SimulationsPlus

Clinical Pharmacology Guidances

Advancing Drug Development and Regulatory Assessment: Role and Opportunities

Xavier Pepin

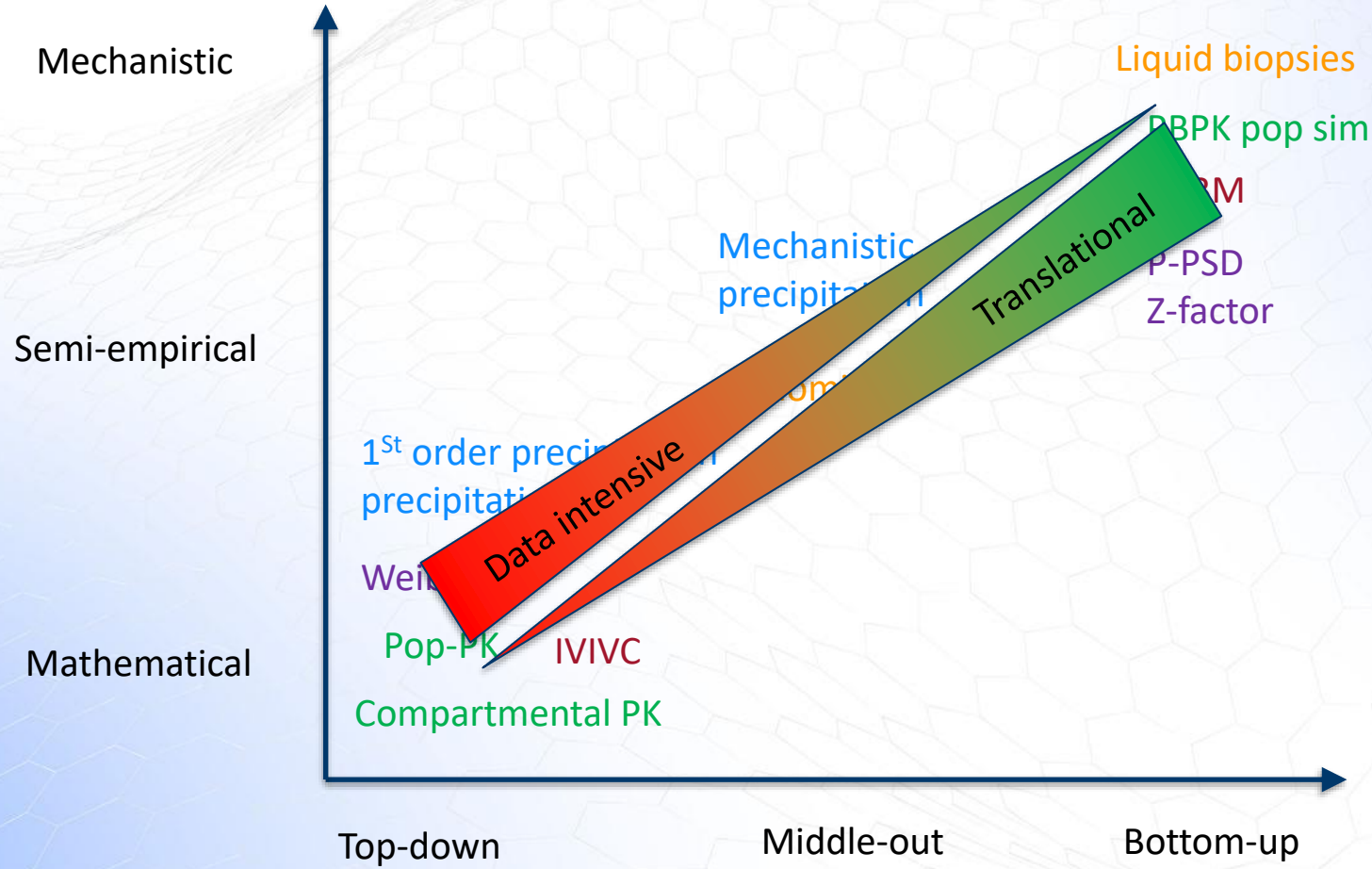
Modeling and simulation lifecycle considerations

9th May 2024

Outline

- Use of M&S tools throughout the drug development process
- Overview of clinical pharmacology (and related) guidances
  Easy wins for more M&S contribution
- Where do we stand on pH-related DDI, food effect predictions and formulation development
- Take home messages

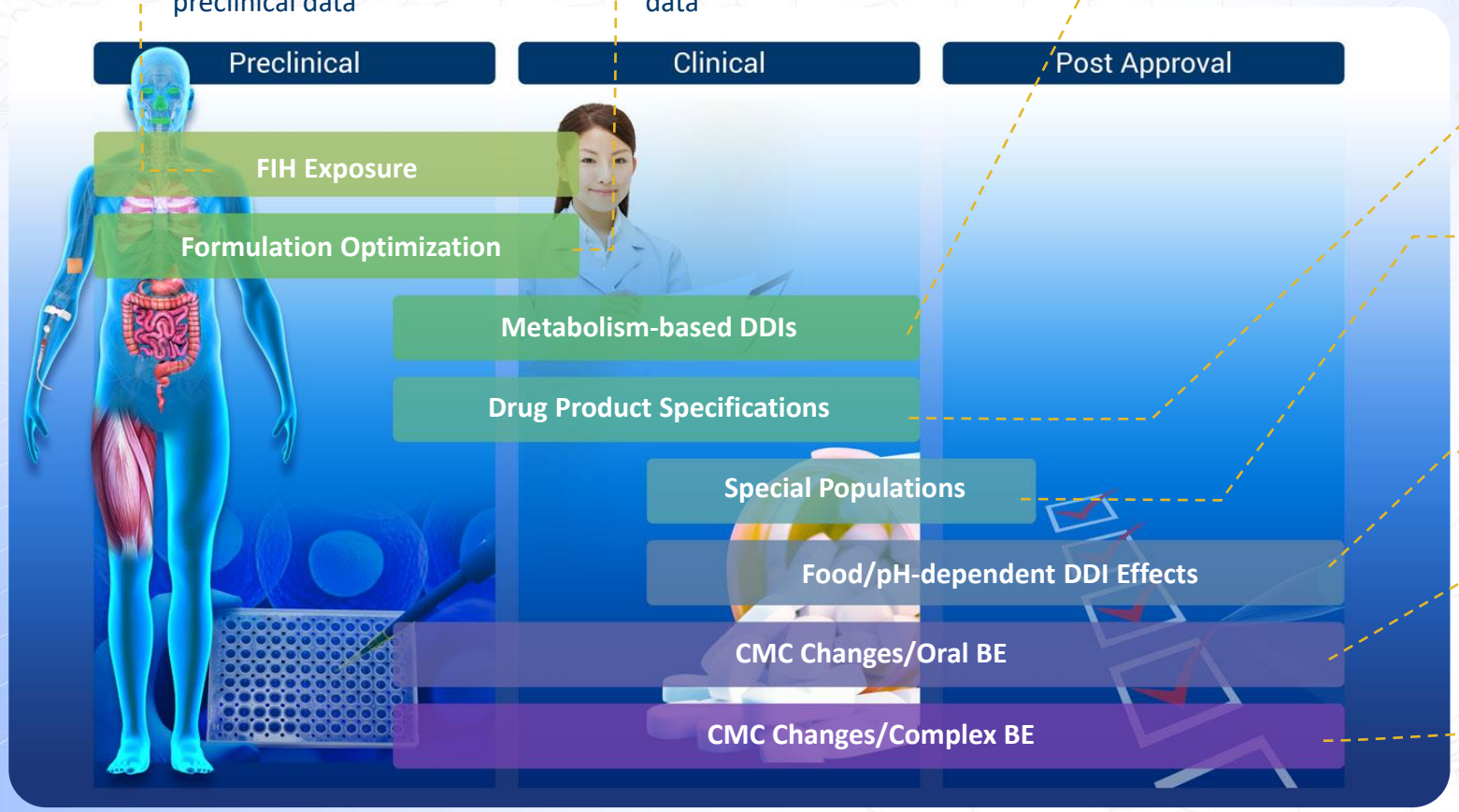
MIDD : How tools classify?



Precipitation
Dissolution (vivo)
Distribution-metabolism
Omics
Biopharmaceutics

Use mechanistic models when required (objective of the model)
→ Wider applicability
→ Less data intensive

Use of PBPK-PBBM along the drug development



FIH dose selection and clinical development plans based on preclinical data

Support for optimal formulation selection based on preclinical data

Predictions of DDI liability; DDI study design support and biowaiver plans

Development of biopredictive dissolution methods and drug product specifications

Simulations to support dose adjustments in special populations and related product labelling

Design studies and biowaiver plans

Design of BE studies and biowaiver plans for oral route of administration

Design of BE studies and biowaiver plan for complex products

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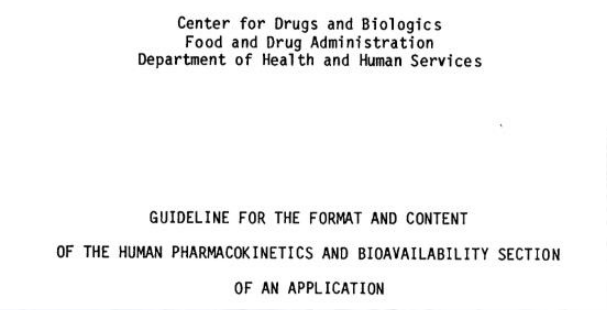
Selected Guidelines : Place of PBPK-PBBM

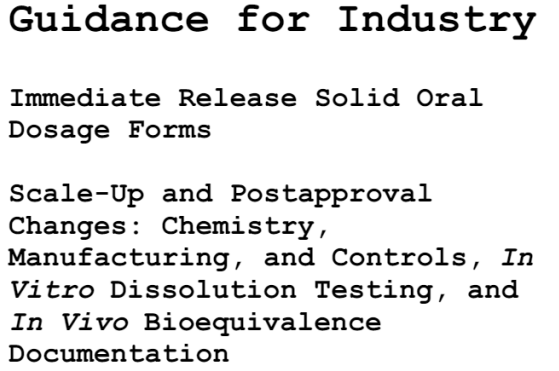
A [redacted] 1987



Center for Drugs and Biologics
Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR THE FORMAT AND CONTENT
OF THE HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION
OF AN APPLICATION

B [redacted] 1995

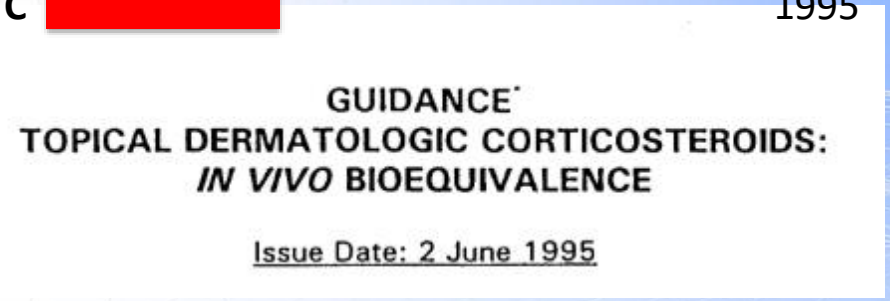


Guidance for Industry

Immediate Release Solid Oral Dosage Forms

Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation

C [redacted] 1995



GUIDANCE
TOPICAL DERMATOLOGIC CORTICOSTEROIDS:
IN VIVO BIOEQUIVALENCE

Issue Date: 2 June 1995

D [redacted] 1997

Guidance for Industry

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

E [redacted] 1997

Guidance for Industry

Dissolution Testing of Immediate Release Solid Oral Dosage Forms

F [redacted] 1997

Guidance for Industry

SUPAC-MR: Modified Release Solid Oral Dosage Forms

Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation

A: https://www.fda.gov/media/71286/download
B: https://www.fda.gov/media/70949/download
C: https://www.fda.gov/media/70931/download
D: https://www.fda.gov/media/70939/download
E: https://www.fda.gov/media/70936/download
F: https://www.fda.gov/media/70956/download

PBPK-PBBM quantitative use is mentioned

PBPK-PBBM is recognized useful but not to waive clinical evaluation

PBPK-PBBM is not mentioned

Selected Guidelines : Place of PBPK-PBBM

G 2003

Guidance for Industry

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

H 2003

Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

I 2013

Guidance for Industry

Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling

J 2016

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

K 2018

Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

L 2018

Physiologically Based Pharmacokinetic Analyses — Format and Content

M 2020

The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

G: https://www.fda.gov/media/70867/download
H: https://www.fda.gov/media/71277/download
I: https://www.fda.gov/media/84923/download
J: https://www.fda.gov/media/88622/download
K: https://www.fda.gov/media/92988/download
L: https://www.fda.gov/media/101469/download
M: https://www.fda.gov/media/142500/download

PBPK-PBBM quantitative use is mentioned

PBPK-PBBM is recognized useful but not to waive clinical evaluation

PBPK-PBBM is not mentioned

Selected Guidelines : Place of PBPK-PBBM

N 2020

Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions

O 2021

M9 Biopharmaceutics Classification System-Based Biowaivers

P 2022

General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products

Q 2022

Bioavailability Studies Submitted in NDAs or INDs — General Considerations

R 2022

Population Pharmacokinetics

S 2022

Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations

T 2023

Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

N: https://www.fda.gov/media/134581/download
O: https://www.fda.gov/media/148472/download
P: https://www.fda.gov/media/129532/download
Q: https://www.fda.gov/media/121311/download
R: https://www.fda.gov/media/128793/download
S: https://www.fda.gov/media/121313/download
T: https://www.fda.gov/media/166156/download

PBPK-PBBM quantitative use is mentioned

PBPK-PBBM is recognized useful but not to waive clinical evaluation

PBPK-PBBM is not mentioned

Easy wins for update: Pre-2000 guidances

- SUPAC-IR, SUPAC-MR, Dissolution testing of IR formulations
  - f_1/f_2, replace/supplement criteria with safe space definition using PBBM, identifying the main CQAs and failure modes for drug product dissolution
  - Dissolution method biopredictive nature could be justified using PBBM and clinically relevant specifications should be set within the safe space
  - Post approval changes could be critically analyzed in terms of impact on dissolution and type of excipient. PBBM can be used in some conditions to support these changes

- IVIVC guideline
  - Consider integration of IR or MR product dissolution in PBBM: capture effect of first pass degradation, metabolism or active transport

- Non-oral, non-systematically active
  - PBBM could be applied to non-oral non-systemically acting drugs with PK-PD + appropriate marker for additional validation

Easy wins for guidance update

2018

Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances

"Additional supportive information could include appropriate in silico modeling in addition to dissolution performance data"

PBBM application could be introduced to define safe space using mechanistic models for dissolution. Scope could also be extended to low solubility products

2021

M9 Biopharmaceutics Classification System-Based Biowaivers

Many drug products belong to more than one category (e.g., depending on dose). PBPK-PBBM could be used to confirm classification using sensitivity analyses or use across class

Easy wins for guidance update

2022

Bioavailability Studies Submitted in NDAs or INDs — General Considerations

Reference made to “IVIVC” only

PBBM could be introduced since it outperforms classical IVIVCs and allows to explain saturable mechanism post release + is applicable to IR on top of MR

2022

Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations

2023

Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

Focus on food effect and pH-related DDI prediction with PBPK-PBBM

Outline

- Use of M&S tools throughout the drug development process
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  Easy wins for more M&S contribution
- Where do we stand on pH-related DDI, food effect predictions and formulation development
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pH-related DDI – Is it only pH ?

ARAs show different interaction potential

[1]		Absorption		Metabolism via Cytochrome P450 System						Transport Systems		Excretion
		Gastric pH-dependent interaction	Chelation	CYP1A2	CYP2A6	CYP2C9	CYP2C19	CYP2D6	CYP3A4	OCT 2	P-gp	Urine Alkalization
Antacid	Sodium bicarbonate	✓										✓
	Calcium carbonate	✓	✓									✓
	Aluminum hydroxide	✓	✓									✓
	Magnesium hydroxide	✓	✓									✓
H2RA	Cimetidine	✓		x			x	x	x	x		
	Ranitidine	✓		s			s	s		x		
	Famotidine	✓								x		
	Nizatidine	✓										
PPI	Omeprazole	✓		i	s	s	×, S'	s	s		x	
	Esomeprazole	✓					×, S'		s			
	Lansoprazole	✓		i		s	s		s		x	
	Dexlansoprazole	✓					s		s			
	Pantoprazole	✓					S'		s		x	
	Rabeprazole	✓					S'		S'			

Legend:

x	Inhibitor
i	Inducer
S'	Major substrate
s	Minor substrate
✓	Elicits pathway

Antacids: Complexation and acid-base reactions

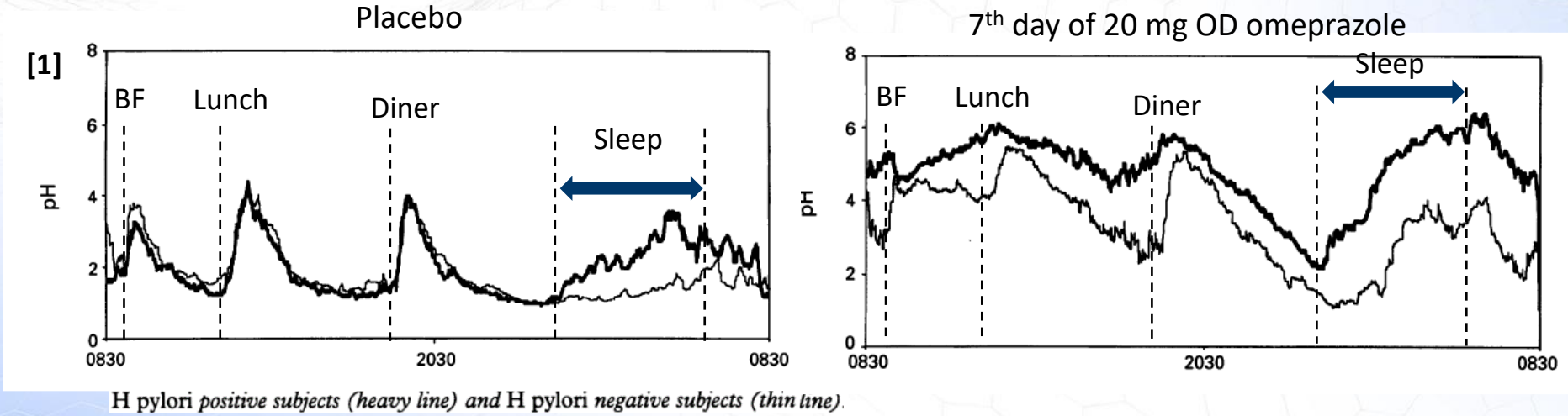
Enzyme-transporter DDI to check

1.Patel, D., et al., A Systematic Review of Gastric Acid-Reducing Agent-Mediated Drug–Drug Interactions with Orally Administered Medications. Clinical Pharmacokinetics, 2020. 59(4): p. 447-462.

pH-related DDI : Mechanisms well incorporated in PBBM

Impact of pH increase

- Predictable : Careful to integrate surface pH for acids, bases and their salts
- Time dependence and co-administration with food (simulation staged administration)



In vitro solubility/dissolution able to capture effect of Antacids, H2RA and PPI [2]

Formulation effects understood [3]

1: Verdú, E. F., et al. (1995). "Effect of Helicobacter pylori status on intragastric pH during treatment with omeprazole." Gut 36(4): 539-543.
2: Segregur, D., et al., Impact of Acid-Reducing Agents on Gastrointestinal Physiology and Design of Biorelevant Dissolution Tests to Reflect These Changes. Journal of Pharmaceutical Sciences, 2019. 108(11): p. 3461-3471.
3: Badawy, S.I., et al., Formulation of solid dosage forms to overcome gastric pH interaction of the factor Xa inhibitor, BMS-561389. Pharm Res, 2006. 23(5): p. 989-96.

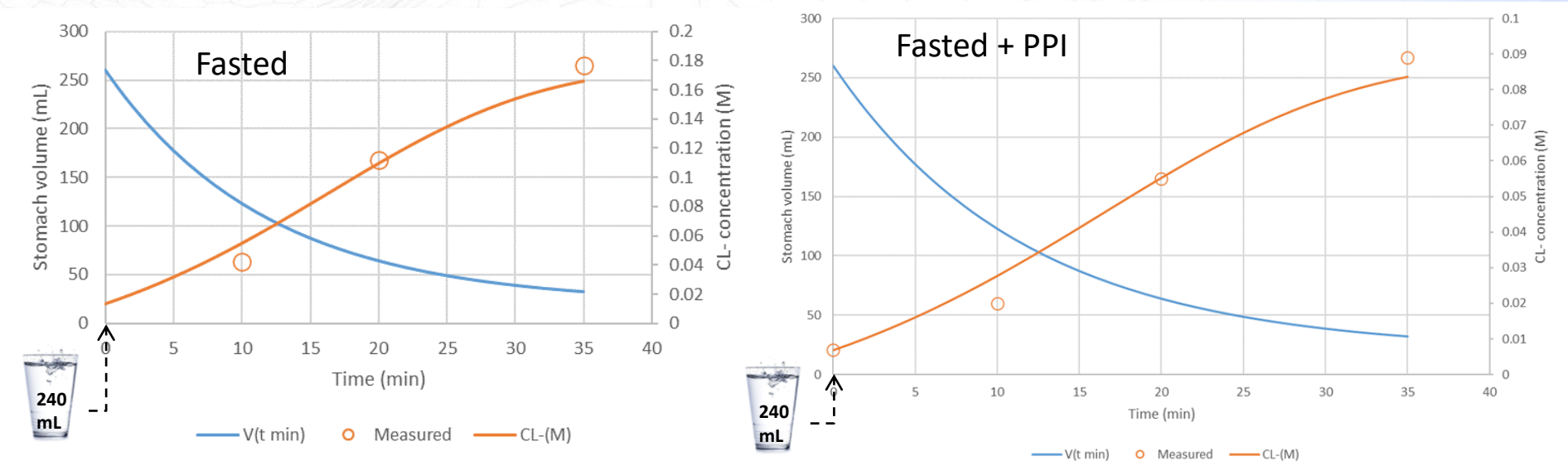
PPI and H2RA reduce secretions

$$K_S = |BH^+| \times |Cl^-|$$

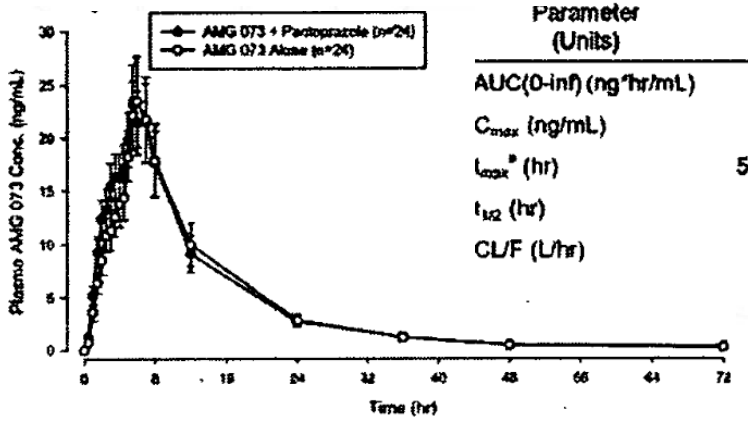
For HCl-salts, solubility can be depressed by luminal chloride concentration

Chloride

- Natural anion highly concentrated in the gastric juice (0.18M) [1,2]
- Common ion to many pharmaceutical salts (HCl)
- Diluted during water administration and secretion depressed (by a factor 2) after H2RA or PPI administration [2]



PPIs reduce chloride concentration and boosts HCl-salts solubility

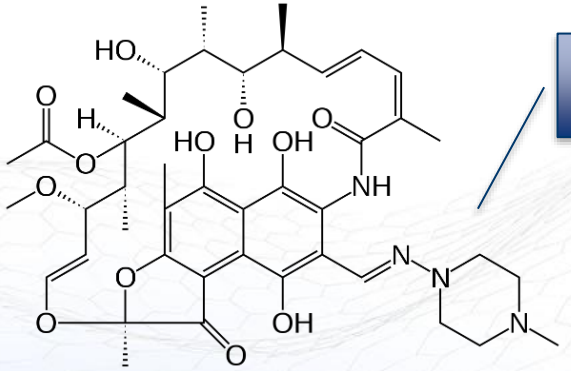


Parameter (Units)	Cinacalcet + Pantoprazole (n = 24)	Cinacalcet Alone (n = 24)
AUC(0-inf) (ng*hr/mL)	305 (252)	294 (256)
C_{max} (ng/mL)	25.8 (18.4)	26.5 (20.9)
t_{max} [a] (hr)	5.50 (2.00-12.0)	5.50 (2.50-12.0)
$t_{1/2}$ (hr)	11.2 (8.91)	9.42 (7.38)
CL/F (L/hr)	614 (628)	632 (802)

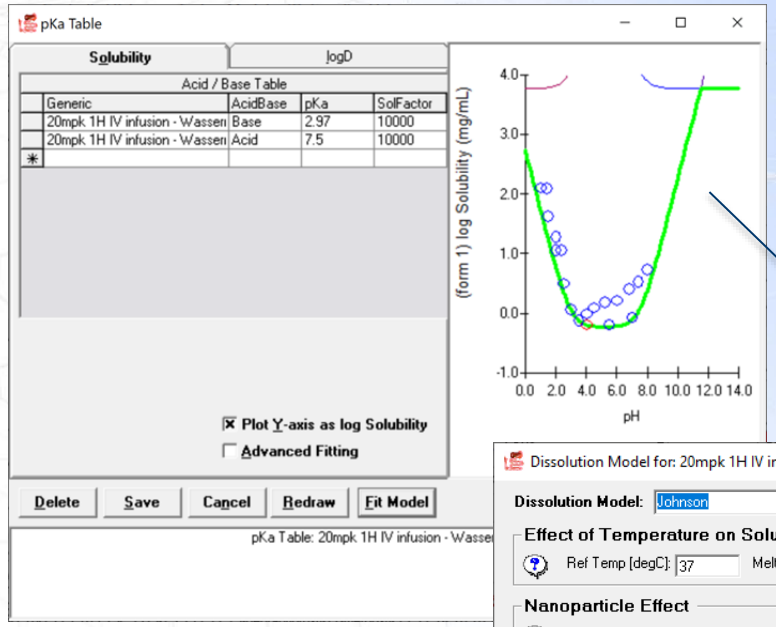
1: Strong, J.A., D. Cameron, and M.J. Riddell, THE ELECTROLYTE CONCENTRATION OF HUMAN GASTRIC SECRETION. Quarterly Journal of Experimental Physiology and Cognate Medical Sciences, 1960. 45(1): p. 1-11.
2:Litou, C., et al., Characteristics of the human upper gastrointestinal contents in the fasted state under hypo-and A-chlorhydric gastric conditions under conditions of typical drug–drug interaction studies. Pharmaceutical research, 2016. 33(6): p. 1399-1412.
3: Study 20010207 - https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-688.pdf_Sensipar_BioPharmr.pdf

Case study : Rifampicin

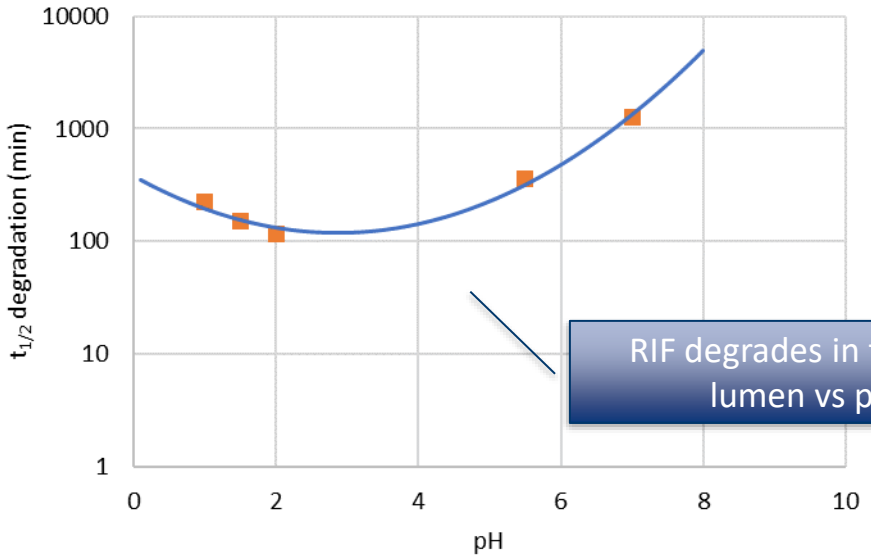
Solubility, luminal degradation and first pass extraction



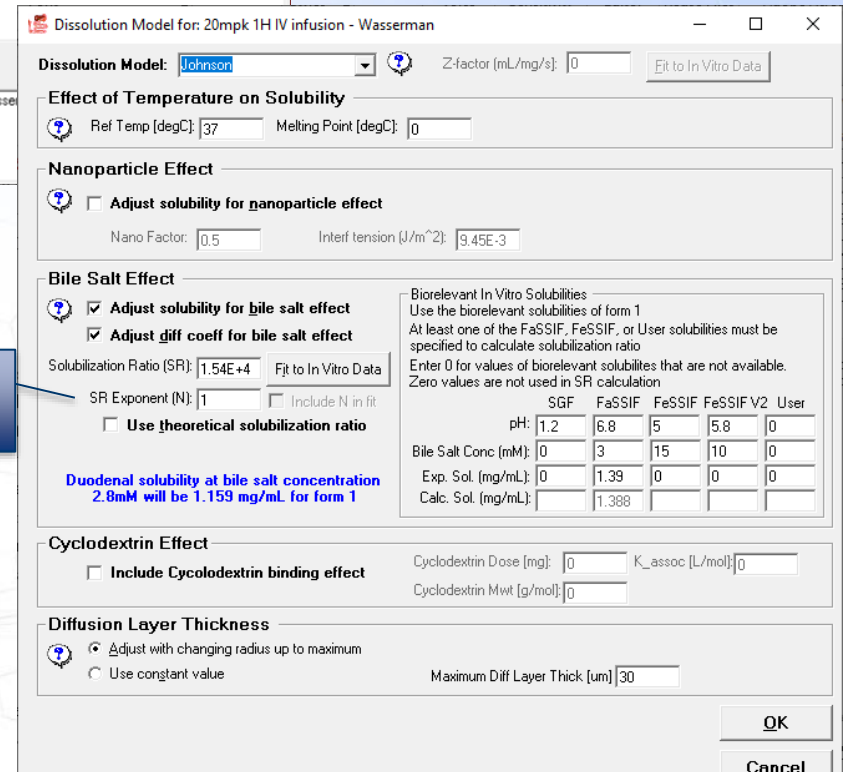
Rifampicin (RIF) is a BCS class 2 drug



RIF solubility vs pH



RIF degrades in the gut lumen vs pH



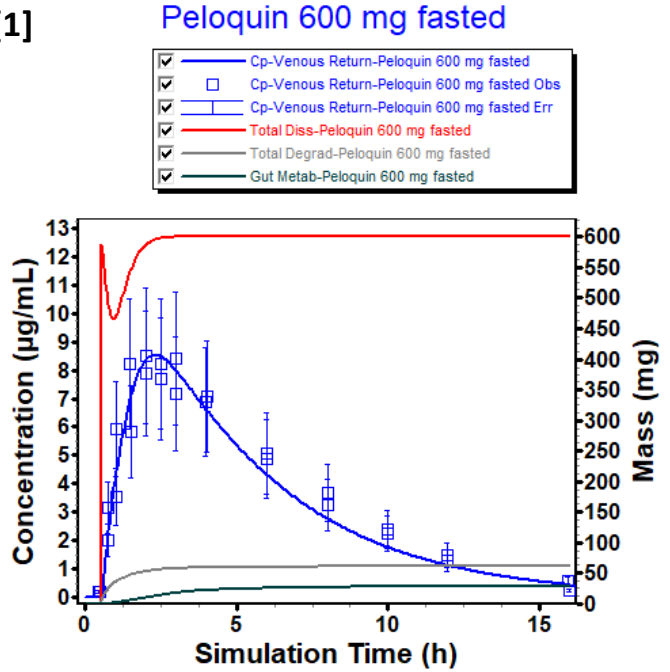
Effects of bile salts

Generic	Enzyme	Location	Data Source	Vmax (mg/s) or (mg/s/mg-enz)	Km (mg/L)	Metabolite	Met_Parer
20mpk 1H IV infusion - Wasse	3A4	Gut	Microsomes	0.014	14.12	NONE	1
20mpk 1H IV infusion - Wasserm	3A4	PBPK	Microsomes	0.000406	14.12	NONE	1
20mpk 1H IV infusion - Wasserm	CES2	Gut	Microsomes	0.014	14.12	NONE	1
20mpk 1H IV infusion - Wasserm	CES2	PBPK	Microsomes	0.000261	14.12	NONE	1

RIF subject to first pass gut metabolism

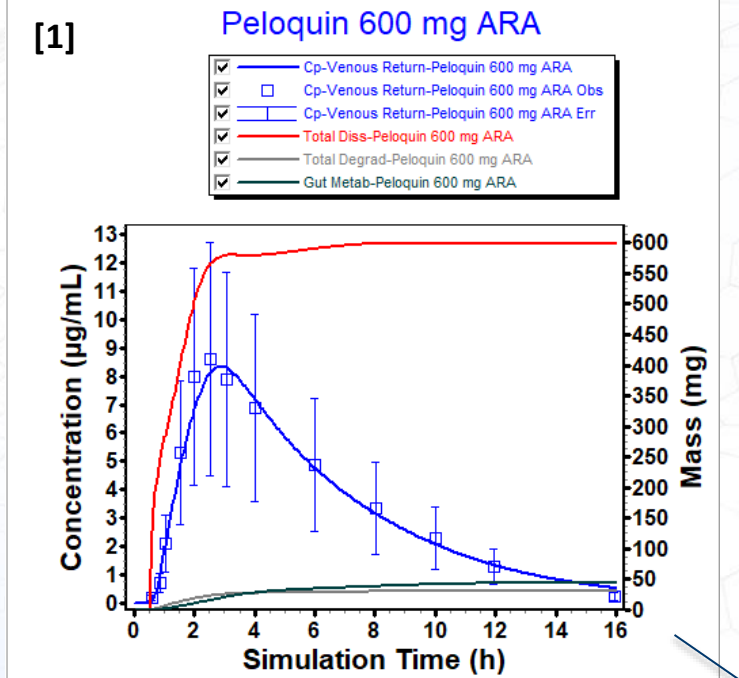
Rifampicin : Effect of acid reducing agents

[1]

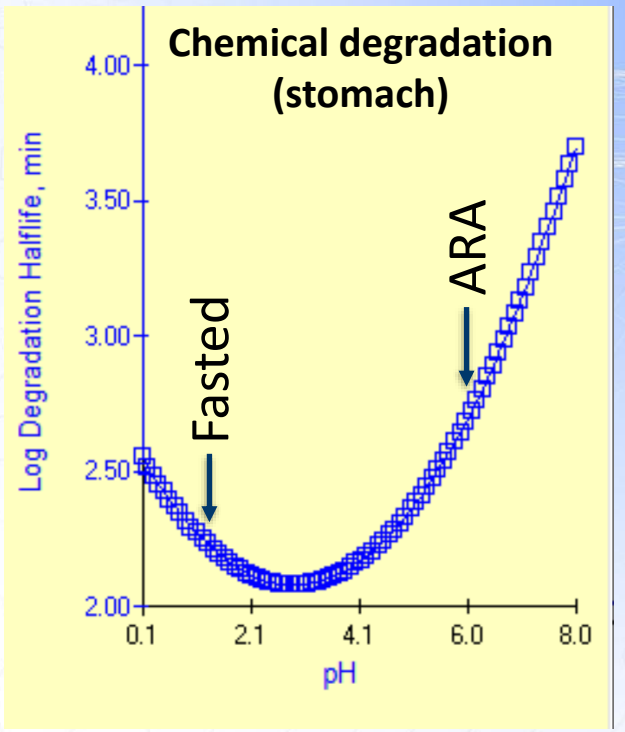


Record: Peloquin 600 mg fasted Total simulation time (h): 16		
Result	Observ	Simul
Fa (%):	0	89.64
FDp (%):	0	84.82
F (%):	0	75.37
Cmax (µg/mL):	8.457	8.528
Tmax (h):	2.005	2.293
AUC 0-inf (µg-h/mL):	58.31	53.25
AUC 0-t (µg-h/mL):	56.76	51.36
CMax Liver (µg/mL):		12.61

[1]



Record: Peloquin 600 mg ARA Total simulation time (h): 16		
Result	Observ	Simul
Fa (%):	0	94.41
FDp (%):	0	86.95
F (%):	0	77.21
Cmax (µg/mL):	8.579	8.334
Tmax (h):	2.538	2.88
AUC 0-inf (µg-h/mL):	54.11	54.50
AUC 0-t (µg-h/mL):	53.46	52.24
CMax Liver (µg/mL):		11.91

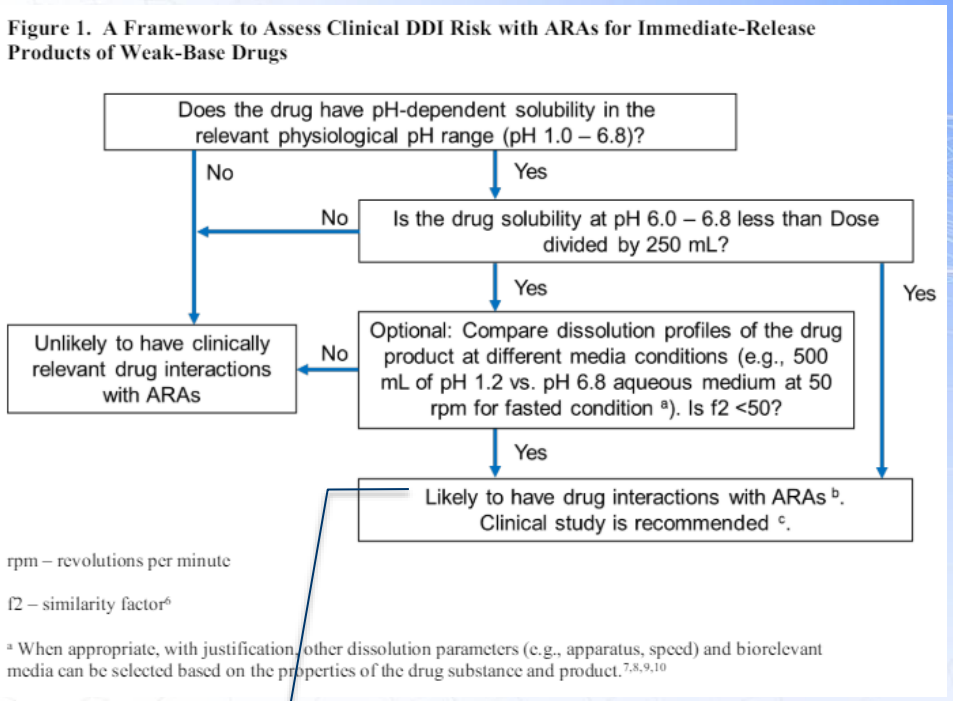


ARA vs Fasted:
Chemical Degradation ↘
Dissolution ↘
Gut metabolism ↗
C_{max} and AUC ↔

1: Peloquin, C.A., et al., Pharmacokinetics of Rifampin Under Fasting Conditions, With Food, and With Antacids. Chest, 1999. 115(1): p. 12-18.

Proposal for pH related DDI

- **Well-understood phenomena**
  - pH effect on drug solubilization
  - First pass degradation
  - Other in vitro interactions can be modeled

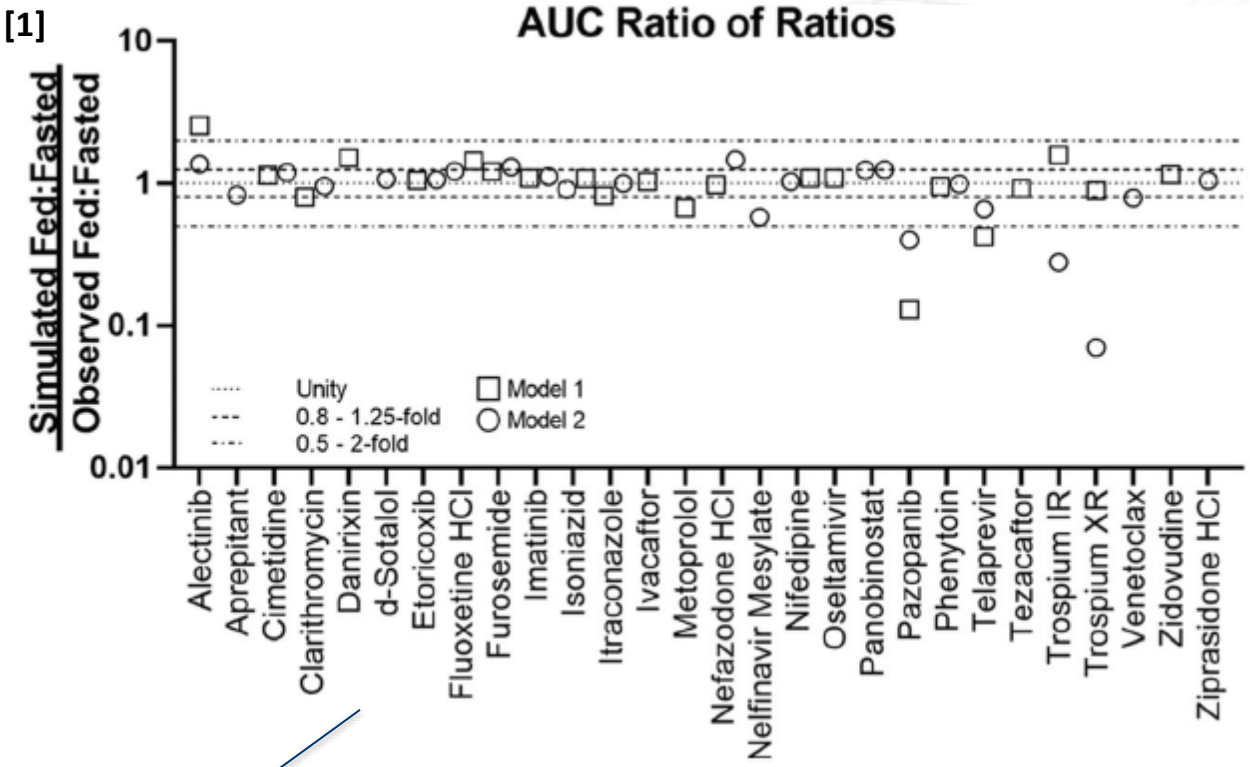


Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

Proposal : Suggestion to introduce PBPK-PBBM step prior to running a clinical evaluation of pH-related DDI. PBBM should be based on mechanistic dissolution models and successfully validated (e.g., in fasted and fed state). Recommend clinical evaluation If the ARA impact is anticipated to be large (e.g., for non-NTI drugs if the AUC fold variation is higher than 2)

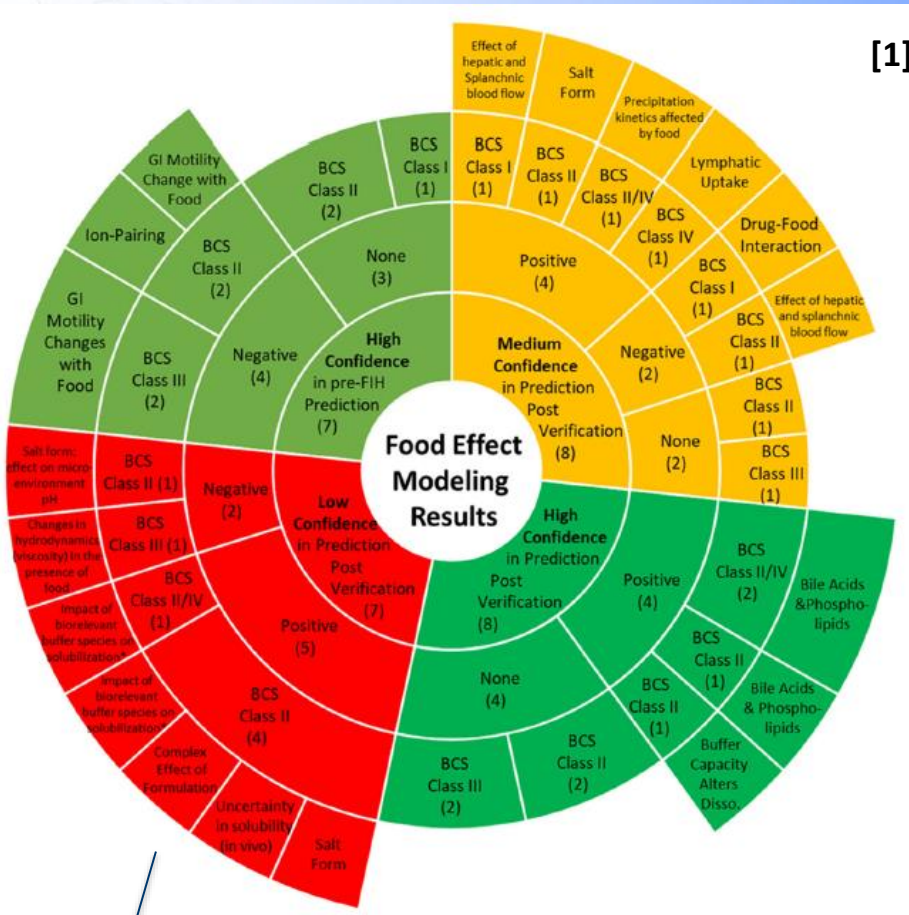
DDI with Food – Where does PBPK-PBBM stand?

[1]



80% of the food effect cases are well predicted by PBPK

[1]

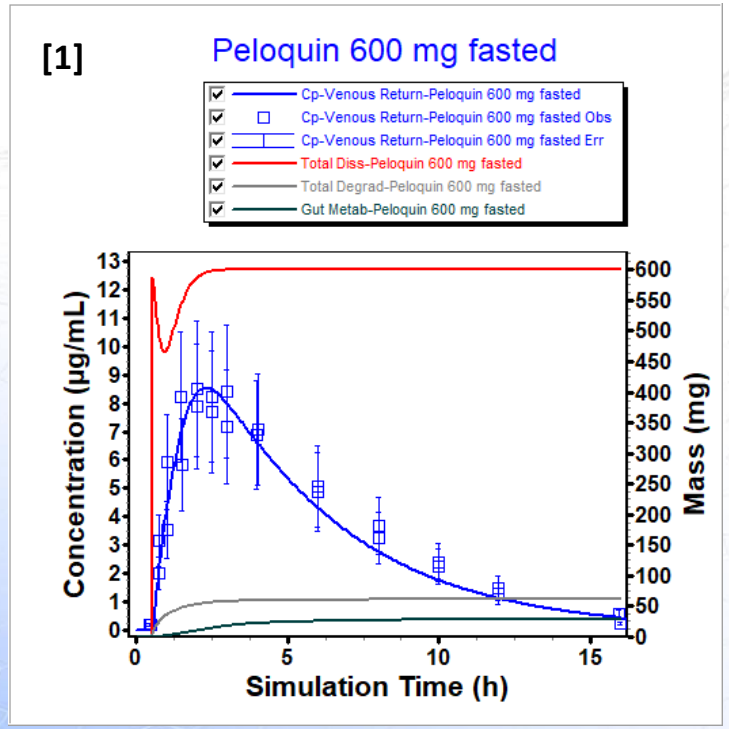


1: Emami Riedmaier, A., et al., Use of PBPK Modeling for Predicting Drug-Food Interactions: An Industry Perspective. The AAPS Journal, 2020. 22(123): p. 1-15.

Failures to predict for complex formulations, complex salt behavior or acid base reactions with biorelevant buffers

Rifampicin : Effect of food

[1]



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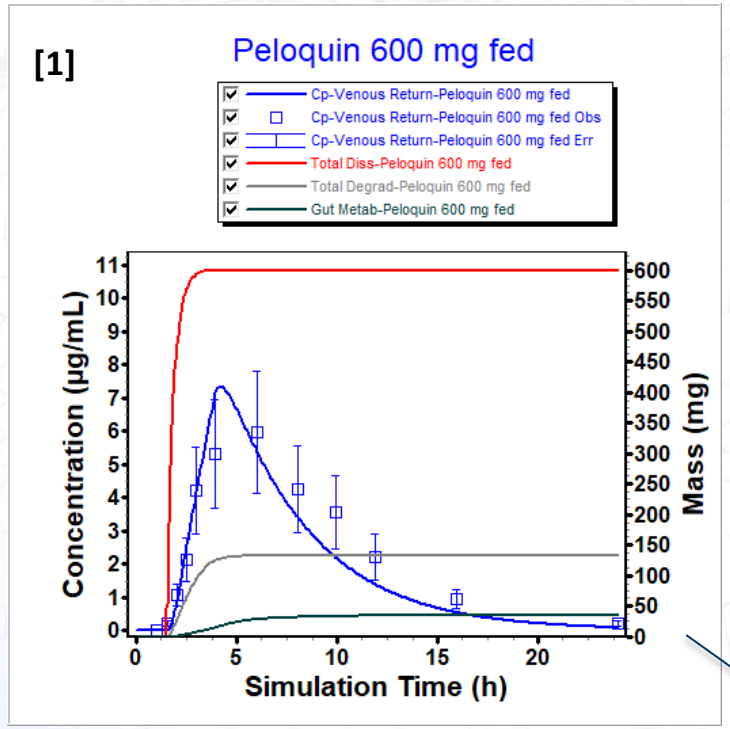
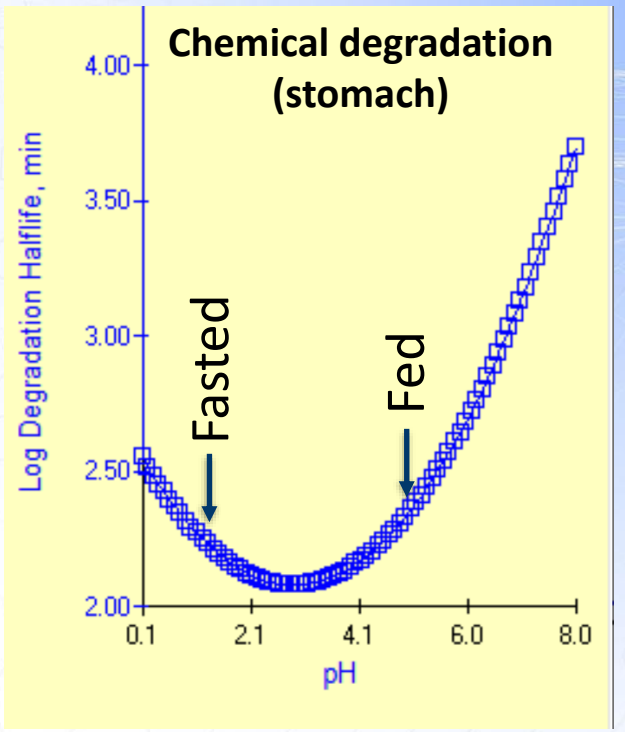


Record: Peloquin 600 mg fed Total simulation time (h): 24		
Result	Observ	Simul
Fa (%):	0	77.70
FDp (%):	0	71.81
F (%):	0	65.53
Cmax (µg/mL):	5.959	7.337
Tmax (h):	6.024	4.16
AUC 0-inf (µg-h/mL):	54.30	44.91
AUC 0-t (µg-h/mL):	53.19	44.58
CMax Liver (µg/mL):		10.42

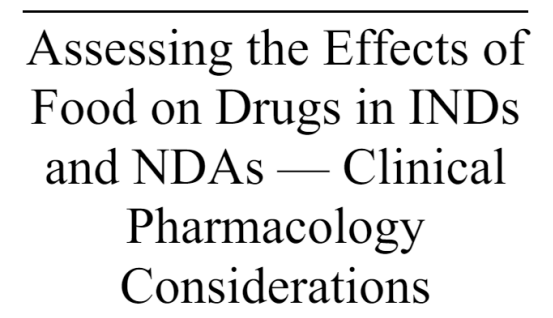


Fed vs Fasted:
Chemical Degradation ↗
Fraction absorbed ↘
Gut metabolism ↗
C_{max} and AUC ↘

1: Peloquin, C.A., et al., Pharmacokinetics of Rifampin Under Fasting Conditions, With Food, and With Antacids. Chest, 1999. 115(1): p. 12-18.

Proposal on food effect prediction

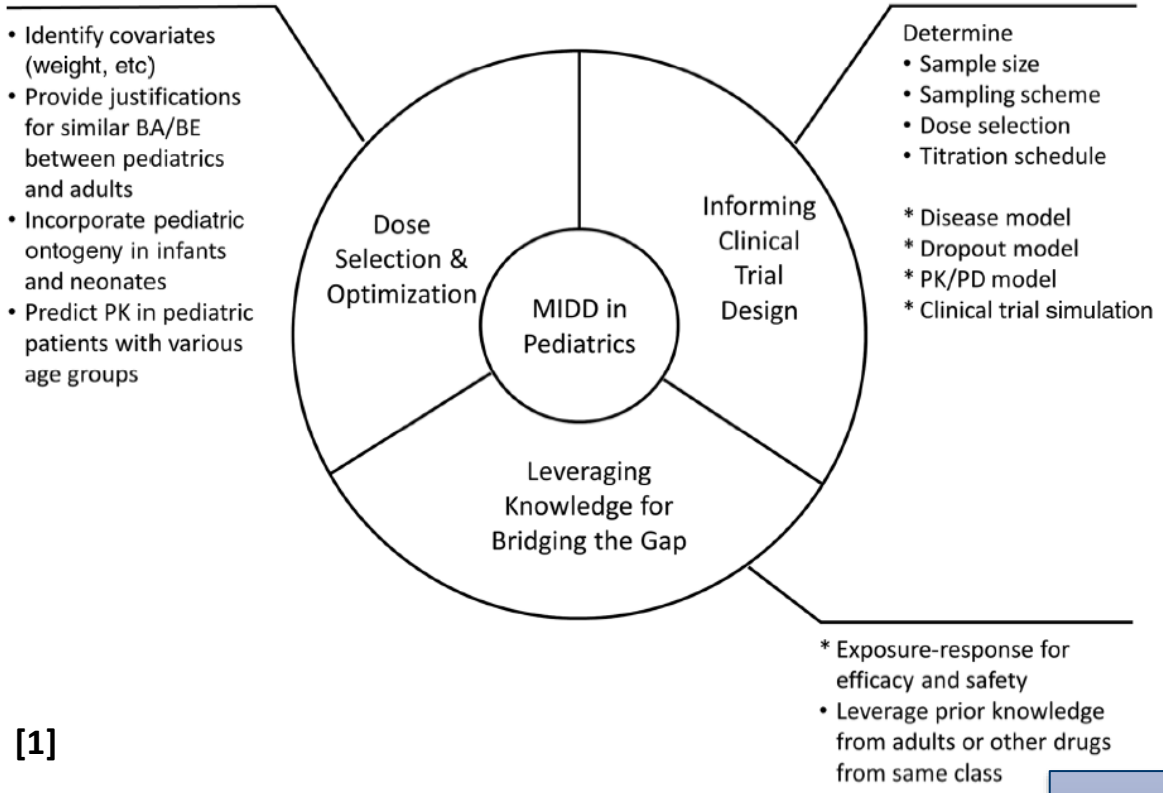
- **Mechanisms integrated in PBBM**
  - pH and bile salt effect on drug solubilization well captured
  - First pass degradation (luminal or metabolic) can be integrated
  - Liver blood flow and first pass liver extraction
- **Gaps**
  - Complex formulations (e.g. lipidic formulations) or formulations comprising solubilizers, permeation enhancers…


Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations

Proposal : Expand clinical FE waiver scope to drugs in simple formulations where a PBBM was previously validated on clinical data and where minimal formulation/process changes were introduced, e.g., minor changes in commercial formulations [1]

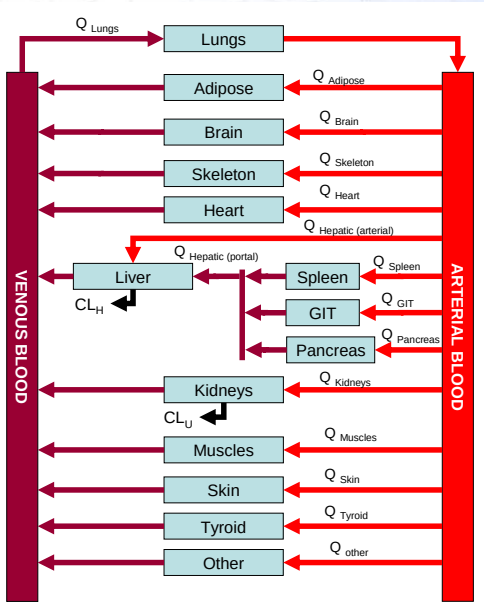
1.Kesisoglou, F., et al., Streamlining Food Effect Assessment — Are Repeated Food Effect Studies Needed? An IQ Analysis. The AAPS Journal, 2023. 25(4): p. 60.

Pediatric dose and formulation development – Isoniazid (INH)

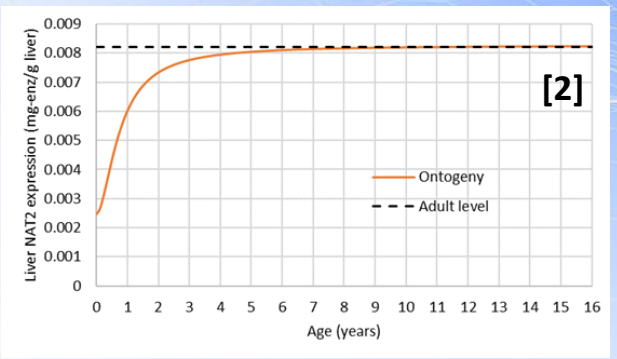


[1]

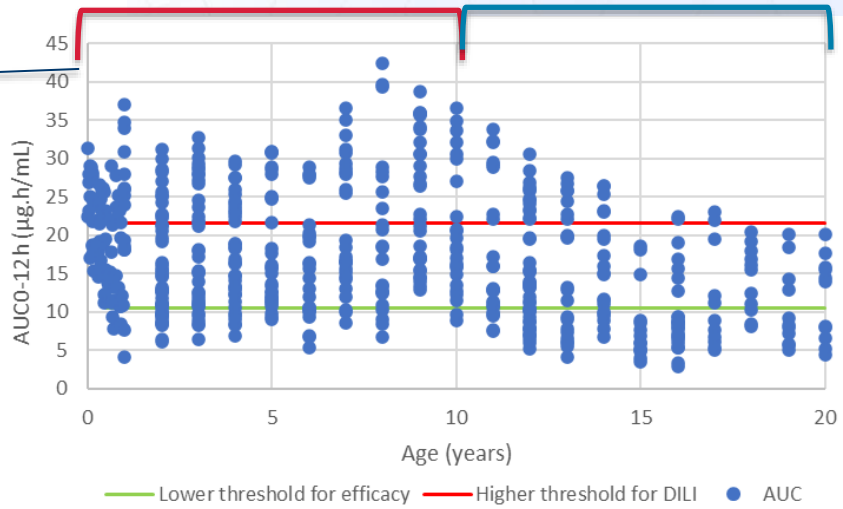
Physiology vs age



NAT2 ontogeny & expression level across the human body



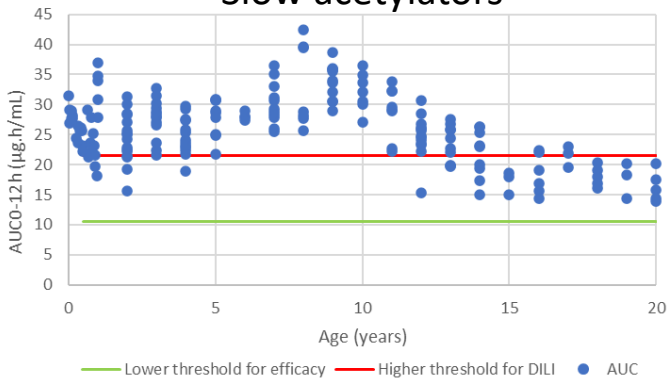
Population simulations across genotypes with age-appropriate formulations



1. Bi, Y., et al., Role of Model-Informed Drug Development in Pediatric Drug Development, Regulatory Evaluation, and Labeling. J Clin Pharmacol, 2019. 59 Suppl 1: p. S104-s111.

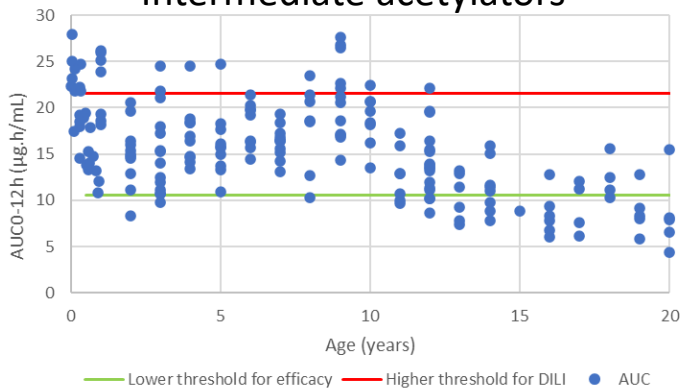
Opportunity to adjust dose to genotype

Slow acetylators



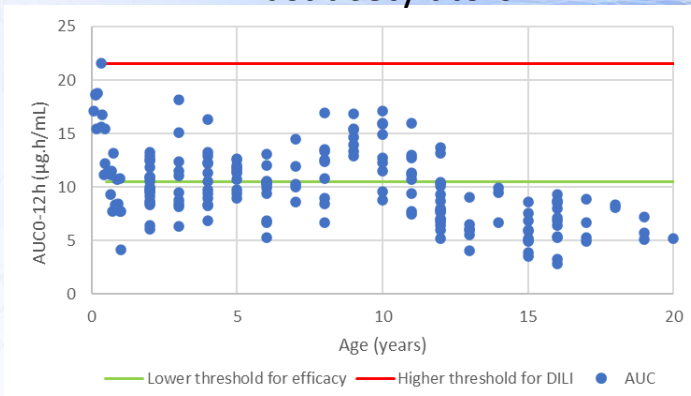
73% > DILI[1] threshold

Intermediate acetylators



12% > DILI threshold

Fast acetylators



0% > DILI threshold

Opportunity to reduce dose in slow acetylators to preserve efficacy and reduce risk to liver

Parameter	Description	Typical genotype distribution		
A	Genotype	SA	IA	RA
B	Frequency of genotype [2]	0.50	0.42	0.09
C	Probability to be over AUC threshold 21.78 µg.h/mL [4]	0.73	0.12	0
D	Probability of DILI above threshold [1]	0.324	0.324	0.324
E	Probability of DILI under threshold [1]	0.09	0.09	0.09
F	Overall DILI in pure genotype [5]	0.261	0.118	0.090
G	Overall DILI risk in population [6]	0.187		

Incidence predicted in pure phenotypes close to reported in the literature [3]

18.7% chance of DILI close to adult incidence (DILI = elevation of ALAT and bilirubin)

1: defined as elevated liver ALAT and bilirubin from Zheng, X., et al., Drug Exposure and Minimum Inhibitory Concentration Predict Pulmonary Tuberculosis Treatment Response. Clinical Infectious Diseases, 2021. 73(9): p. e3520-e3528.
2: Zanrosso, C.W., et al., N -Acetyltransferase 2 Polymorphisms and Susceptibility to Infant Leukemia with Maternal Exposure to Dipyrone during Pregnancy. Cancer Epidemiology, Biomarkers & Prevention, 2010. 19(12): p. 3037-3043.
3: Donald, P.R., Antituberculosis drug-induced hepatotoxicity in children. Pediatr Rep, 2011. 3(2): p. e16.
4: From simulation results
5: $F = C \times D + (1 - C) \times E$
6: $G = F_{SA}B_{SA} + F_{IA}B_{IA} + F_{RA}B_{RA}$

Future wins for guidance update with mechanistic M&S

2022

Population Pharmacokinetics

A population is a collection of individual subjects: PBPK could include individual subjects with adequate biomarkers. This model could translate to any other patient/population

2003

More mechanistic PK-PD models could be built to explore/explain clinical exposure response data, e.g., using quantitative biomarkers for enzyme expression or cell signaling pathways

Outline

- Use of M&S tools along the drug development
- Overview of clinical pharmacology (and related) guidances
  Easy wins for more M&S contribution
- Where do we stand on pH-related DDI, food effect predictions and precision dosing
- Take home messages

Take home messages

- **Mechanistic models (PBBM-PBPK) offer valuable insights and understanding**
  - Enables PK profile understanding
  - Limiting/determining factors can be acted upon : Improve formulation robustness, adapt the dose to patients
  - Models should be validated with well-designed clinical trials
  - Potential to streamline clinical trials

- **There are easy wins to integrate more modeling in FDA Guidances**
  - Replace/supplement f2 testing when it fails with PBBM
  - Replace/supplement IVIVC, especially for drug subject to first pass degradation, metabolism or subject to active efflux with PBBM
  - Understand products beyond the BCS (drugs don't belong to boxes)
  - Support bridging and post approval changes with PBBM
  - Start applying PBBM to non-oral non-systemically active drugs

- **The promise (near-future) of PBBM-PBPK**
  - Predict exposure in age-diverse and genotypically diverse individual subjects
  - Predict dose and scheduling requirements individually
  - Integrate more formulation/process data in the future, e.g. excipients
  - Integrate more pharmacodynamics + biomarker data

Thanks