Orally Inhaled Drug Product PSGs: Considerations for Using Modeling and Simulation with Alternative BE Approaches

Advancing Generic Drug Development 2024:
Translating Science to Approval

Day 1, Session 3: Research to Support Guidance Development for Inhalation Drug Products

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Learning Objectives

- Identify recent product-specific guidance (PSG) documents that include detailed language regarding use of in silico modeling for orally inhaled drug products (OIDPs).
- List potential roles for in silico studies within alternative bioequivalence (BE) approaches for OIDPs.
- Describe recent PSG recommendations for in silico study design and model credibility establishment.

New PSGs – February 2024

- Budesonide; Formoterol Fumarate; Glycopyrrolate Inhalation Metered Aerosol (new drug application [NDA] 212122)
- Formoterol Fumarate; Glycopyrrolate Inhalation Metered Aerosol (NDA 208294)
- Mannitol Inhalation Powder (NDA 022368)
- Mannitol Inhalation Powder (NDA 202049)
- Zanamivir Inhalation Powder (NDA 021036)

New PSGs – Computational Models for Regional Drug Delivery

- As described by Dr. Han, these new PSGs include two options, where the first option does not include a comparative clinical endpoint or pharmacodynamic BE study.
- The PSG for formoterol fumarate; glycopyrrolate inhalation metered aerosol includes detailed language on the potential use of modeling.
- Other new PSGs refer to this PSG with respect to computational modeling.
- Computational modeling is not included in the two BE options for each new PSG, but detailed language is provided to clarify the purposes for using modeling to support BE determination.

What are potential roles for in silico studies within alternative BE approaches for OIDPs?

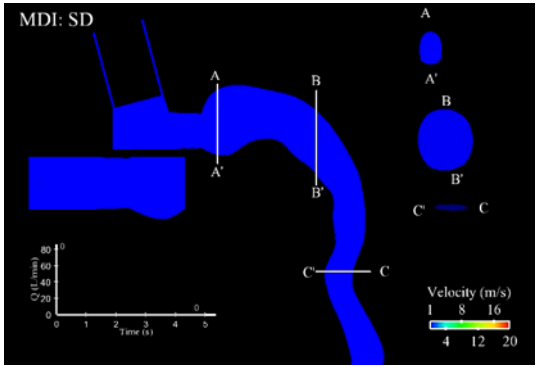
Identify biorelevant limits for BE comparison of key recommended studies by establishing correlations between results of in vitro and/or in vivo studies and in silico regional deposition predictions.

Conduct virtual BE trials using regional deposition predictions.

Design of In Silico Studies

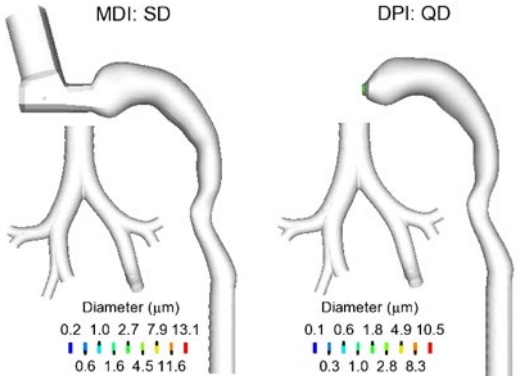
Computational Fluid Dynamics (CFD) Modeling

- Prediction of fluid and particle transport
- Allows for consideration of realistic geometries
- Validated with in vitro or in vivo data



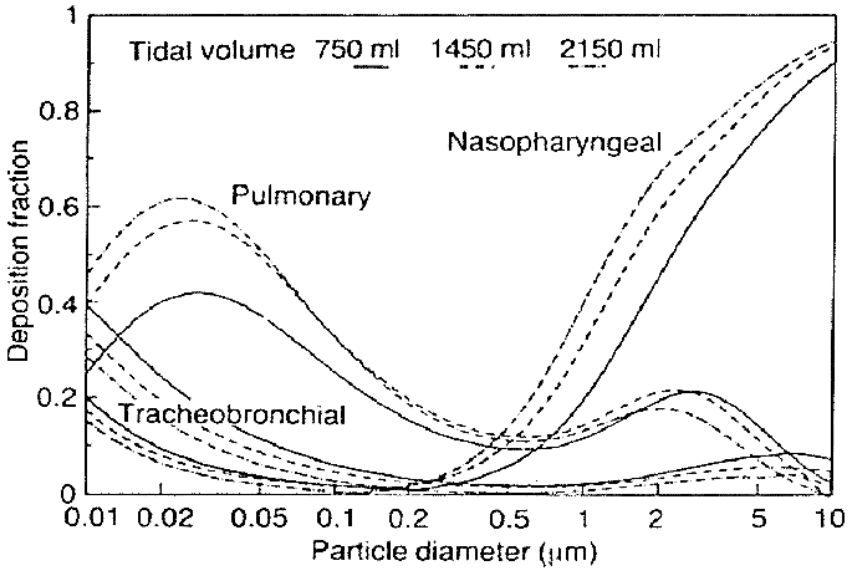
MDI

Simulations from Longest et al.[1]



DPI

Semi-Empirical Regional Deposition Modeling



Deposition fraction predictions in nasopharyngeal, tracheobronchial, and pulmonary regions according to National Council on Radiation Protection and Measurements (NCRP) model (Figure from Phalen et al.[2])

- Algebraic, semi-empirical models
- Branch-specific deposition probability
- Deposition summed across branch levels to obtain regional deposition
- Originally developed for toxicology

Roles of Regional Deposition Modeling

- Biorelevant BE limits
  - Sensitivity of deposition in central and peripheral lung regions to differences in in vitro metrics
    - Aerodynamic particle size distribution (APSD) measured with realistic mouth-throat (MT) models
    - Plume geometry
- Virtual BE trials
  - Provide additional assurance of BE, especially when dissolution and permeation in the lung are expected to be rapid

Connections with In Vitro Data

- APSD results from realistic MT APSD testing may be used as direct inputs for semi-empirical and CFD regional deposition models and MT deposition data may be used to validate CFD model predictions.
- Dissolution data may be used as inputs to assess biorelevance.
- Other relevant studies include plume geometry and spray velocity.
- Ensure that modeling assumptions or results are not in conflict with collected in vitro data.

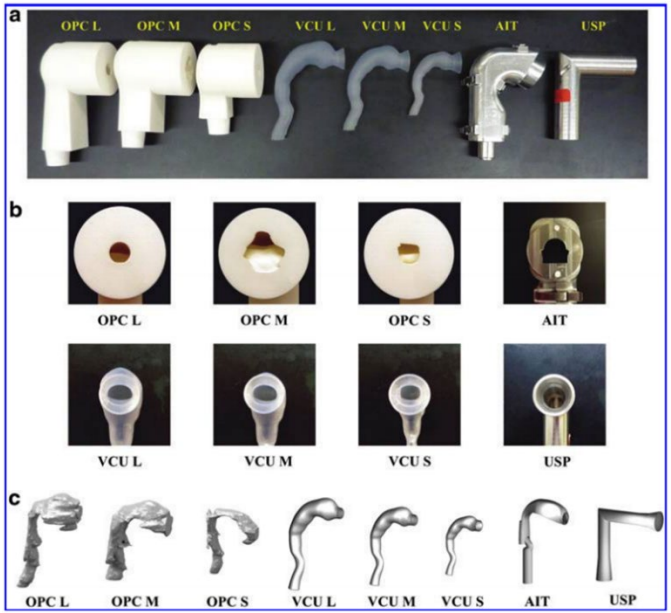
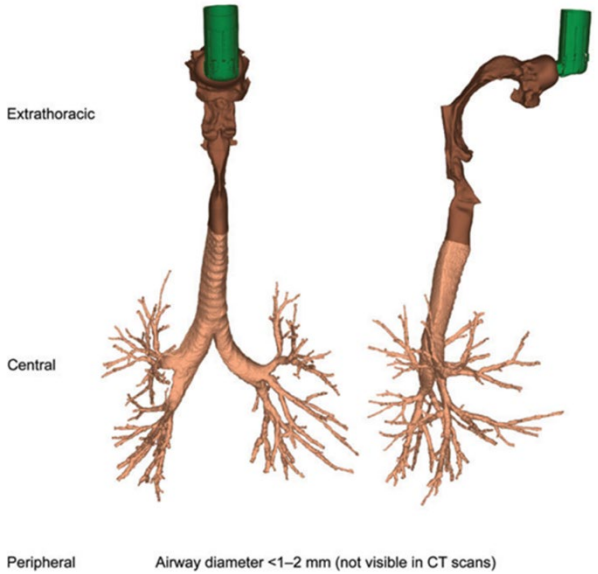


Figure 1 from Wei et al.[3] – Various realistic mouth-throat models include Oropharyngeal Consortium (OPC), Virginia Commonwealth University (VCU), Alberta Idealized Throat (AIT), and United States Pharmacopeia (USP).

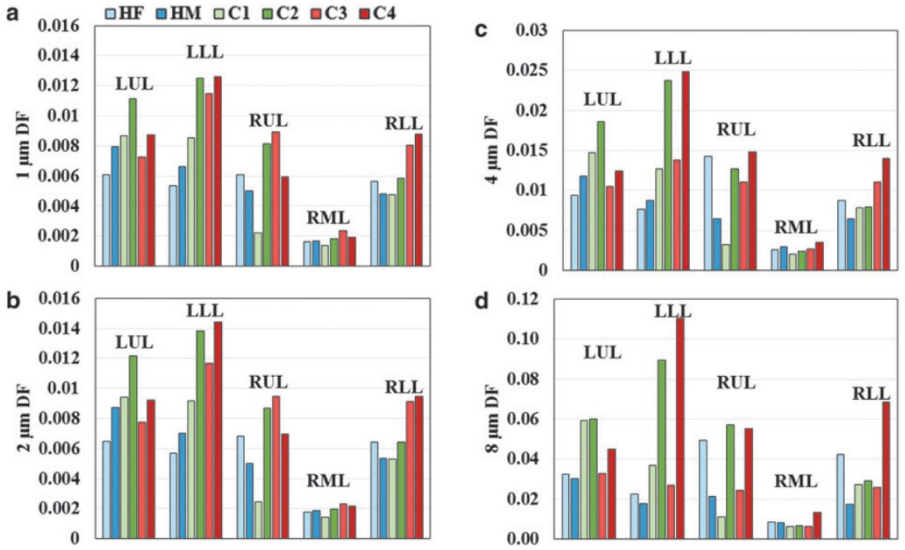
Deposition Prediction Variability – Population Modeling

- Usmani et al.[4] used functional respiratory imaging (FRI) technique to predict regional deposition in 20 patient-specific geometries using CFD.
- FRI allows for using high resolution computed tomography (HRCT) scan data to define patient-specific inhalation profiles.
- Results of Usmani et al.[4] compared regional deposition predictions from two different metered dose inhalers (MDIs).



Patient geometry based on HRCT scan data (Figure 1 from Usmani et al.[4]).

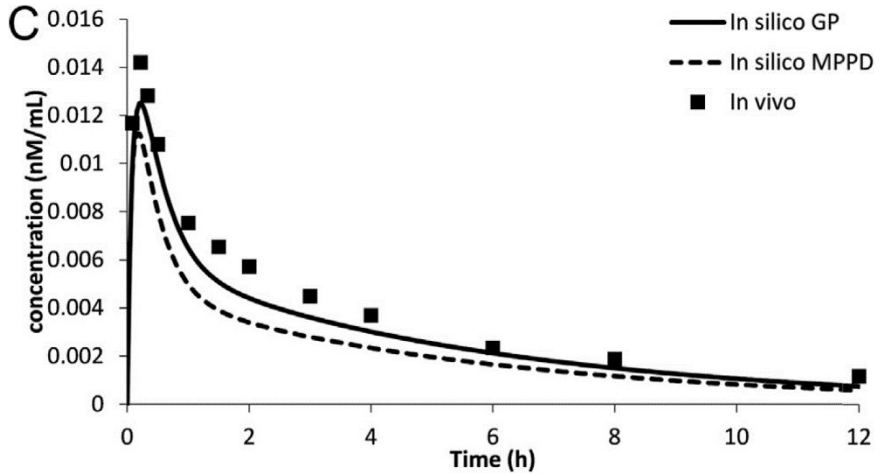
Deposition Prediction Variability – Representative Models



Deposition fraction (DF) predictions in left upper lobe (LUL), left lower lobe (LLL), right upper lobe (RUL), right middle lobe (RML), and right lower lobe (RLL) for different particle sizes (Figure 2 from Choi et al.[5]).

- Generic Drug User Fee Amendments (GDUFA)-funded research
  - University of Iowa (PI: Ching-Long Lin)
  - Grant #1U01FD005837
- Predictions of lobar deposition values using CFD models representing two healthy and eight asthmatic (two for each of four clusters as defined in Choi et al.[5]) subjects
- Monodisperse particle injections

Physiologically Based Pharmacokinetics (PBPK) Modeling



Plasma concentration of albuterol sulfate following administration of an MDI formulation, where GastroPlus (GP) and Multiple Path Particle Dosimetry (MPPD) software packages were used to estimate drug deposition (Figure from Wu et al.[6] with in vivo data from Du et al.[7])

- Compartmental model
- Prediction of local and systemic pharmacokinetics (PK)
  - Dissolution in mucus layer
  - Absorption through lung tissue
  - Metabolism in lung tissue
  - Integration with systemic model
- Validated with in vivo PK data

PBPK Modeling for Understanding Role of Regional Deposition

- While regional deposition is an important component of delivery to the local site of action, it may not always be a surrogate for regional absorption.
- PBPK modeling may be used to understand relative impact of dissolution and permeation on lung absorption.
- May be useful for understanding relationships between charcoal block PK data and regional drug delivery.

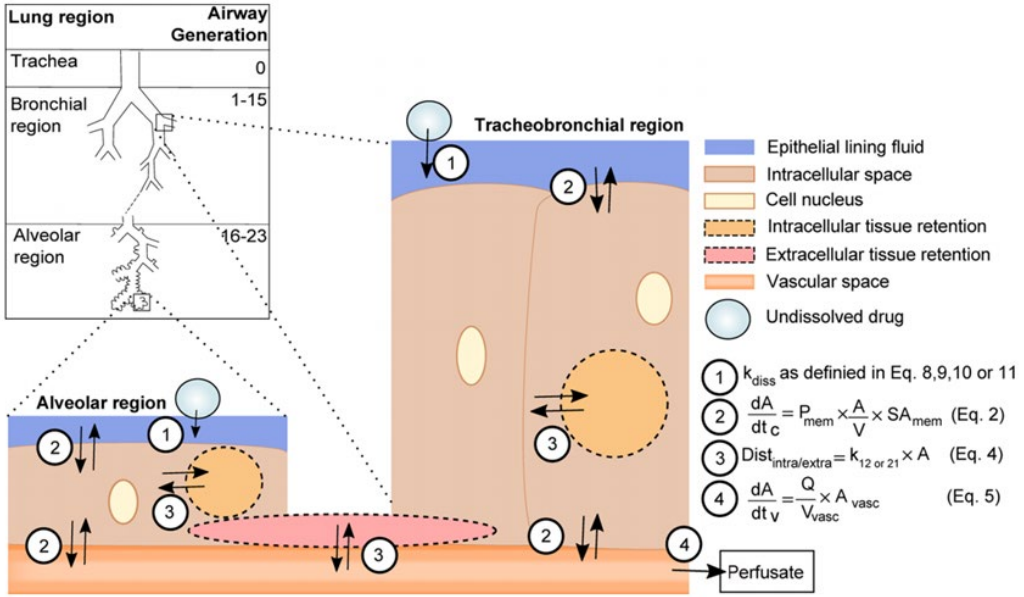
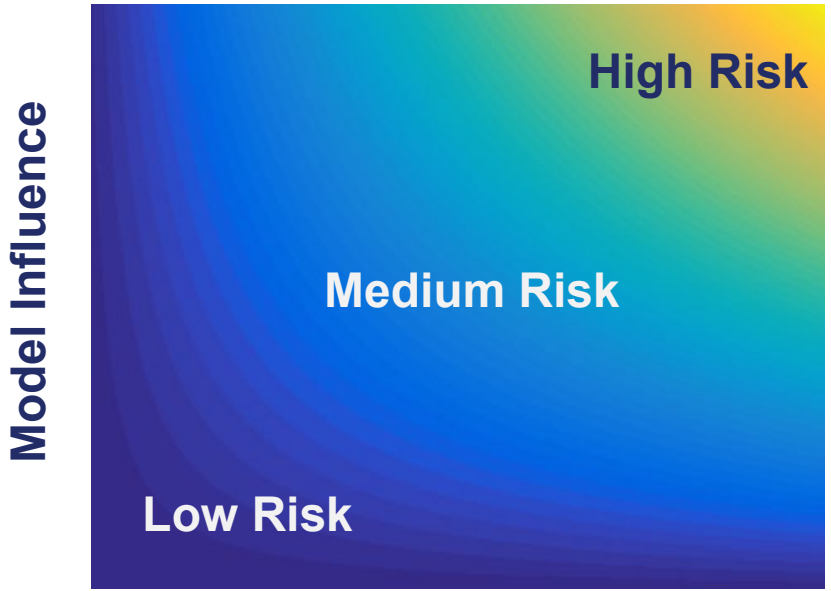


Figure 2 from Eriksson et al.[8] – Model structure for estimating dissolution rate constant (k_{diss}) for pulmonary drug delivery.

Model Credibility

Model Credibility – ASME V&V 40 Concepts

- American Society of Mechanical Engineers (ASME) Verification & Validation (V&V) 40 standard is for computational modeling of medical devices[9]
- Context of Use: Describes what question the model addresses and to what extent
- Model Risk: Determined by decision consequence and model influence
- Credibility: Verification and Validation



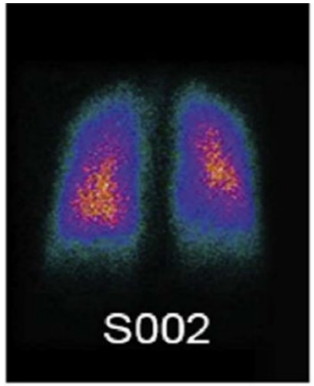
(Figure from Walenga et al.[10])

Model Verification

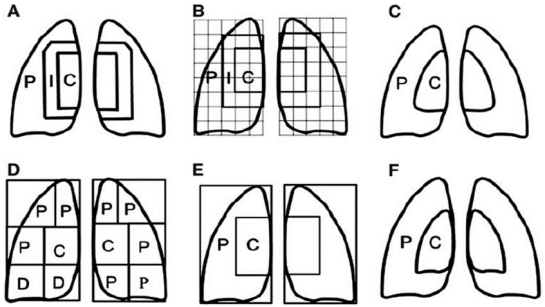
- Ensure that the numerical solutions to the relevant equations are accurate
- CFD models
  - Compare model predictions for simplified scenarios with analytical results
    - For example, may simulate pressure drop in a pipe under turbulent conditions
  - Mesh and time step (i.e., discretization) sensitivity
- PBPK models
  - Check solver settings to ensure minimization of truncation and round-off error for solution of underlying ordinary differential equations

Regional Deposition Validation – Data Sources

- Gamma scintigraphy
  - Two-dimensional image
  - Central-to-peripheral ratio (C/P) for lung deposition
- Single photon emission computed tomography (SPECT)/computed tomography (CT) or positron emission tomography (PET)/CT
  - Three-dimensional information



Gamma scintigraphy image data from glycopyrronium and formoterol fumarate dihydrate developmental metered dose inhaler with ^{81m}Kr ventilation (Figure 4a from Taylor et al.[11])



Several methods for dividing lung into central (C), intermediate (I), and peripheral (P) regions (Figure 4 from Newman et al.[12])

Lung Mapping

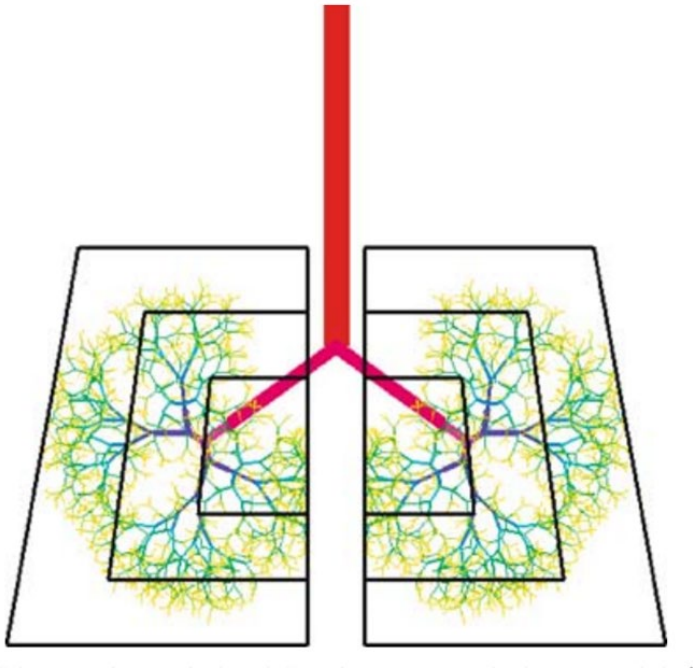


Figure 4 from Schroeter et al.[13] – 3D airway model overlaid with 2D central (inner), intermediate, and peripheral (outer) regional definitions

- In vivo imaging data are typically collected using a two-dimensional (2D) scheme divided into central, intermediate, and peripheral regions.
- There is a lack of precision when comparing three-dimensional (3D) regional deposition predictions with 2D data.
- If CT scan is taken for a subject in addition to deposition data, the subject's lung may be mapped onto 2D regions.

Validation of CFD Modeling

- Deposition should be predicted in all lung regions (especially, central and peripheral).
- Lung region definition should be supported by in vivo data and clinical understanding.
  - Complementary model may be needed for small airways if CFD is used for regional deposition predictions of upper airways.
- Lung mapping was not applied in this study.

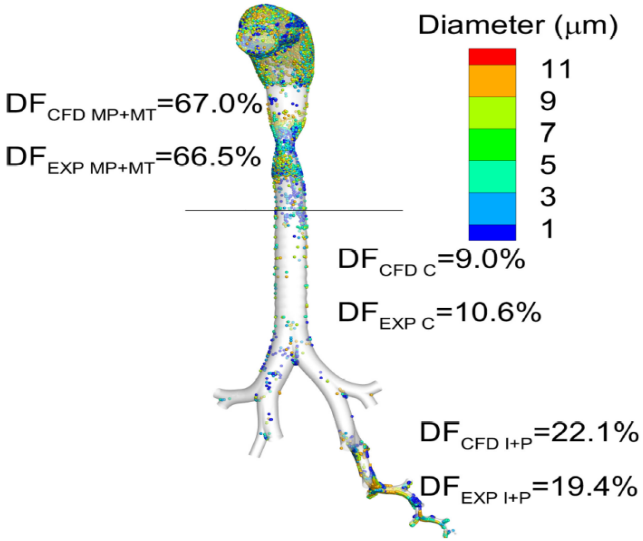


Figure 6 from Tian et al.[14] – Predictions of regional deposition fraction (DF) in mouthpiece (MP), mouth-throat (MT), central (C), intermediate (I), and peripheral (P) regions for DPI, as compared with in vivo gamma scintigraphy data.[15]

Challenge Question #1

What type of in vivo nuclear imaging technique cannot quantify lung deposition in three-dimensional space?

A. SPECT/CT

B. PET/CT

C. Gamma scintigraphy

Challenge Question #2

Which of the following is NOT a potential role for in silico studies within alternative BE approaches for OIDPs?

A. Conduct virtual BE trials using regional deposition predictions.

B. Predict potential adverse events following administration of the proposed generic OIDP.

C. Identify biorelevant limits for BE comparison of key recommended studies by establishing correlations between results of in vitro and/or in vivo studies and in silico regional deposition predictions.

Summary

- Five new PSGs include language describing the use of in silico modeling to support development and approval of generic OIDPs.
- In silico models may be used to establish biorelevant BE limits for recommended in vitro and/or in vivo studies, or to conduct virtual BE trials.
- In silico study designs should consider in vitro data sources and methods for capturing population variability.
- Model credibility should be established using a risk-based approach, such as ASME V&V 40.

Call to Action

Consider using in silico modeling to support development and approval of your generic OIDP.

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Ask me why...

"I make sure that the **generic** drug and the **brand** drug work **the same**."

"The first time I was able to buy my son's inhaler as a generic and realized that my out of pocket dropped, I cried and was able to breathe a sigh of relief."

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