

# Predicting Food Effect

Applications in Clinical Drug Development

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Generic Drug Regulatory Science Initiatives  
Workshop

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# Outline

1

Background

2

Opportunities in the Study of Food Effect

3

Venetoclax Case Study

4

Food Effect IQ Working Group

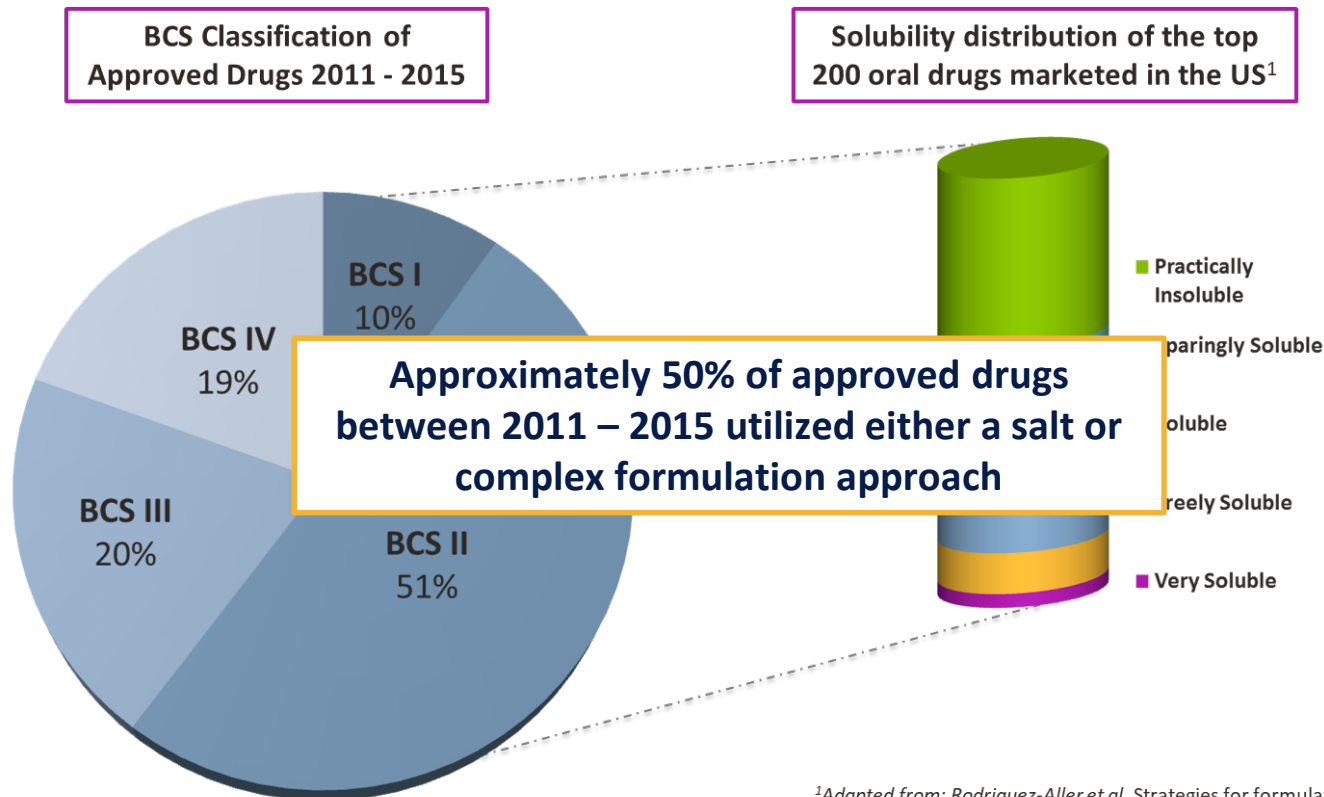
5

Closing Remarks

# Novel Opportunities Have Introduced a New Oral Druggable Space

## Review of Approved Drugs Indicates a Higher Distribution of Class II and IV Compounds

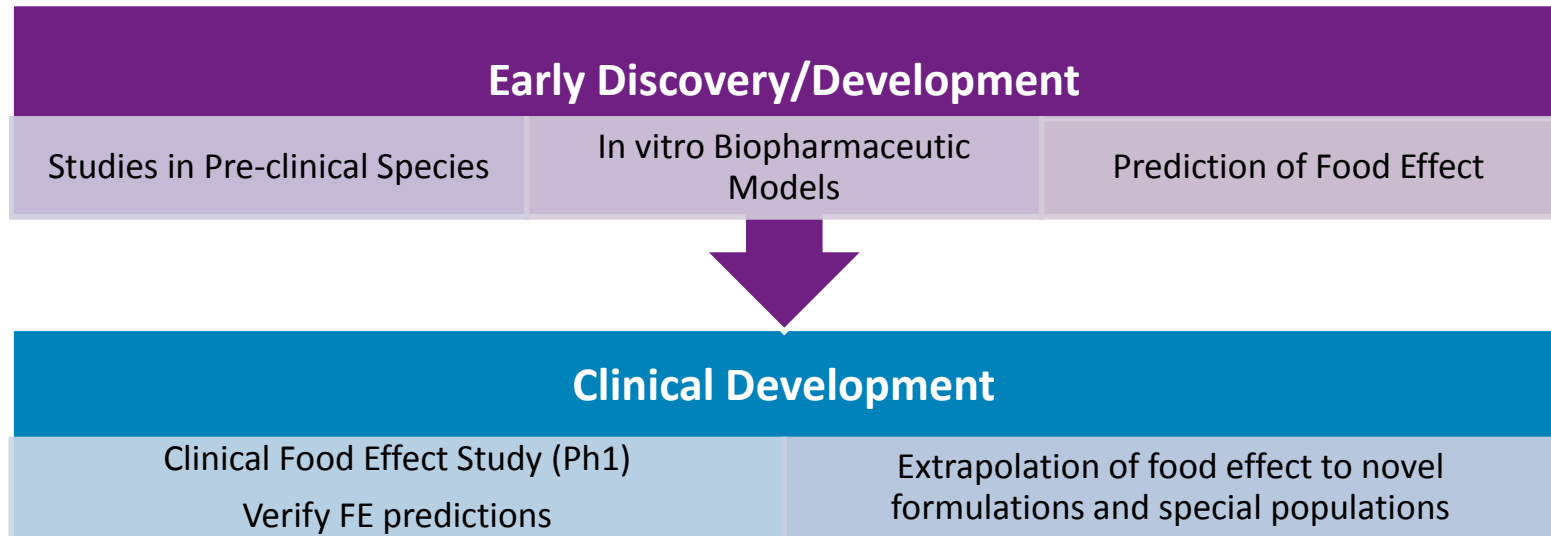
- R&D has been moving towards more complex and hard-to-treat diseases
- Lower tolerance to safety and drug interaction risk, especially for indications where safe drugs already exist
- Novel opportunities have moved the oral druggable space beyond 'rule of 5'



<sup>1</sup>Adapted from: Rodriguez-Aller et al. Strategies for formulating and delivering poorly water-soluble drugs. 2015: JDDST 342-351

# 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 the label recommendations

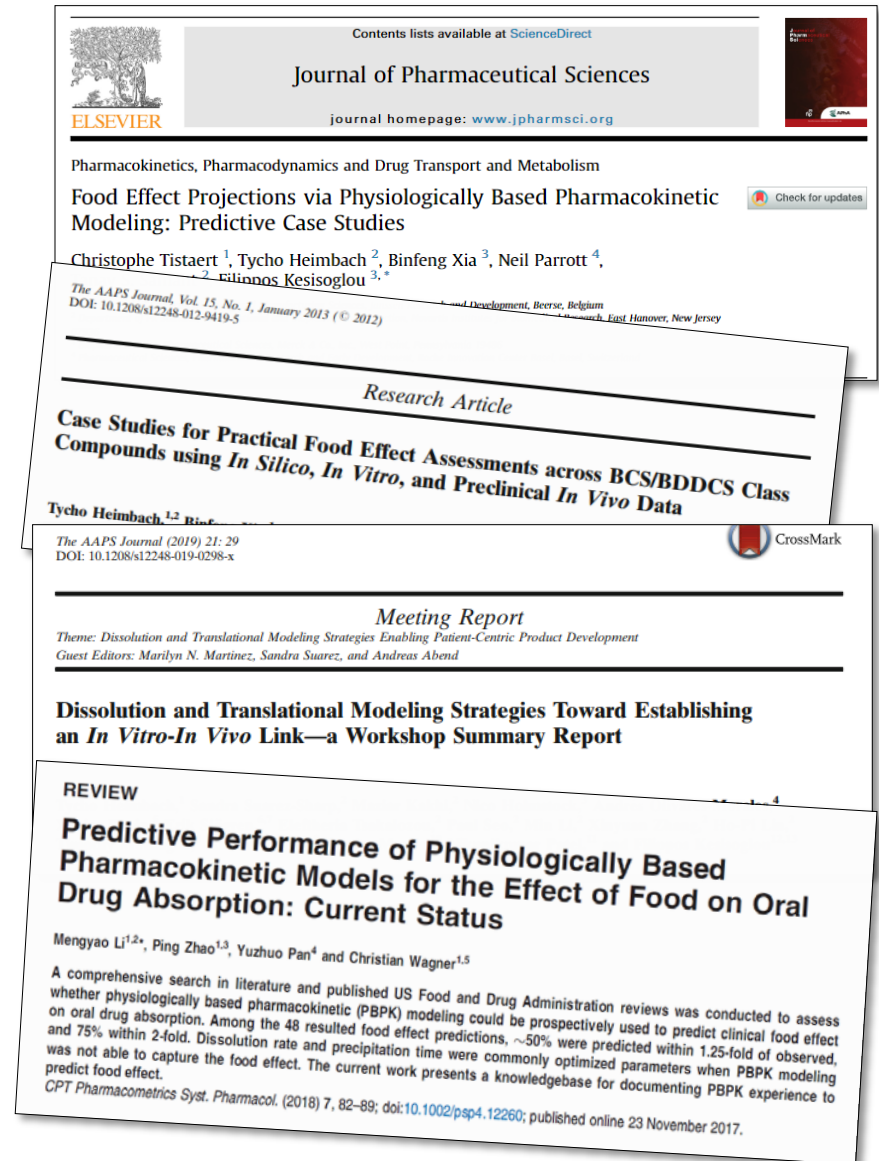


**Given the complex nature of food effect, an integrated approach is required: Physiologically-based absorption models have emerged as a key platform for the support of food effect predictions**

# Prediction of Food Effect

## Industry and Regulatory Confidence

- Various publications from industry, including an IQ paper published in 2015 have demonstrated high to moderate confidence for predicting food effect of compounds where transporters do not play a key role
- Publications from the FDA based on retrospective analysis do not share the same confidence – bottom line: we are not there yet
- Recent FDA guidance on food effect suggests the possible consideration of BCS category (specifically BCS I) to waive FE studies
  - 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



# Venetoclax Case Study

## Predicting the Absorption and Disposition of the BCS IV Compound

**Venetoclax is a selective and orally bioavailable B-cell lymphoma-2 inhibitor developed for the treatment of chronic lymphocytic leukemia (CLL) and other hematological illnesses**

- BCS class IV compound
- Large, lipophilic molecule, highly protein-bound ( $f_{up} = 1.3 \times 10^{-5}$ )
- Poses large challenges to mechanistic modeling and formulation design



Source: Medscape

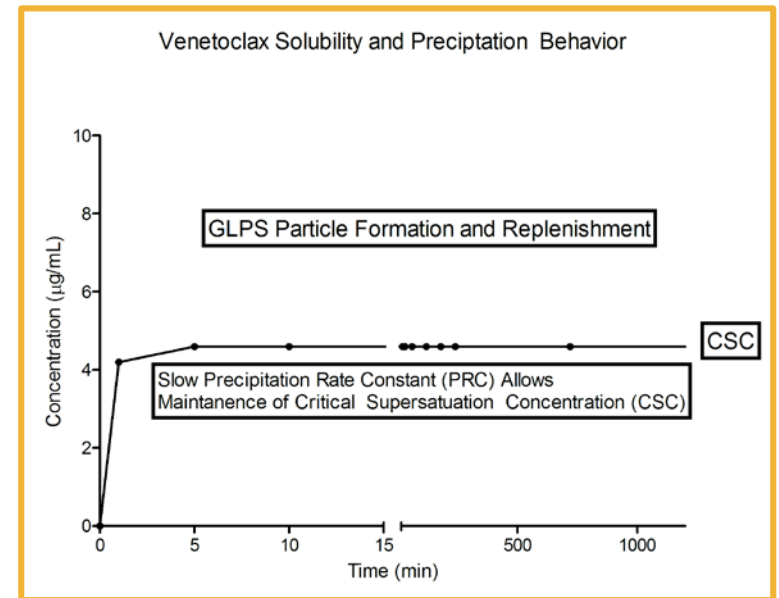
**For BCS class IV compounds, there is a tendency for the application of solubility-enabling formulations to enhance *in vivo* exposure**

- Amorphous solid dispersions (ASDs) may offer significant advantages over crystalline formulations
- Tendency for high molecular weight drugs to be slow crystallizers, which can remain in the supersaturated state

# Venetoclax Case Study

## Predicting the Absorption and Disposition of the BCS IV Compound

- Initial rapid super-saturation of venetoclax to its amorphous solubility occurs at 4.6  $\mu\text{g/mL}$
- Above this concentration, drug-rich particles form and replenish amorphous drug to maintain concentrations at the amorphous solubility



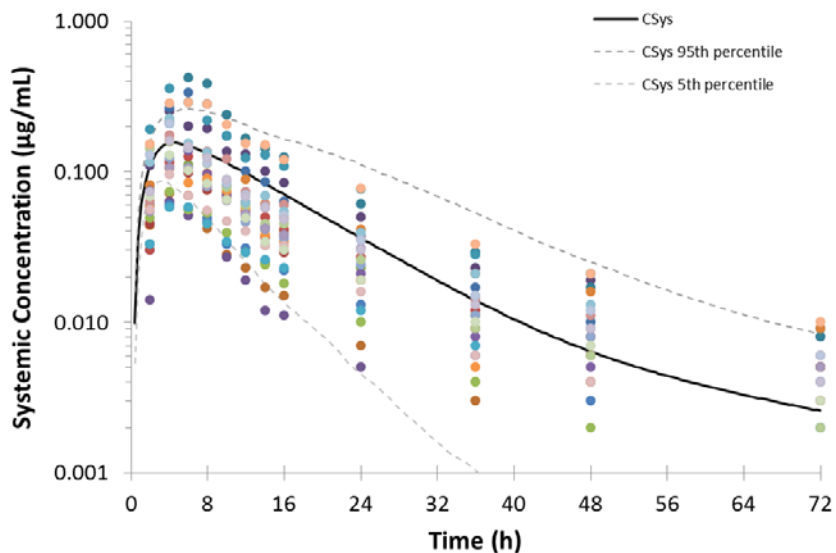
### Key assumptions made based on in vitro data generated within human bio-relevant conditions

- Amorphous solubility measured in buffers was used instead of crystalline solubility
- Dissolution kinetics allowed:
  - Super-saturation to be reached at the amorphous concentrations
  - Precipitation to remain minimal
- Predicted concentrations along the GI tract verified with measured concentrations in simulated GI fluid using the pH dilution method<sup>1</sup>

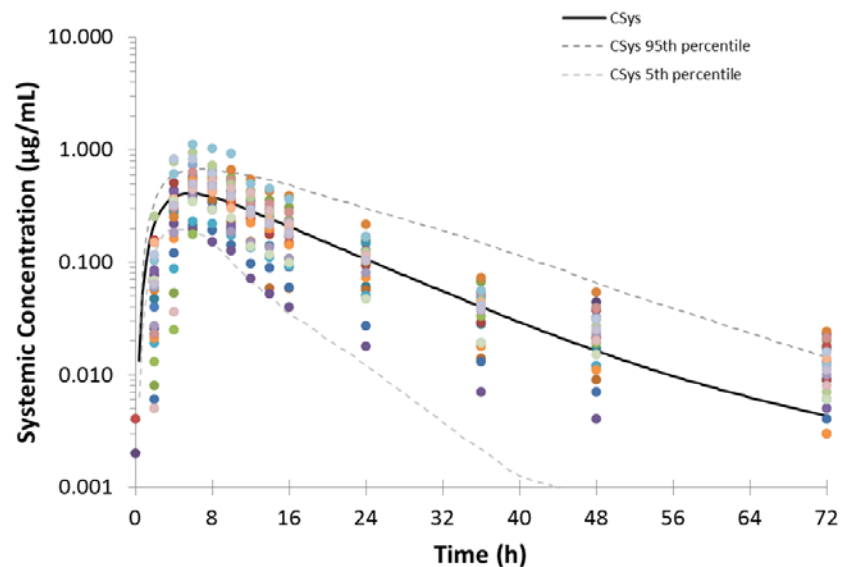
# Venetoclax Case Study

## Verification of fasted and fed profiles in humans

Concentration-time profiles (fasted)



Concentration-time profiles (fed)



Parameter	Fasted	Fed
	Ratio (Predicted:Observed)	Ratio (Predicted:Observed)
$AUC_{0-\infty}$ (µg/mL• hr)	1.10	0.86
$C_{max}$ (µg/mL)	1.01	0.81
$T_{max}$ (hours)	1.02	0.92

**Predicted Bioavailability (fasted) = 6%**  
**Observed Absolute bioavailability (fasted) = 5.4%**  
**Predicted Bioavailability (fed) = 15%**



# 2018 IQ Food Effect Working

## Background

- There are currently no publications assessing the ability of PBPK models to predict absorption and food effect **using a consistent, prospective approach**

## Scope

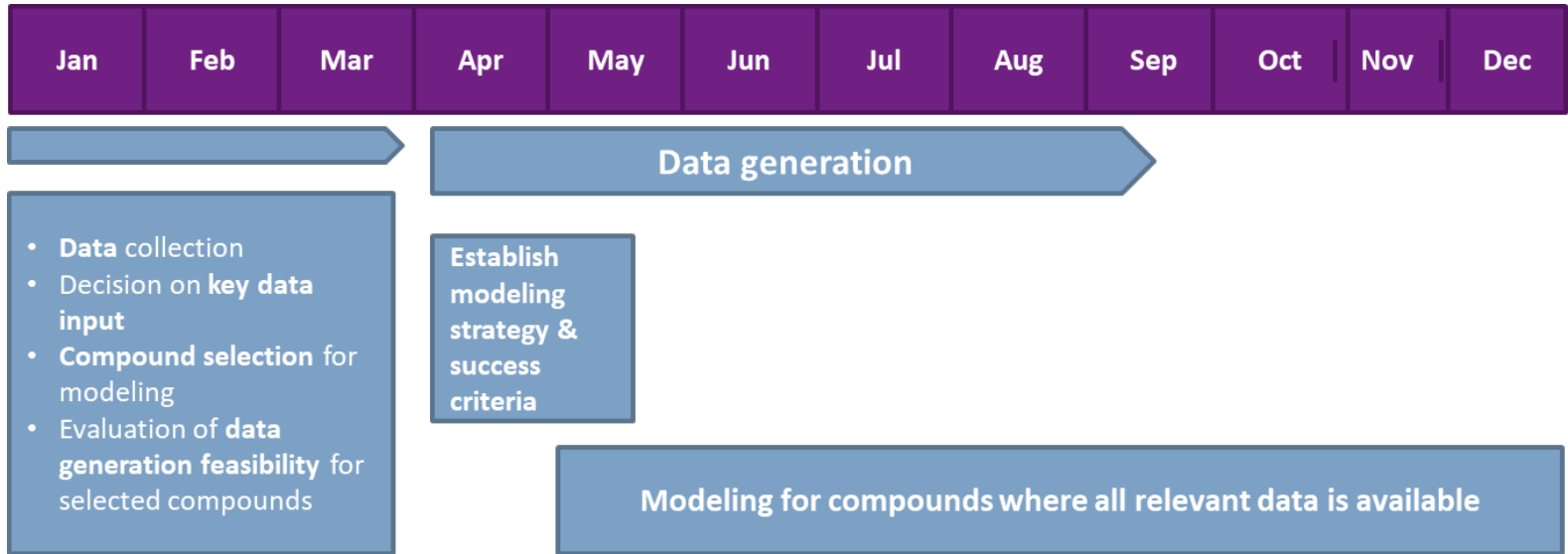
- Cross-functional team of formulation scientists and modelers from 12 pharmaceutical companies
- Establish a consistent workflow for modeling with standardized input data
- Agreed-upon principles, decision trees and data generation methodology
- Appropriate verification of models prior to a food effect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

## Vision

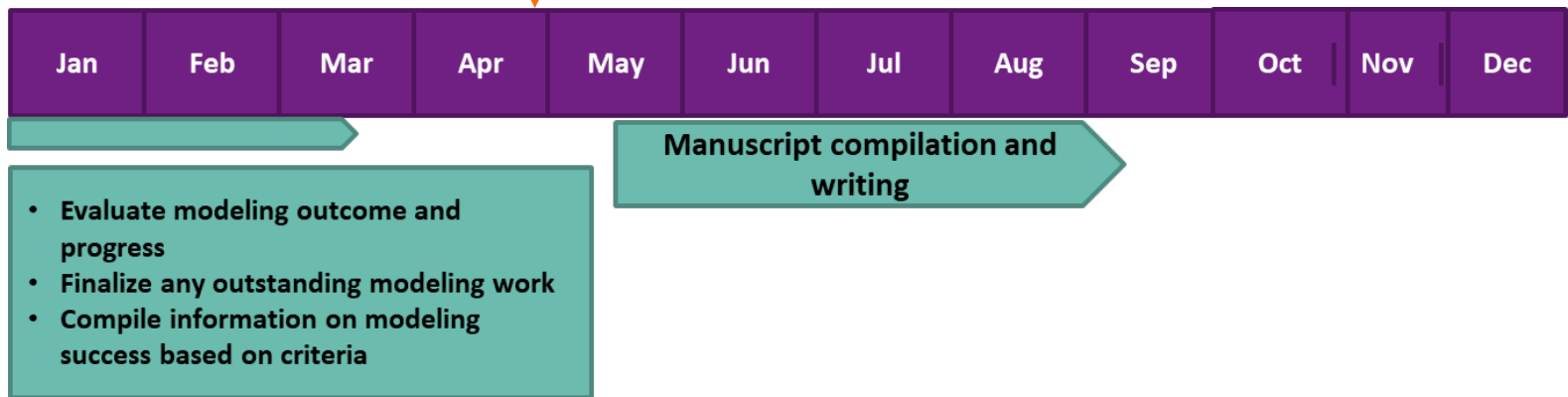
- A well-conducted and published verification study of food effect prediction using PBPK will aid in understanding of modeling applications
- Highlight cases where high vs. moderate-low confidence is expected in predicting food effect
- Provide an aligned industry perspective on cases where modeling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

# 2018 IQ Food Effect Working - Timeline

2018



2019



# Summary and Closing Thoughts

- **Mechanistic, physiologically-based pharmacokinetic models provide an exciting opportunity to utilize an integrated approach for understanding food effect in humans**
- **Proposal for increased confidence in these models:**
  - Application of a consistent workflow with standardized inputs
  - Defined common strategy based on verified models
  - Cross-industry recommendation on best practice based on prospective approach
- **Where models have been verified with clinical food effect data, opportunities exist to utilize PBPK models in the understanding of food effect in:**
  - Early (Ph1) vs. late formulation
  - Different meal types
  - Special populations

# IQ Food Effect Working Group Members

- Christian Wagner (Merck KGaA)
- Filippos Kesisoglou (Merck)
- Sumit Basu (Merck)
- Yuan Chen (Genentech)
- Thuy Tran (GSK)
- Richard Lloyd (GSK)
- James Huckle (Amgen)
- Priyanka Kulkarni (Amgen)
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- Andres Olivares (Roche)
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