observed, and visual inspection indicated good overlay of the PK profiles OR
  - Where the model could accurately capture the fasted and fed PK parameters and profile within 0.8–1.25 range, but only after optimization of absorption parameter(s) as defined in the decision tree
- **Moderate confidence (8 compounds)** was defined as models that:
  - Captured the fasted and fed PK parameters and profile following optimization using fasted data, though it fell outside the conservative criteria defined above, but within 2-fold of observed PK parameters
- **Low confidence (7 compounds)** was defined as models that:
  - Failed to capture the fasted and/or fed PK parameters and profile even after optimization as described in the decision tree

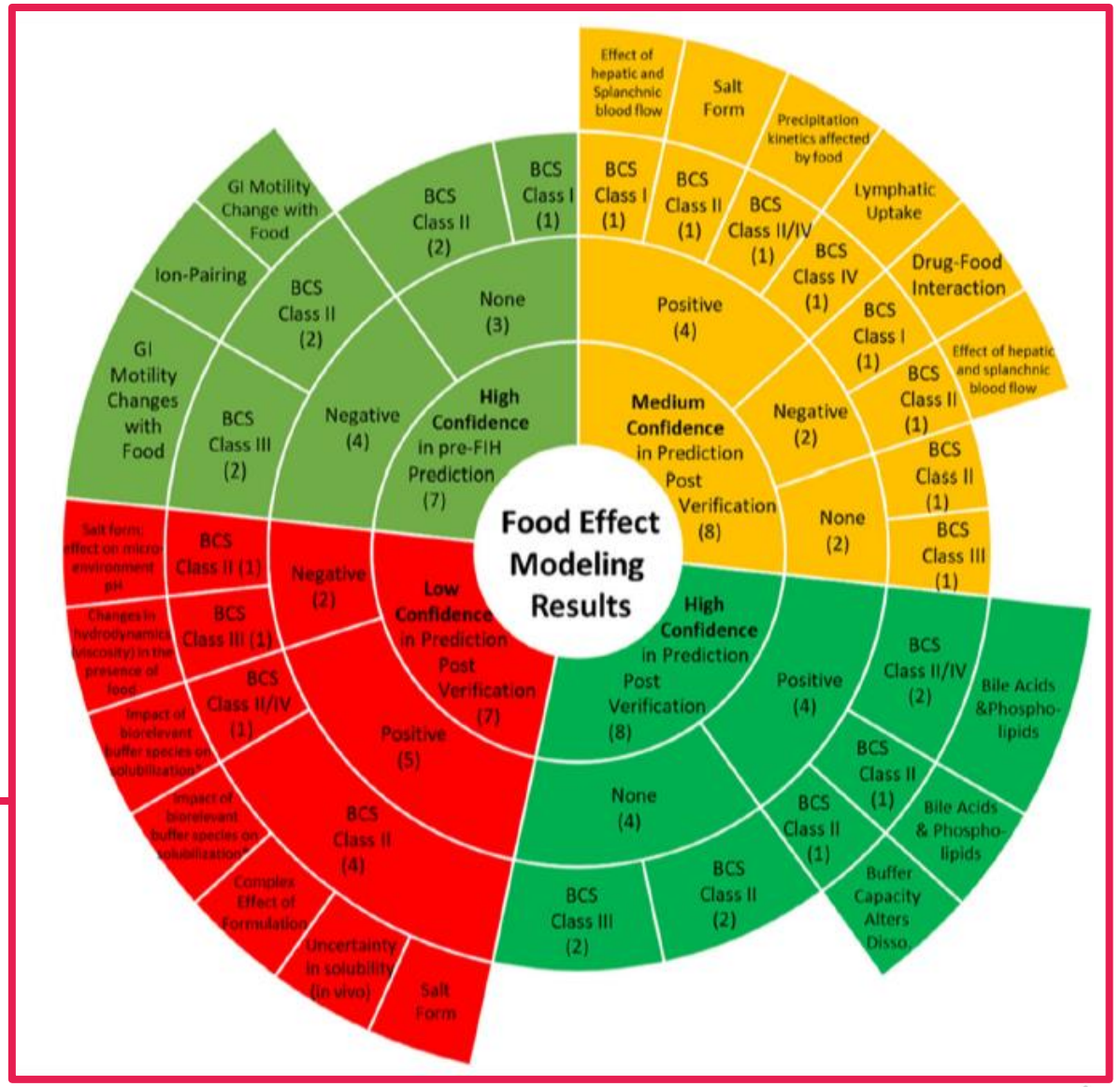
While modeling the low-confidence subset of compounds using a broad, pre-defined decision tree around optimization was not found to be suitable, deviating from the general workflow helped improve the accuracy of some of the models



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





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 Software

- 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)*

Key Takeaways and Future Directions

- This work explored the predictive ability of PBPK models using de novo mechanistic absorption models for 30 compounds:
  - Aligned, pre-defined *in vitro* and modeling methodology
  - Aligned decision tree for model design, verification, and optimization
- PBPK models predicted food effect modeling of most compounds (~80%) with high or moderate confidence
- A smaller subset of compounds showed low (~20%) confidence in food effect prediction
- A correlation was observed between the confidence in the model and the driving mechanism of food effect
- This study was the first step in understanding prediction success of food effect and its correlation with the mechanism(s) driving this effect. Future work will focus on:
  - Further strengthening the validity of these conclusions by expanding this analysis to additional compounds
  - Food type and formulation effect on prediction success