U.S. FOOD & DRUG ADMINISTRATION

*Public Workshop: New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products (OINDPs)*

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# Session 4: Computational Models to Understand In Vivo Performance of OINDPs

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# Computational Modeling in OINDP Development

- Computational modeling provides a connection between in vitro parameters (eg, spray angle and plume geometry) with in vivo deposition and absorption of OINDP aerosols and inform formulation and device designs

- Quantitative methods and modeling can inform regulatory decision-makings that are difficult to make with available in vitro or in vivo data, by predicting
  - Regional deposition of aerosolized drug within individual branches/lobes of the airway
  - Local bioavailability and its relationship with systemic pharmacokinetics

- Computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK) in combination present the next generation modeling toolset

# Computational Fluid Dynamics (CFD) Predictions of OINDP Aerosol Transport and Deposition

- Physics-based modeling framework capable of predicting regional deposition of OINDP aerosols
- Differences in formulation and device design may be predicted, as well as their impact on regional deposition
- Variability dues to orientations, breathing patterns and anatomical differences may be examined

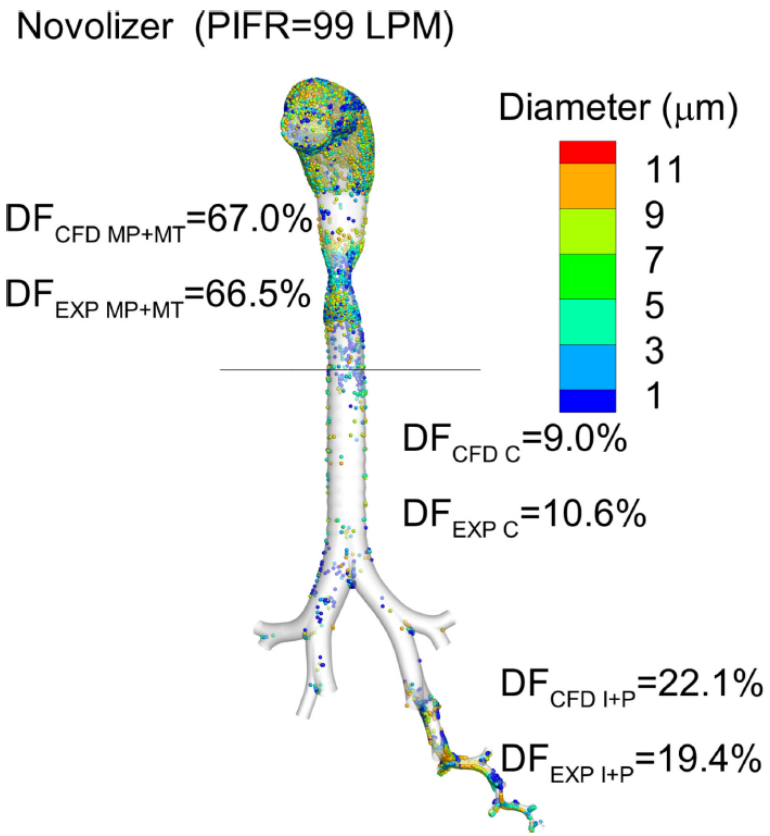
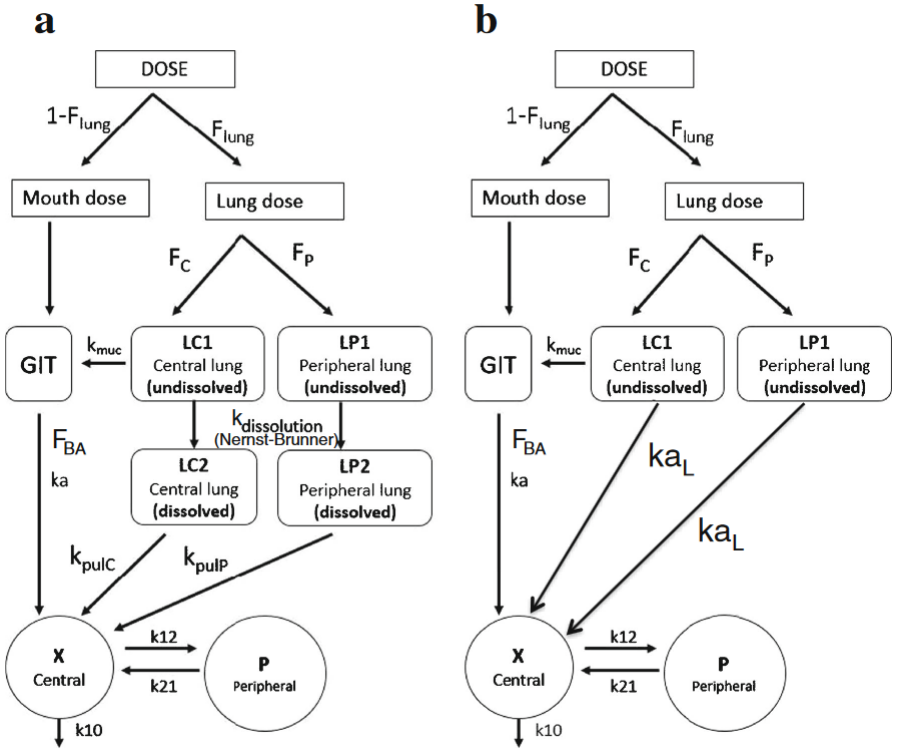



Figure 6 from Tian et al. (2015), showing of CFD predictions of deposition fraction (DF) in human airway model for Novolizer dry powder inhaler, as compared with in vivo data from Newman et al. (2000)


1. Tian G, Hindle M, Lee S, Longest PW. Validating CFD predictions of pharmaceutical aerosol deposition with in vivo data. Pharmaceutical research. 2015;32(10):3170-87.
2. Newman SP, Pitcairn GR, Hirst PH, Bacon RE, O'Keefe E, Reiners M, Hermann R. Scintigraphic comparison of budesonide deposition from two dry powder inhalers. European Respiratory Journal. 2000;16(1):178-83.

# Physiologically Based Pharmacokinetic (PBPK) Predictions of OINDP Absorption

- Compartmental modeling approach used to predict dissolution and absorption of deposited drug particles
- Combination of CFD and PBPK can predict local and systemic absorption
- Useful for determining the extent that in vitro testing is indicative of local and systemic delivery, and for identifying appropriate bioequivalence limits on in vitro parameters




Compartmental model schemes for dry powder inhaler drug delivery from Bhagwat et al. (2017)


3. Bhagwat S, Schilling U, Chen MJ, Wei X, Delvadia R, Absar M, Saluja B, Hochhaus G. Predicting Pulmonary Pharmacokinetics from In Vitro Properties of Dry Powder Inhalers. Pharmaceutical research. 2017 (in press).

# Focus of the Session

- Combination of CFD and PBPK to predict deposition, dissolution, and absorption
  - Impact of in vitro parameters on deposition and absorption
  - Effects of disease state on deposition and absorption
  - Method for predicting mucociliary clearance simultaneously with dissolution and absorption

**Presentation 1:** A CFD-PBPK Approach to Simulate Deposition, Absorption, and Bioavailability of Intranasal Corticosteroids – Jeffry Schroeter, PhD (Applied Research Associates)

**Presentation 2-** A Multiscale Computational Framework for Inhalation Pharmacology and Drug Development – Andrzej Przekwas, PhD (CFD Research Corporation)