

**Session 6a:
FDA Town Hall Update: Modeling and Simulation in
GDUFA Regulatory Science Program**

**Chairs:
Lanyan (Lucy) Fang (FDA), Lei Zhang (FDA)**

**A predictive multiscale computational tool for simulation of lung absorption
and pharmacokinetics and optimization of pulmonary drug delivery**

Narender Singh (CFDRC)

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- ***FDA:** 2014-2017 (1U01FD005214-01/03), Drs. Peng Guo (PI), Narender Singh (PI)
Modeling-based optimization of pulmonary drug delivery
- **NIH:** 2016-2018 (1R43GM108380-01), Dr. Andrzej Przekwas (PI)
A mechanism-based computational tool to optimize pulmonary drug delivery
- **Merck:** 2016-Current, (Multiple), Dr. Andrzej Przekwas (PI)
- **FDA:** 2018-2021 (HHSF223201810182C), Dr. Narender Singh (PI)
A multiscale computational framework for bioequivalence of orally inhaled drugs

References:

- A Quasi-3D compartmental multi-scale approach to detect & quantify diseased regional lung constriction using spirometry data. *IJNMBE, 2018*
- A compartment-quasi-3D multiscale approach for drug absorption, transport, and retention in the human lungs. *IJNMBE, 2017*
- A quasi-3D wire approach to model pulmonary airflow in human airways. *IJNMBE, 2017*
- Pharmaceutical aerosols deposition patterns from a DPI. *Medical Eng & Phy, 2017*
- Particle transport in the human respiratory tract. *IJNMBE, 2015*
- A predictive multiscale computational tool to simulate pulmonary drug delivery. *AAPS Annual Meeting & Exposition, 2017*
- Anthropometry & anatomy-based tools for generation of personalized human respiratory model... *European Aerosol Conference, 2017*
- A multiscale framework for computational inhalation pharmacology. *2nd International Conference on Respiratory and Pulmonary Medicine, 2016*

The Need: OINDP (Orally inhaled & nasal drug products)



OINDPs: Deliver drug(s) to the site of action through inhalation

Thou shalt inhale: Ancient practice. Alkaloids (atropium, 1500BC), Opium (1100BC),...Inhaled epinephrine (1929)

Asthma 235 million people worldwide The most common chronic disease worldwide	COPD >200 million people worldwide Predicted to be the 3rd leading cause of death worldwide by 2030 ¹	Cystic fibrosis (CF) 70,000 people have a diagnosis of CF worldwide ³	Idiopathic pulmonary fibrosis (IPF) 3–9 cases annually per 100,000 in Europe and North America ⁶
Respiratory market size for these conditions⁴ \$28.1 billion in 2015 \$46.6 billion in 2022	Sleep disordered breathing >100 million people worldwide Acute respiratory infection 4 million deaths annually worldwide	Pneumonia is the most common serious respiratory infection, accounting for >1.3 million deaths of children under 5 years of age annually Influenza kills 250,000–500,000 people and costs \$US 71–167 billion annually	Tuberculosis 8.7 million people develop TB annually worldwide Lung cancer 1.37 million people die from lung cancer annually Most common form of cancer

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Benefits

- **Avoid degradation** in GIT and 1st pass metabolism
- **Less drug amount** (compared to oral)
- Lower dose → Fewer **side effects**
- **Suitable** for drugs that are not absorbed orally
- **Rapid** onset of action (large area of lungs)
- Patient **compliance** (painless, less intrusive)
- Better **storage**, no risk of **infection** (compared to IV)

Not limited to respiratory diseases: In past four yrs, 1350 active inhalation studies done on 802 different diseases Afrezza (inhaled insulin), Tobramycin, Relenza & Flumist (influenza), Miacalcin spray (osteoporosis),

OINDP: Effect of various factors on ADME properties



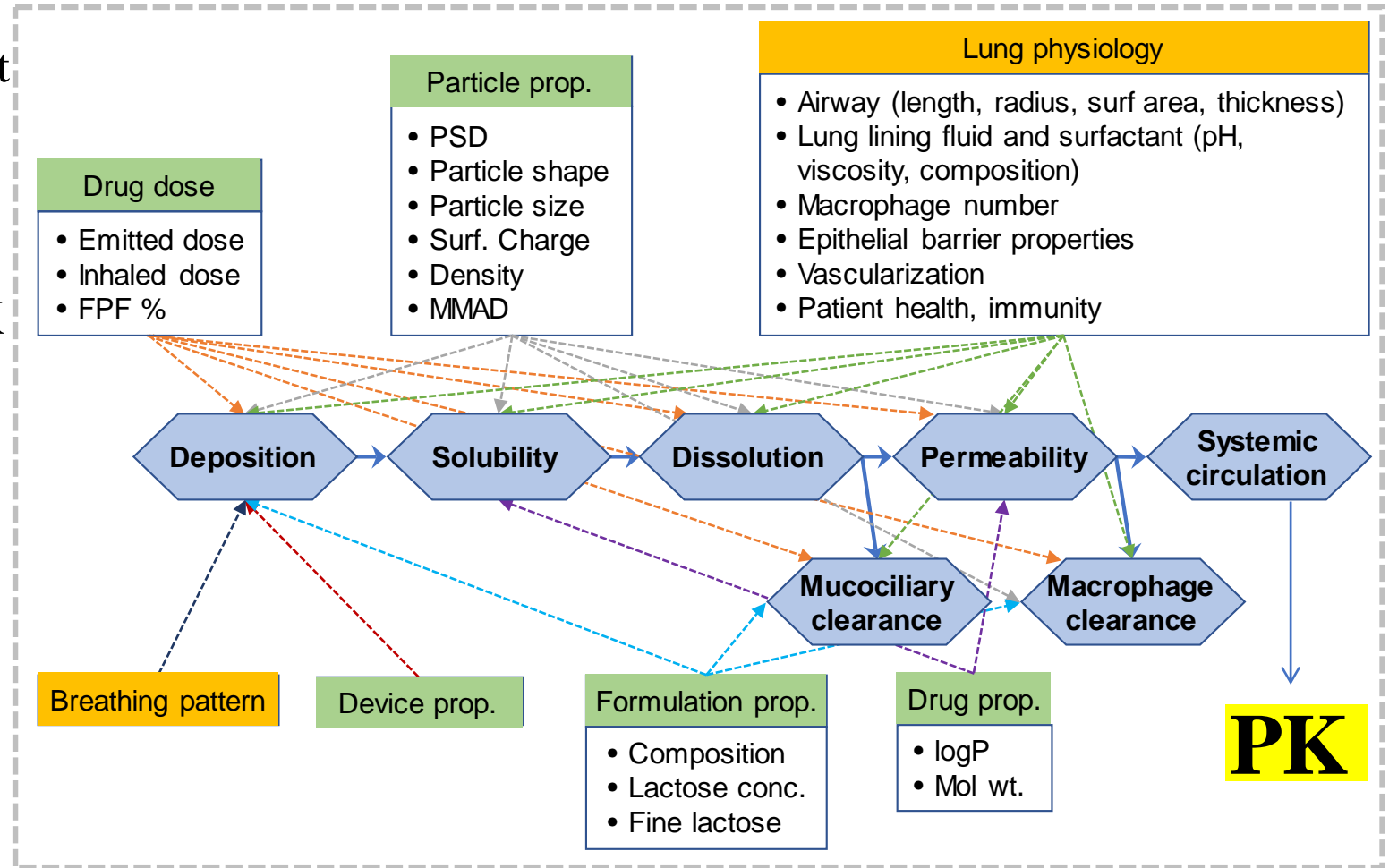
- Future **OINDP success** (new, combination, route switching & generics) depends both on device and formulation advancements, and on understand the detailed effect of OINDP parameters on human physiology/pharmacology

- **Experimentally challenging** to predict the effect of

intrinsic (body related) and

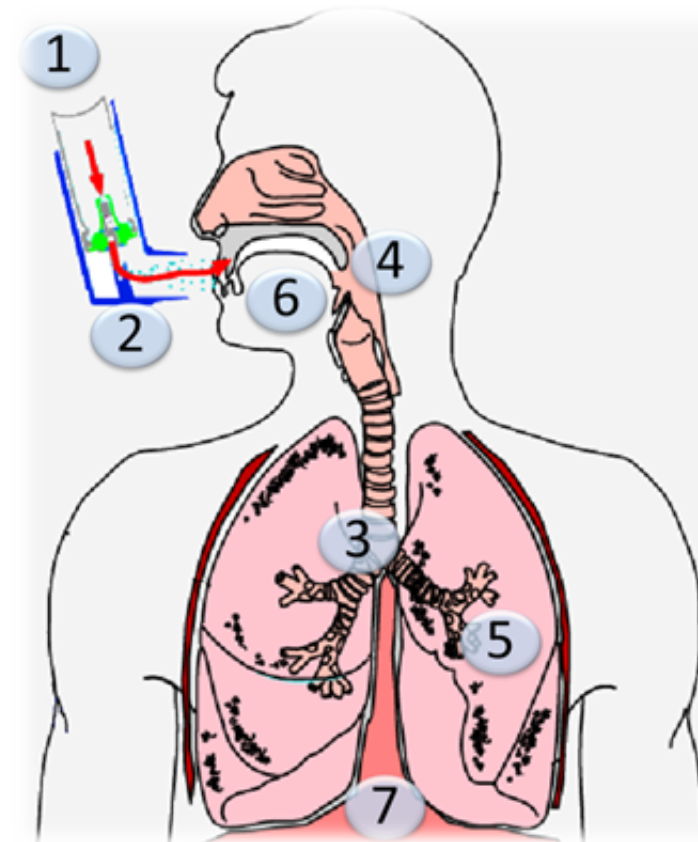
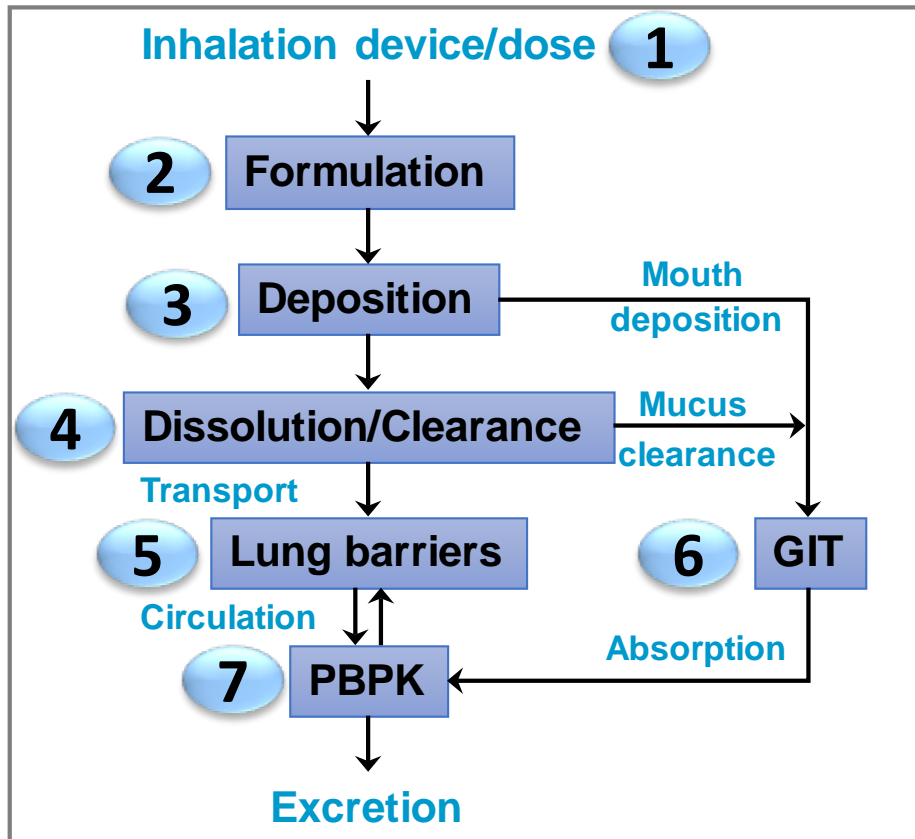
extrinsic (drug related) parameters on PK

- How can **modeling** help?

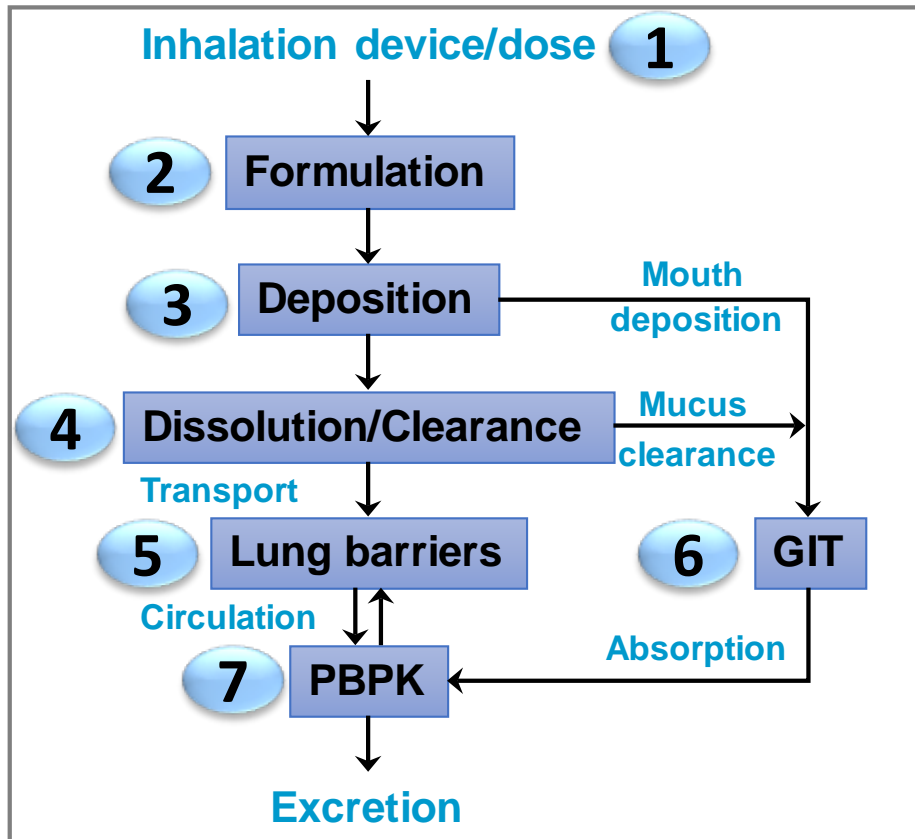


OINDP: Multiscale computational framework

Based on the physiological flow/transport of OINDPs from **inhalation** → **site of action** → **blood** we have developed an **integrated computational framework** for pulmonary drug delivery and PBPK simulations.



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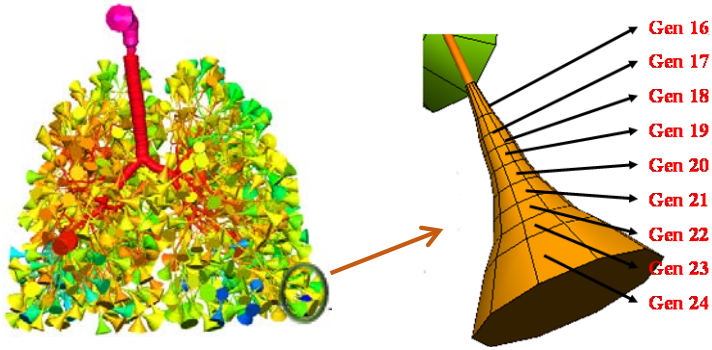
Goal to predict

- Effects of **formulation factors** on PK
 - Particle size, PSD, logP, solubility, mmad, carrier*...
- Effects of **external factors** such as charcoal ingestion
- Effects of **lung physiology**: disease vs healthy PK
- Correlate **local vs systemic** OINDP concentration (PK)
- Ultimately **support product development** → gain confidence before conducting PD BE studies

OINDP: Multiscale computational framework components (shown simplified)

Deposition

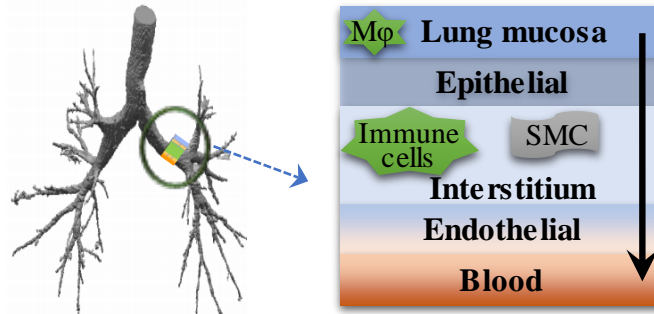
Quasi 3D Model



Under work for spatial-temporal lung deposition (10K faster than CFD)

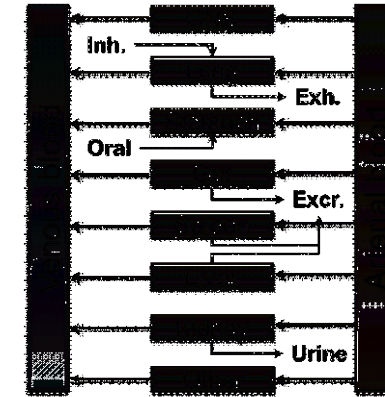
Lung barriers

Rosania barrier model



PBPK

Whole-body Physiology based



Dissolution/Clearance

$$\frac{dm}{dt} = \frac{D}{h} (C_s - C_t) S$$

(Nernst - Brunner eq)

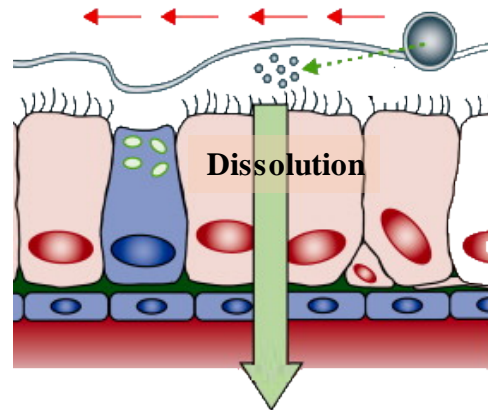
m : Solid mass @ time t
 S : SA of particles
 D : Diffusion coeff.
 h : diffusion layer thickness
 C_s : Drug solubility
 C_t : Drug conc. @ time t

$$m_v = 5.5(1 - e(-0.49621 d^{2.2694}))$$

MCC
 (Exp fit eq.)

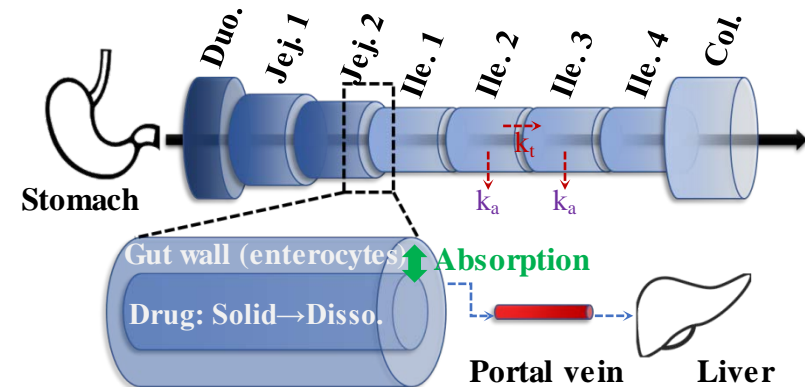
m_v : Mucus vel (mm/min)
 d : Lung gen diameter

Mucociliary clearance (MCC)



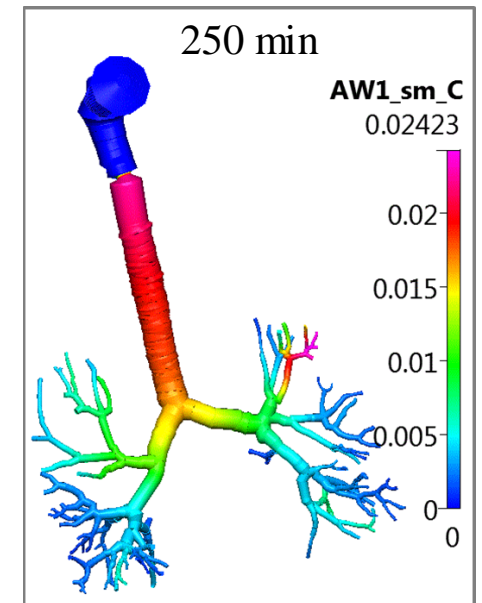
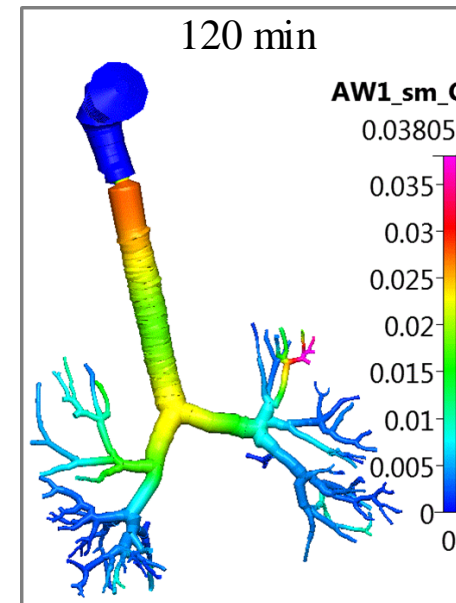
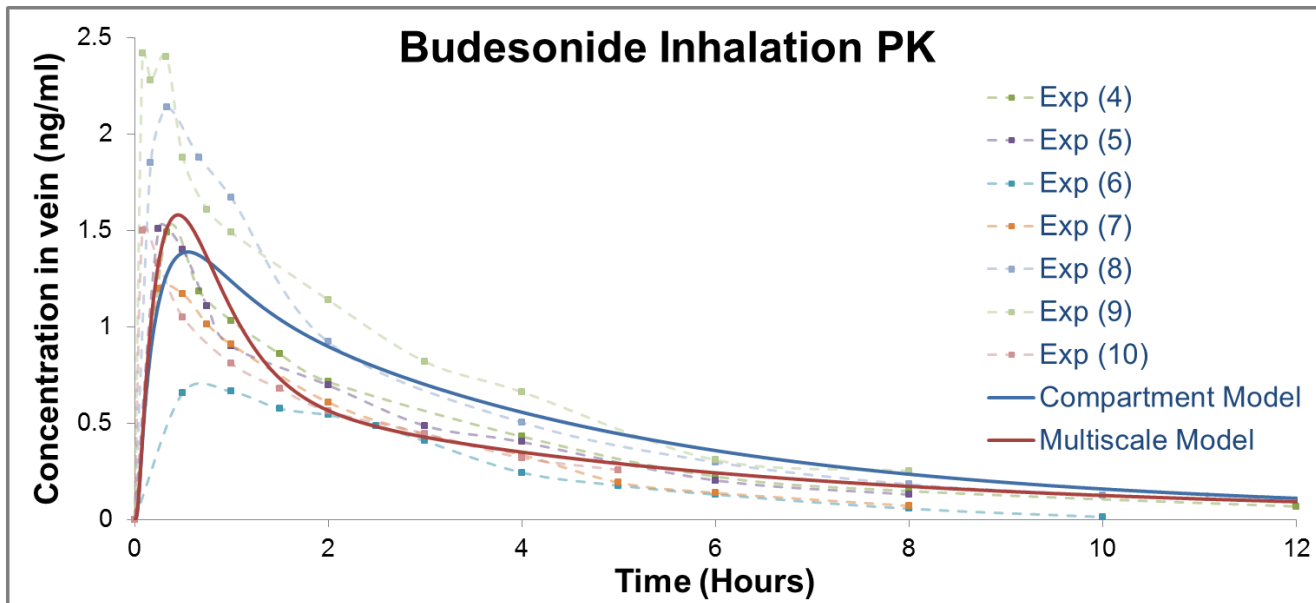
GIT

k_t : Transit rate const.
 k_a : Absorption rate cons.



- **Budesonide:** Predicted PK versus experimental PK (shown for **Compartment-based & Multiscale**)
- Our multiscale framework **can predict the spatio-temporal drug concentration in any given lung layer** (surface lining, Interstitium, & immune, endothelial, epithelial & smooth muscle cells).
- **E.g.**, concentrations shown for in **airway smooth muscle cell (AW_sm)** layers at two different time points (1mg drug inhalation dose) during simulations

Site of action for many inhalation drugs



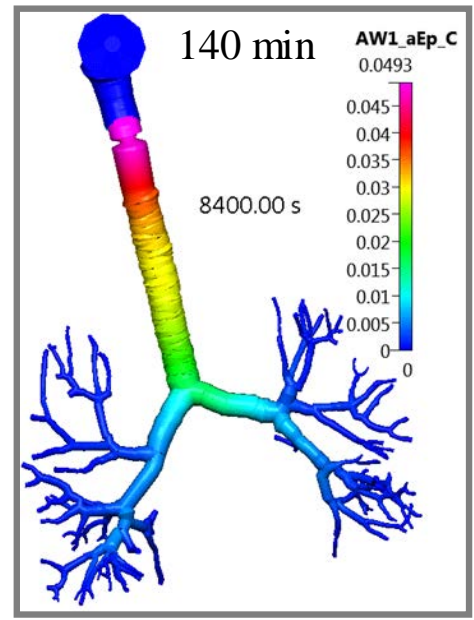
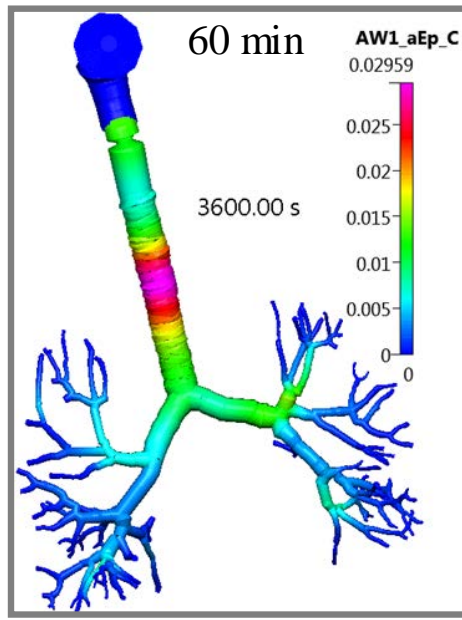
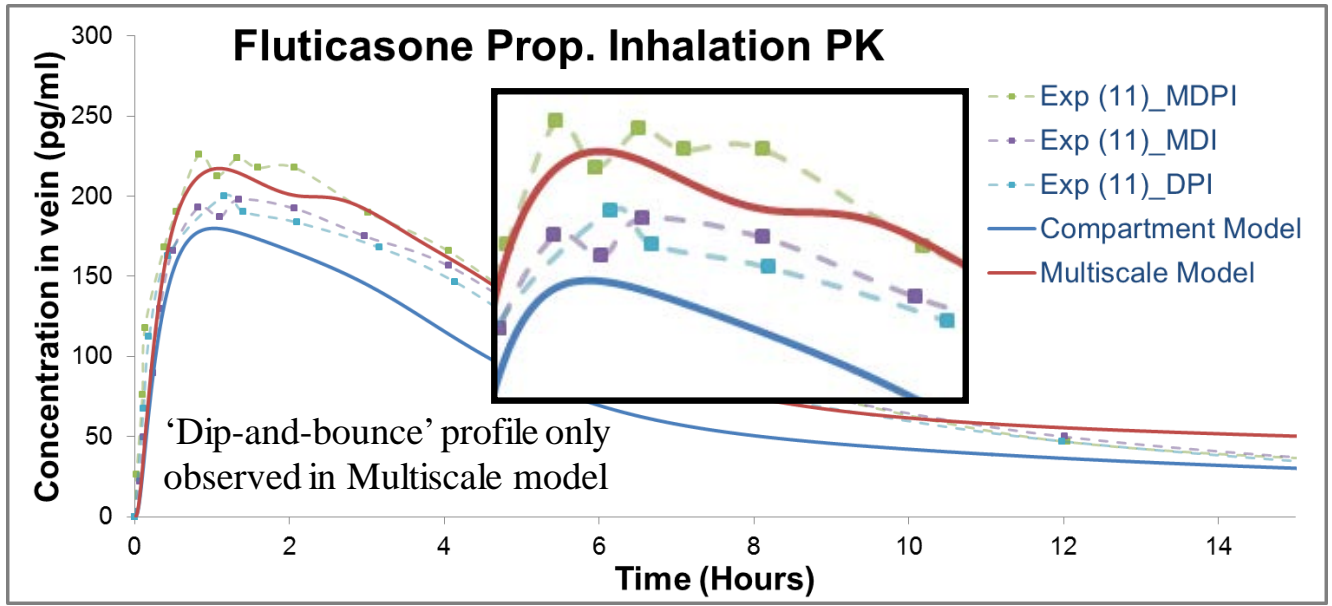
4) Thorsson, BJP, 52(5), 2001
5) Thorsson, ERJ, 7(10), 1994
6) Raaska, CPT, 72(4), 2002

7) Lahema, BJCP, 59(2), 2005
8) Dalby, RR, 10(1), 2009
9) Harrison, Thorax, 58(3), 2003

10) Mortimer, BJCP, 64(4), 2007
11) Vutikullird, JAMPDD, 29(2), 2015

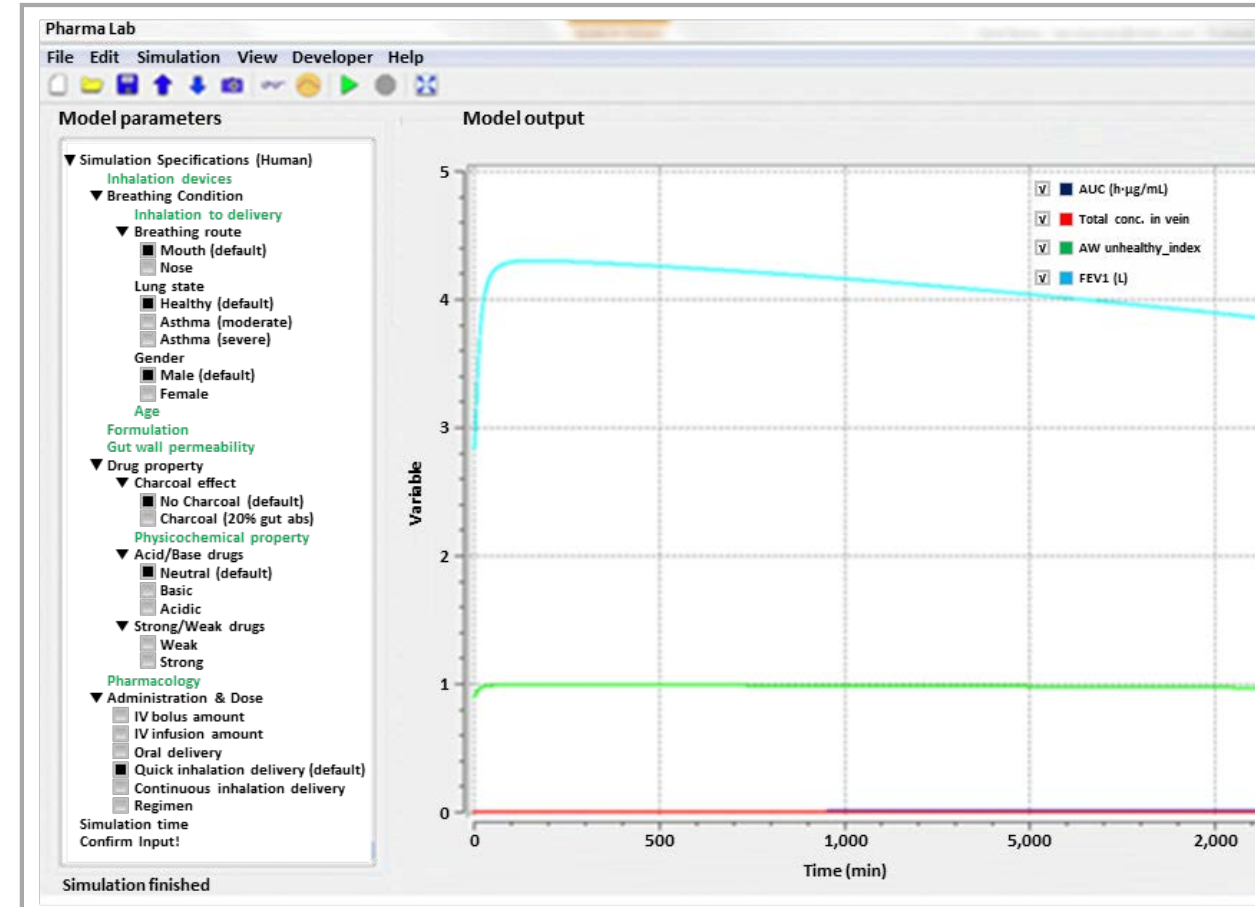
- **Fluticasone Prop:** Predicted PK versus experimental PK (shown for **Compartment-based & Multiscale**)
- Our multiscale framework **can predict the spatio-temporal drug concentration in any given lung layer** (surface lining, Interstitium, & immune, endothelial, epithelial & smooth muscle cells).
- **E.g.**, concentrations shown for in **airway apical epithelial (mucous)** (AW_aEP) layers at two different time points (1mg drug inhalation dose) during simulations

Site of deposition in lung mucosa



4) Thorsson, BJP, 52(5), 2001
 5) Thorsson, ERJ, 7(10), 1994
 6) Raaska, CPT, 72(4), 2002
 7) Lahema, BJCP, 59(2), 2005
 8) Dalby, RR, 10(1), 2009
 9) Harrison, Thorax, 58(3), 2003
 10) Mortimer, BJCP, 64(4), 2007
 11) Vutikullird, JAMPDD, 29(2), 2015

- Our approach can be efficiently used to **predict inhaled drugs PK profiles at multiple lung sites** (e.g. shown for airways epithelial and smooth muscle cells)
- Approach can be **successfully applied** in: Dose optimization, effect of drug's physiochemical properties (logP, mmad, etc.), and ultimately device design and generic drug formulations
- Reduced diameters/thickened mucosa of the lung have been used to model **diseased state PK**
- Models have been integrated in an interactive **GUI interface**



Thank You

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