Leveraging PopPK and PBPK Modeling Approaches to Understand Food/PPI Effects

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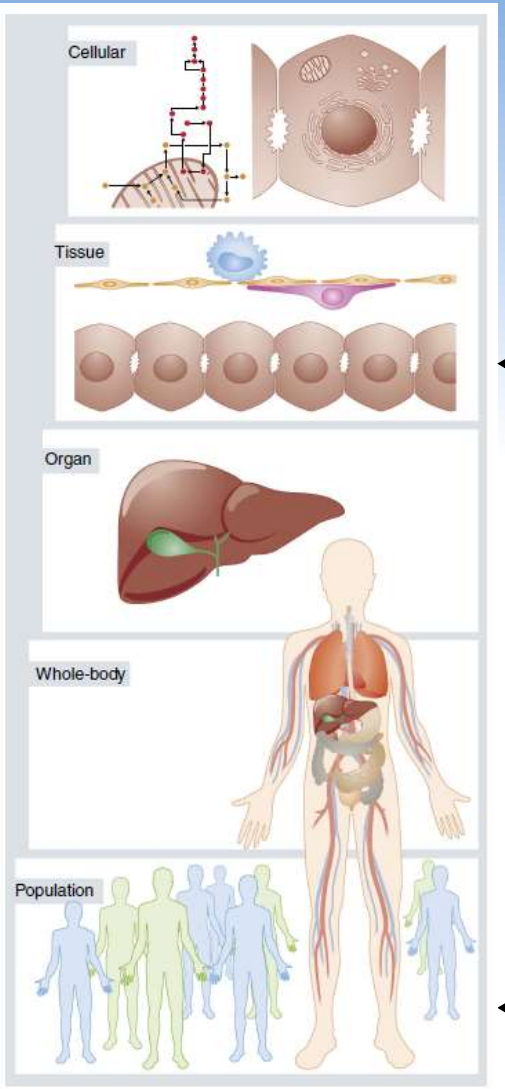
Presentation Outline

- “Bottom-up”/“Top-down” modeling approaches and special considerations for PPIs
- Case study: impact of food and PPIs on pictilisib PK
  - Population PK (PopPK) modeling approach
  - Mechanistic absorption (MAM)/PBPK modeling approach
- Conclusions

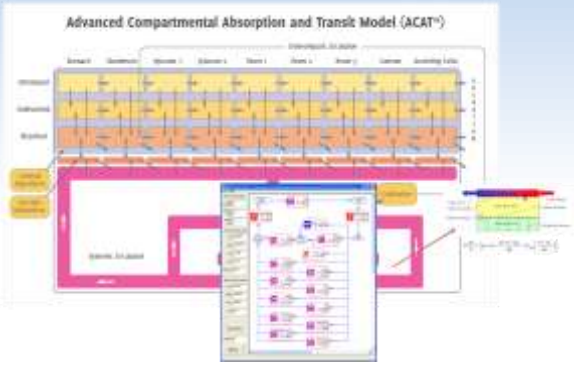
“BOTTOM-UP”/“TOP-DOWN” MODELING APPROACHES AND SPECIAL CONSIDERATIONS FOR PPIS

“Bottom-up” and “Top-down”



Kuepfer 2010, Molecular Systems Biology

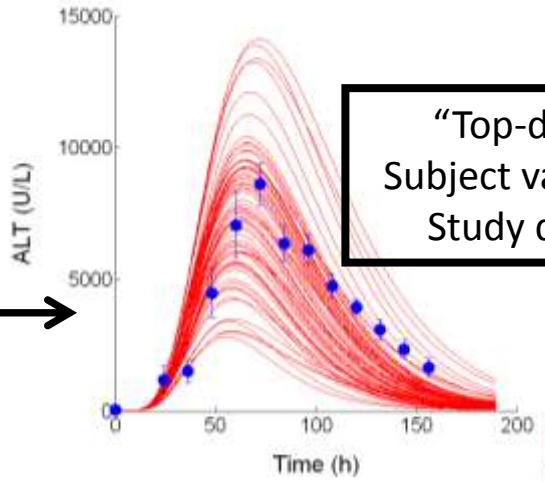
“Bottom-up”
ADME & Physicochemical
Physiology



Drug Specific:
- pKa(s)
- Solubility vs. pH
- logD vs. pH
- Permeability
- Clearance
- Volume of distribution
- Plasma protein binding
- Formulation properties

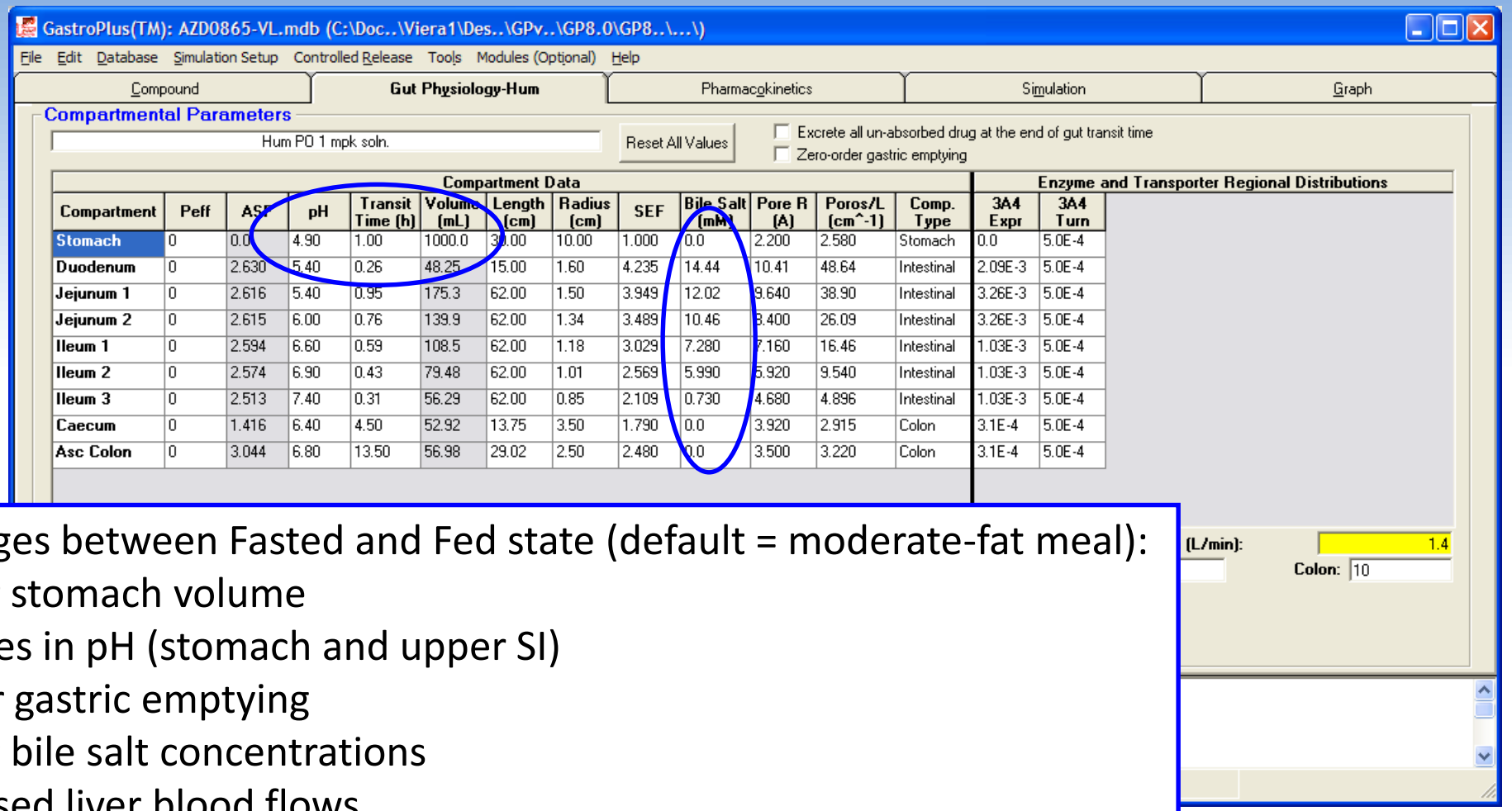
Physiological:
- pH gradients
- Dynamic fluid volumes
- Bile salt distributions
- Residence times
- Microvilli SAE
- Paracellular pore sizes

Tissue properties:
- Specific volume(s)
- Blood perfusion rate
- Enzyme/transporter expression levels
- Volume fractions of lipids & proteins



“Top-down”
Subject variability
Study design

Fed State – ACAT™ Model Changes

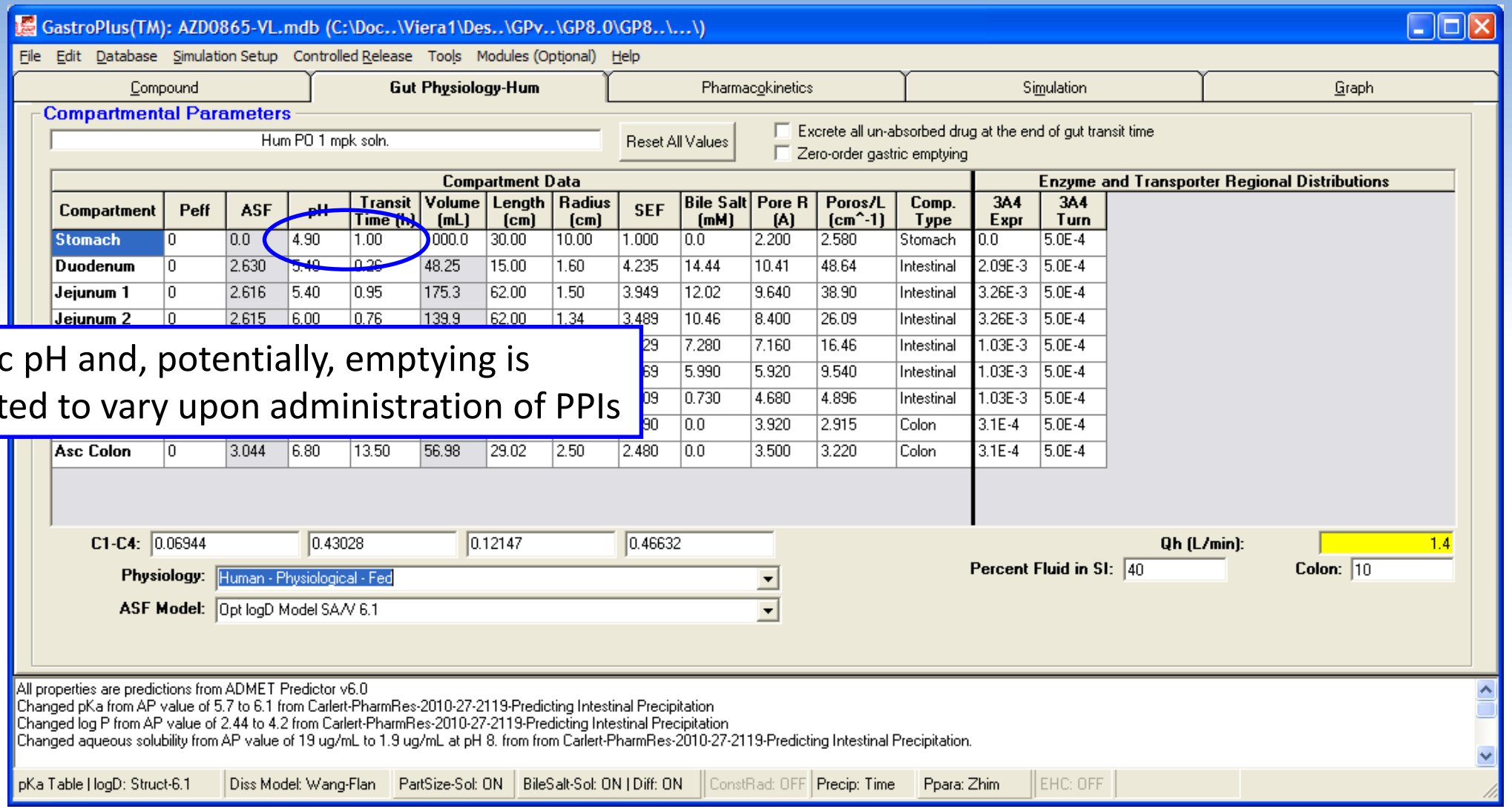


Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	SEF	Bile Salt (mM)	Pore R (A)	Poros/L (cm^-1)	Comp. Type	3A4 Expr	3A4 Turn
Stomach	0	0.0	4.90	1.00	1000.0	30.00	10.00	1.000	0.0	2.200	2.580	Stomach	0.0	5.0E-4
Duodenum	0	2.630	5.40	0.26	48.25	15.00	1.60	4.235	14.44	10.41	48.64	Intestinal	2.09E-3	5.0E-4
Jejunum 1	0	2.616	5.40	0.95	175.3	62.00	1.50	3.949	12.02	9.640	38.90	Intestinal	3.26E-3	5.0E-4
Jejunum 2	0	2.615	6.00	0.76	139.9	62.00	1.34	3.489	10.46	8.400	26.09	Intestinal	3.26E-3	5.0E-4
Ileum 1	0	2.594	6.60	0.59	108.5	62.00	1.18	3.029	7.280	7.160	16.46	Intestinal	1.03E-3	5.0E-4
Ileum 2	0	2.574	6.90	0.43	79.48	62.00	1.01	2.569	5.990	5.920	9.540	Intestinal	1.03E-3	5.0E-4
Ileum 3	0	2.513	7.40	0.31	56.29	62.00	0.85	2.109	0.730	4.680	4.896	Intestinal	1.03E-3	5.0E-4
Caecum	0	1.416	6.40	4.50	52.92	13.75	3.50	1.790	0.0	3.920	2.915	Colon	3.1E-4	5.0E-4
Asc Colon	0	3.044	6.80	13.50	56.98	29.02	2.50	2.480	0.0	3.500	3.220	Colon	3.1E-4	5.0E-4

Main changes between Fasted and Fed state (default = moderate-fat meal):

- Higher stomach volume
- Changes in pH (stomach and upper SI)
- Longer gastric emptying
- Higher bile salt concentrations
- Increased liver blood flows

Proton Pump Inhibitors (PPIs) – Special Considerations



Gastric pH and, potentially, emptying is expected to vary upon administration of PPIs

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Which PPI Dosed is Important…

- Degree of gastric pH elevation is not the same for every PPI (or subject)

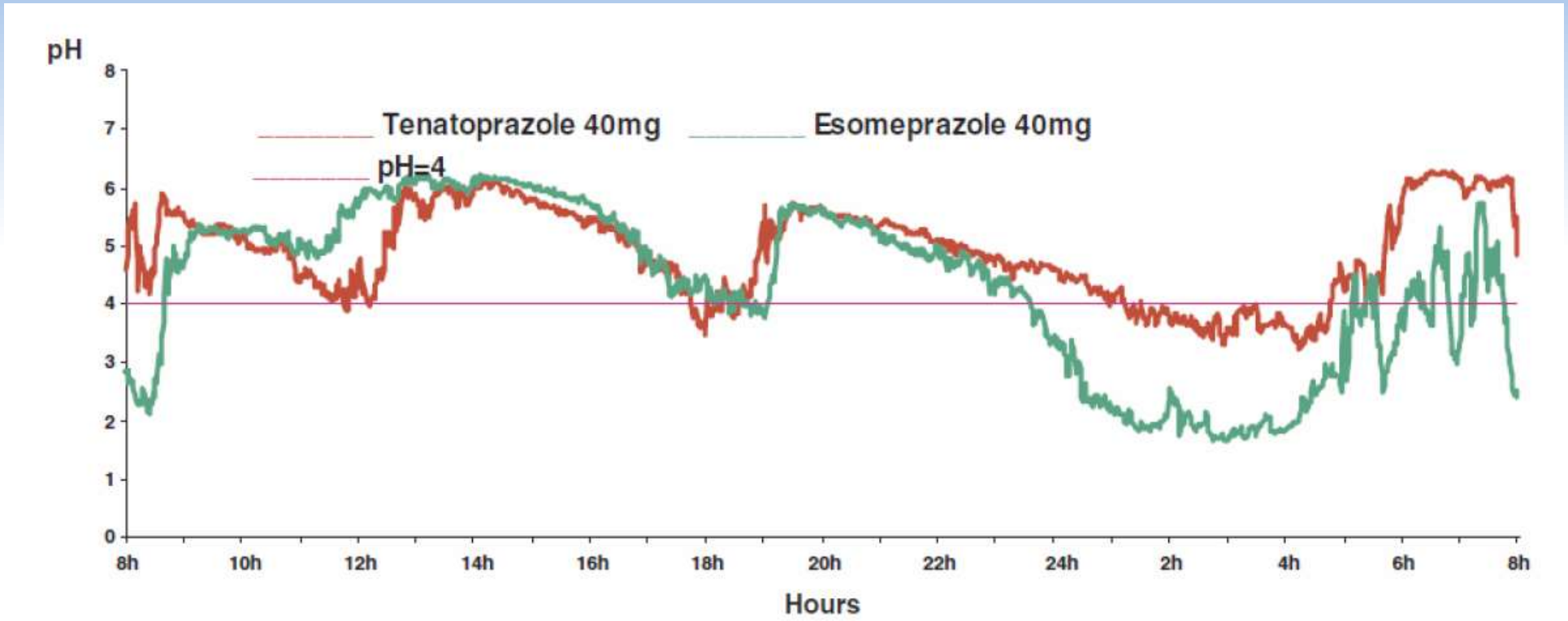


Figure 1. Time course of pH fluctuations [average (mean) of 30 subjects] on day 7.

Hunt et al. Am. J. Gastroenterol. (2005) 100:1949

… As Well as Timing of PPI Administration

- Degree of gastric pH elevation is not the same for every PPI (or subject)

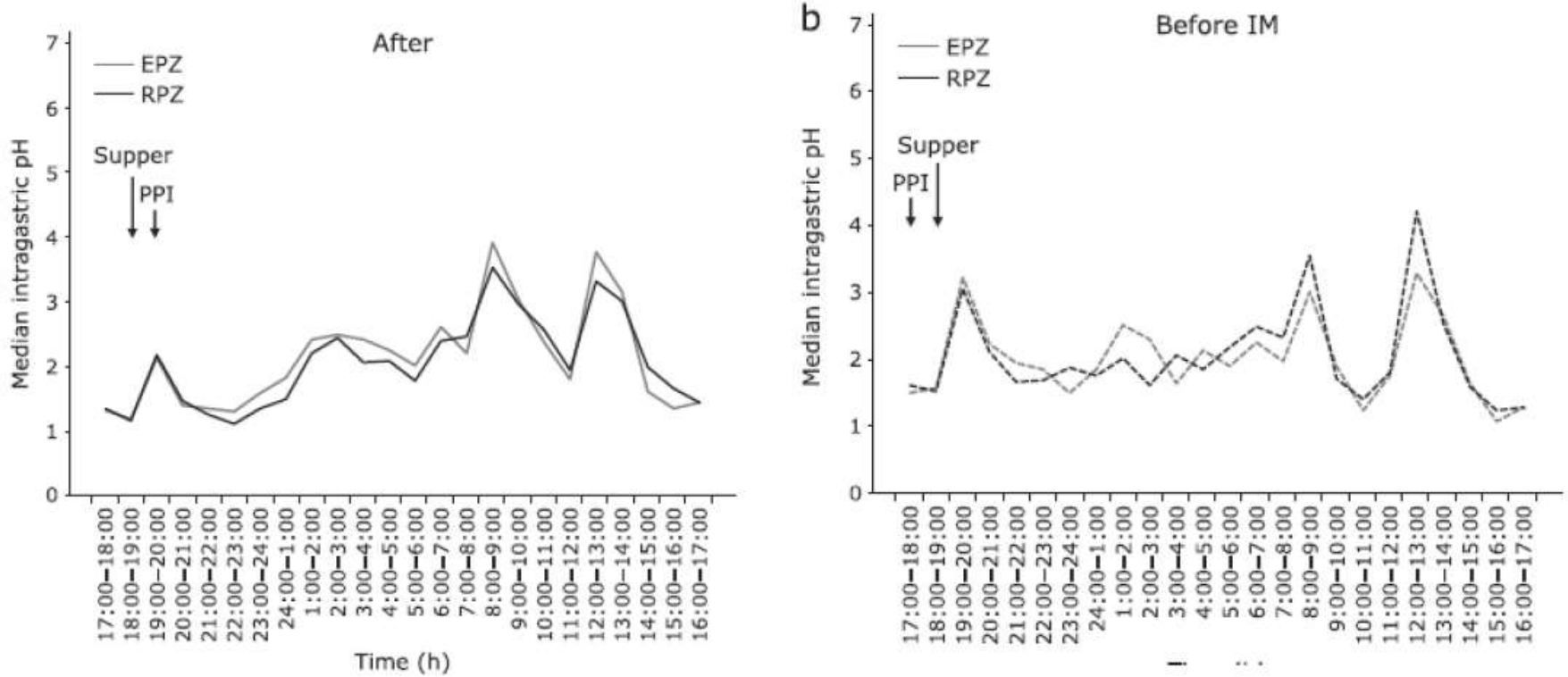
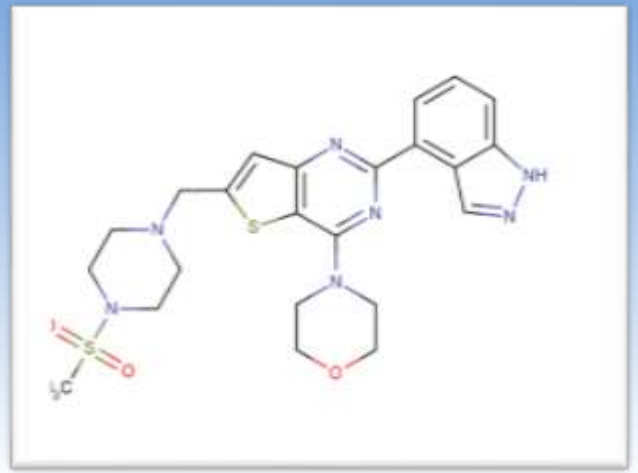


Fig. 4. Median intra-gastric pH during 24-h period after single post-prandial oral administration of 10 mg of rabeprazole (black line) or 20 mg of esomeprazole (gray line). Using a cross-over design, 27 *H. pylori*

Furuta et al. J. Clin. Biochem. Nutr. (2014) 55(3):179

CASE STUDY: IMPACT OF FOOD AND PPI ON PICTILISIB PK

Pictilisib (GDC-0941)



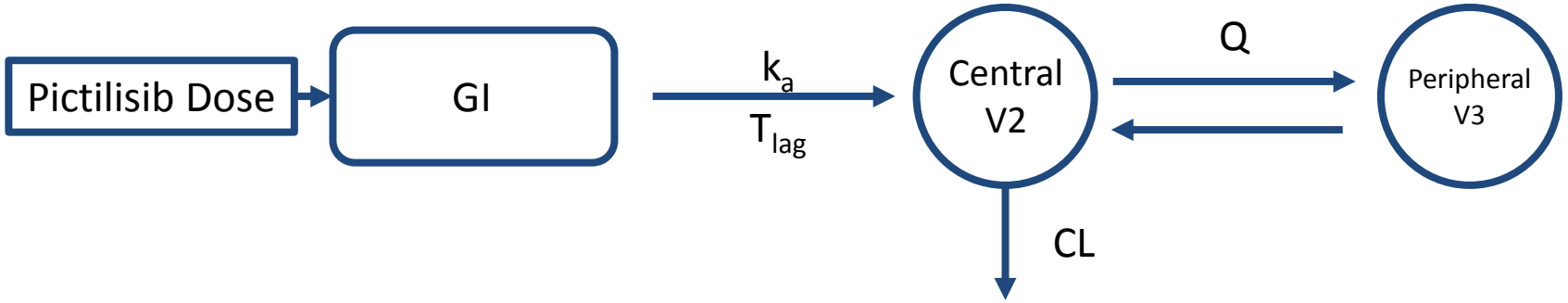
- Potent and selective pan-inhibitor of class I PI3K
- Multiple clinical trials for various cancers
- High permeability/poor solubility at physiological pH
  - Classified as BCS Class II
- Investigate clinical significance of food/PPI administration to enable label recommendations
  - Phase I randomized, open-label study conducted in healthy volunteers
  - Sequence 1: fasted->fed->fasted/PPI->fed/PPI
  - Sequence 2: fed->fasted->fed/PPI->fasted/PPI

Lu et al. CPT Pharmacometrics Syst. Pharmacol. (2017) 6:747

POP-PK MODELING APPROACH

PopPK Analysis

- PopPK analysis and covariate selection conducted on 1,202 plasma samples from 31 subjects
- Models developed in NONMEM®
- Effect of food and PPI on the fixed effect (F_{rel}, K_a, and T_{lag}) and random effect (interindividual variability) were evaluated
- Two-compartment model with first-order absorption, with lag time, and first-order elimination best described data



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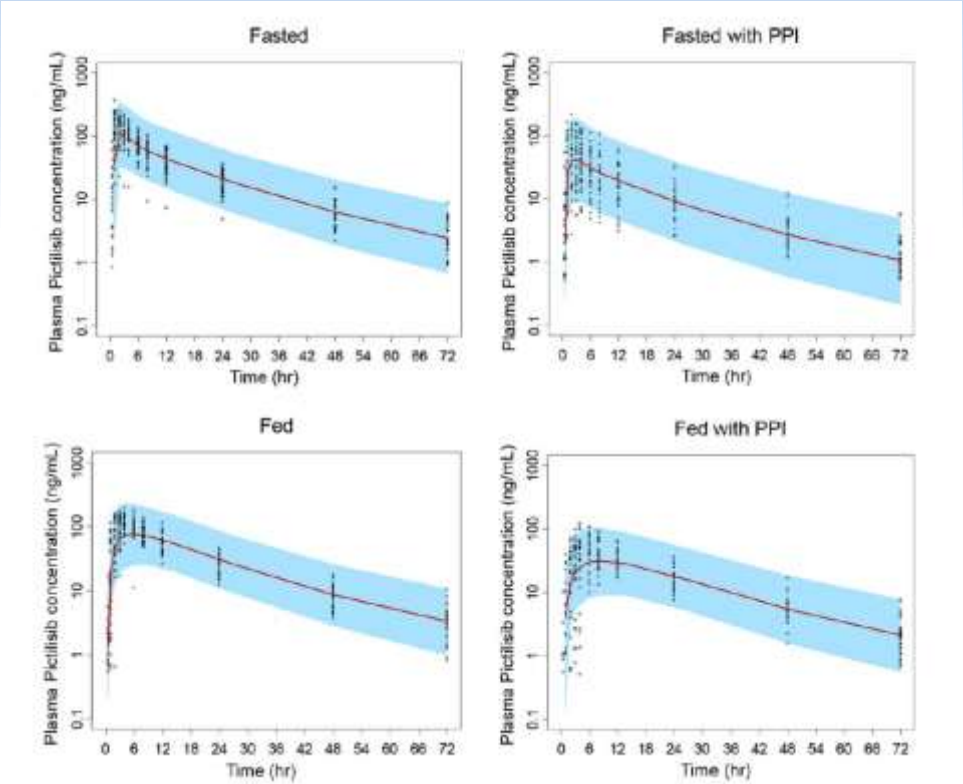
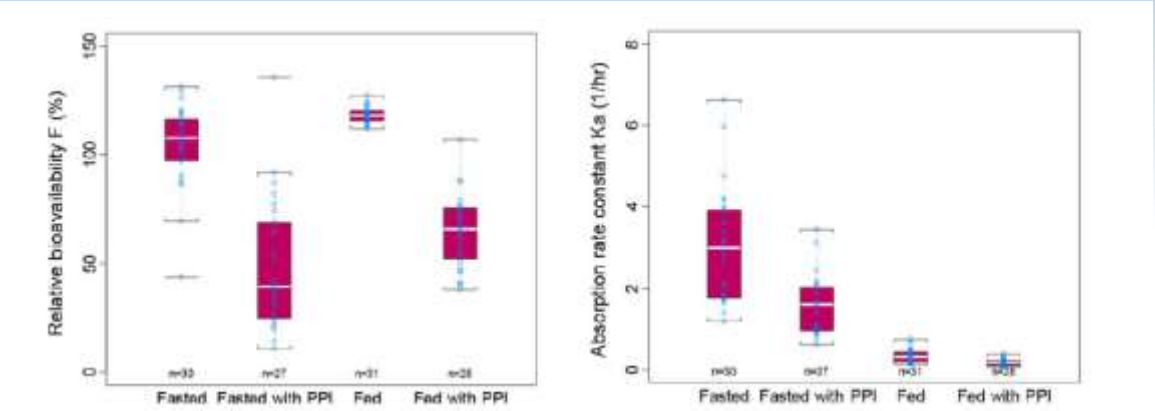
PopPK Results

Visual Predictive Checks



Box Plots for F_{rel} and K_a



- K_a decreased ~80% with food (regardless of PPI)
- K_a decreased ~50% with PPI (regardless of food)

- F_{rel} increased 20-40% with food (regardless of PPI)
- F_{rel} decreased 50-60% with PPI (regardless of food)

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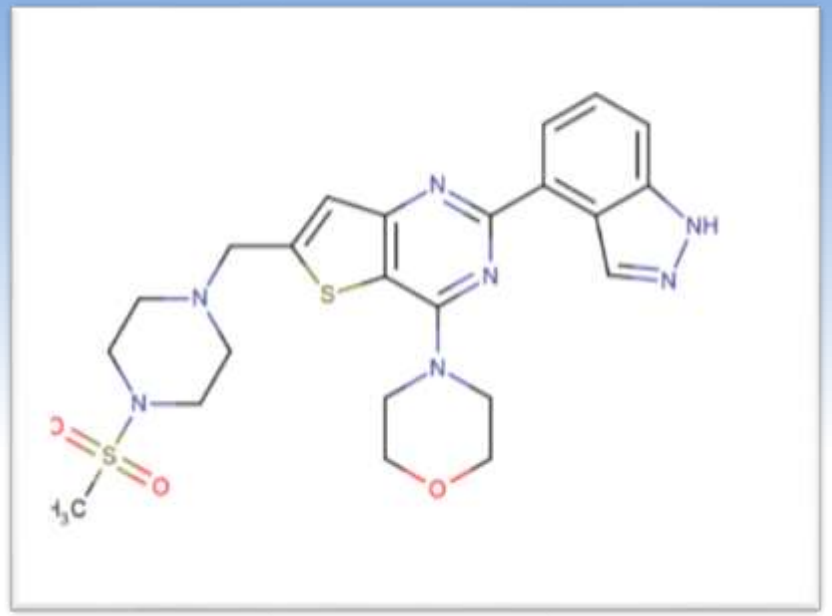
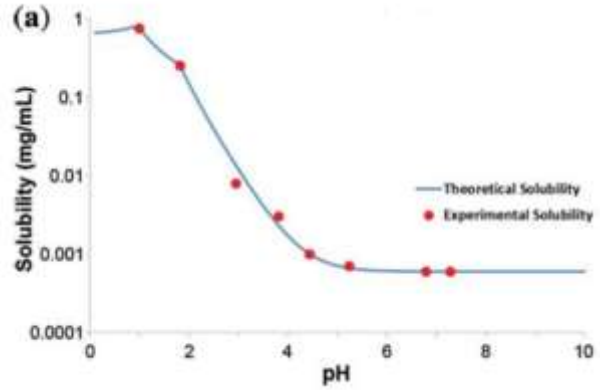
MAM/PBPK MODELING APPROACH

Pictilisib – ADME/Physicochemical Properties





Parameter	Value	Source
logP	3.22	Measured
pKa(s)	4.24 (Base); 1.54 (Base)	Measured
Aqueous solubility	0.001 mg/mL @ pH 6.8	Measured
FaSSIF solubility	0.001 mg/mL	Measured
FeSSIF solubility	0.006 mg/mL	Measured
Human effective permeability	2.26 cm/s *10^-4	Converted from Caco-2 Papp
Particle radius	0.9 µm (SD = 0.48)	Measured
Plasma protein binding	5% unbound	Measured
Blood:plasma concentration ratio	1	Measured
Hepatic/total clearance	5 mL/min/kg	Estimated from *in vitro* HLM and human PK data
PBPK Vss	2.7 L/kg	Calculated from Lukacova Kp method

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MAM/PBPK Modeling Objectives

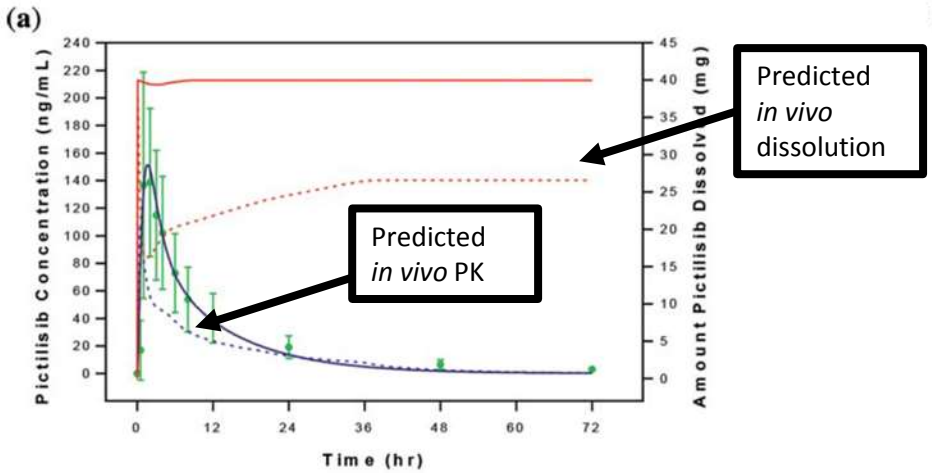
- **Develop** a 'bottom up' MAM/PBPK model using available *in vitro* data and default values in GastroPlus™ to predict food effect
- **Build** a 'top down' MAM/PBPK model using available clinical PK data to determine *in vivo* GI physiology conditions following food/PPI administration
- **Validate** the MAM/PBPK model using clinical PK data not used in the model-building step

‘Bottom Up’ PBPK Model Development – Food Effect

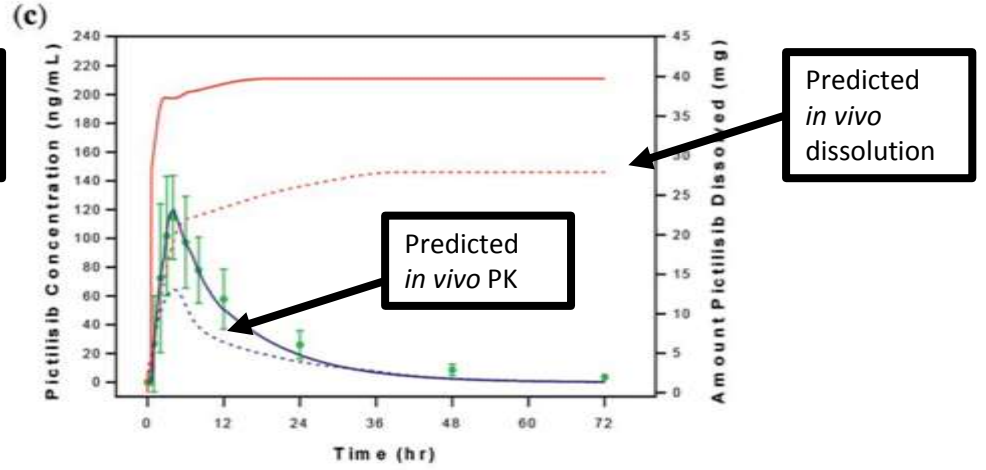
Model building steps:

1. Create virtual human PBPK model according to the subject demographics
2. Define all tissues as perfusion-limited models
3. Estimate tissue partitioning using default Lukacova method in GastroPlus™
4. Extrapolate hepatic clearance using HLM data
5. Define physicochemical property inputs using measured *in vitro* data and/or default settings in GastroPlus™
   a) Mean precipitation time = 900 sec
6. Assume default ACAT™ gut model under fasted or fed conditions

Fasted State



Fed State



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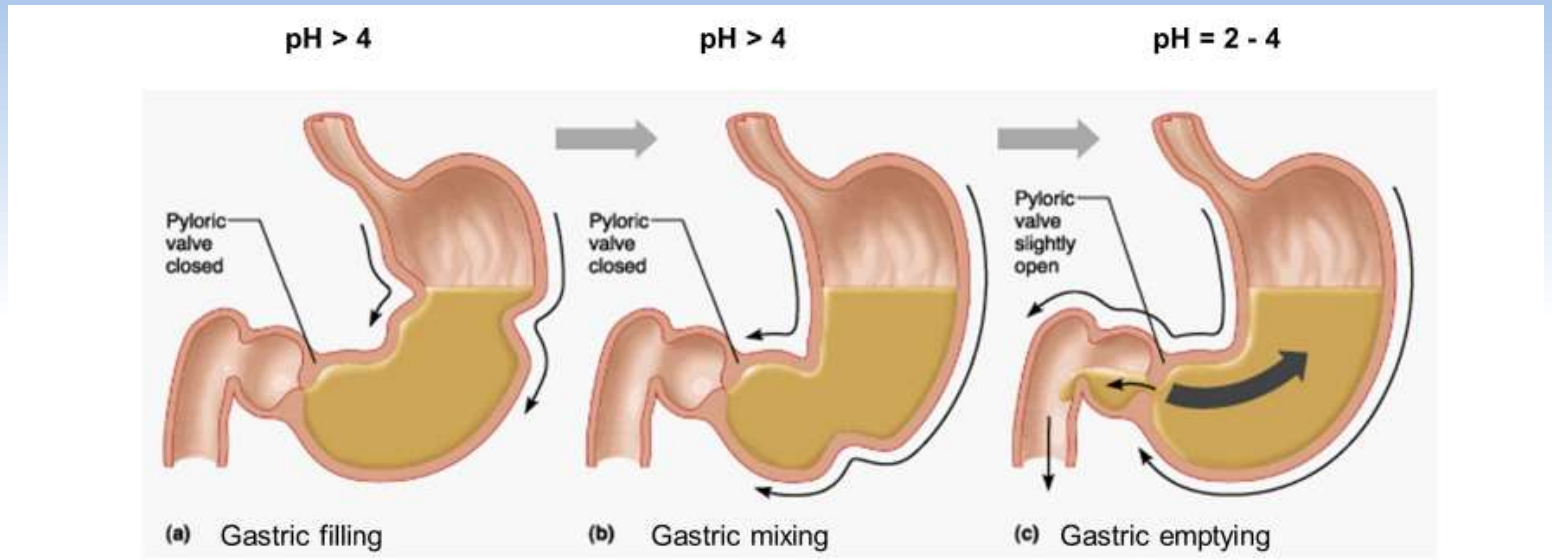
‘Bottom Up’ PBPK Model – Issues

- Fasted state:
  - Default mean precipitation time (900 sec) lead to overprediction of precipitation potential
    - **Justification for changing in model**: ADMET Predictor™ QSAR model predicts “tendency to supersaturate” from chemical structure + observed PK data
  - Default gastric emptying time (0.25 hr) too short
    - **Justification for changing in model**: observed PK data
- Fed state:
  - Default mean precipitation time (900 sec) lead to overprediction of precipitation potential
    - **Justification for changing in model**: ADMET Predictor™ QSAR model predicts “tendency to supersaturate” from chemical structure + observed PK data
  - Default gastric emptying time (1 hr) and pH (4.9) do not provide the necessary ‘low pH’ environment to dissolve
    - **Justification for changing in model**: reported time-/pH-dependent gastric emptying + observed PK data

Gastric Emptying – Time-/pH-Dependent Deconvolution

Gastric emptying does not occur until its contents reach pH 2-4



Approach: utilize clinical PK data under fed conditions to 'deconvolute' the segmental gastric emptying physiology

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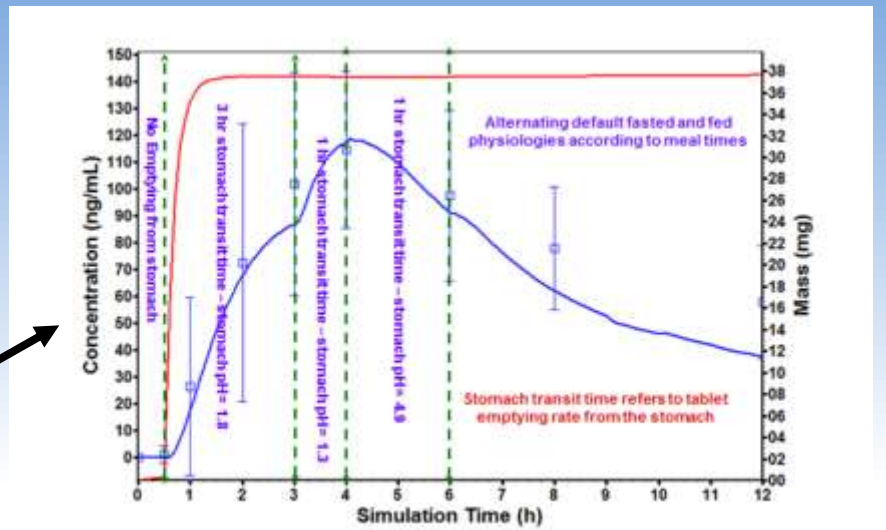
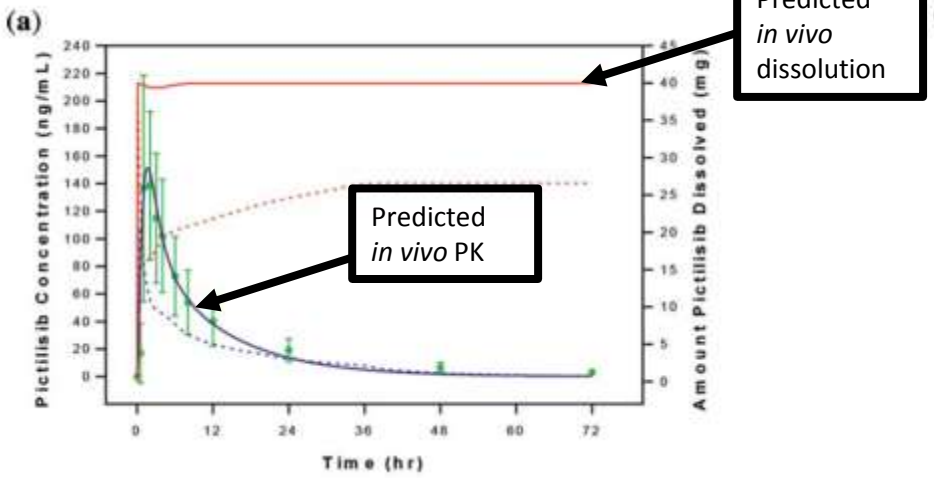
‘Top Down’ PBPK Model Development – Food Effect

Model building steps:

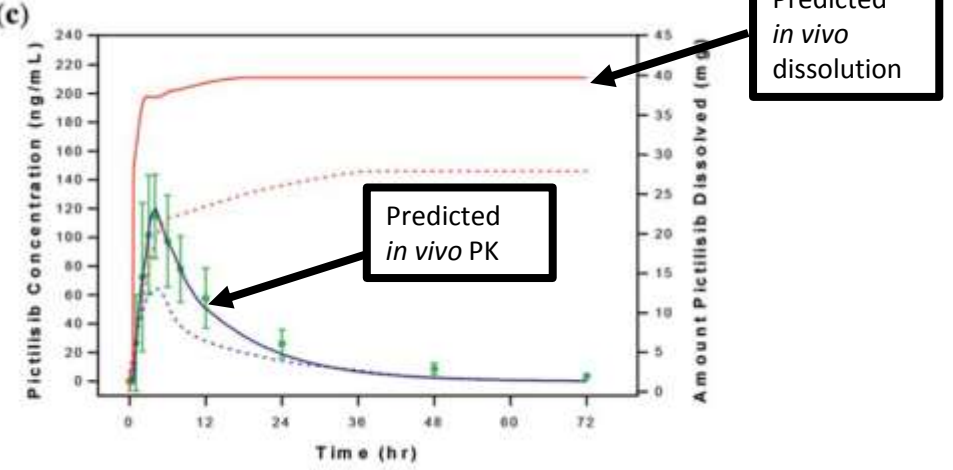
1. Set mean precipitation time to 90,000 sec (create supersaturated environment)
2. Deconvolute gastric emptying time under fasted conditions (1 hr)
3. Deconvolute segmental gastric emptying physiology for fed state



Fasted State



Fed State



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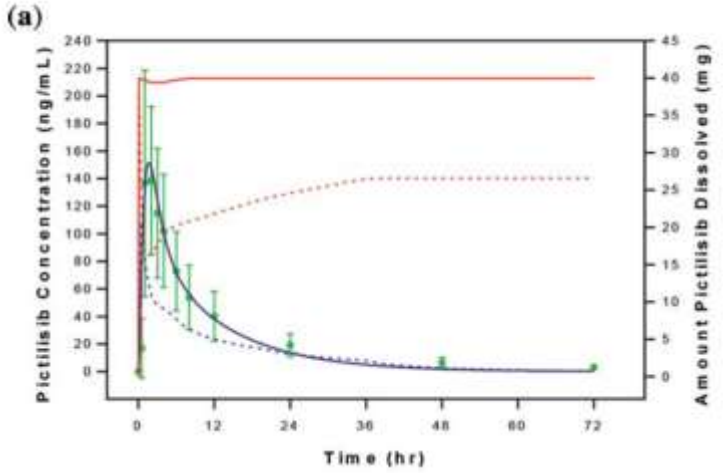
‘Top Down’ PBPK Model Development – PPI Effect

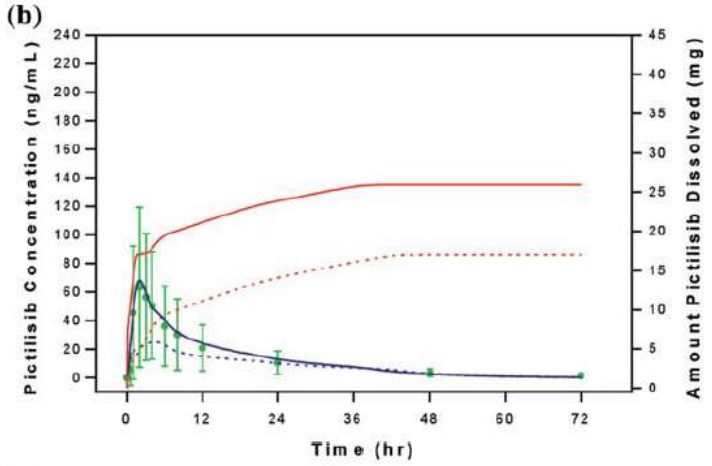
Model building steps – fasted state:

1. Set mean precipitation time to 90,000 sec (create supersaturated environment)
2. Deconvolute gastric emptying time under fasted conditions (1 hr)
3. Initially adjust gastric pH to 4.5 under fasted conditions w/PPI (rabeprazole) – considered upper limit
4. Deconvolute gastric pH to match with clinical PK data (final value = 2.9)

Fasted state



Fasted state w/PPI



Dashed lines represent ‘bottom up’ PBPK model results. Solid lines represent ‘top down’ PBPK model results. (Blue) curves are the plasma concentration-time profiles (left y-axis). Red curves are the simulated *in vivo* dissolution profiles (right y-axis)

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Prospective PBPK Model Predictions – Food+PPI Effects

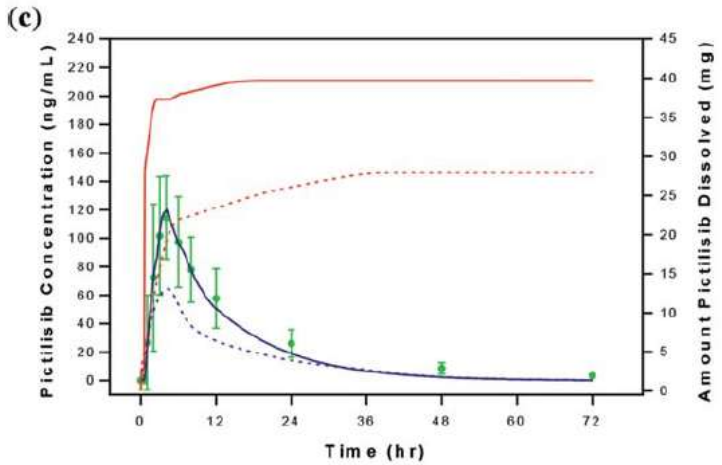
Model building steps – fed state:

1. Set mean precipitation time to 90,000 sec (create supersaturated environment)
2. Apply deconvoluted segmental gastric physiology from fed state PK data
3. Adjust gastric pH levels to reported literature to reflect presence of PPI (rabeprazole)

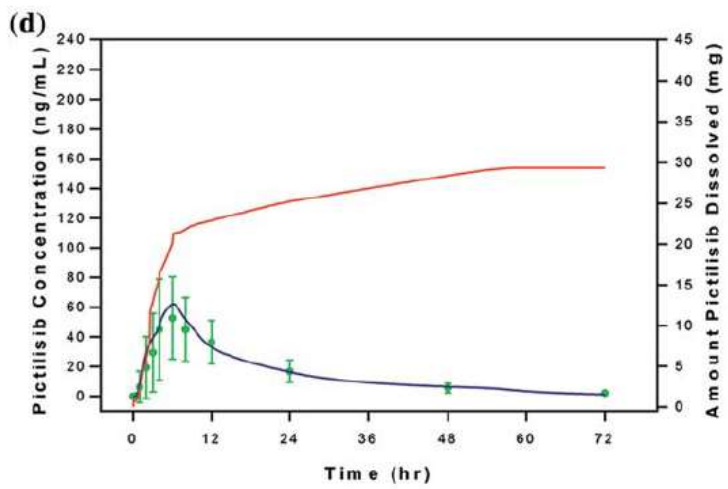
Segmental gastric changes

Time (hr)	STT (hr)	Gastric pH
0	100	4.9
0.5	3	2.8
2.5	1.5	1.3
4	2	4.9
6	1	1.3

Fed state



Fed state w/PPI (prospective prediction)



Segmental gastric changes

Time (hr)	STT (hr)	Gastric pH
0	100	5
0.5	3	5
2.5	1.5	2.9
4	2	5
6	1	2.9

Dashed lines represent 'bottom up' PBPK model results. Solid lines represent 'top down' PBPK model results. (Blue) curves are the plasma concentration-time profiles (left y-axis). Red curves are the simulated *in vivo* dissolution profiles (right y-axis)

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Summary

- 'Bottom up' MAM/PBPK modeling of pictilisib did not capture the observed clinical data under fasted or fed conditions
  - Tendency to supersaturate requires investigation of precipitation kinetics
- Gastrointestinal physiology changes due to presence of food are time dependent
  - Powerful deconvolution methods in GastroPlus™ can capture this with clinical data
- PPI interactions can be modeled through modifications to GI physiology
  - Studying degree of gastric pH elevation for different PPIs will improve prediction confidence
- MAM/PBPK model could be implemented to perform scenario simulations:
  - Sensitivity analysis at clinical dose level in patient group (results not shown)
  - Formulation strategies to mitigate PPI effect (results not shown)
- MAM/PBPK results confirm label recommendations

CONCLUSIONS

Conclusions & General Observations

- Applying both top-down (PopPK and PBPK) and bottom-up (PBPK) modeling approaches can leverage existing data sets and help prospectively answer questions
- Predictions of absorption-related DDIs requires clinical data and close evaluation of the physiological environment
  - Deconvoluting gastric emptying/pH changes vs. time provides clues
  - Population PBPK simulations which implement variability in gastric physiology can best capture expected range of PK endpoints
- Continued collaborations between departments and modeling groups will lead to:
  - Increased confidence in the direction/recommendations of a program
  - Improved opportunities to engage with regulatory agencies on proposed strategies

Acknowledgements

- Simulations Plus, Inc.
  - Grace Fraczkiewicz: Team Leader – Simulation Studies
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Thank you for your kind attention!

Questions?