GastroPlus®

Pulmonary PBPK Modeling for Inhaled Products: Antibiotic Case Studies

2021 ISAM Congress

James Mullin, Sr. Principal Scientist, Simulations Plus, Inc.

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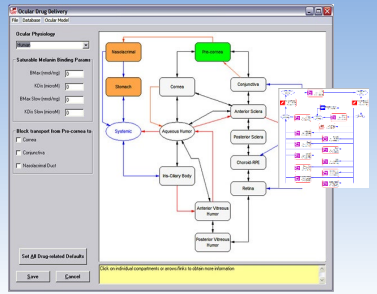
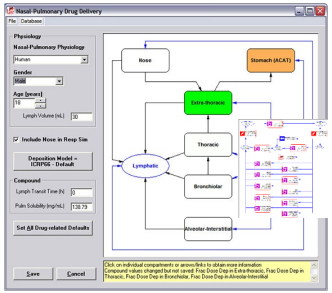
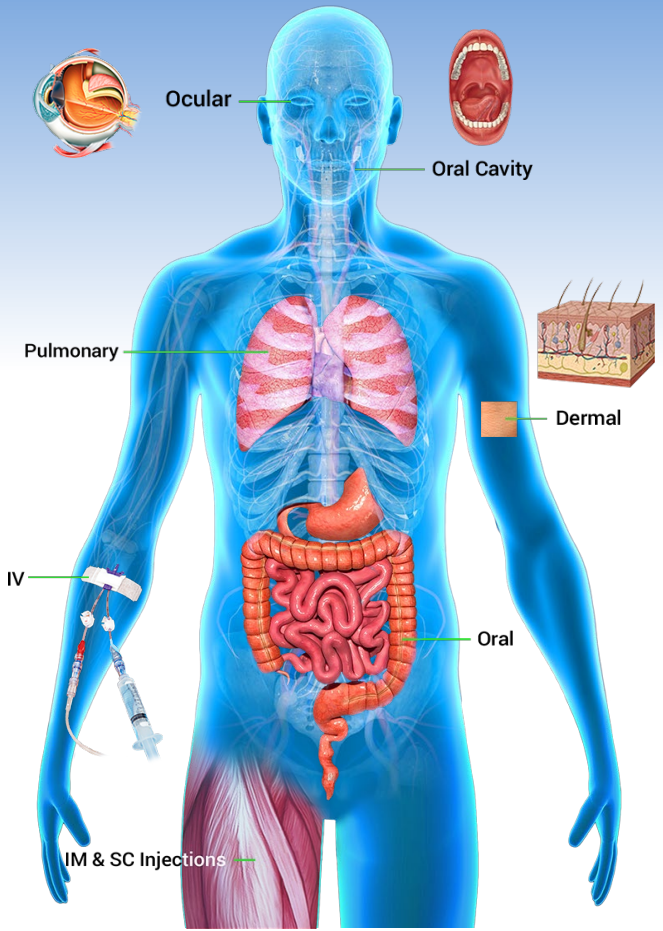
Pathways beyond oral absorption…

Ocular (OCAT™)

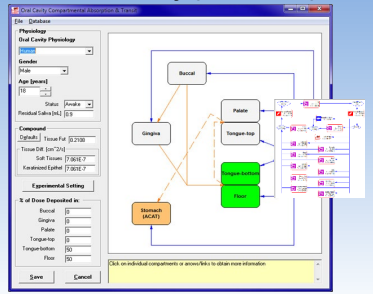


Pulmonary (PCAT™)

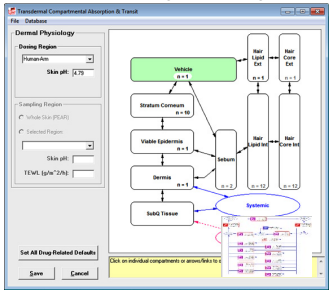




Oral Cavity (OCCAT™)



Dermal (TCAT™)



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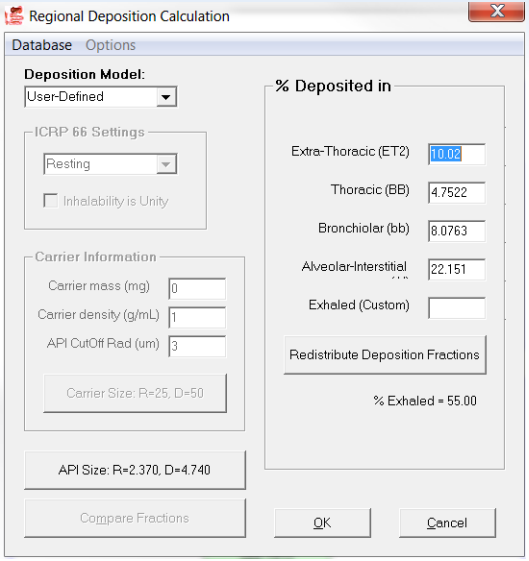
What are we doing for inhaled products today?

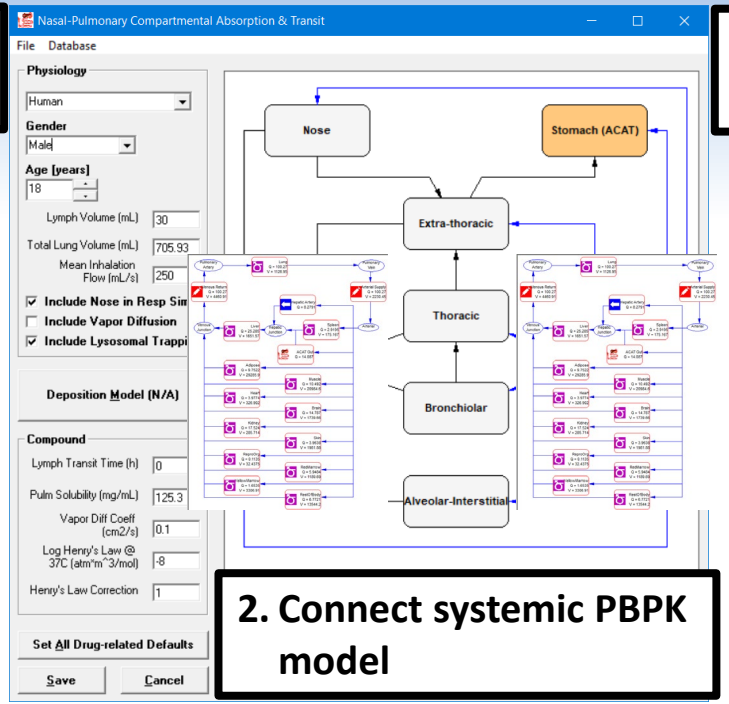
- Ability to assess exposure/concentration in any tissue
- Assessment of therapeutic dose & dose range by linking simulated plasma or tissue concentrations to PD effect
- Evaluation of formulation effects through *Parameter Sensitivity Analysis*
  - ✓ Dosage form
  - ✓ Particle size
  - ✓ Distribution
  - ✓ Density
  - ✓ Shape factor
- Prediction of population variability through the *Population Simulator* mode

Pulmonary Compartmental Absorption and Transit (PCAT™) Model

(as implemented in GastroPlus® - developed in collaboration with GlaxoSmithKline)

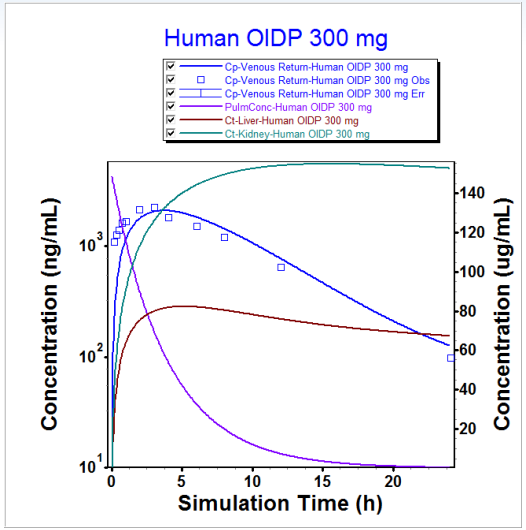
1. Define API properties & deposition fractions





2. Connect systemic PBPK model

3. Predict local and systemic concentrations



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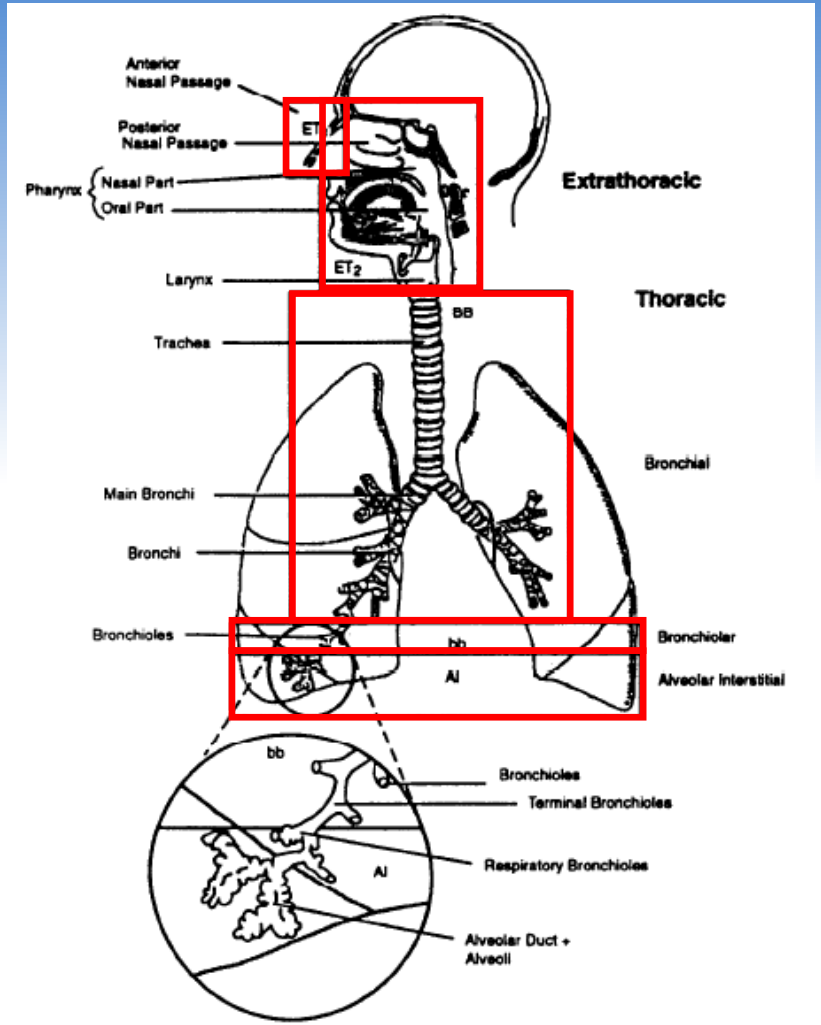
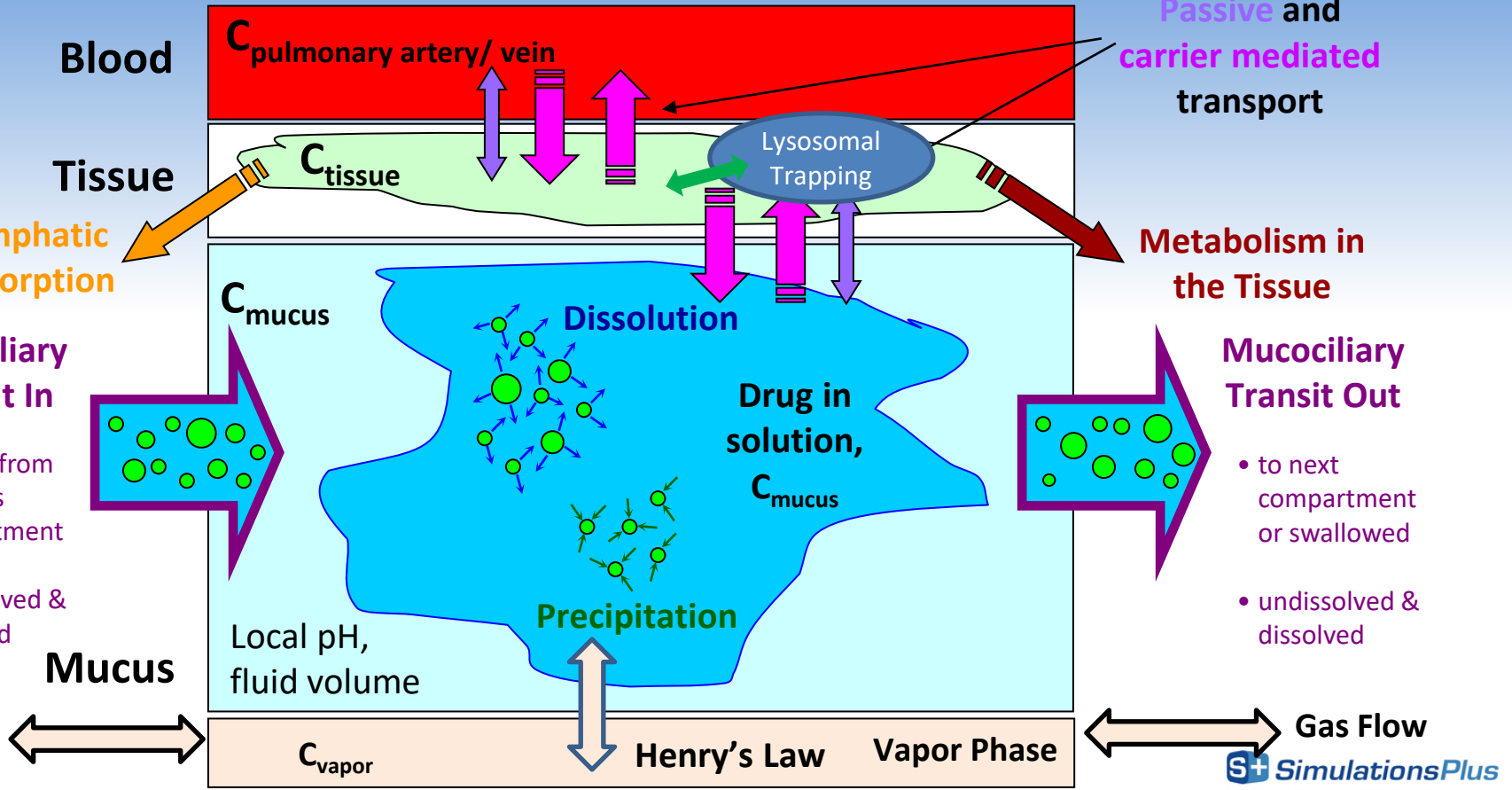


Compartmentalization of the lung (ICRP66)

- ET1 = Anterior nasal passage
- ET2 = Posterior nasal passage, oral cavity, larynx, pharynx, etc.
- BB = Trachea and bronchi
- Bb = Bronchioles (up to terminal)
- AI = Respiratory bronchioles, alveolar duct, alveoli, etc.

Processes Involved in Nasal-Pulmonary Absorption



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Compound Specific & Physiological Parameters

Compound Specific

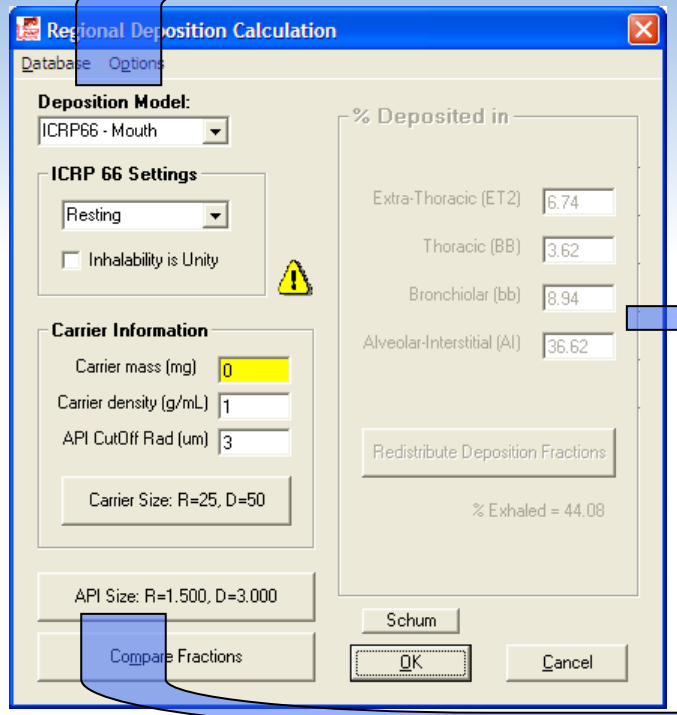
- ✓ Permeability in each tissue
- ✓ Systemic absorption rate from nasal-pulmonary tissues
- ✓ Enzyme and transport parameters
- ✓ Mucus/cell binding

Physiological

- ✓ NEW! Lysosomal fractions
- ✓ NEW! Gas volumes
- ✓ Surface Area
- ✓ Mucus Layer Thickness
- ✓ Tissue Volume
- ✓ Mucociliary Transit Time

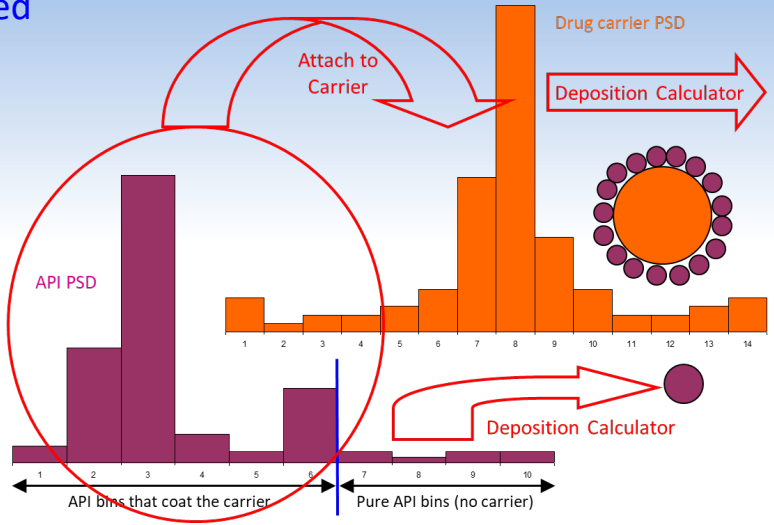
** Human physiology can be scaled based on Gender and Age

Regional Deposition Calculation



Regional lung deposition can be predicted from particle size distribution or specified manually by the user

Output (% deposited) that distributes the administered dose into different lung compartments



Size distribution and additional information for drug carrier (excipient) can be incorporated in calculation of deposition

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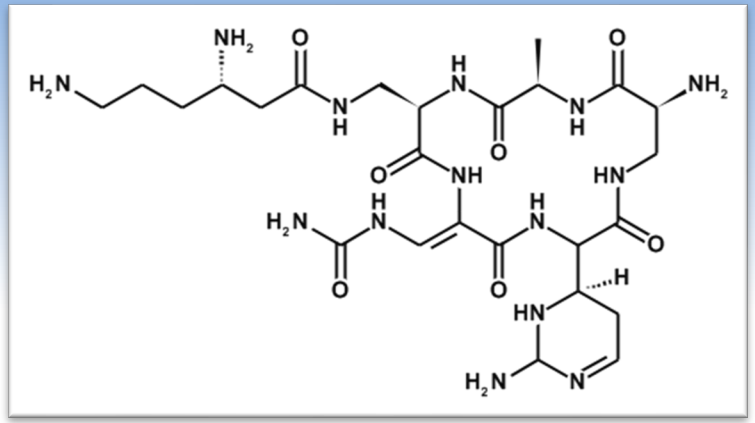
Capreomycin



- Antibiotic used in treatment of tuberculosis
- Poorly permeable compound (BCS Class III)
- Normally administered through injections*
  * poor distribution into lungs

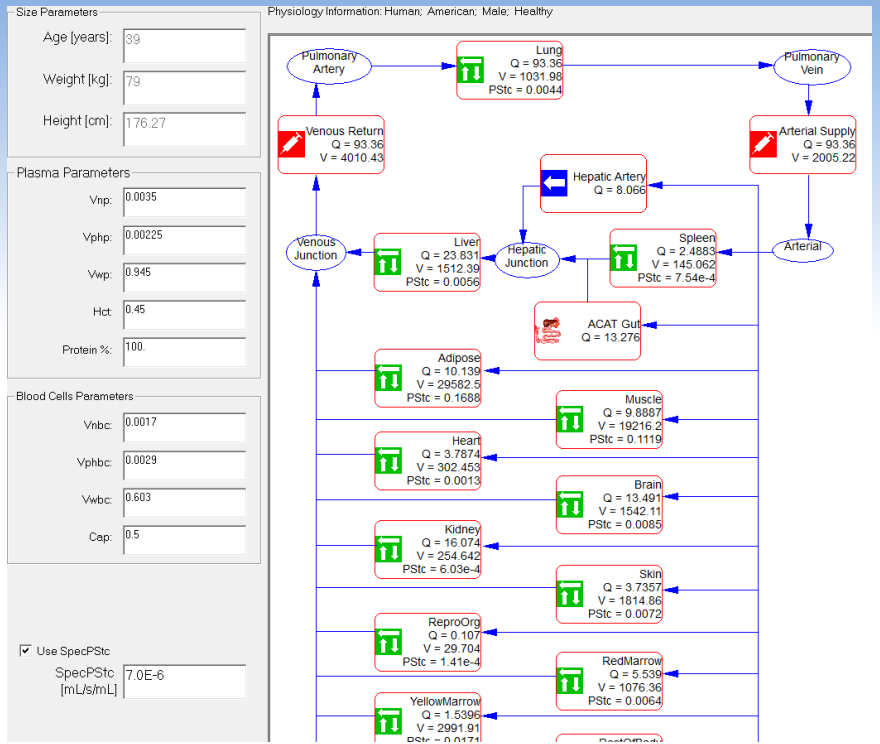
Parameter	Value	Source
logP	-6.34	ADMET Predictor™ v7.2
pKa(s)	8.33 (Base); 11.35 (Acid)	ADMET Predictor™ v7.2
Aqueous solubility	104 mg/mL @ pH 11	ADMET Predictor™ v7.2
GI permeability	0.0686 cm/s *10^-4	ADMET Predictor™ v7.2
Plasma protein binding	60% unbound	Measured [1]
Blood:plasma concentration ratio	1.11	ADMET Predictor™ v7.2
Renal clearance	4.05 L/hr	Calculated [2]
PBPK Vss	51.9 L	Calculated [3]
Specific PStc	7 * 10^-6 mL/s/mL	Optimized [4]

[1] Reisfeld B et al., Antimicrob Agents Chemother 56926-934, 2011.
[2] Calculated from Fup * GFR method; GFR adjusted for different disease states
[3] Calculated from Poulin method for extracellular space partitioning (Poulin et al., 2002)
[4] Optimized using reported PK parameters following intravenous administration

Modeling Objectives

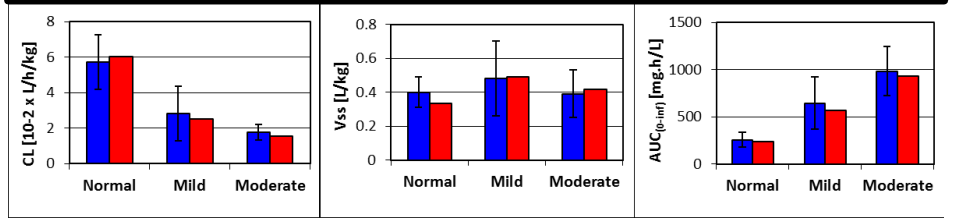
- **Develop** a systemic PBPK model using available PK data following IV administration
- **Build** a MAM/PBPK model for an OIDP at low dose
- **Validate** the MAM/PBPK model for OIDPs at higher doses
- **Apply** the MAM/PBPK model for an OIDP at highest dose to establish product specifications

Baseline Systemic PBPK Model Development



Model building steps:

1. Create virtual humans according to the subject demographics*
2. Define all tissues as permeability-limited models
3. Estimate tissue partitioning using published Poulin method (Poulin et al., 2002)
4. Calculate renal clearance as Fup * GFR
5. Optimize Specific PStc parameter to define tissue permeabilities



Observed (blue) and simulated (red) clearance (A), volume of distribution (B), and AUC (C) in groups of healthy subjects with normal renal function and patients with mild and moderate renal impairment* used to calibrate the capreomycin systemic PBPK model.

* Data from Lehmann CR, Am Rev Respir Dis 138: 1312-1313, 1988.

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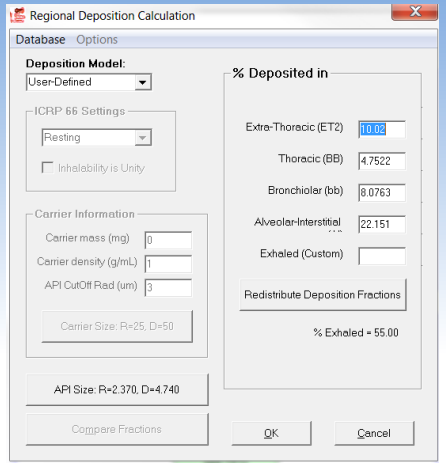
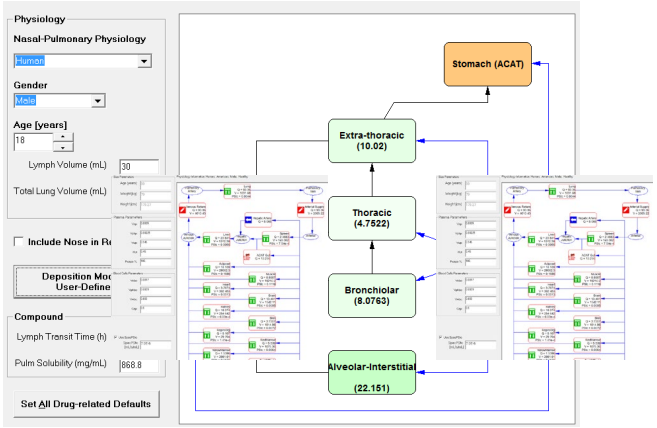
MAM/PBPK Model Building





Model building steps:

1. Define deposition fractions using *in vitro* data, MMAD, and ICRP method*
2. Calculate mucus membrane permeabilities using built-in GastroPlus PCAT™ approach
3. Optimize systemic absorption rate constants for lung compartment using low dose OIDP PK data
4. Predict PK profiles for OIDPs at higher doses to validate model

Parameter	Value	Source
Lung Absorption Rate Constant	8 * 10^-5 / sec	Optimized
Extra-thoracic Permeability	7.61 * 10^-7 cm/sec	GastroPlus PCAT™ model
Thoracic Permeability	6.91 * 10^-7 cm/sec	GastroPlus PCAT™ model
Bronchiolar Permeability	2.53 * 10^-6 cm/sec	GastroPlus PCAT™ model
Alveolar Permeability	6.54 * 10^-5 cm/sec	GastroPlus PCAT™ model
Mass Median Aerodynamic Diameter (MMAD)	4.74 µm	Fiegel J et al., Pharm. Res. 25:805-11, 2008

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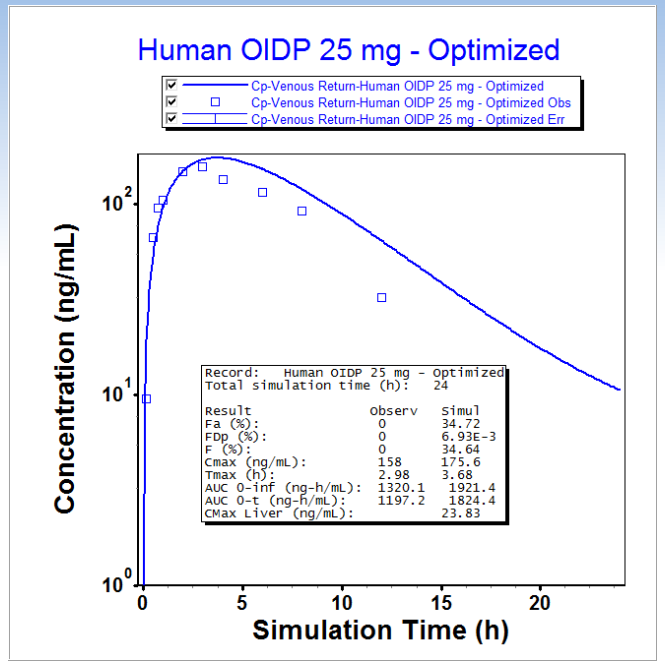
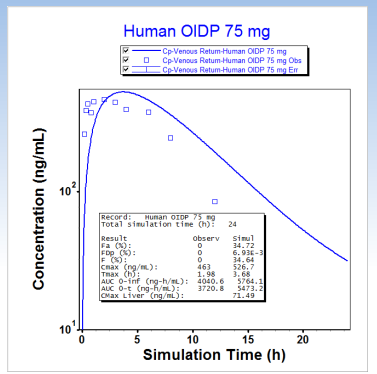
MAM/PBPK Model Validation

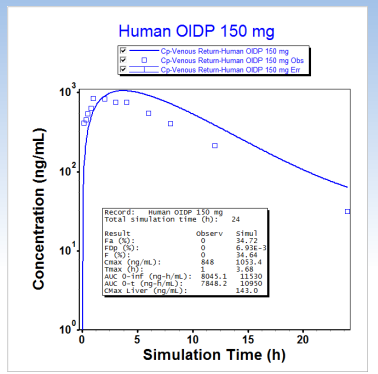
OIDP 25 mg - Optimized



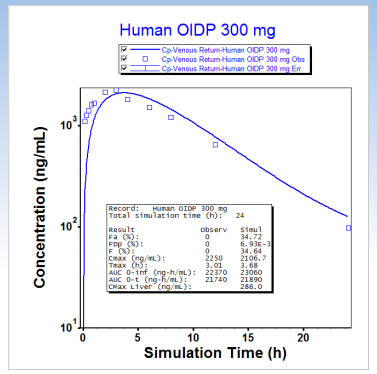
OIDP 75 mg



OIDP 150 mg



OIDP 300 mg



Observed (points) and simulated (lines) systemic PK profiles after 25 mg (A), 75 mg (B) , 150 mg (C), and 300 mg (D) inhaled administration of capreomycin*. The observed Cp-time profile after a 25 mg dose was used to fit the systemic absorption rate coefficient, and the remaining doses were well predicted using the same model parameters.

* Dharmadhikari AS *et al.* Phase I, *Antimicrob Agents Chemother* 57(6): 2613-2619, 2013.

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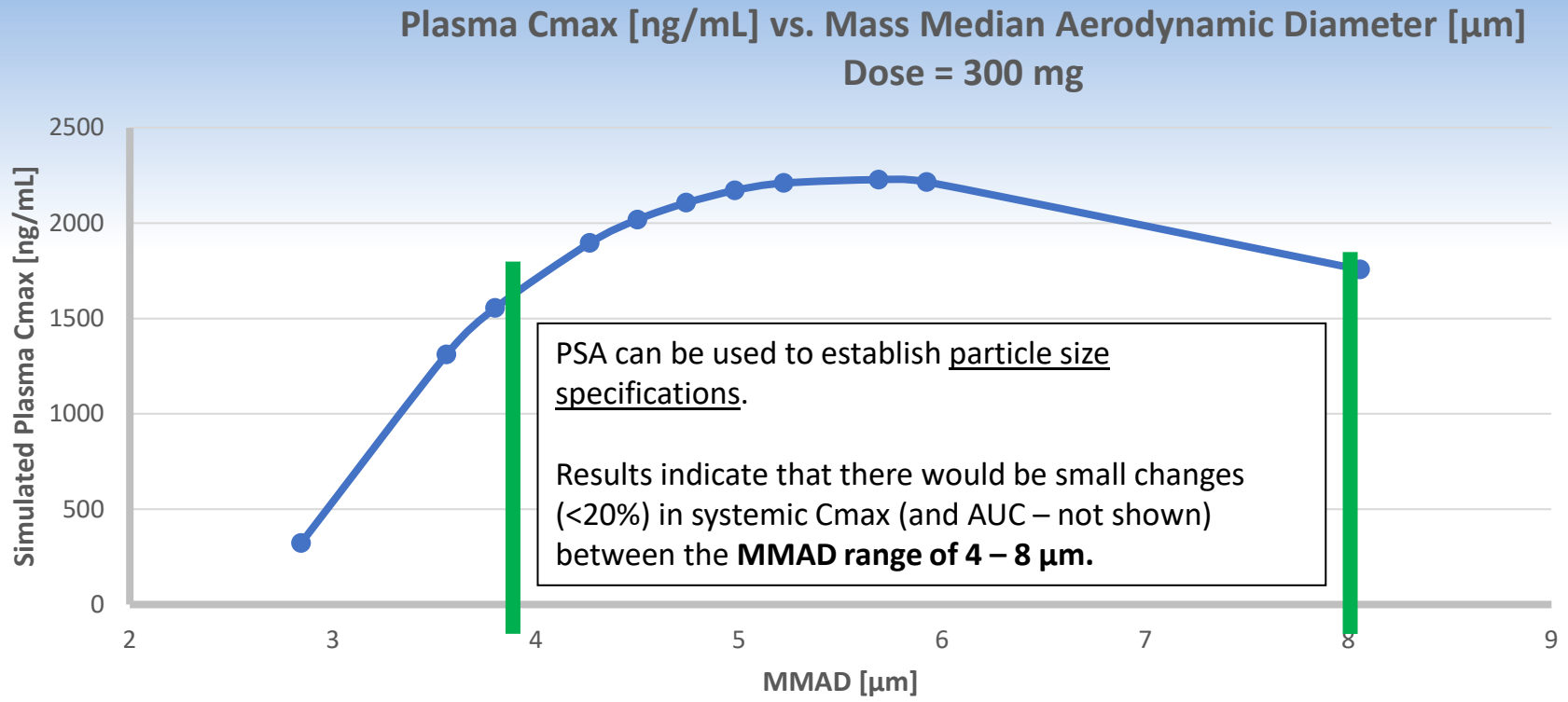
Particle Size Specifications: Sensitivity Analysis



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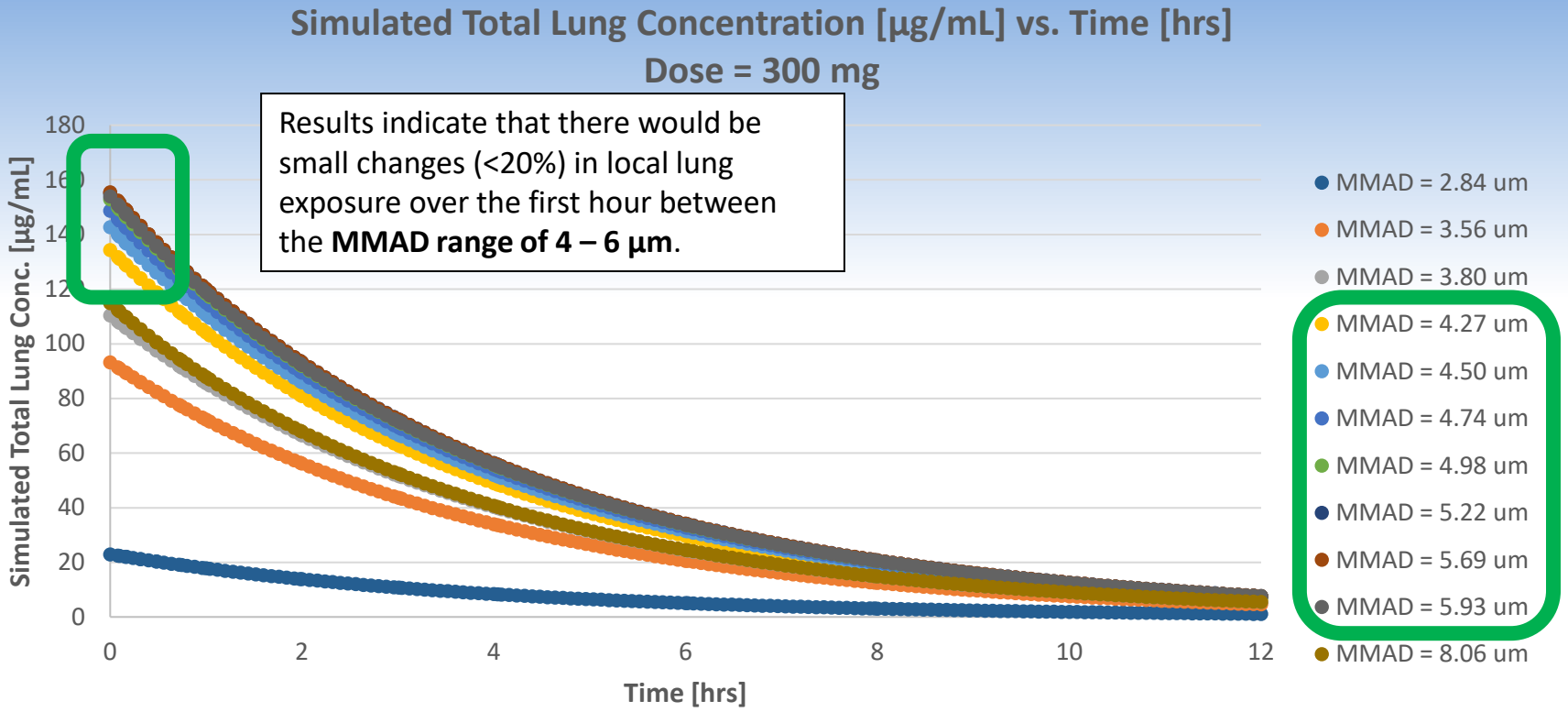
Particle Size Specifications: Local Exposure



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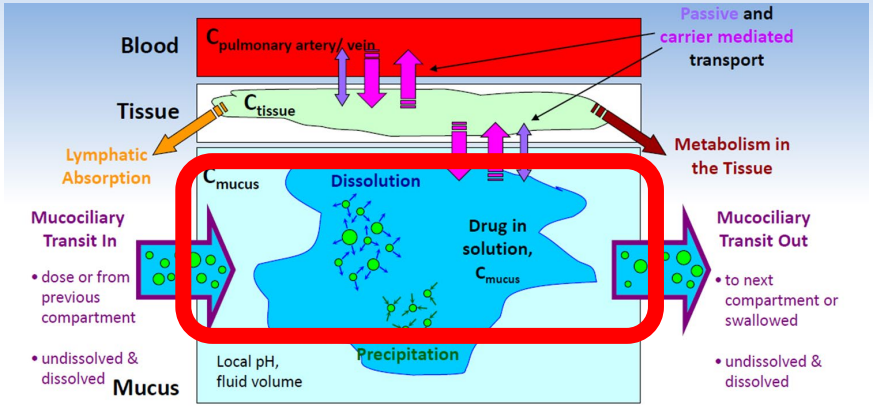
Particle Size Specifications: Dissolution or Deposition?

Are MMAD changes on exposure driven by:

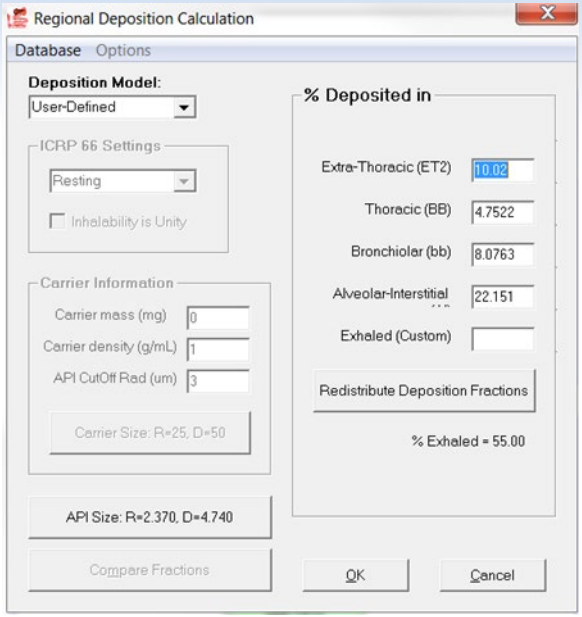
Dissolution Rate?



The phenomena:

- are happening simultaneously
- are repeated in each of the compartments of the nasal-pulmonary model

Deposition?



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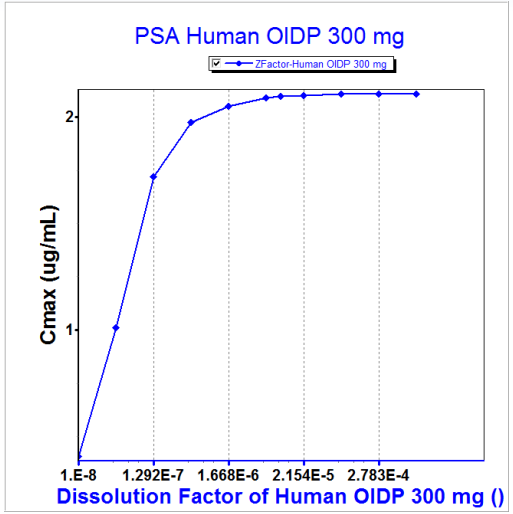
Sensitivity Analysis: Dissolution Rate

Z-Factor Dissolution Model:

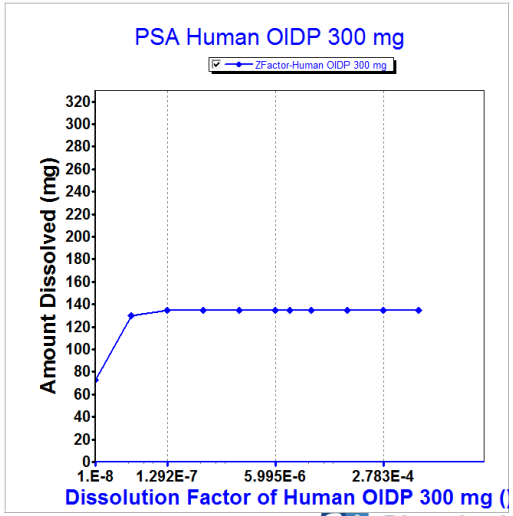
$$Dissolution\ Rate = Z(C_s - C_l) * M_{u(t)}$$

- Z represents z-factor (fitted to *in vivo* or *in vitro* dissolution data);
- Cs is drug solubility;
- Cl is local dissolved drug concentration;
- Mu,t is remaining undissolved drug amount at time t



Sensitivity around Z-Factor (dissolution rate) indicates 2-order magnitude change required to produce similar changes in systemic Cmax seen from MMAD analysis (where MMAD only changed ~50% from baseline)

Indicates that **deposition fractions**, and not dissolution rate, is **driving exposure**.



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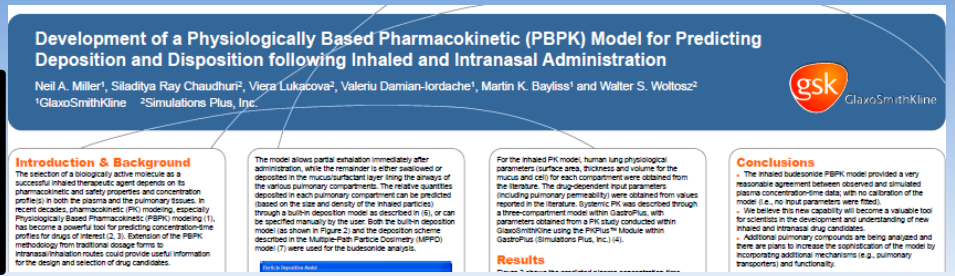
Validation Cases

PBPK models for deposition and disposition following inhaled & intranasal administration (Miller et al., RDD 2010)



Development of a Physiologically Based Pharmacokinetic (PBPK) Model for Predicting Deposition and Disposition following Inhaled and Intranasal Administration

Neil A. Miller[1], Siladitya Ray Chaudhuri[2], Viera Lukacova[2], Valeriu Damian-Iordache[1], Martin K. Bayliss[1] and Walter S. Woltosz[2]

[1]GlaxoSmithKline [2]Simulations Plus, Inc.

GlaxoSmithKline

Introduction & Background

The selection of a biologically active molecule as a successful inhaled therapeutic agent depends on its pharmacokinetic and safety properties and concentration profile(s) in both the plasma and the pulmonary tissues. In recent decades, pharmacokinetic (PK) modeling, especially Physiologically Based Pharmacokinetic (PBPK) modeling (1), has become a powerful tool for predicting concentration-time profiles for drugs of interest (2, 3). Extension of the PBPK methodology from traditional dosage forms to intranasal inhalation routes could provide useful information for the design and selection of drug candidates.

The model allows partial exhalation immediately after administration, while the remainder is either swallowed or deposited in the mucus/surfactant layer lining the airways of the various pulmonary compartments. The relative quantities deposited in each pulmonary compartment can be predicted (based on the size and density of the inhaled particles) through a built-in deposition model as described in (6), or can be specified manually by the user. Both the built-in deposition model (as shown in Figure 2) and the deposition scheme described in the Multiple-Path Particle Dosimetry (MPPD) model (7) were used for the budesonide analysis.

For the inhaled PK model, human lung physiological parameters (surface area, thickness and volume for the mucus and cell) for each compartment were obtained from the literature. The drug-dependent input parameters (including pulmonary permeability) were obtained from values reported in the literature. Systemic PK was described through a three-compartment model within GastroPlus, with parameters obtained from a PK study conducted within GlaxoSmithKline using the PKPlus™ Module within GastroPlus (Simulations Plus, Inc.) (4).

Results

Conclusions

- The inhaled budesonide PBPK model provided a very reasonable agreement between observed and simulated plasma concentration-time data; with no calibration of the model (i.e., no input parameters were fitted).
- We believe this new capability will become a valuable tool for scientists in the development and understanding of new inhaled and intranasal drug candidates.
- Additional pulmonary compounds are being analyzed and there are plans to increase the sophistication of the model by incorporating additional mechanisms (e.g., pulmonary transporters) and functionality.

IVIVE for inhaled products (Salar-Behzadi et al., Int J Pharm 2017)

ELSEVIER

Volume 532, Issue 1, 30 October 2017, Pages 337-344

Research paper

Effect of the pulmonary deposition and *in vitro* permeability on the prediction of plasma levels of inhaled budesonide formulation

Shareen Salar-Behzadi [a], Shengqian Wu [a], Annalisa Mercuri [a, 1], Claudia Meindl [b], Sandra Stranzinger [a], Eleonore Fröhlich [a, b, ⁂]

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Abstract

The growing interest in the inhalable pharmaceutical products requires advanced approaches to safe and fast product development, such as *in silico* tools that can be used for estimating the bioavailability and toxicity of developed formulation. GastroPlus™ is one of the few available software packages for *in silico* simulation of PBPK profile of inhalable products. It contains a complementary module for calculating the lung deposition, the permeability and the systemic absorption of inhalable products. Experimental values of lung deposition and permeability can also be used. This study aims to assess the efficiency of simulation by applying experimental permeability and deposition values, using budesonide as a model substance. The lung deposition values were obtained from the literature, the lung permeability data were experimentally determined by culturing Calu-3 cells under air-liquid interface and submersed conditions to morphologically resemble bronchial and alveolar epithelial cells, respectively. A two-compartment PK model was created for i.v. administration and used as a background for the *in silico* simulation of the plasma profile of budesonide after inhalation. The predicted plasma profile was compared with the *in vivo* data from the literature and the effects of experimental lung deposition and permeability on prediction were assessed. The developed model was significantly improved by using realistic lung deposition data combined with experimental data for peripheral permeability.

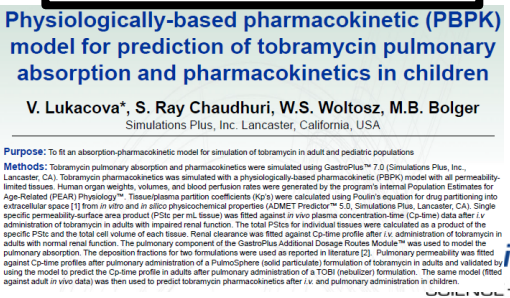
Emerging technologies in inhaled product development (Backman et al., CPT (2014) 95;5)

Advances in Inhaled Technologies: Understanding the Therapeutic Challenge, Predicting Clinical Performance, and Designing the Optimal Inhaled Product

P Bäckman[1], H Adelmann[2], G Petersson[1] and CB Jones[3]

Inhaled medicines are designed mainly to provide safe and efficacious treatment of respiratory diseases, offering the potential advantages of targeted drug delivery such as reduced onset time and increased therapeutic ratio. However, as a flipside of targeted drug delivery, drug levels in the relevant effect compartment cannot be easily assessed. In combination with technical challenges associated with aerosolizing and administering an inhaled medicine, this renders inhalation product development demanding in the regulatory aspect as well. Emerging technologies that could address some of these challenges include (i) mechanistic pharmacokinetic/pharmacodynamic (PK/PD) modeling, which in combination with experimental techniques such as positron emission tomography could provide information on local target engagement; (ii) patient-feedback features in combination with electronic monitoring, which may improve patient adherence as well as patient handling; and (iii) controlled-release formulations and nanotechnology-based formulations with high drug load, which may expand the scope of development of compounds and targets suitable for inhalation product development.

Adult/pediatric PBPK models for pulmonary absorption (Lukacova et al., Rosenon 2010)



Physiologically-based pharmacokinetic (PBPK) model for prediction of tobramycin pulmonary absorption and pharmacokinetics in children

V. Lukacova*, S. Ray Chaudhuri, W.S. Woltosz, M.B. Bolger

Simulations Plus, Inc. Lancaster, California, USA

Purpose: To fit an absorption-pharmacokinetic model for simulation of tobramycin in adult and pediatric populations

Methods: Tobramycin pulmonary absorption and pharmacokinetics were simulated using GastroPlus™ 7.0 (Simulations Plus, Inc., Lancaster, CA). Tobramycin pharmacokinetics was simulated with a physiologically-based pharmacokinetic (PBPK) model with all permeability-limited tissues. Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™. Tissue/plasma partition coefficients (Kp's) were calculated using Poulin's equation for drug partitioning into extracellular space [1] from *in vitro* and *in silico* physicochemical properties (ADMET Predictor™ 5.0, Simulations Plus, Lancaster, CA). Single specific permeability-surface area product (PStc per mL tissue) was fitted against *in vivo* plasma concentration-time (Cp-time) data after *i.v.* administration of tobramycin in adults with impaired renal function. The total PStcs for individual tissues were calculated as a product of the specific PStc and the total cell volume of each tissue. Renal clearance was fitted against Cp-time profile after *i.v.* administration of tobramycin in adults with normal renal function. The pulmonary component of the GastroPlus Additional Dosage Routes Module™ was used to model the pulmonary absorption. The deposition fractions for two formulations were used as reported in literature [2]. Pulmonary permeability was fitted against Cp-time profiles after pulmonary administration of a PulmoSphere (solid particulate) formulation of tobramycin in adults and validated by using the model to predict the Cp-time profile in adults after pulmonary administration of a TOBI (nebulizer) formulation. The same model (fitted against adult *in vivo* data) was then used to predict tobramycin pharmacokinetics after *i.v.* and pulmonary administration in children.

Validation Cases

Physiologically based pharmacokinetic (PBPK) model to describe absorption and disposition of inhaled capreomycin

James Mullin; Viera Lukacova; Michael Bolger; Walter Woltosz
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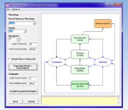
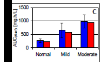


Figure 2: Schematic layout of the compartments in the PCAT model. The numbers in parentheses show estimated percents of the capreomycin dose deposited in different lung regions. The total lung deposition was set to 55%.



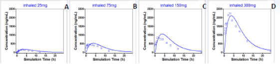


Figure 3: Observed (points) and simulated (lines) Cp-time profiles after 25 mg (A), 75 mg (B), 150 mg (C), and 300 mg (D) inhaled administration of capreomycin. The observed Cp-time profile after a 25 mg dose was used to fit the systemic absorption rate coefficient, and the remaining doses were well-predicted using the same model parameters. Observed data was obtained from literature [2].

Conclusions

PBPK modeling is routinely utilized in the drug development process, mainly for IV and oral administration routes. It, however, also has great potential to help with the development of formulations for other administration routes, and the current work shows an example of a predictive PBPK model for inhaled administration.

PBPK models for deposition and disposition following inhaled administration at different dose levels (Mullin et al., RDD 2016)

Performance evaluation of the GastroPlus™ software tool for prediction of the toxicokinetic parameters of chemicals

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ABSTRACT
The accurate prediction of toxicokinetic parameters arising from oral, dermal and inhalation routes of chemical exposure is a key

ARTICLE HISTORY
Received 2 July 2018
Accepted 30 August 2018

Machine learning+PBPK for inhaled chemicals (Zhang et al., SAR QSAR Environ Res 2018)

Journal of Drug Delivery Science and Technology
Volume 52, August 2019, Pages 803-817

Insights into DPI sensitivity to humidity: An integrated *in-vitro-in-silico* risk-assessment

Snezana Radivojev[a, b, 1], Joana T. Pinto[a, 1], Eleonore Fröhlich[a, b], Amrit Paudel[a, c]

Abstract

Dry pow... storage ... a potential risk. Therefore, an in-vitro-in-silico approach was utilized to assess the risk that patient erroneous storage might pose. For this two commercial DPIs containing lactose and budesonide (Easyhaler® and Novolizer®) were used. These were evaluated in respect to their physical solid-state and micrometric properties as well as their *in-vitro* aerodynamic performance. Testing was carried out at time 0, 14 and 28 days after storage at 60% RH and > 90% RH. Using *in-silico* modeling the potential impact of powder sensitivity to humidity on the biopharmaceutical performance of budesonide was evaluated. Results revealed that the physical and aerodynamic properties of the powders having a smaller carrier particle size and a higher amount of excipient fines were more notably affected. Use of *in-vitro* results as inputs for *in-silico* pharmacokinetic modeling showed that some changes in powder properties can have a potential impact on the pulmonary availability of budesonide. So, it appears that it is important to consider the impact that different product characteristics might have on the physical stability of powders against moisture and their subsequent biopharmaceutical performance.

Risk assessment for DPI products (Radivojev et al., J Drug Del Sci Tech 2019)

The AAPS Journal, Vol. 17, No. 4, July 2015 (© 2015)
DOI: 10.1208/s12248-015-9760-6

Review Article

Pharmacometric Models for Characterizing the Pharmacokinetics of Orally Inhaled Drugs

Jens Markus Borghardt,[1] Benjamin Weber,[2] Alexander Staab,[2] and Charlotte Kloft[1,3]

Received 17 Decembe...

Abstract. During the development, with th... pharmacokinetic proc... for orally inhaled dru... demonstrate the opp... offers. To achieve these objectives, this review (i) discusses pulmonary physiological processes and their impact on the pharmacokinetics after drug inhalation, (ii) provides a comprehensive overview of published pharmacokinetic models, (iii) categorizes these models into physiologically based pharmacokinetic (PBPK) and (clinical data-derived) empirical models, (iv) explores both their (mechanistic) plausibility, and (v) addresses critical aspects of different pharmacometric approaches pertinent for drug inhalation. In summary, pulmonary deposition, dissolution, and absorption are highly complex processes and may represent the major challenge for modeling and simulation of PK after oral drug inhalation. Challenges in relating systemic pharmacokinetics with pulmonary efficacy may be another factor contributing to the limited number of existing pharmacokinetic models for orally inhaled drugs. Investigations comprising *in vitro* experiments, clinical studies, and more sophisticated mathematical approaches are considered to be necessary for elucidating these highly complex pulmonary processes. With this additional knowledge, the PBPK approach might gain additional attractiveness. Currently, (semi-)mechanistic modeling offers an alternative to generate and investigate hypotheses and to more mechanistically understand the pulmonary and systemic pharmacokinetics after oral drug inhalation including the impact of pulmonary diseases.

KEY WORDS: inhalation; mathematical models; physiologically based pharmacokinetic models; population pharmacokinetics; pulmonary absorption.

PBPK models for orally inhaled drugs (Borghardt et al., AAPS J 2015)

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Summary

- MAM/PBPK model for capreomycin explains observed systemic PK for OIDPs across a dose range of 25 – 300 mg
- Sensitivity analysis around MMAD helps establish particle size specifications based on local and systemic PK endpoints
- MAM/PBPK model identifies that MMAD changes impact capreomycin deposition in lung tissues, not dissolution

Q&A

Questions & Answers

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