Acceptability of using alternative PK metrics from systemic pharmacokinetic (PK) data to inform regional deposition for orally inhaled drug products

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Outline

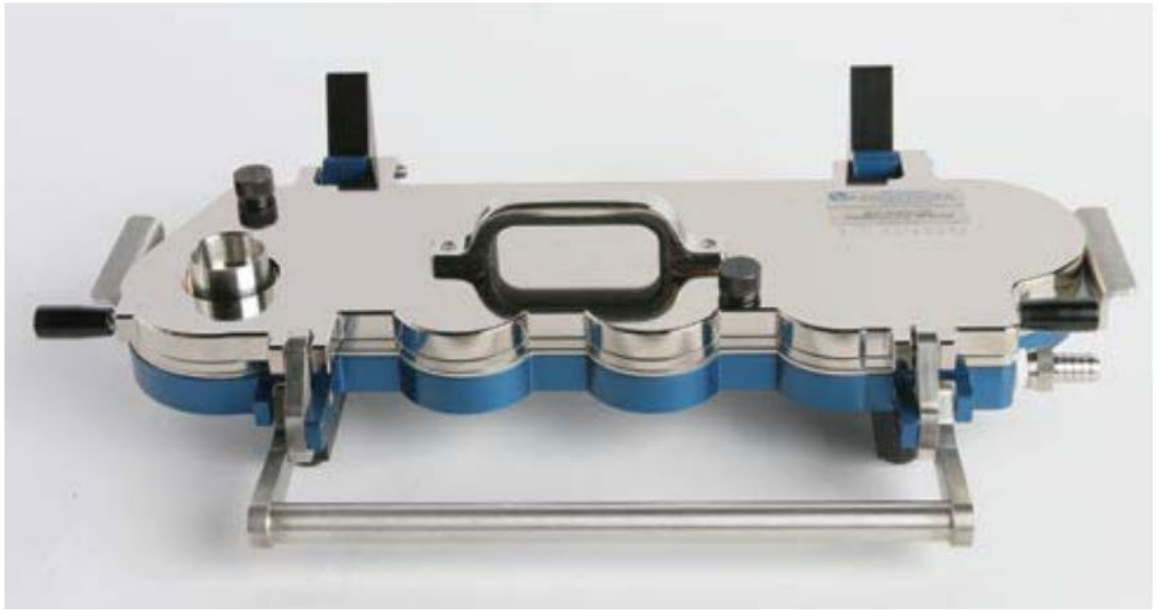
- Introduction
  - Challenges
  - Research in regional lung deposition
- In vitro deposition study and its relationship with systemic PK
- Normalization on lung dose to inform relationship between PK parameters and local lung deposition
- Population PK modeling and partial AUC as alternative PK metrics
- Grant opportunity
- Summary

Introduction

- Challenges
  - FDA applies a weight-of-evidence approach to establish BE for orally inhaled drug products (OIDPs).
  - Both comparative clinical endpoint (CCEP) and pharmacodynamic (PD) bioequivalence (BE) studies can pose a challenge due to its high variability.
  - High PK variability can mask the underlying PK metrics difference when regional deposition was used to identify the formulation difference.
- Research in regional lung deposition
  - Researchers are investigating the feasibility of assessing formulation differences in regional lung exposure based on systemic PK concentration data to establish BE for OIDPs in lieu of CCEP or comparative PD BE studies.

In Vitro Deposition Experiment

Next generation impactor™ (NGI™) – an example



At a flow rate of 39 L/min, stage cutoffs would be as follows:
Stage 1: 10.2 um; Stage 2: 5.58 um; Stage 3: 3.50 um; Stage 4: 2.30 um; Stage 5: 1.18 um; Stage 6: 0.71 um; Stage 7: 0.45 um

https://www.ecotech.com/wp-content/uploads/2015/03/MSP-170-Next-Gen-Impactor.pdf

In Vitro Deposition Significantly Affected by Different Batches of OIDPs

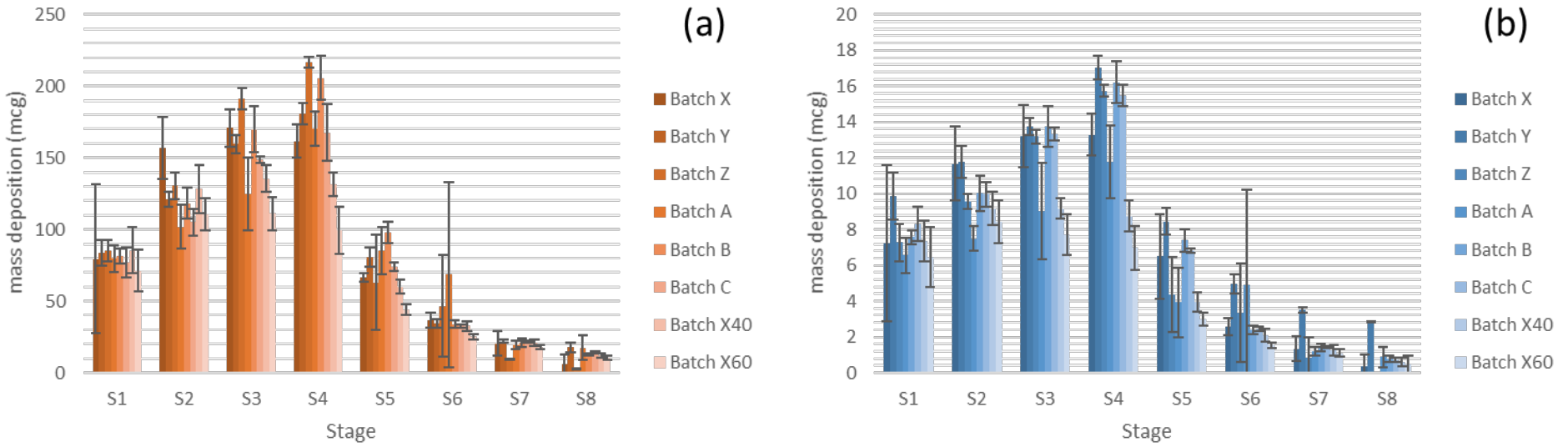
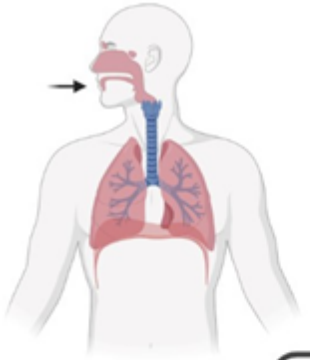


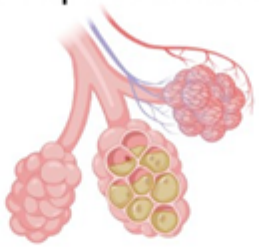
Figure 1: Impactor mass deposition of Fluticasone Propionate (a) and Salmeterol (b) using the NGI at flow rate of 80 L/min for 4 sec. Batch X40 and X60 are the thermally stressed batches. Data represented as mean ± standard deviation (n = 3).

Hefnawy et al. Investigation of the Effects of Physicochemical Properties of Dry Powder Inhalers on Batch-to-Batch Variability, AAPS Pharm Sci 360, 2021

Relationship between Systemic PK and In Vitro Deposition

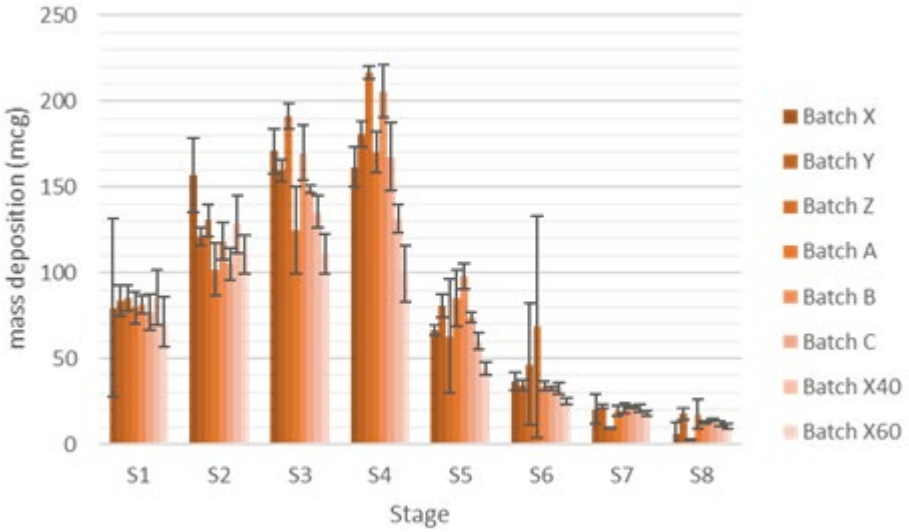


Peripheral airway



Can deposition pattern be lamped into central and peripheral airway?

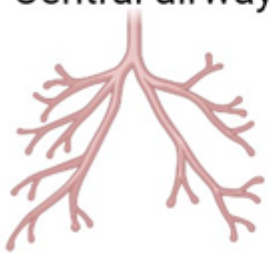
in vitro deposition



A two-pathway absorption model for fluticasone propionate

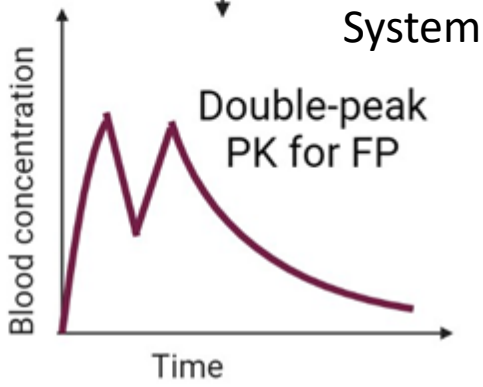
Faster systemic absorption

Central airway



Slower systemic absorption

Systemic PK

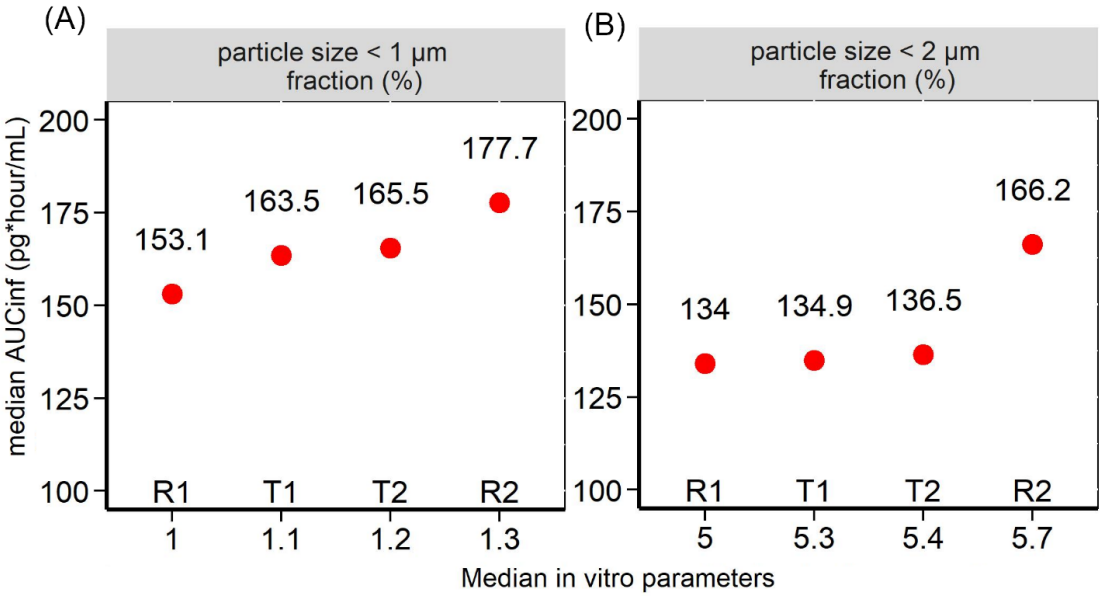


Shuhui Li et al. Population Pharmacokinetic Modeling for Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder in a Bioequivalence Study, ACoP 2020

Positive Relationship Between Particle Size and PK Endpoint

A regression model:

- $AUC_{inf} = 152.9 \times (FPF < 1\mu m)^{0.52}$ where FPF < 1 µm denoted as the fraction of the batch fine particle with an aerodynamic diameter less than 1 µm



Finer particles are more likely to deposit in the peripheral lung deposition, which has less mucociliary clearance and a greater extent of systemic absorption.

(A) The observed batch median fraction of particle with diameter size < 1 um (FPF <1 um) and the observed batch median AUC_{inf} for fluticasone propionate (FP).

(B) the observed batch median fraction of particle with diameter size < 2 um (FPF <2 um) and the observed batch median AUC_{inf} for salmeterol xinafoate (SX).

Shuhui Li et al. Exploring the Relationship Between the In Vitro Properties and the Pharmacokinetic Parameters of Advair Diskus, ACoP 2020

Dose-normalized PK Endpoints

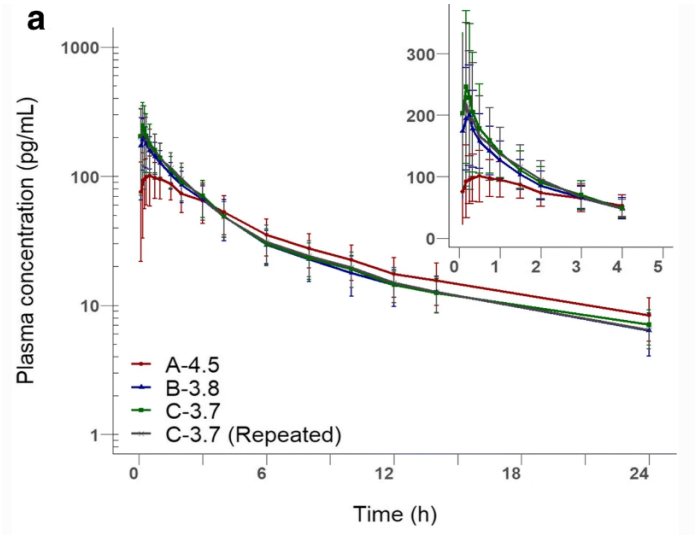
- Three fluticasone propionate (FP) dry powder inhaler (DPI) formulations (A-4.5, B-3.8, and C-3.7), differing only in type and composition of lactose fines, exhibited median mass aerodynamic diameter (MMAD) of 4.5 µm (A-4.5), 3.8 µm (B-3.8), and 3.7 µm (C-3.7) and varied in dissolution rates (A-4.5 slower than B-3.8 and C-3.7).
- In vitro total lung dose ($TLD_{in\ vitro}$) was determined as the average dose passing through three anatomical mouth-throat (MT) models and yielded dose normalization factors (DNF) for each DPI formulation X ($DNF_x = TLD_{in\ vitro,x}/TLD_{in\ vitro,A\text{-}4.5}$).

See, e.g., Hochhaus el ta. Can Pharmacokinetic Studies Assess the Pulmonary Fate of Dry Powder Inhaler Formulations of Fluticasone Propionate? AAPS J. 2021 Mar 25; 23(3):48, doi: 10.1208/s12248-021-00569-x, available at https://link.springer.com/article/10.1208/s12248-021-00569-x.

Results of Dose-normalized PK Endpoints

- The differences in lung-dose-normalized C_{max} could not be explained by differences in in vitro dissolution. This might suggest that C_{max} differences may indicate differences in regional lung deposition.

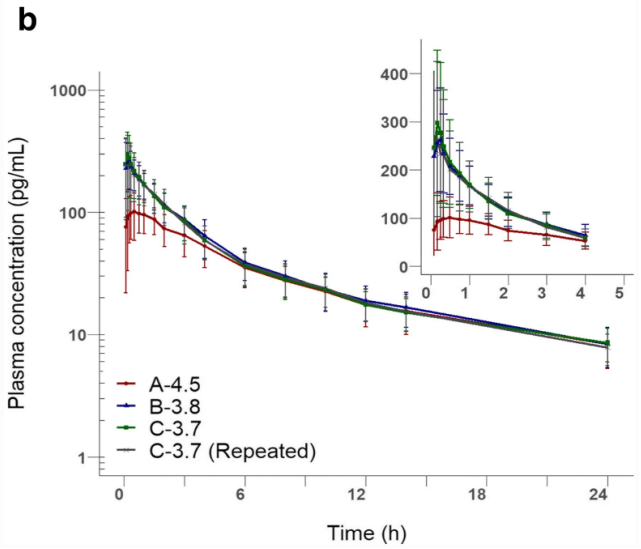
After Dose Normalization



C_{max} – BIE (A/B, A/C)

$AUC_{0\text{-}inf}$ - BE

Before Dose Normalization



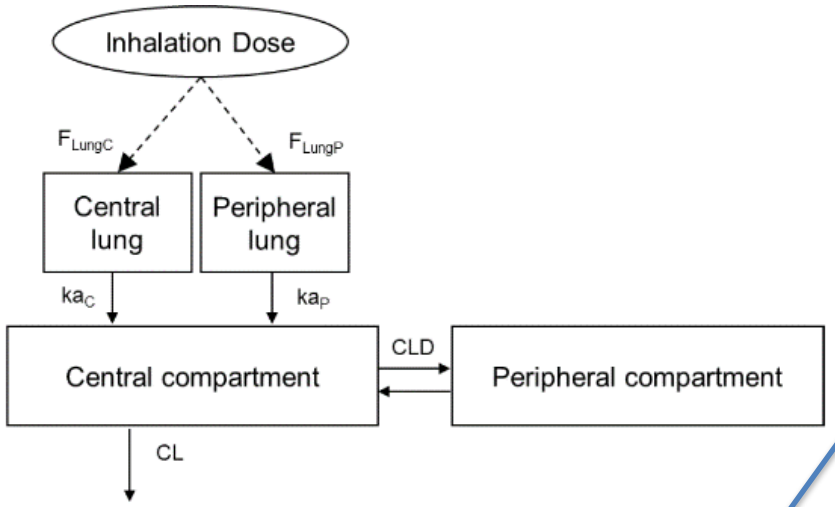
C_{max} - BIE

$AUC_{0\text{-}inf}$ - BIE

Overall, this study has contributed to an improved understanding of the relationship between pharmacokinetic parameters and local lung deposition, including findings on alternative methods in lieu of CCEP or comparative PD BE studies for orally inhaled products.

Population PK Modeling Example for a OIDP

PK model



Systemic PK data of T and R products used to build and validate the model

BE simulation

	S_{WR}	Ratio (%)	90% Lower	90% Upper
$AUC_{central, lung}$	0.35	78.11	71.12	87.12
$AUC_{peripheral, lung}$	0.2	121.12	112.21	131.21
$AUC_{total, lung}$	0.28	93.21	87.21	102.11

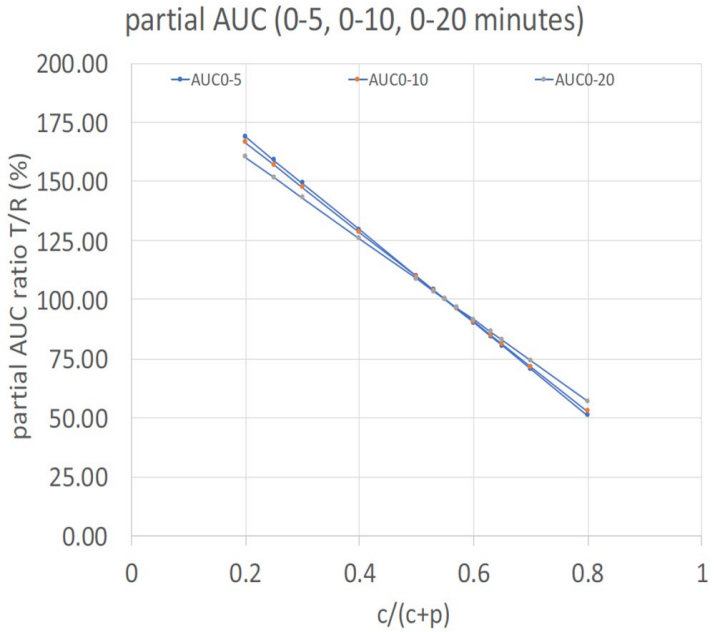
Failed BE in central and peripheral lung compartment

Absorption Half-life

	Test Product (h)	Reference Product (h)
$T_{half, central, lung}$	2.01	1.21
$T_{half, peripheral, lung}$	0.060	0.051

Short absorption half-life

Exploration with Partial AUCs



Simulation predictions based on different proportion of drug deposited to central and peripheral lung compartments

BE Analysis Based on PK Study Data

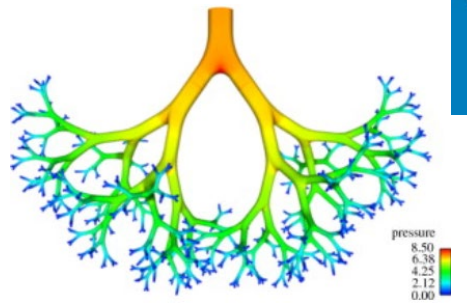
	Time (mins)	T/R ratio	90% CI Lower	90% CI Upper
$AUC_{0\text{-}10mins}$	10	111.10	102.21	122.12
$AUC_{0\text{-}20mins}$	20	108.11	100.12	105.21

- pAUC (of PK study data) T/R ratio is sensitive to detect the formulation difference
- pAUC passes BE criteria

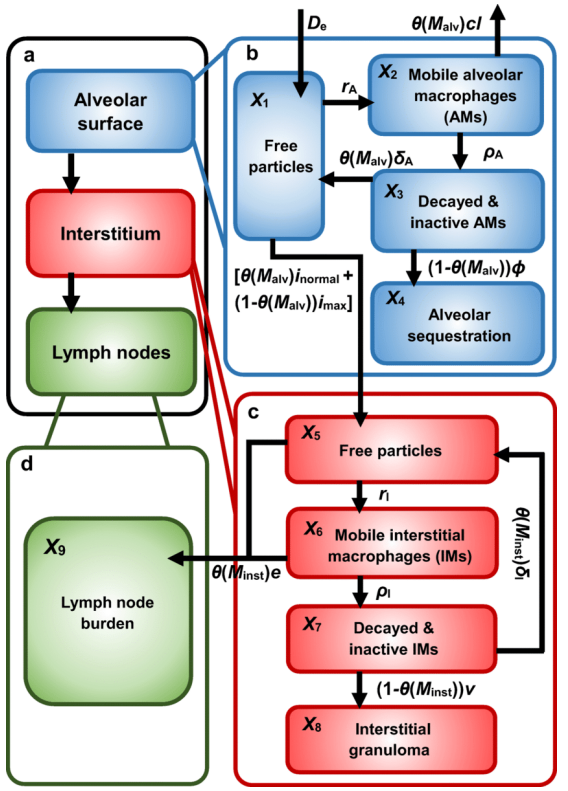
Question: is the pAUC acceptable as an alternative PK endpoint to demonstrate BE in local site of action?

Acceptability of Using Alternative PK metrics to Inform Regional Deposition

- A pAUC-based approach on systemic PK may be possible. But for this example, more detailed information should be provided to support the approach including appropriate validation or rigor.
- The approach should adequately show that bio-inequivalent products would fail by using modeling approach, and be able to demonstrate the clinical significance using the appropriate PK metric such as pAUC.
- It may be more likely to achieve success with a combination of a top-down approach and a fully mechanistic approach that uses a physiologically based pharmacokinetic (PBPK) model that at least includes systemic compartments and regional deposition estimates from either computational fluid dynamics (CFD) or semi-empirical models with in vitro deposition data.



Example: CFD model
Soni et al. Computers & Fluids, (2013)



Example: Compartmentalized physiologically based (PB) lung model – Wang (2021)

Available FDA Grant

- FDA grant: RFA-FD-23-017 - Population Pharmacokinetic Modeling of Systemic Pharmacokinetic Data to Inform Bioequivalence in Regional Lung Exposure
- The purpose of this funding opportunity is to support research that will use modeling and simulation to investigate the feasibility of assessing formulation differences in regional lung exposure based on systemic PK concentration data to establish BE for OIDPs with different drug and product properties.
  - **Task 1**: Create virtual OIDP scenarios (i.e., PK models with more mechanistically-based lung descriptions) based on a combination of different lung regions, regional deposition patterns, absorption rates, and other relevant factors
  - **Task 2**: Build a traditional population PK model that is different from the PK model with more mechanistic lung description developed in task 1 using only the simulated systemic PK data from task 1.
  - **Task 3**: Summarize the key properties of the OIDPs that determine the applicability of the population PK model-based prediction of local lung exposure using systemic PK data in support of establishing BE, in lieu of CCEP or PD studies.

Summary

- There exists challenges for conducting CCEP and PD BE studies for OIDPs.
- Modeling and simulation could provide a solution as alternative PK metrics from systemic PK data to inform regional lung deposition and to show the equivalence in local site of actions. However, sufficient justifications should be provided.
- FDA supports innovated approaches to support the BE approval for OIDPs. Funding opportunities are available in this priority area.

Acknowledgement

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