U.S. FOOD & DRUG ADMINISTRATION

# Computational fluid dynamics modeling of nasally administered drug products in regulatory science research at the U.S. Food and Drug Administration

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# Nasally Administered Drug Products

- Indicated use
  - Nasal sprays
  - Nasal metered aerosols
- Abuse
  - Nasally insufflated opioids


www.sasrx.com


www.wellrx.com

www.drugabuse.com

# NDA vs. ANDA Review Process

| New Drug<br>NDA Requirements | Generic Drug<br>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 | |



NDA: new drug application; ANDA: abbreviated 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

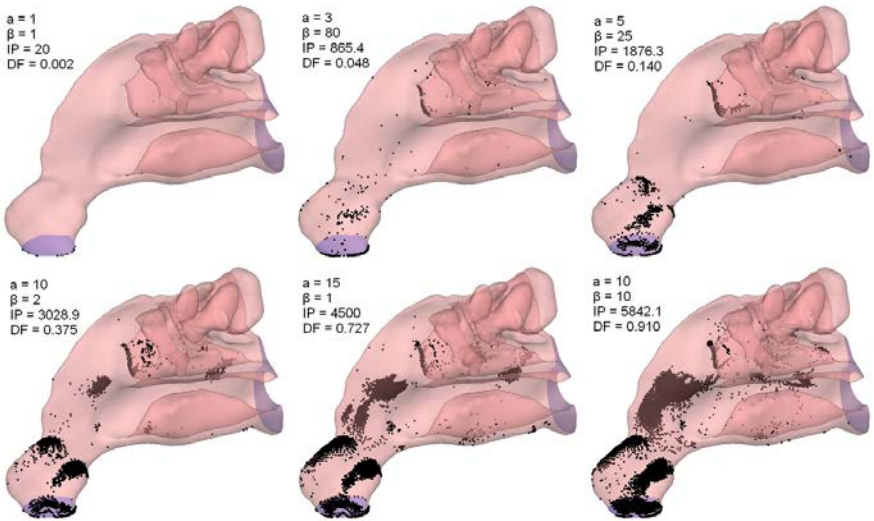
# Generic Drug User Fee Amendments (GDUFA)

- 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
  - www.fda.gov/gdufaregscience



Slide adapted from Dr. Kimberly Witzmann

# Computational Fluid Dynamics (CFD) Modeling of Nasal Drug Products

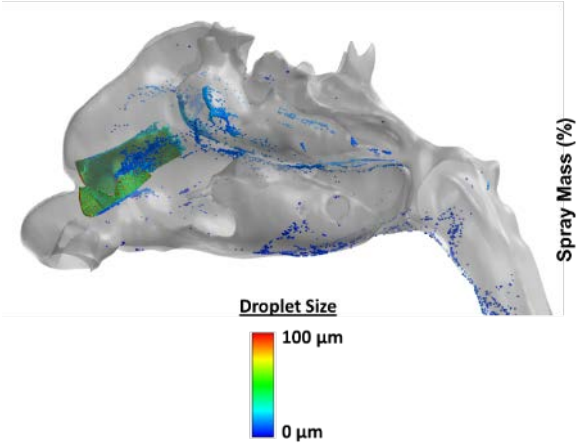



Fiber deposition in nasal cavity, where a is the fiber radius in μm, β is the fiber aspect ratio, IP is the impaction parameter, and DF is the deposition fraction. (Fig. 13 from Dastan et al. (2014))

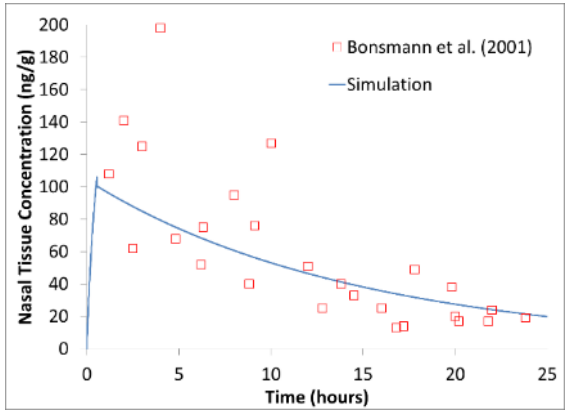
- Predict influence of device and formulation parameters
  - Particle size distribution
  - Regional deposition
    - Intersubject variability
  - Pharmacokinetic (PK) profile
    - Combined with physiologically-based pharmacokinetic (PBPK) modeling

# CFD and PBPK for Nasal Products

- GDUFA funded research
  - Applied Research Associates (PI: Jeffry Schroeter)
  - Grant # 1U01FD005201
- Fully 3D CFD model predicts deposition
- PBPK model for nasal absorption
- Investigation of device and usage parameters

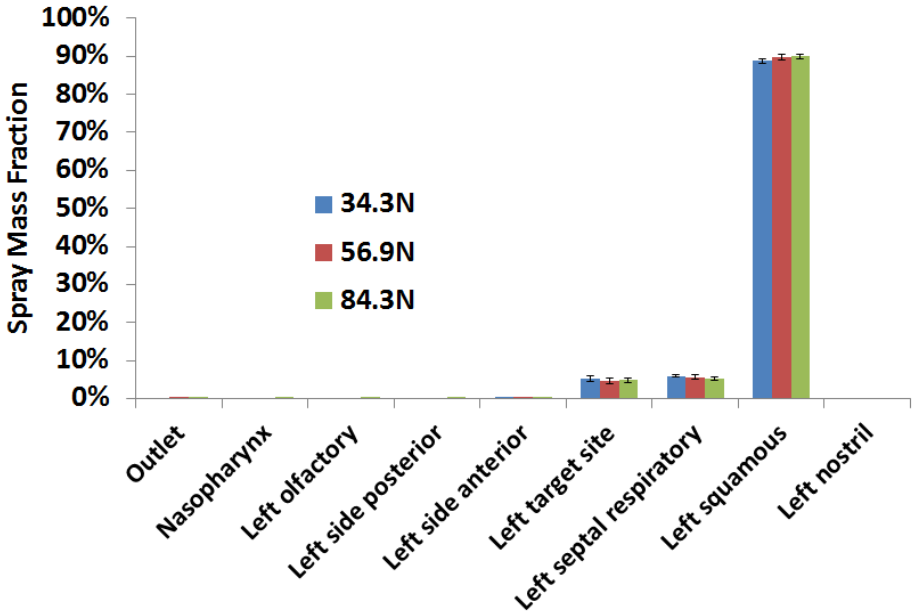



CFD predictions for deposition locations of fluticasone propionate droplets, from Kimbell et al. (2017)




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

# Actuation Force Sensitivity

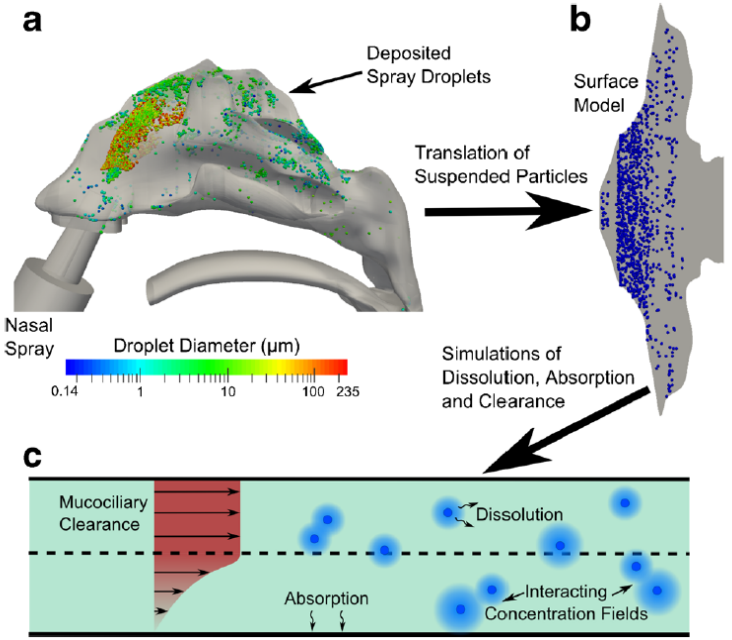



CFD predictions for regional deposition fraction of fluticasone propionate droplets according to differences in actuation force, from Kimbell et al. (2016)

- Steady State Flow
- Three actuation forces chosen: 34.3 N, 56.9 N, and 84.3 N
- Spray velocity based on spray duration measurements
- Droplet size is measured using laser diffraction
- Cone angle is held constant at 70° (Cheng et al. (2001))

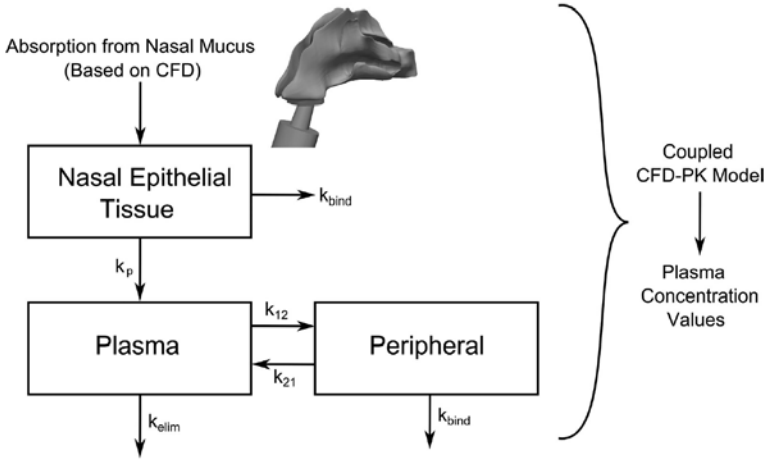
# Nasal Absorption Model Using CFD

- 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

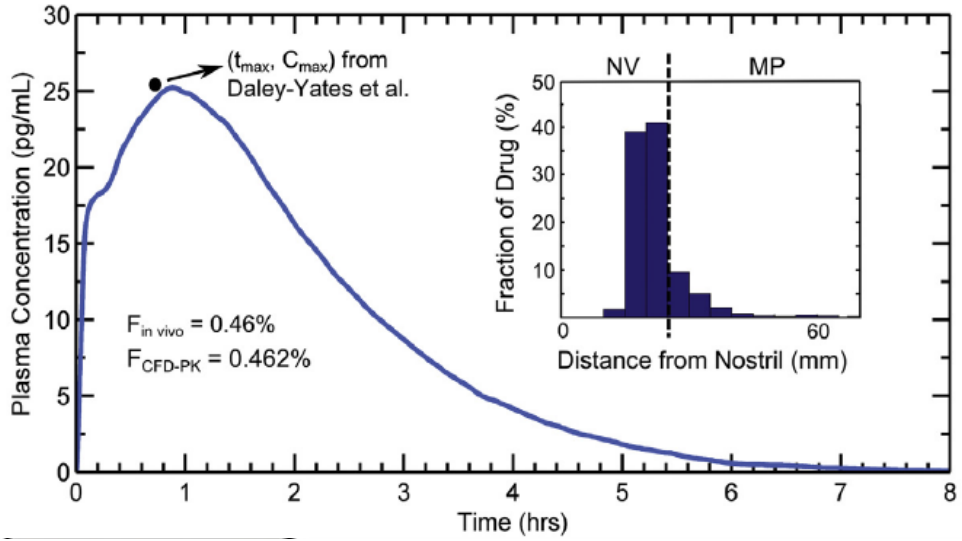



Nasal absorption process, with a) CFD prediction of deposition, b) mucociliary transit model, and c) dissolution, advection, and absorption model. (Fig.1 from Rygg et al. (2016))

# Connection of Nasal Absorption and PK



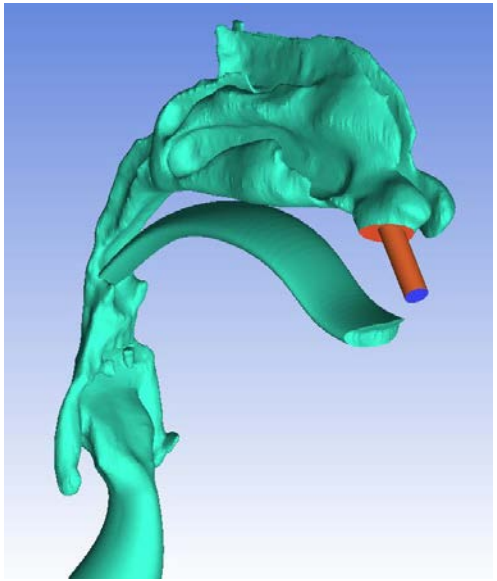

Two-compartment PK model structure. (Fig. 4 from Rygg et al. (2016b)




PK profile prediction as compared with in vivo data from Daley-Yates et al. (2004), 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)

# Nasal Insufflation of Oxycodone HCl Extended Release Tablet

- CFD and PK models to predict intranasal (IN) PK profiles of milled abuse-deterrent formulations (ADFs) in human insufflation PK studies
- Validate with in-house IN PK data
- Predict the IN PK of milled OxyContin tablets as a function of particle size and strength (drug/polymer ratio)
- Ongoing internal research



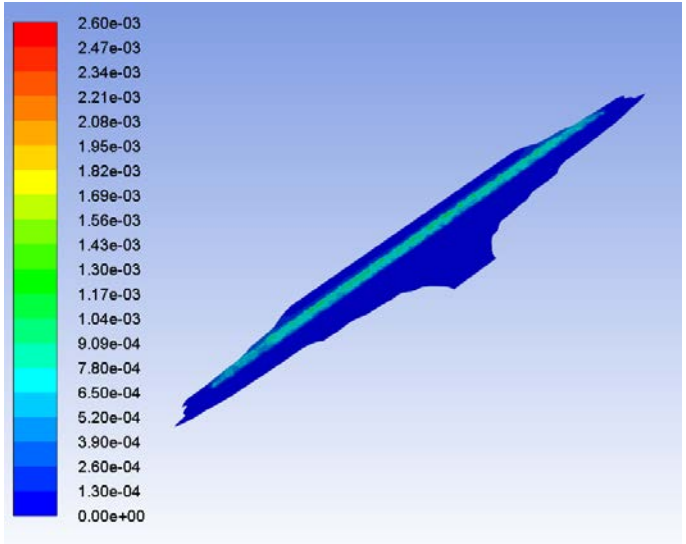
Nasal model based on Subject B model from Walenga et al. (2017)

# Regional Deposition of Insufflated Oxycodone HCl

- Right nostril flow rate 22 L/min – Sobel et al. (2000)
- Steady state
- Reynolds averaged Navier-Stokes (RANS) turbulence
- Neglect particle-wall and particle-particle interactions

- Coarse 30 mg OxyContin deposition fraction (DF)
  - Nasal Cavity: 99.5%
  - Nose: 0.5%
- Fine 30 mg OxyContin DF
  - Nasal Cavity: 99.6%
  - Nose: 0.4%

# PK modeling strategy




Oxycodone HCl mass fraction at epithelial surface

- Translate particles to surface model
- Use experimentally generated in vitro dissolution to model drug release
- Nasal PBPK model with mucus, epithelium, and submucosa compartments
  - Two compartment systemic model
- Investigate
  - Mucociliary transit time
  - Lateral particle distribution density

# Expected Outcomes of Opioid ADF Study

- Understanding of how well a given dissolution method characterizes in vivo dissolution
- Experimental methodology that can accurately assess abuse deterrence of oxycodone HCl formulations
- Validated model that can be used to understand performance of other opioid ADFs

# New GDUFA Funded Research

- Fully 3D CFD nasal mucociliary clearance model to allow for local concentration predictions
  - North Carolina State University (PI: Clement Kleinstreuer), Grant #1U01FD006537
- Nasal in vitro model development that characterizes intersubject variability of nasal spray deposition, supported by CFD predictions
  - Virginia Commonwealth University (PI: Laleh Golshahi), Contract #HHSF223201810144C

# Conclusions

- Development of nasal drug products is challenging due to the potential for device and/or formulation changes during the development process without direct knowledge of the in vivo implications.

- 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.

- In addition to the intended form of use, CFD can be used to assess PK via the abuse route for opioid ADFs.

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