Credibility Establishment for Computational Fluid Dynamics Models of Complex Generic Drug Delivery

Complex Generic Drug Product Development Workshop

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Ross Walenga, Ph.D.

Chemical Engineer

Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs

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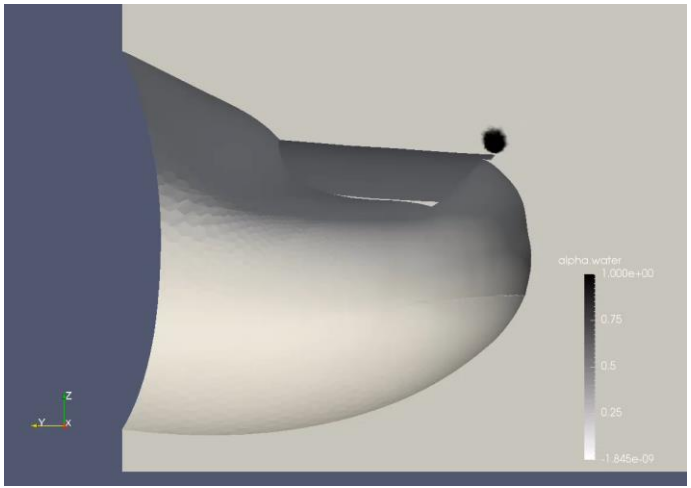
Computational Fluid Dynamics (CFD) Models of Complex Drug Delivery

- In vitro metrics → in vivo performance
  - Often governed by fluid behavior
- Prediction of fluid and particle transport
- Allows for consideration of realistic geometries



Toenail penetration of high surface tension fluid

CFD Solution Strategy

- Navier-Stokes equations of fluid motion
- Domain is subdivided into smaller volumes
- Mesh refers to entire discretized geometry
- Mesh density refers to number of cells

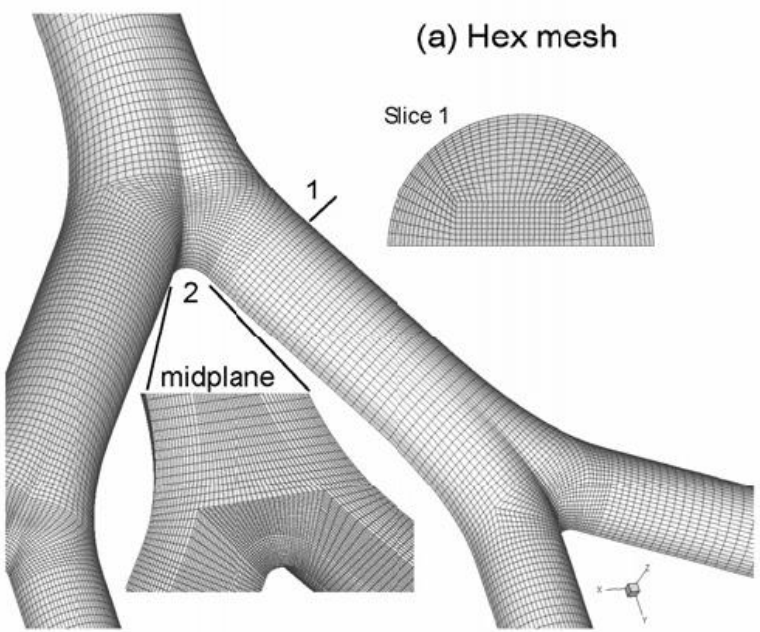
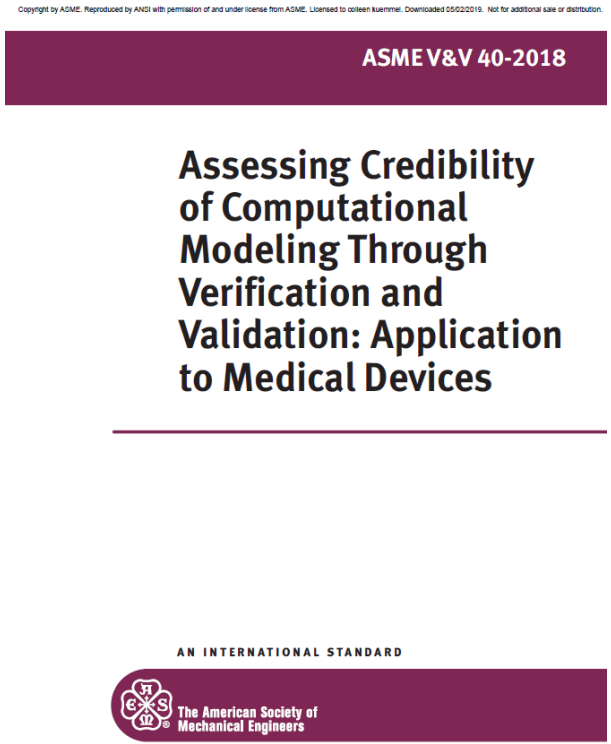


Fig. 2a from Longest and Vinchurkar (2007): Computational mesh of lung bifurcation using hexahedral cells.

Utility of CFD Models

- Applications for generic complex drug products
  - Product development
  - Support alternative bioequivalence (BE) approaches
    - Potentially use in silico models in place of comparative clinical endpoint or pharmacodynamic (PD) study to support BE evaluation.
    - Inform choice of biorelevant in vitro test specifications.
    - Characterize impact of excipient differences on drug absorption.

How to Establish Model Credibility?



- Credibility: Confidence in predictive capability of the model
- Not any one unanimous, universal standard
- American Society of Mechanical Engineers (ASME) Verification and Validation 40 (V&V 40)
  - Intended for computational models of medical devices
  - Useful for variety of complex drug products

ASME V&V 40 Concepts

- Context of Use: Describes what question the model addresses and to what extent
- Model Risk: Determined by decision consequence and model influence
- Credibility: Verification and Validation

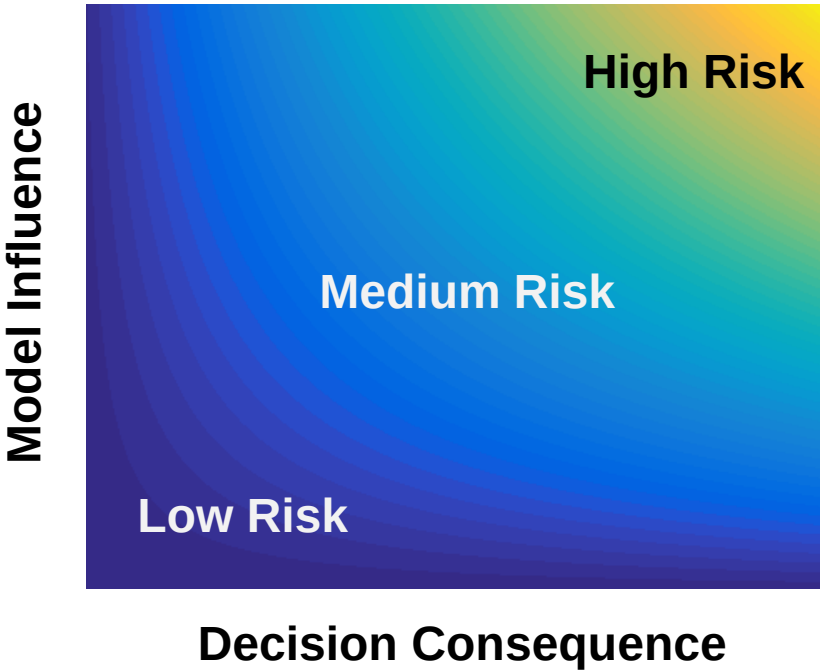


Figure 5 from Walenga et al. (2019)

Example: Dry Powder Inhaler Formulation Change

- Question: Which batch of lactose should be selected prior to particle size distribution (PSD) testing during early product development?
- Context of Use: CFD model will predict PSD from several different batches, which may prevent unneeded repetition of in vitro PSD measurements.
- Model Risk: Decision consequence is low, and model influence is medium, so model risk is low-medium.

Example: Justify Bioequivalence (BE) approach not including a PD Study

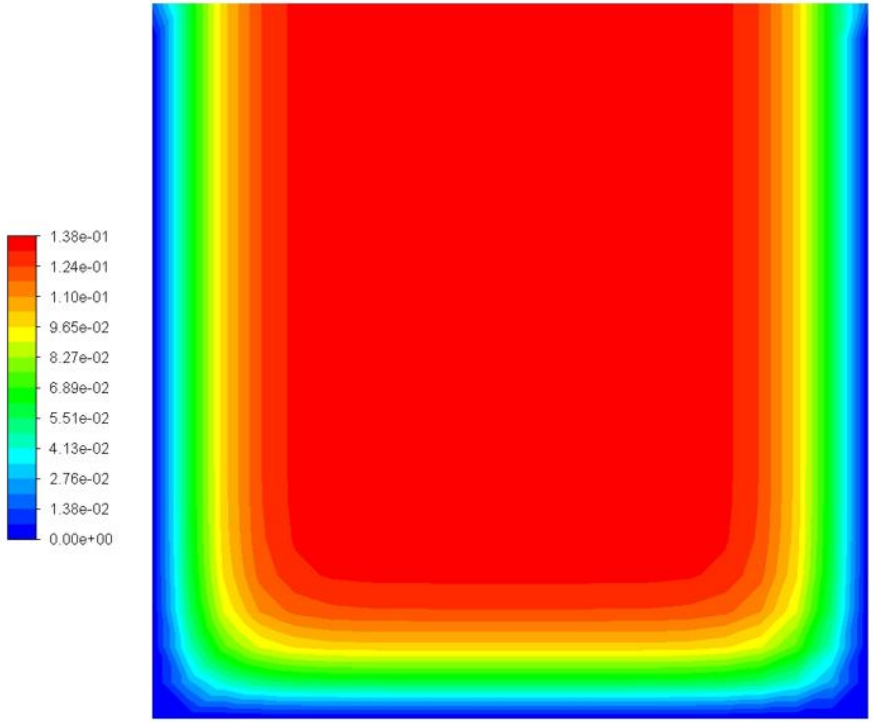
- Question: Is a PD study needed to establish BE for a generic orally inhaled drug product (OIDP)?
- Context of Use: CFD model will predict deposition and physiologically-based pharmacokinetic (PBPK) model will predict drug absorption of OIDP with the ability to capture device and formulation differences. Modeling efforts will establish that in vivo pharmacokinetic and in vitro studies are sufficient to establish BE.
- Model Risk: Decision consequence is high, and model influence is high, so model risk is high-high.

Credibility Factors

- Verification
  - Code
    - Software Quality Assurance
    - Numerical Code Verification
  - Calculation
    - Discretization error
    - Numerical solver error
    - Use error
- Validation
  - Computational Model
  - Comparator
  - Assessment
- Applicability
  - How well does the model reflect metrics of interest?
  - How relevant are the validation activities to the context of use?

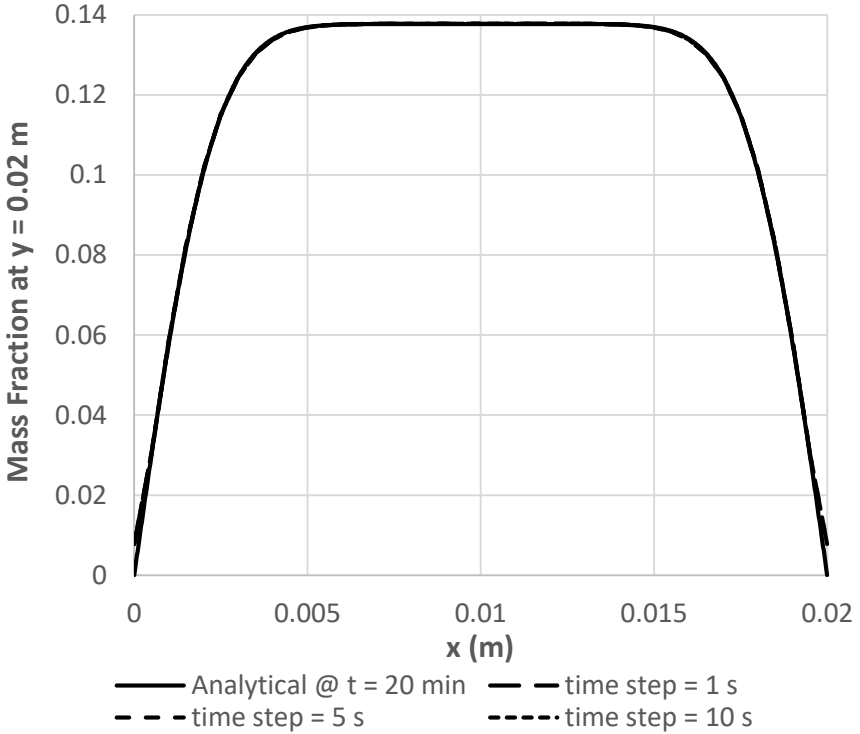
Code Verification

- Ensure adequate numerical accuracy
- Example: Passive diffusion model
- Analytical solution
  - Two dimensional
  - Bounded space (0.02 x 0.02 m)
  - Zero flux on top, zero concentration on other sides



Mass fraction, Y(x,y,t), of active ingredient 20 min after initial condition of Y(x,y,0) = 0.1378 is set, with diffusion coefficient of 1.36e-9 m^2/s.

Code Verification Results

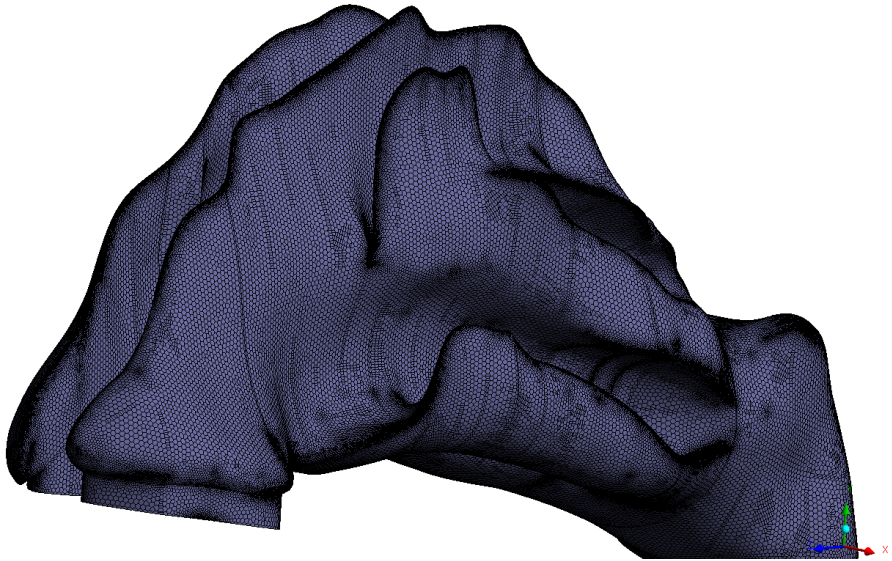


Mass fraction of active ingredient after 20 min, Y(x,H,20 min), with diffusion coefficient of 1.36e-9 m^2/s and mesh size of 1600 cells.

- Top side drug mass fraction
- Variables
  - Diffusion coefficient (1.36e-9, 1.36e-10, 1.36e-11 m^2/s)
  - Mesh size (400 vs. 1600 cells)
  - Time step (1, 5, 10 s)
- Concluded that smaller mesh size was adequate for relevant diffusion coefficient.

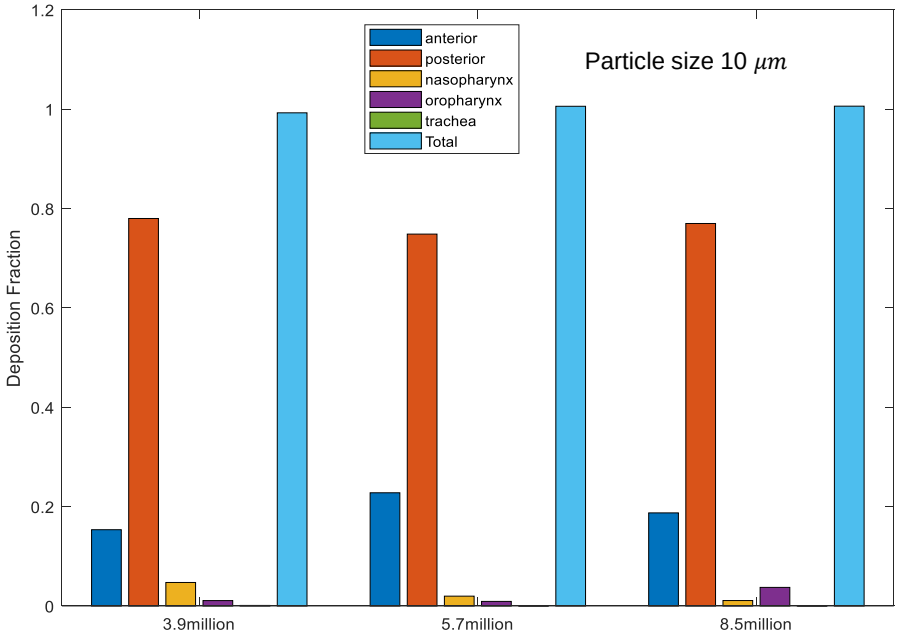
Calculation Verification

- Ensure discretization error does not significantly affect results
  - Spatial
  - Temporal
- Gradually increase discretization resolution until metric of interest does not change
  - Pre-specified tolerance



Nasal mesh, provided courtesy of Arun Kolanjiyil, Worth Longest, and Laleh Golshahi of Virginia Commonwealth University (VCU) for contract #HHSF223201810144C.

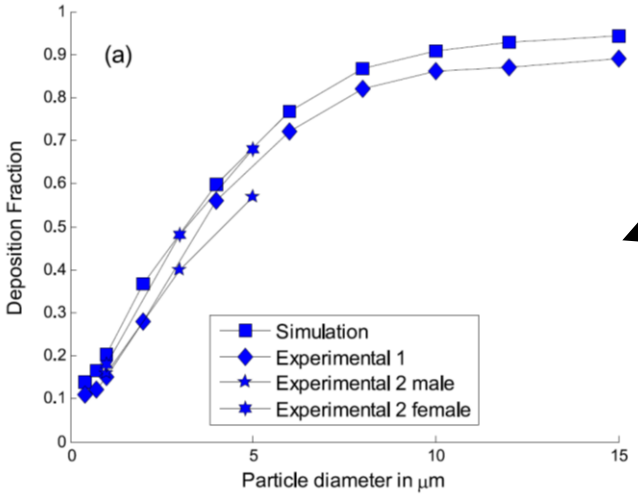
Calculation Verification Results



Nasal mesh sensitivity results for regional deposition fraction, provided courtesy of VCU for contract #HHSF223201810144C.

- Three mesh sizes: 3.9 million, 5.7 million, and 8.5 million cells
- Regional deposition - setup similar to spray injection
- Conclusion was that for total deposition, the 5.7 million cell mesh is adequate
- However, local mesh density in the anterior region (near spray tip) influences particle trajectories
- If regional deposition is of interest, a denser mesh or localized refinement may be needed

Validation

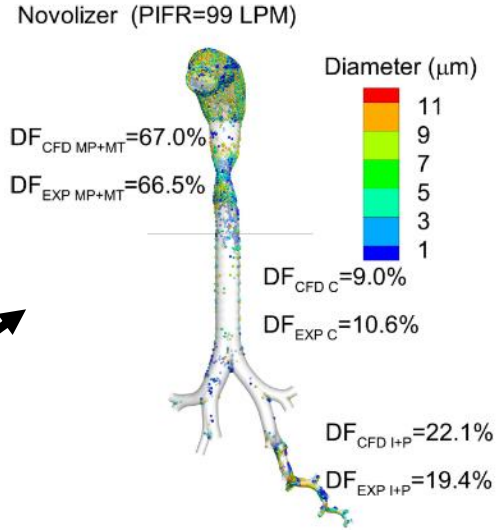


Deposition fraction prediction of general aerosol in realistic mouth-throat and lung geometry, compared with in vitro data from Heyder et al. (1986) and Kim and Hu (2006), from Figure 7a of Kolanjiyil and Kleinstreuer (2016).

In vitro: deposition in rapid prototyped model

In vivo: radiolabeled aerosol with gamma scintigraphy

Uncertainty quantification for either approach



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

Conclusions

- CFD may be useful for product development and alternative BE approaches.
- ASME V&V 40 is a risk-based standard that may be useful for establishing model credibility.
- Verification and Validation, as defined by ASME V&V 40, each require careful consideration for successful implementation.
- Credible models may be used to support product development and/or alternative BE pathways. Alternative BE approaches are encouraged to be discussed via the pre-ANDA meeting process.

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Ongoing Grants and Contracts

Grant/Contract	Institute	Grant or Contract No.
An Integrated Multiscale-Multiphysics Modeling Framework for Evaluation of Generic Ophthalmic Drug Products	CFD Research Corporation	HHSF223201810151C
A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs	CFD Research Corporation	HHS223201810182C
Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalance and Nasal Deposition In Silico and In Vitro	Virginia Commonwealth University	HHS223201810144C
A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways	University of Iowa	1U01FD005837
Modeling Complex Particle Interactions in Dry Powder Inhaler Based Drug Delivery	Princeton University	1U01FD006514
Development of Computational Models to Predict Delivery of Inhalation Drug Powders: From Deagglomeration in Devices to Deposition in Airways	University of Sydney	1U01FD006525
Nasal Mucociliary Clearance affecting local Drug-absorption in Subject-specific Geometries	North Carolina State University	1U01FD006537


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