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Role of Computational Fluid Dynamics and Physiologically-Based Pharmacokinetic Modeling in Development of Orally Inhaled and Nasal Drug Products

Design of Medical Devices Conference

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Computational Modeling & Regulatory Science 2: Respiratory and Nasal Modeling

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Orally Inhaled and Nasal Drug Products (OINDPs)

- Orally Inhaled
  - Metered dose inhalers (MDIs)
  - Dry powder inhalers (DPIs)
  - Nebulizers
- Nasal
  - Nasal sprays
  - Nasal metered aerosols

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NDA vs. ANDA Review Process

New Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Microbiology	4. Microbiology
5. Biopharmaceutics	5. Biopharmaceutics
6. Preclinical Studies	
7. Clin. Pharm.	6. Bioequivalence (BE)
8. Clinical Studies	

ANDA: abbreviated new drug application; NDA: new drug application

Products Delivered to the Respiratory System

- Factors influencing patient-product interactions and drug bioavailability include:
  - Dose percent deposited to nasal mucosa, or in the lungs vs. dose percent swallowed and absorbed from the GI tract
  - Local solubility/permeability
  - Receptor affinity
  - Deposition in central vs. peripheral parts of the pulmonary tree
  - Pulmonary residence time
  - Local clearance (mucociliary transport and reticuloendothelial uptake)
  - Device design
  - Effects of formulation differences on product differences

Slide adapted from Dr. Kimberly Witzmann

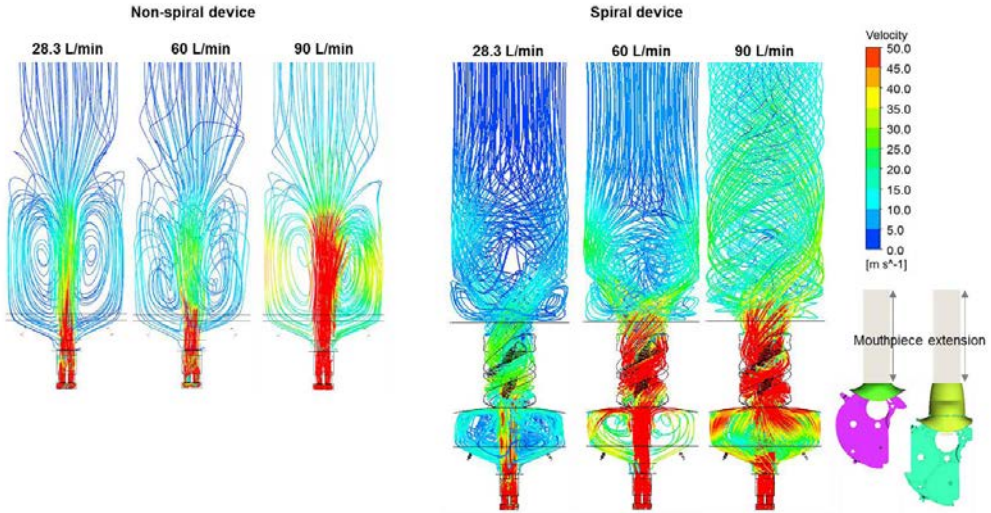
Generic Drug User Fee Amendments (GDUFA)

- Passed in July 2012 to speed access to safe and effective generic drugs to the public, reauthorized in 2017
- Requires user fees to supplement costs of reviewing generic drug applications and provides additional resources, including support for **regulatory science research**
- User fee program which directly supports regulatory science research activities
  - https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Slide adapted from Dr. Kimberly Witzmann

Computational Fluid Dynamics (CFD) Modeling of OINDPs

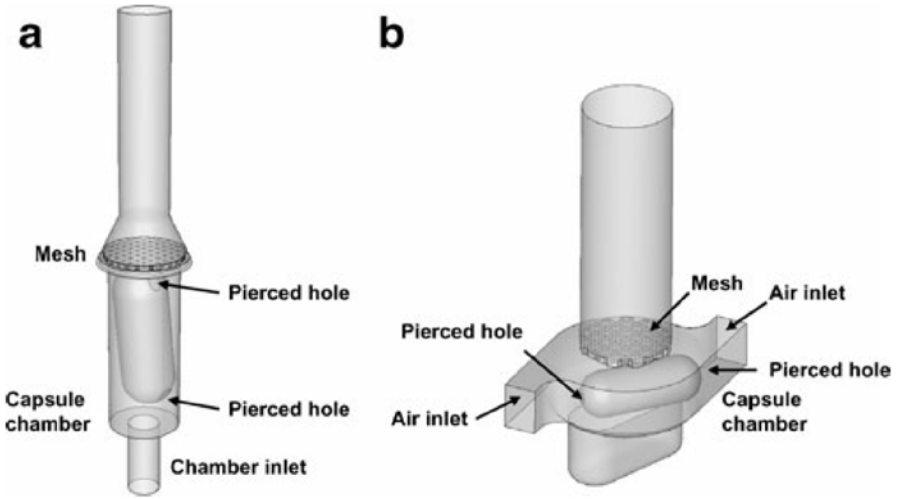
- Predict influence of device and formulation parameters
  - Particle size distribution
  - Regional deposition
    - Intersubject variability
  - Pharmacokinetic (PK) profile
    - Combined with physiologically-based pharmacokinetic (PBPK) modeling



Flow streamlines in non-spiral and spiral versions of ACTIVAIR® dry powder inhaler. (Fig. 6 from Lee et al. (2018))

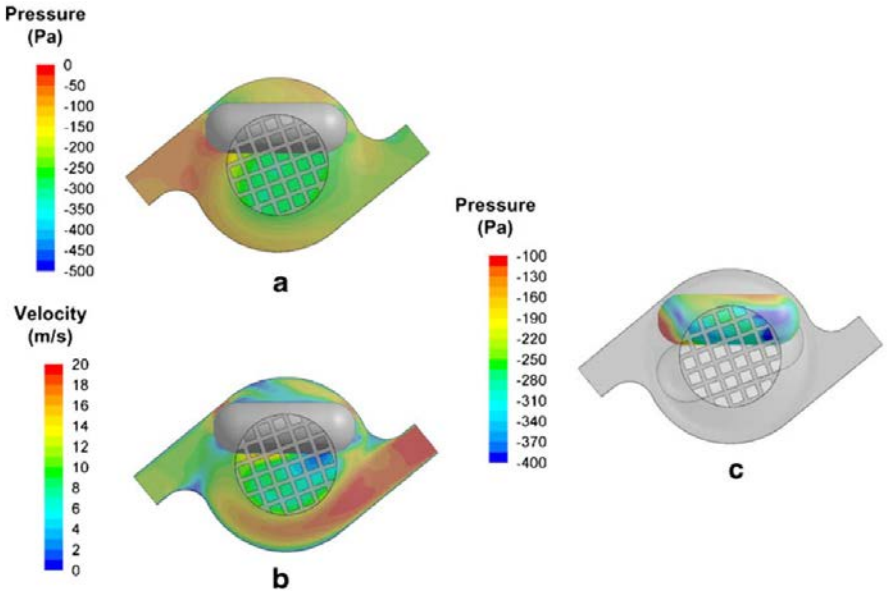
Device Modification to Match In Vitro Performance

- Research funded by the Office of Generic Drugs (OGD)
  - University of Bath (PI: Jagdeep Shur)
- Two capsule-based dry powder inhalers (DPIs) with tiotropium bromide - Handihaler® and Cyclohaler®
- Model flow and particle transport using CFD
- Modify Cyclohaler® to achieve comparable predictions
- Compare in vitro particle size distribution

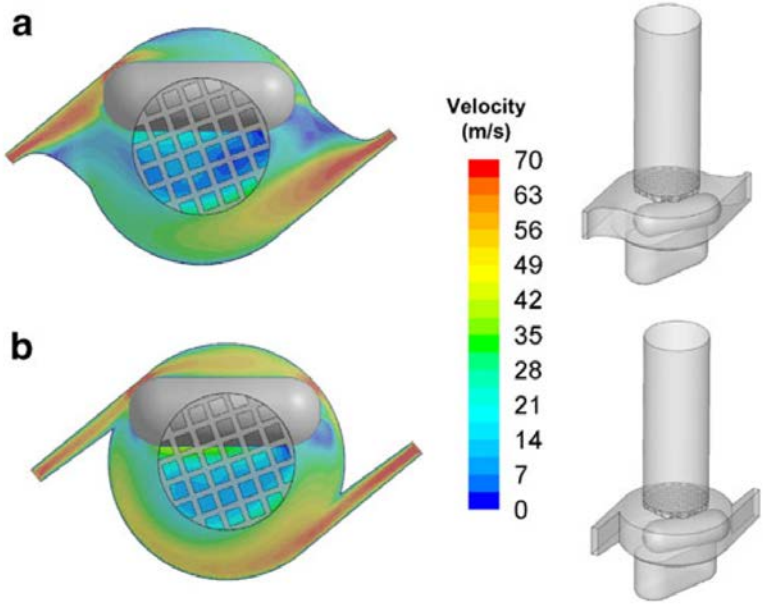


Computer aided design (CAD) representations of a) Handihaler® and b) Cyclohaler®. Fig.1 from Shur et al. (2012)

Velocity Comparison Following Device Modification

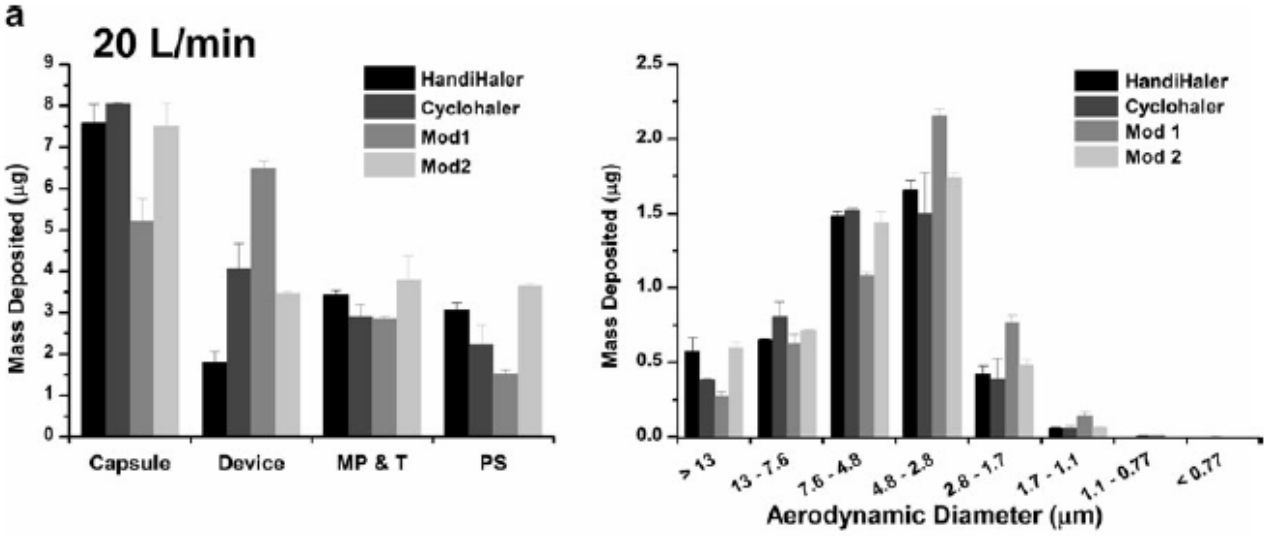


CFD Predictions in unmodified Cyclohaler® for a) device pressure, b) device velocity, and c) capsule pressure. (Fig 3. from Shur et al. (2012))



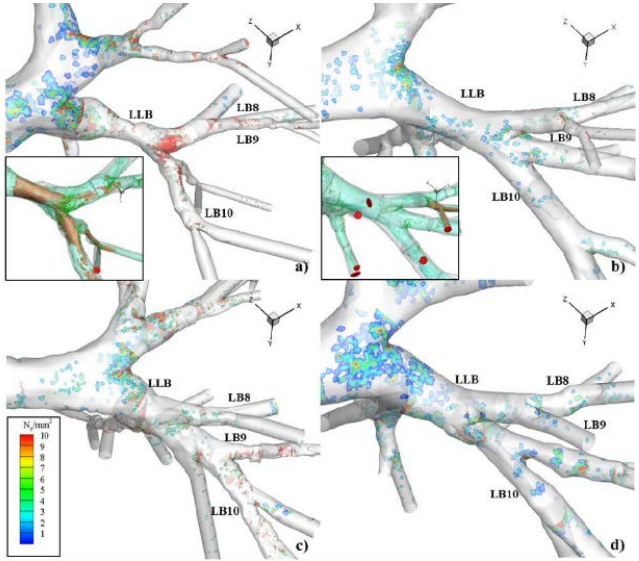
CFD predictions of Cyclohaler® device pressure in a) modification #1, and b) modification #2. (Fig. 4 from Shur et al. (2012))

In Vitro Particle Size Distribution Comparison



Stage measurements in Next Generation Impactor for Handihaler®, Cyclohaler®, and two modifications of Cyclohaler® for flow rate of 20 L/min. Abbreviations: mouthpiece (MP), throat (T), and preseparator (PS). (Fig. 6a from Shur et al. (2012))

Regional Deposition Intersubject Variability

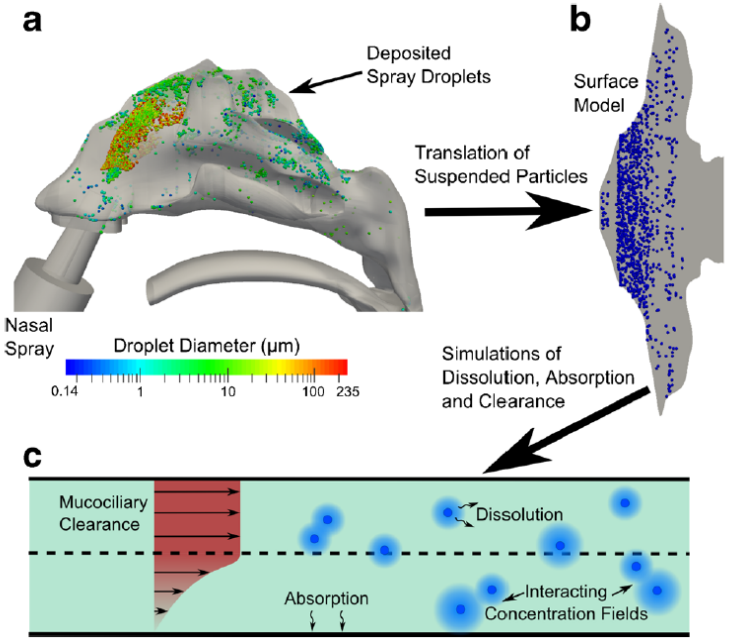


CFD predictions of particle deposition locations in left lower lobe, from Choi et al. (2017)

- GDUFA funded research
  - University of Iowa (PI: Ching-Long Lin)
- Cluster-based approach
  - Asthma patient sub-types
  - Computed tomography (CT) scans from database
- Generate 10 lung models
  - Male and female for healthy and four hypothesized sub-types

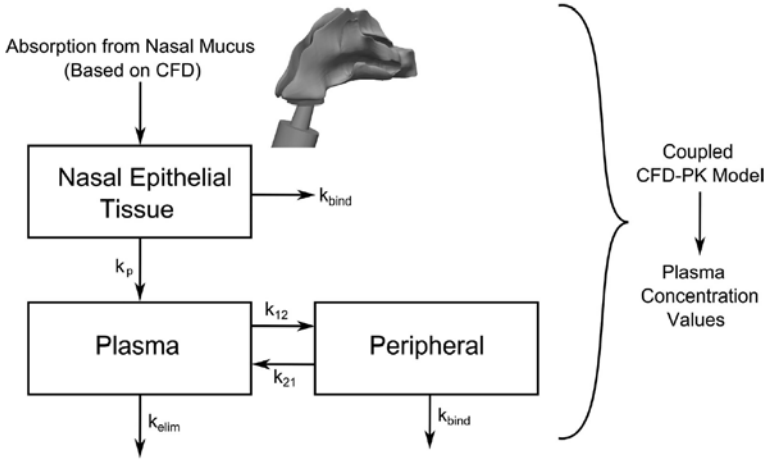
Nasal Absorption Model Using CFD

- GDUFA funded research
  - Virginia Commonwealth University (PI: P. Worth Longest)
- Predict local delivery of nasal suspension spray droplet using CFD
- Predict mucociliary transit and dissolution using CFD with 2D surface model

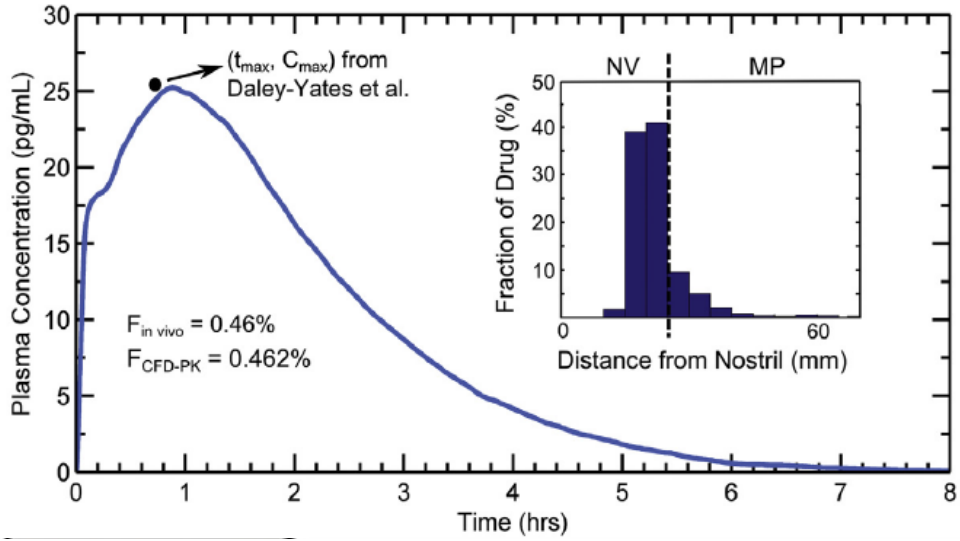


Nasal absorption process, with a) CFD prediction of deposition, b) mucociliary transit model, and c) dissolution, advection, and absorption model. (Fig.1 from Rygg et al. (2016))

Connection of Nasal Absorption and PK



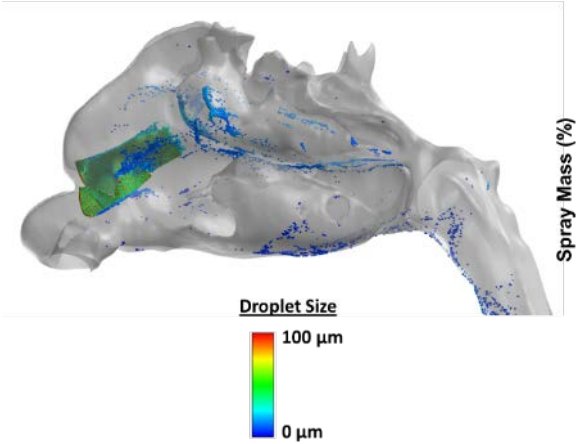
Two-compartment pharmacokinetic (PK) model structure. (Fig. 4 from Rygg et al. (2016b)



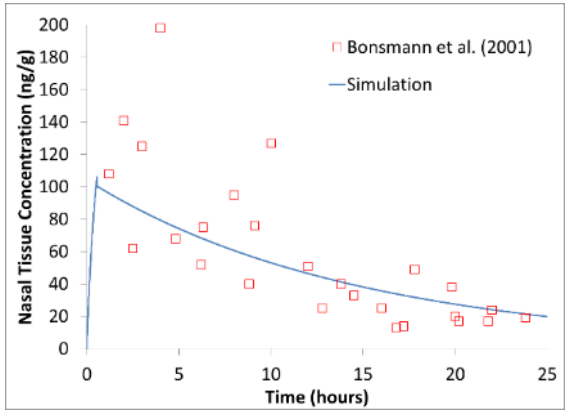
Pharmacokinetic (PK) profile prediction as compared with in vivo data from Daley-Yates et al. (), as well as comparison of bioavailability (F). The inset bar-graph shows distance of drug deposited from nostril in either the nasal vestibule (NV) or the middle passage (MP). (Fig. 6 from Rygg et al. (2016b)

CFD and PBPK for Nasal Products

- GDUFA funded research
  - Applied Research Associates (PI: Jeffry Schroeter)
- Fully 3D CFD model predicts deposition
- Physiologically-based pharmacokinetic (PBPK) model for nasal absorption
- Investigation of device and usage parameters



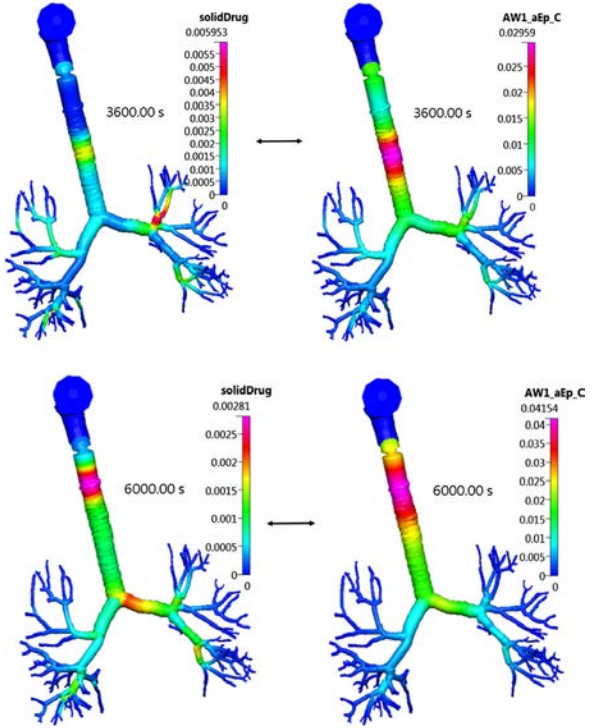
CFD predictions for deposition locations of fluticasone propionate droplets, from Kimbell et al. (2017)



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

Quasi-3D CFD Model for Lung Absorption

- GDUFA funded research
  - CFD Research Corporation (PI: Narender Singh)
- Fully 3D CFD model to predict regional deposition
- Quasi-3D model to predict mucociliary transit, dissolution, absorption
- Coupled with PBPK model



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

New GDUFA Funded Research

- CFD modeling combined with discrete element modeling (DEM) to predict drug-carrier particle interactions of DPIs
  - Princeton University (PI: Jari Kolehmainen)
  - University of Sydney (PI: Kim Chan)
- Fully 3D CFD nasal mucociliary clearance model to allow for local concentration predictions
  - North Carolina State University (PI: Clement Kleinstreuer)

New GDUFA Funded Research (cont'd)

- Further development of quasi-3D model for lung absorption
  - CFD Research Corporation (PI: Narender Singh)
- Nasal in vitro model development that characterizes intersubject variability of nasal spray deposition, supported by CFD predictions
  - Virginia Commonwealth University (PI: Laleh Golshahi)

Internal GDUFA Funded Research

- CFD models of droplet formulation from metered dose inhaler (MDI)
- CFD models of OINDPs based on Respimat® device
- Development of CFD-PBPK models for opioid nasal insufflation for assessment of abuse deterrence

Conclusions

- Development of OINDPs is challenging due to the need for multiple device and formulation changes without knowledge of their impact.
- CFD may be used to predict the influence of device and formulation changes on metrics of interest, including particle size distribution, PK, and drug concentration at the site of action.
- Intersubject variability may be examined using CFD with several realistic lung models from a given population.
- It is expected that when CFD is used concurrently with OINDP development, the process will be more effective and efficient.

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