Complex Nasal Suspensions: Utilization of In Silico Studies to Support Development and Approval

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 2: Noteworthy Guidances for Nasal Suspension and Inhalation Products

Ross Walenga, Ph.D.
Senior Chemical Engineer
Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA

September 13, 2023

Learning Objectives

- Describe the utility of computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK) modeling for nasal drug product development.
- Understand how CFD and PBPK models for nasal suspension drug products are validated.
- Identify in vitro metrics that are predicted to influence posterior nasal cavity drug delivery.

BE Approach for Nasal Suspension Drug Products

Bioequivalence (BE) recommendations from the U.S. Food and Drug Administration (FDA) include two options for nasal suspension drug products.

- Option 1 includes only in vitro studies
  - Qualitative (Q1) and quantitative (Q2) sameness
  - Test (T) device is appropriate for an abbreviated new drug application (ANDA)

In vitro studies

- Single Actuation Content
- Droplet Size Distribution by Laser Diffraction
- Drug in Small Particles/Droplets
- Spray Pattern
- Plume Geometry
- Priming and Repriming
- Drug Particle Size Distribution
- Dissolution

BE Approach for Nasal Suspension Drug Products (cont'd)

Option 2 includes in vitro and in vivo studies as listed below but does not include Q1/Q2 sameness.

In vitro studies	In vivo studies
❖ Single Actuation Content ❖ Droplet Size Distribution by Laser Diffraction ❖ Drug in Small Particles/Droplets ❖ Spray Pattern ❖ Plume Geometry ❖ Priming and Repriming	❖ Comparative PK with fasting, two-way crossover design in healthy subjects ❖ Comparative Clinical Endpoint

PK - pharmacokinetics

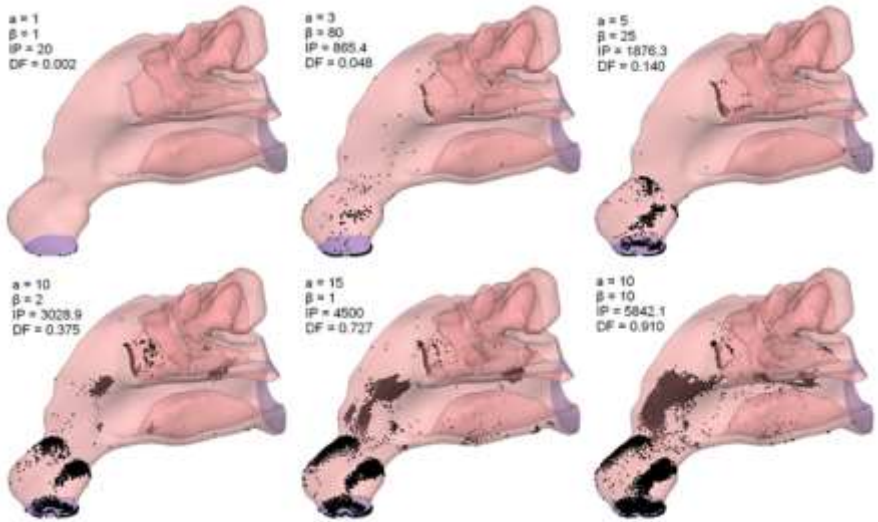
Why is Modeling Useful?

Value of In Silico Models

- Influence of device and formulation differences on regional deposition and absorption
  - If Option 2 is selected for demonstrating BE, modeling can predict impact of formulation and device changes on PK.
  - Current modeling techniques may be modified to predict in vitro study outcomes.
- Prediction of olfactory region absorption for nose-to-brain drug delivery

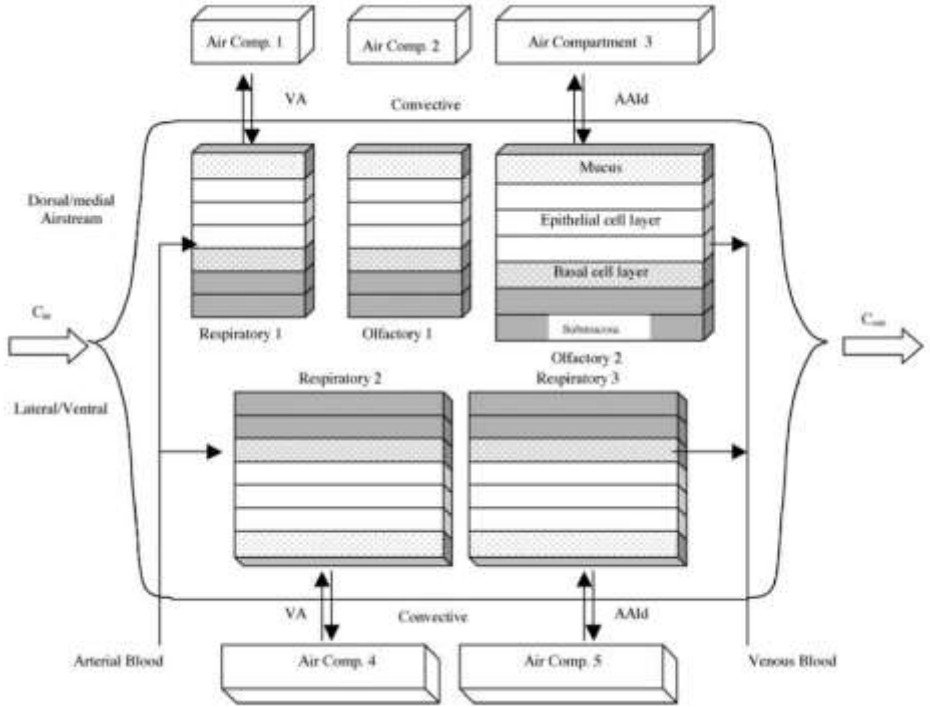
Computational Fluid Dynamics (CFD) Modeling of Nasal Drug Products

- Predict influence of device and formulation parameters on drug delivery to the site of action
  - Particle size distribution, spray angle, spray velocity
  - Regional deposition
    - Intersubject variability
  - PK profile
    - Combined with PBPK modeling



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. (Figure 13 from Dastan et al.[1])

PBPK Modeling of Nasal Drug Products

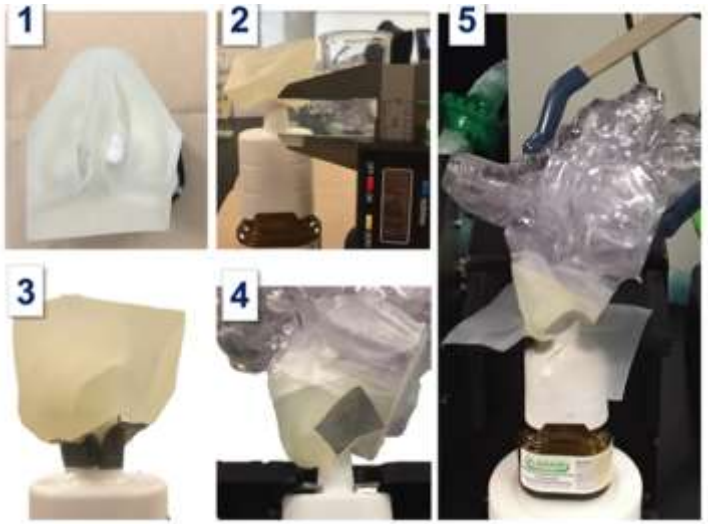


- Compartmental model
- Regional deposition inputs (in vivo, in vitro, or in silico)
- Prediction of local and systemic PK
  - Dissolution in mucus layer
  - Absorption through nasal tissue
  - Metabolism in nasal tissue
  - Integration with systemic model
- Validated with in vivo systemic or tissue PK data

Nasal PBPK model structure as shown in Figure 2 of Andersen et al.[2]

Case Study – CFD and PBPK Modeling with Adult and Pediatric Subjects

Adult and Pediatric Nasal Models

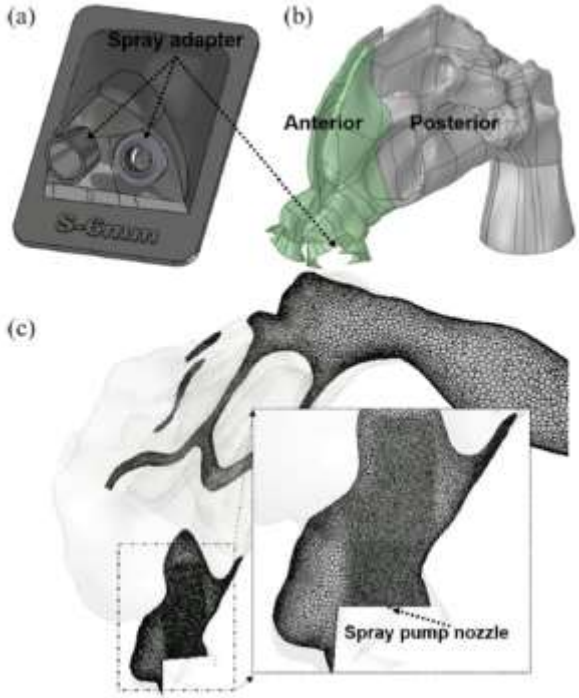


Experimental setup for measuring deposition following actuation of fluticasone propionate nasal spray. (Figure 2 of Manniello et al.[3])

- Virginia Commonwealth University (VCU)
  - PI: Laleh Golshahi
  - Contract #HHSF223201810144C (adult models)
  - Contract #75F40120C00172 (pediatric models)
  - Develop two sets of in vitro models for adult and pediatric subjects (three models for each – low, medium, and high deposition)
  - Intersubject variability for nasally inhaled corticosteroids
- Relationships of in vitro metrics of spray properties with regional deposition

CFD Model Development

- One average adult nasal model from Manniello et al.[3] was used to develop CFD model[4]
- Model is decomposed into computational mesh
- Two methods used to couple fluid and particle motion
- Results compared to in vitro data



(a) Spray adapter used for positioning of nasal suspension drug product, (b) computer aided design model of adult nasal model, and (c) interior computational mesh. (Figure 2 of Kolanjiyil et al.[4])

CFD Model Validation

Deposition predictions using two CFD methods with fluticasone furoate nasal spray and fluticasone propionate nasal spray as compared with in vitro data (n = 5). (Based on Table 6 of Kolanjiyil et al.[4])

	Fluticasone Furoate		Fluticasone Propionate	
	Anterior (%)	Posterior (%)	Anterior (%)	Posterior (%)
CFD quasi two-way coupling	93.4	6.6	89.5	10.5
CFD one-way coupling	92.6	7.4	94.0	6.0
In vitro	94.1 ± 1.9	5.9 ± 1.9	85.8 ± 5.4	14.2 ± 5.4
Relative error (quasi two-way coupling) (%)	0.7	11.9	4.3	26.1
Relative error (one-way coupling) (%)	1.6	25.4	9.6	57.7

- One-way coupling
  - Effect of airflow on particle motion
- Two-way coupling
  - Also includes effect of particle motion on airflow
- Improvement of predictions may be possible by considering spray-wall interaction and post-deposition liquid motion.[5]

Parameter Sensitivity Analysis

Parameter sensitivity analysis cases for spray cone angle, spray average velocity, and plume ovality. (Table 2 of Kolanjiyil et al.[6])

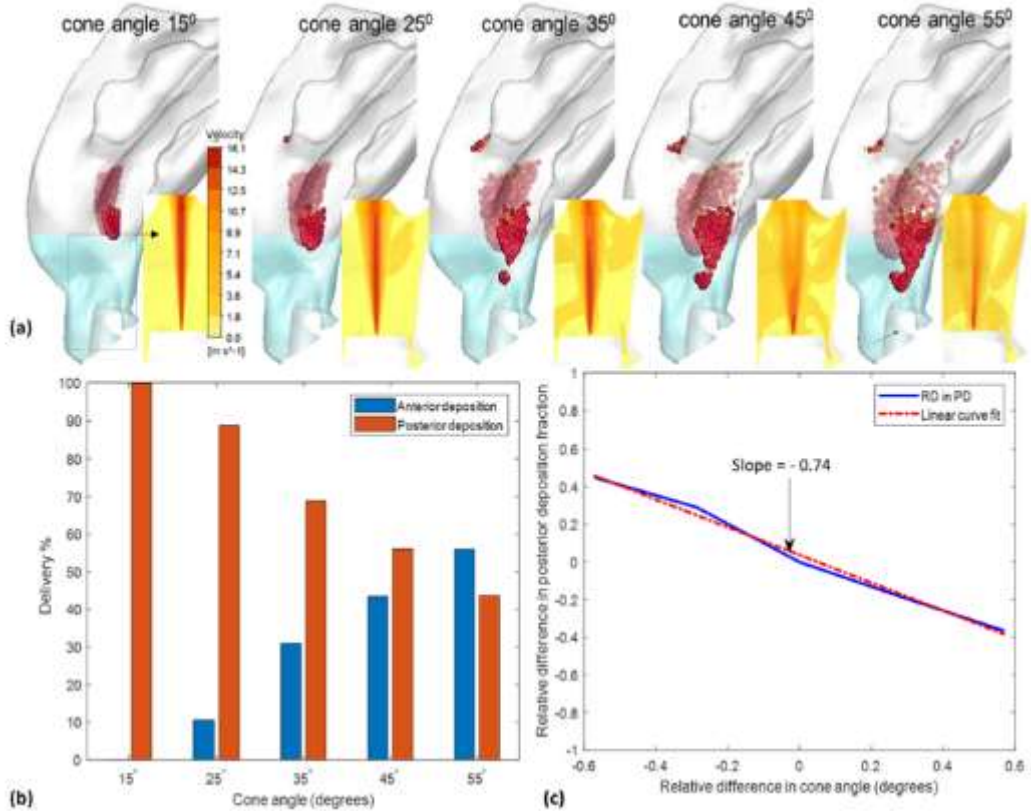
In vitro metrics	Case I	Case II	Case III	Case IV	Case V
Spray cone angle	55^0	45^0	35^0	25^0	15^0
Spray average velocity	8.4 m/s	11.4 m/s	14.4 m/s	17.4 m/s	20.4 m/s
Plume ovality (major axis diameter : minor axis diameter)	Ovality = 0.5 (maj:min 0.5:1)	Ovality = 0.67 (maj:min 0.67:1)	Ovality = 1 (maj: min 1:1)	Ovality = 1.5 (maj:min 1:0.67)	Ovality = 2 (maj:min 1:0.5)

Parameter sensitivity analysis cases for particle size distribution. (Table 3 of Kolanjiyil et al.[6])

In vitro metrics	Case I	Case II	Case III	Case IV	Case V
n	1.4	1.9	2.3	2.8	3.3
d_{bar}(μm)	49.6	66.2	82.7	99.3	115.8

- Parameter sensitivity analyses were conducted with spray cone angle, spray average velocity, plume ovality, and particle size distribution.[6]
- Fluticasone furoate nasal spray
- Medium and high deposition adult models were considered with three insertion conditions.
- Baseline condition included spray injection velocity = 14.4 m/s, average cone angle = 35°, and ovality = 1.

Influence of Spray Cone Angle



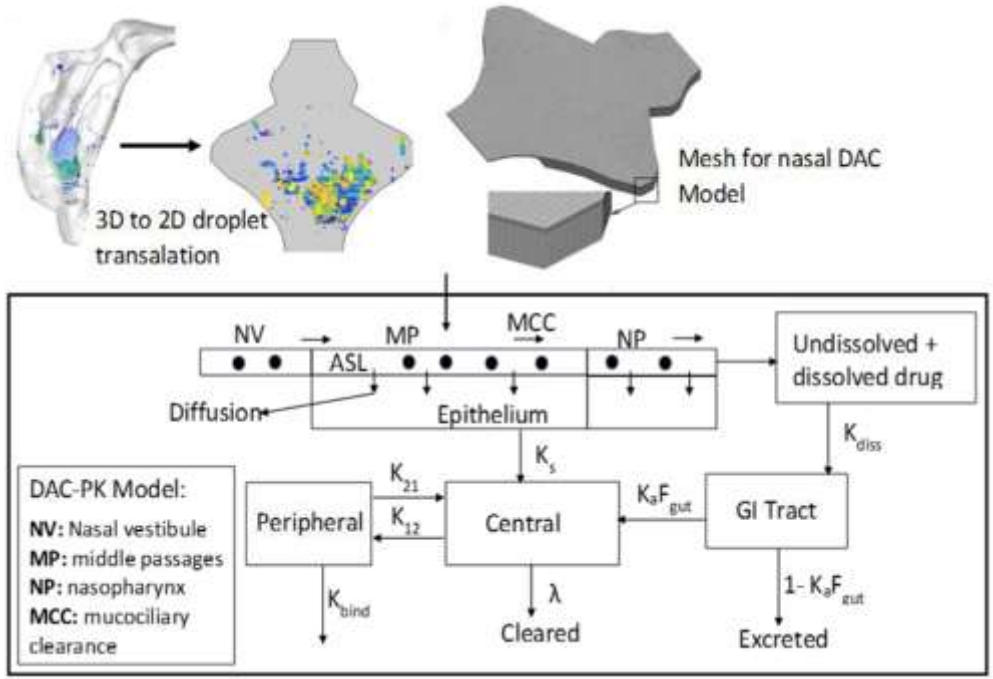
CFD simulation results with medium nasal model and Insertion Condition II with fluticasone furoate nasal spray, shown as (A) variation in spray cone angle input parameter, (B) anterior and posterior deposition percentage predictions, and (C) relative difference (RD) in posterior deposition fraction (PD) as varied by relative difference in spray cone angle (baseline of 35^{o}). (Figure 9 of Kolanjiyil et al.[6])

Overall Results – Parameter Sensitivity Analysis

- Spray cone angle showed the largest influence on posterior nasal cavity drug delivery.
- Plume ovality showed some influence that was dependent on insertion condition.
- Spray velocity showed little effect.
- Particle size distribution showed some effect, depending on which of two parameters were adjusted.
- Trends were similar between nasal models, with some slight differences for particle size distribution.

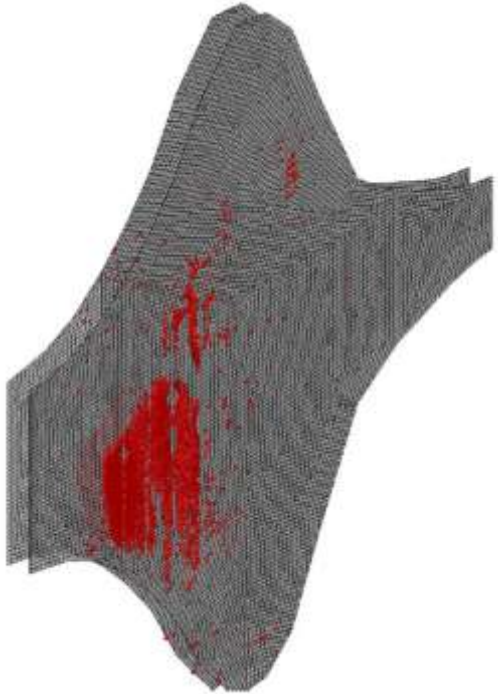
PBPK Model Development

- Deposition predictions are transferred to dissolution, absorption, and clearance (DAC) CFD model.
- DAC model is quasi-2D with varying width based on nasal cavity perimeter.
- Originally based on Rygg et al.[8]
- DAC model is coupled with two-compartment PK model and simplified gastrointestinal (GI) tract model.



Method for translating CFD predictions to nasal dissolution, absorption, and clearance (DAC) model (top) and compartmental structure of PBPK model as it interacts with DAC model (bottom). (Figure 1 of Dutta et al.[7])

PBPK Model Development (cont'd)

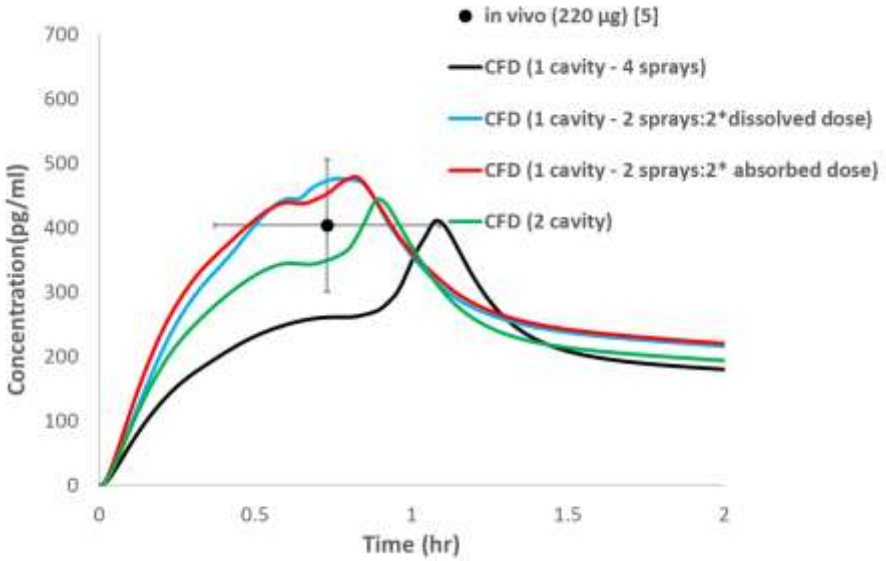


Computational mesh of two cavity DAC model with deposited particles. (Figure 3 of Dutta et al.[7])

- Predictions were made with 3D CFD and DAC models using adult medium deposition nasal model.
- Previous model built by Rygg et al.[8] used one model based on both nasal cavities.
  - New model separated geometry into one or two single nasal cavity models
- Absorption is based on nasal permeability, which is optimized to provide best match with available in vivo PK data for triamcinolone acetonide nasal spray.
- Distribution and clearance parameters were based on available intravenous PK data for triamcinolone acetonide.
- Deposition predictions were validated in a similar manner as described previously.

PBPK Results

- Plasma concentration predictions were obtained for 110 µg (one spray in each nostril) and 220 µg (two sprays in each nostril) doses and compared with available in vivo PK data.[9]
- For 220 µg dose, several approaches with one cavity included four sprays, two sprays with doubled post-dissolution dose, and two sprays with doubled absorbed dose.
- Two-cavity model was generally superior to one-cavity model, with some modified one-cavity model approaches also acceptable.



Predicted plasma concentration values using one- and two-cavity approaches for 220 µg dose, as compared with in vivo data from publicly available Clinical Pharmacology review of new drug application (NDA) 20468.[9] (Figure 5 of Dutta et al.[7])

How May a Firm Adopt the Use of Modeling?

- Develop capability
  - Internal, contract research organization, academia
- Build model early in development
- Explore impact of formulation or device changes
  - May consider impact on PK or develop models to replicate certain in vitro studies (e.g., spray pattern, plume geometry, etc.)

Challenge Question #1

Which in vitro metric was predicted to have the greatest influence on posterior nasal cavity drug delivery?

A. Spray average velocity

B. Plume ovality

C. Spray cone angle

D. Particle size distribution

Challenge Question #2

Which of the following statements is NOT true?

A. If Option 2 is selected for demonstrating bioequivalence (BE), modeling can predict impact of formulation and device changes on pharmacokinetics (PK) predictions.

B. Computational fluid dynamics (CFD) models may only be validated using in vivo deposition data.

C. It is most useful to build a computational model to support product development early in the process, rather than the middle or end of the process.

Conclusions

1. CFD and PBPK modeling of nasal suspension drug products may be used to understand the impact of formulation and device changes on systemic PK or in vitro metrics.
2. A combination of in vitro and/or in vivo data may be used to validate CFD and PBPK models of nasal suspension drug products.
3. Model predictions suggested that spray cone angle has the largest influence on posterior nasal cavity drug delivery, among the considered in vitro metrics.

Call to Action

Consider developing the capability to use CFD and PBPK modeling to support development of your generic nasal suspension drug product.

Acknowledgements

- FDA/CDER/OGD/ORS
  - Khondoker Alam
  - Andrew Babiskin
  - Betsy Ballard
  - Elizabeth Bielski
  - Susan Boc
  - Steven Chopski
  - Sneha Dhapare
  - Liangfeng Han
  - Anubhav Kaviratna
  - Jae Ho (Mike) Lee
  - Abhinav Mohan
  - Bryan Newman
  - Mingliang Tan
  - Eleftheria Tsakalozou
  - Miyoung Yoon
- FDA/CDER/OGD/ORS
  - Lanyan (Lucy) Fang
  - Myong-Jin Kim
  - Darby Kozak
  - Liang Zhao
  - Markham Luke
  - Lei Zhang
  - Robert Lionberger
- FDA/CDER/OGD/OSCE
  - Kimberly Witzmann
  - Sharon Ahluwalia
  - Denise Conti
- FDA/CDER/OPQ/OLDP
  - Srinivas (Ravindra) Behara
  - Qiang (Jason) Wang
- FDA/CDER/OPQ/ONDP
  - Renishkumar Delvadia
- FDA/CDER/OPQ/OTR
  - Geng (Michael) Tian
  - Maziar Kakhi
- FDA/CDER/OPQ/OTR
  - Changning Guo
  - Nicholas Holtgrewe
  - Xiaofei Liu
- FDA/CDER/OTS/OCP
  - Sneha Dhapare
- Otsuka Pharmaceutical Companies
  - Bhawana Saluja
- VCU
  - Worth Longest
  - Arun Kolanjiyil
  - Rabijit Dutta
  - Laleh Golshahi
  - Michael Hindle

We Are OGD

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."

www.fda.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

References

1. Dastan A, Abouali O, Ahmadi G. CFD simulation of total and regional fiber deposition in human nasal cavities. Journal of Aerosol Science. 2014;69:132-49.
2. Andersen ME, Green T, Frederick CB, Bogdanffy MS. Physiologically based pharmacokinetic (PBPK) models for nasal tissue dosimetry of organic esters: assessing the state-of-knowledge and risk assessment applications with methyl methacrylate and vinyl acetate. Regulatory Toxicology and Pharmacology. 2002;36(3):234-45.
3. Manniello MD, Hosseini S, Alfaifi A, Esmaeili AR, Kolanjiyil AV, Walenga R, Babiskin A, Sandell D, Mohammadi R, Schuman T, Hindle M. In vitro evaluation of regional nasal drug delivery using multiple anatomical nasal replicas of adult human subjects and two nasal sprays. International Journal of Pharmaceutics. 2021;593:120103.
4. Kolanjiyil AV, Hosseini S, Alfaifi A, Farkas D, Walenga R, Babiskin A, Hindle M, Golshahi L, Longest PW. Validating CFD predictions of nasal spray deposition: Inclusion of cloud motion effects for two spray pump designs. Aerosol Science and Technology. 2022;56(4):305-22.
5. Kolanjiyil AV, Alfaifi A, Aladwani G, Golshahi L, Longest W. Importance of Spray–Wall Interaction and Post-Deposition Liquid Motion in the Transport and Delivery of Pharmaceutical Nasal Sprays. Pharmaceutics. 2022;14(5):956.

References (cont'd)

6. Kolanjiyil AV, Walenga R, Babiskin A, Golshahi L, Hindle M, Longest W. Establishing quantitative relationships between changes in nasal spray in vitro metrics and drug delivery to the posterior nasal region. International Journal of Pharmaceutics. 2023;635:122718.
7. Dutta R, Kolanjiyil AV, Golshahi L, Longest W. Development of a CFD PK nasal spray model with in vivo human subject validation. Poster Presentation at Respiratory Drug Delivery (RDD) 2022 (May 1, 2022). Orlando, FL, USA. (Poster and conference paper)
8. Rygg A, Hindle M, Longest PW. Linking suspension nasal spray drug deposition patterns to pharmacokinetic profiles: A proof-of-concept study using computational fluid dynamics. Journal of Pharmaceutical Sciences. 2016;105(6):1995-2004.
9. Clinical Pharmacology Review – NDA 20468 SE05, S-24. 2007.