PBPK Modeling - Knowledge Gaps and Challenges

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Physiologically-based Disease Models – Knowledge Gaps

Systemic changes caused by the diseases can be measured *in vivo* and accounted for by the models but local (specific tissue) changes are not defined that well and often have to be deconvoluted from drug plasma concentrations

- **Cancer – it is not a single disease, different types of cancer cause different systemic and local changes**

  Progression of the disease and prior treatments produce changes in GI tract that affect drug absorption:

  - Stomach emptying – typically prolonged due to disease, PPIs and opioid pain medications but might be also shortened
  - Elevated stomach pH (caused by disease, PPIs co-administered with cancer drugs)
  - Intestinal permeability often affected by tissue inflammation
  - Changes in enterocytes – their volumes and binding can be lower due to damage caused by prior treatments
  - Expression of enzymes (typically lowered) and transporters is affected
  - GI tract specific cancers have more profound effect on absorption – GI surgeries must be considered by modifying gut physiology

Currently, many of these local changes have to be deconvoluted from *in vivo* plasma concentrations by modeling individual cancer subjects – subjects' history of the disease and prior treatments must be known for this purpose. Often, lack of IV data and PO data in healthy subjects makes model development more difficult.

Predictability of Food Effects

- **Food Effect - BCS Class III, IV and some of the BCS Class II compounds pose challenges**

  While fat and caloric content impact of the meal on the extent of food effect can be predicted, the direct food-drug interactions are still not fully understood or quantifiable

  - food media composites: peptides, amino acids, and sugars effect on viscosity of the media and water diffusivity [Radwan et al. 2013]
  - impact of food on permeability is still not fully understood

  Better *in vitro* assays are needed to understand these interactions and to predict them *in vivo*, Dog model is still a must

  – Time scale of stomach pH and emptying changes during the absorption process needs to be implemented in models for compounds with pH-dependent solubility - especially for those showing drastic changes in solubility between stomach and intestinal pH (e.g. weak bases with pKas ~2-4) [Lu et al. 2017]

  – Pediatric food effects are different than adult ones due to different type of food administered (liquid meals in neonates and infants) and higher frequency of feeding

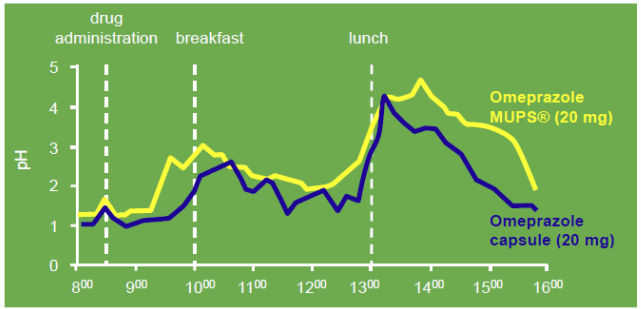
  – The difference in bile salt concentrations between pediatric and adult subjects is not known

  Not sure how to get this information due to ethical issues

Can we predict PPI/ARA DDIs?

- **Most of the PPI/ARA effects on absorption/PK can be predicted if we take into consideration:**
  - **the degree of stomach pH elevation not the same for every PPI/ARA and every subject**
    can be found in literature, however, variability in response needs to be considered, more *in vivo* data for different PPIs is required
  - **timing of PPI/ARA administration in respect to the drug and meal**
    often not provided to modelers together with clinical data (typical modelling pitfall: maximum stomach pH elevation is assumed)
  - **stomach emptying is also affected under fed condition (prolonged due to the lower acid output)**
    insufficient information is available about the extent of delay in stomach emptying for different PPIs

FIGURE 6: MEDIAN PH MONITORING PROFILE ON THE FIRST DAY OF PROTON PUMP INHIBITOR TREATMENT - COMPARISON OF OMEPRAZOLE CAPSULE VS MUPS® (Adapted from Reference 8).



Aubert et al., *SelfCare* 2011;2(S1):1-14

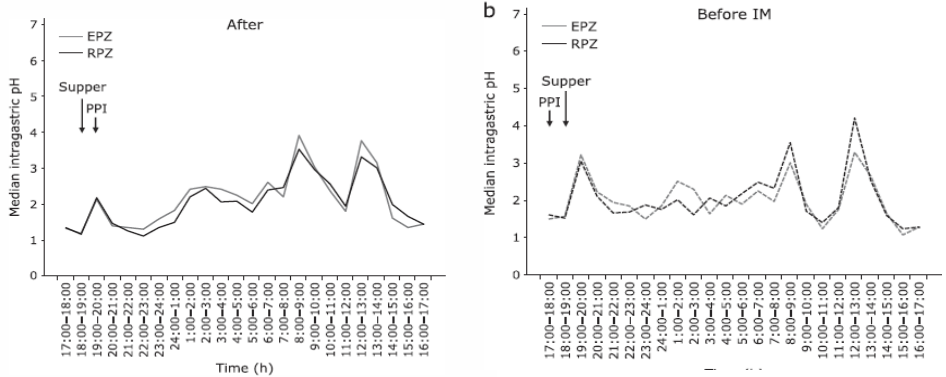


Fig. 4. Median intra-gastric pH during 24-h period after single post-prandial oral administration of 10 mg of rabeprazole (black line) or 20 mg of esomeprazole (gray line). Using a cross-over design, 27 *H. pylori*

Furuta et al., J. Clin. Biochem. Nutr. 2014, vol. 55, no. 3, 179

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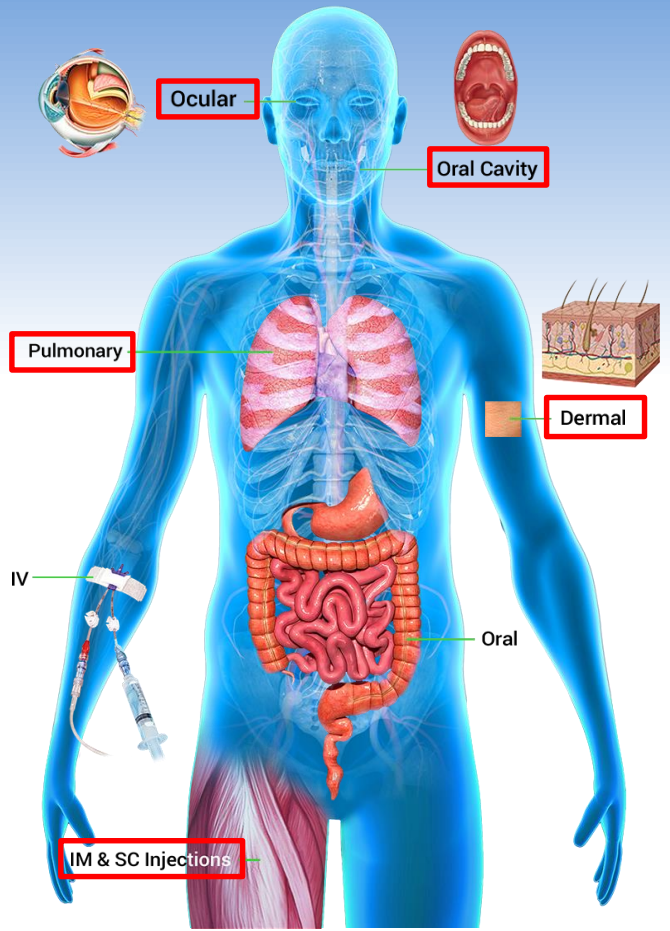
What about non-oral dosage routes?

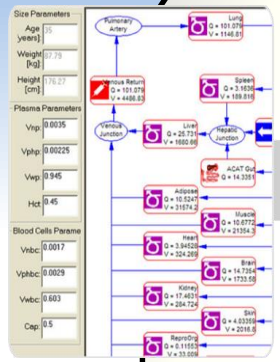
Great advancements have been made in the understanding of non-oral dosage routes but there are still many needs:

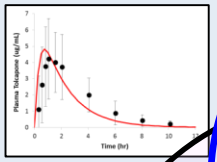
- **Better definition of physiology of the dosing site**
- **Differences in absorption from the specific site between different ethnicities**
- **Understanding impact of excipients**

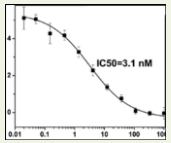


- **Physiological information is hard to get, typically obtained by painstaking literature searches**
- **Better translation of *in vitro* assays data to *in vivo* is needed**
- **Lack of sufficient information about metabolism and transport in the administering tissue**
- **Lack of satisfactory amount of *in vivo* data for validation purposes**

Future: Integration of PBPK/PD and QSP Models





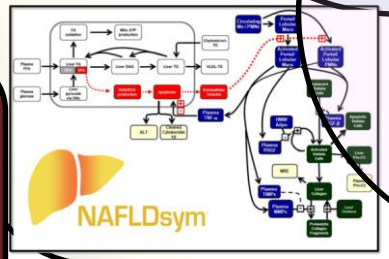


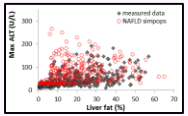
Exposure

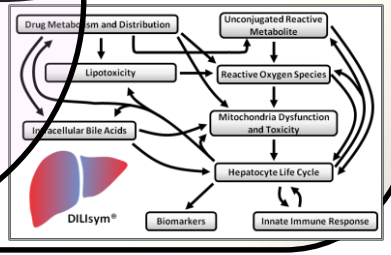
Drug Effects

Efficacy

Liver Biochemistry/ Pathophysiology







PD effects and interactions with underlying biochemistry unique for most compounds; QSP model needs to be flexible to provide ability to represent these effects

Mechanistic representation of underlying biochemistry describing pathophysiology is foundation of QSP models

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Proprietary Modeling Platforms – The Reality…

- **Code/version/quality control**
  - ✓ Strict SOPs when implementing 'Voice-of-Customer' selected functionality
  - ✓ Feature/bug reports logged and assigned to different teams
  - ✓ New versions and patches released annually
- **'Real world' implementation & compliance considerations**
  - ✓ Consistent system validation procedures (to ensure compliance)
  - ✓ Access privilege definitions (administrator, user, reviewer)
  - ✓ Global support staff to address technical questions and train users

- **Platform qualification provides 'reproducibility confidence'**
  - ✓ Software is fully documented and referenced: product manual is an open book – equations & references available for review. Peer-reviewed journal articles, scientific posters, and conference presentations showcase predictability for different applications
  - ✓ No need for computer scientists on regulatory staffs to review logic code, variable definitions, etc. Can instead efficiently review the model's fit-for-purpose

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