Computational fluid dynamics (CFD) modeling for product development of generic OINDPs and for supporting novel BE approaches

Complex Generic Drug Product Development Workshop

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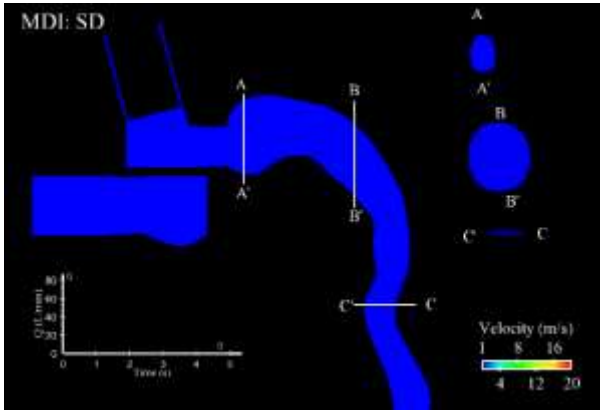
CDER | US FDA

Regulatory Impacts/Applications of CFD

- Generic OINDP Product Development
  - Reduce number of device design changes
- Regulatory Utility
  - Support alternative bioequivalence (BE) approaches including not conducting clinical endpoint studies
  - Product specific guidance (PSG) development

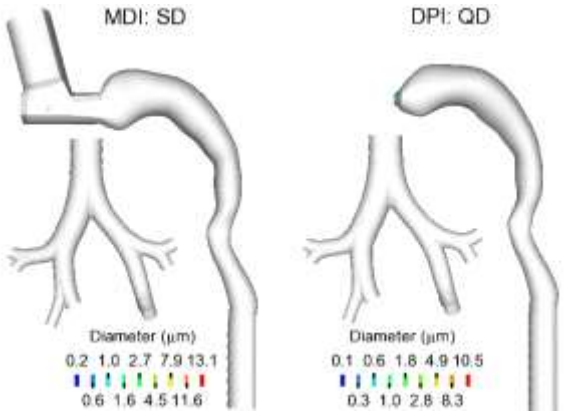
Computational Fluid Dynamics (CFD)

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



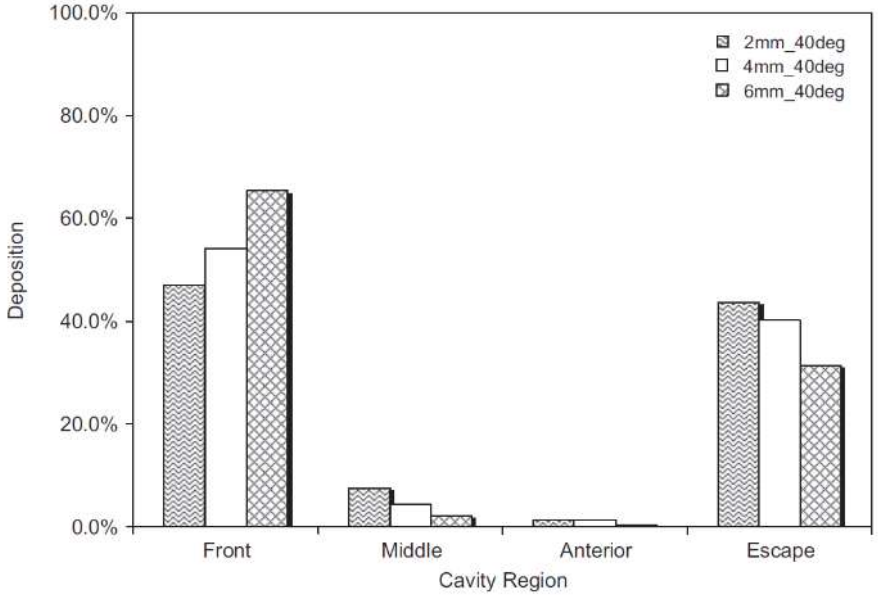
Metered Dose Inhaler (MDI)

Simulations from Longest et al. (2012)



Dry Powder Inhaler (DPI)

In Vitro to In Vivo



Regional nasal deposition fraction of 10 µm particles with different spray cone diameters (Fig. 10 from Inthavong et al. (2008)

- Several in vitro parameters are commonly measured
- Effect on drug deposition largely unknown
- CFD can predict influence of these parameters

Product Development

Fig. 1 from Shur et al. (2012) – a) Handihaler and b) Cyclohaler

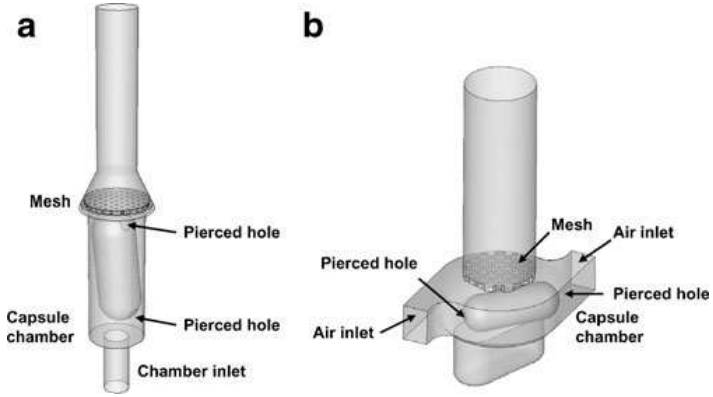
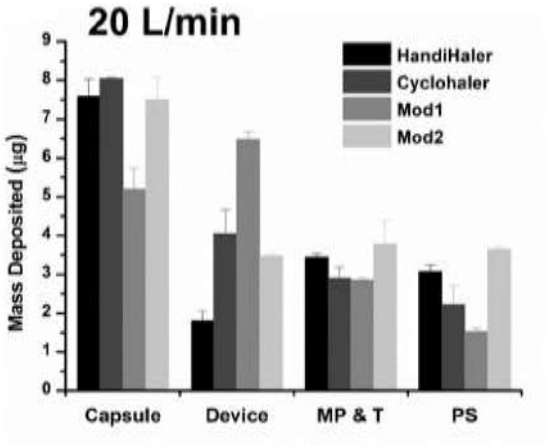


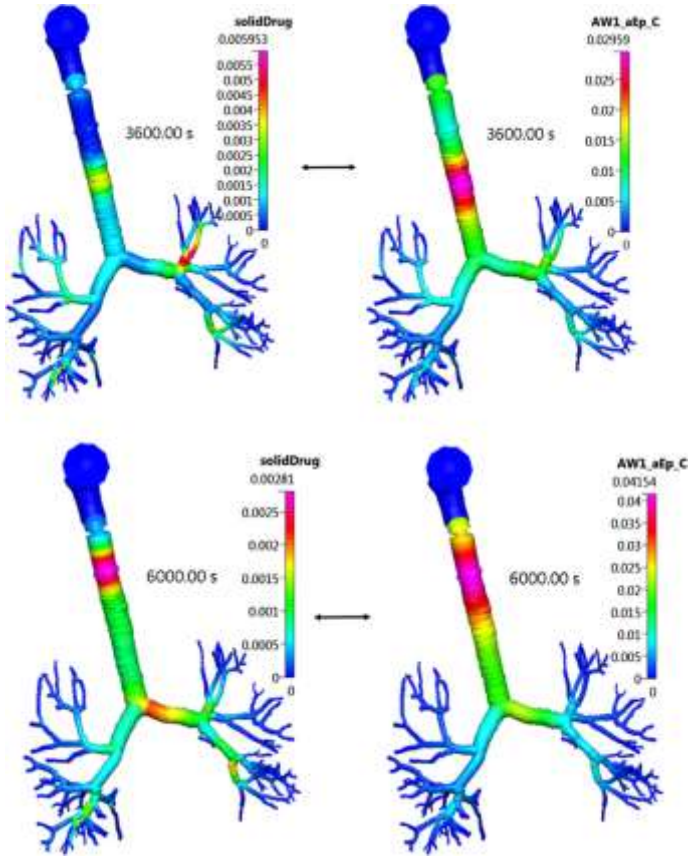
Fig. 6a from Shur et al. (2012) – NGI data at 20 L/min



- FDA Contract #HHSF223200910017C
- Two different devices (Handihaler and Cyclohaler)
- Two modifications made to Cyclohaler, CFD used to optimize

Lung PBPK

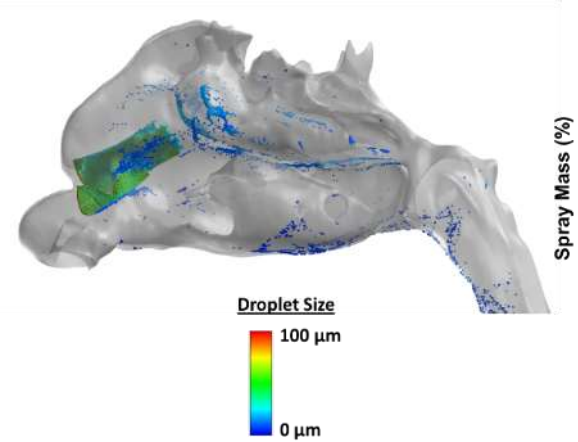
- FDA Grant #1U01FD005214
- Physiologically-based pharmacokinetic (PBPK) model for lung absorption
- Fully 3D CFD predicts deposition, Quasi-3D CFD for absorption



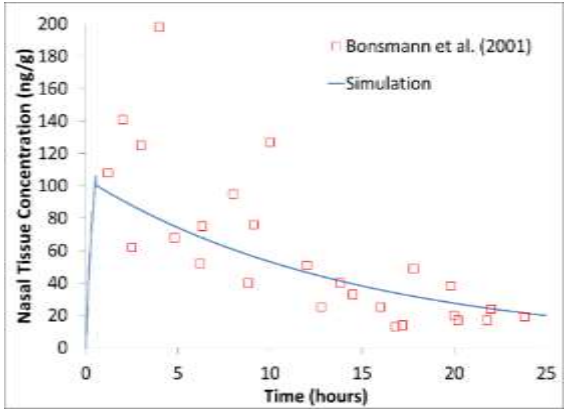
Local drug concentration predictions of solid and dissolved fluticasone propionate Fig. 15 from Kannan et al. (2018)

Nasal PBPK

- FDA Grant #1U01FD005201
- PBPK model for nasal absorption
- Fully 3D CFD predicts deposition, compartmental model for absorption

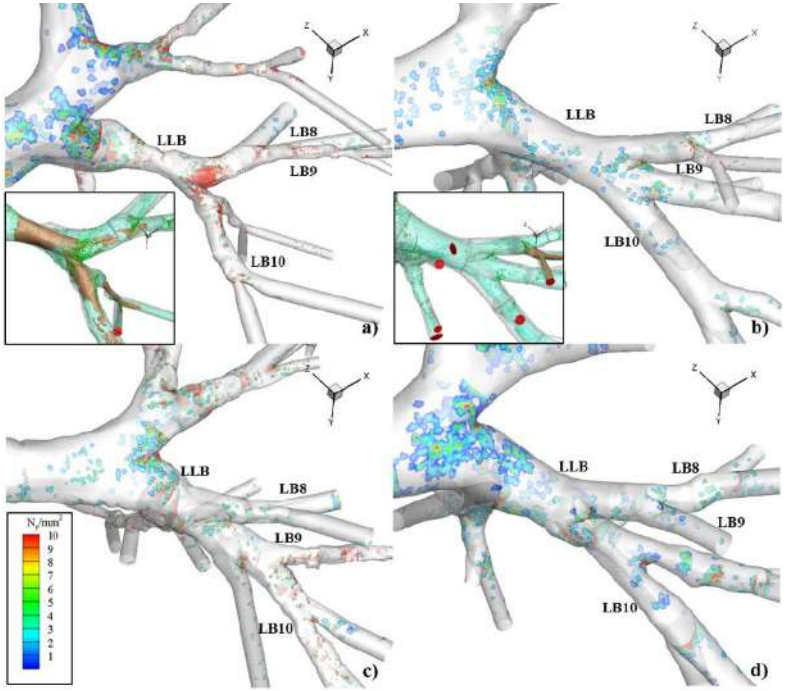


CFD predictions for deposition locations of fluticasone propionate droplets, from Kimbell et al. (2017)



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

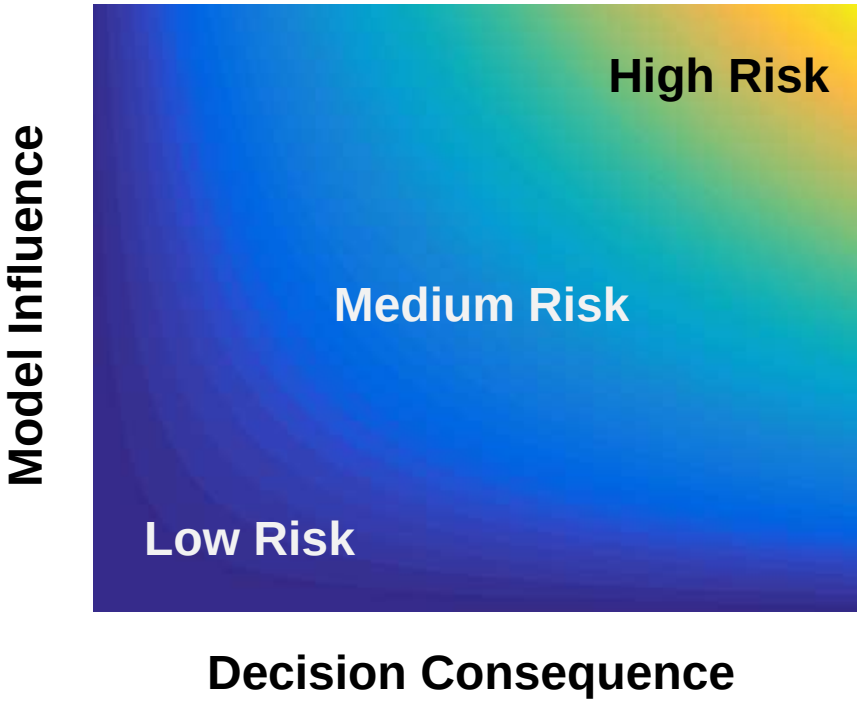
Novel Bioequivalence Approaches



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

- Pre-ANDA product development meeting
- Effects of in vitro parameter differences on regional deposition and PK
- CFD is capable of capturing small airway deposition

Context of Use

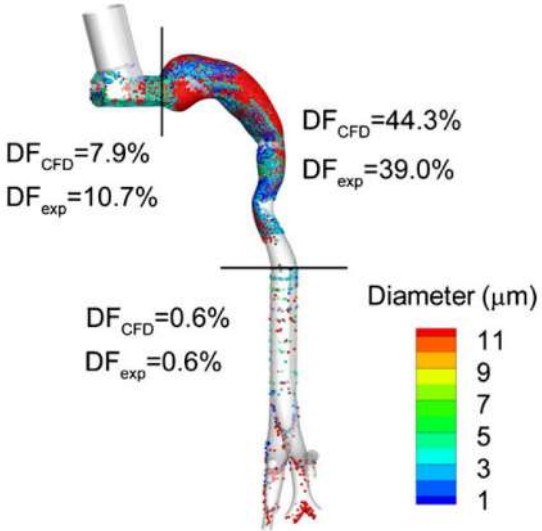


- American Society of Mechanical Engineers (ASME) Verification and Validation 40
- Model influence – how much model is used
- Consequence of a wrong decision

Credibility Assessment

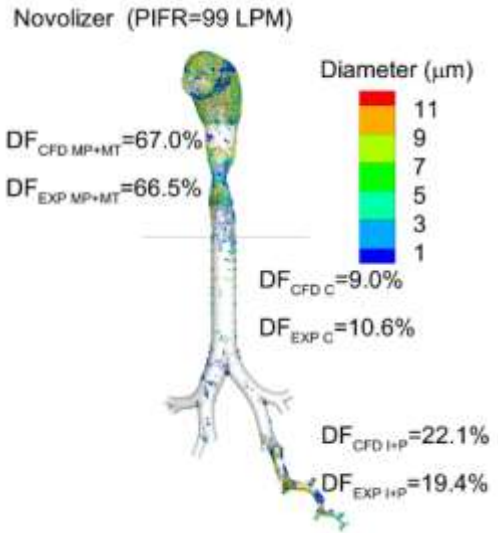
- Verification – quality of computational model
- Validation – ability of computational model to represent reality
- Uncertainty quantification – sensitivity of model result to parameter uncertainty

Validation



Deposition fraction prediction in fluticasone propionate MDI, compared with in vitro data, from Figure 5 of Longest et al. (2012)

- In vitro – deposition in rapid prototyped model
- In vivo – radiolabeled aerosol with gamma scintigraphy



Deposition fraction prediction in budesonide DPI, compared with in vivo data, from Figure 6 of Tian et al. (2015)

Conclusion

- Computational fluid dynamics (CFD) is capable of predicting effects of device and in vitro parameters on in vivo performance
- Product development – reduce number of device changes
- Support alternative bioequivalence (BE) approaches including not conducting clinical endpoint studies

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