Impact of Orally Inhaled and Nasal Drug Product PBPK Models on Product Development and Regulatory Decision Making

ASCPT 2019 Annual Meeting Pre-Conference:
PBPK Modeling for the Development and Approval of Locally Acting Drug Products

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Session 1: Orally Inhaled and Nasal Drug Products

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA

Regulatory Impacts/Applications of PBPK for OINDPs

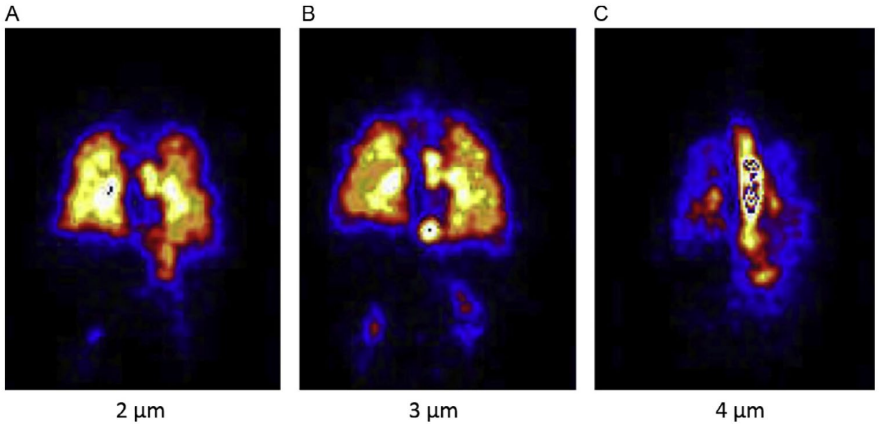
- Generic Orally Inhaled and Nasal Drug Product (OINDP) Development
  - Inform product design and development
- Regulatory Utility
  - Product specific guidance (PSG) development
  - Potentially support alternative bioequivalence (BE) approaches including not conducting comparative clinical endpoint BE studies

Why PBPK for OINDP Development?

- Product Specific Guidance (PSG) documents for generic locally-acting OINDPs
  - Often recommend “weight of evidence” approach
  - May include pharmacodynamic or comparative clinical endpoint BE studies
- Model to integrate formulation development, device development, and increase chance of showing BE for multiple studies

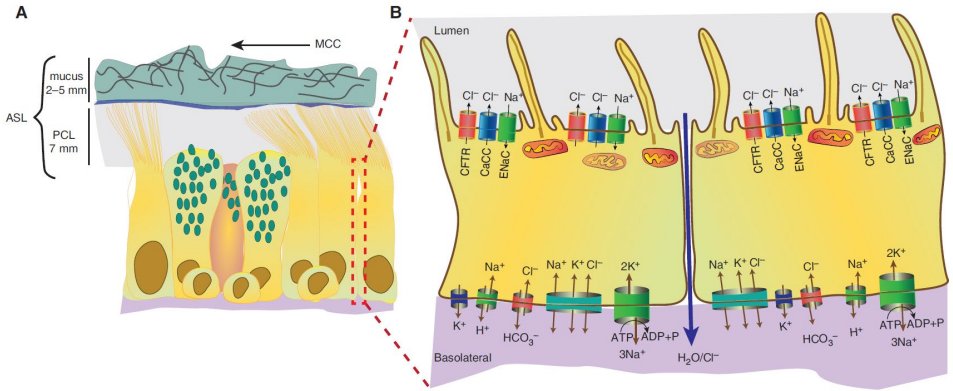
Modeling Considerations for Locally-Acting OINDPs (Part 1)

Regional Deposition



Single-photon emission computerized tomography (SPECT) images – Figure 1 of Kwok et al. (2019)

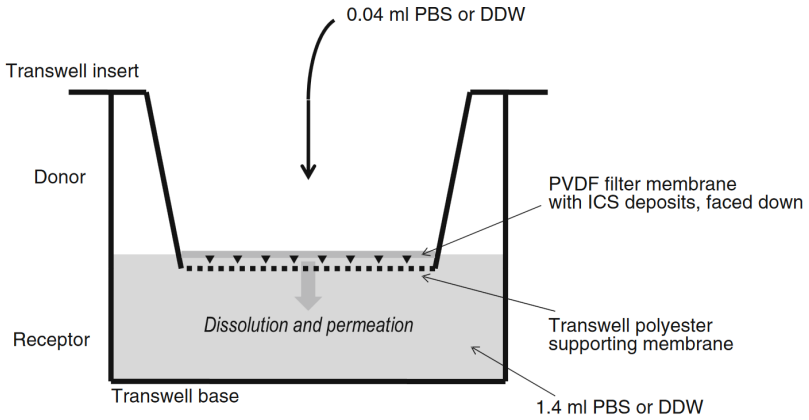
Mucociliary Clearance



Mucociliary clearance mechanisms – Figure 2 of Bustamente-Marin and Ostrowski (2017)

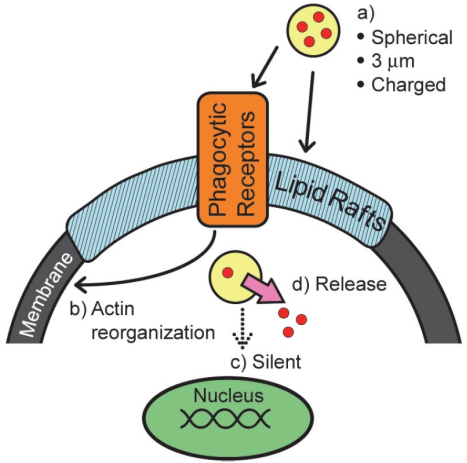
Modeling Considerations for Locally-Acting OINDPs (Part 2)

Dissolution and Permeation



Transwell volume-limited dissolution apparatus – Figure 2 of Arora et al. (2010)

Macrophage Uptake



Macrophage uptake – Figure 2 of Hirota and Terada (2012)

PBPK Modeling for Locally-Acting OINDPs – Case Studies

- Poorly soluble compounds
  - Regional transit due to mucociliary clearance
- Formulation changes for dry powder inhalers (DPIs)
  - Carrier particle modification

Case Study 1: Poorly Soluble OIDP Compound

- This case study describes work by Bäckman et al. (2017)
- New selective glucocorticoid receptor modulator, AZD5423
- Poorly soluble in water, highly lipophilic
- PK data available for model building
  - Study 1: Intravenous (IV), oral, two different nebulizers
  - Study 2: IV, oral, two different nebulizers, two different DPIs
- PBPK: Relationship between in vitro parameters and PK exposure
  - GastroPlus 9.0
- In vitro parameters: delivered dose, ex-mouth throat model (ex-MTM) dose, particle size distribution

Delivered Dose and Ex-MTM Dose do not Predict AUC

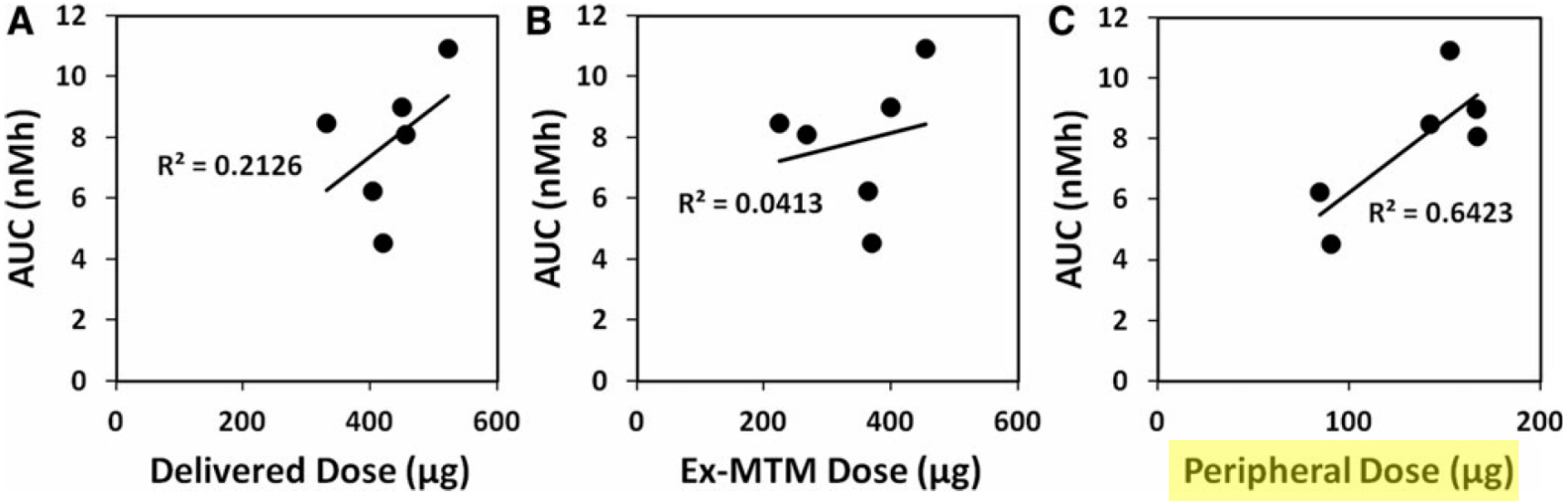


Figure 3 from Bäckman et al. (2017): For OIDP-delivered drug, correlations between area under the curve (AUC) and A) delivered dose to the lung, B) ex-mouth-throat-model (ex-MTM) dose, and C) peripheral dose computed using semi-empirical model.

PBPK Predictions of AUC and C_{max} Correlate Well with PK Data

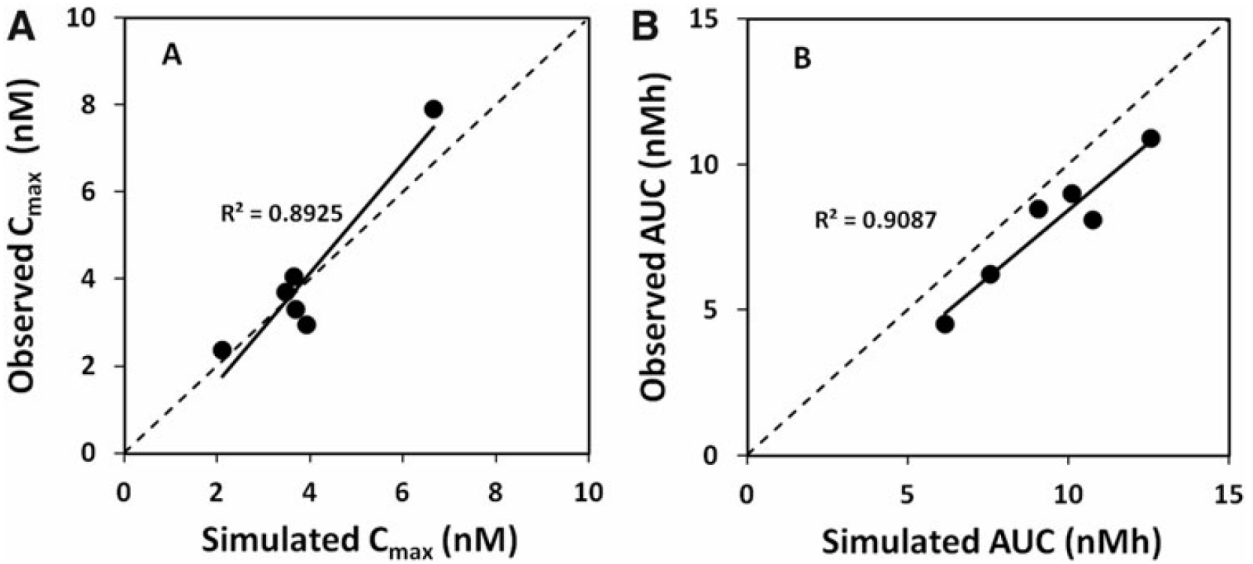


Figure 4 from Bäckman et al. (2017): For OIDP-delivered drug, correlations between observed and simulated A) maximum plasma concentration (C_{max}) and B) area under the curve (AUC).

Case Study 2: Carrier Surface Modification for DPI Development

- This case study describes work by Wu et al. (2016)
- Albuterol sulfate delivered from Cyclocaps®
- Carrier particle surface modification
  - Glass beads as carrier particle substitutes
- Particle size characterized using Next Generation Impactor
- PBPK model: Relationship between particle size and PK exposure
  - GastroPlus 8.6

PK Data Available for Model Building

- IV data from Goldstein et al. (1987) used to parameterize two compartment PK model
- Oral solution data and Ventolin® MDI data (Du et al. (2002) used to validate model
  - No Cyclocaps® PK data available

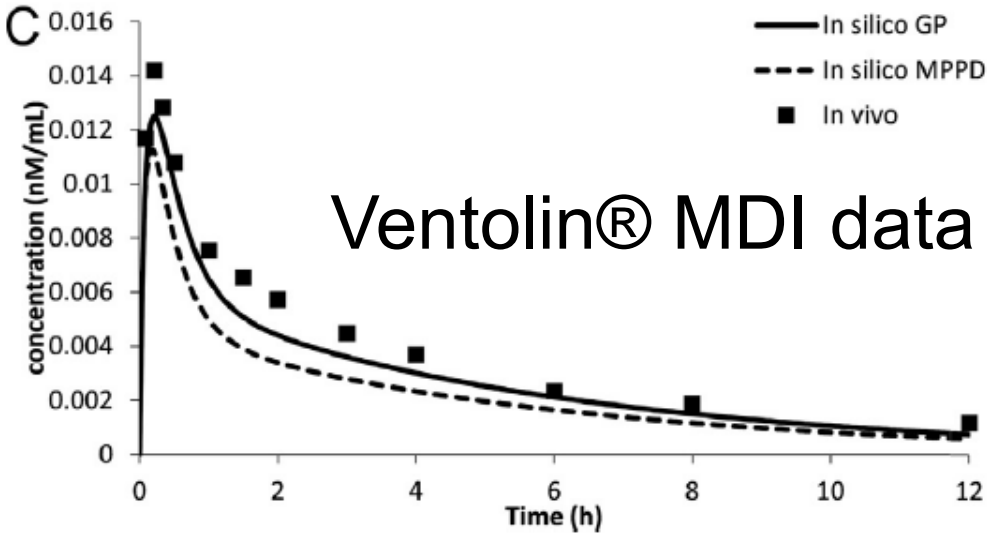


Figure 4C from Wu et al. (2016): Comparison of model Ventolin® MDI data from Du et al. (2002), where the built-in GastroPlus regional deposition predictor was used as well as the Multiple-Path Particle Dosimetry (MPPD) for regional deposition estimates.

Predictions Show Greater C_{max} with Surface Engineered Glass Beads

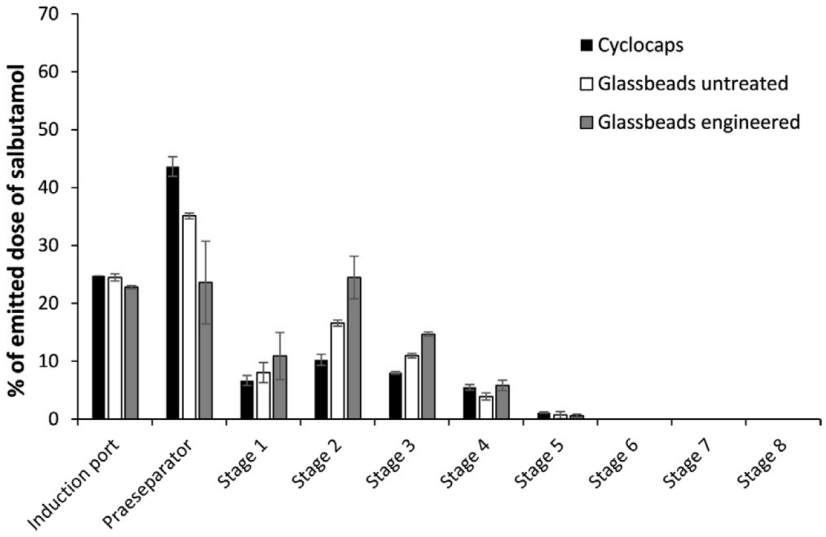


Figure 3 from Wu et al. (2016): Particle size distribution data for Cyclocaps®, formulation with untreated glass beads, and formulation with treated glass beads, where standard deviation bars are given for each stage (n = 3) and results are presented with respect to emitted dose.

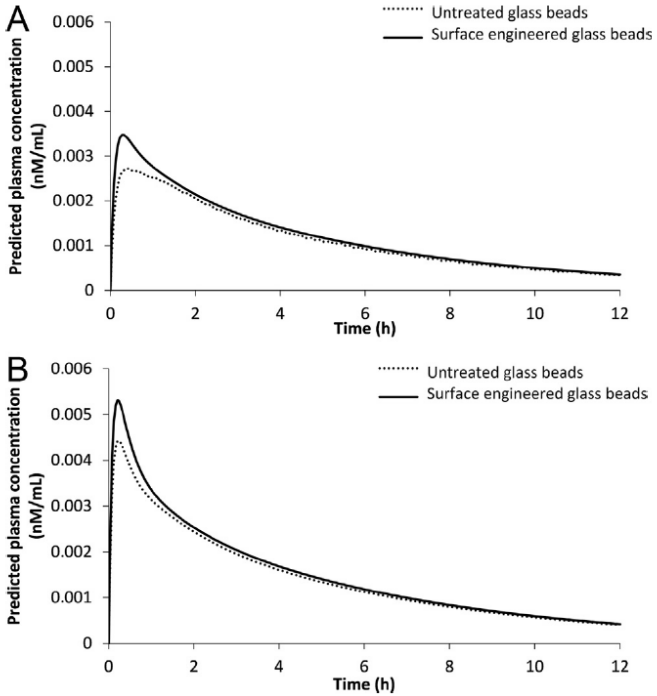


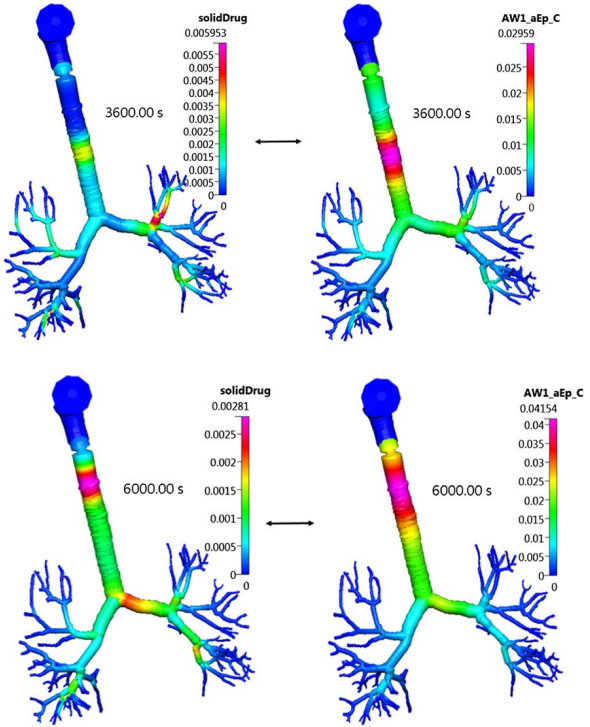
Figure 6 from Wu et al. (2016): Predicted plasma concentration for formulations with untreated and surface engineered glass beads using A) GastroPlus built-in regional deposition predictor and B) MPPD model.

Enhancement for PBPK Models of OINDPs Using CFD

- Many PBPK models use semi-empirical models
  - Cannot consider formulation and device differences on regional deposition
- Computational fluid dynamics (CFD)
  - Capable of modeling product differences
  - More precise mucociliary clearance modeling

Quasi-3D CFD Model for Lung Absorption

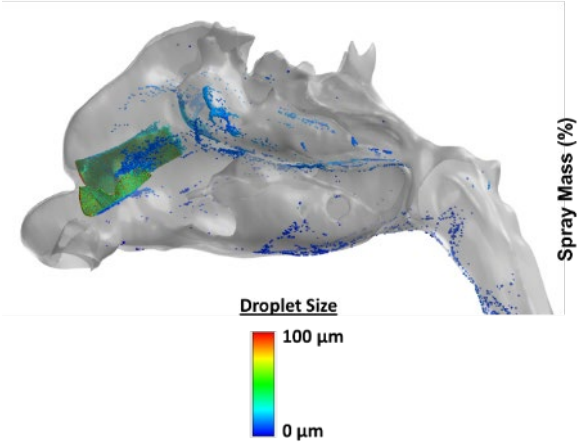
- Computational fluid dynamics (CFD)
  - Regional deposition estimates
  - Quasi-3D absorption model
- FDA Grant #1U01FD005214
  - Generic Drug User Fee Amendments (GDUFA)
- New GDUFA-funded contract (#HHS223201810182C) based on same model



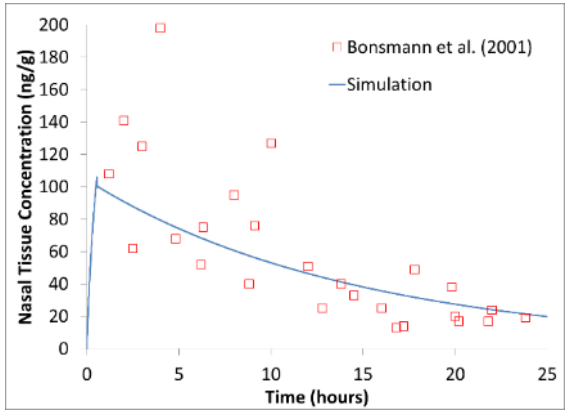
Local drug concentration predictions of solid and dissolved fluticasone propionate Fig. 15 from Kannan et al. (2018)

CFD and PBPK for Nasal Products

- PBPK model for nasal absorption
- Fully 3D CFD model predicts deposition
- FDA Grant #1U01FD005201
  - GDUFA



CFD predictions for deposition locations of fluticasone propionate droplets, from Kimbell et al. (2017)



Pharmacokinetic (PK) predictions of fluticasone propionate nasal spray, from of Schroeter et al. (2017)

Support Alternative Bioequivalence (BE) Approaches

- Local concentration predictions may identify more precise in vitro and/or PK studies
- Evidentiary burden would be much higher than for product development
- Pre-ANDA meeting

Conclusions

- PBPK models can be used to inform product design and development of locally-acting OINDPs.
- Practical applications of PBPK for locally-acting OINDPs have considered a poorly soluble compound and a carrier particle modification.
- Computational fluid dynamics (CFD) is capable of predicting regional deposition while considering product differences.
- Alternative bioequivalence (BE) approaches for locally-acting OINDPs may be potentially supported by PBPK.

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