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

Narender Singh (CFDRC)

CFDRC: Inhalation Pharmacology Modeling Framework

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)

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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), …..

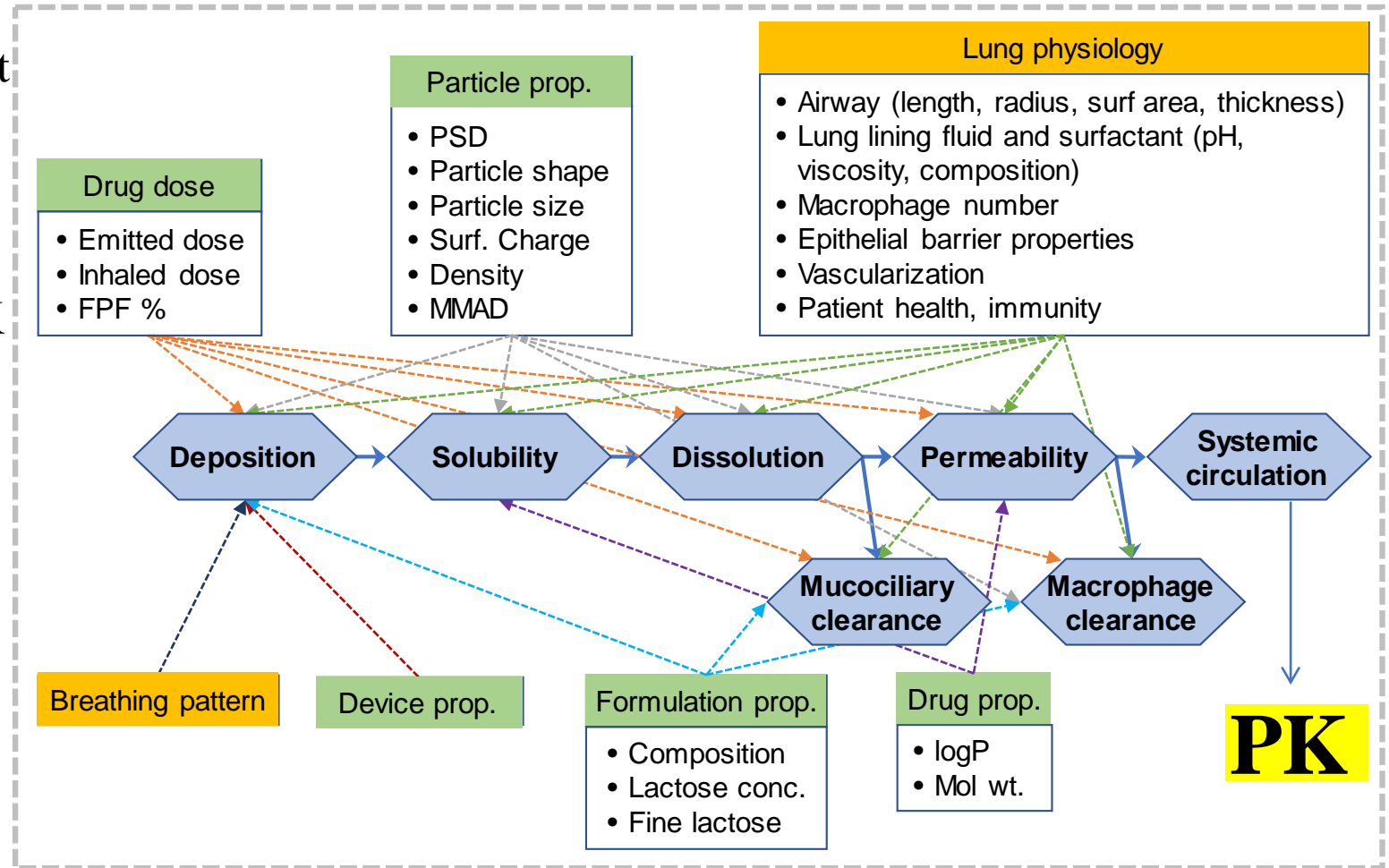# OINDP: Effect of various factors on ADME properties

- 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?

Lung physiology
- Airway (length, radius, surf area, thickness)
- Lung lining fluid and surfactant (pH, viscosity, composition)
- Macrophage number
- Epithelial barrier properties
- Vascularization
- Patient health, immunity

Particle prop.
- PSD
- Particle shape
- Particle size
- Surf. Charge
- Density
- MMAD

Drug dose
- Emitted dose
- Inhaled dose
- FPF %

Deposition → Solubility → Dissolution → Permeability → Systemic circulation

Mucociliary clearance → Macrophage clearance

Breathing pattern

Device prop.

Formulation prop.
- Composition
- Lactose conc.
- Fine lactose

Drug prop.
- logP
- Mol wt.

PK

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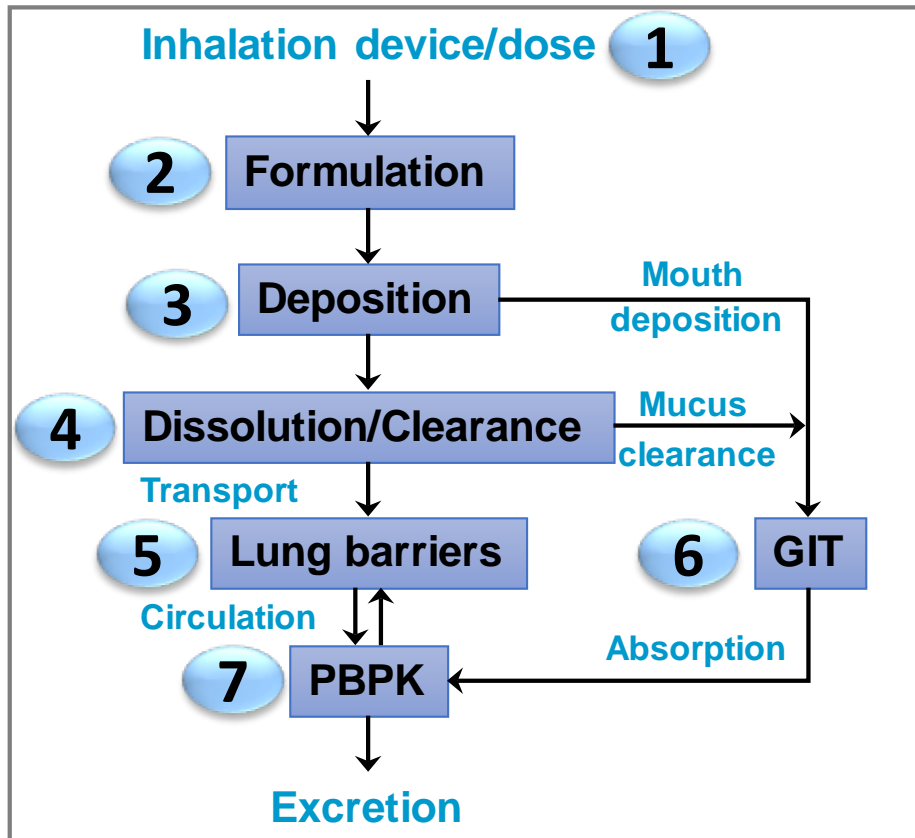
OINDP: Multiscale computational framework
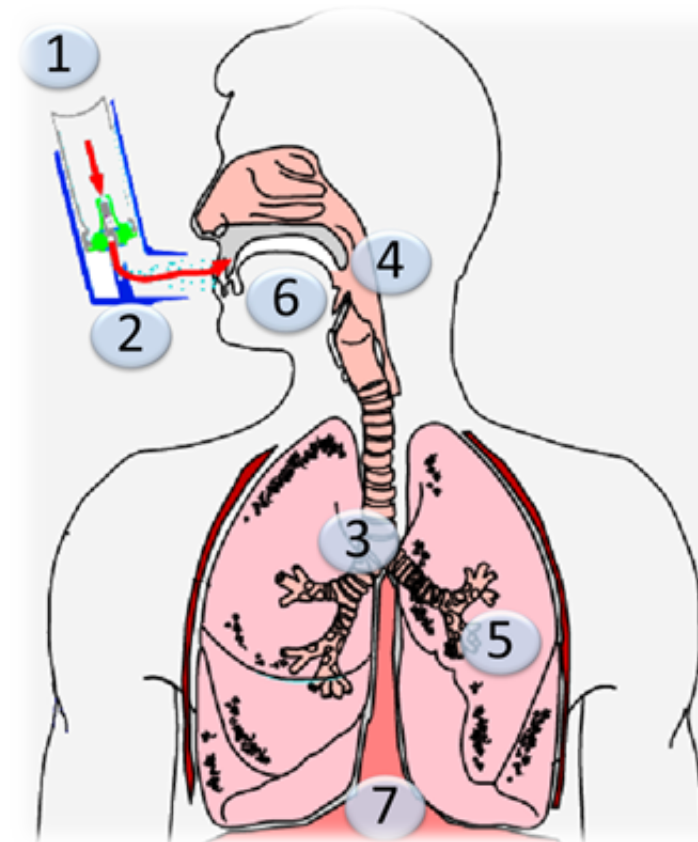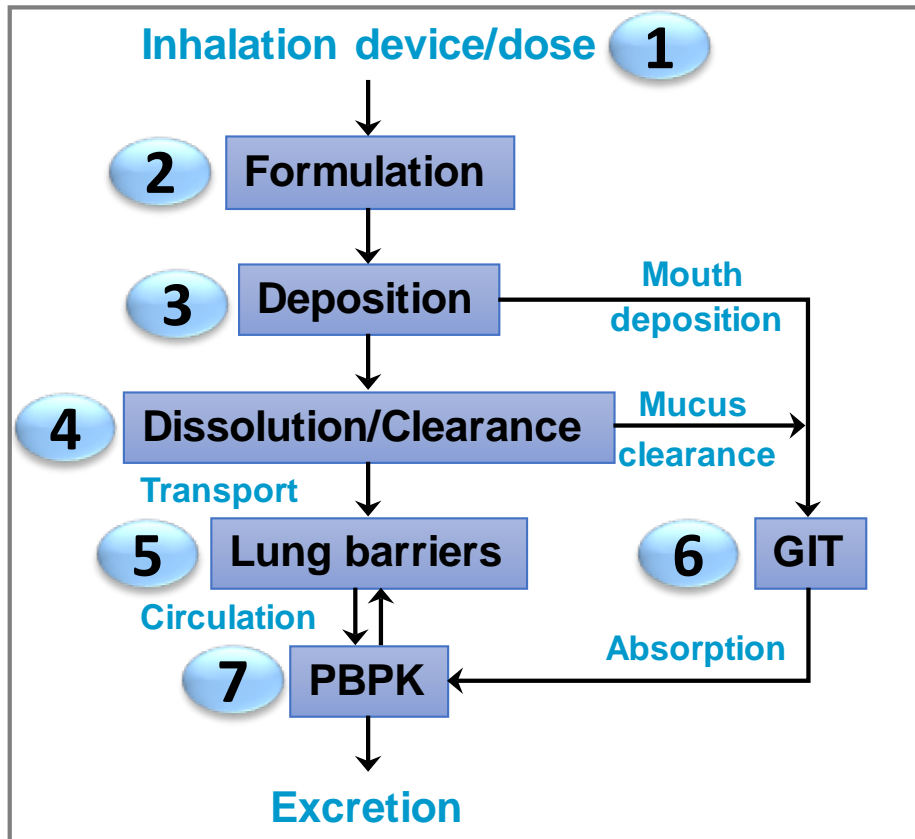
Based on the physiological flow/transport of OINDPs from **<u>inhalation → site of action → blood</u>** we have developed an **integrated computational framework** for pulmonary drug delivery and PBPK simulations.


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)
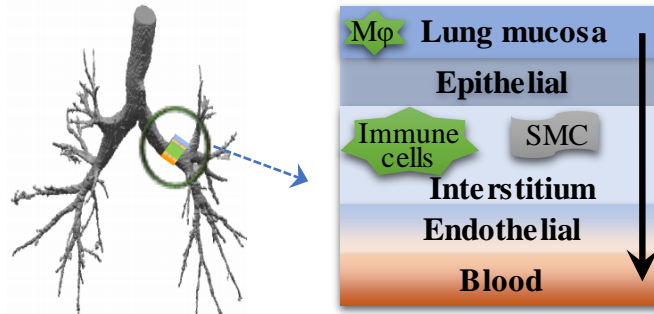
Deposition
Quasi 3D Model

Gen 16
Gen 17
Gen 18
Gen 19
Gen 20
Gen 21
Gen 22
Gen 23
Gen 24
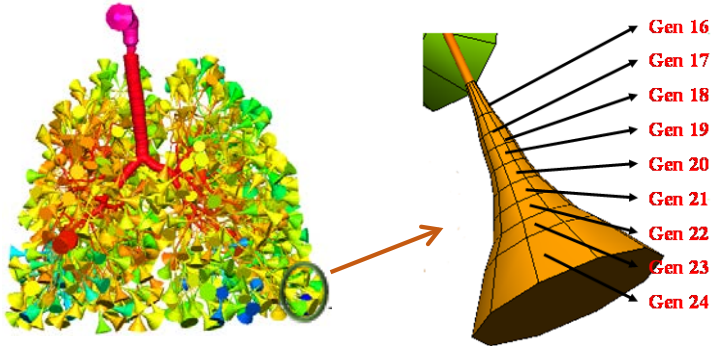
Under work for spatial-temporal lung deposition (10K faster than CFD)

Lung barriers
Rosania barrier model

Mφ — Lung mucosa
Epithelial
Immune cells — SMC
Interstitium
Endothelial
Blood

PBPK
Whole-body Physiology based

Inh.
Exh.
Oral
Excr.
Urine
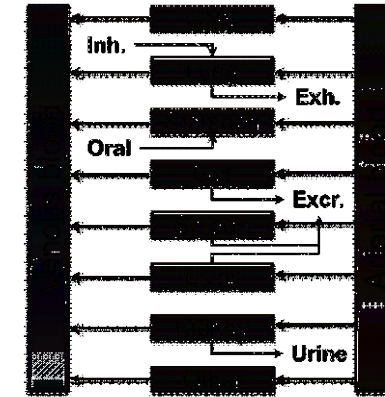
Dissolution/Clearance

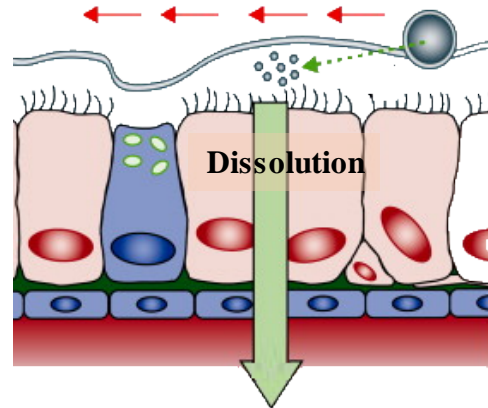$$\frac{dm}{dt} = \frac{DS}{h}*(C_s - C_t)$$

Dissolution
(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

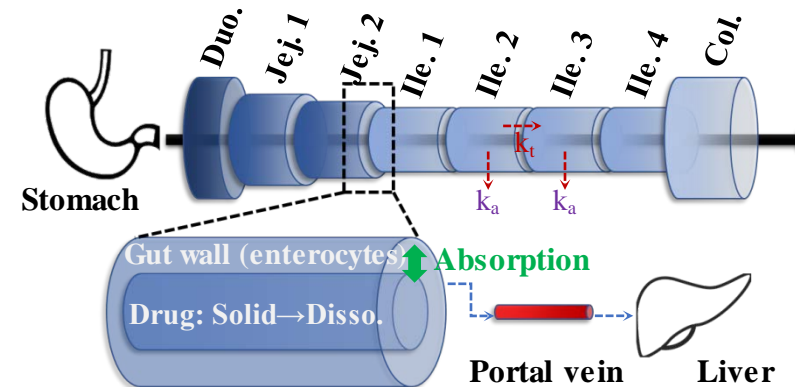$$m_v = 5.5(1 - e^{(-0.49621\, d^{2.2694})})$$

MCC
(Exp fit eq.)

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

Mucociliary clearance (MCC)


Dissolution

GIT

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

Duo. Jej. 1 Jej. 2 Ile. 1 Ile. 2 Ile. 3 Ile. 4 Col.

Stomach

k_t
k_a k_a

Gut wall (enterocytes) — Absorption
Drug: Solid→Disso.

Portal vein — Liver

- **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
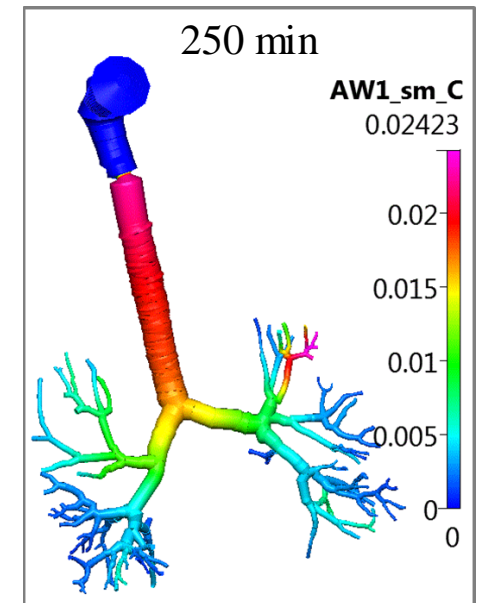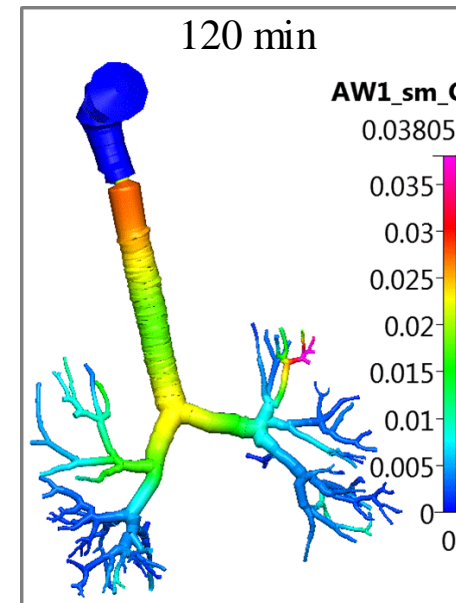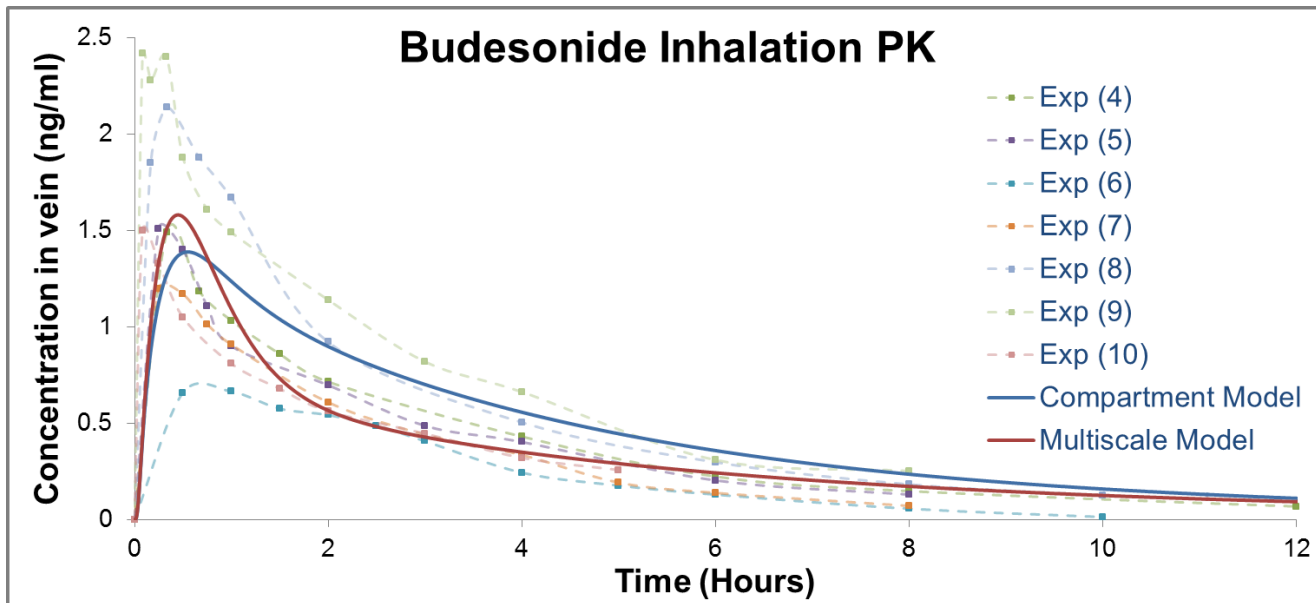
Budesonide Inhalation PK

120 min

250 min

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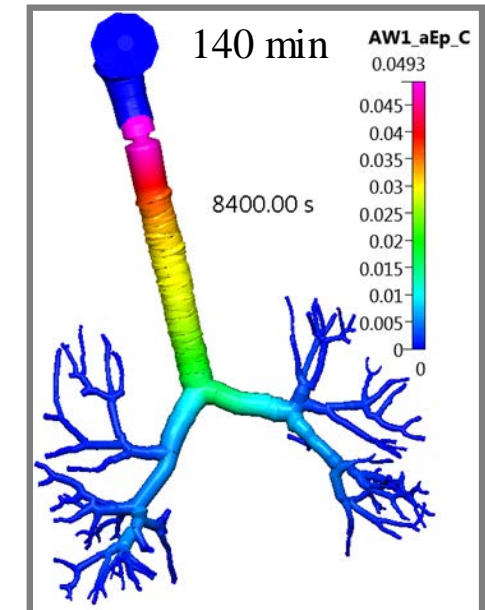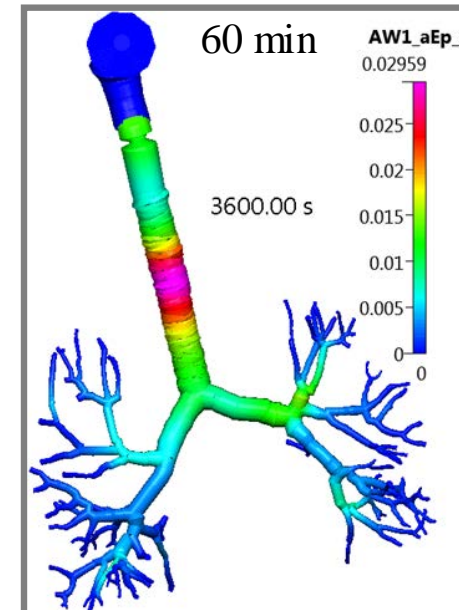7) Lahema, BJCP, 59(2), 2005
8) Dalby, RR, 10(1), 2009
9) Harrison, Thorax, 58(3), 2003
10) Mortimer, BJCP, 64(4), 2007
11) Vutikullird, JAMPDD, 29(2), 2015

- **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

Fluticasone Prop. Inhalation PK

- - - Exp (11)_MDPI
- - - Exp (11)_MDI
- - - Exp (11)_DPI
—— Compartment Model
—— Multiscale Model

'Dip-and-bounce' profile only observed in Multiscale model

60 min — 3600.00 s — AW1_aEp_C 0.02959

140 min — 8400.00 s — AW1_aEp_C 0.0493

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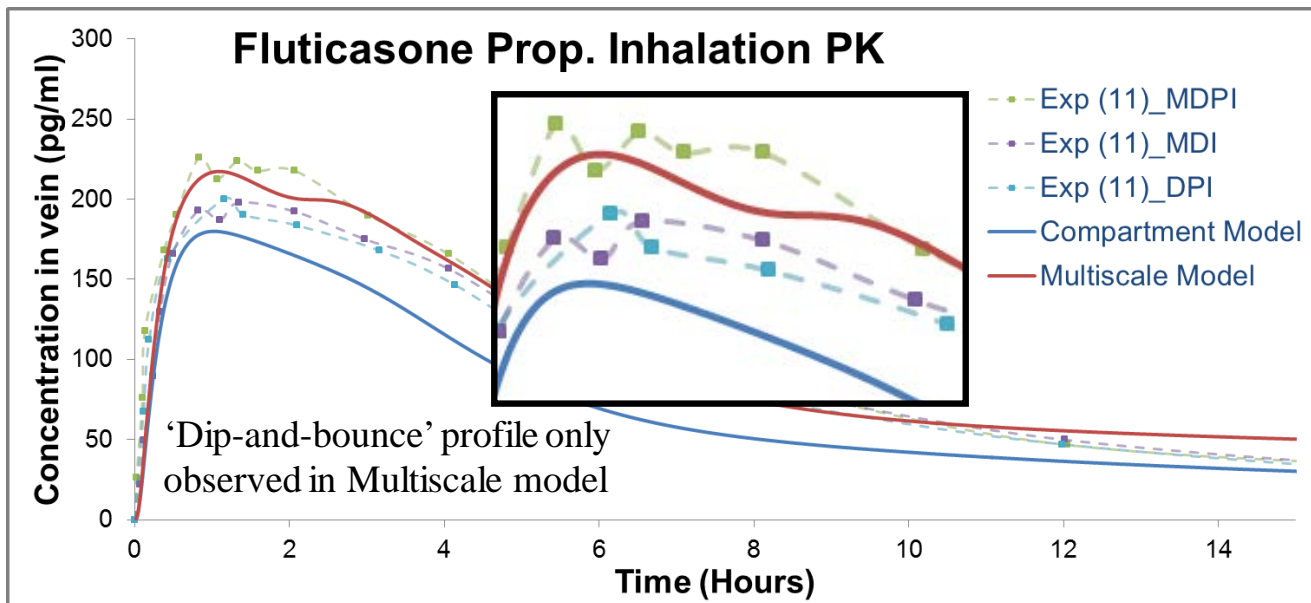5) Thorsson, ERJ, 7(10), 1994
6) Raaska, CPT, 72(4), 2002
7) Lahema, BJCP, 59(2), 2005
8) Dalby, RR, 10(1), 2009
9) Harrison, Thorax, 58(3), 2003
10) Mortimer, BJCP, 64(4), 2007
11) Vutikullird, JAMPDD, 29(2), 2015

- 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**
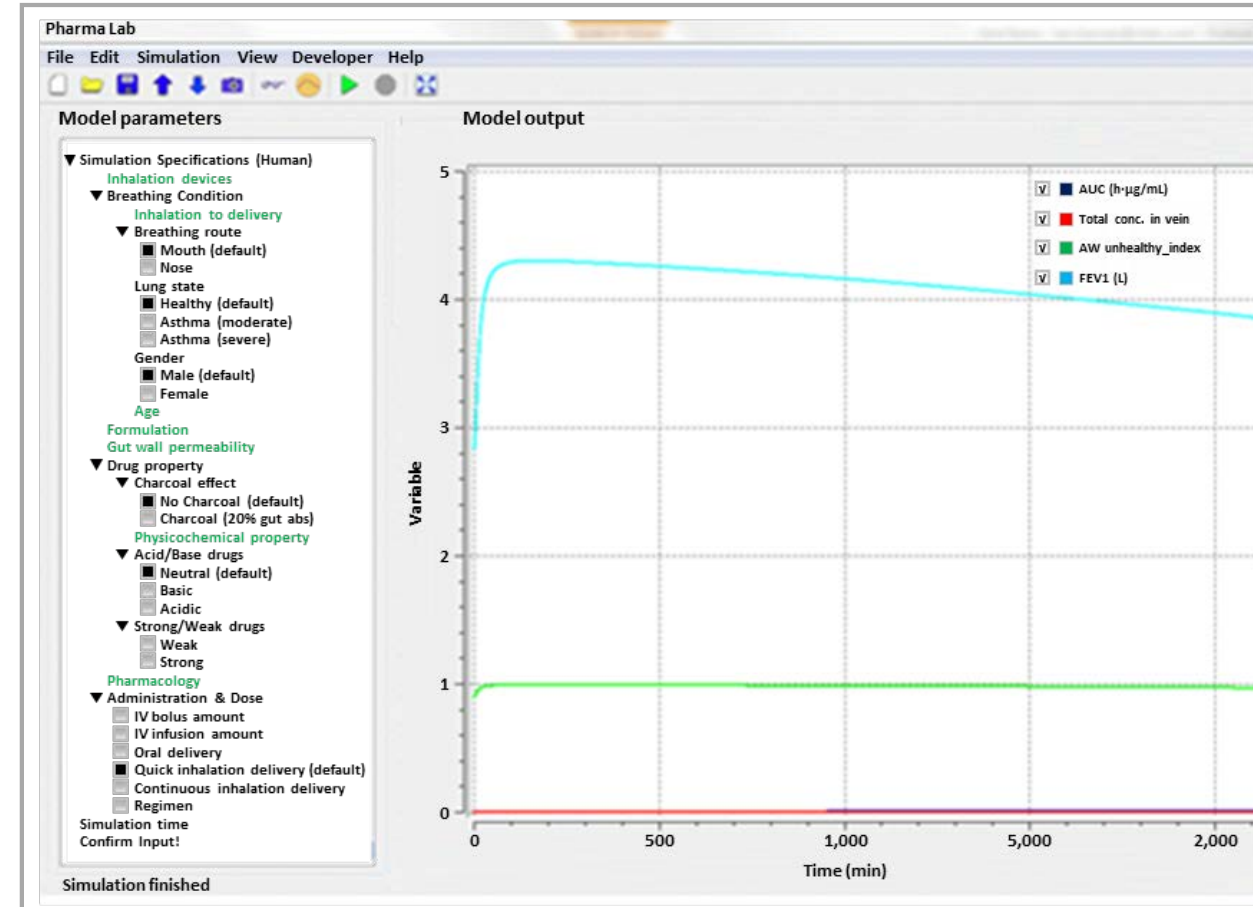
Thank You

CFDRC Team

Andrzej Przekwas (Sr. VP, Group Leader CMB)

Narender Singh (Principal Engineer)

Ravi Kannan (Principal Engineer)

FDA Team

Renishkumar Delvadia (FDA CDER)

Ross Walenga (FDA CDER)

Tian Geng (FDA CDER)