

SimulationsPlus

Enhanced PBPK-Based In Vitro to In Vivo Extrapolation Method to Support the Development of Pulmonary Drug Products

Maxime Le Merdy. Ph.D, Pharm.D.

Director, PBPK Research & Collaborations

Fiscal Year 2025 Generic Drug Science and Research Initiatives Public
Workshop

03 June, 2025

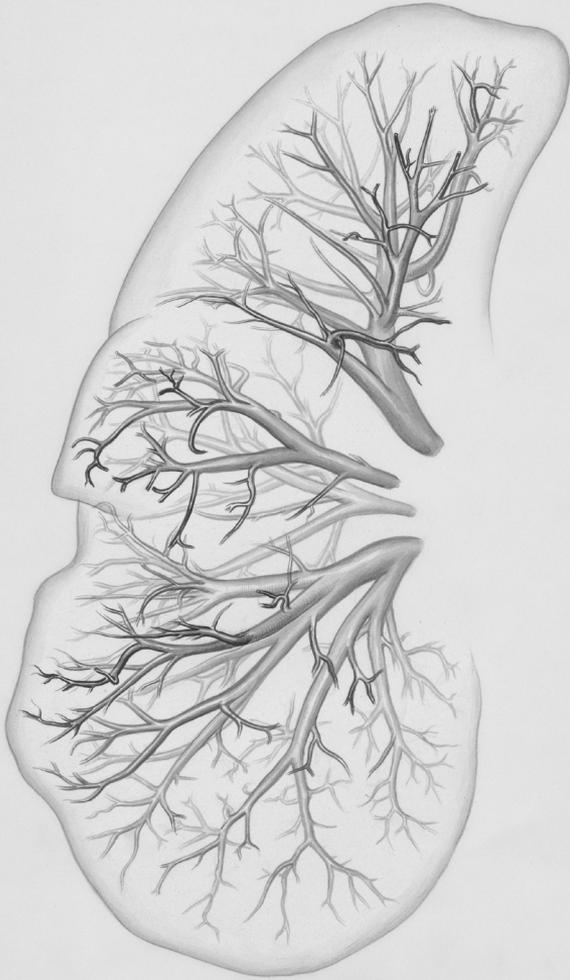


Orally inhaled drug products (OIDPs) are used to treat pulmonary respiratory diseases:

- Asthma: about **25 million** (7.7% of the U.S. population) had asthma in 2021
- Chronic Obstructive Pulmonary Disease (COPD): **1 of the top 10** causes of death in the U.S.

OIDPs are considered **complex generics** drug products.





OIDPs absorption occurs in **three** phases:

- Deposition: where and how much of the inhaled drug **settles** in the different parts of the respiratory tract
- Dissolution: API **dissolution** into the lung fluid
- Permeation: **movement** of dissolved API across the lung epithelium

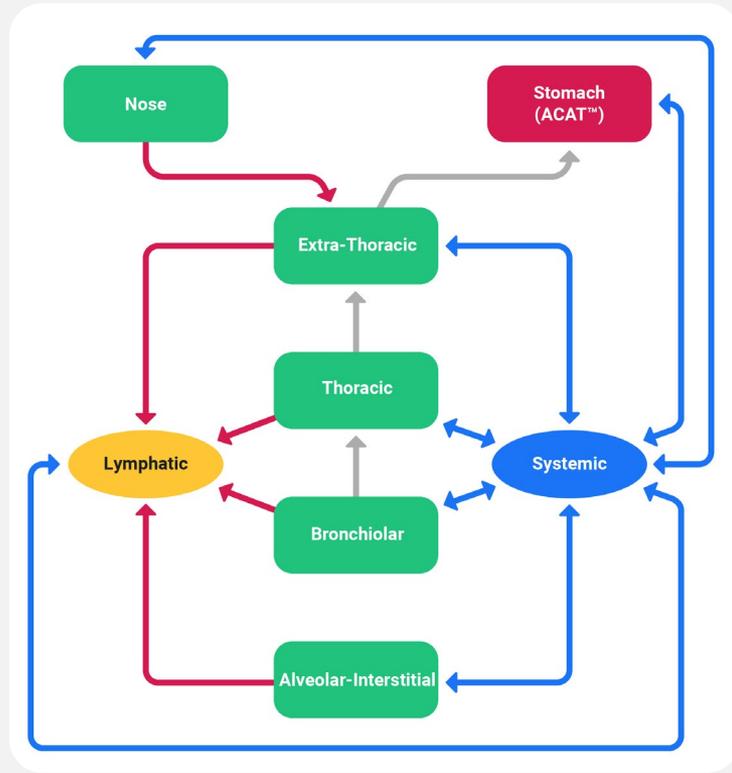
Understanding the relationship between these three phases and the resulting **local** and **systemic** pharmacokinetic (PK) profiles is a necessity for the regulatory assessment of new and generic OIDPs.

Challenge: Predicting local and systemic human exposure for OIDs is challenging as the deposition, dissolution, and permeability are **difficult** to estimate using **in vitro** or **in vivo** testings.

PBPK models can support OIDs generic development:

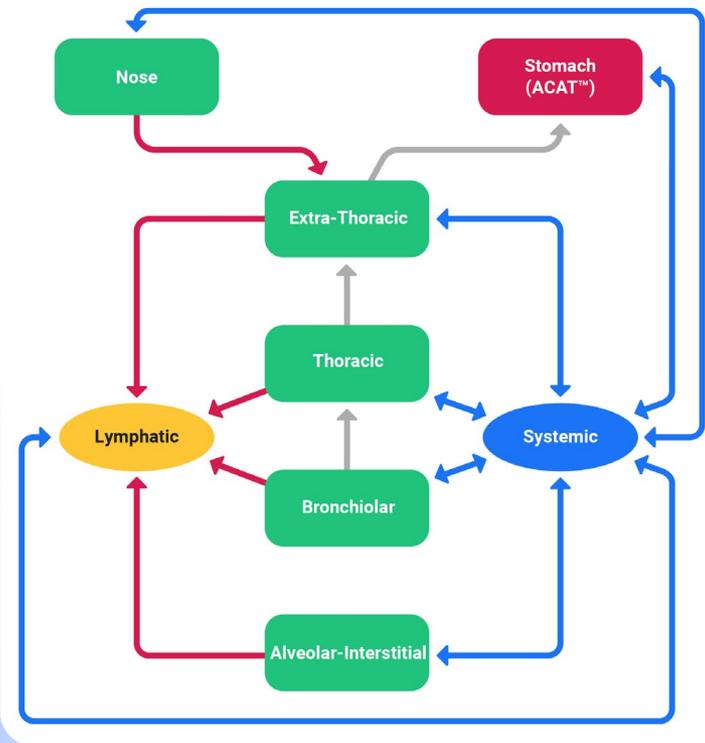
- It includes regional **deposition** in the lung tissues, API **dissolution** rate and **permeability**.
- It presents an integrated solution to **predict** local and systemic API PK.

PBPK model **parametrization** can be challenging for locally acting drug products.

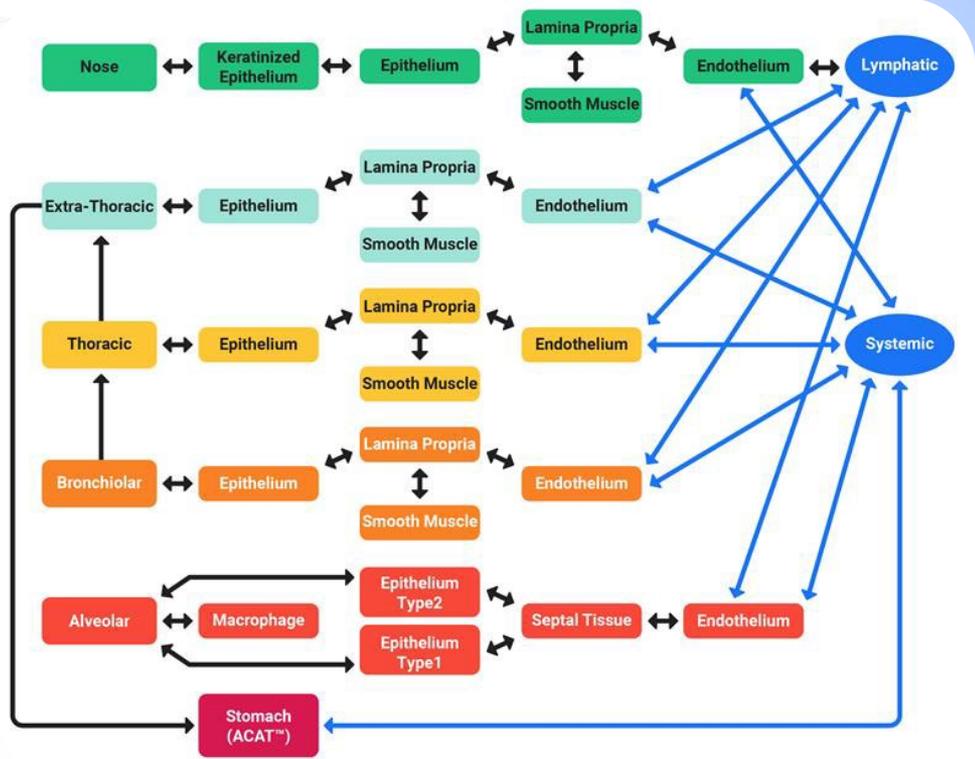


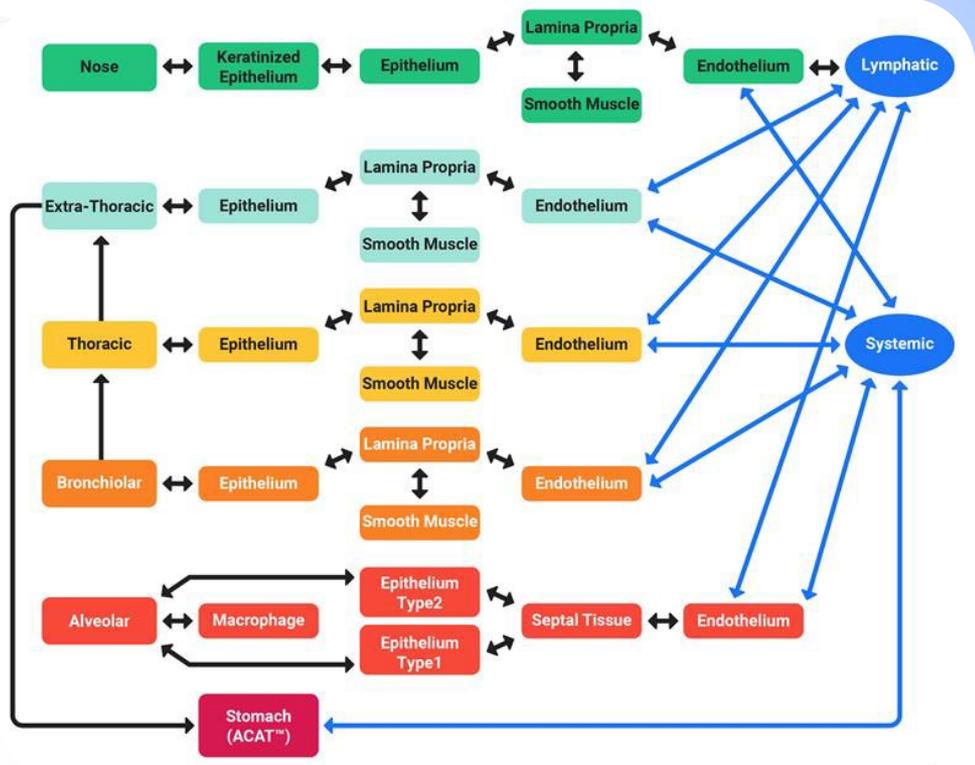
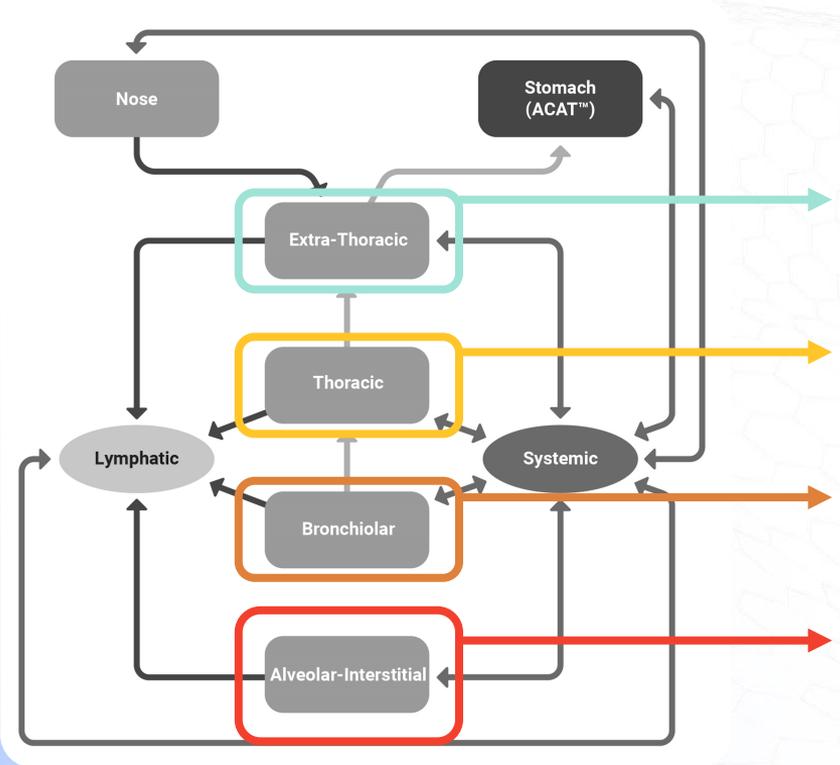
Evaluate the use of *in vitro* lung cell permeability assays
to parameterize the model and predict *in vivo* PK





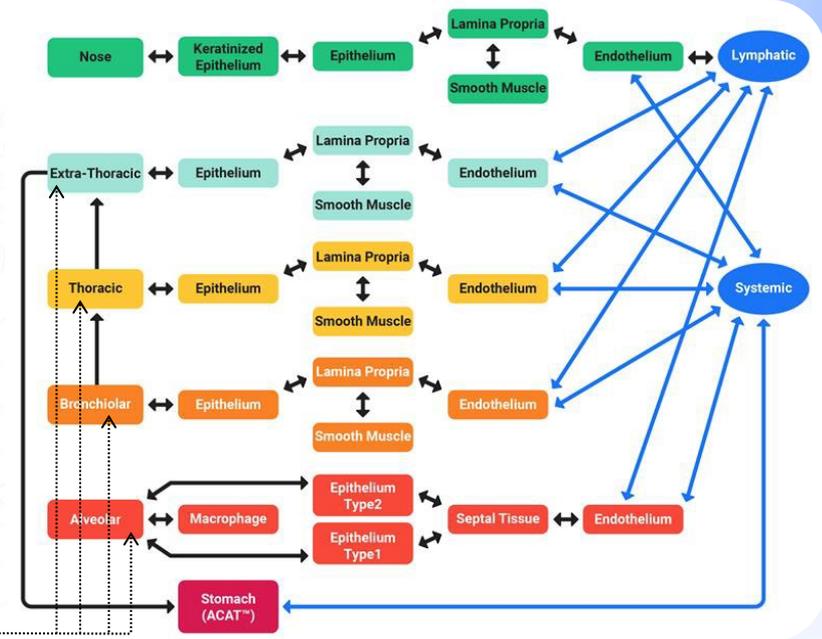
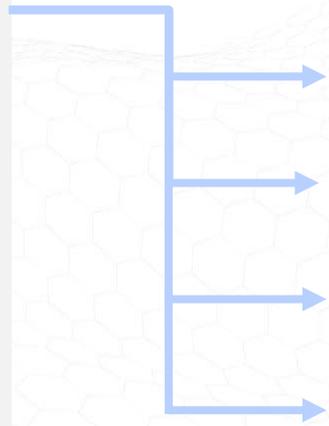
Single tissue layers





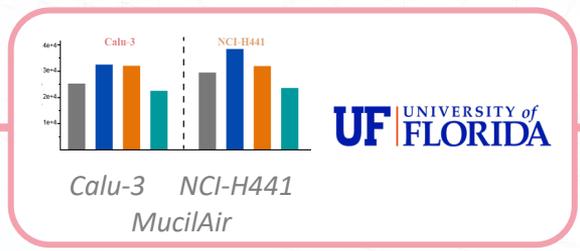
Separate diffusion sublayers for epithelium, lamina propria, smooth muscle, and endothelium

Deposition: combination of *in vivo*, *in vitro* and *in silico*

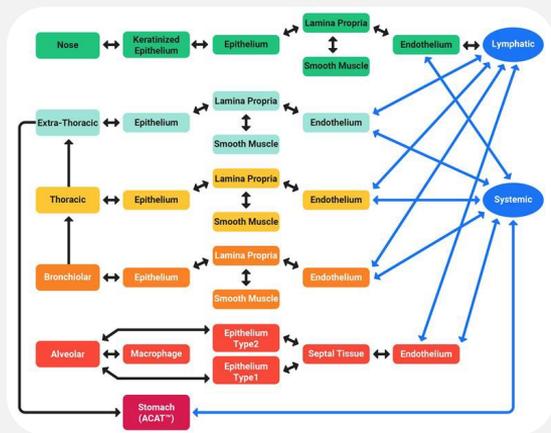


Dissolution: *in silico* and *in vitro* predictions

Permeability: *in vitro* cell-based permeability systems



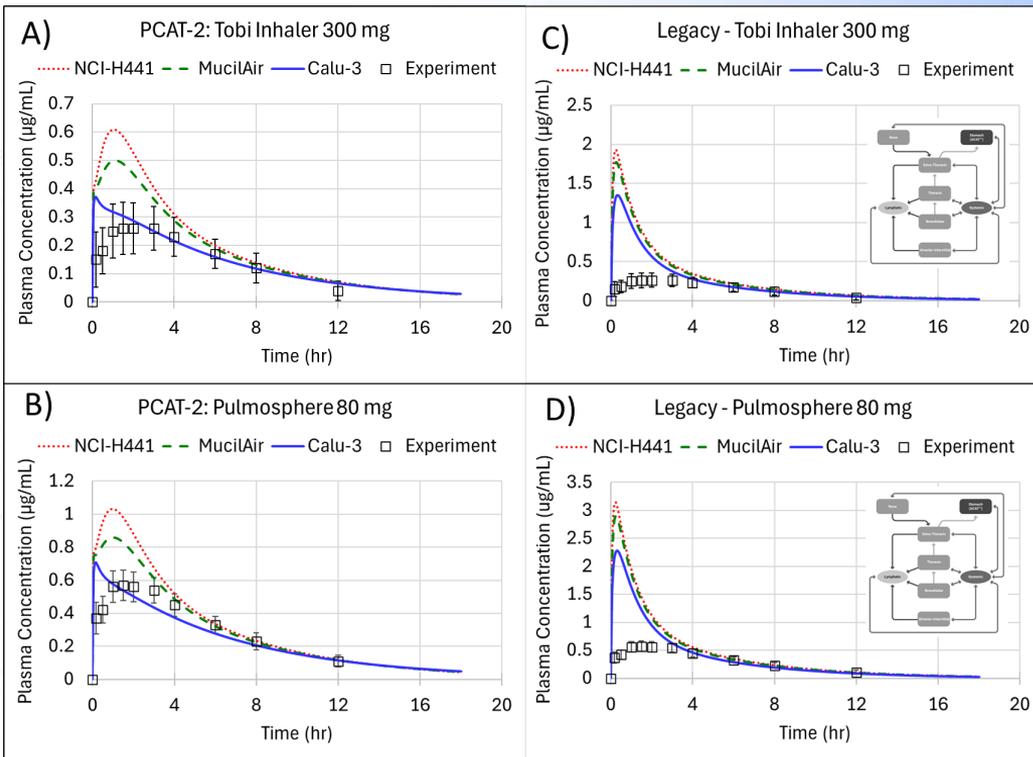
Tobramycin



Deposition: 2D scintigraphy

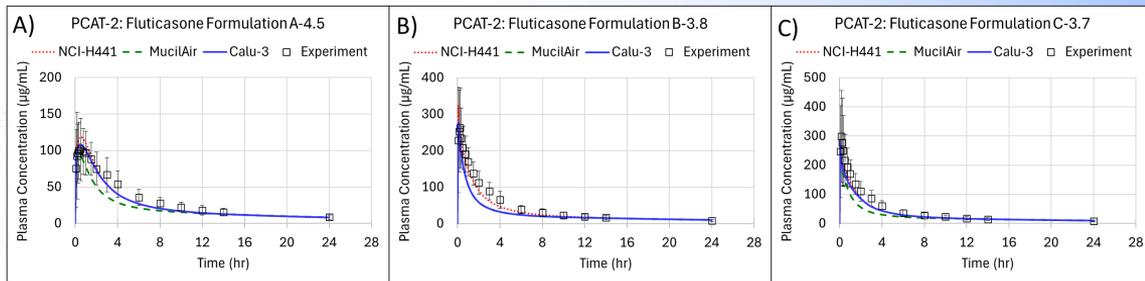
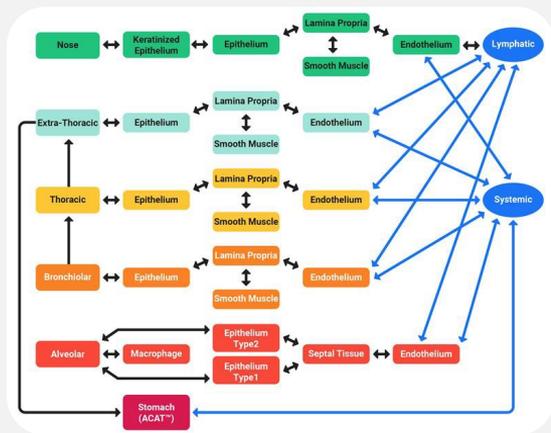
Dissolution: solubility predicted from ADMET Predictor and measured particle distribution

Permeability: in vitro cell-based permeability systems

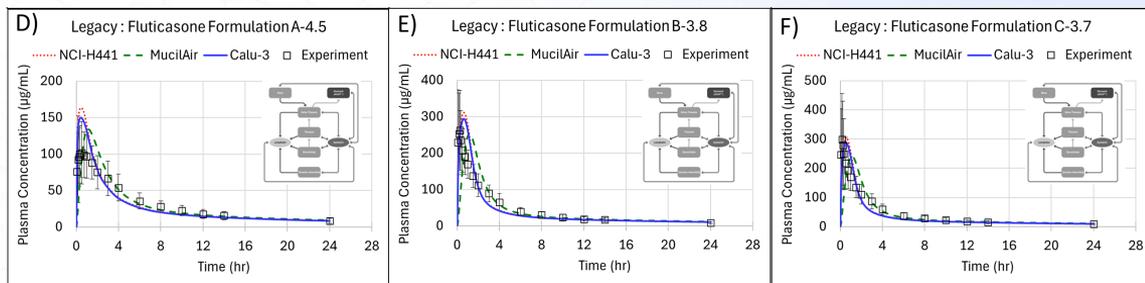


	Tobi Inhaler 300 mg			Pulmosphere 80 mg		
	MucilAir	Calu	NCI-H441	MucilAir	Calu	NCI-H441
Cmax Error %	134.0	43.3	92.1	81.1	24.6	51.0
Tmax Error %	30.7	89.3	25.3	33.3	89.3	33.3
AUCt Error %	61.5	10.1	45.0	21.7	13.5	10.6

Fluticasone propionate



	PCAT-2 Model: Fluticasone Propionate								
	MucilAir			Calu-3			NCI-H441		
	A-4.5	B-3.8	C-3.7	A-4.5	B-3.8	C-3.7	A-4.5	B-3.8	C-3.7
Cmax Error %	5.83	6.19	18.85	6.85	22.01	7.01	17.10	23.26	5.96
Tmax Error %	34.0	60.0	39.4	4.0	71.0	56.1	0.0	71.0	56.1
AUC Error %	29.4	29.6	34.1	14.5	14.9	20.2	11.9	12.5	17.8

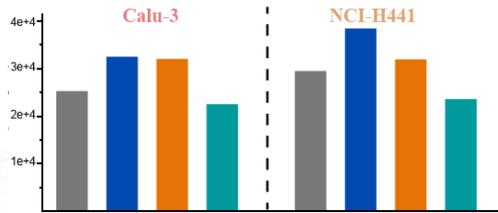


	Legacy Model: Fluticasone Propionate								
	MucilAir			Calu-3			NCI-H441		
	A-4.5	B-3.8	C-3.7	A-4.5	B-3.8	C-3.7	A-4.5	B-3.8	C-3.7
Cmax Error %	32.16	4.04	19.14	47.48	11.77	3.53	60.89	18.76	2.61
Tmax Error %	124.0	348.0	578.8	20.0	156.0	203.0	4.0	156.0	239.4
AUC Error %	1.78	3.07	1.54	6.78	5.07	10.52	2.85	1.36	6.53

Deposition: Next Generation Impactor (NGI) measurements

Dissolution: USP paddle dissolution test

Permeability: in vitro cell-based permeability systems



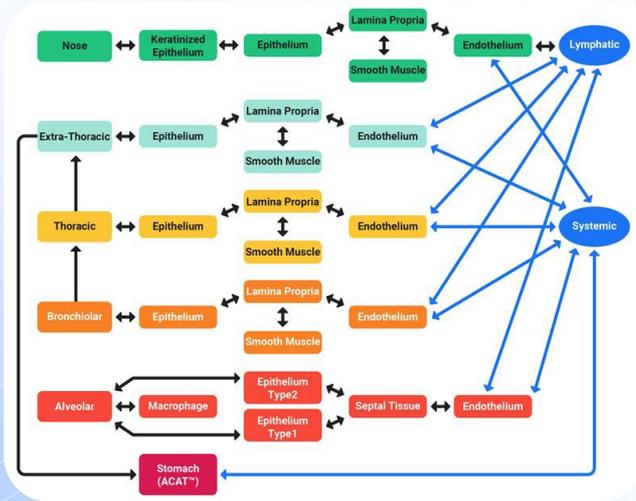
- The PCAT-2 model, with improved lung physiology, enhanced IVIVE predictions in both case studies.

- Calu-3 permeability was most predictive in the Tobramycin study.

- For Fluticasone, Calu-3 worked best with the legacy model; NCI-H441 worked best with PCAT-2.

- More compounds will be tested to confirm these findings and the model's improvements.

- Best practices for in vitro permeability assays will be developed to improve lung PBPK predictions for OIDP absorption.



- Dr. Ross Walenga
- Dr. Steven Chopski
- DQMM/ Locally acting PBPK Team



- Dr. Rodrigo Cristofolletti
- Dr. Juergen Bulitta
- Dr. Guenther Hochhaus
- All others



- Jim Mullin
- Dr. Viera Lukacova
- Dr. Conner Sandefur

