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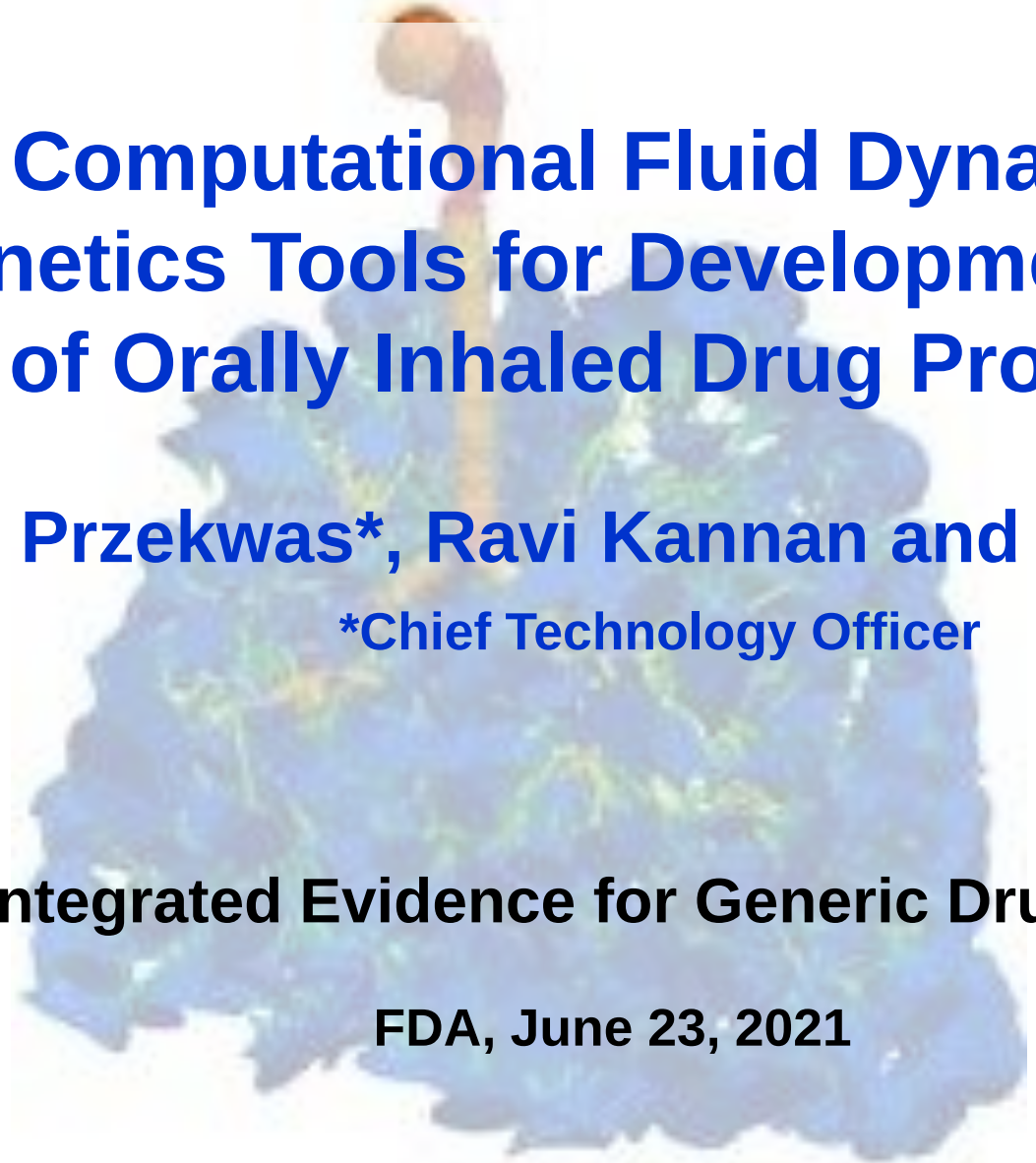

Integrated Computational Fluid Dynamics-Physiology-Pharmacokinetics Tools for Development and Evaluation of Orally Inhaled Drug Products

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***Chief Technology Officer**

Model-Integrated Evidence for Generic Drug Development

FDA, June 23, 2021

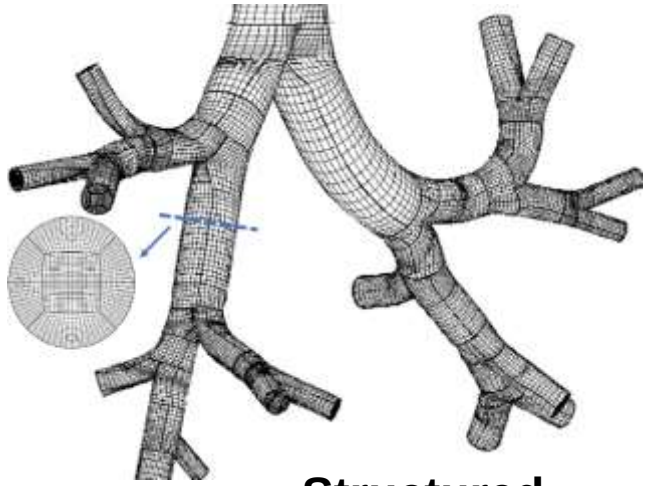
Outline

- CFD in generic dug (GD) development
- Multiscale CFD-PBPK pipeline
- Generation of human airway model
- Bioaerosol inhalation/deposition model: E-L or E-E?
- Q3D airway barrier model
- PBPK
- CFD-PBPK Validation
- Summary, Recommendations

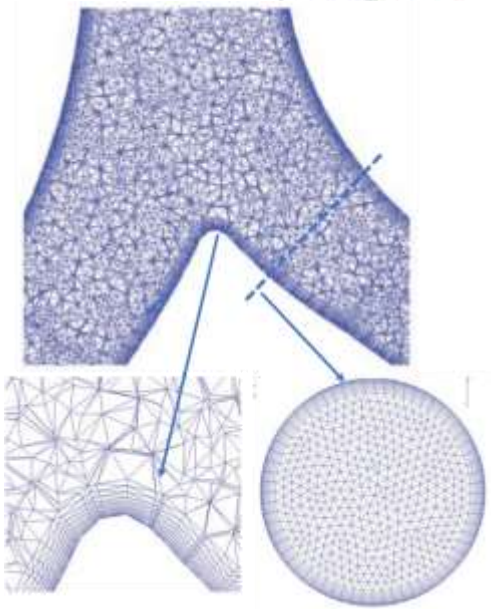
Computational Fluid Dynamics (CFD)

CFD software tools solve 3D Navier-Stokes equations along with species and particle transport

- Geometry represented as mesh
- Airway meshing – not trivial



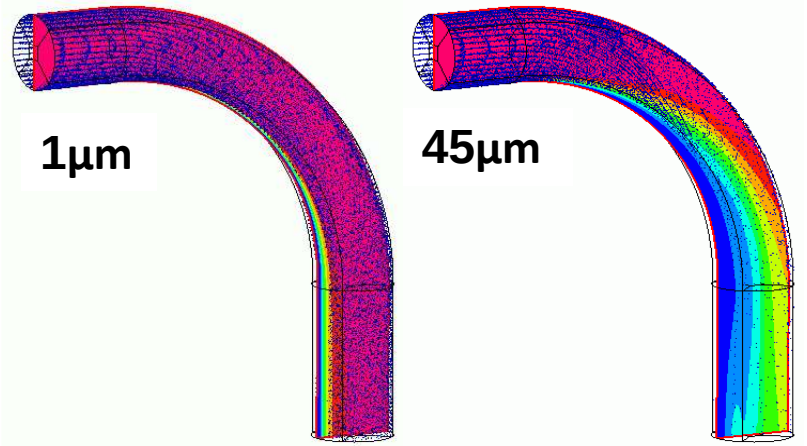
Structured



Unstructured

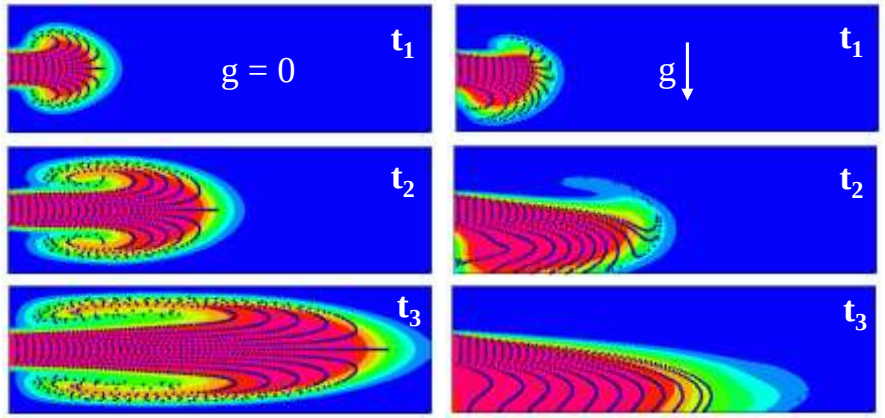
CFD Particle transport models

- **Euler-Lagrange (E-L)- tracks individual particles**
- **Euler-Euler (E-E) - solves particle concentration transport equations**



• • • E-L

E-E



CFD in Generic Drug (GD) Development

- **Inhaler device - drug particles emission**

  formulation, velocity profile, PSD (impactor), API release, …

- **In vitro dissolution-permeation**

  biophysics models with minimum or no calibration

- **In vitro mucosal barrier (lung-on-chip)**

- **Aerosol inhalation and airway wall deposition (sec)**

  CFD model validation on airway phantoms for **DPI** vs **MDI**

- **Airway barrier (transport) model (min)**

  Particle dissolution, escalator, transport, binding, systemic

- **Multiscale Barrier-PBPK model (hrs)**

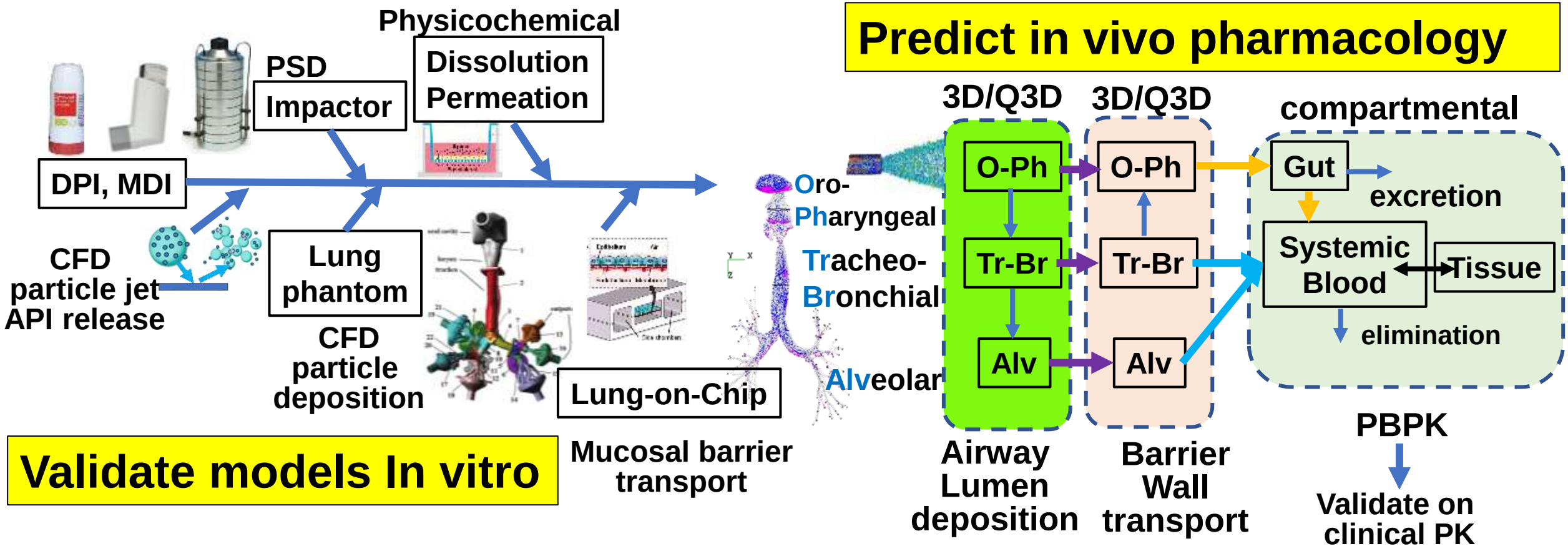
  lung barrier ↔ blood

DPI- Dry Powder Inhaler
- Breath actuated

MDI- Metered Dose Inhaler
- Pressure activated

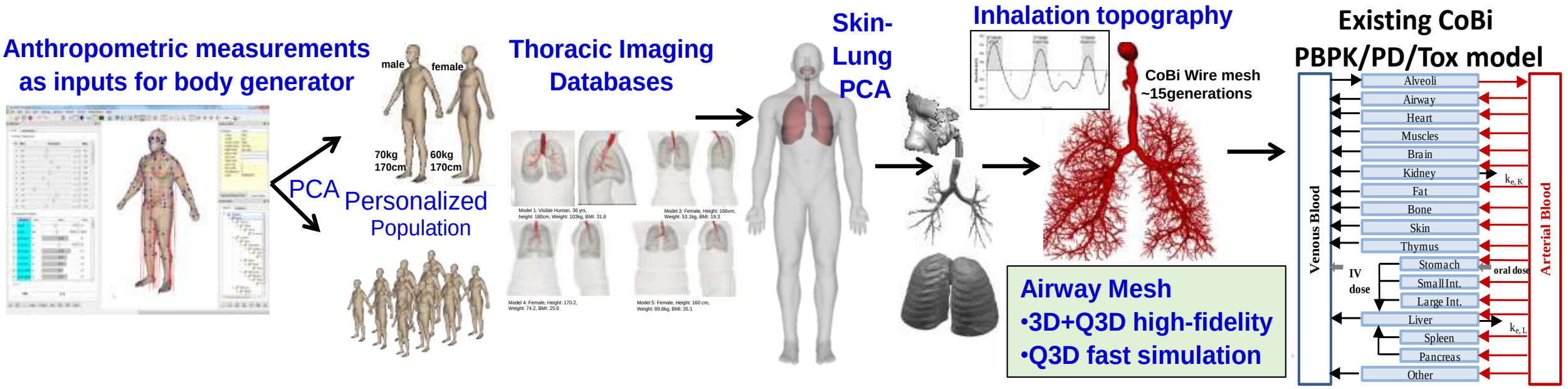
Multiscale CFD - PBPK pipeline

- **Can in vitro validated CFD model linked to PBPK predict inhaled drug lung tissue and systemic PK?**



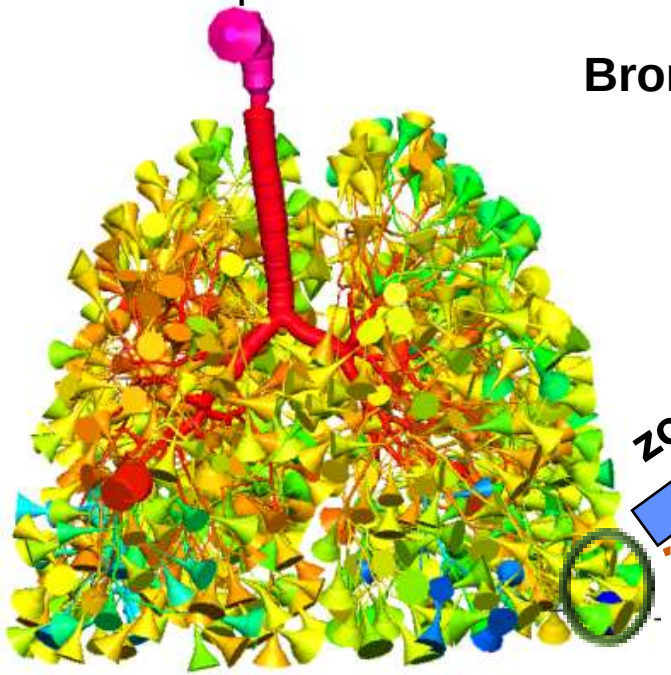
Generation of human airway model

- **Huge variability of human respiratory system - airway size, shape, morphology, physiology, disease status**
- **Population Inhalation-deposition model needed**
- **Anthropometry + Spirometry based airway model can be generated**



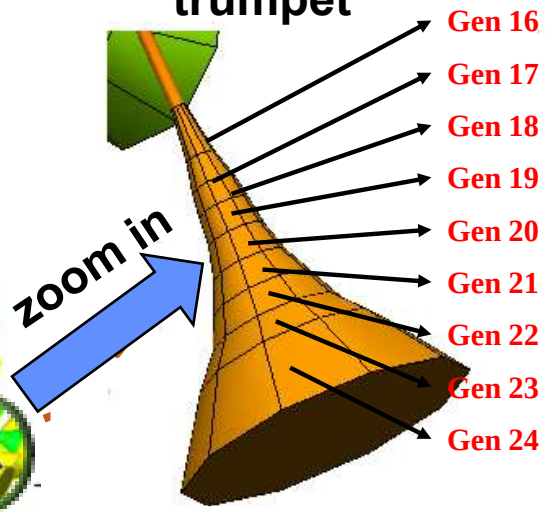
Bioaerosol inhalation/deposition model E-L or E-E

- **CoBi whole-body airway model**
  - Multiple lung anatomy models available
- **E-L:** particle inertia (++), dispersion (--), large number ~10^7 of particles needed, computationally slow (explicit)
- **E-E:** particle inertia (--), dispersion (++), fast implicit solution of particle concentration equations

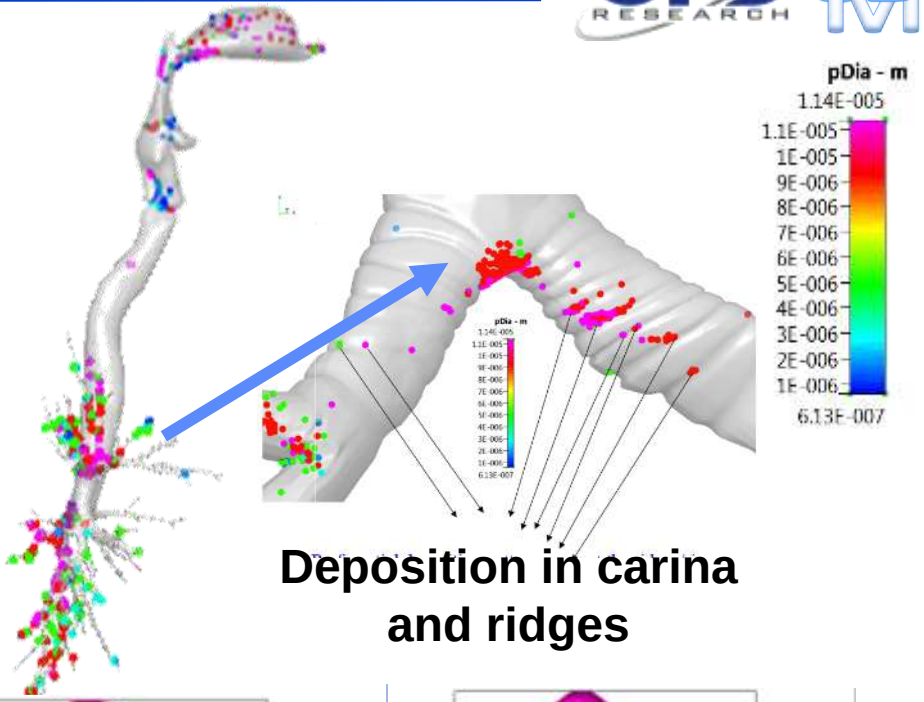


Q3D E-E whole lung deposition

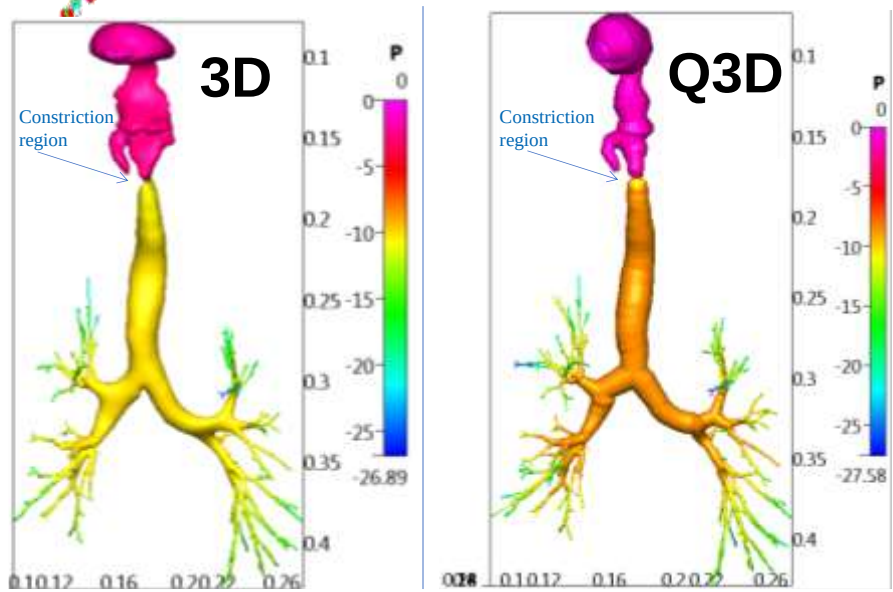
Bronchial tree termination "trumpet"



Q3D E-E alveolar deposition



Deposition in carina and ridges



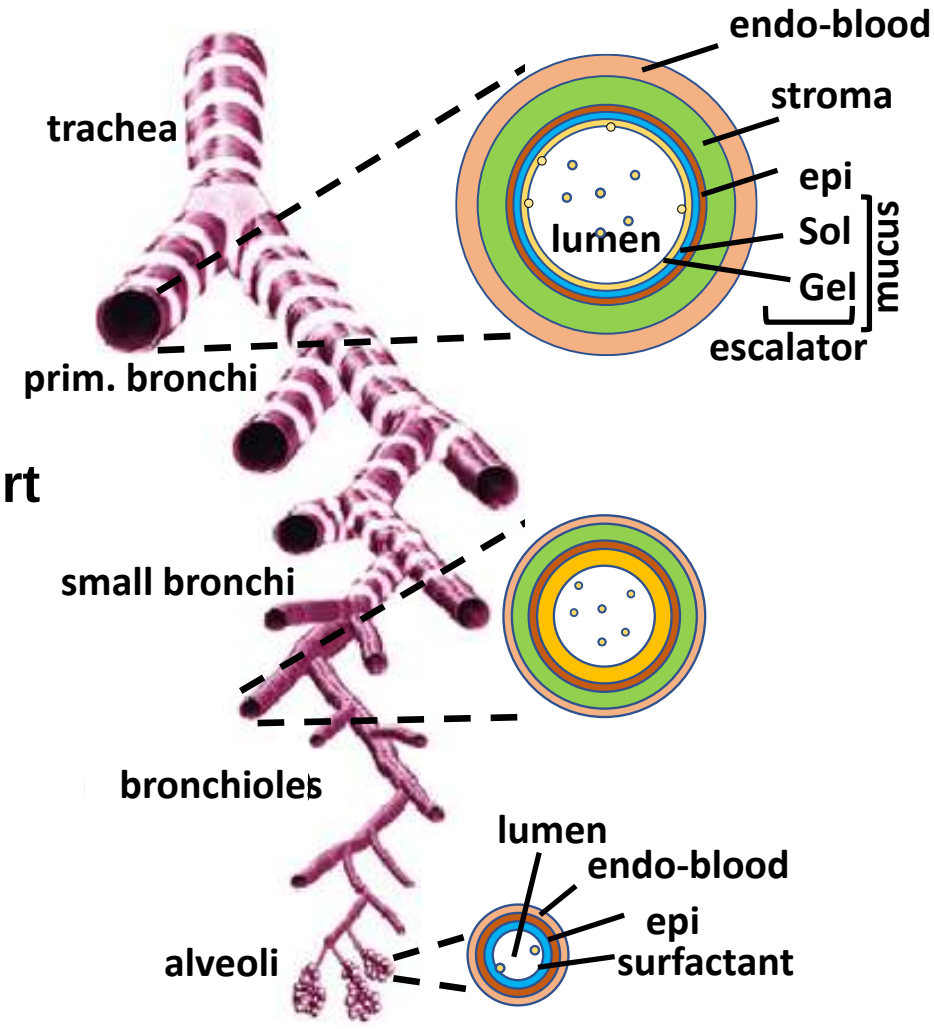
Q3D airway barrier model

- **The Q3D airway tree wall subdivided**
  - axially into large number of cells,
  - radially into serval layers (variable thickness/morphology)

- **Deposited particles dissolve in mucus, undergo mucociliary clearance into GIT, and trans-mucosal transport**

- **Dissolved API crosses all layers, binds to targets, absorbed to systemic circulation**
  - Spatial-temporal drug distribution in the lung wall barrier

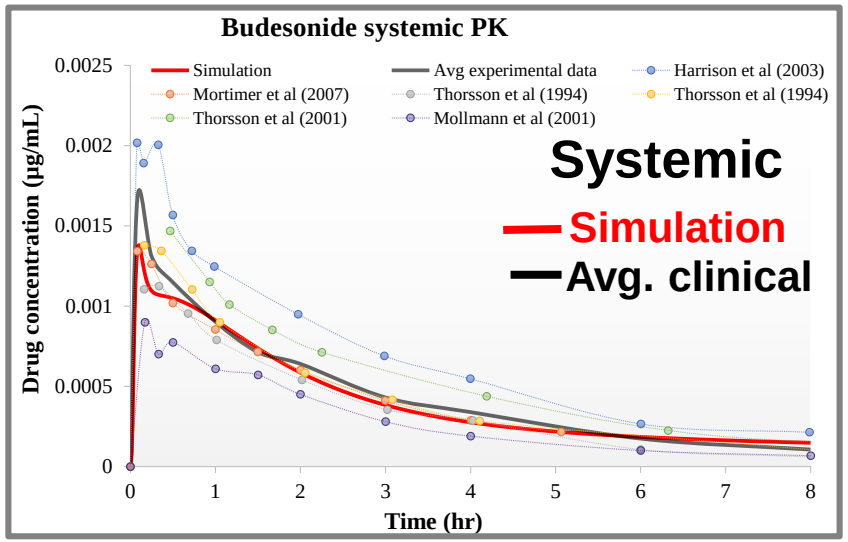
- **Barrier model linked to whole body PBPK**

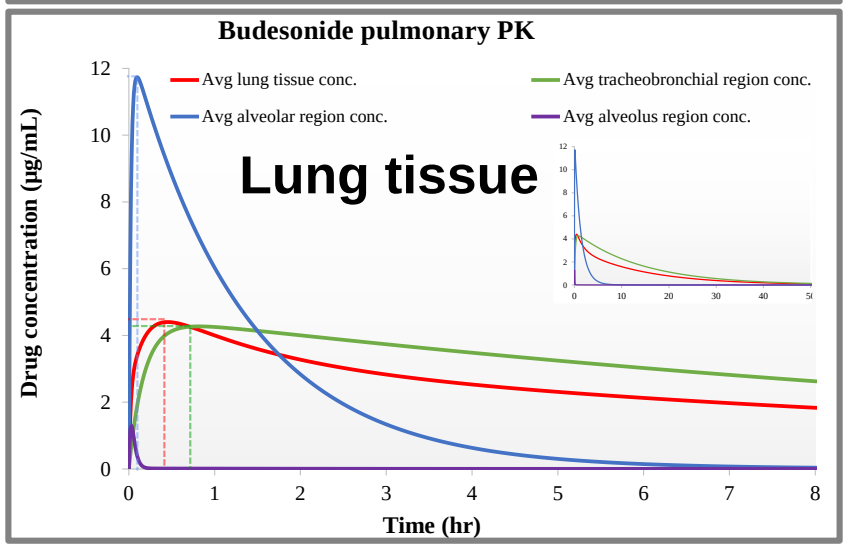


OIDP: CFD-PBPK Corticosteroid Validation

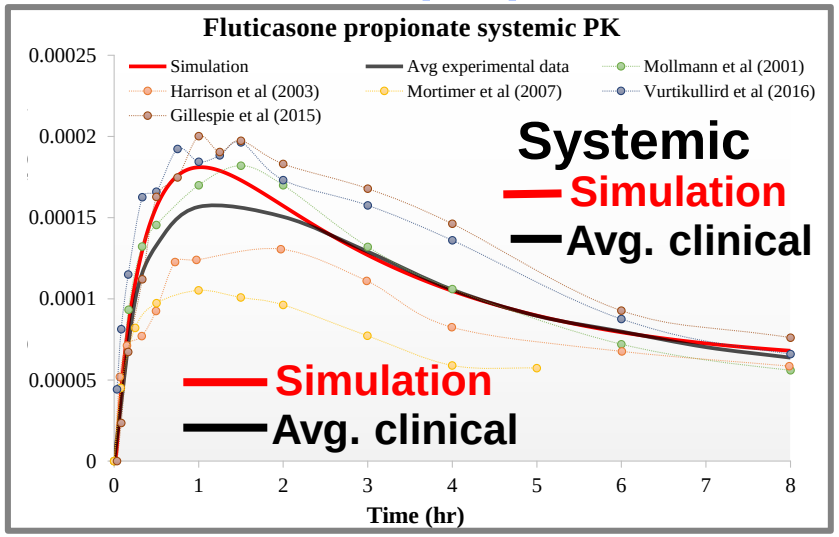
- **Budesonide (high soluble) and Fluticasone (practically insoluble)**

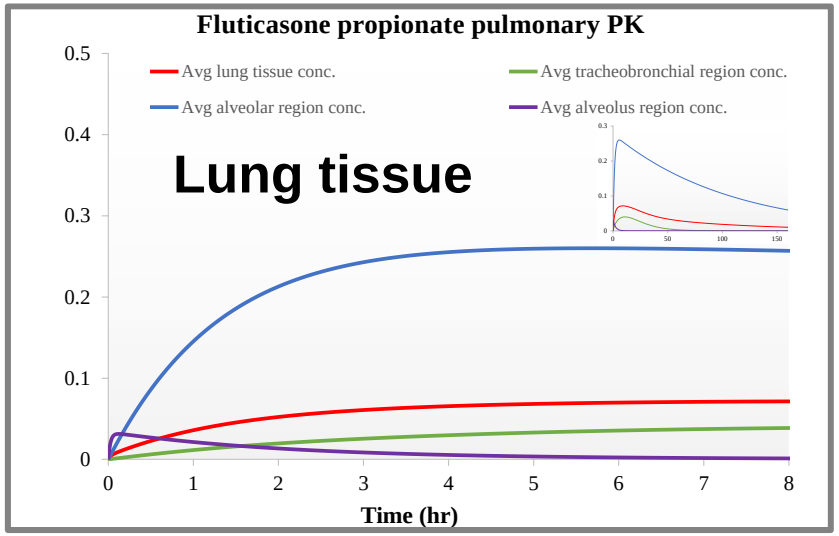
Budesonide



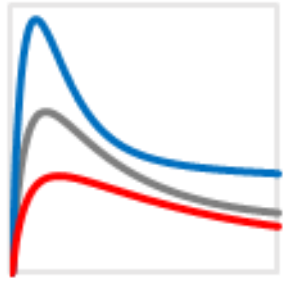


Fluticasone propionate

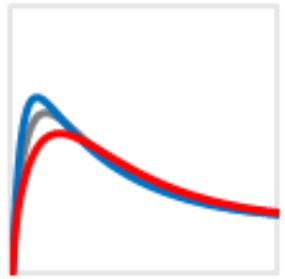




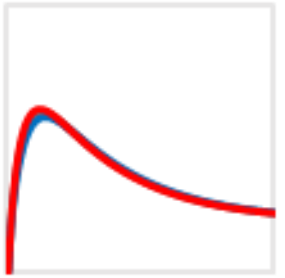
Rapid parameter sensitivity assessment



logP



B2P ratio



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Summary and Recommendations

- **CFD-based models of in vitro devices needed for development of OIDP**
- **Validation protocols on in vitro data for:**
  - aerosolization, deposition, dissolution, permeability,
  - bronchi-on-chip, alveoli-on chip devices for validation of mucosal barrier models
- **CFD tools enable simulation of in vivo deposition, dissolution and absorption of OIDPs**
- **Predictive capabilities still need to be validated**
- **CFD-PBPK simulates drug distribution between systemic and lung tissue**
  - spatially resolved entire airway wall barrier feasible
- **CFD-PBPK model needs further validation on clinical data for innovator OIDPs**
  - novel methods data collection: pulmonary imaging, biomarkers, …