Development of a CFD-PK Nasal Spray Model with *In Vivo* Human Subject Validation

Rabijit Dutta[1], Arun V Kolanjiyil[1], Laleh Golshahi[1] and Worth Longest[1,2]

[1]VCU Department of Mechanical & Nuclear Engineering
[2]VCU Department of Pharmaceutics

Regulatory Approval Pathways for Generic Nasal Sprays

- Because several commercial nasal spray products have passed their period of patent exclusivity, there is an opportunity for new generic nasal sprays
- For the regulatory approval of generic sprays in the US, bioequivalence (BE) studies comparing the generic product to a reference listed product are necessary
- For approval of solution based nasal spray products U.S. Food and Drug Administration (FDA) guidance recommends six *in vitro* tests:
    - E.g., single actuation content, droplet size distribution by laser diffraction, spray pattern, plume geometry) [1, 2]
- It is currently recommended that suspension nasal spray products use a weight-of-evidence approach for establishing BE:
    - Based on equivalent *in vitro* performance similar to solution products, equivalent systemic exposure based on pharmacokinetic (PK) studies, and comparative clinical endpoint or pharmacodynamics (PD) studies [2].
    - Alternative approaches to conducting the comparative clinical endpoint or PD-BE studies are based on advanced methodologies for assessing the particle size distribution (PSD) of suspended drug particles within the product

[1] US_FDA. Draft guidance for industry: Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action, US Food and Drug Administration, Washington, DC, 2003.
[2] Li BV, Jin F, Lee SL, Bai T, Chowdhury B, Caramenico HT, and Conner DP: Bioequivalence for locally acting nasal spray and nasal aerosol products: standard development and generic approval. The AAPS Journal 2013,15:875-883.

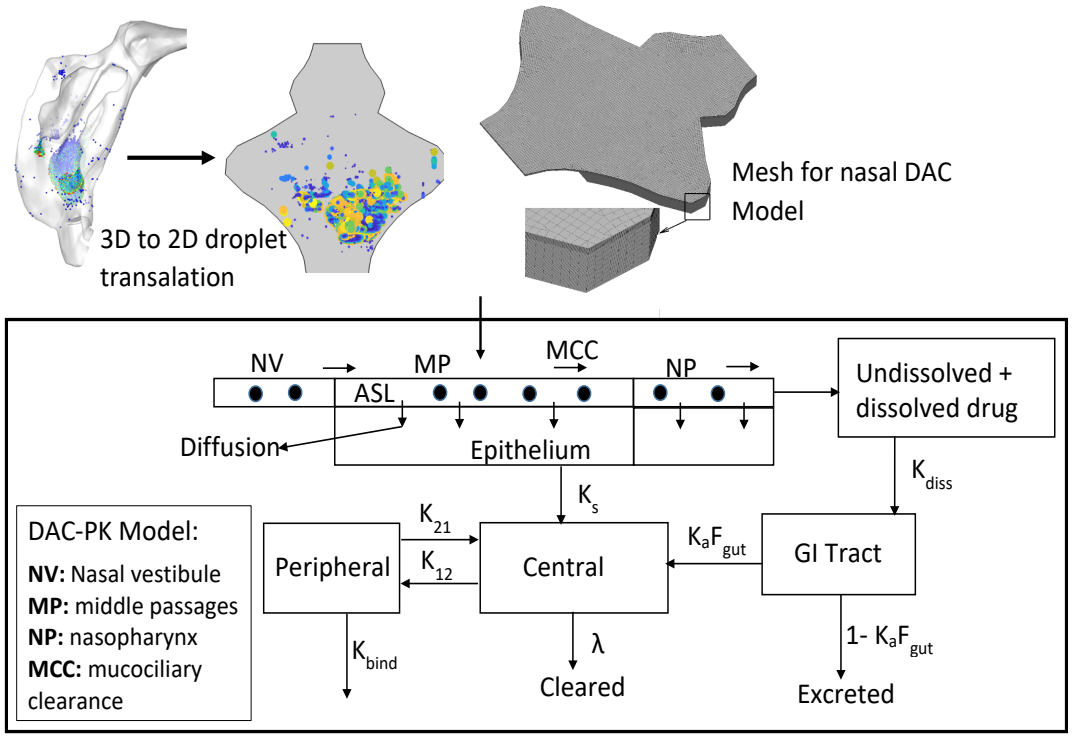
Objective

- Advancements in modeling and simulation have potential in supporting alternative BE approaches for nasal spray products, which may reduce the need for human subject testing when establishing BE
- The objective of this study is to develop a complete nasal transport *in silico* model to correlate drug deposition and plasma concentration for a representative nasal spray product, Nasacort® AQ (triamcinolone acetonide) nasal spray
- The transport model was developed by extending the CFD-PK approach proposed by Rygg et al. [3]:
  - CFD modeling is used to predict spray droplet deposition locations in a 3D nasal cavity
  - Droplets are translated to a nasal dissolution, absorption and clearance (nasal-DAC) model and coupled with a compartmental PK model

[3] Rygg A, Hindle M, and 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 2016,105:1995-2004.

Methods

- The spray droplet deposition patterns in the nasal airways were predicted using a newly developed 'quasi two-way coupled simulation' approach [4]
  - The initial and boundary conditions of the CFD model were based on *in vitro* measured data for Nasacort® AQ
- For creating the nasal-DAC model, a 2D surface representation of the 3D nasal geometry was created based on the perimeter of the cross-sections
  - 2D surface geometry was extruded to create an airway surface liquid (ASL) layer and an epithelium layer (in the posterior region)



- Drug dissolution in the ASL region was modeled by the Noyes-Whitney equation
- Behavior of the dissolved drug in the model was governed by an advection-diffusion equation
- A mass source was implemented to model mucociliary clearance rate of ~ 6mm/min
- The diffusion across ASL/epithelium membrane is modeled as:

$$V_{ep}\frac{dC_{ep}}{dt} = PS_{nose}\left(C_{muc}f_{um} - \frac{C_{ep}}{K_{pu}}\right)$$

[4] Kolanjiyil AV, Hosseini S, Alfaifi A, Hindle M, Golshahi L, and Longest PW: Importance of cloud motion and two-way momentum coupling in the transport of pharmaceutical nasal sprays. Journal of Aerosol Science 2021,156:105770.

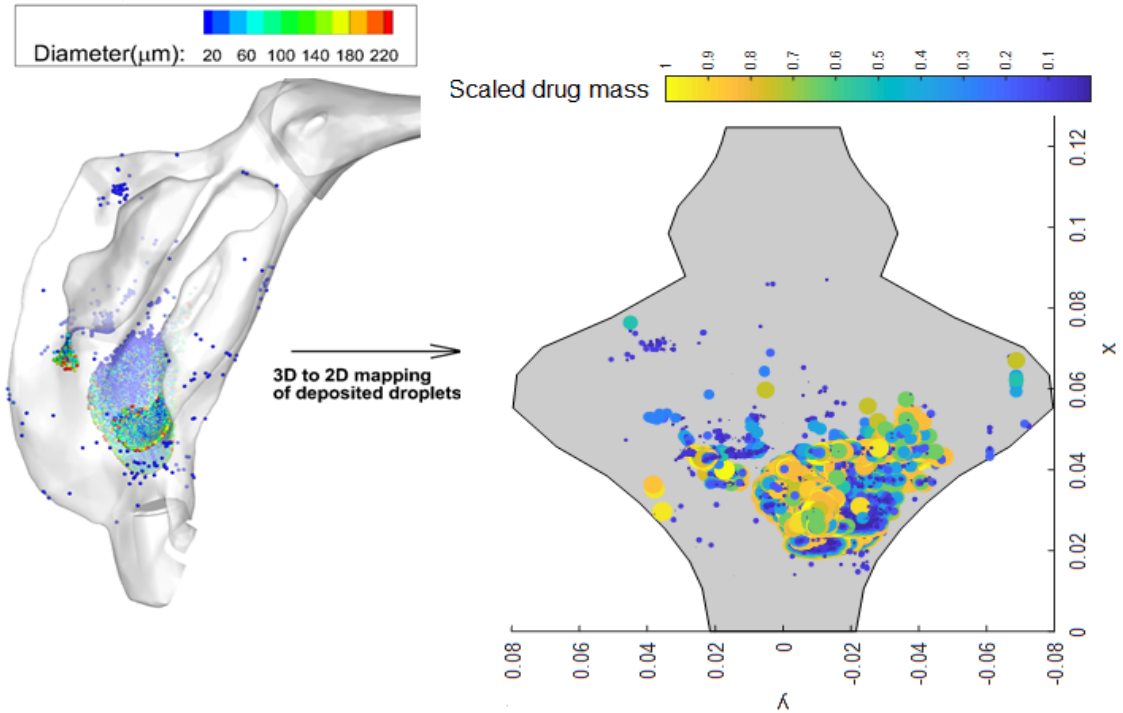
Methods

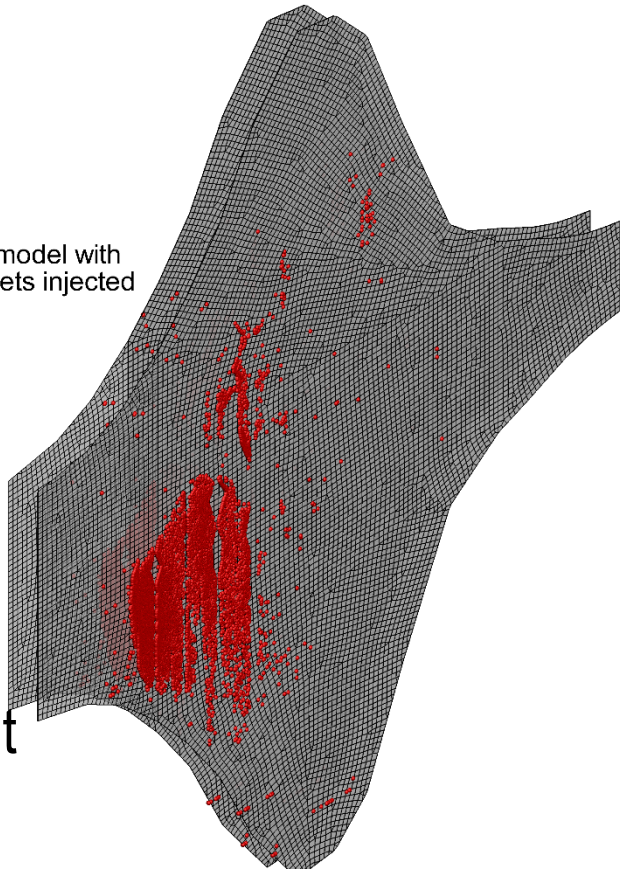
- The PK model rate constants were estimated using IV bolus PK data for triamcinolone acetonide [5]
- The new PK model also accounts for the absorption of the swallowed drug mass using a simple GI tract absorption model
  - Model parameters for oral absorption were estimated from oral dose data [5]
- The nasal systemic absorption constant (K_s) was specified using Gastroplus v9.8 (Simulations Plus, Inc., Lancaster, CA, USA) predicted value
  - The permeability value (in the DAC model) was adjusted to correctly capture *in vivo* PK values for 110 µg Nasacort® AQ dose
  - This optimization is necessary since the model assumes a Gastroplus predicted value of K_s

[5] Derendorf H, Hochhaus G, Rohatagi S, Möllmann H, Barth J, Sourgens H, and Erdmann M: Pharmacokinetics of triamcinolone acetonide after intravenous, oral, and inhaled administration. The Journal of Clinical Pharmacology 1995,35:302-305.

Methods

- A new algorithm was developed in MATLAB 2018a for the translation of deposited droplet locations from the 3D CFD model to the airway surface liquid (ASL) layer, which can resolve deposition hotspots



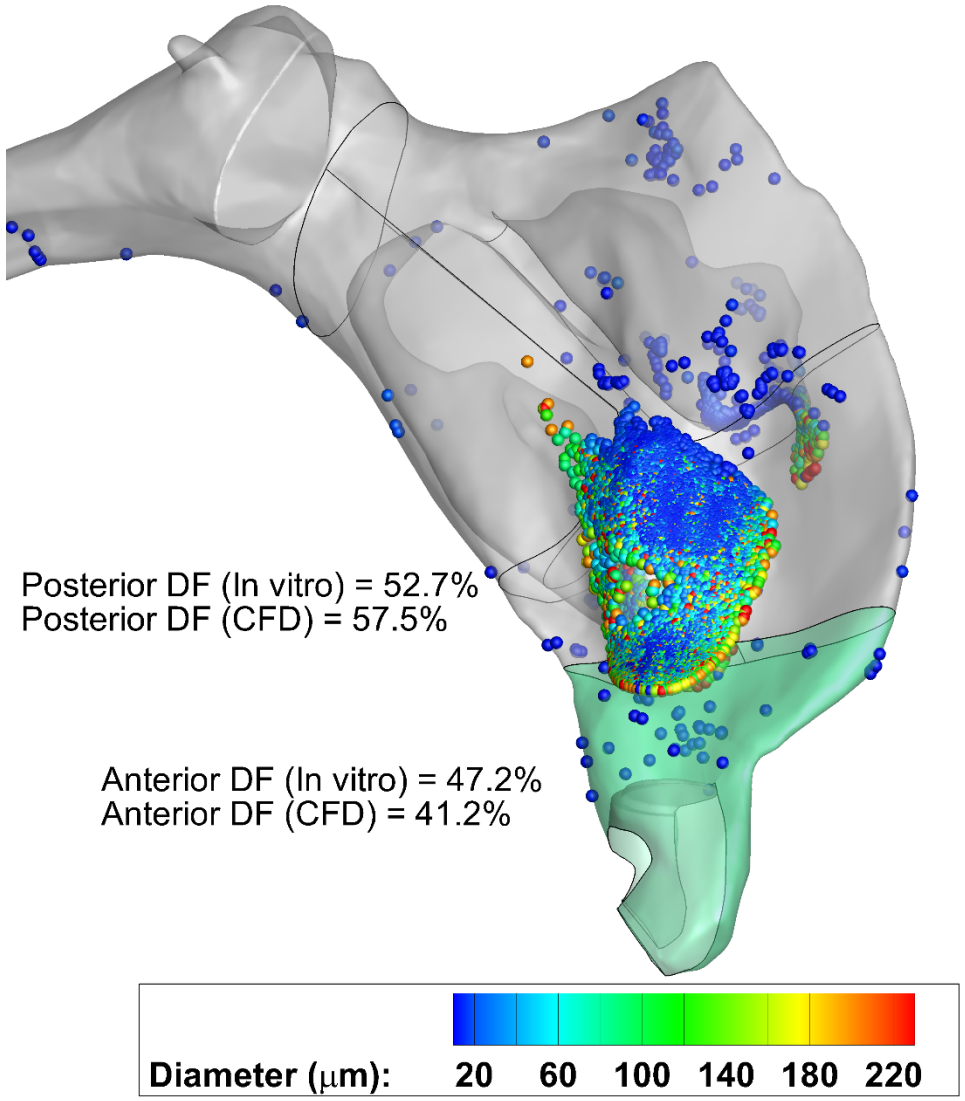


- Preliminary DAC model was developed by translating a 3D nasal geometry that consisted only the left nasal cavity (one-cavity model)
  - To simulate *in vivo* conditions, an updated DAC model was developed with two symmetric nasal cavities (two-cavity model)

Results and Discussion

➢ CFD *in vitro* validation

- *In vitro* deposition measurement was conducted using a representative adult nasal airway model (Model 7L from Manniello et al. [6])
- The CFD predicted anterior and posterior deposition results using the quasi two-way coupled model showed good agreement with the *in vitro* data
  - Accurate implementation of the *in vitro* positioning data was highly important
  - Nozzle tip diameter was accurately estimated (340 μm) using micro-CT imaging

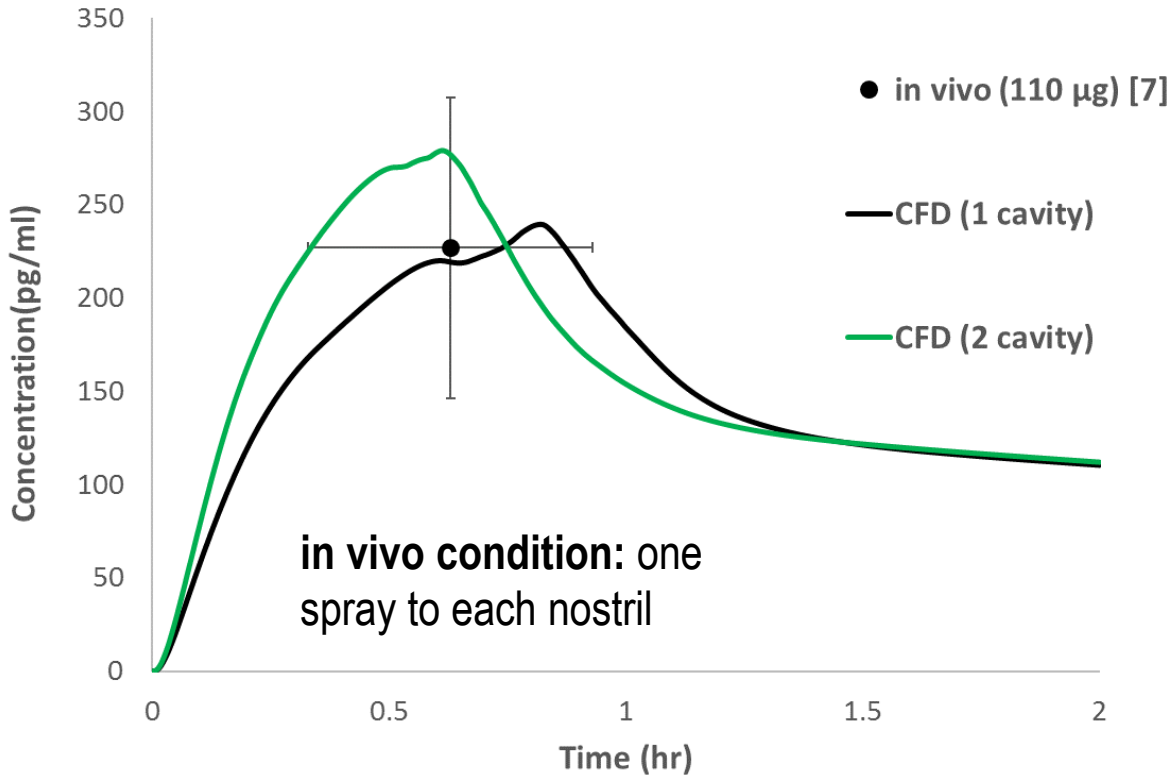


[6] Manniello MD, Hosseini S, Alfaifi A, Esmaeili AR, Kolanjiyil AV, Walenga R, Babiskin A, Sandell D, Mohammadi R, and Schuman T: In vitro evaluation of regional nasal drug delivery using multiple anatomical nasal replicas of adult human subjects and two nasal sprays. International Journal of Pharmaceutics 2021,593:120103.

Results and Discussion

➢ *In vivo* PK comparison (110 µg)

- *In vivo* delivery conditions were one spray (55 µg) to each nostril
- Both one-cavity and two-cavity approaches predicted similar PK profiles with slightly different peak plasma concentration (Cmax) and time to Cmax (i.e., Tmax) values



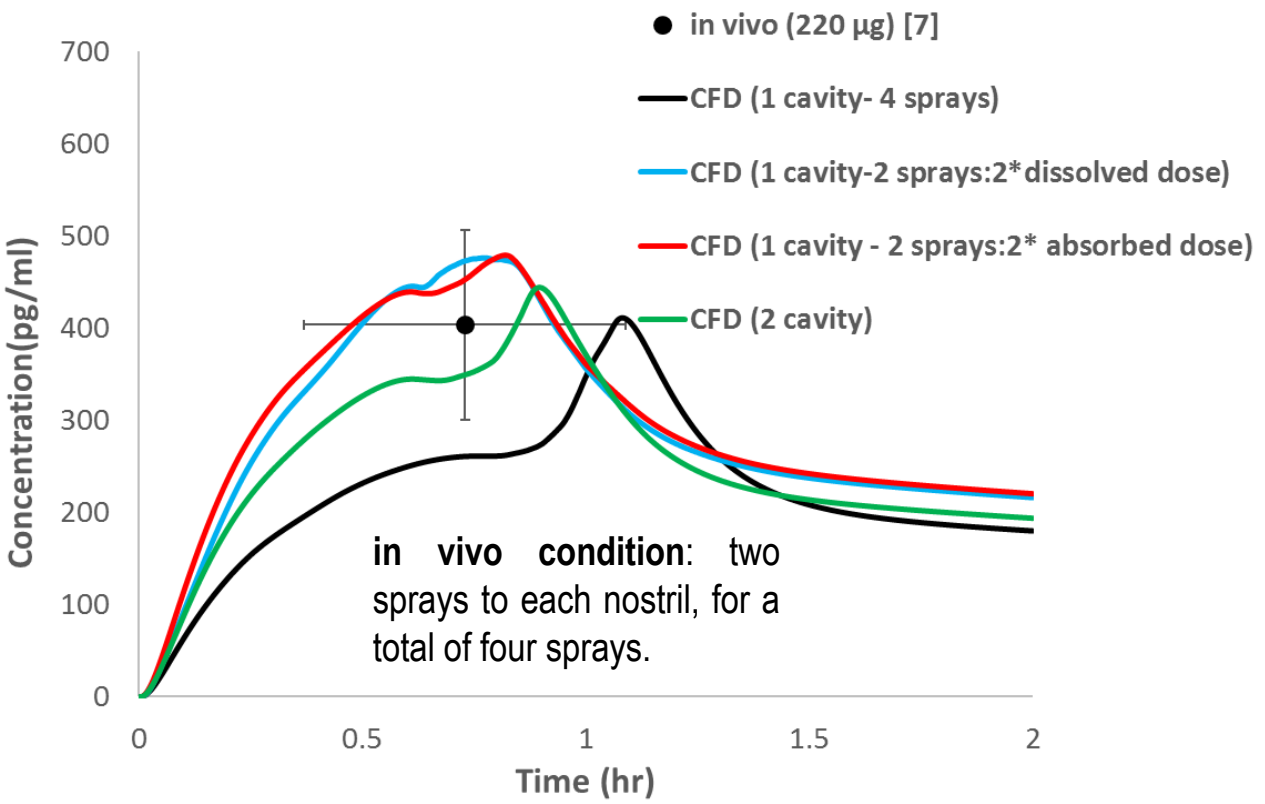
- Two-cavity model simulated the *in vivo* conditions **more realistically** (i.e., one spray to each nostril) and, therefore, **<u>better predicted the Tmax value</u>**
- One-cavity model showed an inaccurate effect of drug concentration buildup as indicated by delaying drug release and an appearance of the Cmax at a later time

[7] Roy P, Qiu W, and Tornoe C. FDA-Nasacort®AQ Clinical Pharmacology Review - NDA 20468 SE05, S-24. 2007.

Results and Discussion

➢ *In vivo* PK comparison (220 µg)

- *In vivo* delivery conditions were two sprays (110 µg) to each nostril
- 220 µg dose with the one-cavity model was modeled by injecting droplet mass corresponding to four sprays, which changed the dissolution and absorption physics and gave poor agreement with the *in vivo* data



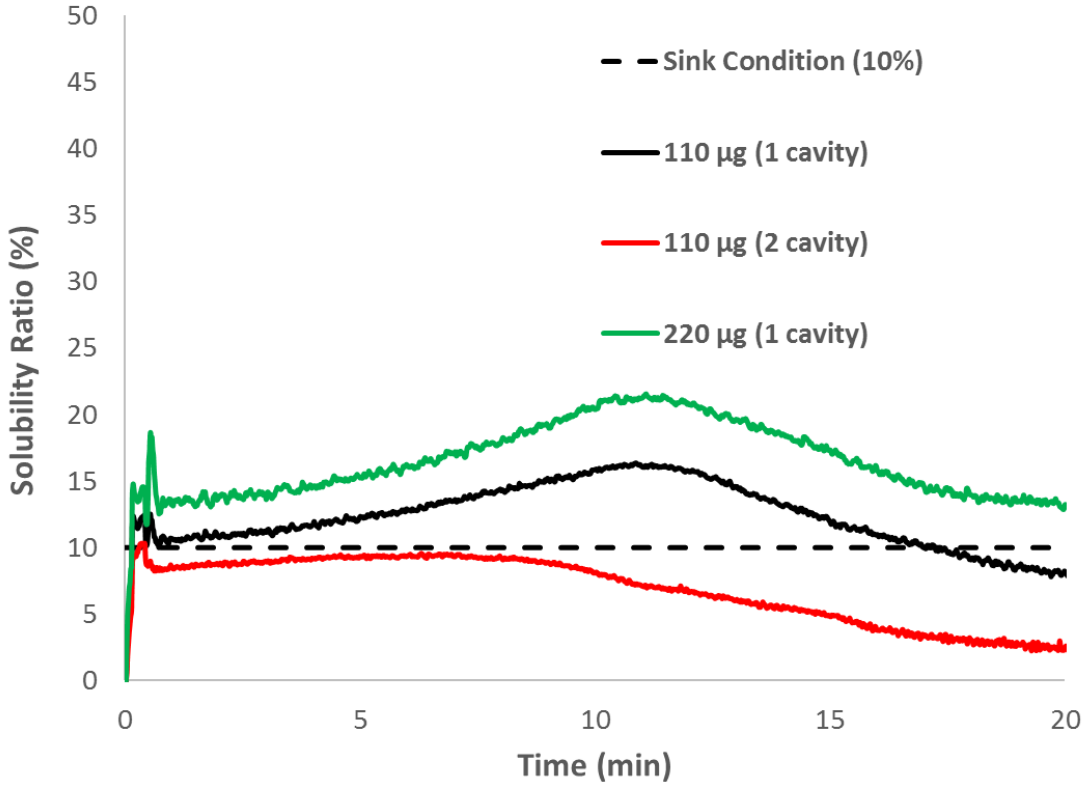
- The two-cavity model showed better agreement with the *in vivo* data
- Additional one-cavity approaches were also found to give adequate results:
  - By doubling the mucus dose post-dissolution or by doubling the absorbed dose
  - Both of these approaches showed reasonable agreement with the *in vivo* data

[7] Roy P, Qiu W, and Tornoe C. FDA-Nasacort®AQ Clinical Pharmacology Review - NDA 20468 SE05, S-24. 2007.

Results and Discussion

➢ Drug concentrations in the mucus

- We investigated the ratio of dissolved drug concentration in the ASL region to the drug solubility
  - The drug concentration in the ASL layer was calculated by volume averaging the local drug concentrations in this region
  - If the drug concentration is less than 10% of the solubility of the drug, sink conditions can be considered (effect of saturation concentration can be neglected)



- Solubility ratio was studied for the initial 20 min:
  - Two-cavity model resulted in sink conditions for the 110 µg case
  - One-cavity model deviates from the sink conditions case for initial 15 minutes (110 µg)
  - Concentration buildup becomes more apparent for the 220 µg case with one-cavity model

Conclusion

- A nasal CFD model of a representative suspension-based spray product was combined with a transport model for nasal dissolution absorption and clearance, which was then coupled with a compartmental PK model to generate blood concentration profiles
- Modeling *in vivo* conditions with a one-cavity nasal model (left cavity of an adult nose) delayed drug release and the Cmax appeared at a later time compared to the *in vivo* data
- The two-cavity model, which was developed by mirroring the one-cavity model to mimic *in vivo* physiological and drug delivery conditions showed very good agreement with the *in vivo* data
- The proposed CFD-DAC approach needs to be tested with other nasal geometries to predict variability in PK predictions
    - Further validations with other nasal spray products are needed to complement the findings of this study
- The CFD-DAC *in silico* tool presented here may, in the future, help with establishing BE and guide the design of new nasal spray products

Acknowledgements

Funding was provided by Contract 75F40120C00172, from the Department of Health and Human Services, U.S. Food and Drug Administration. This presentation reflects the views of the author and should not be construed to represent FDA's views or policies. The authors are grateful to Ross Walenga, Sneha Dhapare, Bryan Newman, Abhinav Mohan and Sharon Ahluwalia (U.S. FDA) for useful discussions.

Thank you