Sandoz
Product Development

Modeling to Support Regulatory Needs of Orally Inhaled Drug Products (OIDPs)

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2021 FDA Workshop on Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

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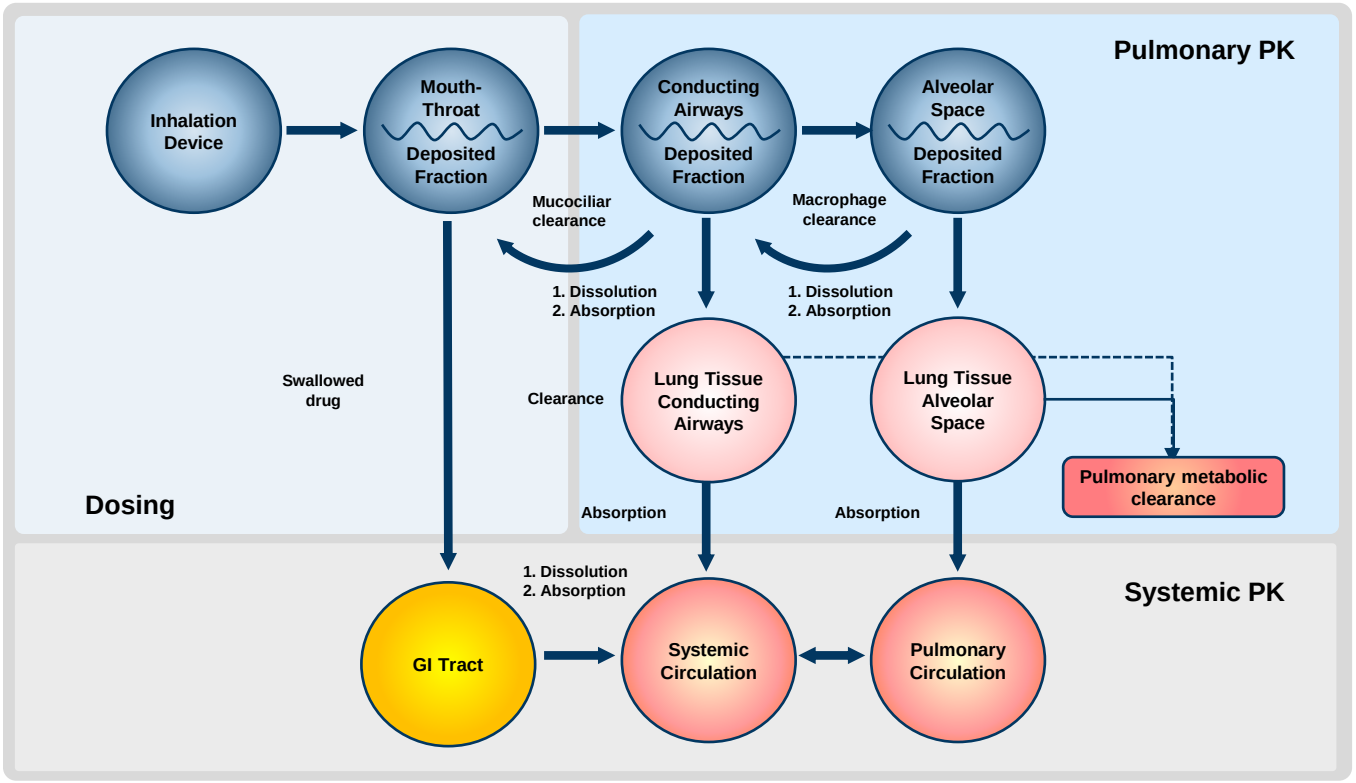
Content

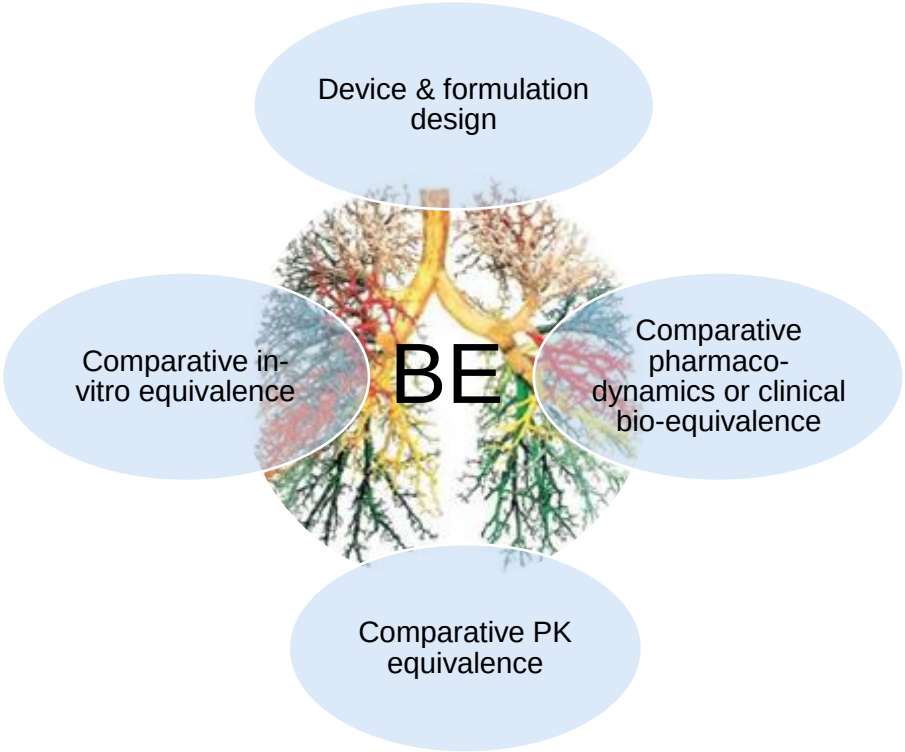
- Absorption of OIDPs
- FDA's weight of evidence approach & challenges
- Modeling as alternative & critical factors for modeling OIDPs
- In-vitro based in-silico modeling approaches
- PBPK & semi mechanistic modeling for internal decisions
  - In-vitro in-silico approach, MPPD + Gastroplus
  - Identification of suitable prototype & RLD batch
- Deposition modeling to understand formulation differences
- Dissolution modeling for local and systemic exposure
- Conclusions

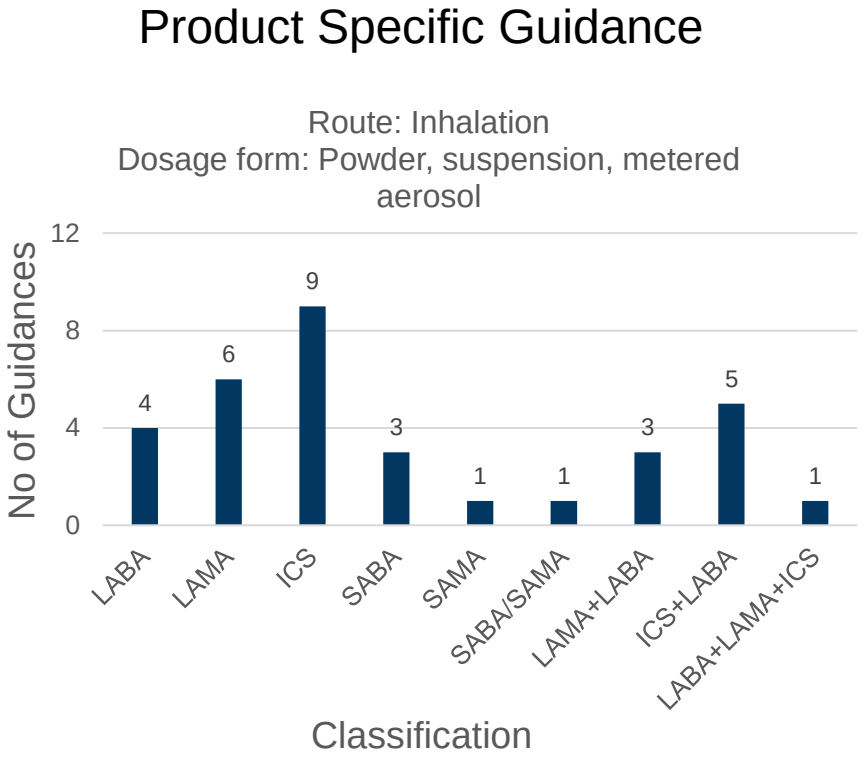
Drug Absorption via Inhalation Route



Adapted from Hatipoglu et al, Int J Pharm 2018, 549, 306-316

FDA's Weight of Evidence Approach

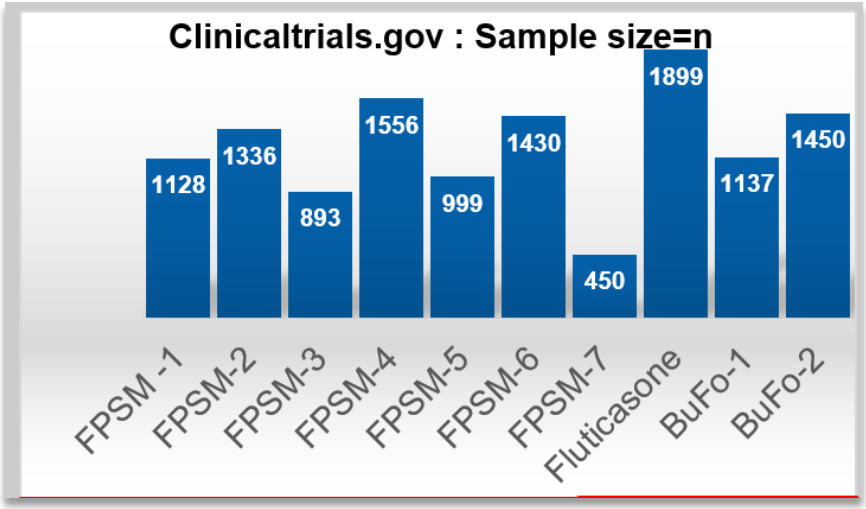




Challenges with Weight of Evidence Approach

Mainly with clinical endpoint BE studies:

- Large sample size due to high variability
- High cost & longer time
- Less sensitivity to formulation differences



Kerwin et al, J Aero Med and Pulm Drug Delivery, 2020, 33(2), 99-107

Longphre et al, An ATS, 2017,14 (2), 182-189

Guidance where FDA Recommends Modeling as one of the Alternate Route

Beclomethasone Dipropionate HFA MDI, 2020

Additional supportive in vitro studies may include, but are not limited to, (i) more predictive APSD testing using representative mouth-throat models and breathing profiles, (ii) characterization of emitted aerosol sprays with respect to velocity profiles and evaporation rates, (iii) dissolution, and (iv) morphology imaging comparisons, including characterization of the full range of residual drug particle sizes. Prospective applicants may also consider the use of quantitative methods and modeling (for example, physiologically-based PK and computational fluid dynamic studies) and alternative in vivo PK BE studies.

Momentasone Furoate & Fluticasone Furoate Nasal spray, 2020

(PSD) in aerosols and sprays using commonly used analytical methods. Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to systemic circulation. If drug PSD in the T and R products can be accurately measured using a validated analytical method such as morphology-directed Raman spectroscopy or any other advanced methodology, prospective applicants may submit comparative particle size distribution data as part of their drug characterization within their ANDA application. In such

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

... Some more products

Critical Factors for Modeling OIPs

Modeling: Mechanistic and biophysical modeling must take Device, Formulation and Patient Characteristics into consideration

FORMULATION

- Physico-chemical properties of API and Excipients
- Carrier functionality
- Blend properties
- Manufacturing Process

DEVICE

- Device geometry
- Aerosol engine
- Airflow resistance
- Dosing principle
- Energy source
- Human factors

SUBJECT/PATIENT

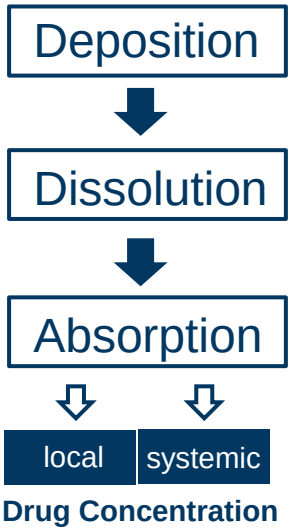
- Inhalation effort
- PIF
- Training
- Age, Gender
- User interface
- (Disease state)

MODEL INPUTS

- In-vitro performance and aerosol characteristics SAC, APSD)
- CFD for regional deposition
- Systemic exposure (PK)

In-vitro Based In-Silico Modeling Approaches – Separated Model

Processes



Characterization

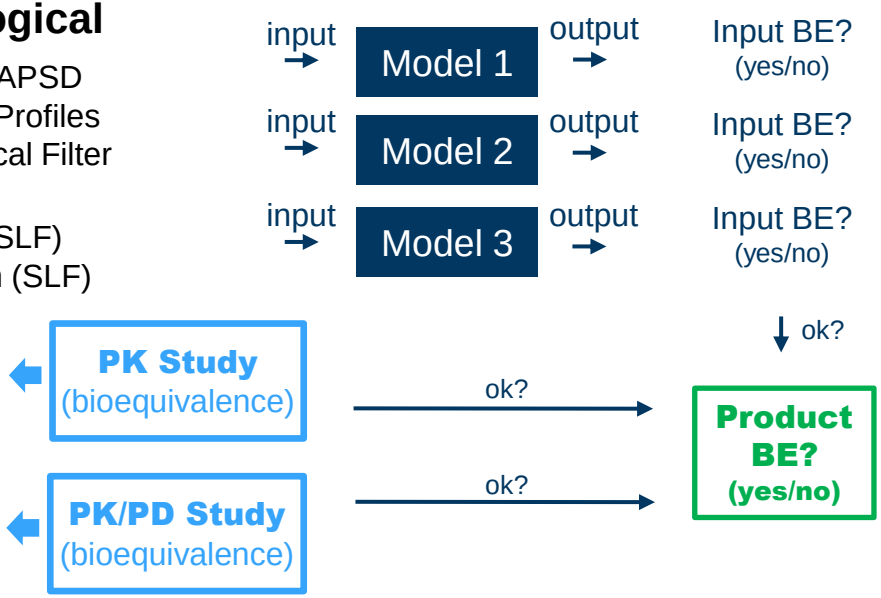
Technical

APSD
Powder Emission
Inhaler Resistance
....
Solubility (PBS)
Dissolution (PBS)
....
?

Physiological

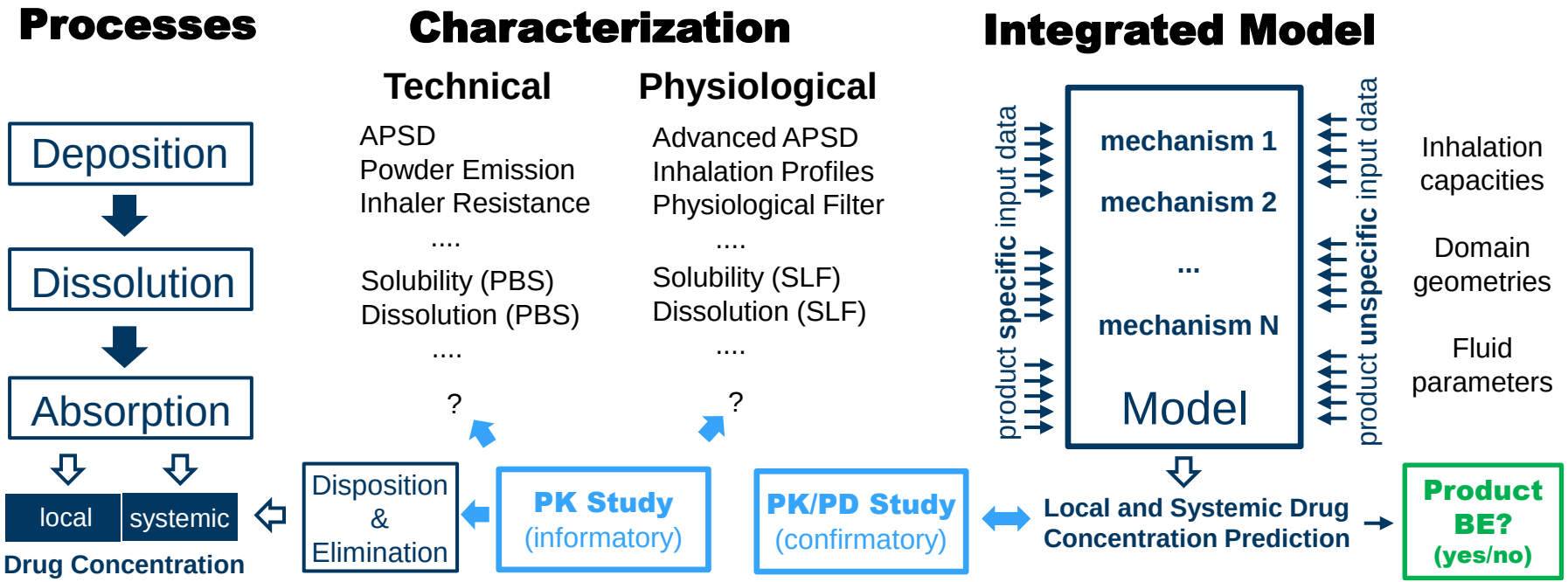
Advanced APSD
Inhalation Profiles
Physiological Filter
....
Solubility (SLF)
Dissolution (SLF)
....
?

Separated Models



PBS: phosphate-buffered saline; SLF: simulated lung fluids

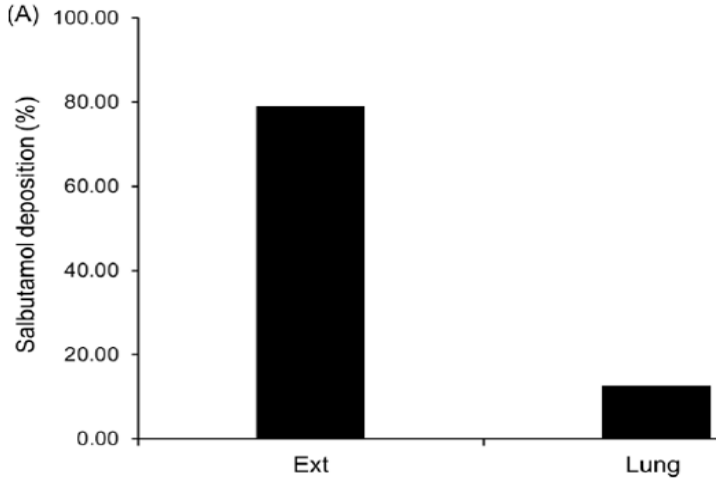
In-vitro Based In-Silico Modeling Approaches – Integrated Model

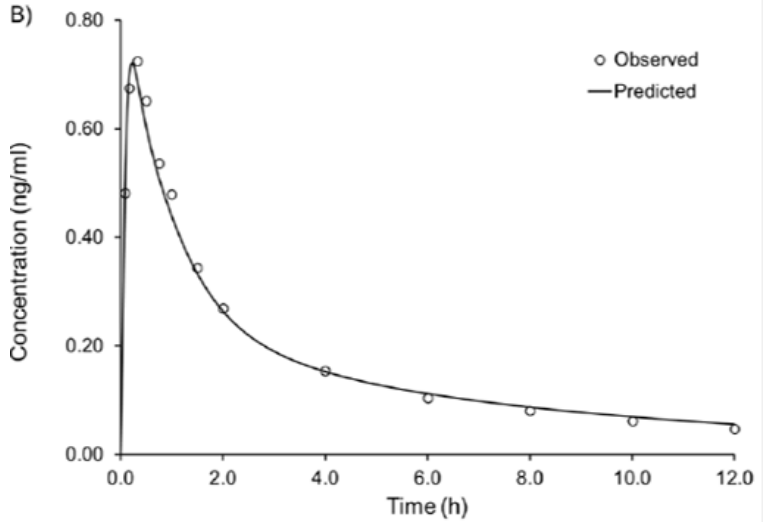


PBS: phosphate-buffered saline; SLF: simulated lung fluids

In-vitro In-Silico Approach to Achieve PK-BE

- PBPK model – MPPD coupled with Gastroplus
- MMAD & GSD to predict deposition & plasma profile of RLD – Diskus
- Impact of different carrier (lactose) on PK is predicted. Applicable for soluble drugs

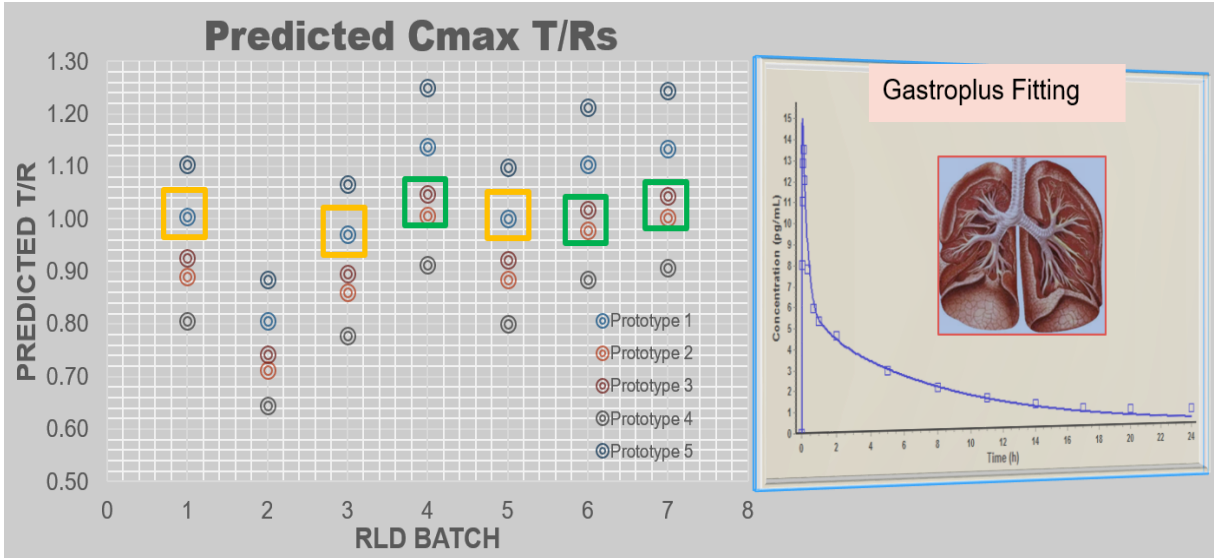




Pinto et al, 2021, Pharmaceutics, 13, 297

Identification of Suitable Prototype & RLD Batch

- Semi mechanistic model using APSD data



More suitable prototype (1) against RLD batch 1,3 & 5

More suitable prototypes (2 & 3) against RLD batch 4, 6 & 7

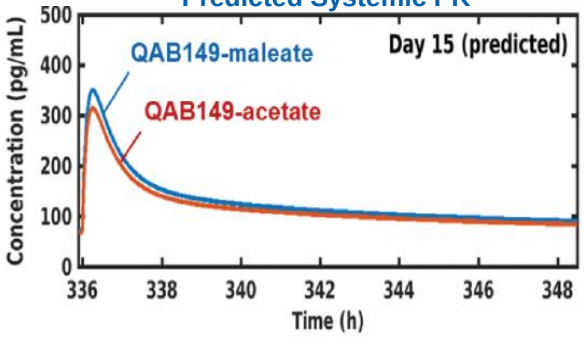
Deposition Models – Examples

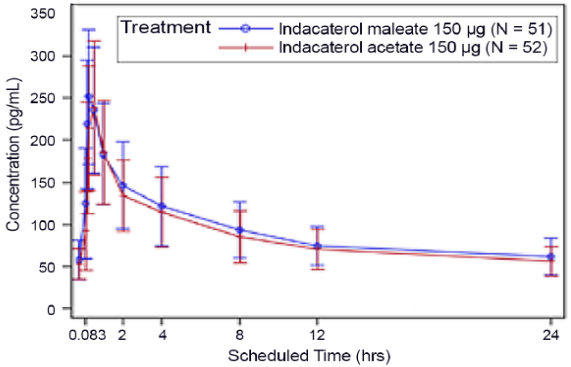
Modeling sensitive enough to predict formulation difference and reflect it to clinical objectives for PK-BE

Delivery Predicted for 90 L/min

Simulation	Maleate	Acetate
Capsule & Device	25.3	24.9
Mouth-Throat	57.6	53.7
Bronchial Model	7.6	7.3
Deep Lung (< 2mm)	12.8	11.3

Predicted Systemic PK





Observed (Clinical) Data

Study	Maleate	Acetate
T max (h)	0.25	0.47
Cmax (pg/ml)	264	236
AUC 0-24h (h*pg/ml)	2300	2050

Predicted vs Observed Ratios

	Acetate/Maleate (simulation)	Acetate/Maleate (clinical study)
C_{max},ss	0.9	0.89
AUC,ss	0.92	0.89

Jauernig et al, Respiratory Drug Delivery Europe, 2019, 1-4.

Deposition Models - Examples

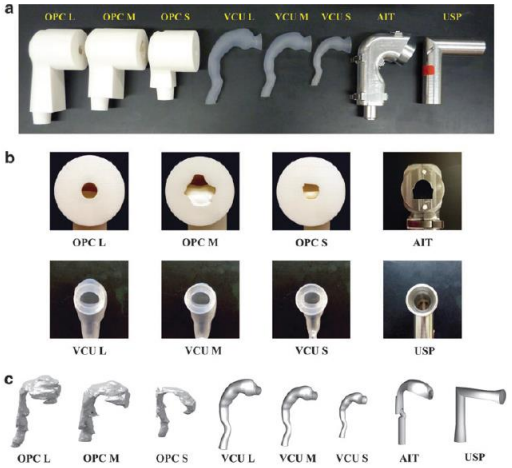
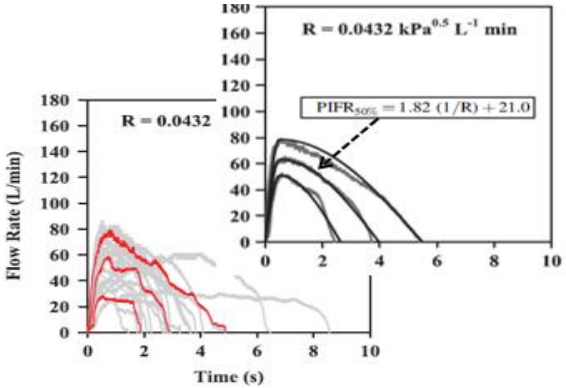
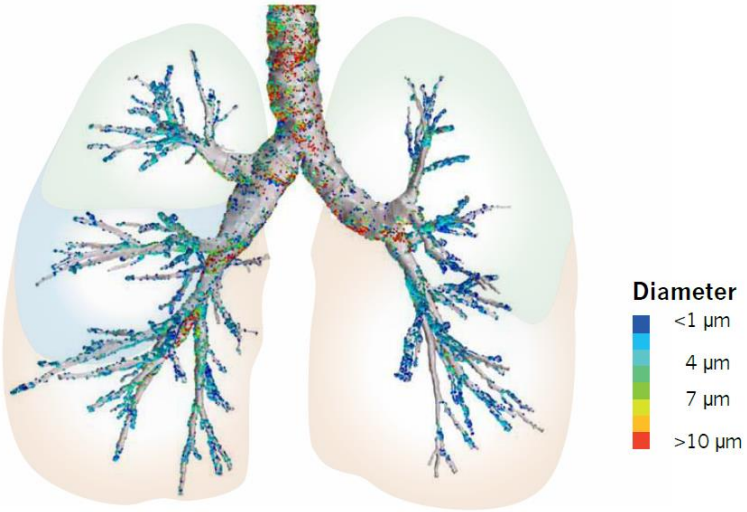


FIG. 1. Realistic MT models developed for inhaler *in vitro* testing: OPC Large (OPC_L), OPC Medium (OPC_M), OPC Small (OPC_S), VCU Large (VCU_L), VCU Medium (VCU_M), VCU Small (VCU_S), AIT (Medium), and USP Induction Port. **(a)** side view; **(b)** view from the mouth entry; **(c)** internal geometry. MT, mouth–throat; OPC, Oropharyngeal Consortium; VCU, Virginia Commonwealth University; AIT, Alberta Idealized Throat; USP, United States Pharmacopeia.



Regional lung dose is the foundation for PD-BE assessment and is probably sufficient for soluble drugs

Figure 4. Particle deposition analysis for IND/GLY in the bronchial tree



Wei et al, J Aer Med and Pulm Drug Delivery, 2018, 31 (6), 358-371
Dolovich et al, Int J Pharm, 2019, X1, 100018
Kuttler et al, 2015, European Respiratory Society International Congress
Delvadia et al, J Aer Med and Pulm Drug Delivery, 2016, 29 (2), 196-206

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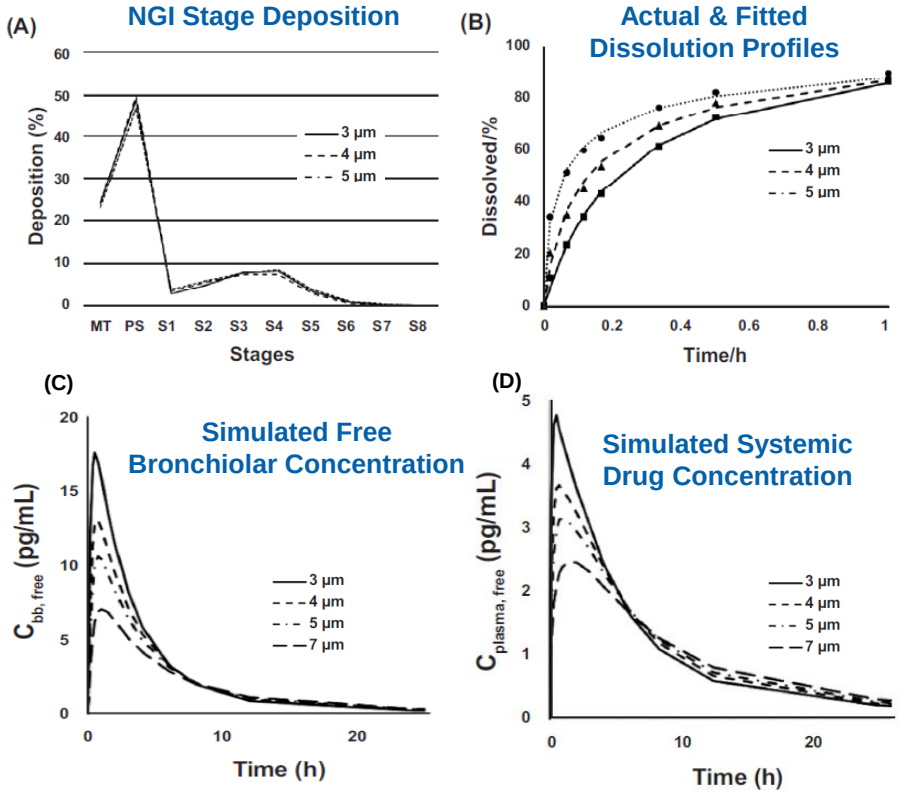
Dissolution Modeling for Local & Systemic Exposure of Poorly Soluble Drug

Fluticasone Propionate (Advair)



- ❑ Absorption rate into the blood depends on solubility & dissolution rate
- ❑ Relationships between dissolution/release rate and local and systemic exposure

Carry Home Message

- Complement to and potentially alternate to PK & PD studies

Bäckman et al, Resp Drug Delivery, 2020,113-122

Take Home Message (Conclusions)

- Modeling helps to identify in-vitro characteristics reflecting in-vivo
- Today, modeling plays a key role in drug product design and internal decision making processes
- Biophysical deposition model has capacity to integrate multiple experimental, device and formulation characteristics
- Modeling of local and systemic concentration has a huge potential to alternate some clinical studies in the future

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Thank you

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