Prediction of pH-Dependent DDI for Basic Drugs using Physiologically Based Biopharmaceutics Modeling: Industry Case Studies

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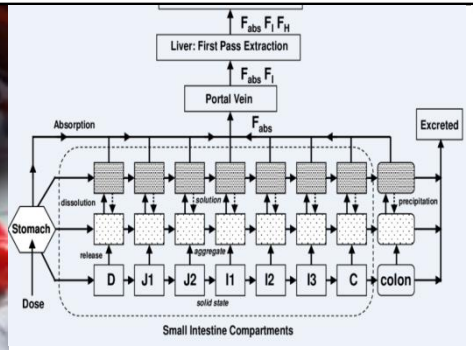
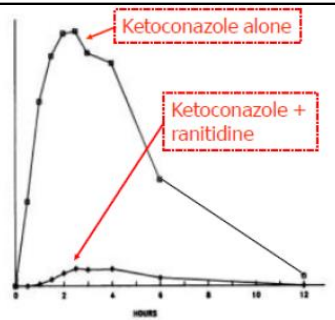




Overview

- Background to pH-dependent DDI
- Predicting the Effect of Acid Reducing Agents with PBBM
  - *Workflow for ARA prediction*
- Case Studies
- Future outlook
- Questions

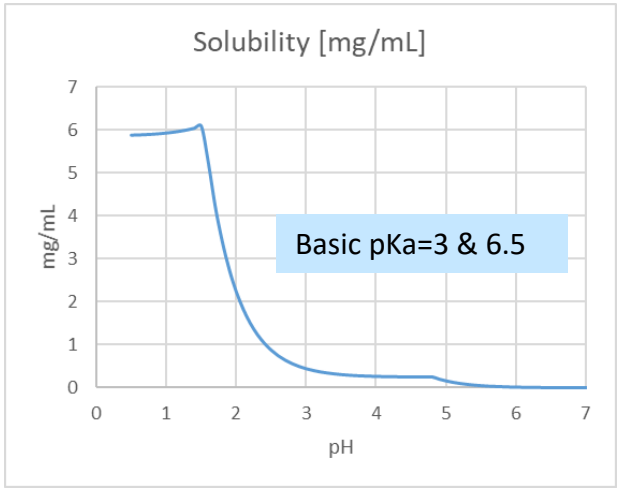
Background

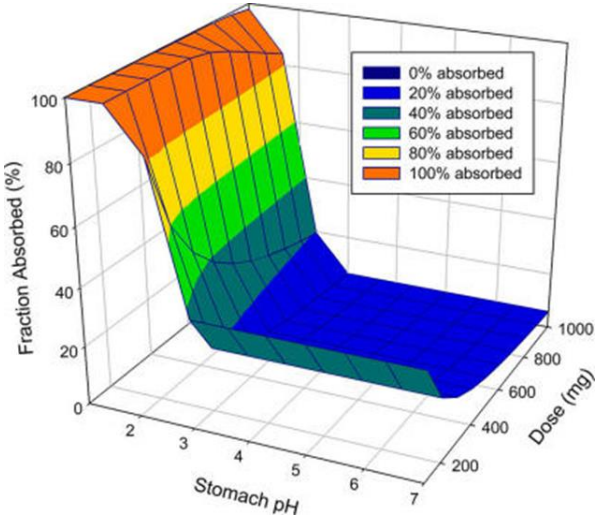
- PK DDIs can cause toxicity or poor efficacy
- Adverse drug events contribute to patient harm and healthcare costs*
- PBPK used to predict and manage metabolic DDIs and inform labels
- Absorption-related DDIs may equal the magnitude of metabolic DDI effects but PBPK is having less impact in this area

* up to $177.4 billion annually. Ernst and Grizzle. J Am Pharm Assoc (Wash), 2001. **41**(2): p. 192-9

The Effect of Acid Reducing Agents

- pH-dependent DDI may occur in the stomach when a poorly soluble weakly basic drug with pH dependent solubility is co-administered with an acid reducing agent (ARA) e.g. proton pump inhibitor (PPI), histamine 2 receptor antagonist (H2RA) or antacid





pH-dependent DDI for Poorly Soluble Weak Bases

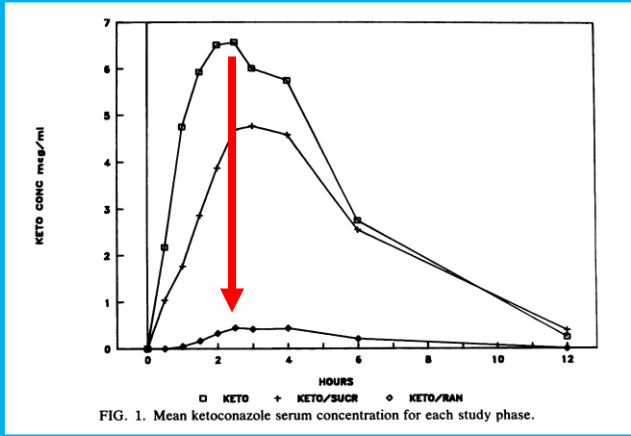
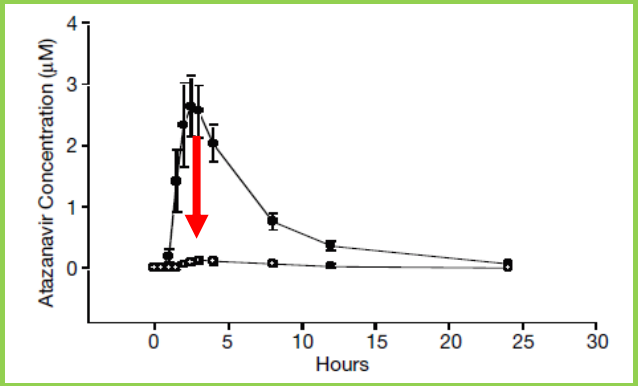


FIG. 1. Mean ketoconazole serum concentration for each study phase.

ketoconazole exposures↓ 95%
2 hours after ranitidine

Piscitelli, S.C., et al. (1991). *Effects of ranitidine and sucralfate on ketoconazole bioavailability.* Antimicrobial agents and chemotherapy. **35**(9): p. 1765-1771.



atazanavir exposures↓ 95%
after lansoprazole

Tomilo, D. L., et al. (2006). *Inhibition of Atazanavir Oral Absorption by Lansoprazole Gastric Acid Suppression in Healthy Volunteers.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 26(3): 341-346.

Impact on Label

2 DOSAGE AND ADMINISTRATION

General Dosing Recommendations:

- REYATAZ Capsules must be taken with food.
- Do not open the capsules.
- The recommended oral dosage of REYATAZ depends on the treatment history of the patient and the use of other coadministered drugs. When coadministered with H_2-receptor antagonists or proton-pump inhibitors, dose separation may be required [see *Dosage and Administration (2.1)*].

Table 13: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies[a] or Predicted Interactions (Information in the table applies to REYATAZ with or without ritonavir, unless otherwise indicated)

Concomitant Drug Class: Specific Drugs	Effect on Concentration of Atazanavir or Concomitant Drug	Clinical Comment
Proton-pump inhibitors: omeprazole	↓ atazanavir	Plasma concentrations of atazanavir were substantially decreased when REYATAZ 400 mg or REYATAZ 300 mg/ritonavir 100 mg once daily was administered with omeprazole 40 mg once daily, which may result in loss of therapeutic effect and development of resistance. ***In treatment-naive patients:*** The proton-pump inhibitor dose should not exceed a dose comparable to omeprazole 20 mg and must be taken approximately 12 hours prior to the REYATAZ 300 mg with ritonavir 100 mg dose. ***In treatment-experienced patients:*** Proton-pump inhibitors should not be used in treatment-experienced patients receiving REYATAZ.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021567s026lbl.pdf

Regulatory View

Applications of PBBM in Prediction of ARA Effect

Effect of Gastric pH on the Pharmacokinetics of a BCS Class II Compound in Dogs: Utilization of an Artificial Stomach and Duodenum Dissolution Model and GastroPlus,™ Simulations to Predict Absorption

SHOBHA N. BHATTACHAR,[1] EVERETT J. PER

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[2]Eli Lilly and Company, Drug Disposition, Lilly Research Laboratories, Indianapolis, Indiana 46285

Preclinical assessments of ARA

Using Absorption Simulation and Gastric pH Modulated Dog Model for Formulation Development To Overcome Achlorhydria Effect

Amitava Mitra,[*,†] Filippos K

Development of Improved Formulation

Drug Discovery—Development Interface

Prediction of ARA/PPI Drug-Drug Interactions at the Drug Discovery and

Stephanie Dodd [1], , , Hyungchul Kim [1], Qingshuo Meng [4], Stefania Beato [5], Tycho Heimbach [3]

De-risking compound selection

Virtual bioequivalence for achlorhydric subjects: The use of PBPK modelling to assess the formula lorhydria

Kosuke Doki[a,b,*], Adam S. ı Rostami-Hodjegan[a,c]

[a] Centre for Applied Pharmacokinetic Research, Division of Pharmacy & Optometry, University of Manchester, Manchester, UK
[b] Department of Pharmaceutical Sciences, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan
[c] Simcyp Limited (A Certara Company), Sheffield, UK

Investigation of BE

Characteristics of the Human Upper Gastrointestinal Contents in the Fasted State Under Hypo- and A-chlorhydric Gastric Conditions Under Conditions of Typical Drug – Drug Interaction Studies

Chara Litou [1] • Maria Vertzoni • Constantinos Goumas • Vassilis Vasdekis • Wei Xu • Filippos Kesisoglou • Christos Reppas [1]

Characterization of GI contents

Impact of Acid-Reducing Agents on Gastrointestinal Physiology and Design of Biorelevant Dissolution Tests to Reflect These Changes

Domagoj Segregur [1], Talia Flanagan , James Mann , Andrea Moir , Eva M. Karlsson [4], Matthias Hoch [5], David Carlile [5], Sakina Sayah-Jeanne [6], Jennifer Dressman [1,*]

Proposed biorelevant media

Assessment of Bioequivalence of Weak Base Formulations Under Various Dosing Conditions Using Physiologically Based Pharmacokinet ons. Case Examples: Ketoconazole and Posaconazole

Rodrigo Cristofoletti [1,2], Nikunjkumar Patel [3], Jennifer B. Dressman [2,*]

Understanding variability

Journal of Pharmaceutical Sciences

Article in Press

janssen | Pharmaceutical Companies of Johnson & Johnson | Roche

Prediction of pH-Dependent Drug-Drug Interactions for Basic Drugs using Physiologically based Biopharmaceutics Modeling: Industry Case Studies

Amitava Mitra[1], Neil Parrott[2], Neil Miller[3], Richard Lloyd[4], Christophe Tistaert[5], Tycho Heimbach[6], Yan Ji[7], Filippos Kesisoglou[8,*]

PlumX Metrics

DOI: https://doi.org/10.1016/j.xphs.2019.11.017

7 Case Studies from 5 Pharmaceutical Companies

Key Input Parameters of Compounds

Parameter	Molecule 1	Etoricoxib	JNJ-X	Danirixin		GSK1	Erlotinib	Ribociclib
Molecular weight	356.4 g/mol	358.9 g/mol	434 g/mol	441.9 g/mol		463.5 g/mol	393.45 g/mol	434.55 g/mol
Log P	3.58	2.28 (log D, pH 7.0)	3.03	3.45		6.52	2.7	1.954
pKa		4.5 (base)	3.8 (base)	4.8 (acid), 8.1 (base)		9.96 (base) 2.95 (base)	5.65 (base)	8.6 (base) 5.5 (base)
BCS Class	2	2	4	4		2/4	2	4
pH – solubility profile (mg/mL)	5.75 (pH 1.2) 1.25 (pH 2.1) 0.48 (pH 3.0) 0.012 (pH 4.0) 0.005 (pH 6.0) 0.005 (pH 8.0)	25.1 (pH 2.0) 2.01 (pH 3.1) 0.70 (pH 3.5) 0.3 (pH 4.0) 0.14 (pH 4.5) 0.09 (pH 5.0) 0.08 (pH 5.5) 0.05 (pH 6.9)	6.2 (pH 1.3) 0.23 (pH 4.9) 0.31 (pH 6.5, FaSSIF) 0.64 (pH 5.0, FeSSIF)	Freebase 0.601 (pH 2.0) 0.021 (pH 4.0) 0.004 (pH 6.0) 0.005 (pH 8.0) 0.715 (SGF, pH 1.2) 0.009 (FaSSIF, pH 6.5) 0.019 (FeSSIF, pH 5.0)	HBr salt 0.605 0.685 0.194 0.052 0.757 0.459 0.724	32 (SGF) 4.3 (pH 2.0) 0.7 (pH 4.0) 0.05 (pH6.0) 0.02 (pH 7.0) 0.02 (pH 8.0)	0.6 (pH 2.5) 0.32 (pH 3.4) 0.015 (pH 5.0) 0.0058 (pH 6.5) 0.0085 (FaSSIF, pH 6.4) 0.0533 (FeSSIF, pH 5)	2.4 (≤pH 4.5) 0.8 (pH 6.8) 0.3 (pH 7.5) 2.4 (FaSSIF, pH 6.5) 2.2 (FeSSIF, pH 5.0)
Dose	50 mg	120 mg	1000 mg	100 mg	50 mg	100 mg	150 mg	600 mg
Effective human permeability (cm/sec)	3.25×10^{-4}	4.75×10^{-4}	0.4×10^{-4}	0.91×10^{-4}		0.8×10^{-4}	4.32×10^{-4}	0.9×10^{-4}
Permeability Source	Rat Intestinal Perfusion	Caco-2	MDR1-MDCKII	ADMET Predictor		Fit to Cp-time profile	Caco-2	
Precipitation time (sec)	900	10000	14872	90000 (freebase) 900 (HBr salt)		900	900	900
Particle size (radius)	d10 = 10 µm d50 = 20 µm d90 = 40 µm	20 µm (mean)	d50 = 5 µm	0.9 µm (mean, freebase) 5.7 µm (mean, HBr salt)		25 µm (mean)	d50 = 27 µm	60 µm (mean)
Disposition model parameters	Vc = 0.299 L/kg CL = 0.034 L/hr/kg	Vc = 0.507 L/kg CL = 0.046 L/h/kg V2 = 1.132 L/kg k_{12} = 0.617 1/h k_{21} = 0.276 1/h Elimination t1/2 = 26.7 hr	N/A (fraction absorbed was simulated)	Vc = 0.082 L/kg V_{max} = 0.013 mg/s K_m = 0.214 mg/L k_{12} = 0.221 1/h k_{21} = 0.173 1/h		Perfusion limited PBPK model for distribution Mean CLsys = 2.2 L/h	Vc = 0.826 L/kg CL = 0.15 L/h/kg V2 = 1.138 L/kg Vmax = 4.47E-4 mg/s Km = 0.232 µg/mL k_{12} = 0.182 1/h k_{21} = 0.132 1/h	Vc = 5.0 L/kg CL = 0.596 L/h/kg k_{12} = 0.07 1/h k_{21} = 0.041 1/h

Workflow for Prediction of ARA effect for BCS 2/4 Compounds

Criteria Supporting the Reliability of PBBM Simulation for Acid Reducing Agents (ARAs)

- Mechanism of interaction related primarily to changes in gastric pH (i.e. no chelation effects and/or metabolic interaction between API and ARA)
- Clinical data under normal dosing conditions available for model verification
- Free form of the API is used in a conventional dosage form (may be more difficult to model formulations containing salts or acidulants)

Predict likelihood of ARA effect pre-FIH

1. Physicochemical properties (full pH solubility, biorelevant solubility) and In Vitro/Preclinical data as Input

Develop and validate PBBM

1. Physicochemical properties and/or dissolution data
2. Clinical PK, when available from FIH (& IV data if available)
3. Simulate with default physiology & verify vs. observed data
4. Optimize model

Predict ARA effect

1. Apply validated human model adjusting for pH effect of ARA (e.g. pH 4-5 for PPIs in fasted conditions)
2. Due to variability in ARA effect, conduct PSA across the physiological pH range
3. If possible, verify model against clinical experience (e.g. if dedicated ARA study available or if popPK model available demonstrating clinically relevant covariate effect on AUC &/or C_{max})

Apply Developed Model

1. If significant effect predicted, conduct dedicated ARA study and verify model. If needed further optimize model (repeat step 2)
2. If no significant effect predicted, consider whether model can be used to inform label
3. Use model to inform impact of future formulation changes as needed

CASE STUDIES

Alectinib

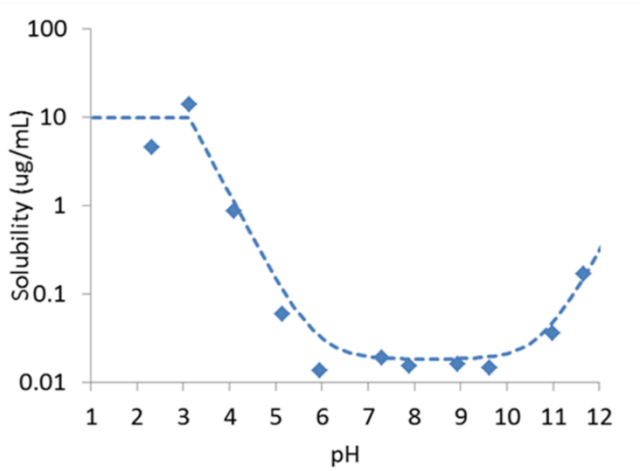
Table S1. Summary of published case studies on the application of PBBM in prediction of ARA effect

Property	**Value**
logD	1.96 at pH 3.575
pKa	7.05 base
Permeability	2.5 *10-4 cm/s
Kinetic solubility of granules in clinical capsules measured at 37° C in 50 mL of biorelevant media after 4 hours stirring with a paddle speed of 50 rpm . Five milligram of RO5424802 was applied.	FaSSIF (23 µg/mL) FeSSIF (77 µg/mL)
Clinical Dose	600 mg

Physiologically Based Absorption Modeling to Explore the Impact of Food and Gastric pH Changes on the Pharmacokinetics of Alectinib

Neil J Parrott,[1,5] Li J Yu,[2] Ryusuke Takano,[3] Mikiko Nakamura,[4] and Peter N. Morcos[2]

The AAPS Journal (2016)



Model Changes for PPIs

- Fasting gastric pH increased to 4.5
- Postprandial gastric pH increased to 6.5

Fasted pH	Compartment	Fed pH
4.5 → 1.30	Stomach	6.5 → 4.90
6.00	Duodenum	5.40
6.20	Jejunum 1	5.40
6.40	Jejunum 2	6.00
6.60	Ileum 1	6.60
6.90	Ileum 2	6.90
7.40	Ileum 3	7.40
6.40	Caecum	6.40
6.80	Asc Colon	6.80

Prediction

- Negligible effect of elevated gastric pH predicted
  - Very limited dissolution in the stomach irrespective of pH
  - Solubility of alectinib at normal healthy gastric pH << 2.4 mg/mL (the value needed for complete dissolution of the dose in a glass of water (600 mg dose / 250 mL))
- Solubility decreases with increased gastric pH have little effect
- This prediction was useful to design pivotal study w.r.t. patient exclusion criteria
- Prediction was later confirmed by clinical study

Potential to use PBBM to waive clinical study

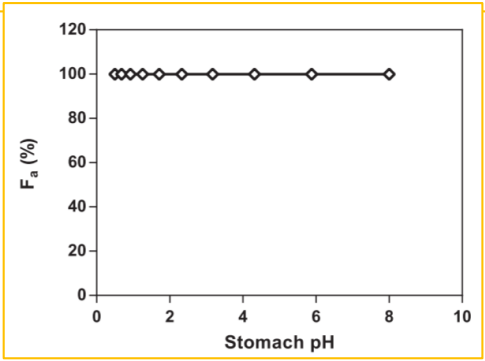
PBBM simulations supplemented with PopPK analyses may lead to waiving of dedicated PPI clinical pharmacology trials

Ribociclib Bioavailability Is Not Affected by Gastric pH Changes or Food Intake: *In Silico* and Clinical Evaluations

Tanay S. Samant[1], Shyeilla Dhuria[2], Yasong Lu[1], Marc Laisney[3], Shu Yang[1], Arnaud Grandeury[3], Martin Mueller-Zsigmondy[3], Kenichi Umehara[3], Felix Huth[3], Michelle Miller[1], Caroline Germa[1] and Mohamed Elmeliegy[1]

Case Study 2: etoricoxib
Case Study 5: GSK-1
Case Study 7: Ribociclib

lack of pH sensitivity across the pH range 2-8.



Pabinostat FDA Review

" Model simulations suggested the lack of effect of elevating gastric pH on panobinostat oral absorption and PK. No dedicated clinical study pursued"

Case Study 3: JNJ-X

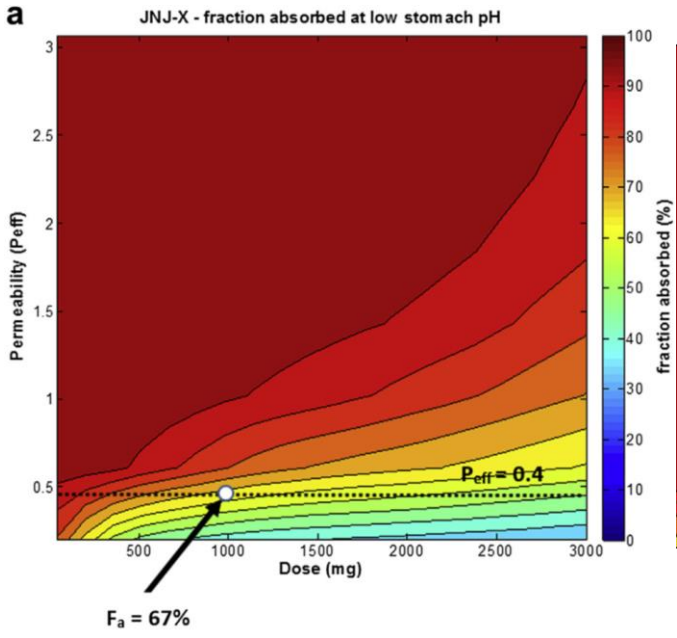
A BCS class 4 weakly basic compound with intermediate lipophilicity and pKa of 3.8 given at a high dose

Parameter	JNJ-X
Molecular weight	434 g/mol
Log P	3.03
pKa	3.8 (base)
BCS Class	4
Solubility (mg/mL)	6.2 (pH 1.3) 0.23 (pH 4.9) 0.31 (pH 6.5, FaSSIF) 0.64 (pH 5.0, FeSSIF)
Dose	1000 mg
Peff (cm/sec)	0.4×10^{-4}
Precipitation time (sec)	14872

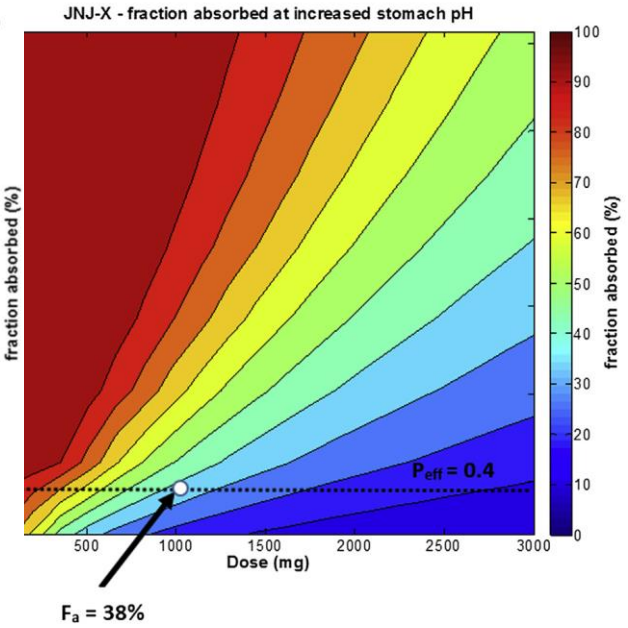
Case Study 3: Early risk evaluation

3D PSA varying Dose, Peff & pH

pH 1.3



pH 5.0



DDI liability confirmed by clinical PPI study

Demonstrates value of PBBM for PPI liability in early development

PBBM models verified with PPI data might be used to waive studies after formulation changes

Case Study 6: Erlotinib

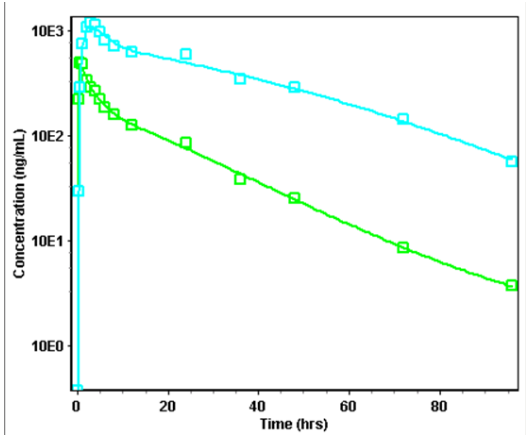
- Lipophilic with high permeability and low solubility
- CYP3A4 & CYP1A2 substrate
- The effect of omeprazole and ranitidine on erlotinib has been studied clinically. Modelling was done retrospectively

Parameter				
$logP_{(O/W)}$	2.7			
pk_a	5.65			
fu	0.046			
B/P	0.55			
Permeability (cm/s)	caco-2 $33.6x10^{-6}$ -> human Peff $4.3x10^{-4}$			
Buffer solubility at different pH (mg/ml)	pH	mg/mL		
	2.5	0.6		
	3.4	0.32		
	5	0.0145		
	6.5	0.0058		
Biorelevant solubility at 37°C (mg/ml)	Media	start pH	end pH	mg/mL
	FaSSIF	6.5	6.4	0.0085
	FeSSIF	5	5	0.0533

Step 1: Disposition Model

- Mean Cp(t) for IV and PO crossover study 150-mg tablet vs 25-mg 30 minute intravenous infusion in 20 healthy mainly female subjects
- 2 compartmental model with **nonlinear clearance** fit gives best fit
- Bioavailability estimated with saturable clearance is **59%** vs 106% based on a simple non-compartmental analysis

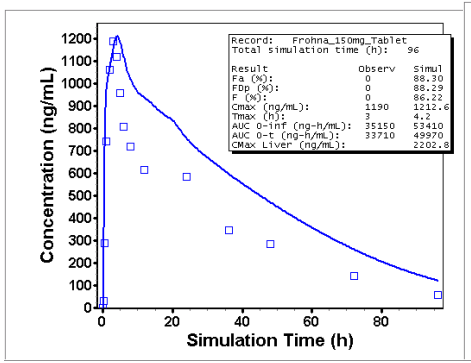
nonlinear model fit in PKPlus

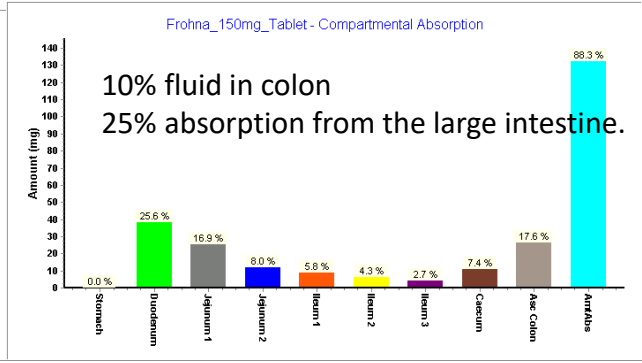


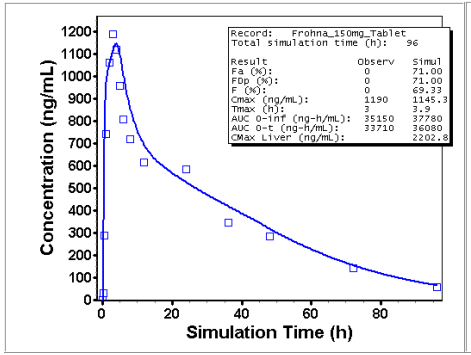
Vc/kg=	0.826	L/kg	CV= 26%
CL2/kg=	0.150	L/h/kg	CV= 54%
V2/kg=	1.138	L/kg	CV= 33%
Vmax =	**4.47E-4**	**mg/s**	**CV= 53%**
Km =	**0.232**	**µg/mL**	**CV= 77%**
K12 =	0.182	1/h	CV= 60%
K21 =	0.132	1/h	CV= 63%
Tlag =	0.228	h	CV= 19%
Ka =	0.731	1/h	CV= 53%
F =	**59.27**	%	CV= 19%

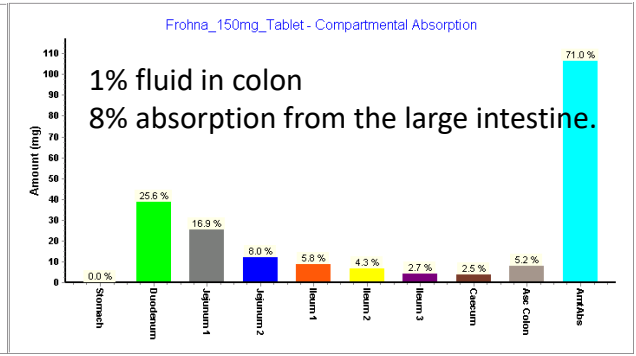
Step 2: Oral Tablet Simulation (Fasted State)

- Vmax and Km transferred to the enzyme table accounting for changed units and free fraction in plasma
- Default model simulation over estimates observed Cp(t)
- Reduction in %fluid colon improves match



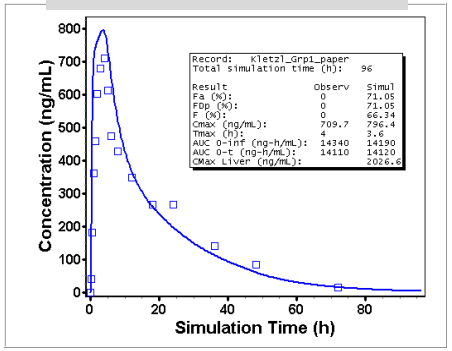




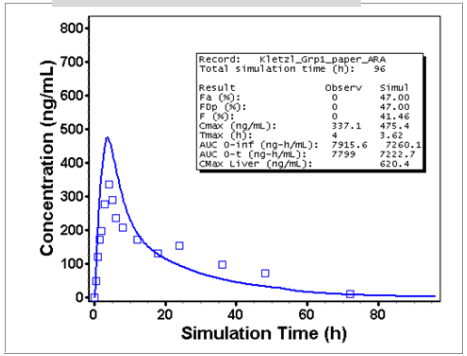


Step 3: Simulation with/without ARA

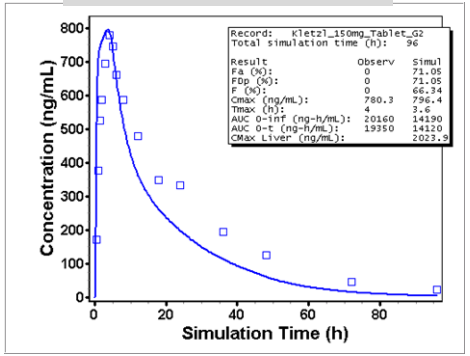
Without omeprazole



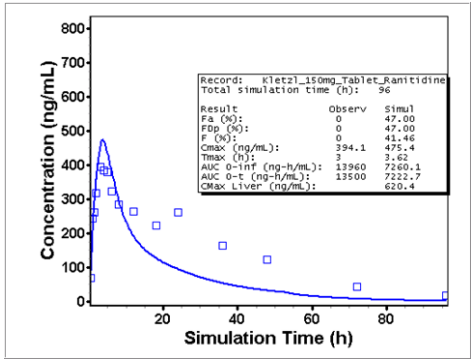
With omeprazole



Without ranitidine



With ranitidine

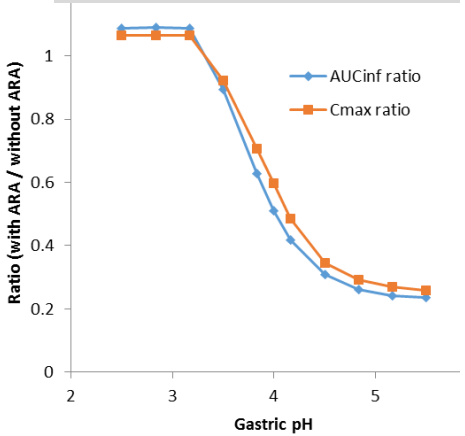


- Stomach pH changed from 1.3 to 4.0
- Gastric transit increased from 0.25h to 0.5h

AUCinf	omeprazole	ranitidine
Observed	54%	67%
Simulated	51%	51%

Cmax	omeprazole	ranitidine
Observed	39%	46%
Simulated	60%	60%

Sensitivity to gastric pH



Erlotinib Conclusions

- PBBM indicates high risk of pH-dependent DDI
- Precise prediction of extent of effect is challenging
  - Complex non-linear PK
  - HCl salt dosed
  - Uncertainty in colonic absorption
  - High sensitivity to gastric pH in range 3 – 5
- Model verification with clinical data recommended
- Subsequent application of a verified PBBM for waiver can be envisaged
  - Formulation changes
  - Different patient populations

PBBM for ARA DDI Risk & Formulation Development

- PBBM should play a role in integrating physicochemical, in vitro, in vivo and physiological data into a mechanistic framework to yield fuller understanding of pH dependent DDIs
- A bottom-up approach and PSA is useful for early internal decisions
- Multiple PBBM examples support the value during clinical development
- Wider application to streamline drug development and waive unnecessary studies is warranted

Acknowledgements

- Co-authors – Neil Miller (GSK), Richard Lloyd (GSK), Christophe Tistaert (Janssen), Tycho Heimbach (Novartis), Filippos Kesisoglou (Merck)

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