Predicting Food Effect

Applications in Clinical Drug Development

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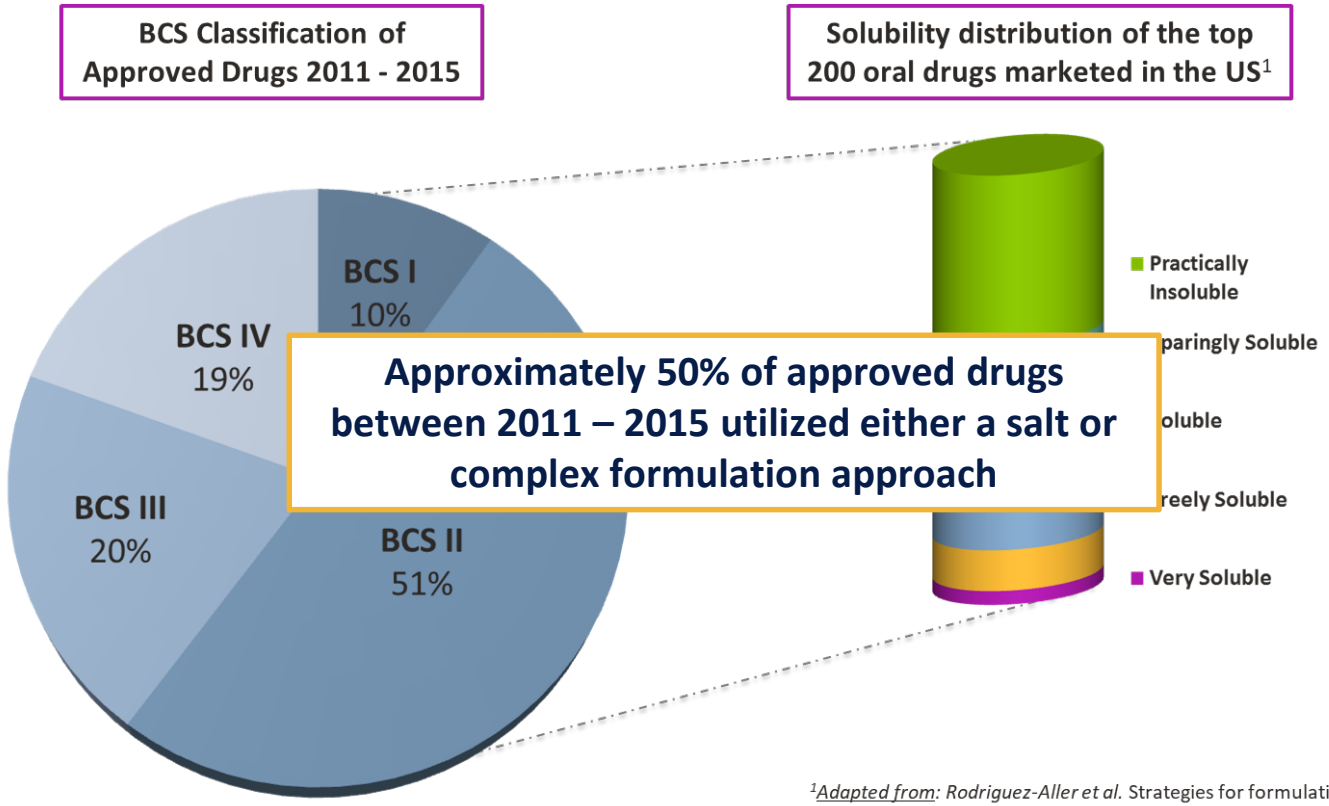
Outline

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

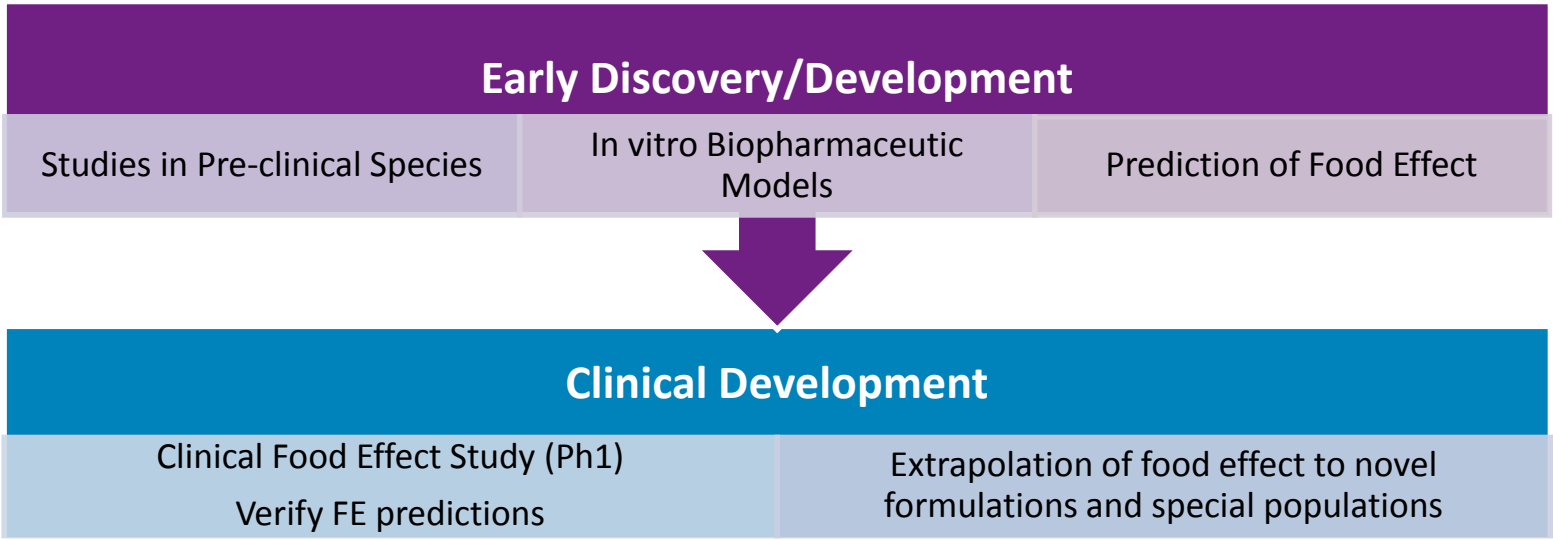
- R&D has been moving towards more complex and hard-to-treat diseases
- Lower tolerance to safety and drug interaction risk, especially for indications where safe drugs already exist
- Novel opportunities have moved the oral druggable space beyond 'rule of 5'



[1]*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 (fu_p = 1.3 x 10^{-5})
- Poses large challenges to mechanistic modeling and formulation design

Source: Medscape

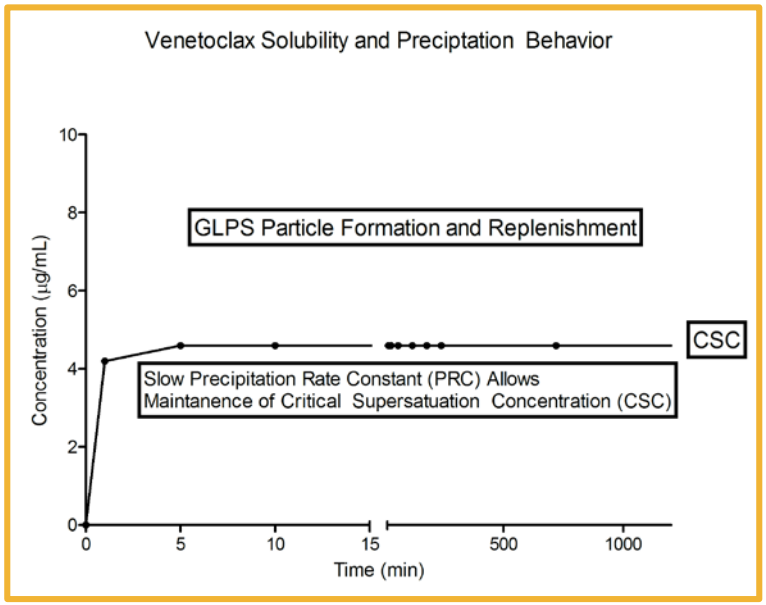
For BCS class IV compounds, there is a tendency for the application of solubility-enabling formulations to enhance *in vivo* exposure

- 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 µg/mL
- Above this concentration, drug-rich particles form and replenish amorphous drug to maintain concentrations at the amorphous solubility



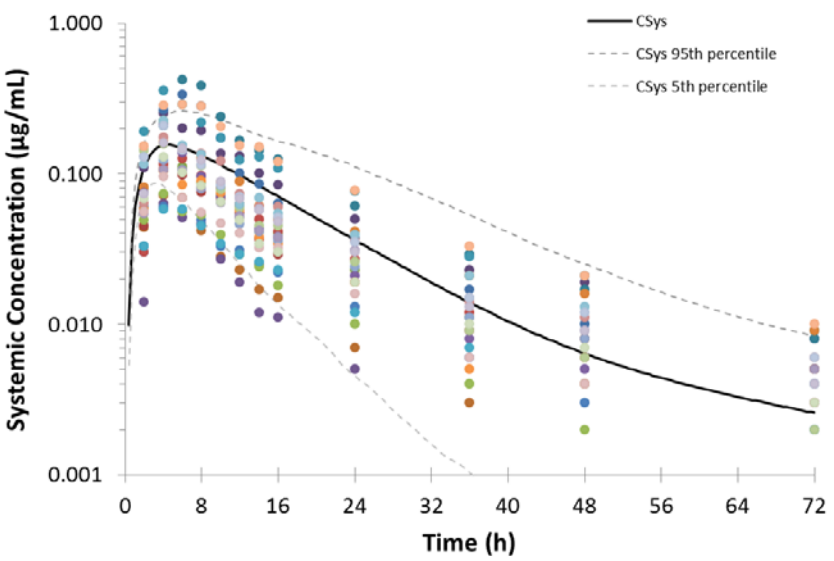
Key assumptions made based on in vitro data generated within human bio-relevant conditions

- 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 method1

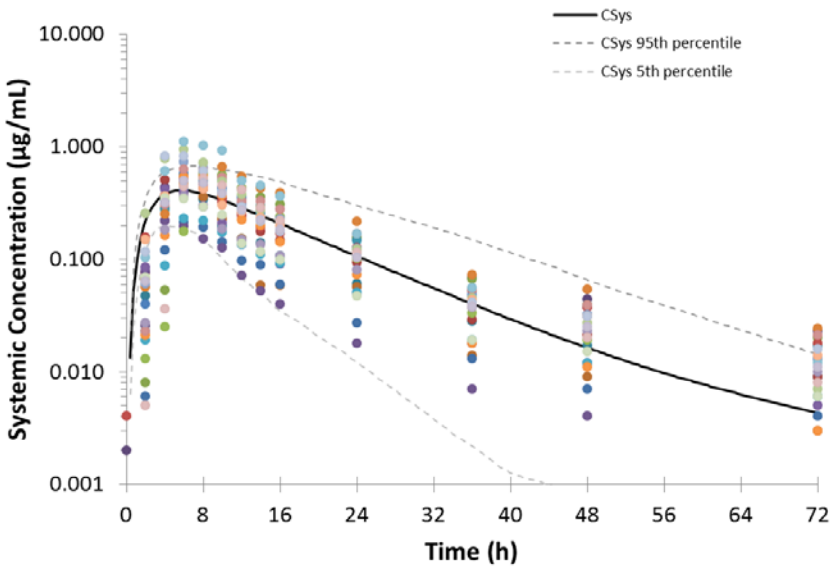
Venetoclax Case Study

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**

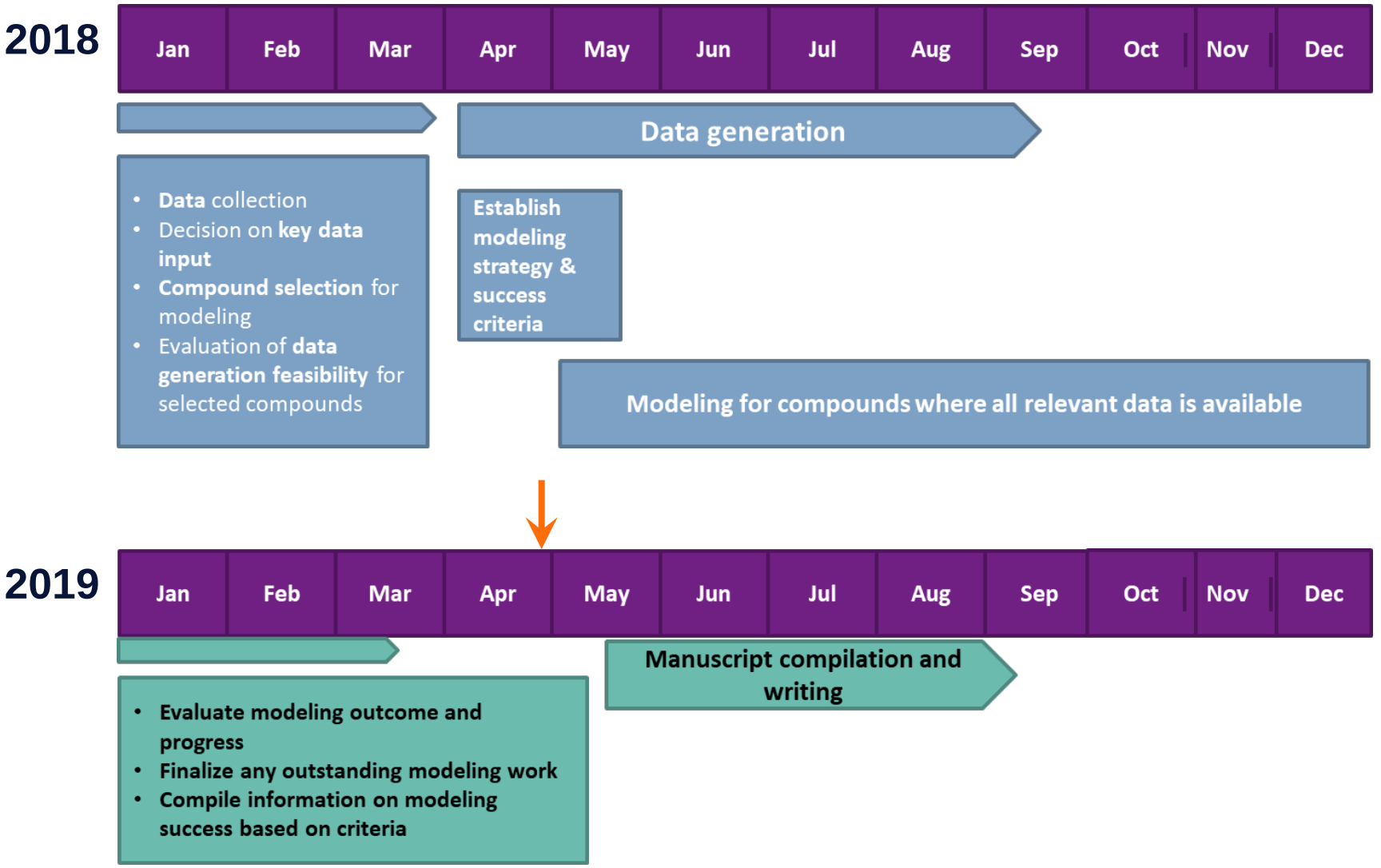
Scope

- 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



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)
- Chi-Chi Peng (Amgen)
- Andres Olivares (Roche)
- Cordula Stillhart (Roche)
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- Stephanie Dodd (Novartis)
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- David Lindley (AbbVie)
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