Using PBPK modeling to assess the impact of diseases on oral drug absorption: case study in HIV-infected patients

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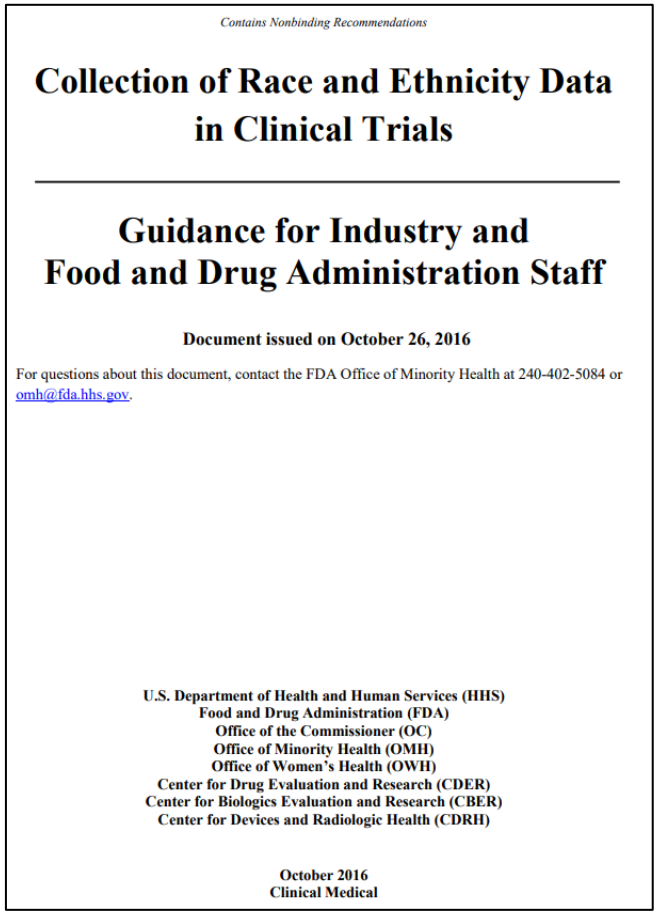
Outline

- Background
  - Efforts to enhance diversity of clinical trial populations
  - Challenges
- PBPK modeling & extrapolation
  - Separation between drug- and system-related parameters
  - Reverse translation approach
- Case study – ketoconazole
  - Translating *in vitro* biopharmaceutics data
  - IVIVE of precipitation
  - IVIVE of dissolution
  - Forward projection: PK in HIV-infected patients

Background

- 2012 - Food and Drug Safety and Innovation Act (FDASIA)
- Sec. 907 requires the FDA to provide Congress with an action plan enhancing diversity of clinical trial populations



Contains Nonbinding Recommendations

Collection of Race and Ethnicity Data in Clinical Trials

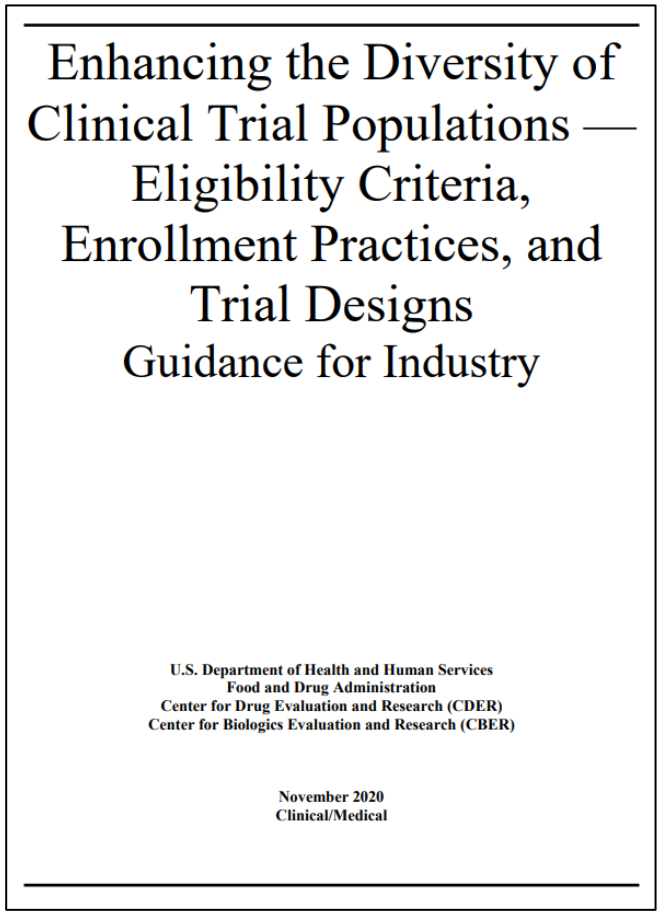
Guidance for Industry and Food and Drug Administration Staff

Document issued on October 26, 2016

For questions about this document, contact the FDA Office of Minority Health at 240-402-5084 or omh@fda.hhs.gov.

U.S. Department of Health and Human Services (HHS)
Food and Drug Administration (FDA)
Office of the Commissioner (OC)
Office of Minority Health (OMH)
Office of Women's Health (OWH)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiologic Health (CDRH)

October 2016
Clinical Medical



Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2020
Clinical/Medical

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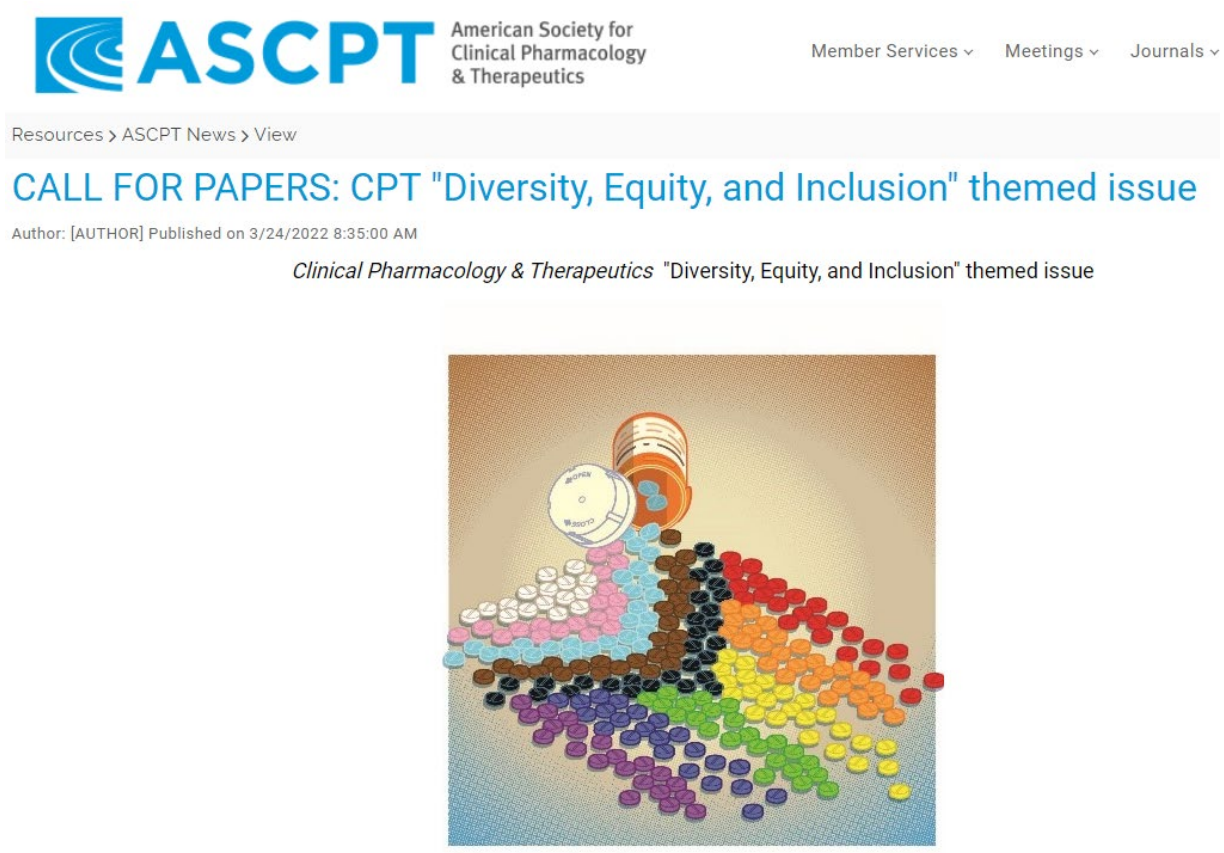
Background

- Significant efforts have been made by patient organizations, academicians and clinical pharmacology societies



- Clinical pharmacology in vulnerable populations
- Transgender studies
- Pharmacogenomic studies in minority populations
- **Challenges** and **opportunities** for clinical pharmacology research in minority populations

Source: https://www.ascpt.org/Resources/ASCPT-News/View/ArticleId/27720/CALL-FOR-PAPERS-CPT-Diversity-Equity-Inclusion-themed-issue

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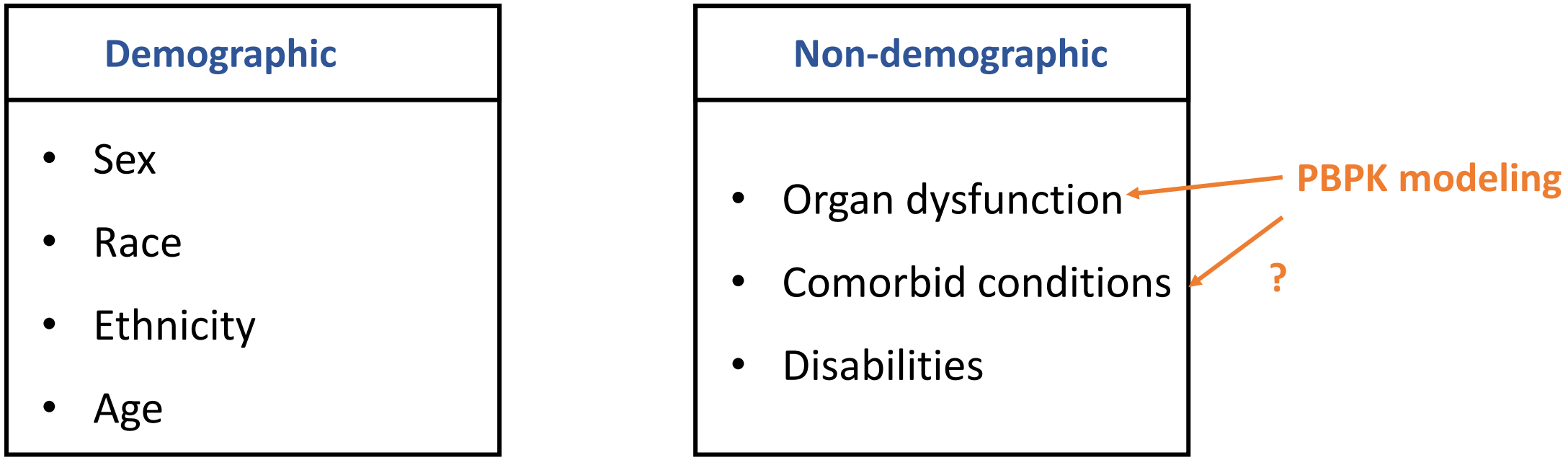
Background

- Two complementary perspectives



- Enhancing diversity may be challenging for drugs showing a wide "prescribability" potential
  - Antimicrobials
  - Anti-inflammatory drugs

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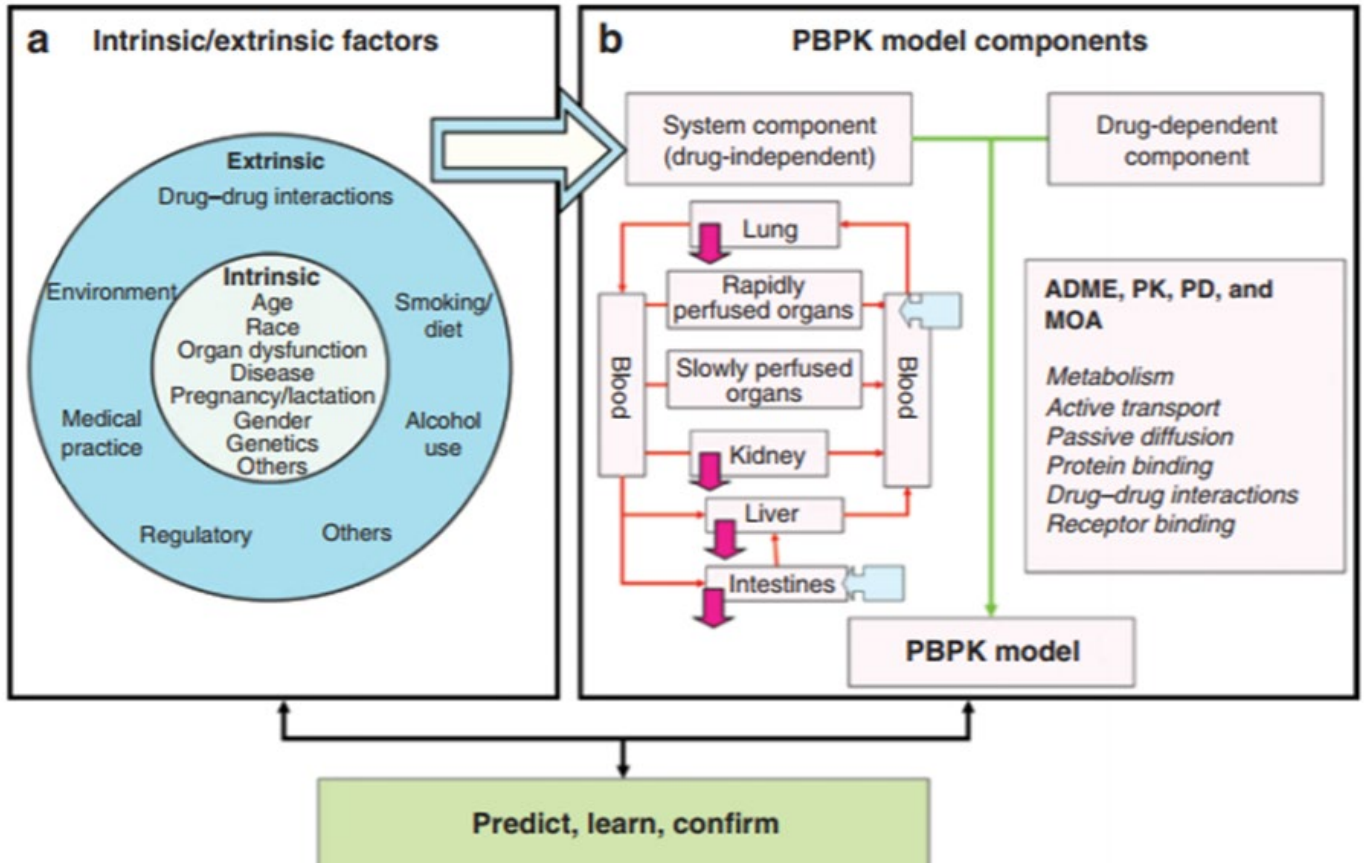
PBPK modeling & extrapolation

- Separation between drug- and system-related parameters



Zhao et al, *Clin Pharmacol Ther* 2011;89(2):259-67

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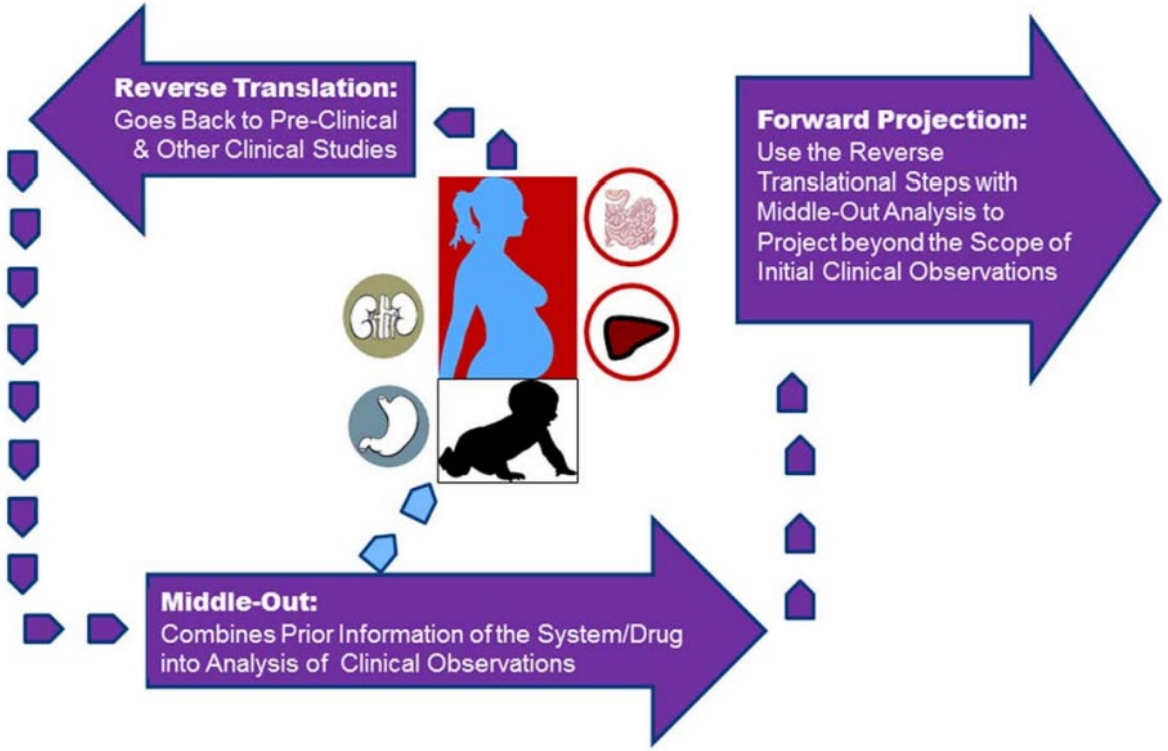
PBPK modeling & extrapolation

- Reverse translation approach



Rostami AH 2018, *Clin Pharmacol Ther* 103(2):224-232

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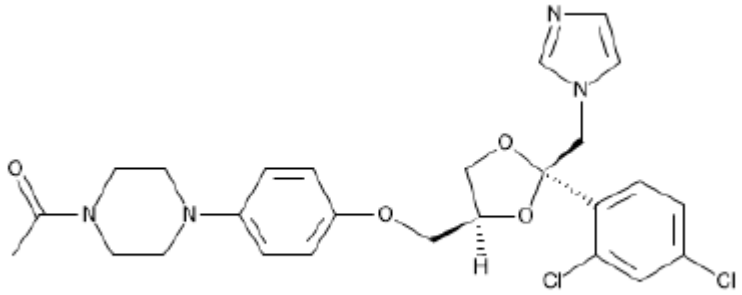
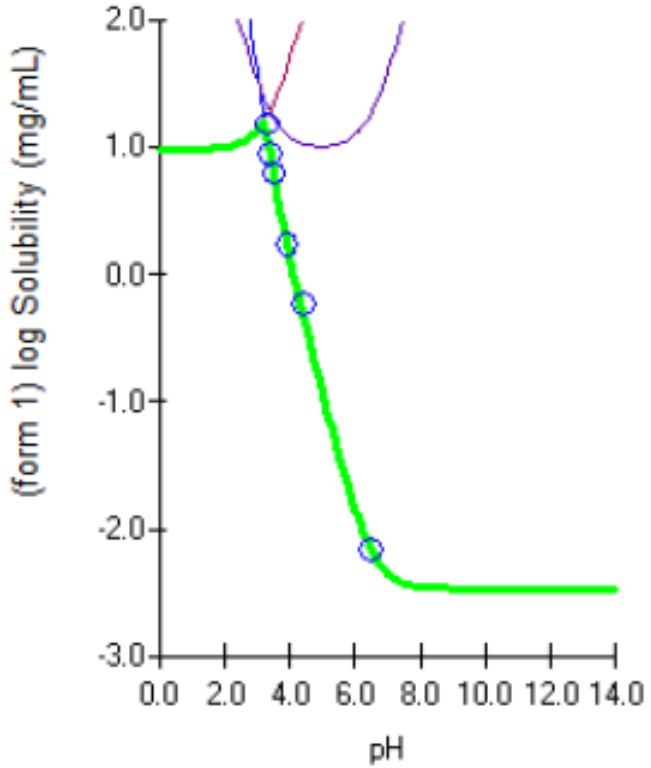
Case study

- Ketoconazole (BCS II weak base)
  - Dose-dependent precipitation kinetics
  - Dose-dependent metabolism
  - LogP = 3.73
  - pka = 3.4 and 6.51
  - f_u = 1%
  - BP = 0.6





Walter & Kurz, 1988. *J Pharm Pharmacol* 40:689-693; Daneshmend et al, 1988. *Clin Pharmacokin* 14:13-34; Matthew et al, 1994. Pharm Res 10(3):418-422; Pathak et al, 2017. *Mol Pharmaceutics* 14:4305−4320; Galia et al, 1998. *Pharm Res* 15(5):698-705.

Model-based analysis of *in vitro* data

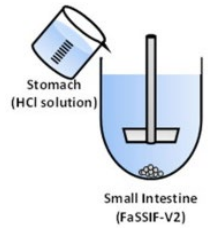
- Estimate fundamental parameters (deconvolution)

Process	In vitro system	Models	Fundamental parameters
Metabolism	Hepatocytes, human liver microsomes or recombinant enzymes	Michaelis-Menten model	K_m and V_{max}
Uptake Transport	Overexpressing cell lines suspended or plated	Mechanistic compartmental uptake models	CL_{diff}, $f_{u,cell}$, K_m and V_{max}
Dissolution / Precipitation	One- or multi-stage dissolution apparatuses	Diffusion layer models, Z-factor, Mooney model, biphasic dissolution model, transfer model, transmembrane flux model, etc.	Dependent on apparatus and model choice

IVIVE of precipitation

- Model-based analysis of *in vitro* precipitation data from different systems
  - Ketoconazole fully dissolved in the donor compartment

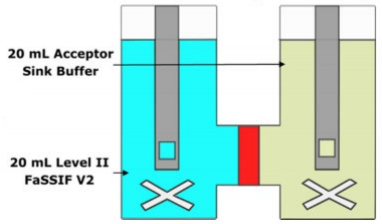
Dumping test

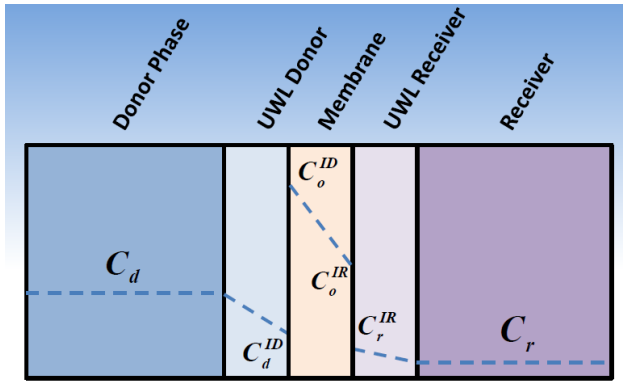


Closed system

$$\frac{dM_i}{dt} = \left(\frac{V_i}{T_{precip}}\right)(C_i - S_i)$$

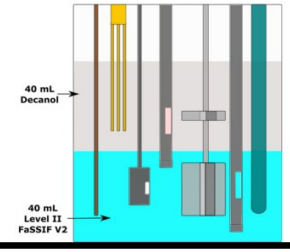
Transmembrane flux

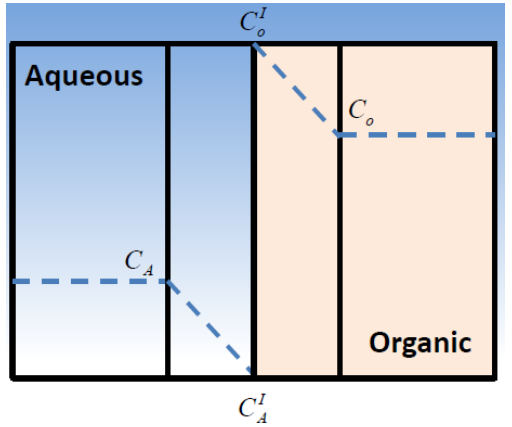




$$j_{overall} = \frac{D_A D_o D_R K_{od}}{D_A D_R h_o + D_o\left(D_R h_d K_{od} + D_A h_r K_{or}\right)}\left(C_d - K_r C_r\right)$$

Biphasic dissolution





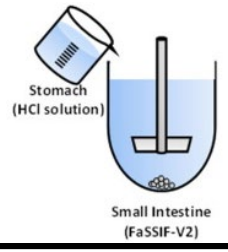
$$\frac{dm_o}{dt} = \frac{k_A k_o K_{o:w}}{k_A + k_o K_{o:w}} A_I \left(C_A - \frac{C_o}{K_{o:w}}\right)$$

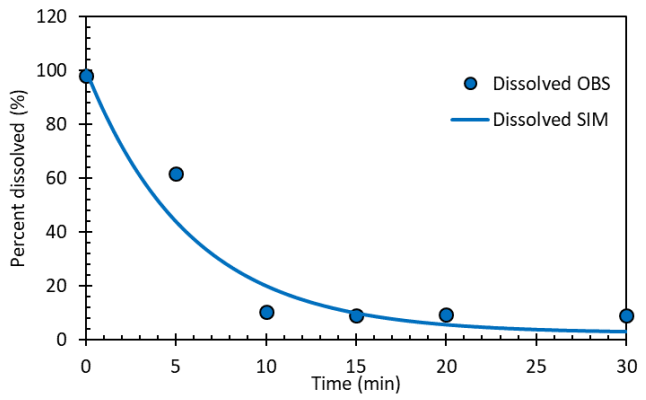
Kambayashi et al, 2016. *Eur J Pharm Biopharm* 103:95-103; Mullin, 2021. *Best Practices for Membrane & Biphasic In Vitro Dissolution with DDDPlus™& GastroPlus®*

IVIVE of precipitation

- Model-based analysis of *in vitro* precipitation data from different systems
  - First-order precipitation model

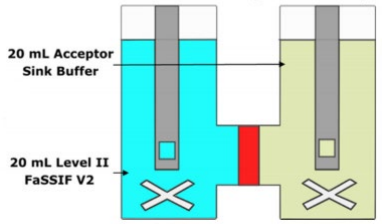
Dumping test

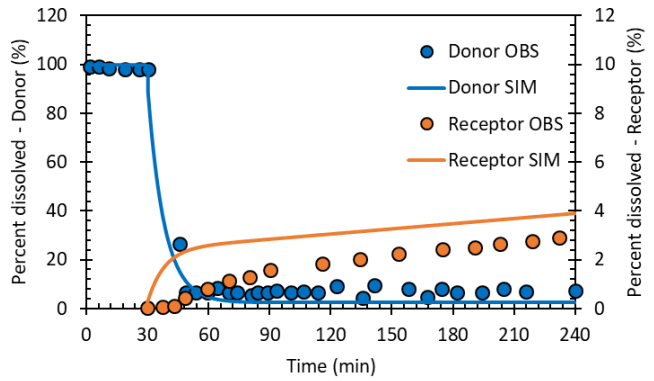




Mean precipitation time = 350 s

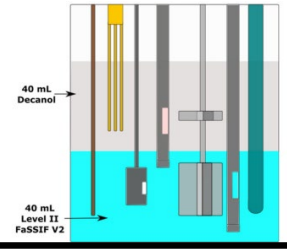
Transmembrane flux

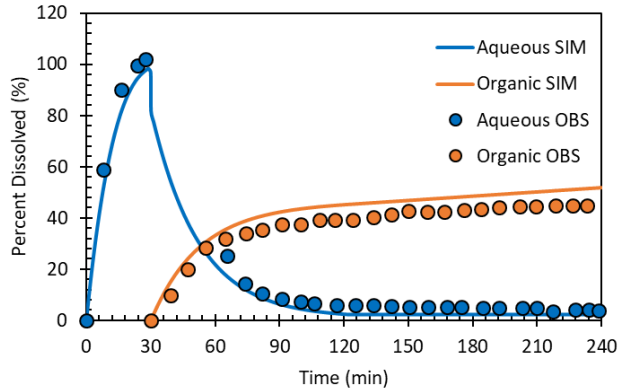




Mean precipitation time = 500 s
Surface area = 1.54 cm²

Biphasic dissolution





Mean precipitation time = 2850 s
Surface area = 19.63 cm²

Kambayashi et al, 2016. *Eur J Pharm Biopharm* 103:95-103; O'Dwyer et al, 2020. *Pharmaceutics* 12:272.

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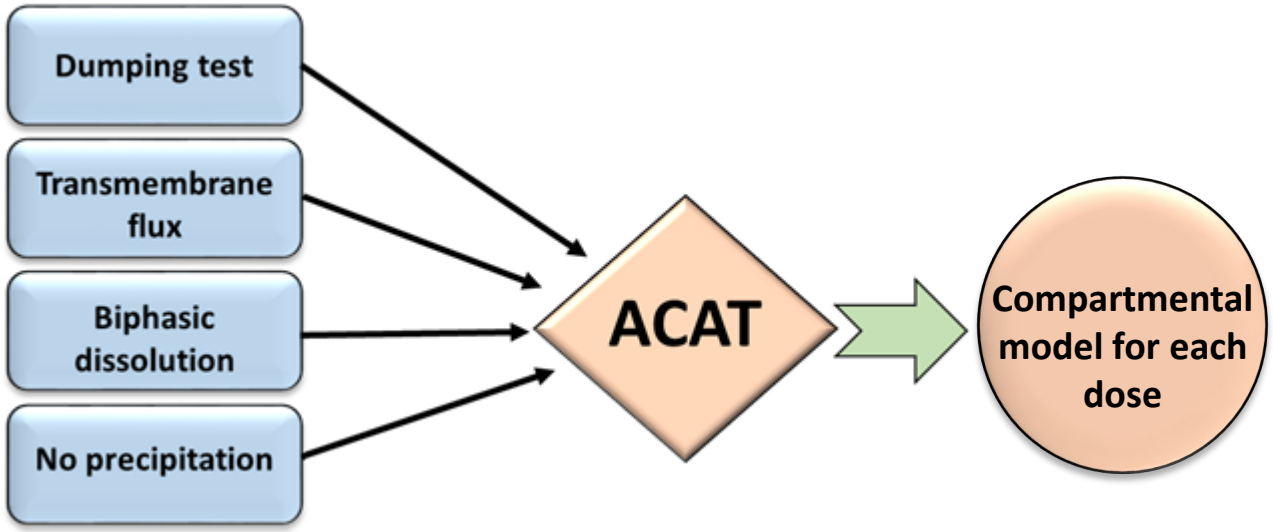
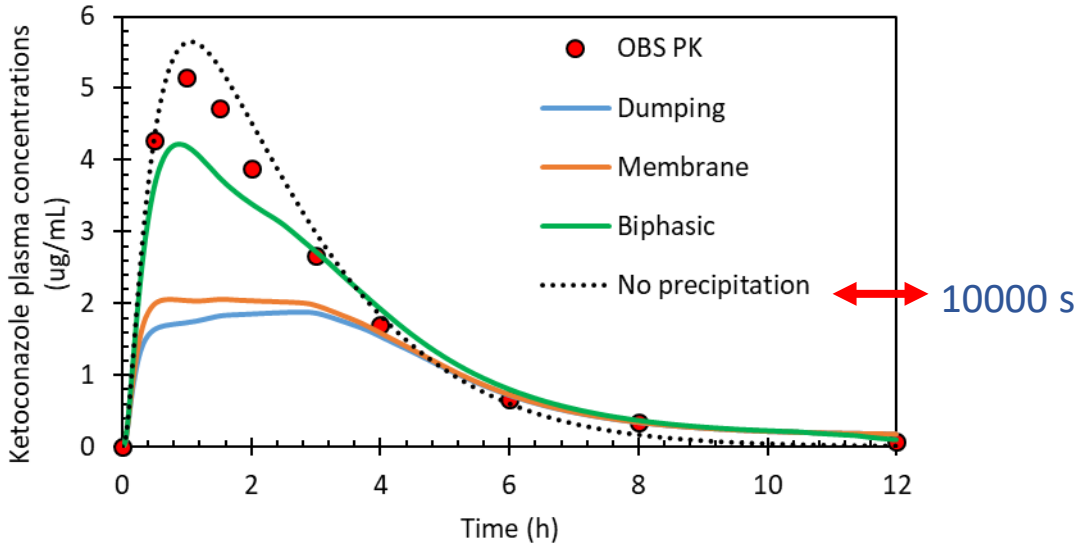
IVIVE of precipitation

- IVIVE-PBPK modeling
  - Ketoconazole <u>solution</u> 200 mg – healthy adults under fasting conditions
    - Different *in vitro* systems, different results



pH-solubility profile, pKa, P_{app} and SR
Default C1-C4

Hepatic and intestinal FPE (preclinical), f_u and BP



200 mg

OBS $AUC_{0\text{-inf}}$ = 17.9 ug.h/mL

SIM $AUC_{0\text{-inf}}$ = 12.7 ug.h/mL

CL/F = 12 L/h

Psachoulias et al, 2011. *Pharm Res* 28:3145-3158; Huang et al, 1986. *Antimicrob Agents Chemother* 30(2):206-210; Pathak et al, 2017. *Mol Pharm* 14(12):4305-4320; Cristofoletti et al. 2017 *J Pharm Sci* 106(2):560-569.

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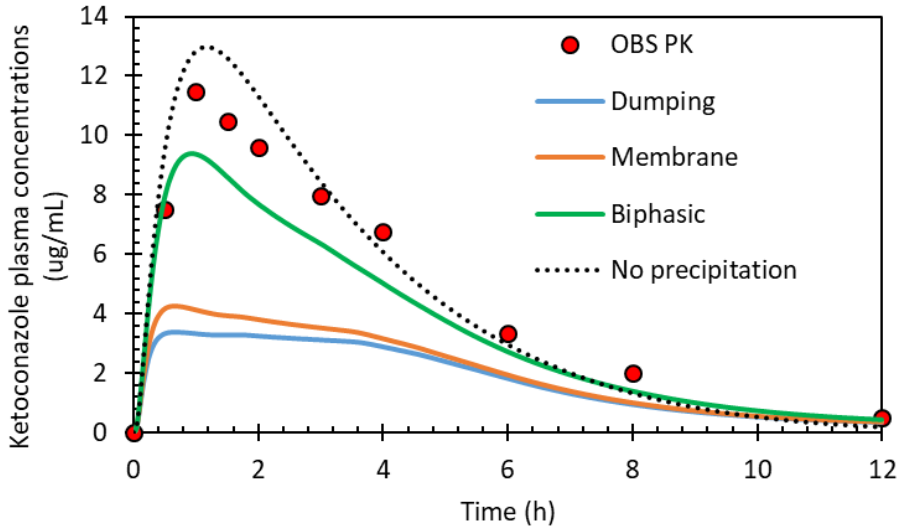
IVIVE of precipitation

- IVIVE-PBPK modeling
  - Ketoconazole <u>solution</u> 400 and 800 mg – healthy adults under fasting conditions
    - Dose-dependent precipitation rate

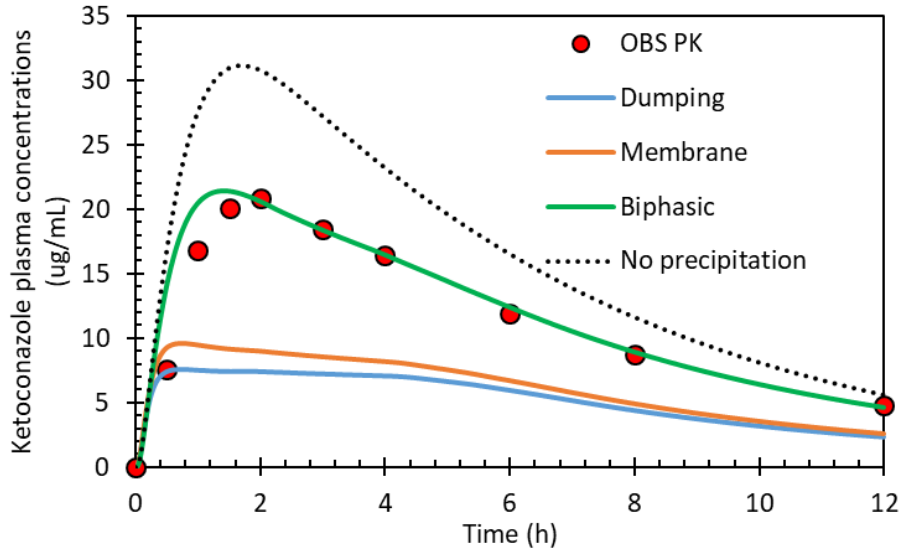


400 mg

OBS $AUC_{0\text{-}inf}$ = 55 ug.h/mL

SIM $AUC_{0\text{-}inf}$ = 42 ug.h/mL

CL/F = 7.3 L/h



800 mg

OBS $AUC_{0\text{-}inf}$ = 172 ug.h/mL

SIM $AUC_{0\text{-}inf}$ = 176 ug.h/mL

CL/F = 4.5 L/h

Huang et al, 1986. *Antimicrob Agents Chemother* 30(2):206-210.

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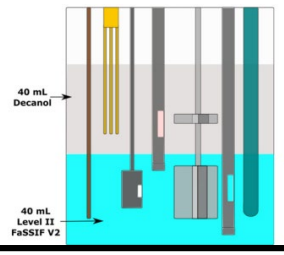
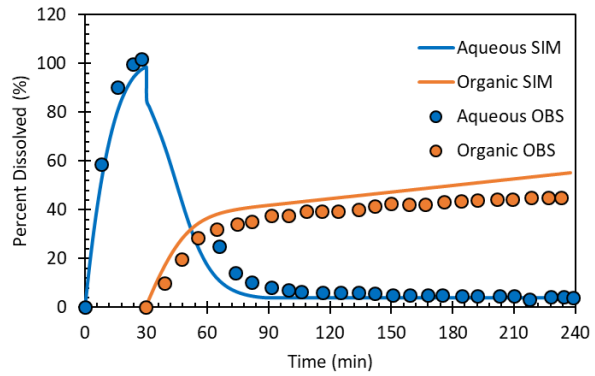
IVIVE of precipitation

- Mechanistic model-based analysis of *in vitro* biphasic dissolution data

Lindfors model





Surface Int Factor (λ) = 0.3 µm
Exp Correc Factor = 0.155

Fitted

$$J = \text{Pre-exponential Term} * e^{\text{Exponential Term}}$$

Pre-exponential Term:

$$D_{mono} N_{Av} c^2 \left(\frac{k_B T}{\gamma}\right)^{1/2} \ln\left(\frac{c}{S}\right) \frac{R^*}{R^* + \lambda}$$

Exponential Term:

$$-ExpCorr \frac{16\pi}{3} \left(\frac{\gamma}{k_B T}\right)^3 \frac{v_m^2}{\ln\left(\frac{c}{S}\right)^2}$$

O'Dwyer et al, 2020. *Pharmaceutics* 12:272
Lindfors et al, 2008. *Colloid Interf Sci* 325(2):404

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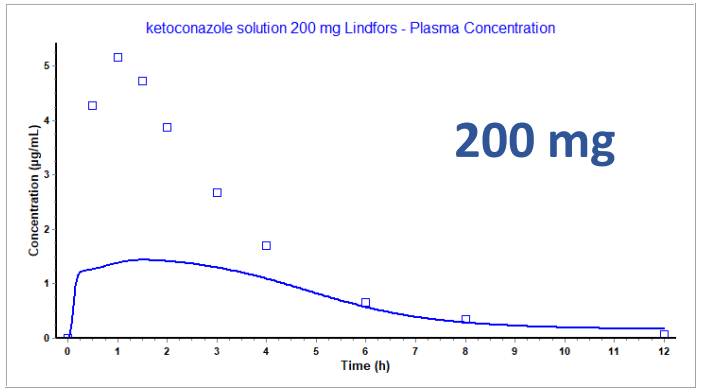
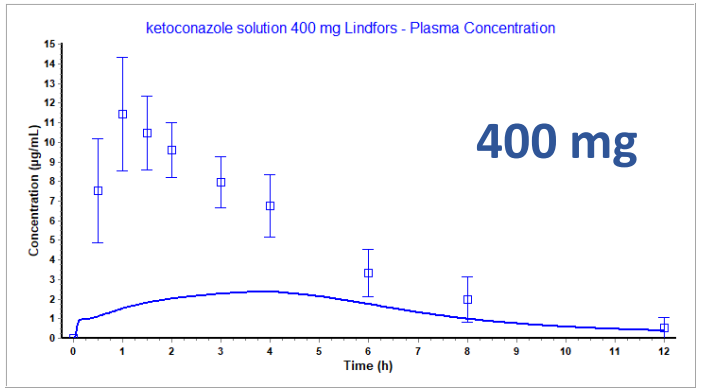
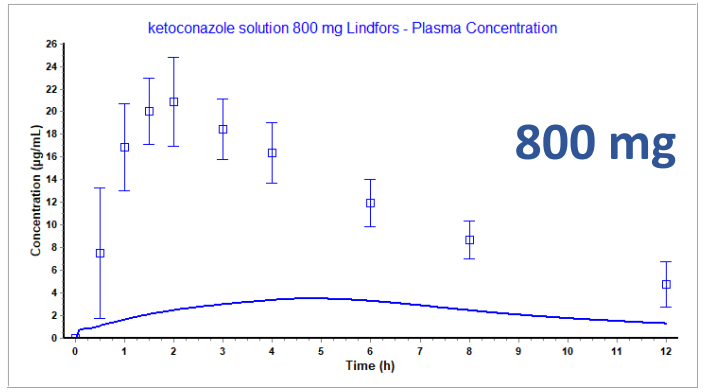
IVIVE of precipitation

- 200 – 800 mg oral solution
- Lindfors parameters estimated from *in vitro* data
  - Interf_Tension = 0.0191 J/m^2; Surface Int Factor = 0.3 µm; Exp Correc Factor = 0.155
  - Forward IVIVE failed







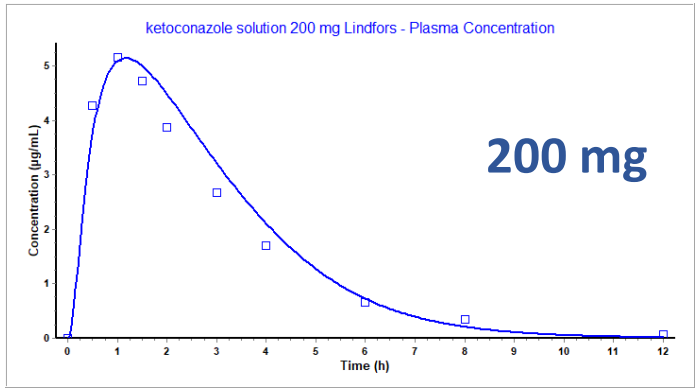
Comp Name	Rad of 1st Nucl (um)	Max Rad of Nucl (um)	SSR at Nucl	Time Nucl (h)	SSR Max	Time SSR Max (h)
Stomach	-1	-1	-1	-1	-1	-1
Duodenum	3.01E-3	8.292	9.231	0.028	23.62	0.116
Jejunum 1	0.796	5.654	1.510	0.084	3.623	0.185
Jejunum 2	-1	-1	-1	-1	-1	-1
Ileum 1	-1	-1	-1	-1	-1	-1
Ileum 2	-1	-1	-1	-1	-1	-1
Ileum 3	-1	-1	-1	-1	-1	-1
Caecum	-1	-1	-1	-1	-1	-1
Asc Colon	-1	-1	-1	-1	-1	-1

Comp Name	Rad of 1st Nucl (um)	Max Rad of Nucl (um)	SSR at Nucl	Time Nucl (h)	SSR Max	Time SSR Max (h)
Stomach	-1	-1	-1	-1	-1	-1
Duodenum	2.96E-3	6.400	9.605	0.013	31.97	0.060
Jejunum 1	0.868	3.392	1.516	0.056	2.583	0.097
Jejunum 2	-1	-1	-1	-1	-1	-1
Ileum 1	-1	-1	-1	-1	-1	-1
Ileum 2	-1	-1	-1	-1	-1	-1
Ileum 3	-1	-1	-1	-1	-1	-1
Caecum	-1	-1	-1	-1	-1	-1
Asc Colon	-1	-1	-1	-1	-1	-1

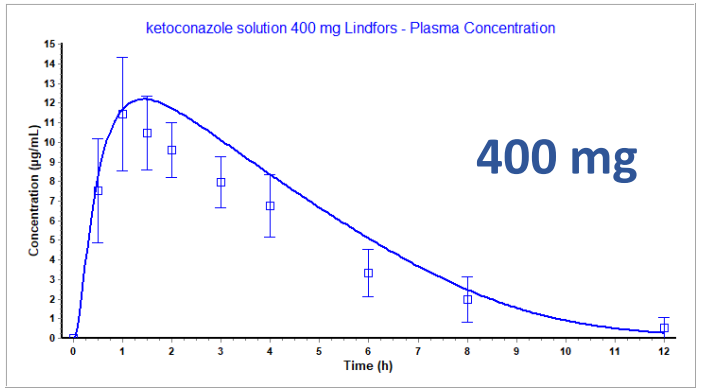
Comp Name	Rad of 1st Nucl (um)	Max Rad of Nucl (um)	SSR at Nucl	Time Nucl (h)	SSR Max	Time SSR Max (h)
Stomach	-1	-1	-1	-1	-1	-1
Duodenum	2.93E-3	5.601	9.815	6.55E-3	41.13	0.034
Jejunum 1	0.965	2.385	1.510	0.038	1.957	0.060
Jejunum 2	-1	-1	-1	-1	-1	-1
Ileum 1	-1	-1	-1	-1	-1	-1
Ileum 2	-1	-1	-1	-1	-1	-1
Ileum 3	-1	-1	-1	-1	-1	-1
Caecum	-1	-1	-1	-1	-1	-1
Asc Colon	-1	-1	-1	-1	-1	-1

IVIVE of precipitation

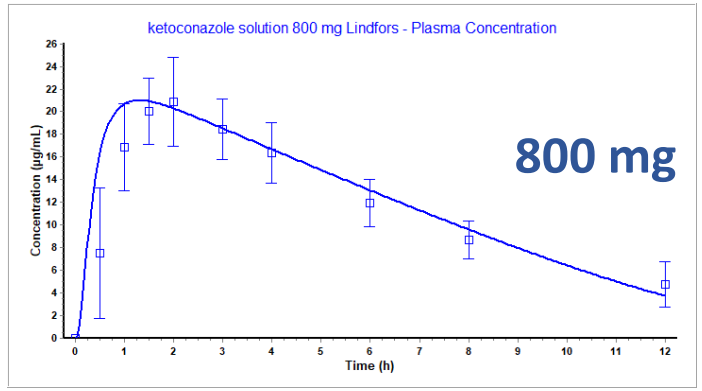
- 200 – 800 mg oral solution
- Lindfors' parameters fitted to 200-800 mg oral PK profile
  - Gaining confidence using a reverse translation approach



Comp Name	Rad of 1st Nucl (um)	Max Rad of Nucl (um)	SSR at Nucl	Time Nucl (h)	SSR Max	Time SSR Max (h)
Stomach	-1	-1	-1	-1	-1	-1
Duodenum	-1	-1	-1	-1	-1	-1
Jejunum 1	-1	-1	-1	-1	-1	-1
Jejunum 2	-1	-1	-1	-1	-1	-1
Ileum 1	-1	-1	-1	-1	-1	-1
Ileum 2	-1	-1	-1	-1	-1	-1
Ileum 3	-1	-1	-1	-1	-1	-1
Caecum	-1	-1	-1	-1	-1	-1
Asc Colon	-1	-1	-1	-1	-1	-1

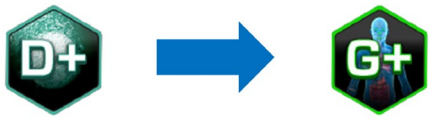


Comp Name	Rad of 1st Nucl (um)	Max Rad of Nucl (um)	SSR at Nucl	Time Nucl (h)	SSR Max	Time SSR Max (h)
Stomach	-1	-1	-1	-1	-1	-1
Duodenum	1.65E-3	48.78	54.30	0.164	55.21	0.199
Jejunum 1	8.309	47.46	13.29	0.262	17.64	0.475
Jejunum 2	26.12	44.81	7.249	0.613	7.736	0.763
Ileum 1	35.13	42.25	4.667	1.141	4.667	1.141
Ileum 2	38.55	38.86	2.521	1.679	2.521	1.679
Ileum 3	-1	-1	-1	-1	-1	-1
Caecum	-1	-1	-1	-1	-1	-1
Asc Colon	-1	-1	-1	-1	-1	-1



Comp Name	Rad of 1st Nucl (um)	Max Rad of Nucl (um)	SSR at Nucl	Time Nucl (h)	SSR Max	Time SSR Max (h)
Stomach	-1	-1	-1	-1	-1	-1
Duodenum	7.09E-3	110.3	62.46	0.054	110.0	0.194
Jejunum 1	1.950	93.43	4.890	0.074	32.06	0.402
Jejunum 2	12.01	88.29	2.248	0.184	12.66	0.640
Ileum 1	30.13	84.59	2.244	0.377	7.231	0.875
Ileum 2	44.90	81.12	2.232	0.623	4.462	1.085
Ileum 3	43.89	83.01	2.228	0.680	6.095	1.266
Caecum	58.04	74.25	2.240	1.136	2.860	1.480
Asc Colon	-1	-1	-1	-1	-1	-1

IVIVE of precipitation



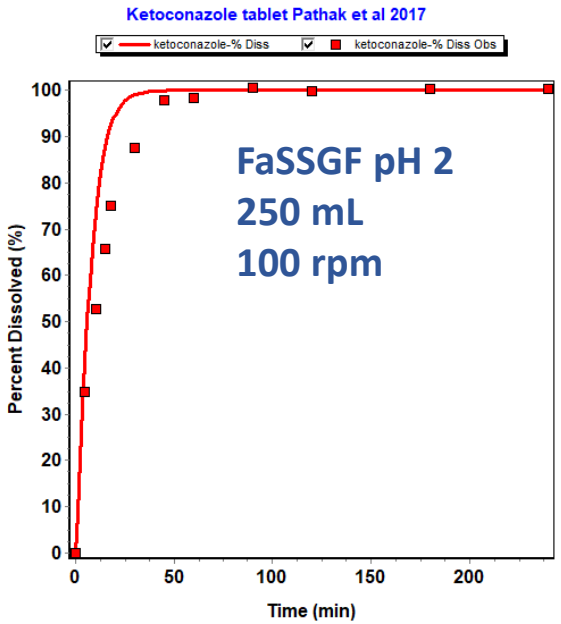
- From a ACAT-compartmental to a full PKPK model
- Simultaneous fit of 200-800 mg data
  - V_{max}
  - K_m
- Captured non-linear metabolism
  - 4-fold increase in dose
  - 9-fold increase in $AUC_{0\text{-}inf}$

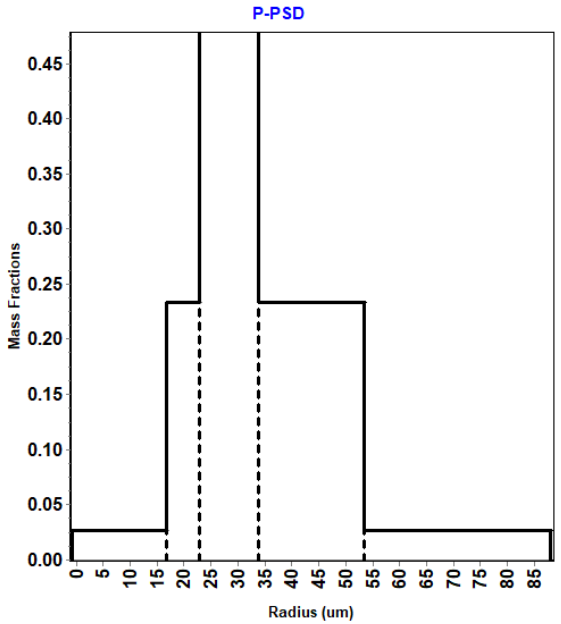
Doses	Parameter	SIM	OBS	Ratio
200 mg	C_{max}	5.1	5.2	0.98
	$AUC_{0\text{-}inf}$	18.4	17.9	1.03
	$AUC_{0\text{-}inf}$/dose	0.092	0.0895	1.03
400 mg	C_{max}	12.2	11.5	1.06
	$AUC_{0\text{-}inf}$	64.7	55.2	1.17
	$AUC_{0\text{-}inf}$/dose	0.162	0.138	1.17
800 mg	C_{max}	21.0	20.9	1.00
	$AUC_{0\text{-}inf}$	161.5	172.3	0.94
	$AUC_{0\text{-}inf}$/dose	0.202	0.215	0.94

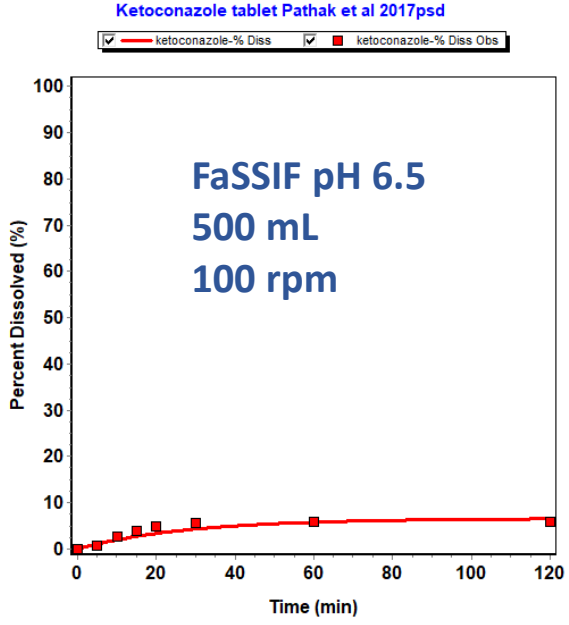
IVIVE of dissolution

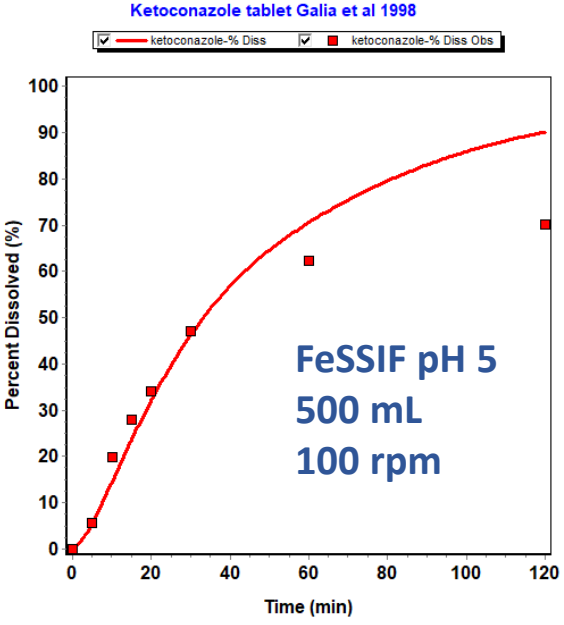
- Model-based analysis of *in vitro* dissolution data
  - Johnson model (modified version of the Nernst-Bruner model): dissolution of spherical and cylindrical particles
  - Derive P-PSD

$$\frac{dM_D}{dt} = \frac{D_w}{\rho h r_t}\frac{(1+2s)}{s}(C_s - C_l)M_{u,t}$$









Pathak et al, 2017. *Mol Pharmaceutics* 14:4305−4320; Galia et al, 1998. *Pharm Res* 15(5):698-705.

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IVIVE of dissolution

- Integrating drug and formulation parameters with physiology (convolution)
  - Simulating *in vivo* dissolution profiles

Drug and formulation parameters

- pH-solubility profile
- **P-PSD**
- P_{app}
- Precipitation kinetics

Gastrointestinal physiology

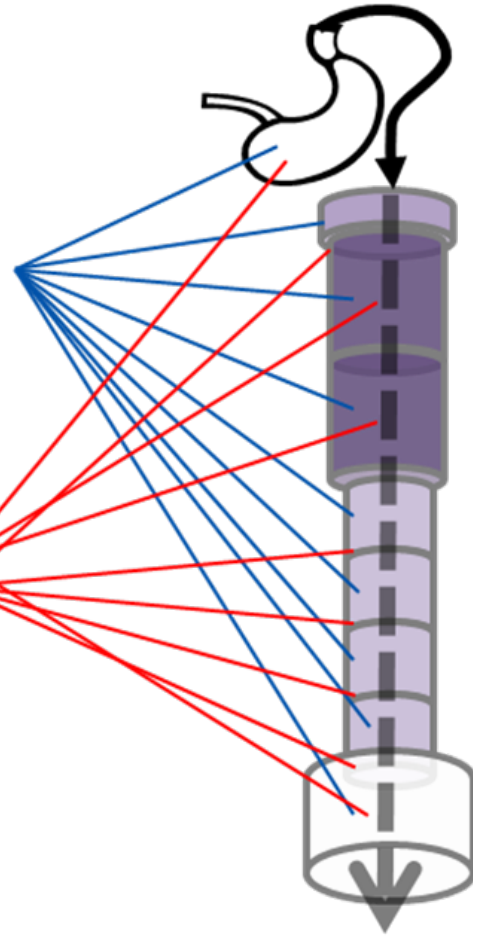
- Intraluminal pH
- Buffer capacity
- Intestinal fluid volume

Subject 1
Intraluminal
Dissolution

Subject 2
Intraluminal
Dissolution

.
.
.

Subject n



Cristofoletti et al, 2019. *J Pharm Sci* 108:3842-3847.

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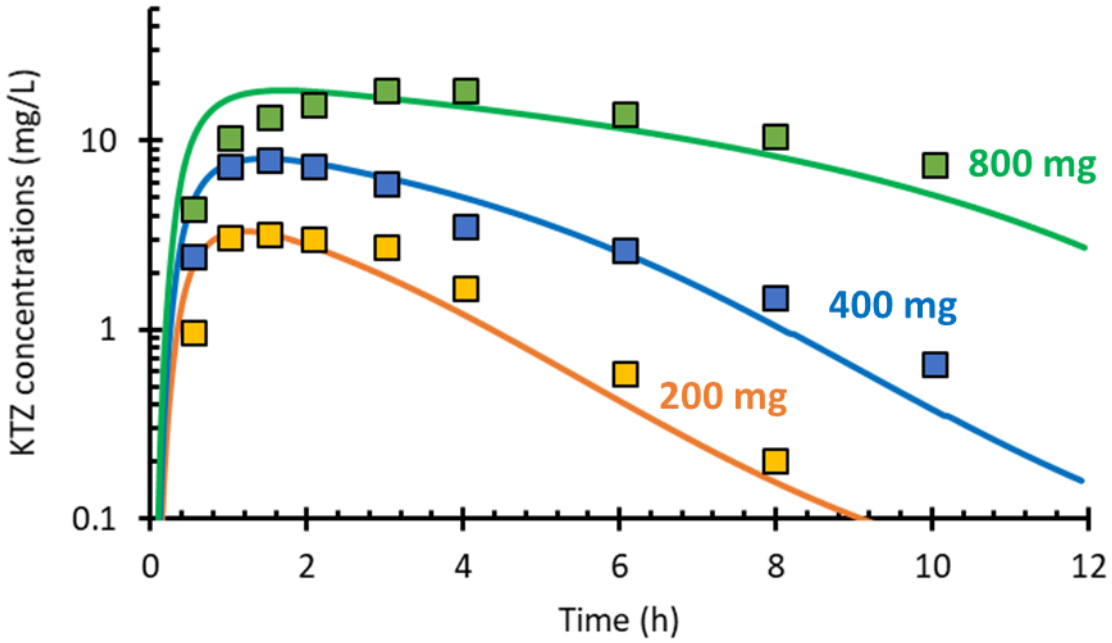
IVIVE of dissolution

- Ketoconazole tablets 200 – 800 mg <u>fasted</u> PK profiles
  - P-PSD

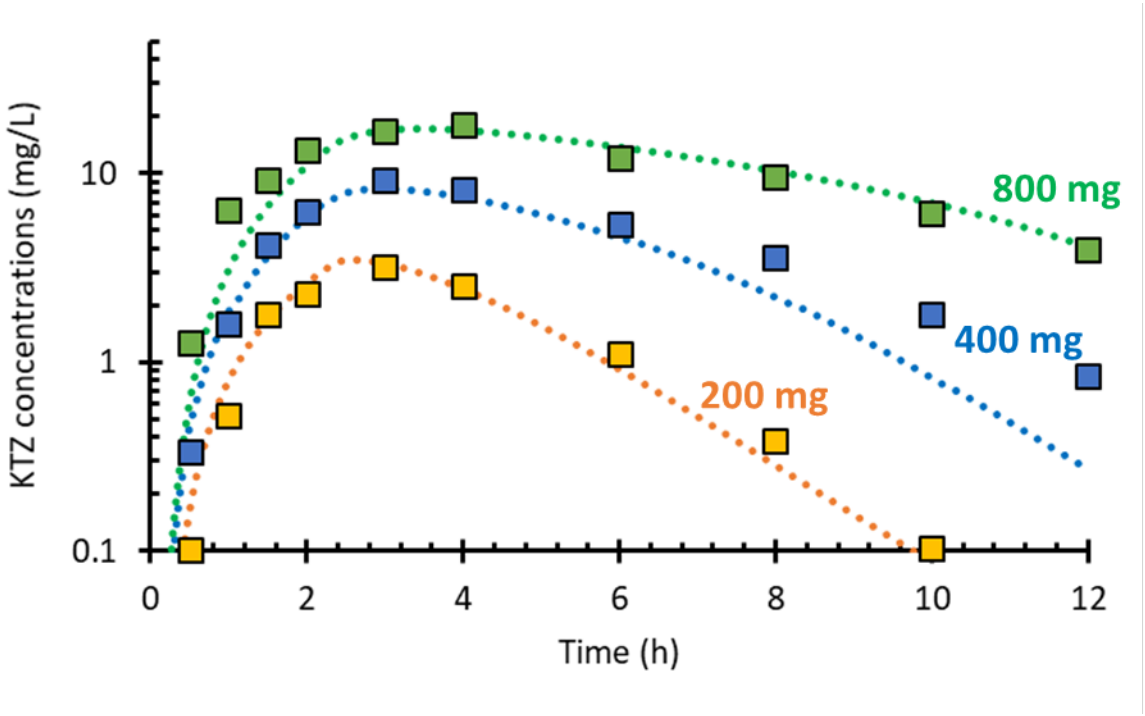


Doses	Parameter	SIM	OBS	Ratio
200 mg	C_{max}	3.3	3.2	0.95
	AUC_{0-t}	11.1	12.5	0.89
	AUC_{0-inf}	11.3	12.9	0.88
	T_{max}	1.2	1.5	0.8
400 mg	C_{max}	8.0	7.9	1.01
	AUC_{0-t}	36.2	35.2	1.03
	AUC_{0-inf}	36.5	35.8	1.02
	T_{max}	1.4	1.6	0.88
800 mg	C_{max}	18.4	18.5	0.99
	AUC_{0-t}	134.2	159.2	0.84
	AUC_{0-inf}	127.4	140.1	0.91
	T_{max}	1.8	3	0.6

Pathak et al, 2017. *Mol Pharmaceutics* 14:4305−4320; Daneshmend et al, 1984. *Antim Agents Chemother* 25:1-3.

IVIVE of dissolution

- Ketoconazole tablets 200 – 800 mg <u>fed</u> PK profiles
  - P-PSD



Doses	Parameter	SIM	OBS	Ratio
200 mg	C_{max}	3.5	3.2	1.01
	AUC_{0-t}	12.8	13.0	0.98
	AUC_{0-inf}	12.9	13.2	0.98
	T_{max}	2.6	3.0	0.87
400 mg	C_{max}	8.2	9.2	0.89
	AUC_{0-t}	41	51.5	0.80
	AUC_{0-inf}	41.3	53.8	0.80
	T_{max}	2.9	3.0	0.97
800 mg	C_{max}	17.4	17.9	0.97
	AUC_{0-t}	123.5	120.9	1.02
	AUC_{0-inf}	136.3	138.7	0.98
	T_{max}	3.5	4	0.88

Pathak et al, 2017. *Mol Pharmaceutics* 14:4305−4320; Daneshmend et al, 1984. *Antim Agents Chemother* 25:1-3.

Forward projection - application

- HIV-infected individuals with CD4 T cell count > 200 cells/µl
  - Less susceptible to infections in the GI tract
  - Weighted mean gastric pH = 3.46 and SD = 0.35

- HIV-infected individuals with CD4 T cell count < 200 cells/µl (AIDS)
  - Weak immune systems
  - Susceptible to infections in the GI tract
  - Weighted mean gastric pH = 4.85 and SD = 1.29

- Control individuals
  - No infection
  - Gastric pH 1.5 – 2.9

Lake-Bakaar et al, 1988. *Ann Intern Med* 109(6):502-504; Geragthy et al, 2015. *PLoS One* 10(8):e0132043; Welage et al, 1995. *Clin Infect Dis* 21(6): 1431-1438; Wilcox et al, 1999. *Gut* 44:101-105; Kelly et al, 2010. *BMC Gastroenterol* 10:72.

Forward projection - application

- HIV-infected individuals with CD4 T cell count < 200 cells/µl
  - GET is ≈ 3-fold slower in the presence of opportunistic GI infection

TABLE 1. CLINICAL CHARACTERISTICS AND GASTRIC EMPTYING DATA OF HIV SEROPOSITIVE SUBJECTS AND HIV SERONEGATIVE CONTROLS*

				HIV(+)		
	Controls	*HIV(+)*	P	*Enteric pathogens*	*No enteric pathogens*	P
Subjects (*N*)	12	54		20	34	
Age (yr)	30.9 (0.75)	38.0 (1.14)	0.0052	39.95 (2.02)	36.85 (1.34)	0.19
CD4 (count/mm^3)	NA	166.1 (26.74)		44.8 (18.4)	237.5 (35.9)	0.0002
Gastric symptoms (15)	0.08 (0.08)	6.55 (0.5)	<0.0001	7.47 (0.79)	6.45 (0.58)	0.29
BMI (kg/m^2)	23.42 (0.37)	20.8 (0.38)	0.0022	20.1 (0.6)	21.2 (0.46)	0.15
Weight loss (%)	0	8.41 (1.44)		12.4 (2.6)	6.1 (1.5)	0.007
Gastric T½ (min)	65.67 (5.07)	116.4 (11.9)	0.0024	163.4 (26.3)	88.8 (8.1)	0.0128
SI (min)	−3.9 (5.94)	3.01 (4.79)	0.52	13.03 (10.4)	−2.89 (4.36)	0.17
GE gradient (%/min)	−0.751 (0.044)	−0.499 (0.032)	0.0007	−0.42 (0.04)	−0.57 (0.03)	0.0038
Proximal/total GE gradient (%/min)	1.033 (0.084)	1.367 (0.083)	0.07	1.38 (0.17)	1.36 (0.09)	0.93

* Results are expressed as mean (SE).

Lake-Bakaar et al, 1988. *Ann Intern Med* 109(6):502-504; Neild et al, 2000. Digestive Dis Sci 45(8):1491-1499

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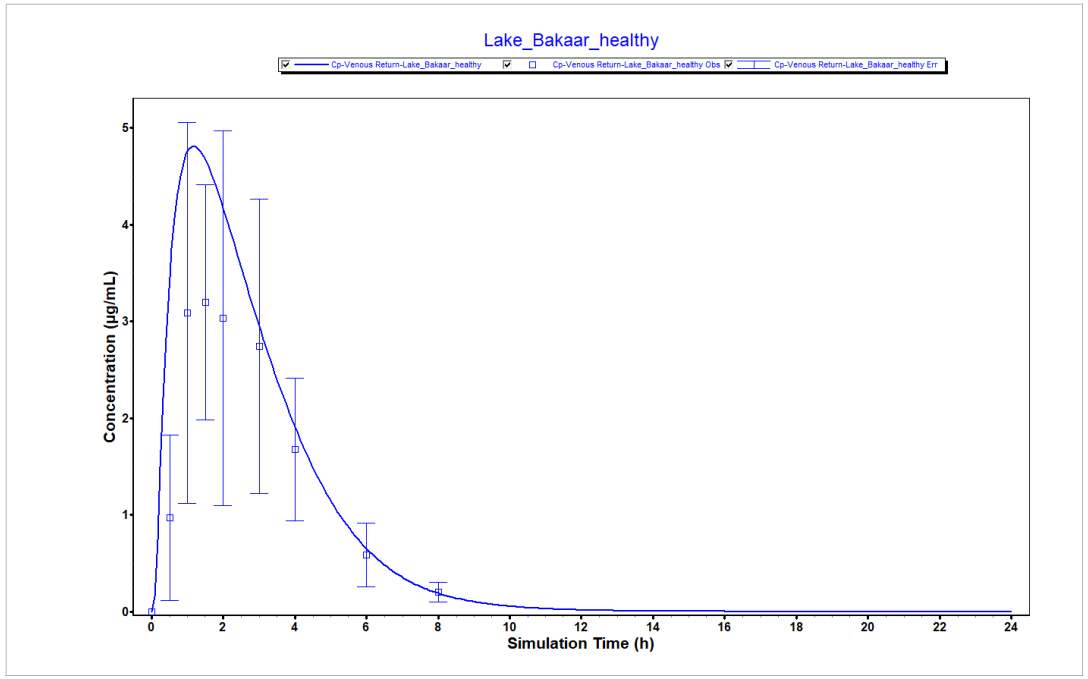
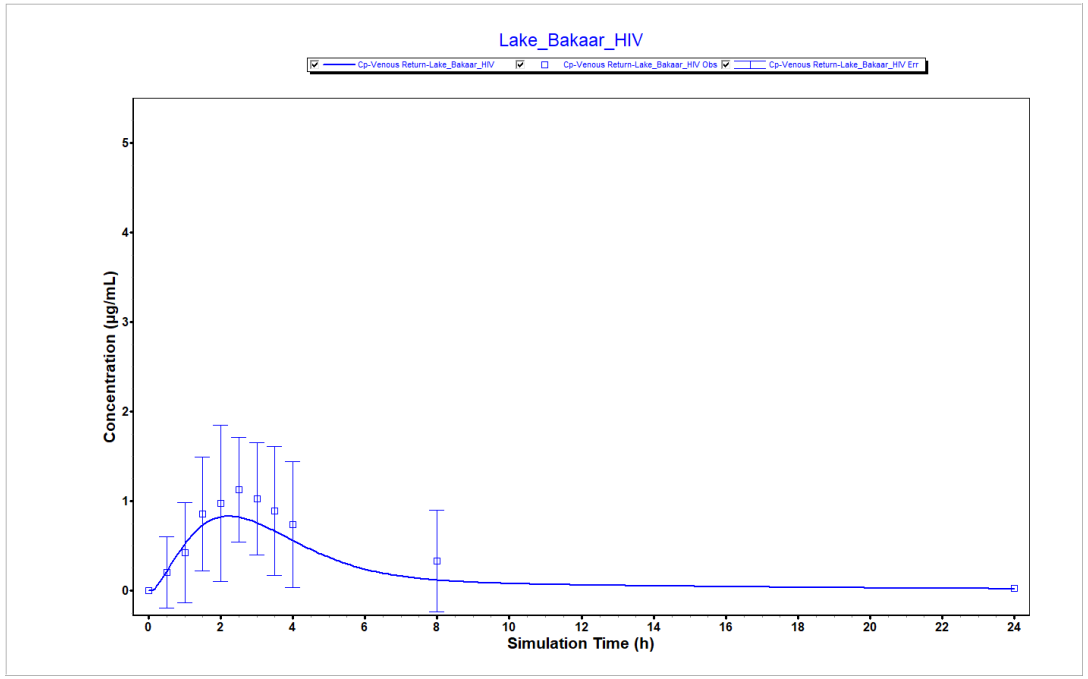
Forward projection - application

- HIV-infected individuals with CD4 T cell count < 200 cells/µl
  - Ketoconazole tablets 200 mg (fasting)





Lake-Bakaar et al, 1988. *Ann Intern Med* 109(6):502-504

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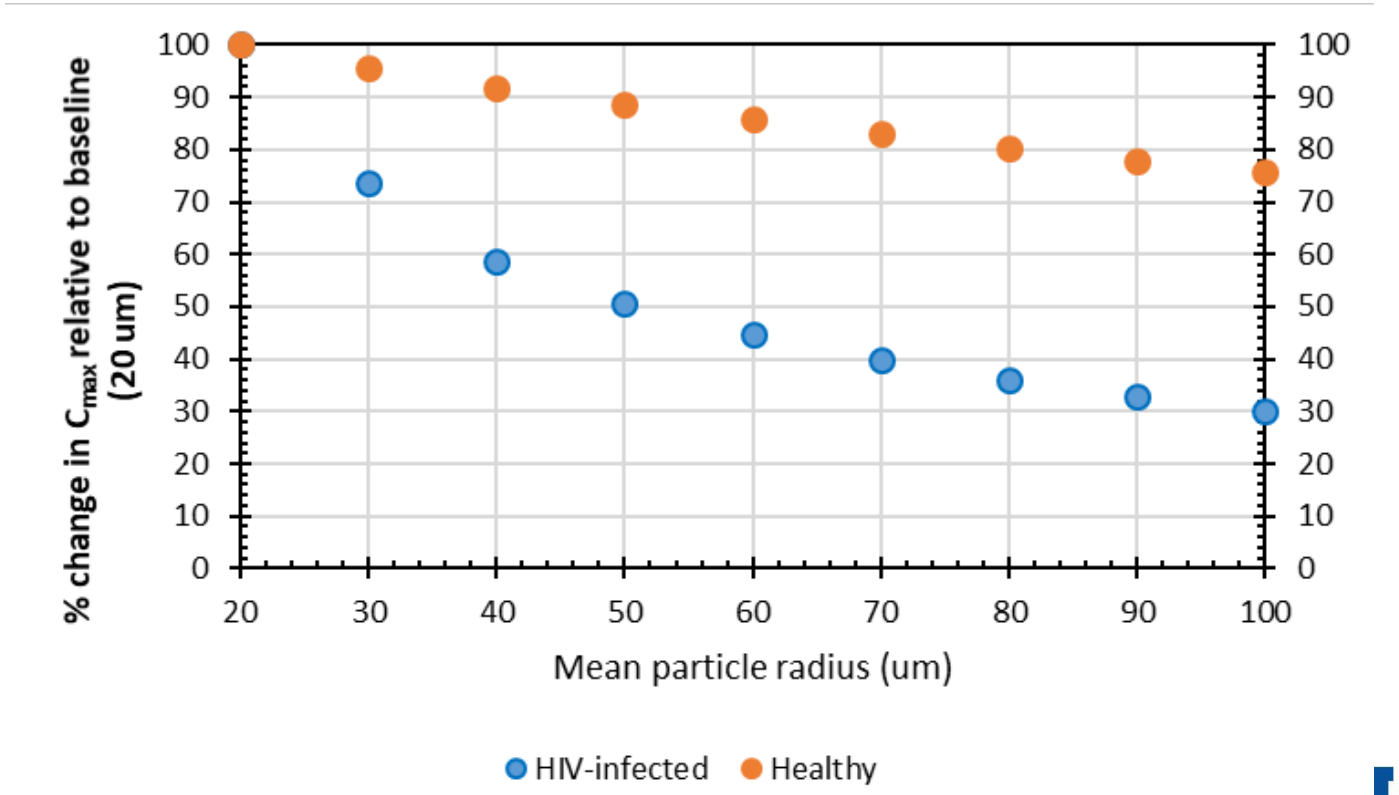
Forward projection - application

- HIV-infected individuals with CD4 T cell count < 200 cells/µl
  - PSA
  - C_{max} in HIV-infected is more sensitive to P-PSD than C_{max} in healthy adults



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Summary

- Model-based analysis of *in vitro* data is helpful to derive fundamental input parameters for PBPK models;
- Generalization of first-order precipitation rate across different doses is not straightforward;
  - Dose-dependent precipitation
- Forward translation of *in vitro* precipitation data using Lindfors model requires further research;
- Gaining experience in the translatability of drug-specific parameters is needed to inform forward projections;
- We were able to recapitulate the impact of HIV infection on ketoconazole oral absorption;
  - Model performance may be limited by knowledge gaps related to system parameters
- PBPK modeling may be useful to gain mechanistic insights on the impact of comorbid conditions on the exposure of the investigational drug and help assessing the risks related to enhancing diversity of clinical trial populations

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  - Lais Silva, PhD
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Thank you!

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