Bridging the Gap Between Regional Deposition and Systemic Pharmacokinetic Data of OINDPs with Modeling and Simulation

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop

Session 3: Future Directions, Emerging Technology, and Current Thinking on Alternative BE Approaches

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Learning Objectives

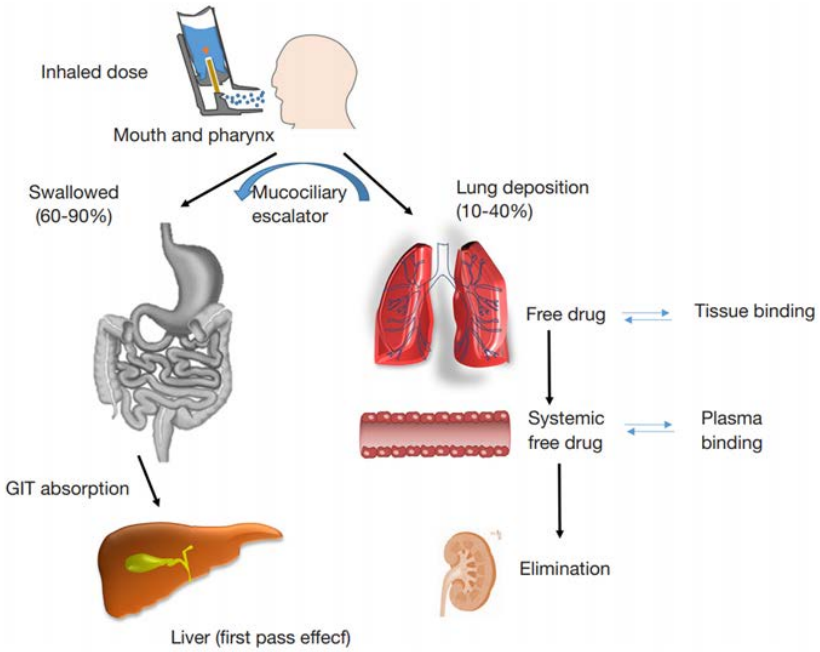
- Identify the sites of action for various orally inhaled and nasal drug products (OINDPs)
- Describe different in vitro and in vivo methods for regional deposition data collection
- Determine strengths and limitations of various modeling techniques for prediction of regional deposition
- Formulate strategies for evaluating differences in rate and extent of drug delivery to the site of action of OINDPS with modeling

Bioequivalence (BE) Regulation

21 CFR 314.3 –"Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

BE at the Site of Action

- For locally acting orally inhaled drug products (OIDPs), lung tissue concentration is the site of action
- Nasal cavity tissue is the site of action for locally acting nasal drug products
- Regional deposition is upstream of local tissue concentration and systemic pharmacokinetics (PK) is downstream



Drug delivery, absorption, distribution, metabolism, and elimination of OIDPs (Figure from de Pablo et al.[1])

Pre-Abbreviated New Drug Application (ANDA) Communication

- Several firms have contacted the Office of Generic Drugs (OGD) at FDA regarding alternative BE approaches for OIDPs
- In more than one case the alternate BE approach focused on systemic PK of OIDPs, but did not address local lung tissue PK
- Another approach is to infer regional deposition based on systemic PK without validation of regional deposition values
- Ideal approach is to validate both regional deposition and systemic PK predictions and bridge the two components to credibly predict local tissue PK

Small Airway Definition

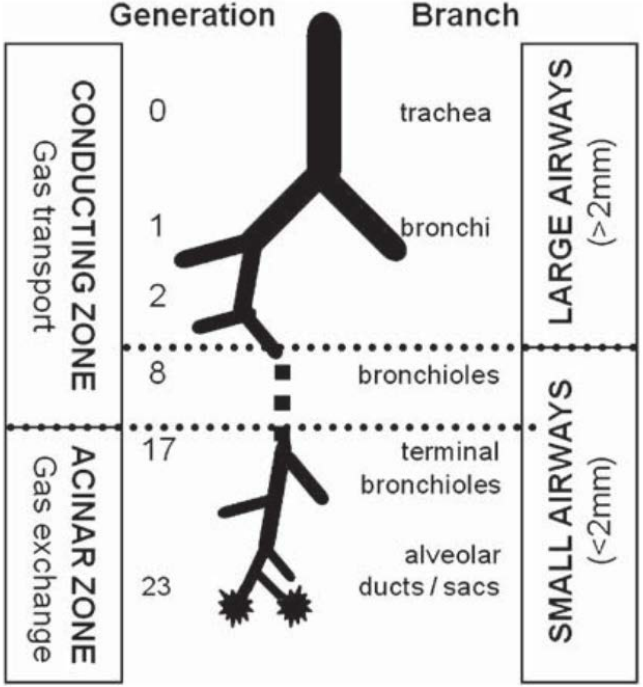
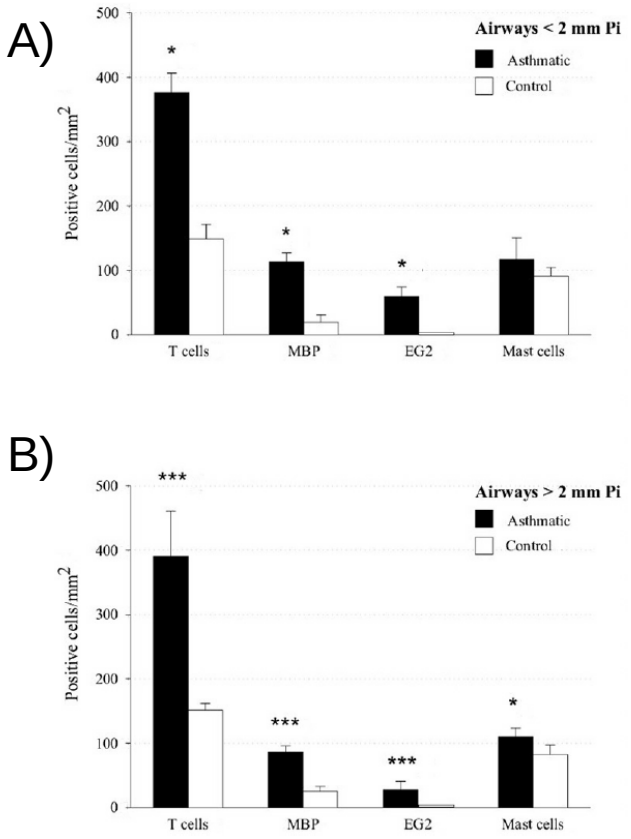


Diagram of lung regions (from Usmani and Barnes[2])

- Bronchi, bronchiole, alveolar regions
- Small airway cutoff
  - After bronchi[2]
  - Airways smaller than 2 mm in diameter[2]
  - Cutoff for 2 mm airways may be beyond bronchioles[3]

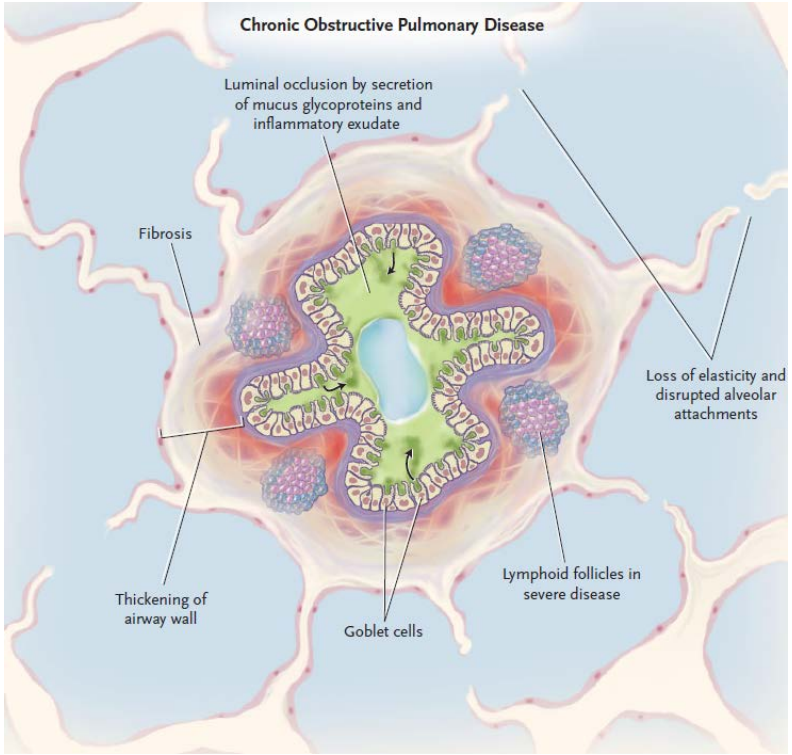
Targeted Drug Delivery for Asthma

- Asthma
  - Large and small airways[4,5]
- Locally acting OIDPs
  - Bronchodilators
    - β_2-agonists
    - Anti-muscarinic
  - Corticosteroids



Immuno-cytochemical cell markers in
A) small airways (< 2 mm diameter) and
B) large airways (> 2 mm diameter)
(From Tulic et al.[4] and Hamid et al.[5])

Targeted Drug Delivery for COPD

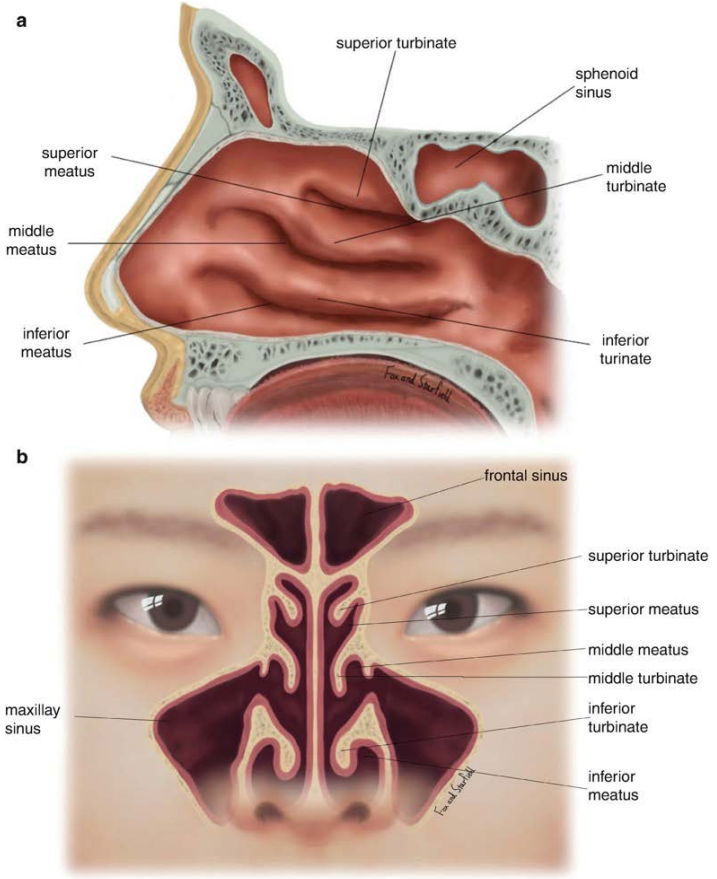


Small airway changes due to COPD (Figure from Barnes[6])

- Chronic Obstructive Pulmonary Disease (COPD)
  - Small airways[6]
- Locally-acting OIDPs
  - Bronchodilators
    - β_2-agonists
    - Anti-muscarinic
  - Corticosteroids

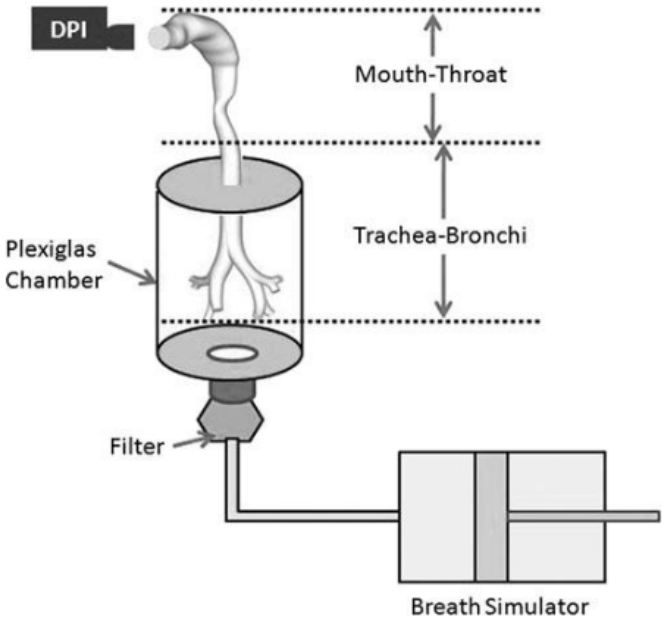
Locally Acting Nasal Drug Delivery

- Allergic Rhinitis[7]
  - Inferior turbinate
- Nasal Polyps
  - Middle meatus[8]
  - Middle and superior turbinates[8]



Nasal anatomy (Figure from Suh[9])

Regional Deposition – In Vitro

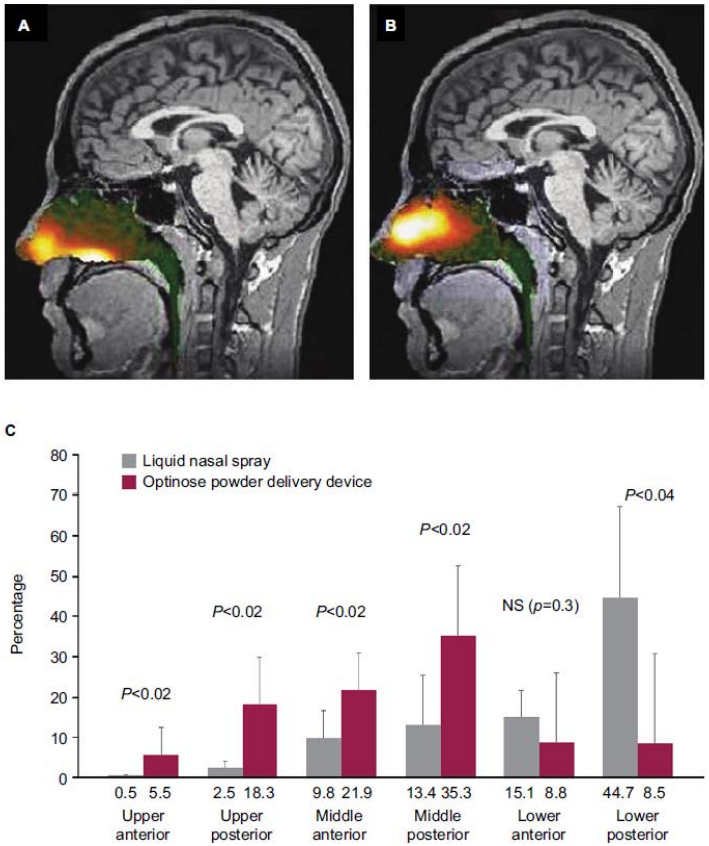


Mouth-throat and lung model in vitro setup (Figure from Delvadia et al.[10])

- Realistic mouth-throat models
  - Rapid prototyping
  - High performance liquid chromatography
  - May include tracheobronchial region but limited to larger airways
- Nasal models
  - Difficult to section precisely

Regional Deposition – In Vivo

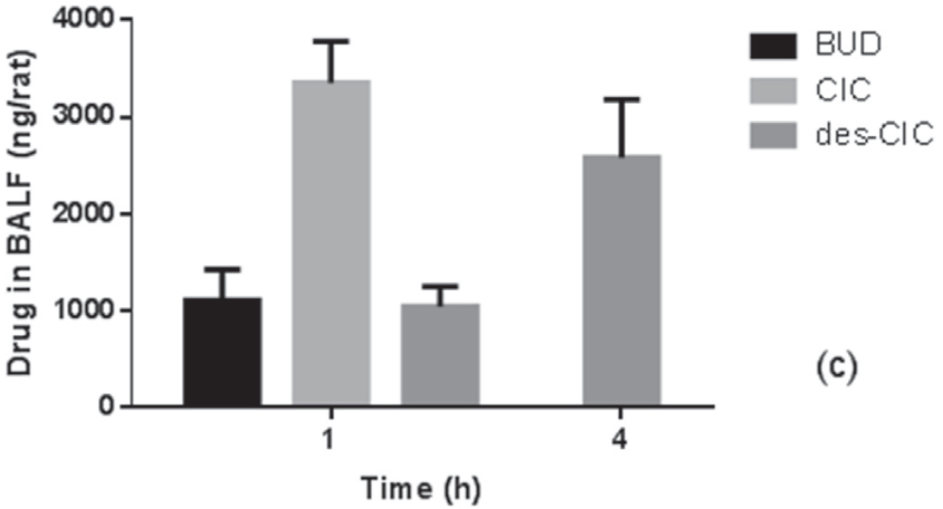
- Gamma scintigraphy
  - Two-dimensional image
  - Central-to-peripheral ratio (C/P) for lung deposition
- Single positron emission computed tomography /computed tomography
  - Three-dimensional information



Regional deposition of liquid nasal spray and Optinose powder delivery system using gamma scintigraphy (Figure from Tepper and Johnstone[11])

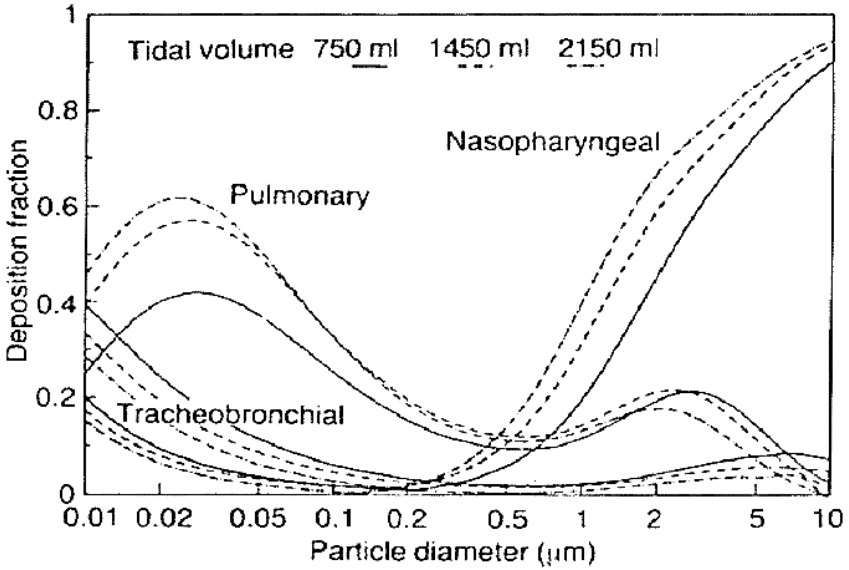
PK Data

- Systemic PK: plasma concentration
- Local tissue PK
  - Difficult to obtain due to ethical concerns
  - Bronchoalveolar lavage (BAL) for lungs
  - Nasal surgery



Drug in bronchoalveolar lavage fluid (BALF) after administration of budesonide (BUD), ciclesonide (CIC), and des-ciclesonide (des-CIC) in rats (Figure from Fu et al.[12])

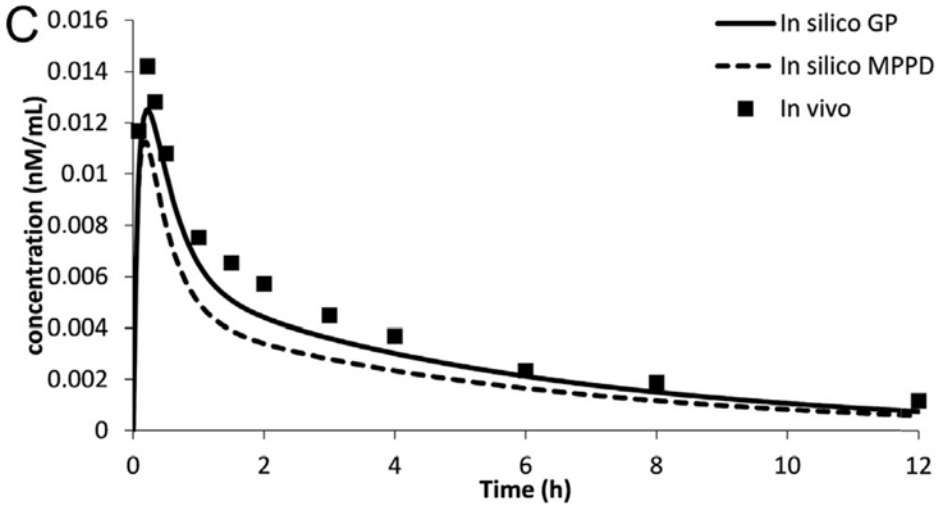
Semi-Empirical Regional Deposition Modeling



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.[13])

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

Physiologically Based Pharmacokinetics (PBPK) Modeling

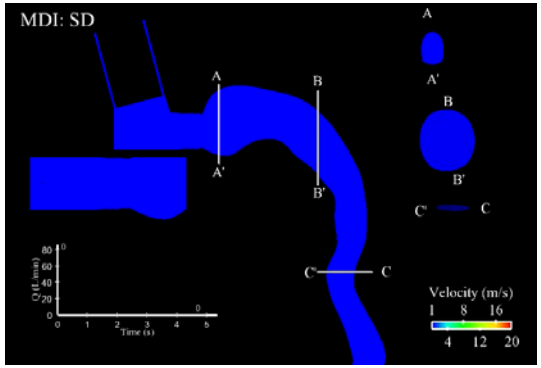


Plasma concentration of albuterol sulfate following administration of an Metered Dose Inhaler (MDI) formulation, where GastroPlus (GP) and Multiple Path Particle Dosimetry (MPPD) software packages were used to estimate drug deposition (Figure from Wu et al.[14] with in vivo data from Du et al.[15])

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

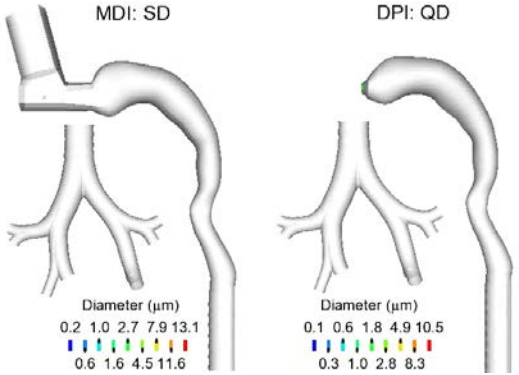
Computational Fluid Dynamics (CFD) Modeling

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



Metered Dose Inhaler (MDI)

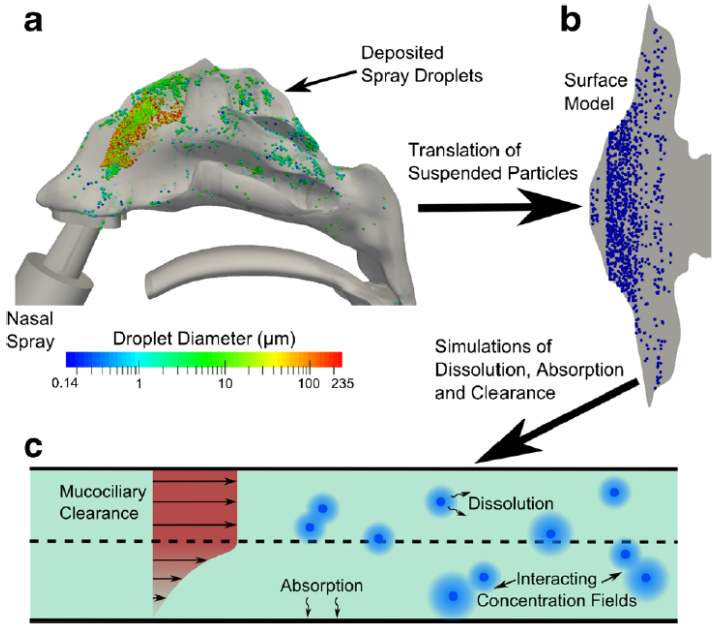
Simulations from Longest et al.[16]



Dry Powder Inhaler (DPI)

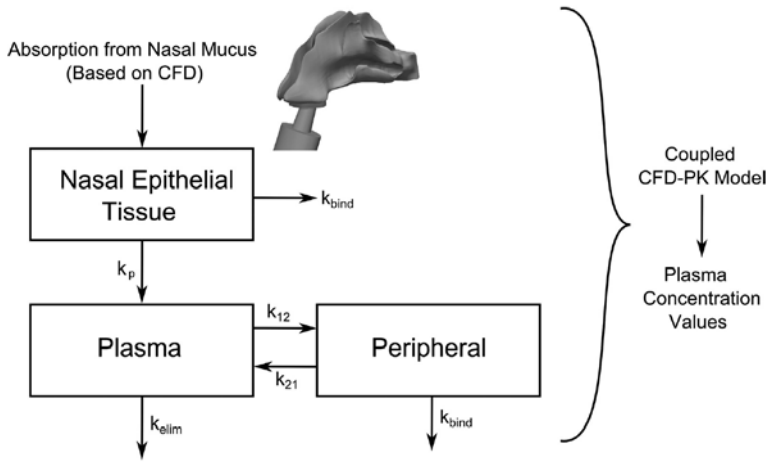
Nasal Absorption Model Using CFD

- Generic Drug User Fee Amendments (GDUFA)-funded research
  - Virginia Commonwealth University (PI: P. Worth Longest)
  - Grant #1U01FD004570
- Predict local delivery of nasal suspension spray droplet using CFD
- Predict mucociliary transit and dissolution using CFD with 2D surface model

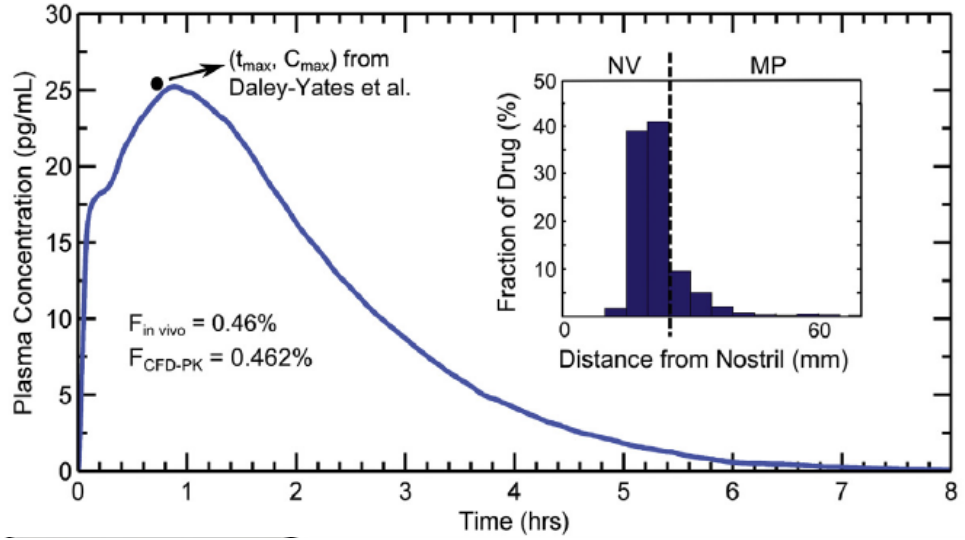


Nasal absorption process, with a) CFD prediction of deposition, b) mucociliary transit model, and c) dissolution, advection, and absorption model (Figure from Rygg et al.[17])

Connection of Nasal Absorption and PK



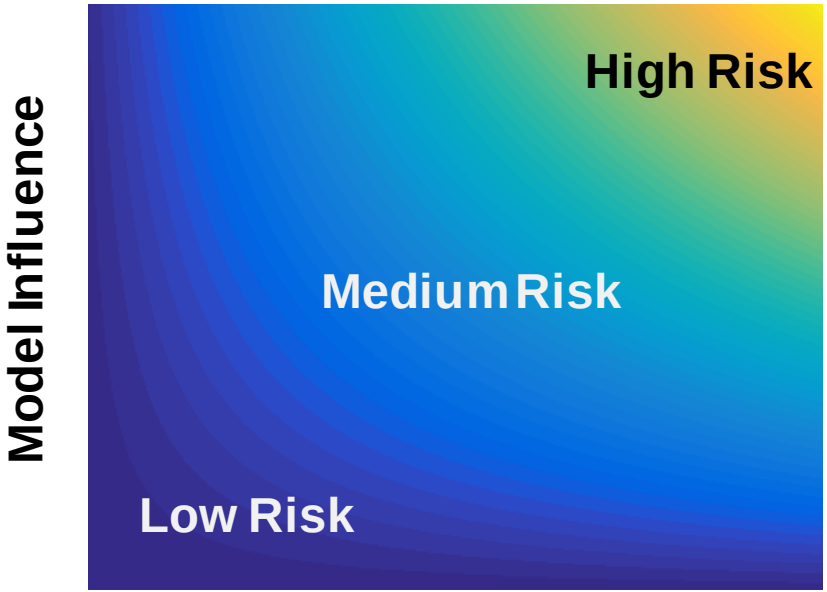
Two-compartment PK model structure (Figure from Rygg et al.[19])



PK profile prediction as compared with in vivo data from Daley-Yates et al.,[18] as well as comparison of bioavailability (F). The inset bar-graph shows distance of drug deposited from nostril in either the nasal vestibule (NV) or the middle passage (MP) (Figure from Rygg et al.[19])

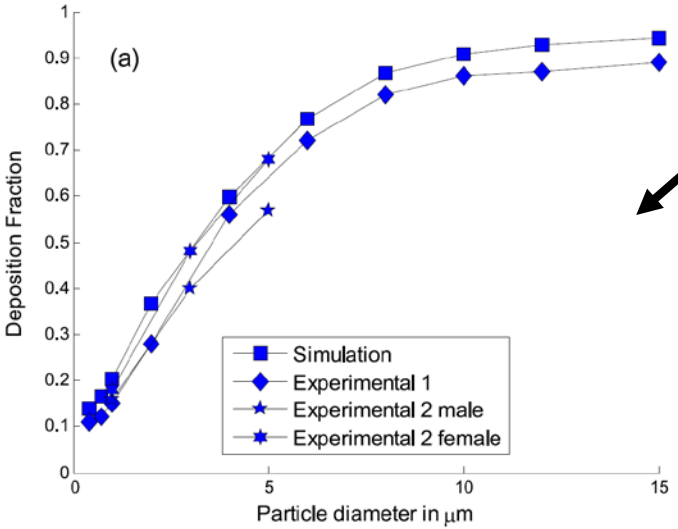
ASME V&V 40 Concepts

- American Society of Mechanical Engineers (ASME) Verification & Validation 40 standard[20]
- 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.[21])

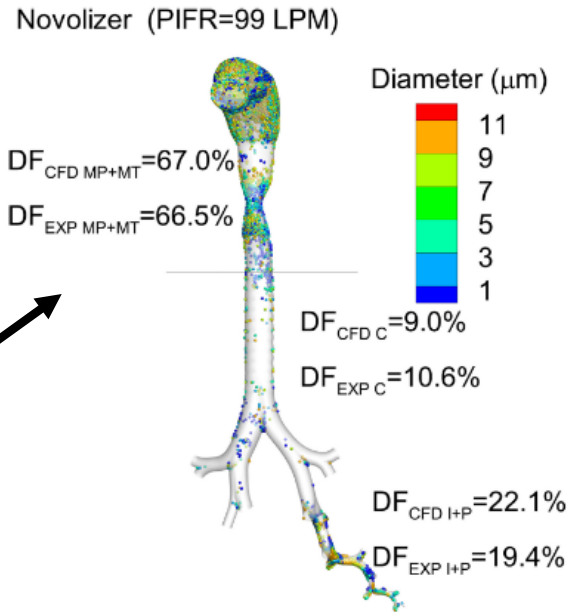
Regional Deposition Validation



Deposition fraction prediction of general aerosol in realistic mouth-throat and lung geometry using CFD, compared with in vitro data from Heyder et al.[22] and Kim and Hu[23] (Figure from Kolanjiyil and Kleinstreuer[24])

In vitro: deposition in rapid prototyped model

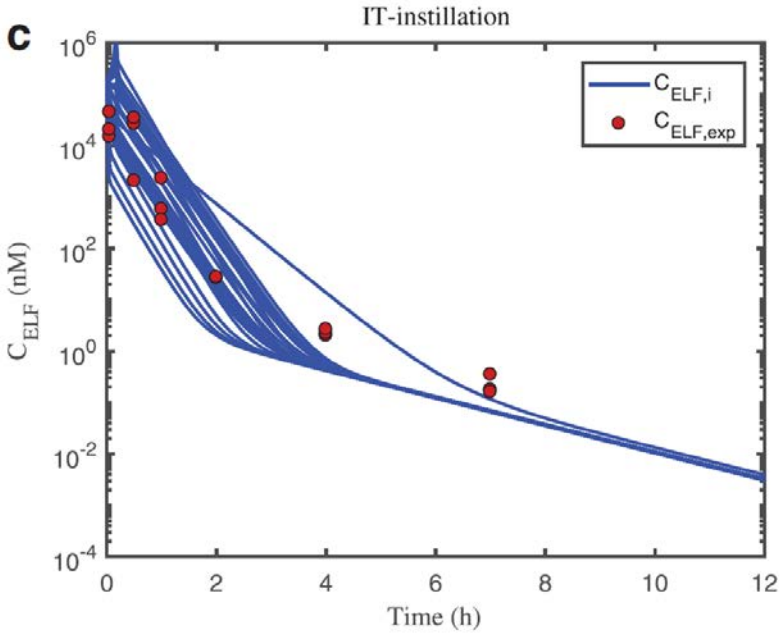
In vivo: radiolabeled aerosol with gamma scintigraphy



Deposition fraction prediction in budesonide DPI using CFD, compared with in vivo data (Figure from Tian et al.[25])

Local Lung Tissue Concentration

- Target region for generic BE comparison
- Systemic PK is more easily validated
- Lung tissue PK may be validated with animal data, or human bronchoalveolar lavage (BAL) data, if available



Branch level specific epithelial lining fluid concentration (C_{ELF}) predictions of albuterol sulfate following intra-tracheal (IT) instillation in rats as compared with mean experimental data (Figure from Boger and Fridén[26])

Challenge Question #1

The site(s) of action for OIDPs that treat COPD is(are) the

A. Small airways
B. Large airways
C. Large and small airways
D. Nasal cavity

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Conclusions

- Rate and extent of delivery to the site of action for locally acting OINDPs is best reflected by local tissue concentration.
- Regional deposition, CFD, and PBPK, may be used in various combinations to predict local tissue concentration.
- Validation of local drug delivery may be bridged with in vivo deposition and systemic PK when BAL data or other local tissue PK data are not available.

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