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PBPK Modeling for Identifying and Mitigating Absorption Risks in Early Drug Development

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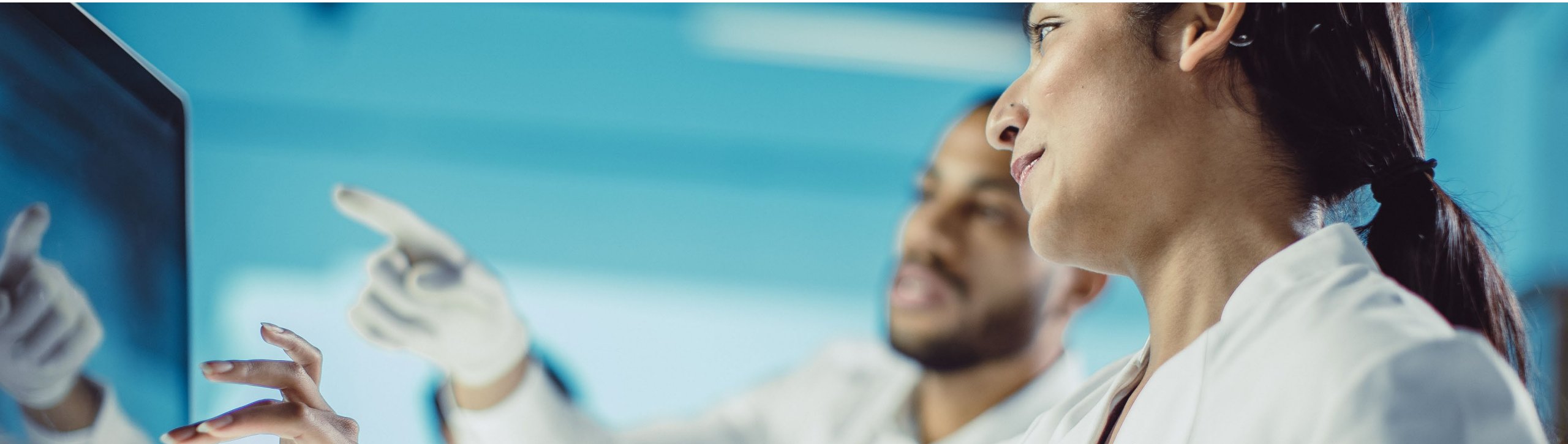
John DiBella, President, SLP Division, Simulations Plus

27 April 2023

Public



Agenda

- The State of PBPK Modeling
- Oral Absorption Risks and Mitigation Strategies
- Lonza PBPK Modeling Services Overview
- PBPK Case Studies

The State of PBPK Modeling

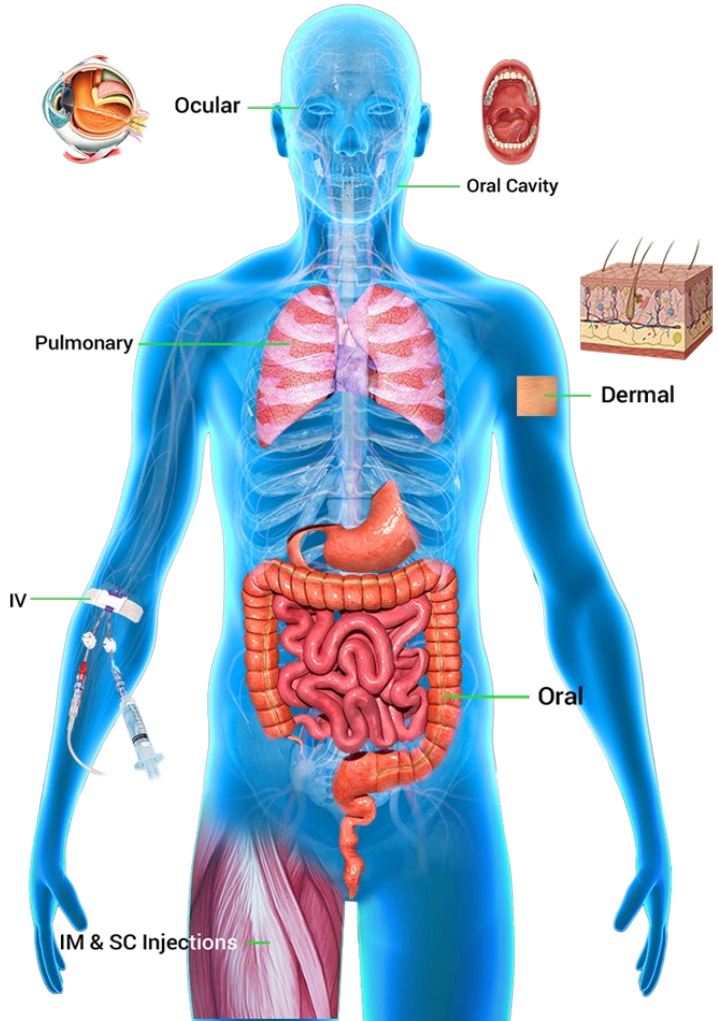
27 April 2023

What Do We Mean When Describing PBPK Modeling?

- Physiologically based pharmacokinetic (PBPK) models represent animals and humans virtually as a collection of organs and tissues, each defined by a system of mathematical equations

- PBPK models are developed using quantitative values ("parameters") and equations that describe characteristics (e.g., body weight, blood flow rate, physicochemical properties, formulation) and mechanisms (e.g., dissolution, precipitation, absorption, metabolism)

- PBPK models built for animals can often be extrapolated to humans – and, in a similar vein, models built for healthy adults can often be extrapolated to other populations (e.g., pediatrics, disease states)



Evolving Relationship Between PBPK Modeling and Pharmaceutical R&D

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Model "supported" (first questions 20 years ago):

- Will modeling and simulation help?

Model "based" (questions 5 years ago):

- How can I maximize the value of modeling and simulation in my development program?

Model "informed" (questions today):

- How do I change the R&D process to reflect the availability of in silico tools and techniques?

PBPK Modeling to Support Regulatory Interactions: The Push!

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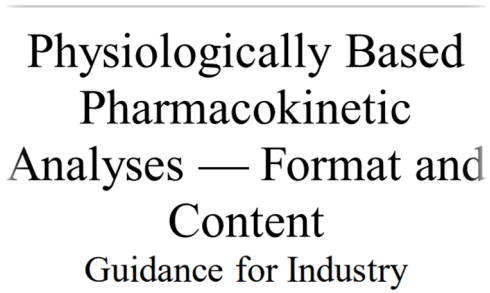
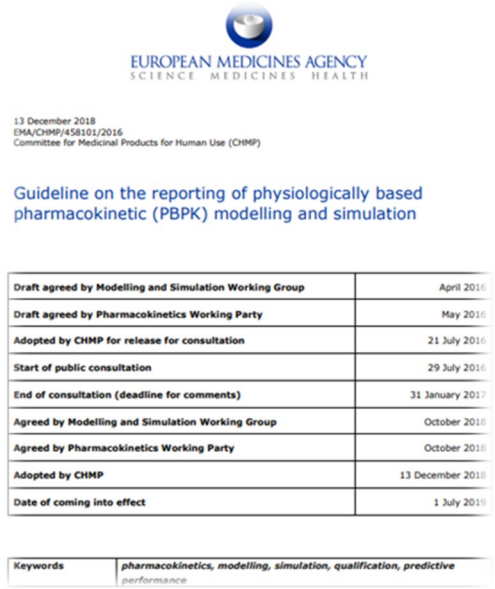

Physiologically Based Pharmacokinetic Analyses — Format and Content
Guidance for Industry

2018

https://www.fda.gov/media/101469/download


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

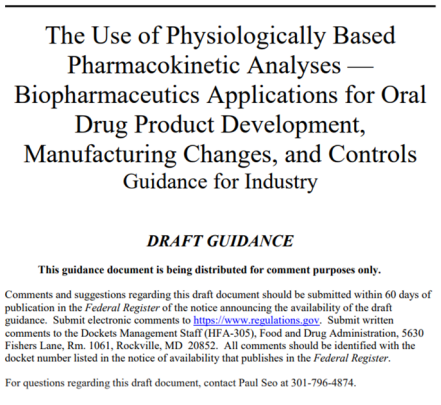
Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetics Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017
Agreed by Modelling and Simulation Working Group	October 2018
Agreed by Pharmacokinetics Working Party	October 2018
Adopted by CHMP	13 December 2018
Date of coming into effect	1 July 2019

Keywords	*pharmacokinetics, modelling, simulation, qualification, predictive performance*

2018

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf


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

DRAFT GUIDANCE

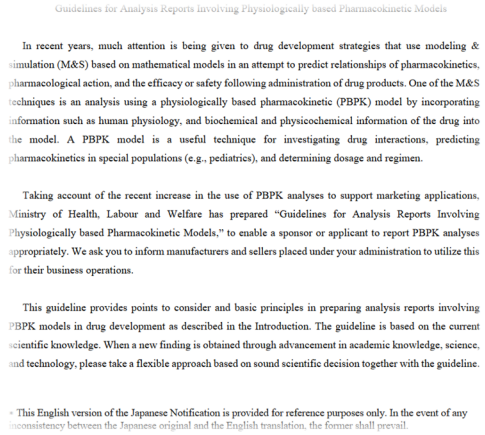
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Paul Seo at 301-796-4874.

2020

https://www.fda.gov/media/142500/download


Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models

In recent years, much attention is being given to drug development strategies that use modeling & simulation (M&S) based on mathematical models in an attempt to predict relationships of pharmacokinetics, pharmacological action, and the efficacy or safety following administration of drug products. One of the M&S techniques is an analysis using a physiologically based pharmacokinetic (PBPK) model by incorporating information such as human physiology, and biochemical and physicochemical information of the drug into the model. A PBPK model is a useful technique for investigating drug interactions, predicting pharmacokinetics in special populations (e.g., pediatrics), and determining dosage and regimen.

Taking account of the recent increase in the use of PBPK analyses to support marketing applications, Ministry of Health, Labour and Welfare has prepared "Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models," to enable a sponsor or applicant to report PBPK analyses appropriately. We ask you to inform manufacturers and sellers placed under your administration to utilize this for their business operations.

This guideline provides points to consider and basic principles in preparing analysis reports involving PBPK models in drug development as described in the Introduction. The guideline is based on the current scientific knowledge. When a new finding is obtained through advancement in academic knowledge, science, and technology, please take a flexible approach based on sound scientific decision together with the guideline.

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

2020

https://www.pmda.go.jp/files/000239317.pdf

PBPK Modeling Submissions to the FDA

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Supplement Article

ACCP

The Journal of Clinical Pharmacology 2020, 60(S1) S160–S178
Published 2020. This article is a U.S. Government work and is in the public domain in the USA.
DOI: 10.1002/jcph.1767

Application of PBPK Modeling and Simulation for Regulatory Decision Making and Its Impact on US Prescribing Information: An Update on the 2018-2019 Submissions to the US FDA's Office of Clinical Pharmacology

Xinyuan Zhang, PhD, Yuching Yang, PhD, Manuela Grimstein, PhD, Jianghong Fan, PhD, Joseph A. Grillo, PharmD, Shiew-Mei Huang, PhD, Hao Zhu, PhD, and Yaning Wang, PhD

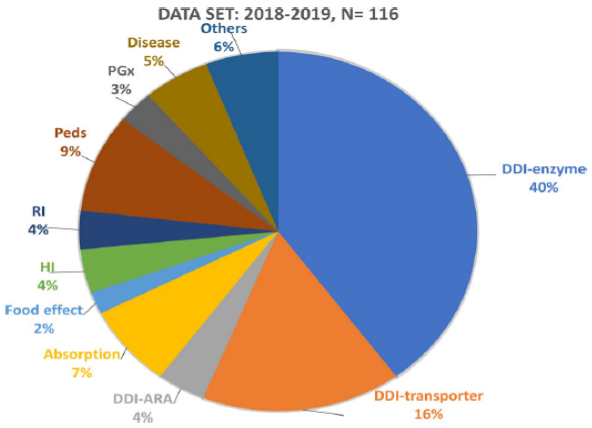

Figure 3. Distribution of physiologically based pharmacokinetic submissions by application areas (2018-2019). DDI-ARA, acid-reducing agent-mediated drug-drug interaction; DDI-enzyme, enzyme-mediated drug-drug interaction; DDI-transporter, transporter-mediated drug-drug interaction; HI, hepatic impairment; peds, pediatrics; PGx, pharmacogenomics; RI, renal impairment.

Zhang et al. J Clin Pharm 2020

Commentary

Biopharmaceutics Applications of Physiologically Based Pharmacokinetic Absorption Modeling and Simulation in Regulatory Submissions to the U.S. Food and Drug Administration for New Drugs

Fang Wu,[1,2,9] Heta Shah,[3] Min Li,[1] Peng Duan,[3] Ping Zhao,[4,5] Sandra Suarez,[3] Kimberly Raines,[1] Yang Zhao,[1,6] Meng Wang,[1,7] Ho-pi Lin,[1] John Duan,[3] Lawrence Yu,[8] and Paul Seo[1,9]

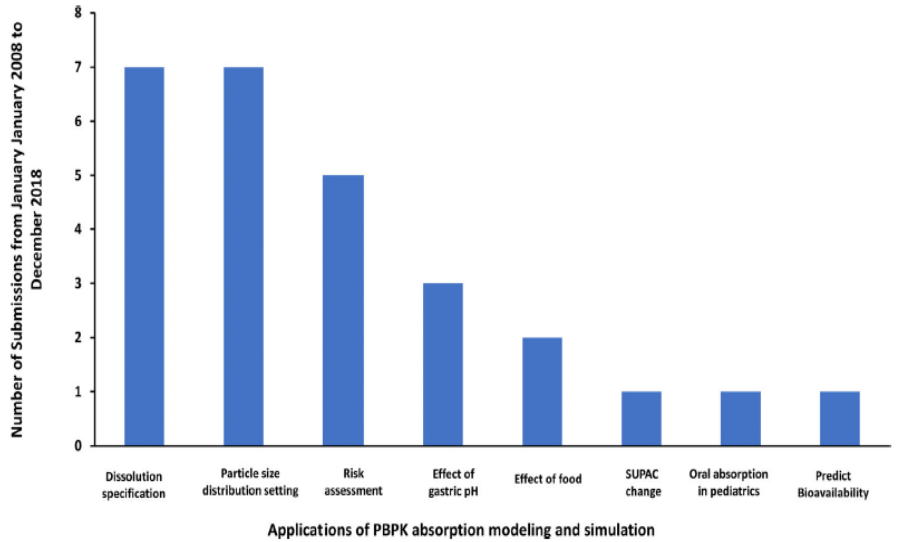

Fig. 2. Applications of PBPK absorption modeling and simulations in the new drug applications submissions*. Abbreviations: SUPAC, scale-up and post-approval changes. *Note that in some cases, the same model was used for multiple purposes, e.g., setting of both particle size specification and dissolution acceptance criteria

Wu et al. AAPS J 2021

Examples of Approved Drugs Supported By PBPK Modeling

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ALECENSA® alectinib 150 mg capsules

pH-dependent DDI

BRAFTOVI® + MEKTOVI®

(encorafenib) 75 mg capsules (binimetinib) 15 mg tablets

metabolic DDI

CALQUENCE®

(acalabrutinib) 100 mg capsules

drug product specifications / pH - dependent DDIs

FARYDAK®

(panobinostat) capsules

10mg/15mg/20mg

pH-dependent DDI

Inlyta®

axitinib 1mg and 5mg tablets

transporter DDI

KISQALI®

ribociclib 200 mg tablets

pH-dependent DDI

Opsumit®

macitentan tablets 10 mg

drug product specifications

Mekinist™

(trametinib)

transporter DDI

Tamiflu®

oseltamivir phosphate

Prescription for flu

drug product specifications

Invokana®

(canagliflozin) tablets

drug product specifications

PIQRAY®

(alpelisib) tablets

50 mg · 150 mg · 200 mg

food effect

ZURAMPIC™

lesinurad tablets

pediatric dose support

Common PBPK Modeling Industrial Applications

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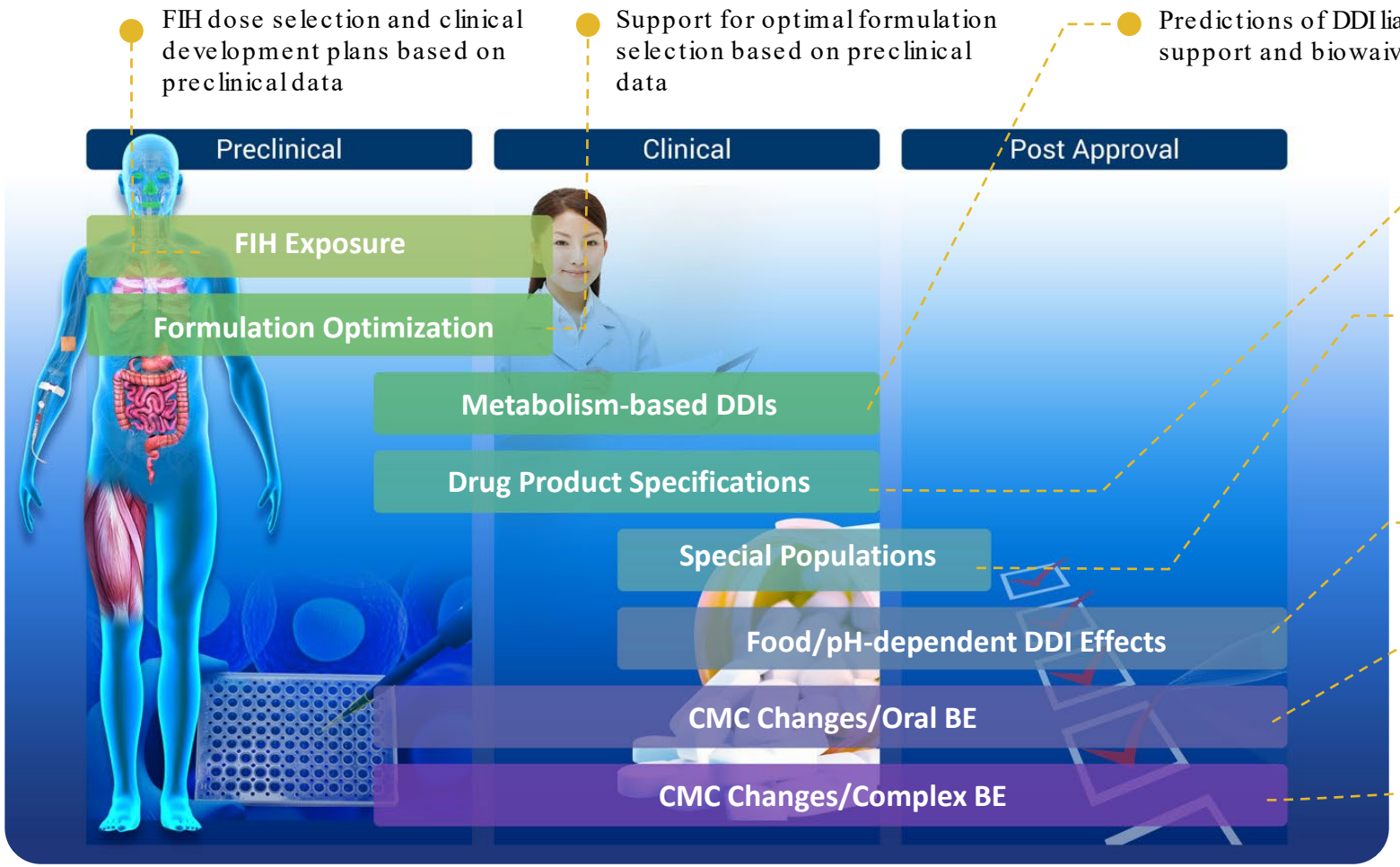

FIH dose selection and clinical development plans based on preclinical data

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

PBPK Modeling to Support FIH Exposure Predictions: in Vitro-in Vivo Extrapolation (IVIVE)

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Predicting Concentration vs Time Profiles in Man From In Vitro and Pre-clinical Data - An Evaluation of PBPK

Summary of IV profile prediction accuracy

APPROACH	PROFILE	Vss		CL	
	Weighted sum of squares (RANK)	AFE	% within 2-fold error (3-fold error)	AFE	% within 2-fold error (3-fold error)
GastroPlus	-11.7 (1)	1.4	90 (100)	1.6	80 (85)
PKSim	-6.4 (2)	1.7	70 (90)	1.6	80 (85)
Current Pfizer Approach	-3.8 (3)	1.6	75 (85)	1.6	80 (85)
SimCYP – hlm	5.6 (4)*	1.5	80 (95)	2.5	58 (74)
SimCYP – rhCYP	7.8 (5)*	1.5	80 (95)	2.4	55 (65)
ChloePK	8.5 (6)*	-	-	1.7	70 (80)

Summary of Oral profile prediction accuracy

AFE➔ Average Fold Error

APPROACH	PROFILE	AUC		Cmax	
	Weighted sum of squares (RANK)	AFE	% within 2-fold error (3-fold error)	AFE	% within 2-fold error (3-fold error)
GastroPlus	-9.8 (1)	2.7	50 (72)	2.0	67 (72)
Current Pfizer Approach	-5.3 (2)	3.9	33 (56)	2.5	44 (61)
SimCYP - rhCYP	-3.7 (3)	3.0	56 (67)	2.2	61 (72)
SimCYP - hlm	5.7 (4)*	3.6	41 (53)	2.7	53 (59)
PKSim	6.1 (5)*	4.7	22 (39)	5.0	17 (33)
ChloePK	7.0 (6)*	2.8	39 (50)	2.4	50 (61)

Cole et al., 2008 – Asian ISSX Meeting
Jones et al. 2011. Clin. Pharmacokinet. 50(5): 331

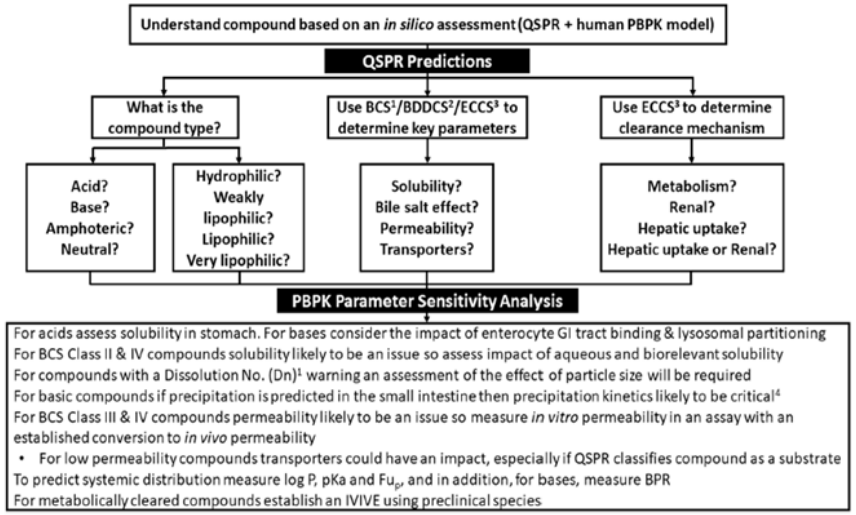
Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-019-00741-9

REVIEW ARTICLE

Check for updates

Physiologically Based Pharmacokinetic Modelling for First-In-Human Predictions: An Updated Model Building Strategy Illustrated with Challenging Industry Case Studies

Neil A. Miller[1] · Micaela B. Reddy[2] · Aki T. Heikkinen[3] · Viera Lukacova[4] · Neil Parrott[5]



Miller et al., (2019) Clin Pharmacokinet 58(6):727-746

Pharmaceutical Risk Assessment Strategy: Proposed by Roche in 2006

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EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES 27 (2006) 91–99

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journal homepage: www.elsevier.com/locate/ejps

A strategy for preclinical formulation development using GastroPlus™ as pharmacokinetic simulation tool and a statistical screening design applied to a dog study

Martin Kuentz, Sonja Nick, Neil Parrott, Dieter Röthlisberger*

F. Hoffmann-La Roche Ltd., Pharmaceutical and Analytical R&D, Bldg./Lab. 072/338, Grenzacherstr., CH-4070 Basel, Switzerland

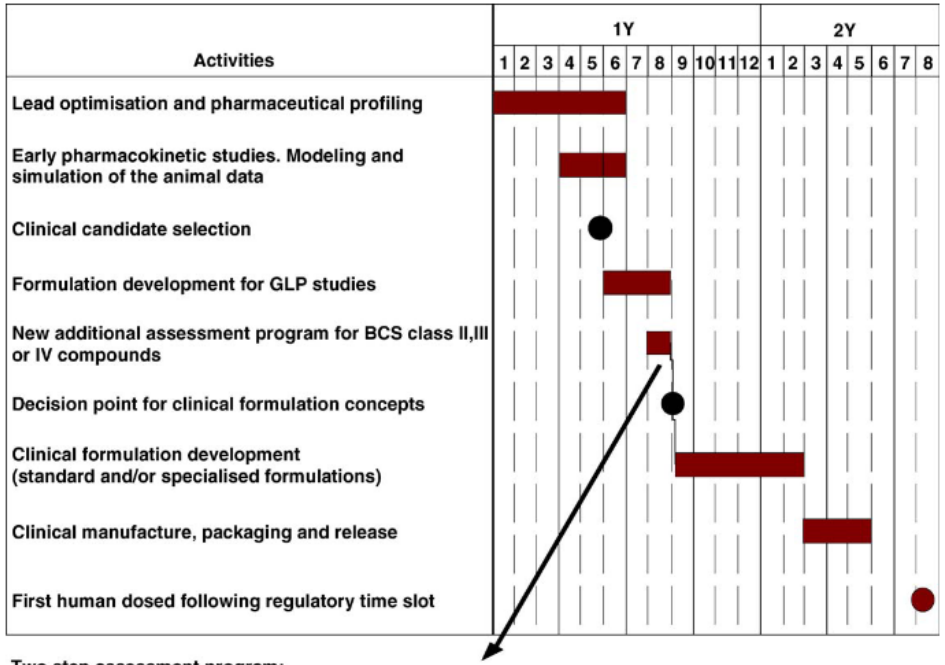

Fig. 1 – Gantt chart of the relevant formulation development activities including the new additional biopharmaceutical assessment program.

Key takeaways:

- Relevant formulation development activities should include additional PBPK modeling step
- Meaningful development resources can be assigned one year before the first-in-human study

Kuentz et al. Eur. J. Pharm. Sci. 2006. 27:91-99

Pharmaceutical Risk Assessment Strategy: BCS Class II Case Study

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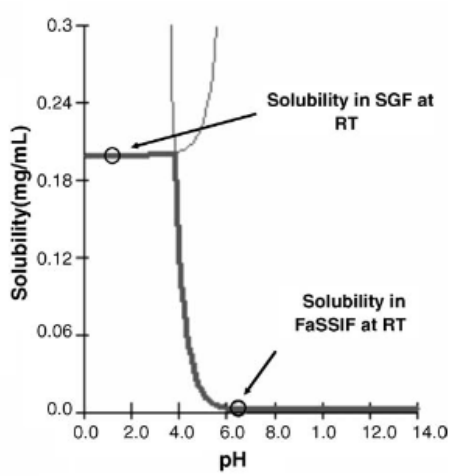

Fig. 3 – Drug solubility vs. pH profile used as lower limit of the solubility values of a set of computer simulations.

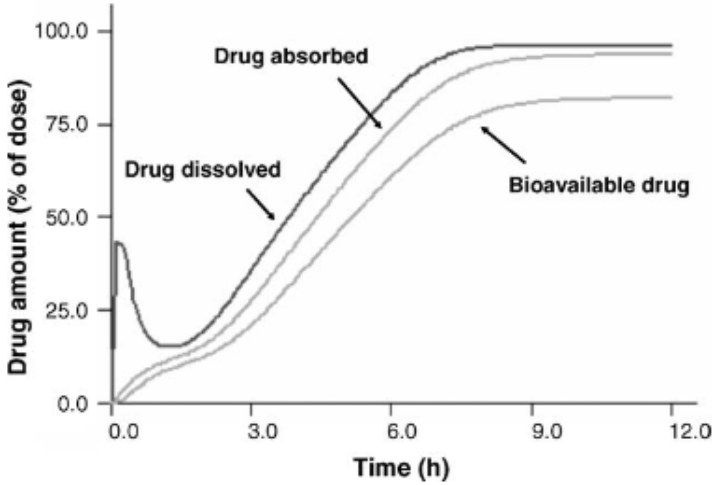

Fig. 4 – Simulated drug amounts (%) for the 160 mg dose of R1315 in human.

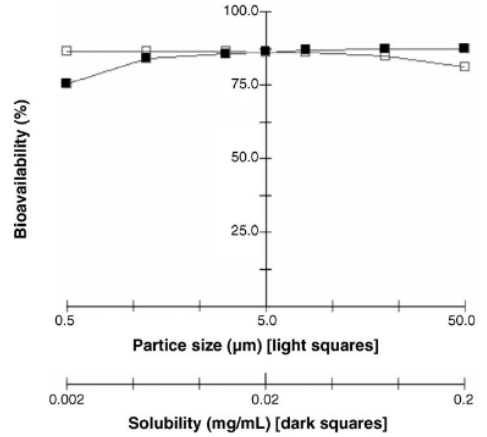

Fig. 6 – Parameter sensitivity analysis of the oral bioavailability (%) as a function of reference solubility at pH 6.5 (mg/mL) [dark squares], as well as effective particle radius (µm) [light squares] at a dose of 160 mg R1315.

- BCS assessment suggested solubility enhancement would improve oral bioavailability
- Mechanistic Parameter Sensitivity Analysis was performed to assess the impact of changes to particle size and solubility:
  - 0.5 um ⩽ particle size ⩽ 50 um
  - 0.002 mg/ml ≤ solubility ≤ 0.2 mg/ml
- Simulation results indicated that particle size reduction or solubility enhancement by technological means may not lead to improved bioavailability

Kuentz et al. Eur. J. Pharm. Sci. 2006. 27:91-99

Pharmaceutical Risk Assessment Strategy: BCS Class II Case Study

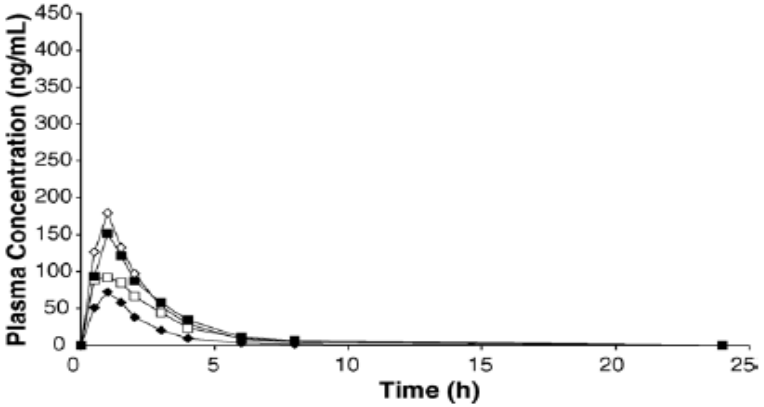

Fig. 7 – Plasma levels of individual dogs that received a solution. Diamonds hold for profiles of 2 mg/kg dose, whereas those of the 4 mg/kg dose are represented by squares. The light symbols hold for the fasted condition and the bold symbols for fed dogs.

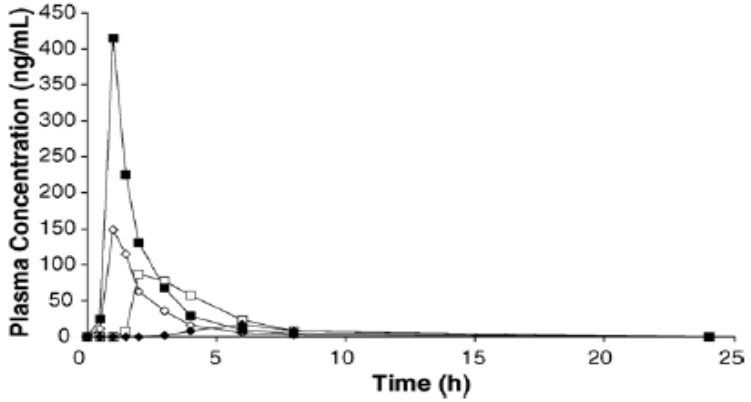

Fig. 8 – Plasma levels of individual dogs that received a capsule. Diamonds hold for profiles of 2 mg/kg dose, whereas those of the 4 mg/kg dose are represented by squares. The light symbols hold for the fasted condition and the bold symbols for fed dogs.

- Based upon the predictions from GastroPlus®, in vivo dog PK studies were performed using two different formulations
  - "Best" formulation: Cremophor vehicle solution
  - "Worst" formulation: Pure drug substance in capsule
- While variability is high, there is no significant difference in AUC between the two formulations

Kuentz et al. Eur. J. Pharm. Sci. 2006. 27:91-99.

Formulation Screening and Dissolution Method Selection in Preclinical Species

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RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2015, 5, 19844

Interspecies prediction of oral pharmacokinetics of different lacidipine formulations from dogs to human: physiologically based pharmacokinetic modelling combined with biorelevant dissolution

Chunnuan Wu,[a] Longfa Kou,[a] Panqin Ma,[b] Lifang Gao,[a] Bo Li,[a] Ran Li,[a] Cong Luo,[a] Jianzhong Shentu,[c] Zhonggui He[a] and Jin Sun*[ad]

Baseline model development for lacidipine: rat and dog IV and PO suspension studies

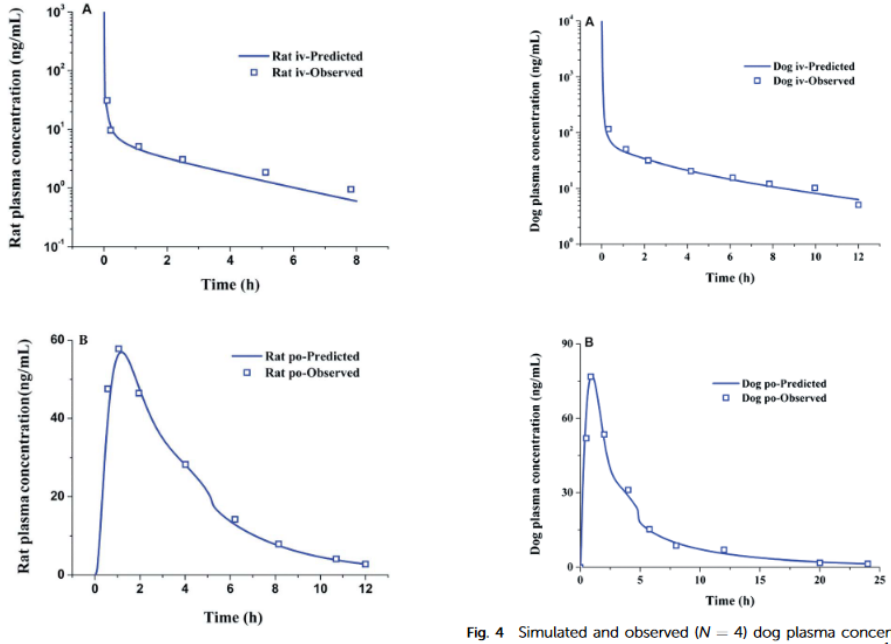

Fig. 3 Simulated and observed ($N = 4$) rat plasma concentration–time profiles after iv bolus administration of a 0.05 mg kg^{-1} dose of lacidipine (A) and oral administration of a 2.5 mg kg^{-1} dose of lacidipine suspension (B) (the observed data were collected form literature[24]).

Fig. 4 Simulated and observed ($N = 4$) dog plasma concentration–time profiles after iv bolus administration of a 0.5 mg kg^{-1} dose of lacidipine (A) and oral administration of a 2 mg kg^{-1} dose of lacidipine suspension (B) (the observed data were collected form literature[24]).

Formulation Screening and Dissolution Method Selection in Preclinical Species

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Dog PK data after PO administration of different tablet formulations was used to select the biopredictive in vitro dissolution experiment

Table 1 Compositions of blank FaSSIF, FaSSIF and FaSSIF-V2

Composition	Blank FaSSIF	FaSSIF	FaSSIF-V2
Sodium taurocholate (mM)	—	3	3
Lecithin (mM)	—	0.75	0.2
Maleic acid (mM)	—	—	19.12
NaH_2PO_4 (mM)	14.33	14.33	—
NaCl (mM)	52.87	52.87	68.62
NaOH (mM)	4.35	4.35	34.8
pH	6.5	6.5	6.5

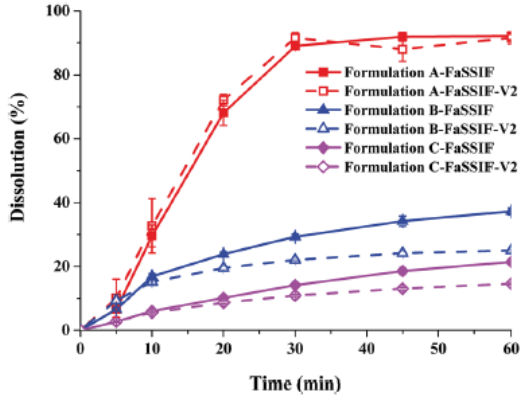
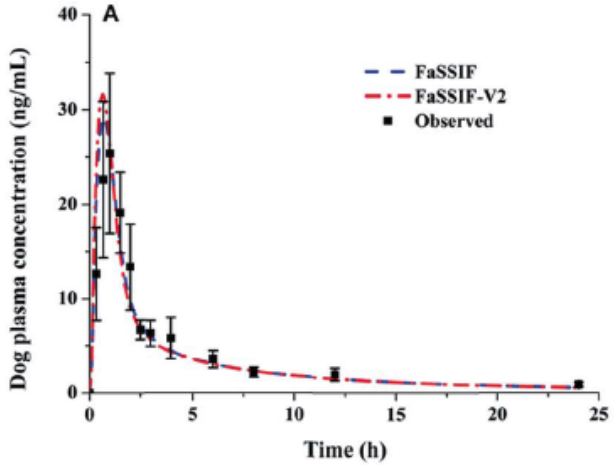
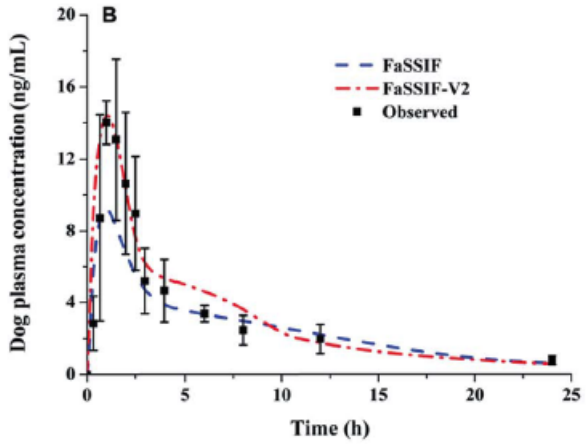


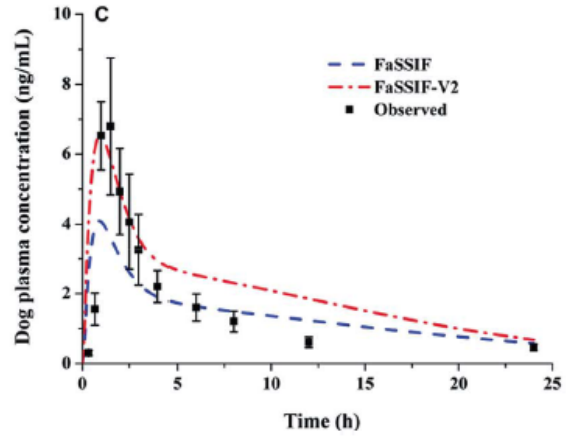
Fig. 1 Dissolution profiles of three lacidipine formulations in bio-relevant dissolution media (data are mean ± S.D., $n = 3$).

Table 3 The Z-factor values in different dissolution media for the three lacidipine formulations (unit: mL mg^{-1} s^{-1})

	Formulation A	Formulation B	Formulation C
FaSSIF	0.010	0.059	0.021
FaSSIF-V2	0.012	0.199	0.045







Wu et al. RSC Adv. (2015) 5;19844

Formulation Screening and Dissolution Method Selection in Preclinical Species

- Dog ACATÏ and PK model translated to human
- Data from biopredictive *in vitro* dissolution experiment used to successfully predict human PK

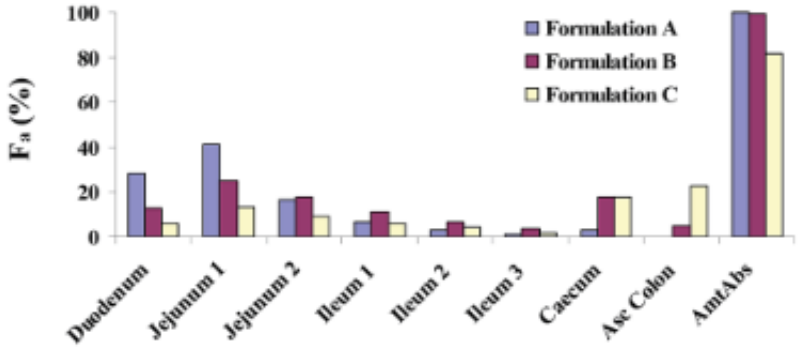


Fig. 10 Human compartmental absorption of the three lacidipine tablets.

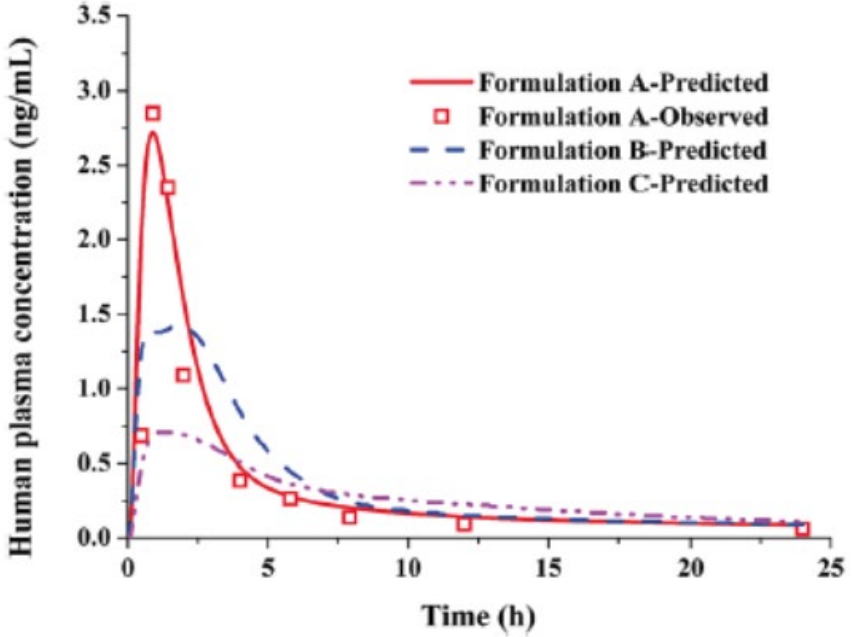


Fig. 8 The simulated and observed human *in vivo* PK profiles for the three lacidipine formulations using the *Z*-factor form FaSSIF-V2 dissolution media.

Wu et al. RSC Adv. (2015) 5;19844

The GastroPlus® PBPK Platform Is Validated Throughout Your Drug Product's Lifecycle

(1000+ peer-reviewed journal articles reference GastroPlus® applications)

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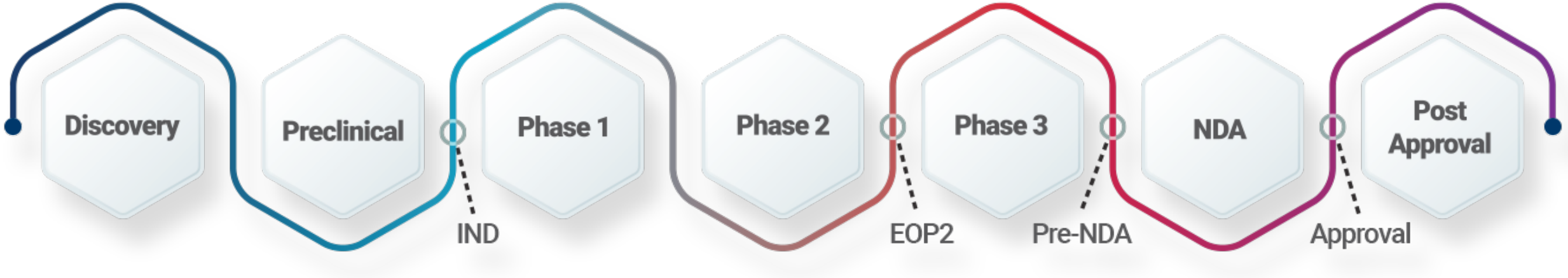
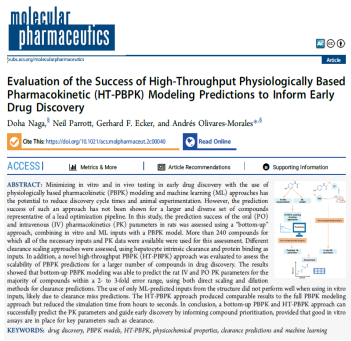


LEAD SELECTION

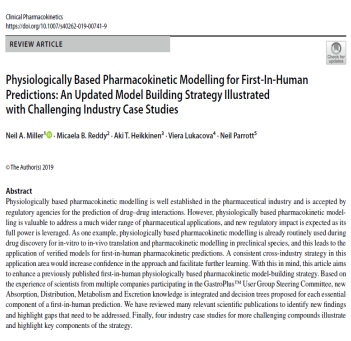

molecular pharmaceutics

Evaluation of the Success of High-Throughput Physiologically Based Pharmacokinetic (HT-PBPK) Modeling Predictions to Inform Early Drug Discovery

Doha Naga, Neil Parrott, Gerhard F. Ecker, and Andrés Olivares-Morales

Naga et al. (2022)
2300+ downloads!

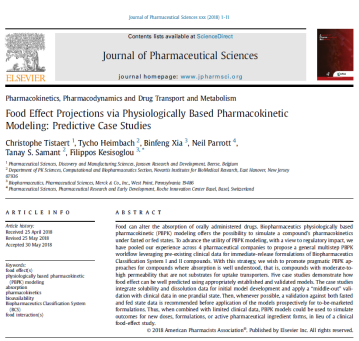
FIRST-IN-HUMAN


Physiologically Based Pharmacokinetic Modelling for First-In-Human Predictions: An Updated Model Building Strategy Illustrated with Challenging Industry Case Studies

Neil A. Miller, Micaela B. Reddy, Aki T. Heikkinen, Viera Lukacova, Neil Parrott

Miller et al. (2019)
80+ citations!

FOOD EFFECTS

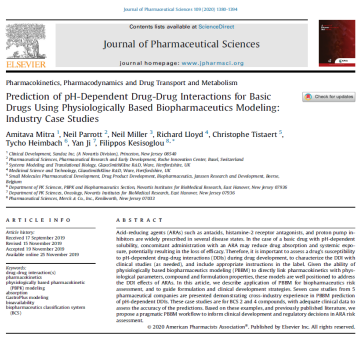

Journal of Pharmaceutical Sciences

Food Effect Projections via Physiologically Based Pharmacokinetic Modeling: Predictive Case Studies

Christophe Tistaert, Tycho Heimbach, Binfeng Xia, Neil Parrott, Tanay S. Samant, Filippos Kesisoglou

Tistaert et al. (2018)
40+ citations!

pH-DEPENDENT DDI

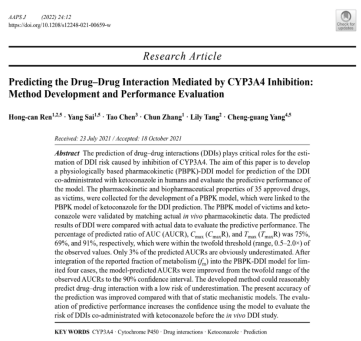

Journal of Pharmaceutical Sciences

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

Amitava Mitra, Neil Parrott, Neil Miller, Richard Lloyd, Christophe Tistaert, Tycho Heimbach, Yan Ji, Filippos Kesisoglou

Mitra et al. (2020) 26 citations!

METABOLIC DDI


Research Article

Predicting the Drug–Drug Interaction Mediated by CYP3A4 Inhibition: Method Development and Performance Evaluation

Hong-can Ren, Yang Sai, Tao Chen, Chun Zhang, Lily Tang, Cheng-guang Yang

Ren et al. (2022)
780+ downloads!

BIOEQUIVALENCE


Journal of Pharmaceutical Sciences

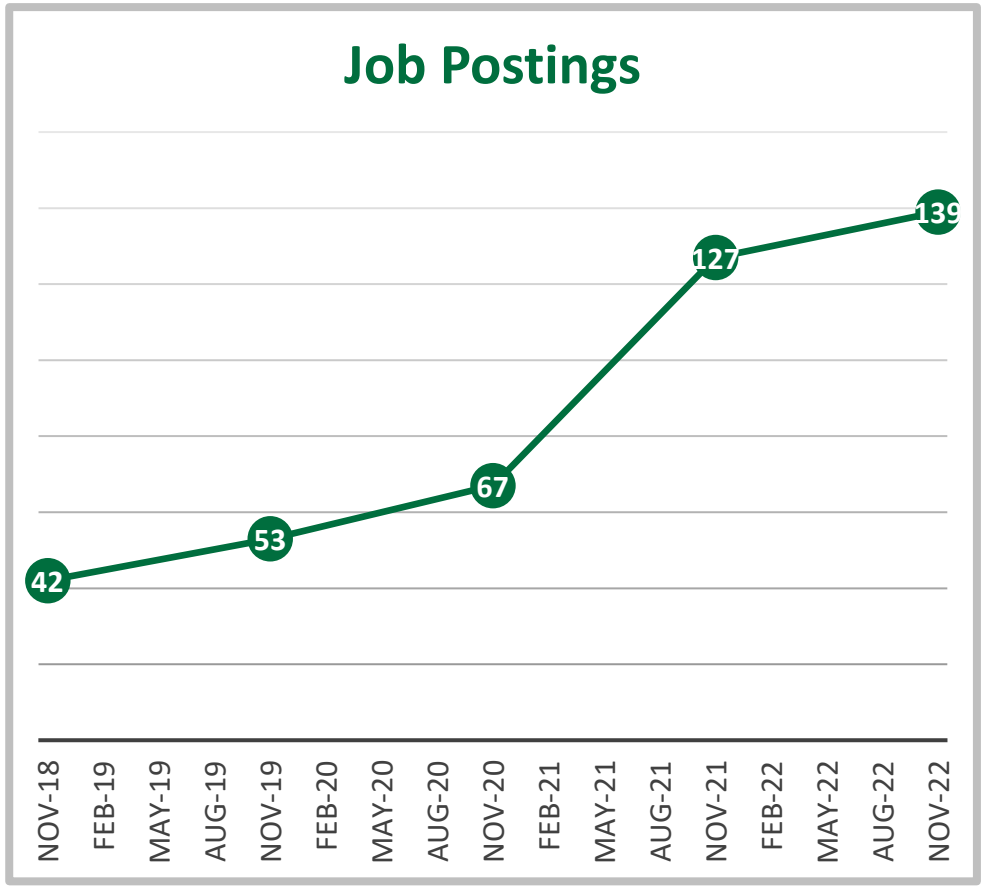
Establishing the Bioequivalence Safe Space for Immediate-Release Oral Dosage Forms using Physiologically Based Biopharmaceutics Modeling (PBBM): Case Studies

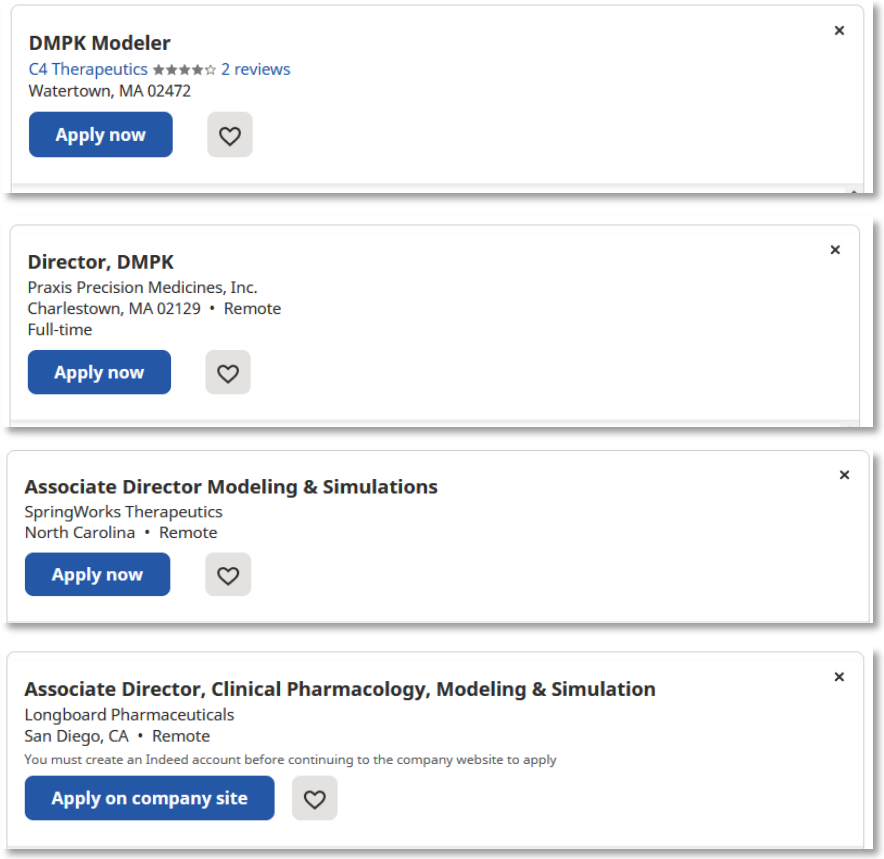
Tycho Heimbach, Filippos Kesisoglou, Jasmina Novakovic, Christophe Tistaert, Martin Mueller-Zsigmondy, Sivacharan Kollipara, Tausif Ahmed, Amitava Mitra, Sandra Suarez-Sharp

Heimbach et al. (2021)
18 citations!

Professional Development:
What a Great Time to be a PBPK Modeler

Lonza
Small Molecules





PBPK Modeling Saves Resources in R&D and Regulatory Interactions

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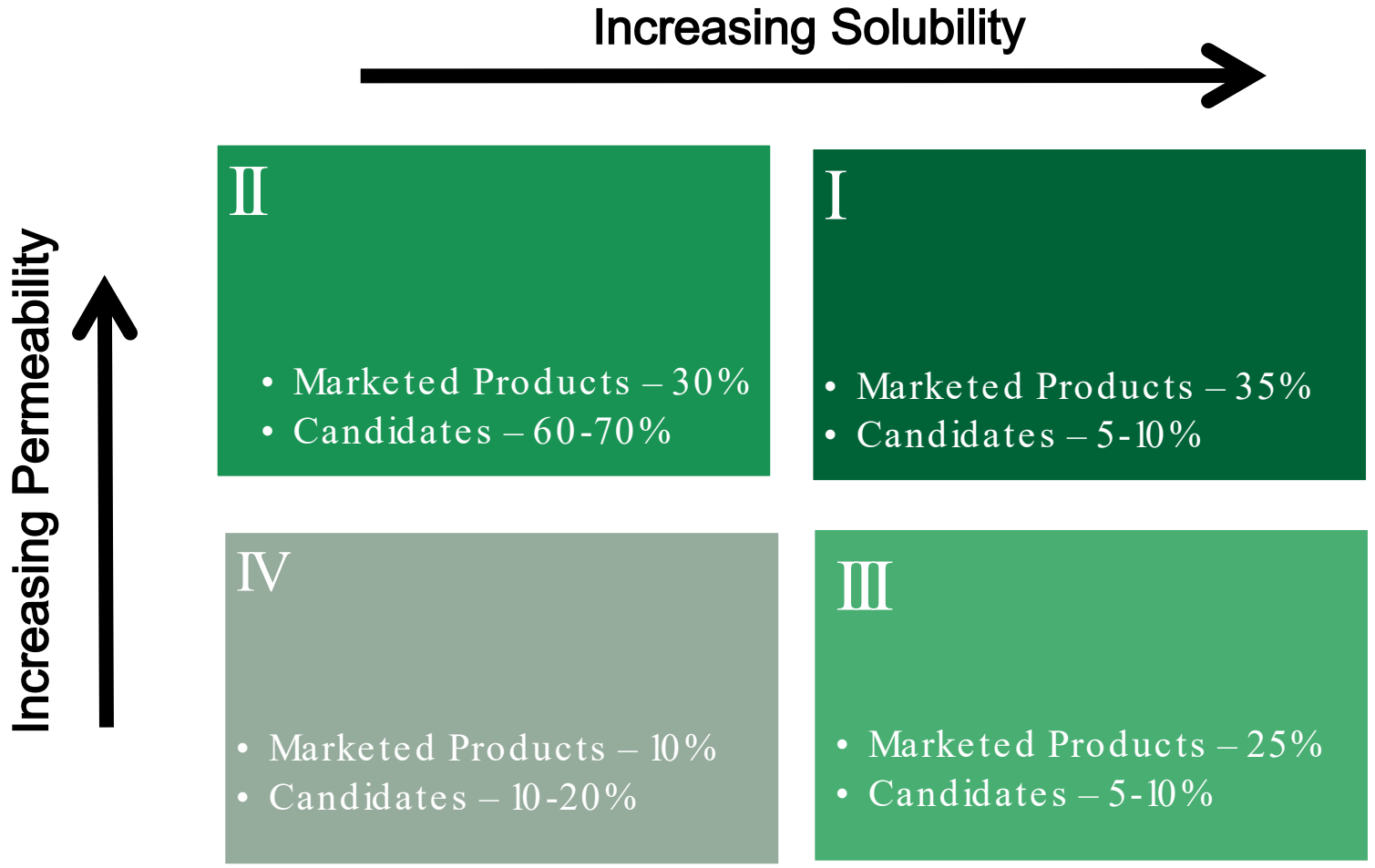
1. Prioritize and **make better investments**
2. Integrate data to **tell a compelling story**
3. Eliminate **unnecessary animal/human studies**
4. Improve productivity to be the **first to market**
5. Reduce **regulatory burden**
6. Improve **patient lives**

Oral Absorption Risks and Mitigation Strategies

27 April 2023

Solubility and Permeability are Key Underlying Mechanisms of Poor Oral Absorption

Lonza Small Molecules



Reference 1 – Rene Holm (Lundbeck) 2010 Improving Solubility, Reference 2 – Pharma A – Internal Data; 2004 – 2008, Reference 3 – M.E. Brewster 3rd Annual Congress on Strategies to Enhance Solubility and Drug Absorption 2008, Reference 4 – Pharma B – Internal Data; Oncology and AntiInfectives

Solubility and Permeability Depend on Drug Physicochemical Properties and GI Physiology

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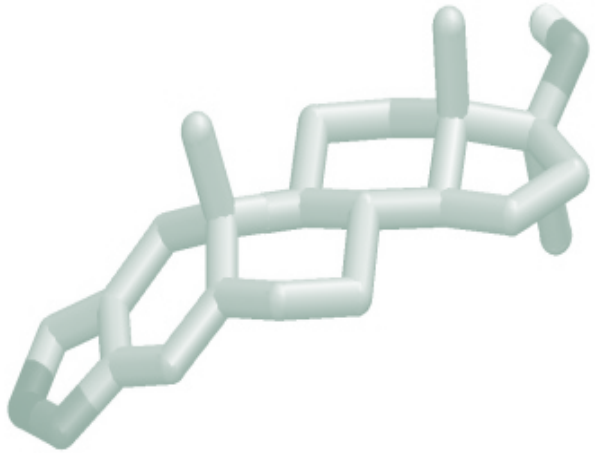
Drug Properties



Physiological Properties

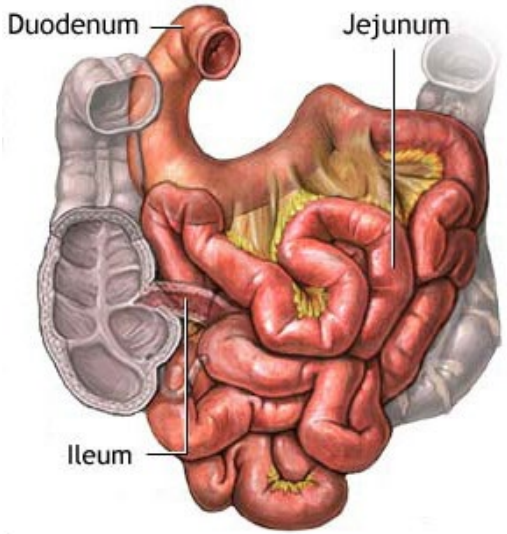


Image source: daviddarling.info

Poor Solubility and Permeability can Negatively Impact in Vivo Oral Absorption and Plasma Exposure

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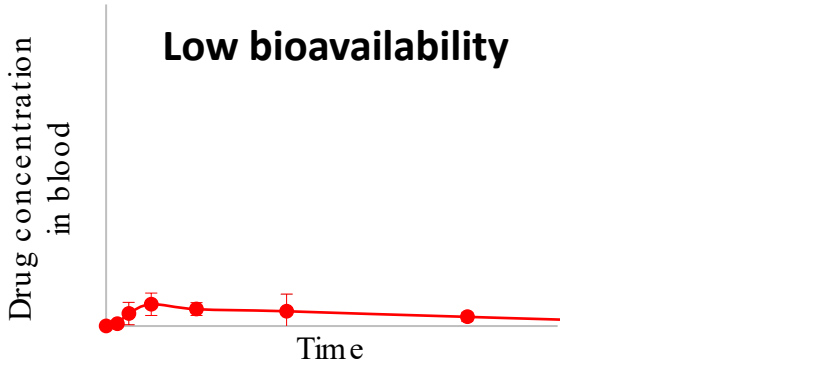
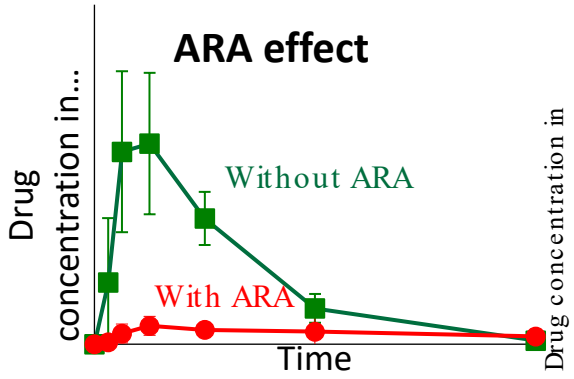
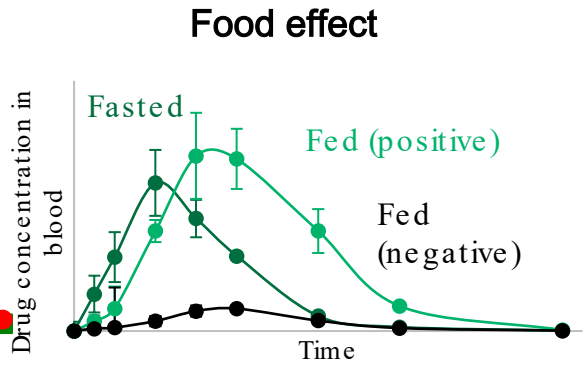
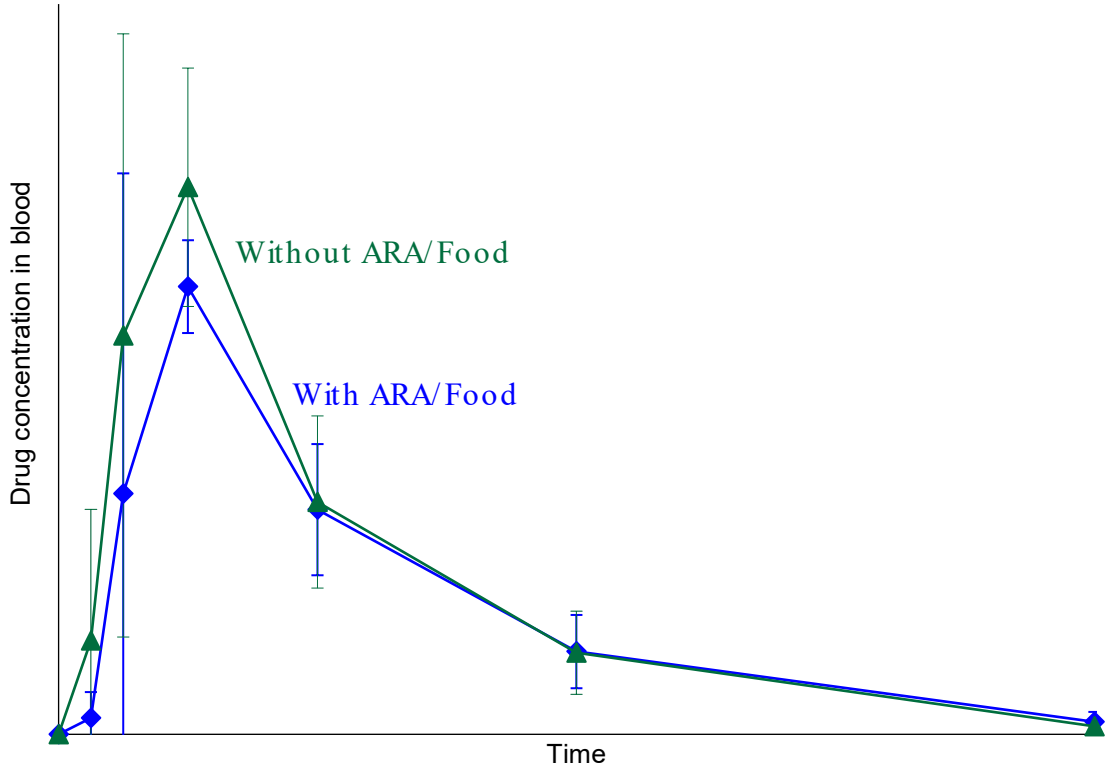
Potential oral exposure risks







With form/formulation mitigation



Several Formulation Strategies Exist for Mitigating Poor Oral Absorption Through Solubility Enhancement

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Solid-State Alteration: Form, Particle Size

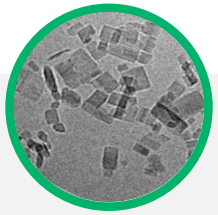
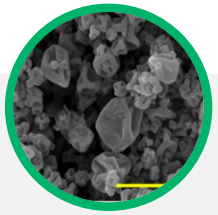
- Polymorphs
- Amorphous solid dispersions
- Micronized drug
- Nanocrystals

New crystalline compound

- Co-crystals
- Salts

Solvation, Complexation

- Co-solvents
- Surfactants
- Cyclodextrins
- Lipids



H.D. Williams et al. "Strategies to Address Low Solubility in Discovery and Development," Pharmacol Rev, 65(2013)315-499

Lonza PBPK Modeling Services

27 April 2023

Lonza PBPK Modeling Services Key Outputs for our Clients

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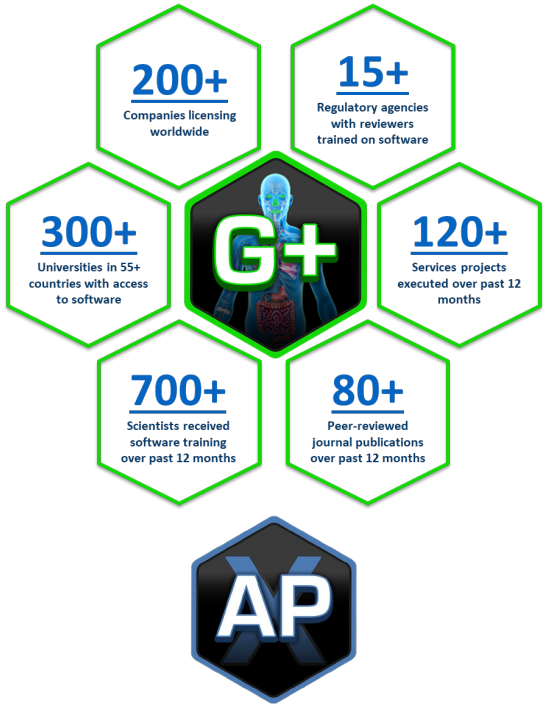
1	Identify drug absorption risks	e.g. solubility, dissolution rate, permeability, food effect, pH-dependent ARA effect
2	Recommend absorption risk mitigation strategies	e.g. salt, cocrystal, amorphous solid dispersion 
3	Inform/De -risk preclinical/clinical study outcomes	e.g. dose, formulation, food, pH-dependent ARA impacts on exposure

Lonza PBPK Modeling Services Key Components

Lonza Small Molecules

Established ADMET Predictor® and GastroPlus® modeling and simulation software†



†Simulations Plus, Lancaster, CA (Simulations Plus | Modeling & Simulation Software (simulations-plus.com))

An expansive set of custom and off-the shelf in-vitro performance tests

Vast experience in API synthesis, solubility enhancement, & formulation development

- **> 10** ASDs developed that have progressed to market
- **> 20** patent families in ASD/SDD space
- **> 230** therapies in clinical development in 2022
- **~140** commercial scale small molecule projects supported in 2022

Lonza's Custom and Off-The-Shelf in Vitro Bioperformance Toolkit

Lonza Small Molecules

Amorphous solubility

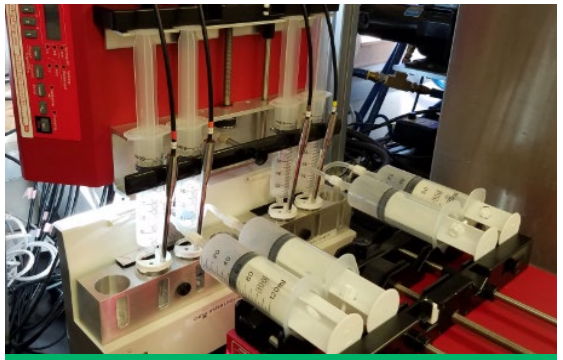
- Amorphous "solubility"
- Precipitation risk

Dissolution

- Dissolution rate
- Precipitation rate
- Speciation

Membrane flux

- Impact of dissolved species on diffusion
- Rate-limiting step to absorption

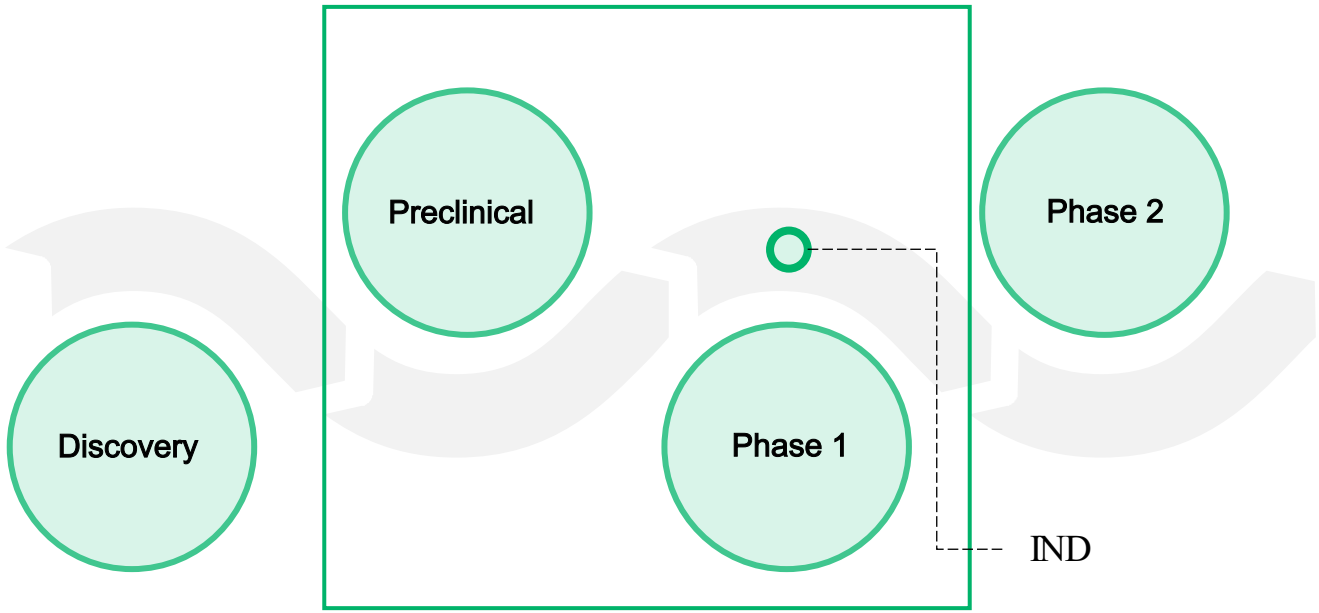


Controlled transfer dissolution

- Impact of dynamic pH and transit on dissolution precipitation rate

PBPK is Part of a Suite of Lonza Services that Streamline Drug Development

Lonza
Small Molecules



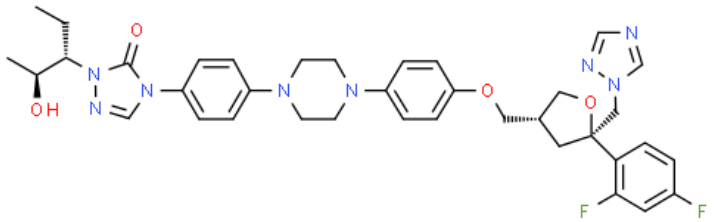
Case Study – Early API Absorption Risk Assessment

27 April 2023

Early API Absorption Risk Assessment – Model Drug Posaconazole

Lonza Small Molecules

Posaconazole



- Azole antifungal agent
- Brand name NOXAFIL®
- Oral dosages of 100 – 400 mg per administration†

†Multiple daily dosing

Inputs

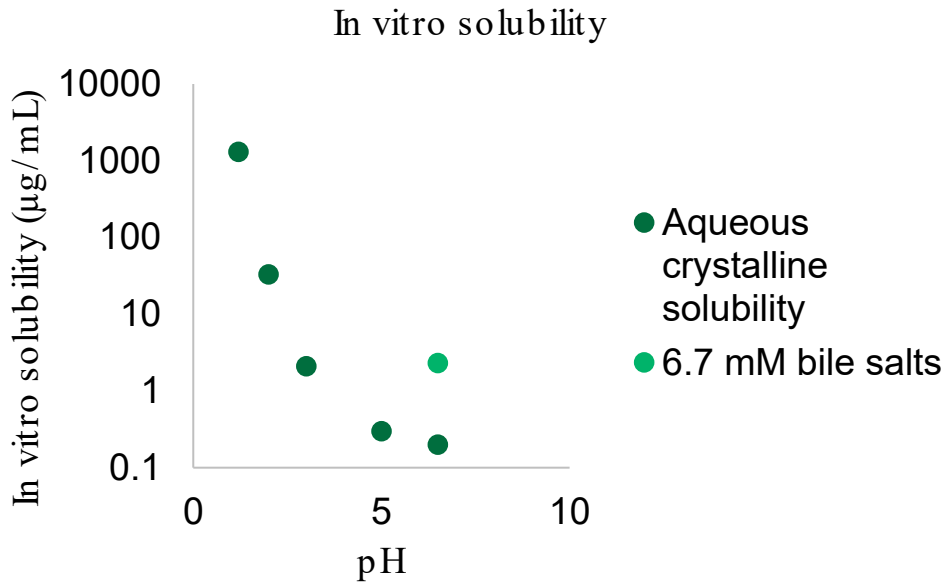
- API structure
- Crystalline solubility
- Amorphous solubility

In house calculator

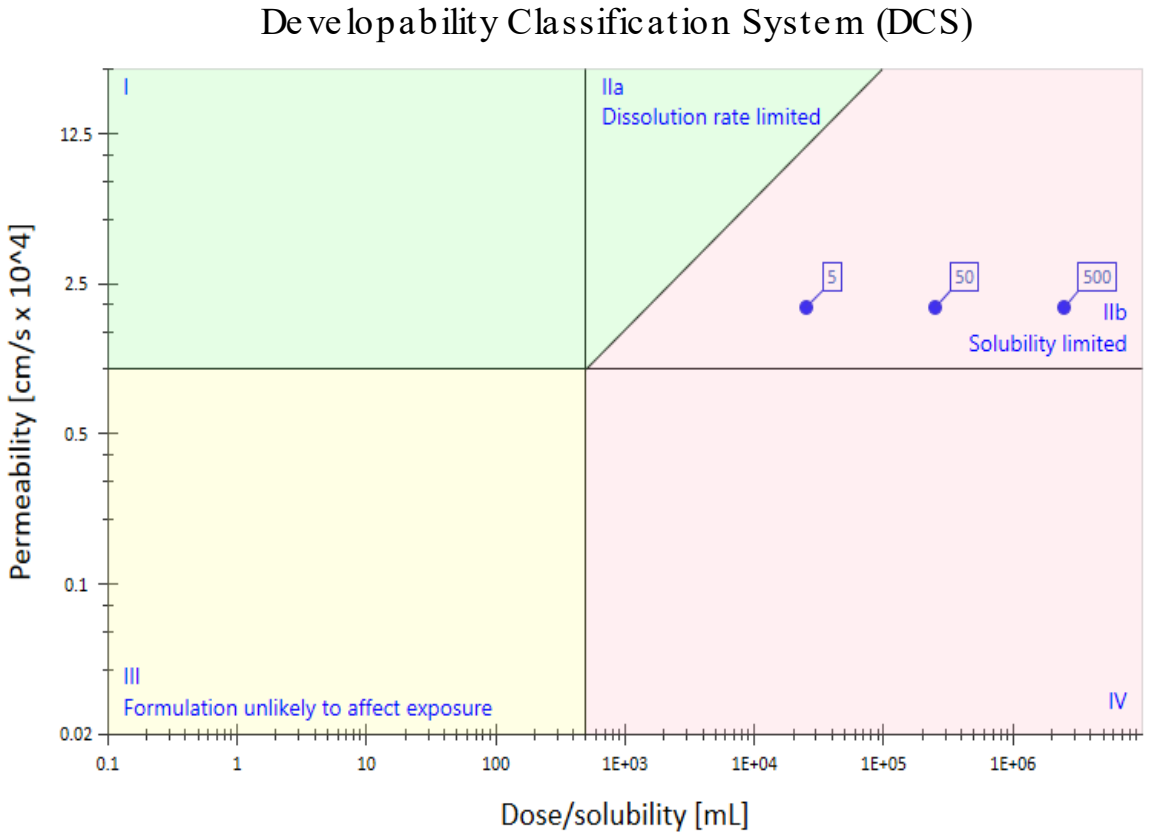
Outputs

- Barriers to absorption
- Percent dose absorbed
- Potential food/acid-reducing agent (ARA) effects

Posaconazole is a Lipophilic Weak Base with Solubility-Limited Absorption



- pH-dependent solubility
- Potential for precipitation
- High extent of bile salt micelle partitioning



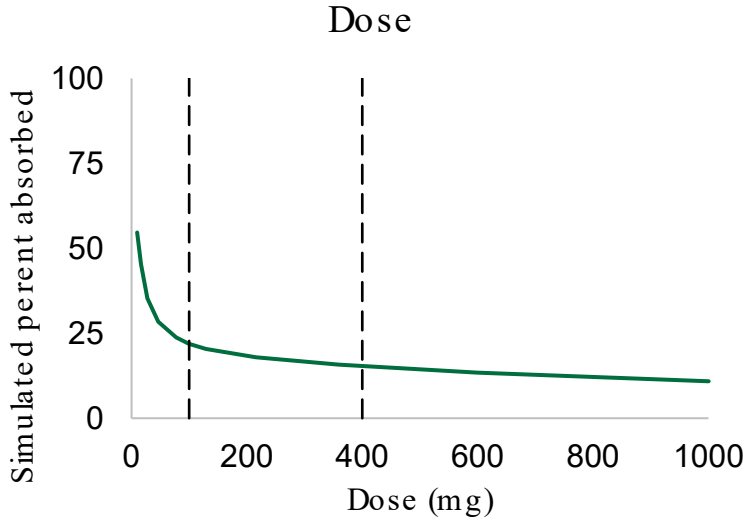
Ref: Butler & Dressman J Pharm Sci, 2010

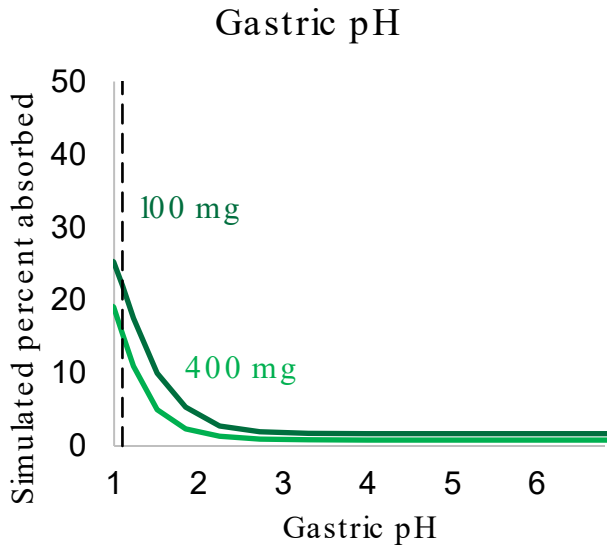
Projected Percent Dose Absorbed in Fasted Humans is Low and Sensitive to Key Variables

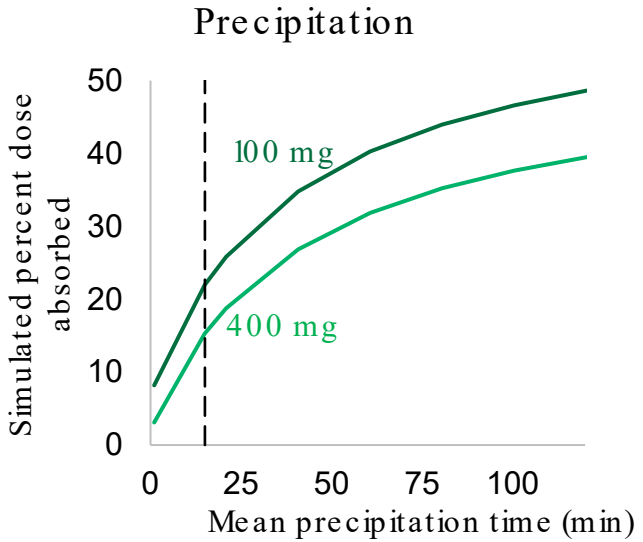
Lonza Small Molecules

Parameter sensitivity analyses

- Fasted human physiology
- IR tablet
- 25 µm particle radius
- S+ $P_{eff} = 2 \times 10^{-4}$ cm/s







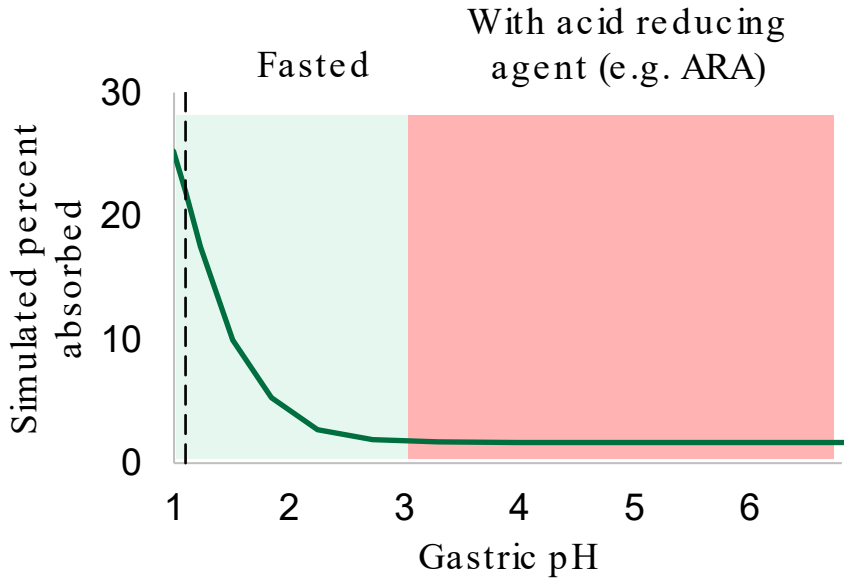
NOXAFILOS (crystalline oral suspension) bioavailability: ~8%–47%*

*Ref: Lipp, Mycoses. 2008

Posaconazole has Potential for pH-dependent DDIs with ARAs and Food-Drug Interactions

Lonza Small Molecules

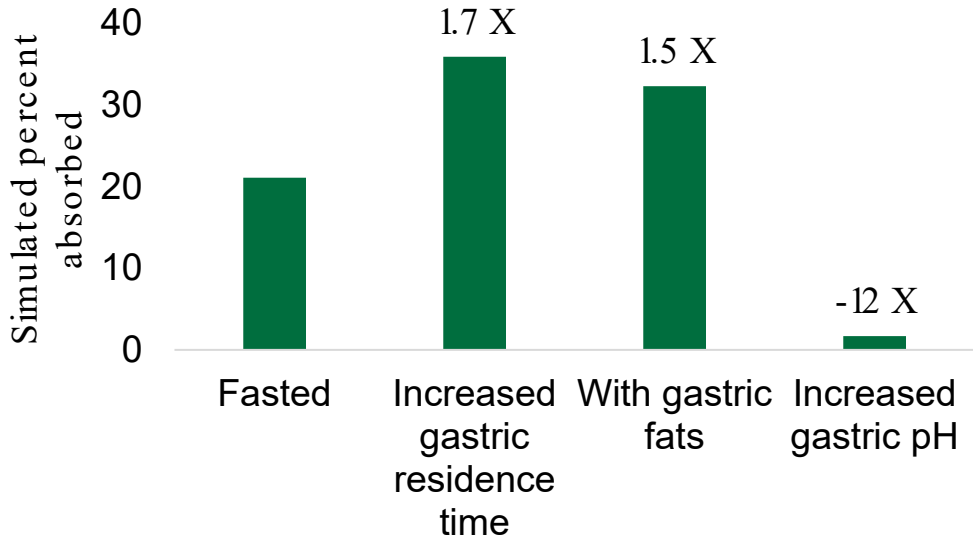
Change in % absorbed with ARA-induced physiology (100-mg dose)



NOXAFIL OS: exposure ↓ 30% w/ARA*

*400 mg single dose, ref: FDA label

Change in % absorbed with fed-induced physiology (100-mg dose)

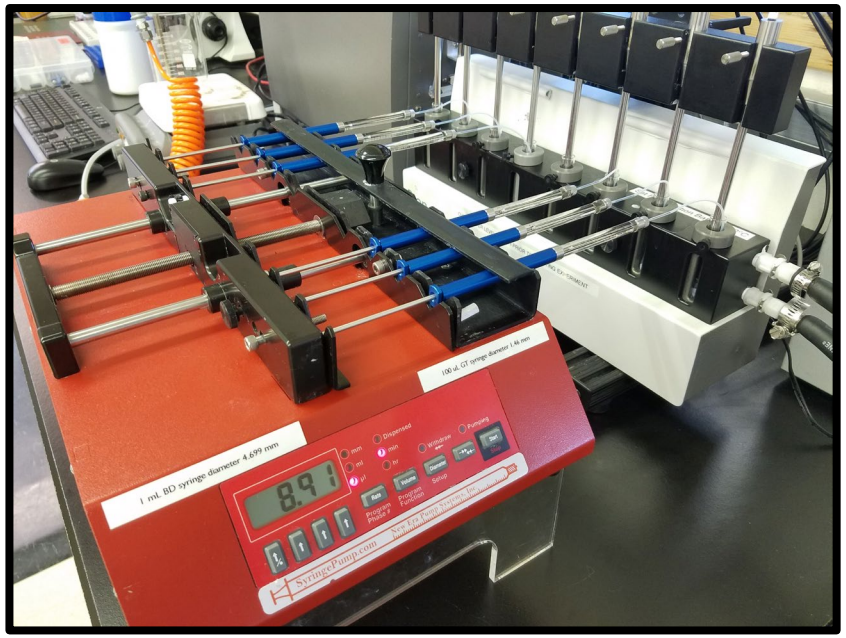


NOXAFIL OS: exposure ↑ 2.5- to 3-fold with a meal**

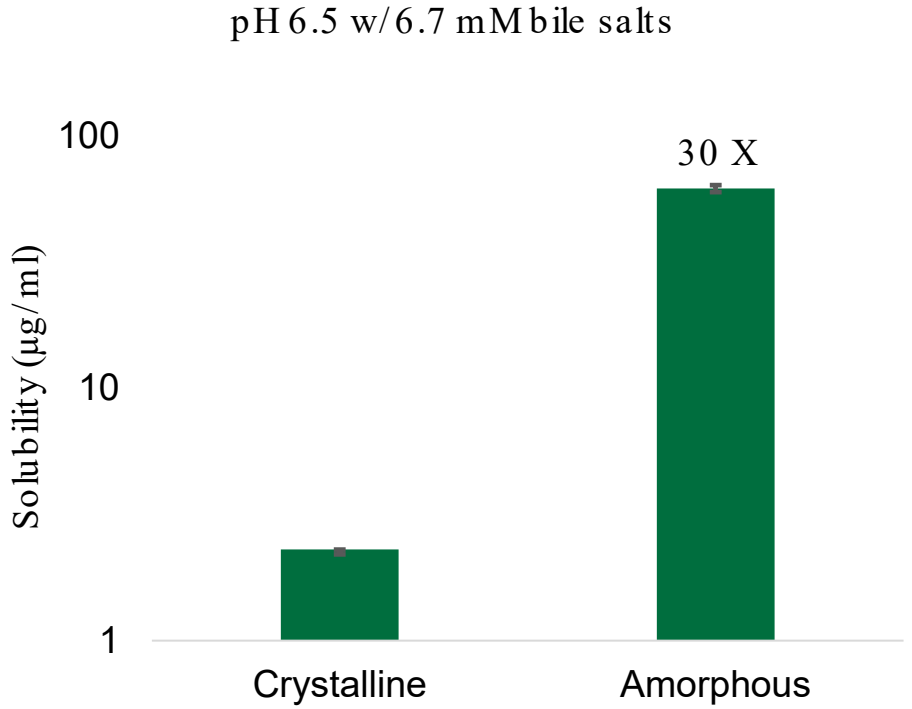
*100 mg, single dose, ref: Krishna et. al. Antimicrob. Agents Chemother., 2012

Evaluating Amorphous Form of Posaconazole to Mitigate Absorption Risks

- Measure posaconazole amorphous solubility



Lonza custom in vitro solvent shift UV assay

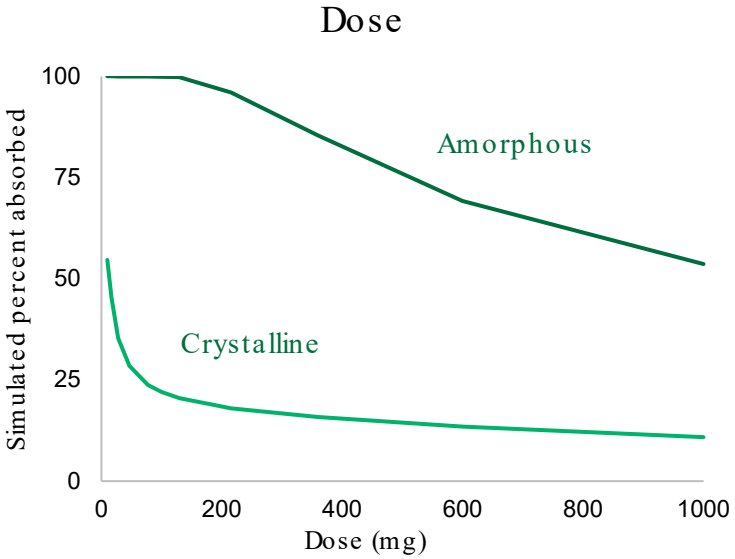


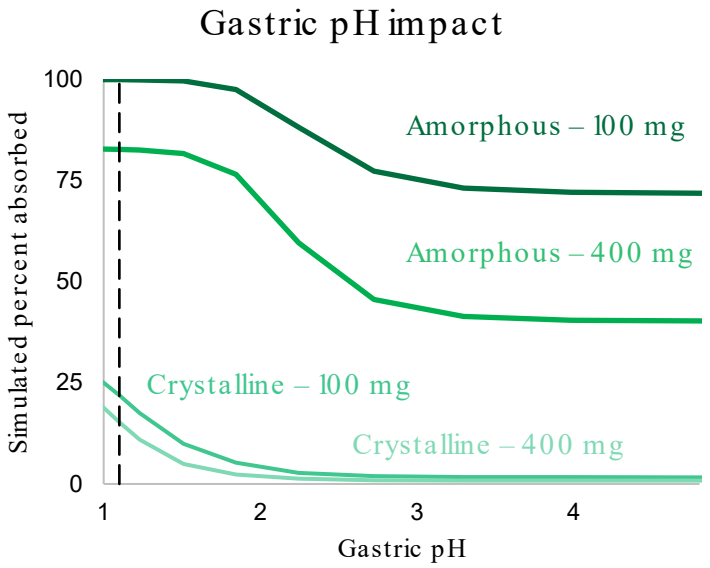
Projected Percent Dose Absorbed is Improved for Amorphous Form Compared to Crystalline Free Base

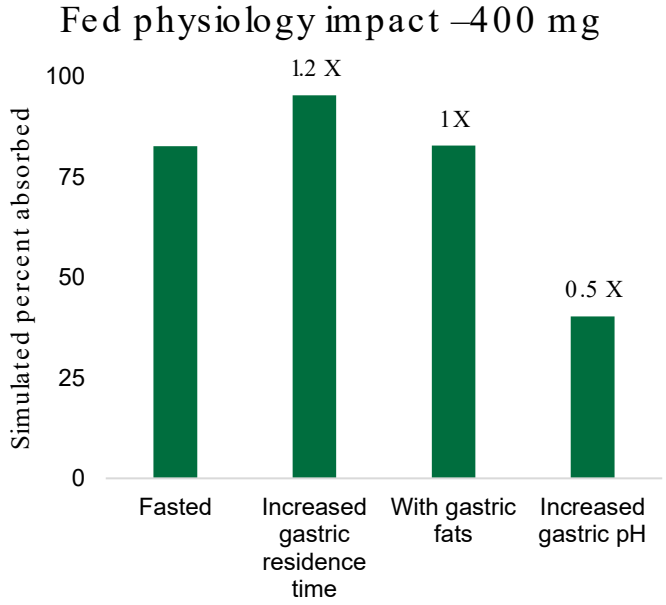
Lonza Small Molecules

Parameter sensitivity analyses

- Fasted human physiology
- IR tablet
- 25 µm particle radius





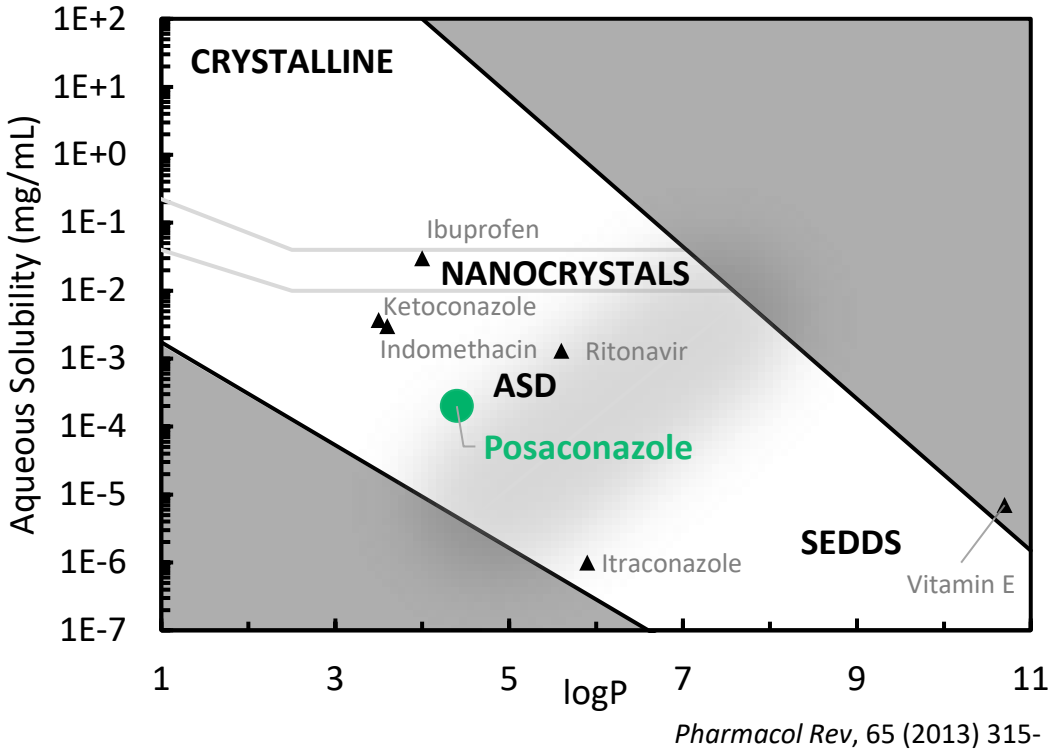


NOXAFIL delayed release (DR) tablet (amorphous):

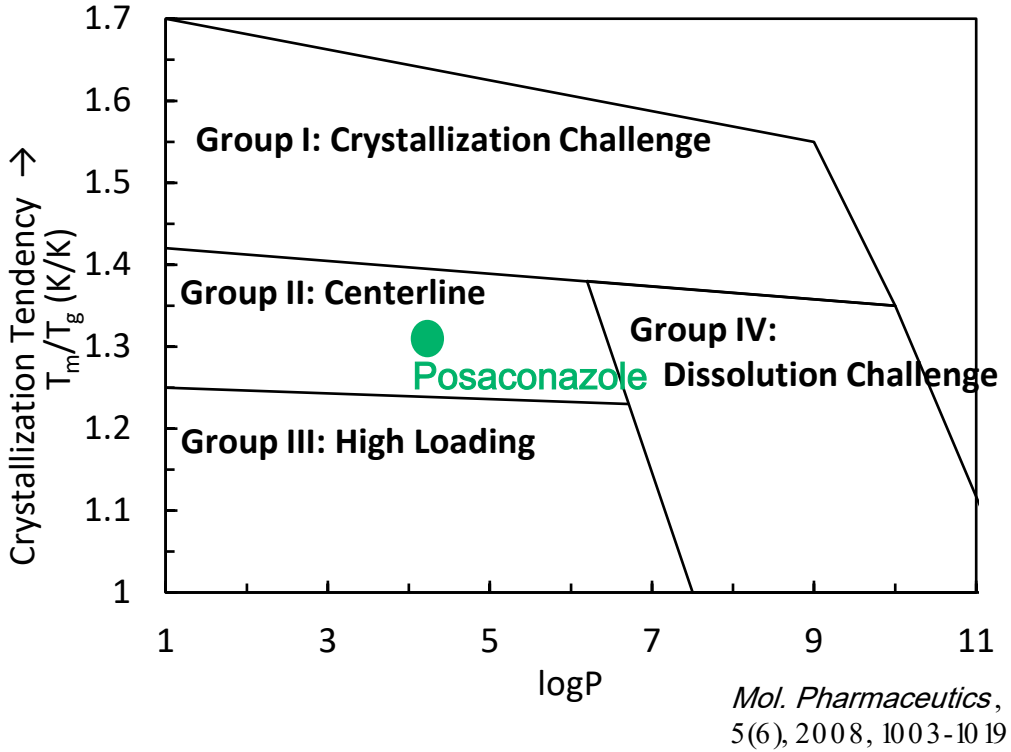
- Exposure ↑ 3fold vs. NOXAFIL OS fasted*
- Exposure 1.1- to 1.5-fold with food*†
- Exposure Λ with ARA**

*100 mg, single dose, ref: Krishna et. al, Antimicrob. Agents Chemother., 2012
†300 mg, single doe, ref: Kersemaekers et. al, Antimicrob. Agents Chemother., 2015
**400 mg, single dose, ref: Kraft et. al, Antimicrob. Agents Chemother., 2014

Posaconazole Projected to be a Favorable ASD Candidate



Pharmacol Rev, 65 (2013) 315-



Mol. Pharmaceutics, 5(6), 2008, 1003-1019

Posaconazole ASD Tablet Outperforms Crystalline Oral Suspension In Vitro

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Small Molecules

Posaconazole ASD tablet

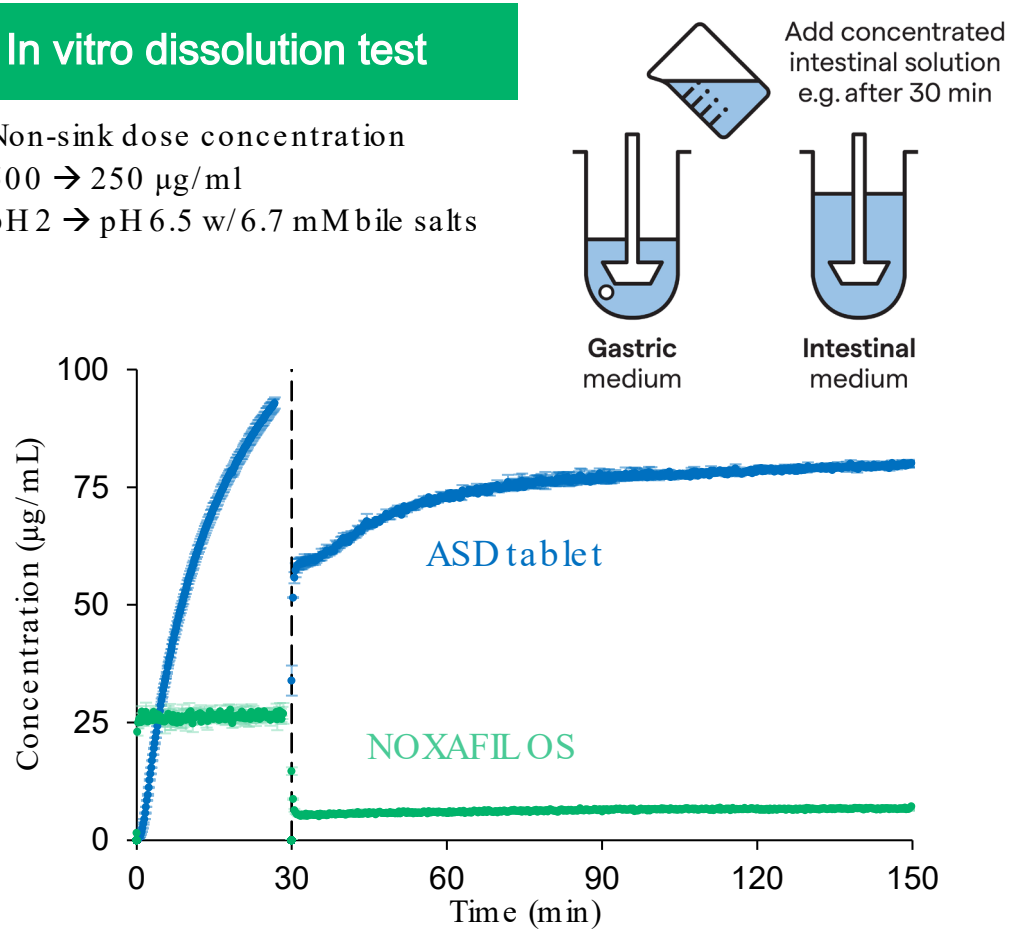
- 75/25 (w/w) posaconazole/Eudragit® L100 ASD granulated with HPMCAS-H
- 25% drug loading in tablet
- IR tablet (1-min disintegration)
- Physically stable ASD

NOXAFIL® OS

- 40 mg per mL crystalline posaconazole
- IR suspension

In vitro dissolution test

- Non-sink dose concentration
- 500 → 250 µg/ml
- pH 2 → pH 6.5 w/ 6.7 mM bile salts



Using PBPK Modeling for Preclinical Study Design & Risk Mitigation

Lonza
Small Molecules

Posaconazole
Drug product formulations

ASD tablet

NOXAFIL OS

Image: media.empr.com

PBPK inputs

- API structure
- Crystalline solubility
- Amorphous solubility
- **In vitro dissolution**
- **Caco-2 P_{app}***
- **In vivo data (IV bolus)****

AP G+

Lonza internal calculator

Outputs

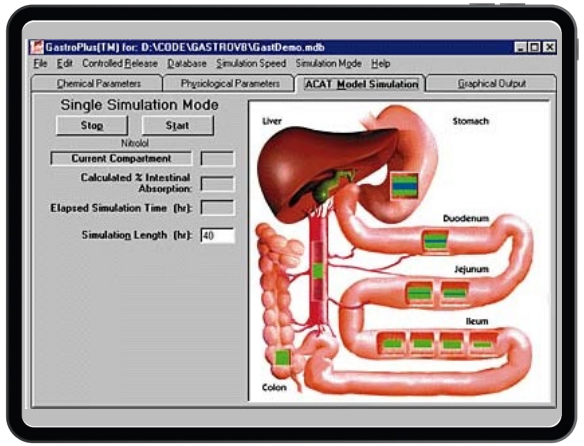
- Plasma exposure
- Amorphous enhancement
- Sensitivity to physiological & formulation variables

* Hens et. al, *Mol Pharm*, 2017, **Nomier et. al., Antimicrob. Agents Chemother., 2000

ASD tablet projected to outperform crystalline suspension in fasted dogs

Lonza Small Molecules

PBPK model - GastroPlus® v9.6

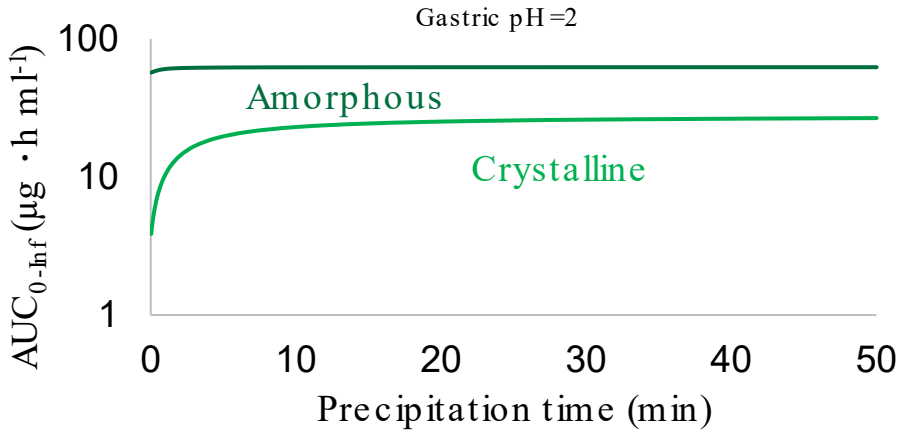


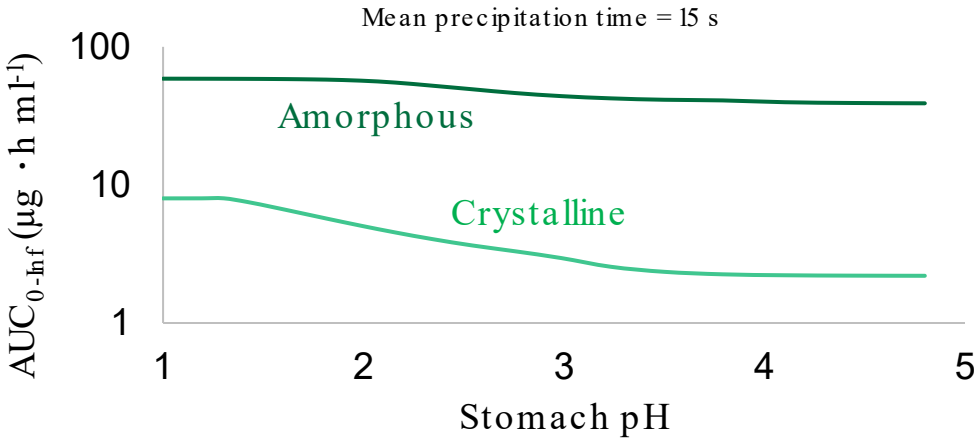
- Fasted dog physiology
- 100 mg single dose
- Bottom-up
- No optimization

PSA results: ASD tablet vs NOXAFIL OS:

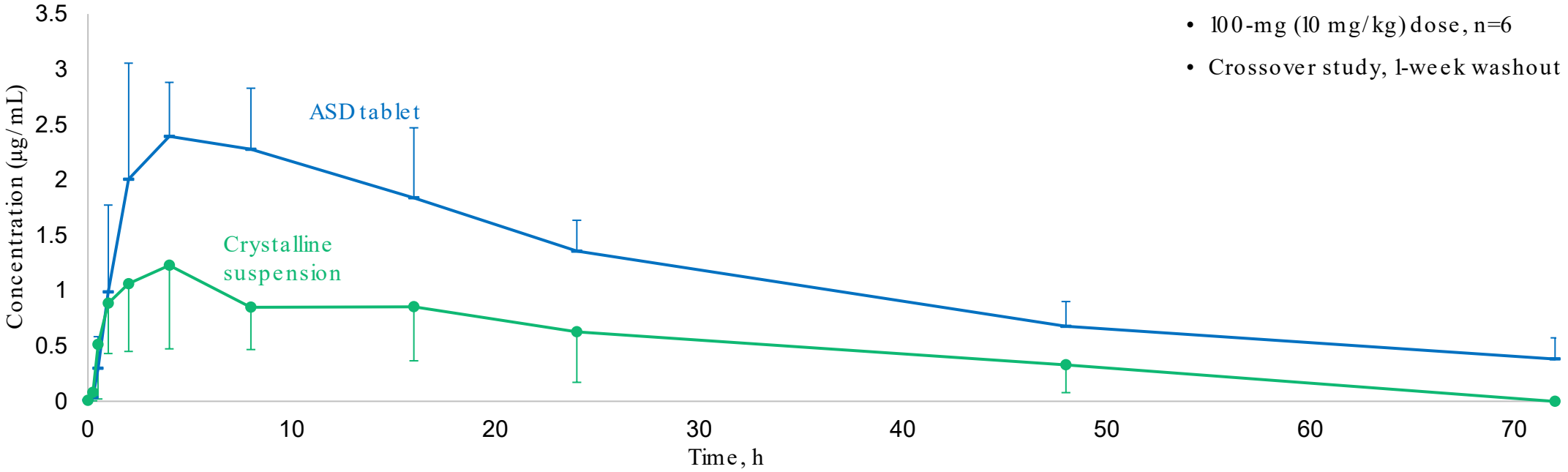
↓ Sensitivity to gastric pH & precipitation

↑ AUC by 2- to 15-fold (gastric pH 1-2)





ASD Tablet Achieves 2-Fold Improvement in AUC in Pentagastrin-Treated Dogs in Line with PBPK Projections



- 100-mg (10 mg/kg) dose, n=6
- Crossover study, 1-week washout

Treatment	C_{max} (µg/ml)	$AUC_{0\text{-}72\ h}$ (µg*h/ml)	AUC p-value (relative to crystalline)	PBPK simulated range in AUC
ASD tablet	2.7	82	0.008	57-63
Crystalline suspension	1.3	37	n/a	3.9 - 37

Mudie et al. *Mol Pharm* 2020, 17, 12

Conclusions

Posaconazole Case Study

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Successfully used PBPK modeling and in house in vitro tools to:

- Identify poor oral absorption of posaconazole
- Forecast amorphous form as viable strategy to increase absorption and decrease sensitivity to physiological variables

Milligrams of API
~1 week
no in vivo data

- Develop robust posaconazole ASD tablet formulation that outperforms crystalline suspension
- Set expectations for dog study by forecasting exposure enhancement of ASD tablet compared to NOXAFIL OS

Grams of API
~3 months
1 preclinical study

Case Study – Preclinical Study De-risking

27 April 2023

Preclinical Study De-risking – Acalabrutinib Case Study

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CALQUENCE® (acalabrutinib) 100 mg capsules

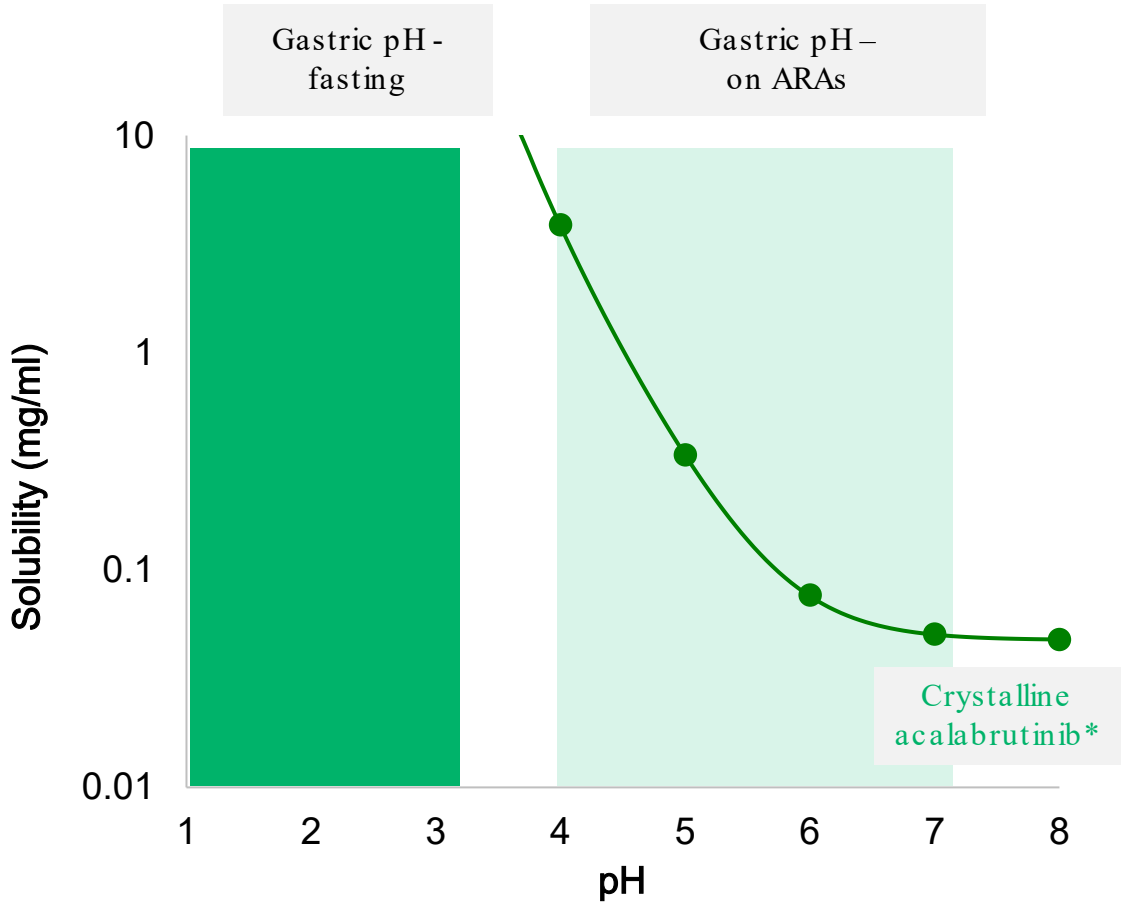
100 mg
Not actual capsule size.

12 hours

- Bruton tyrosine kinase inhibitor indicated for oncology
- Plasma AUC reduced by 43% when taken with PPI*
- Patients must avoid taking with PPIs or other ARAs

Images from www.Calquence.com (accessed June 8, 2021)

*Calquence FDA label



*Pepin et al. *Eur J Pharm Biopharm* 2019 Sep;142

Acalabrutinib ASD Tablet Developed to Overcome pH Effect

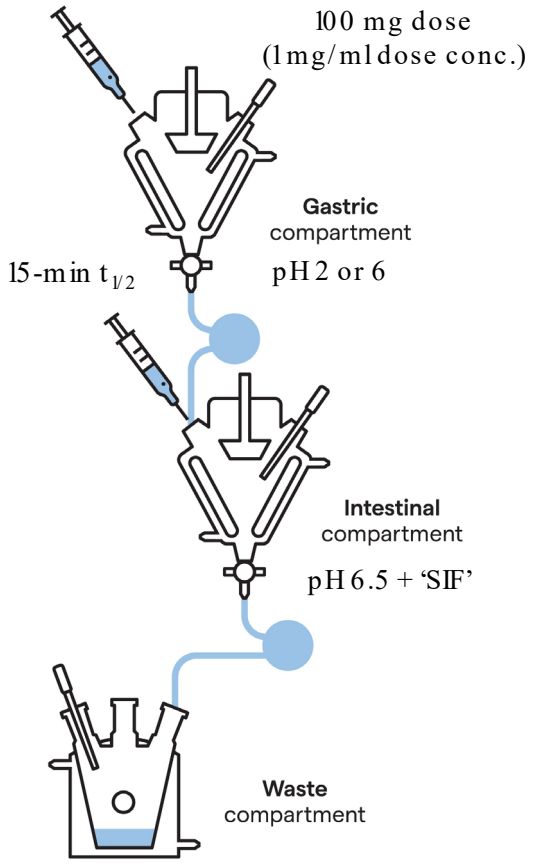
ASD tablet design

- 50/50 acalabrutinib/HPMCAS-H ASD in IR tablet
- Good stability
- 60% smaller than Calquence capsules

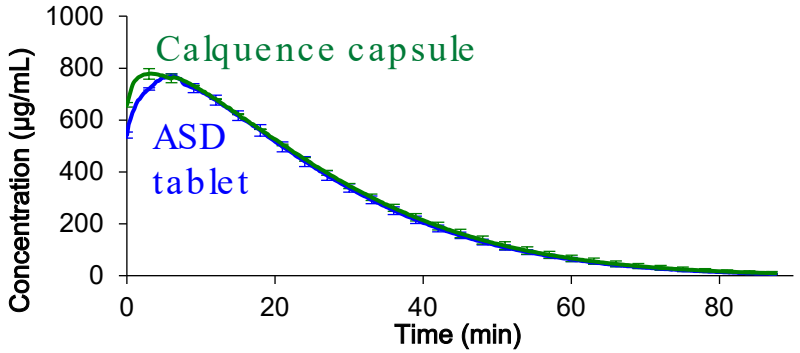
In vivo study goals

- Mitigate pH effect using ASD tablet
- Match plasma exposure of fasted CALQUENCE® using ASD tablet
- Show pH effect with Calquence

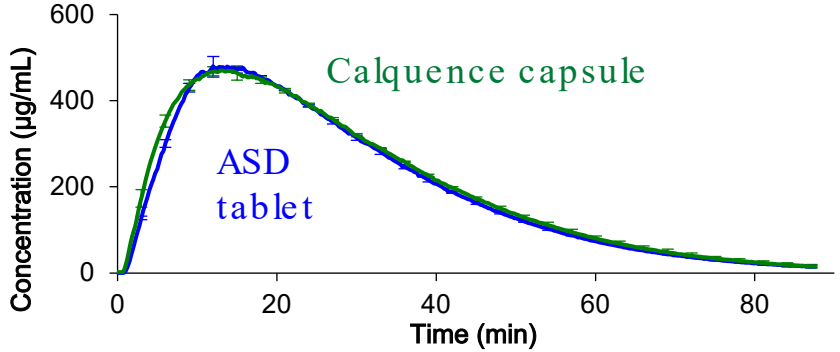
ASD Tablets Achieve Performance Goals In Vitro



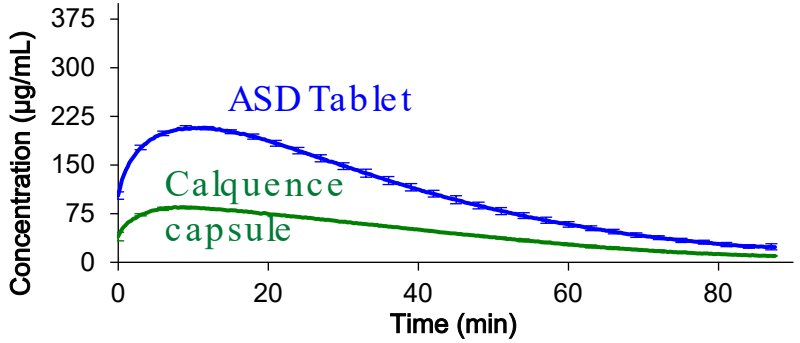
Gastric Compartment, pH 2



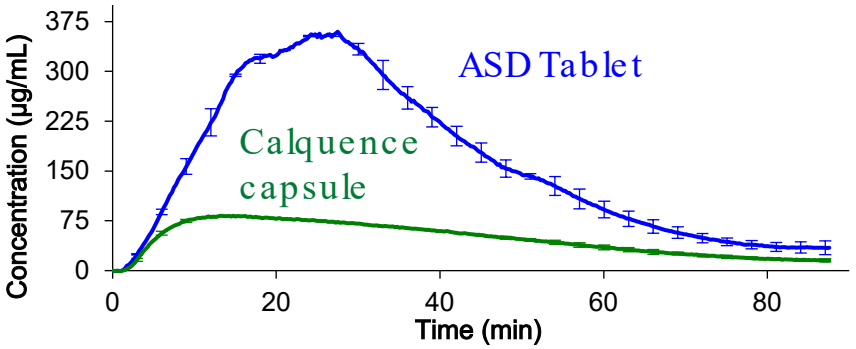
Intestinal Compartment



Gastric Compartment, pH 6



Intestinal Compartment



Mudie et al. *Pharmaceutics* 2021, *13(4)*, 557

PBPK Predictions – Gain Confidence in Formulation Identified From in Vitro Testing

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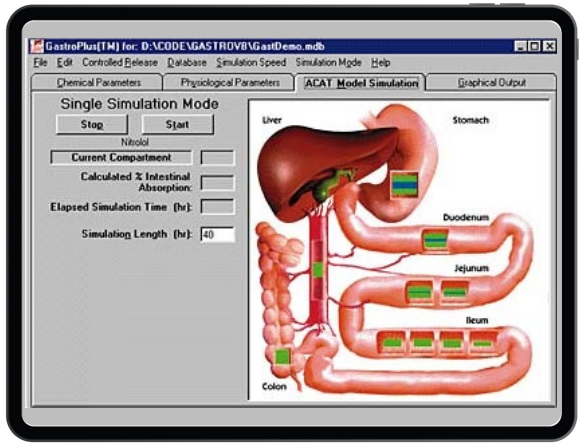
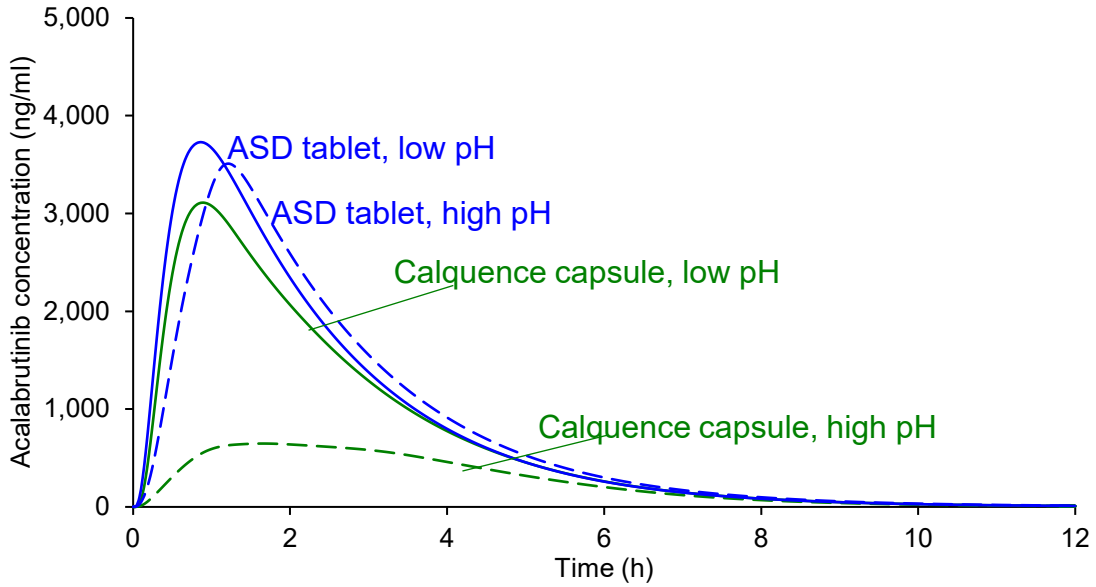
PBPK model - GastroPlus® v9.8



- Fasted dog physiology
- 100 mg single dose
- Bottom-up
- No optimization



Model inputs†

- API structure
- Crystalline solubility
- Amorphous solubility
- In vitro dissolution
- MDR1-MDCK P_{app}*
- In vivo data (oral solution)**

Simulation results†

✓ Mitigate pH effect
✓ Match exposure of Calquence at low pH
✓ Show Calquence pH effect

†Mudie et al. *Pharmaceutics* 2021, *13* 1257, *Pepin et al. *Eur J Pharm Biopharm* 2019 Sep;142, ** Podoll et. al, *Drug Metab Dispos*, 47 2019

In Vivo Data Matches Bottom – up PBPK Predictions for Successful Pre-Clinical Study

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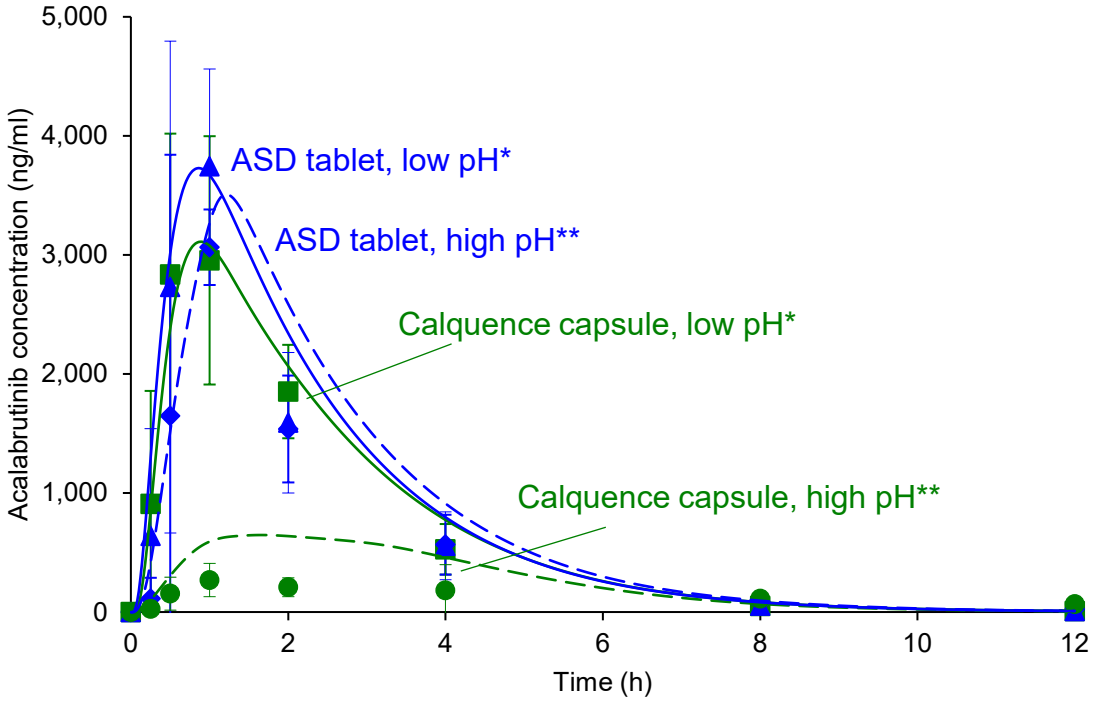
100 mg dose

Overnight fast, n = 6, crossover study, 1 – wk washout



- $AUC_{0\text{-inf}}$ within 10% for ASD tablet at low and high pH
- Good prediction accuracy (absolute average fold error of $AUC_{0\text{-inf}} < 2$)
- Overcame pH effect on the first try using PBPK

* 6 µg/kg subcutaneous pentagastrin, ** 40 mg oral famotidine

Mudie et al. *Pharmaceutics* 2021, *13*(4), 557 & Mudie et al. *Pharmaceutics* 2021, *13*, 1257

Overall Conclusions

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Small Scale and Early

Absorption Risk Assessments

- 1 week assessment time
- 10 – 100 mg API

Informed

Root cause analysis

- e.g. solubility, dissolution, permeability limited

Mitigation strategies

- e.g. ASD, salt, cocrystal, micronization

Saving Time and Money

Reduce the need for reformulation and/or repeated in vivo studies

- ~0.5-2.0M$ & 6-9 months for reformulation, clinical readiness and clinical supplies

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- Christopher Craig
- David Lyon
- Kimberly Shepard
- Nishant Biswas
- Molly Adam

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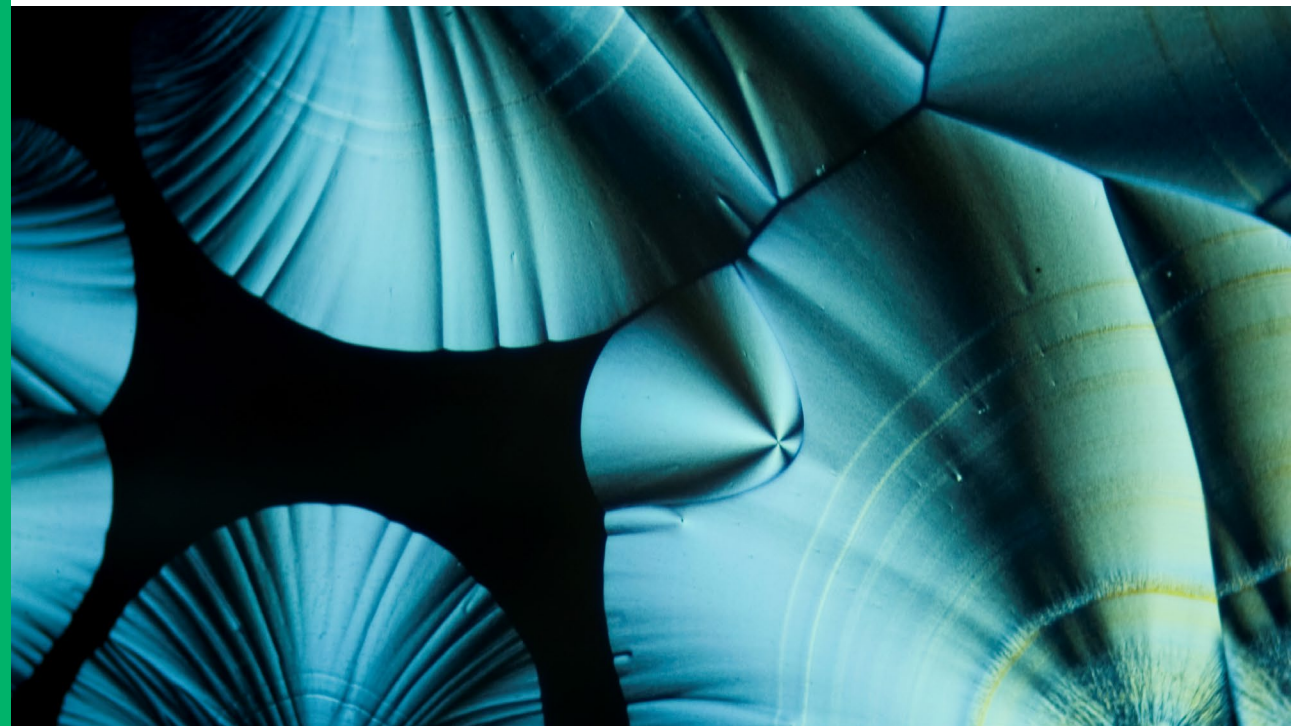
Q&As



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27 April 2023