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

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PURPOSE

- Orally inhaled drug products (OIDPs) are used to treat pulmonary diseases. OIDP absorption occurs in three phases: deposition, dissolution, and permeation.
- Understanding the relationship between these three phases and the resulting local and systemic pharmacokinetic (PK) profiles is important for both pharmaceutical development and regulatory assessment of new and generic OIDPs.
- Predicting local and systemic human exposure for OIDPs is challenging, because deposition, dissolution, and permeability are difficult to estimate using *in vitro* or *in vivo* methods.
- Physiologically based pharmacokinetic (PBPK) modeling is an integrated solution to predicting local and systemic PK, which can support OIDP development. It includes regional deposition in the lung tissues, pulmonary physiological conditions, and active pharmaceutical ingredient (API) physicochemical characteristics that affect the API dissolution rate and permeability.
- To support the capability of an existing state-of-the-art lung PBPK model to accurately model permeability, this study aimed to evaluate the use of *in vitro* lung cell permeability assays to parameterize the model and predict *in vivo* PK. Tobramycin and fluticasone propionate were selected as validation case studies for this *in vitro* to *in vivo* extrapolation (IVIVE) method.

METHODS

- The Pulmonary Compartmental Absorption and Transit (PCAT™) model within GastroPlus® version 9.8.3 (Simulations Plus, Inc., Lancaster, California, USA) was used to build the lung PBPK models.
- Two versions of the PBPK model were used: (1) The legacy PCAT model (Figure 1-A) which utilizes only mucus and single tissue layers for each compartment including nose, extra-thoracic, thoracic, bronchioles, and alveoli, and (2) PCAT-2 (Figure 1-B) which enhances the complexity of each lung tissue compartment by adding separate diffusion sublayers for epithelium, lamina propria, smooth muscle, and endothelium.
- A combination of *in vivo* and *in vitro* deposition from aerodynamic particle size distribution data using various mouth-throat models and a Next Generation Impactor (NGI) was utilized [1,2,3]. NGI deposition fractions, cup cutoff diameters in mass median aerodynamic diameter (MMAD), and the ICRP 66 model [4] were utilized to calculate deposition in PCAT model.
- API dissolution was determined based on product specific particle size distribution (P-PSD) based on *in vitro* dissolution [5].
- To validate the IVIVE, the prediction ability of three *in vitro* cell-based permeability systems (Calu-3, NCI-H441, and MucilAir Bronchial) were compared for the tobramycin and fluticasone propionate models.

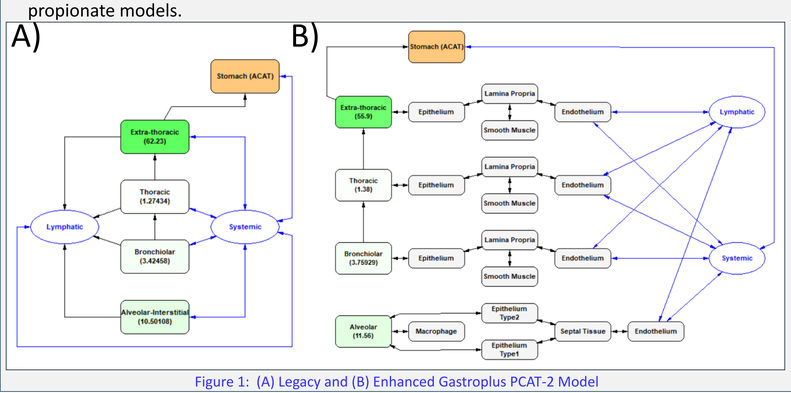

Figure 1: (A) Legacy and (B) Enhanced Gastroplus PCAT-2 Model

RESULTS

Tobramycin

- Tobramycin PK predictions using both the legacy PCAT and PCAT-2 models with the three cell-based permeability assays are shown in Figure 2.
- The tobramycin model utilizes two-dimensional scintigraphy deposition measurements to determine the amount of tobramycin deposited in the lung. Dissolution was determined by solubility predicted from ADMET Predictor and measured particle distribution.
- PCAT-2 provides a better prediction of maximum concentration (C_{max}) and area under the curve (AUC) when the IVIVE is done with the Calu-3 cell line data. The error results are displayed for PCAT-2 model in Table 1.

Table 1: Pulmonary PBPK absolute prediction error [100xABS(pred-obs)/obs] for three different cell-based assays including MucilAir, Calu-3, and NCI-H441 utilizing new PCAT-2 pulmonary model for two formulations of tobramycin including 300 mg Tobi nebulized inhaler and 80 mg Pulmosphere DPI.

	Tobi Inhaler 300 mg			Pulmosphere 80 mg		
	MucilAir Bronchial	Calu-3	NCI-H441	MucilAir Bronchial	Calu-3	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

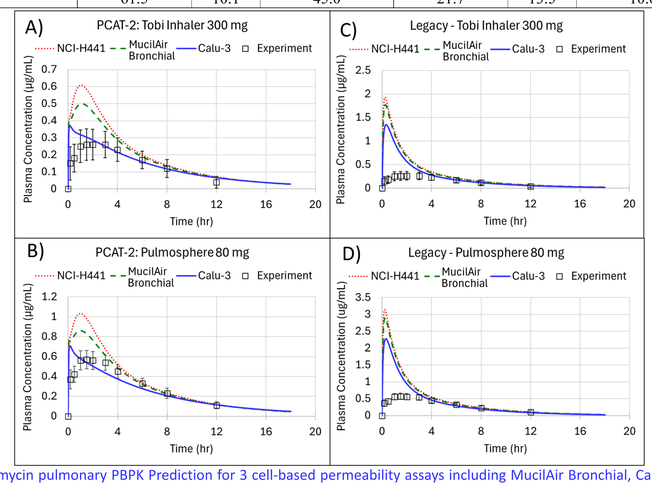

Figure 2: Tobramycin pulmonary PBPK Prediction for 3 cell-based permeability assays including MucilAir Bronchial, Calu-3, and NCI-H441 for PCAT Version 2 (A. B) and legacy (C, D) models for 300mg Nebulized Tobi formulation and 80 mg Pulmophere DPI.

Fluticasone propionate

- NGI measurements of three fluticasone propionate formulations with mass median aerodynamic diameter (MMAD) values of 4.5 µm, 3.8 µm, and 3.7 µm were used to predict lung deposition.
- USP paddle dissolution test was used to extract P-PSD to calculate *in vivo* dissolution [5].
- PCAT-2 model predicts the data better than the legacy model as shown in Figure 3.

Table 2: Pulmonary PBPK absolute prediction error [100xABS(pred-obs)/obs] for three different cell-based assays including MucilAir Bronchial, Calu-3, and NCI-H441 utilizing original legacy pulmonary model for three formulations of fluticasone A-4.5, B-3.8, and C-3.7. Here the formulation labels refer to the particle size of the formulation.

	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

Table 3: Pulmonary PBPK absolute prediction error [100xABS(pred-obs)/obs] for three different cell-based assays including MucilAir Bronchial, Calu-3, and NCI-H441 utilizing new PCAT-2 model for three formulations of fluticasone A-4.5, B-3.8, and C-3.7.

	PCAT-2 Model: Fluticasone Propionate								
	MucilAir Bronchial			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	6.66	18.66	6.85	25.93	4.65	17.10	27.09	3.78
Tmax Error %	34.0	63.3	44.4	4.0	80.0	64.6	0.0	80.0	64.6
AUC Error %	29.4	29.6	34.1	14.5	14.9	20.2	11.9	12.5	17.8

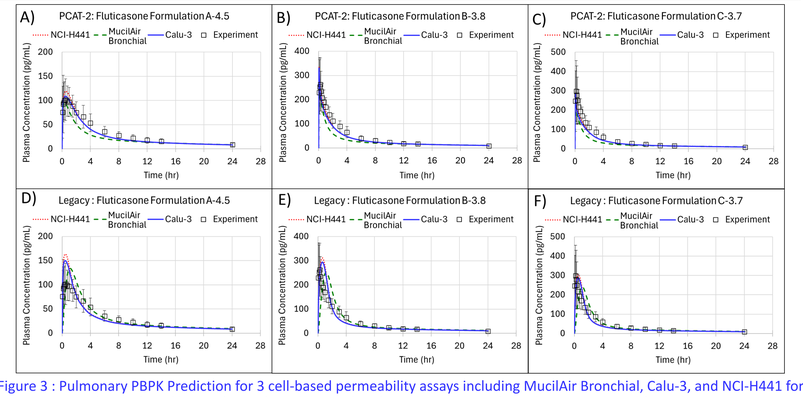

Figure 3 : Pulmonary PBPK Prediction for 3 cell-based permeability assays including MucilAir Bronchial, Calu-3, and NCI-H441 for PCAT Version 2 (A, B, C) and legacy (D, E, F) model including formulation A-4.5, formulation B-3.8, and formulation C-3.7.

CONCLUSIONS

- The PCAT-2 model with enhanced lung physiology provides an improved IVIVE of pulmonary exposure in both case studies.
- For the tobramycin case study, the Calu-3 permeability experiment was most predictive.
- For fluticasone, the Calu-3 permeability experiment was most predictive with the legacy model, while the NCI-H441 was most predictive with PCAT-2 model.
- We have not yet determined why Calu-3 seems to most often be the most predictive. We believe more clarity will come once we test the model on more compounds and scale the permeabilities with measured cell layer thicknesses rather than using literature assumption for the *in vitro* cell layer thickness.
- Best practices for the type of *in vitro* permeability assays to use for a successful IVIVE will be determined for lung PBPK prediction of OIDPs absorption predictions.

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