Scientific Gaps that Impact the Prediction of Fed BE Studies

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Current Fed BE Study Recommendations

- For an IR product, FDA generally recommends a fed BE study, when recommending a fasting BE study
  - except when the RLD labeling states that the product should be taken on an empty stomach or when serious adverse events are anticipated under fed conditions
  - only a fed study is recommended when serious adverse events are anticipated with fasting administration
- For all MR products, FDA recommends a fed BE study, in addition to a fasting BE study, irrespective of dosing instructions in the RLD labeling
  - a fed or fasting study is not recommended when serious adverse events are anticipated under fed or fasting conditions, respectively

What Modeling and Simulation of a Fed Study Can Support?

- Identify critical product quality attributes (e.g., drug substance attributes, formulation attributes, manufacturing process parameters)
- Explore potential failure modes during generic drug development and improve the success rates of generic drugs
- Develop dissolution and drug product quality specifications
- Assess risk associated with post-approval changes
- Support Not conducting fed BE studies

Origins of Food Effects

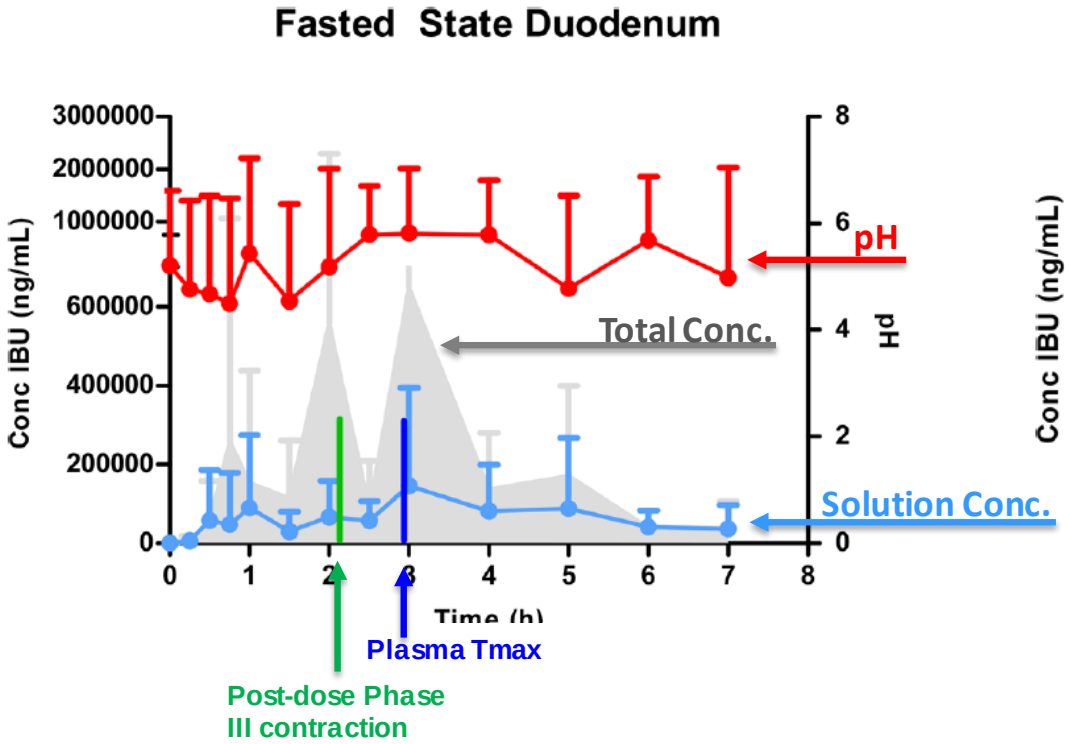
- Gastrointestinal (GI) motility and transit time
- Bile salt concentration
- GI pH and buffer capacity
- GI liquid volume and distribution
- Splanchnic blood flow
- Pre-systemic metabolism and transport
- Direct interaction of food with API and/or excipients
- Meals with different fat or caloric content
- Others

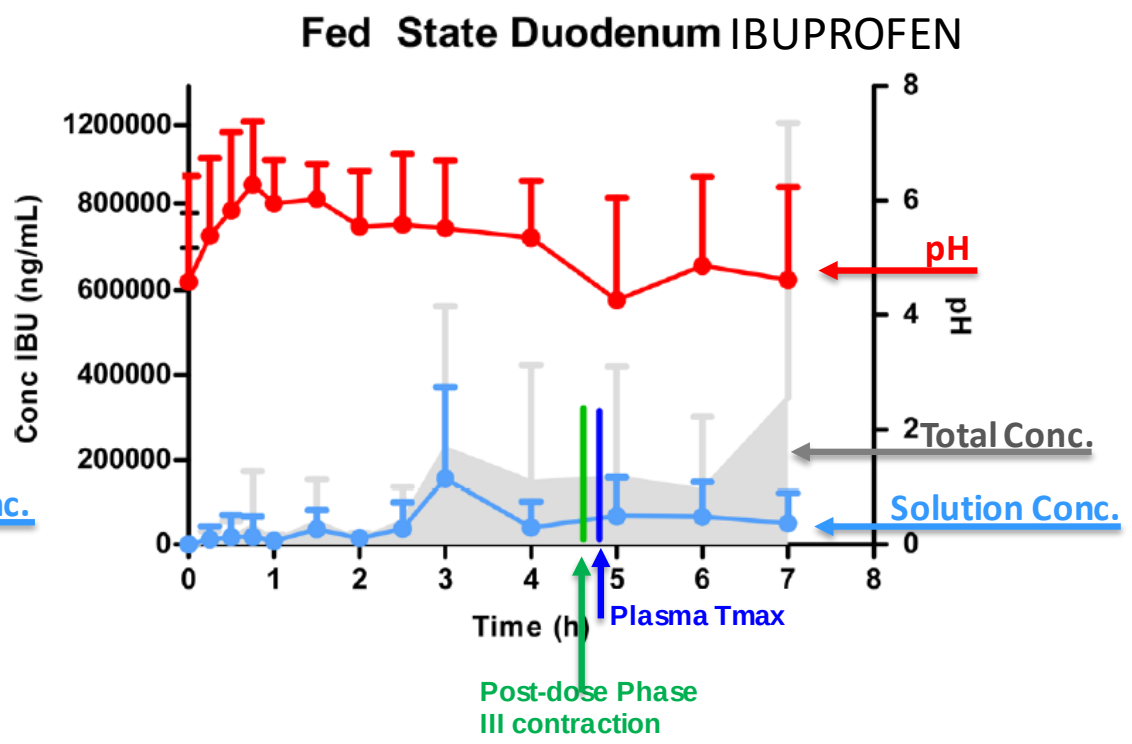
Virtual BE Simulations for Fed Studies

Based on Mechanistic Modeling Approaches

- Goal: to predict food effects on PK for both T and R (predict fed BE) products based on fasting PK data
- Virtual population for BE study should account for both intra-subject and inter-subject variability in the GI **physiology**
  - **Potential scientific gap: food-induced changes in GI physiology**
  - **Potential scientific gap: measure of population variability**
- The model must incorporate **formulation** variables that can represent the difference between the T and R products
  - **Potential scientific gap: Bio-predictive in vitro testing results as modeling input(s)**
  - **Potential scientific gap: Impact of excipient differences on the size of food effect**

Translate Food-induced Changes in GI Physiology into Drug Intraluminal and Systemic Behaviors





- Large inter-subject variability in GI pH and buffer capacity, dynamic changes in pH and buffer capacity (Intra-subject variability), and alternating GI motility pattern
- Research is needed to look into more drug products (different BCS classes, dosage forms and release mechanisms)
- Mechanistic model can ideally describe intraluminal behavior of different drug products

Hens B et. al. Mol. Pharmaceutics 2017, 14, 4281–4294

Formulation Factor(s) and/or Bio-predictive in vitro Testing Results as Modeling Input(s)

- Drug substance attributes (e.g., particle size distribution, polymorphic form)
- Formulation attributes (e.g., release controlling excipient levels/types)
- Processing parameters (e.g., granule particle size)
- In vitro dissolution (e.g., In vivo predictive dissolution)
  - Potential interaction between food and formulation

Excipient Effect(s) on Drug Absorption

- Current PBPK models do not fully characterize excipient effect on drug absorption
  - Some excipients can impact the GI transit time (e.g., sodium acid Pyrophosphate and mannitol) and can potentially change GI motility
  - Excipients may change the response of the formulation to exposure to food
- Drug-excipient interaction(s) may occur through physical and/or chemical interactions
  - In vitro studies indicate excipients have complex effects on solubility and crystalline formation of API with low solubility with and without food
- Food-excipient interaction(s) may effect the rate of absorption of IR products
- **Absorption modeling needs further research to characterize potential in vivo excipient effects with and without food!**

In Vitro Study Suggests Complex Excipient Effects on Behaviors of API with Low Solubility

Solubility of posaconazole in different media

Medium	Crystalline solubility (µg/mL)	Amorphous solubility (µg/mL)	Amorphous/crystalline solubility ratio
FaSSGF	117.76	2107.98	17.9
FaSSIF V1	2.23	46.18	20.7
FaSSIF V2	0.97	19.52	20.1
FeSSIF V1	7.80	160.89	20.6
FeSSIF V2	7.26	139.52	19.2

Impact of medium composition and vehicles on the solubility and crystallization time of posaconazole

Composition	Amorphous Solubility	Crystallization Time
Xanthan gum	=	=
Titanium dioxide	=	=
Polysorbate 80	↑↑↑	↓↓↓
HPMCAS	=	↑↑↑
Sodium taurocholate (STC)	↑	↑
Lecithin (+ STC)	↑↑	↓↓
FaSSIF (STC + Lecithin)	↑↑	↓↓
HPMCAS + FaSSIF	↑↑	↑↑

- **This study indicates excipients may have complex effects on solubility and crystalline formation of API with low solubility with and without food in vivo**

Courtesy of Dr. Lynne Taylor

Food Effect Simulations – A Published Literature Review

Literature Summary

- Among the 48 food effect simulation cases (27 compounds, 36 PBPK models), ~50% of total cases (23 of 48) were predicted within 1.25-fold of observed, and 75% within 2-fold (36 of 48).
- Among optimization cases(9/48), dissolution rate and precipitation time were the most commonly adjusted parameters to match the observed food effect, when PBPK modeling was not able to capture the food effect.
- Given the limited number of BCS class I and III compounds in, it is difficult to generalize the predictability of PBPK within each BCS class, whereas similar predictabilities of PBPK models were shown for BCS class II and class IV drugs

Limitations:

- Limitations in fed physiology implemented in the current platforms (e.g., food-included GI physiology changes and variability, excipient effects, and the effect of different food components)
- Lack of BE (fasting and fed) simulations
- It is always important to consider the ‘‘publication bias’’ because only the ‘‘good’’ results tend to be published or submitted, whereas the ‘‘true’’ picture may be lost

Li M et. al. Mol. Pharmacometrics Syst. Pharmacol. (2018) 7, 82–89

Summary

- Fed BE simulations can aid generic drug development and review, and their successful implementations can support both product development and regulatory decision makings
- Both challenges and opportunities still exist in
  - Understanding food-induced changes in GI physiology
    - the link between food-induced changes and intraluminal and systemic behavior of different drug products
    - the link between intra-subject variability in GI physiology and intra-subject variability in in vivo PK metrics
  - Understanding formulation factors that change food effects
    - Identifying formulation factor(s) and/or bio-predictive in vitro testing results as modeling input(s) for in vivo PK prediction

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