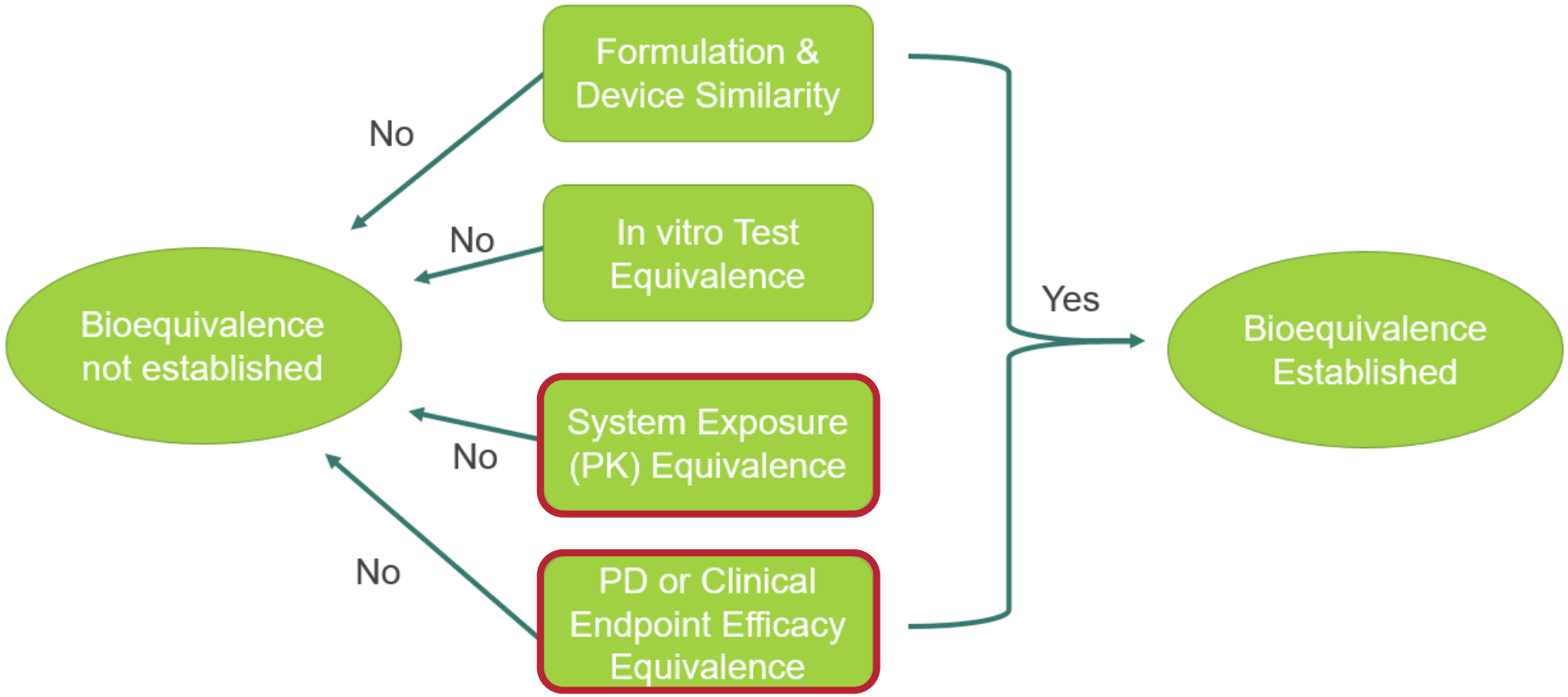
Utilizing Modelling approaches to support regulatory submission for orally inhaled drug products: case example

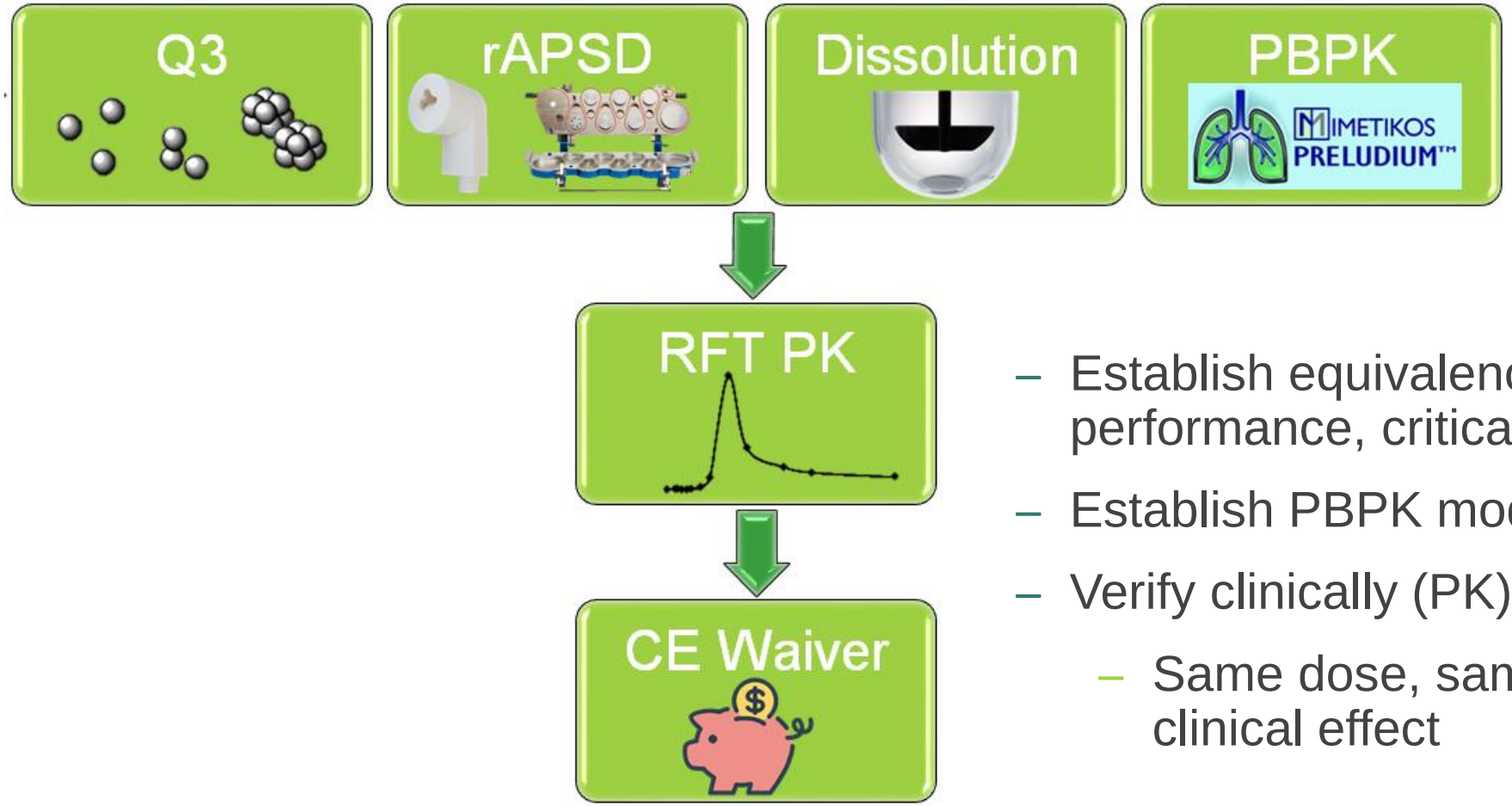
Marc Kelly CRCG-FDA Workshop 27Oct2022

Bioequivalence – traditional paradigm

"PD BE study is the only reliable tool to establish equivalence in clinical effect at the local sites of action within the lung"



Alternative Approach Condensed

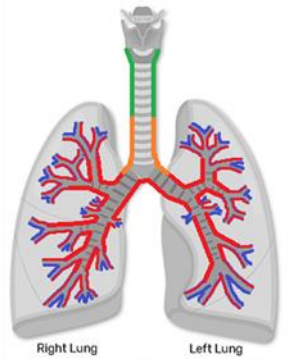


- Establish equivalence; composition, performance, critical design attributes
- Establish PBPK model
- Verify clinically (PK)
  - Same dose, same distribution, same clinical effect

CASE study – solution pMDI, soluble API

- Solution-phase pMDI containing a single highly soluble API (30 mg/mL in PBS at 37°C)
  - One excipient, two volatile components
- Proposed generic Q1 and Q2 equivalence, device comparable for all critical parameters; componentry and patient use
- Modelling approach developed to support PK success and propose alternative to PD study

System Exposure (PK) Equivalence

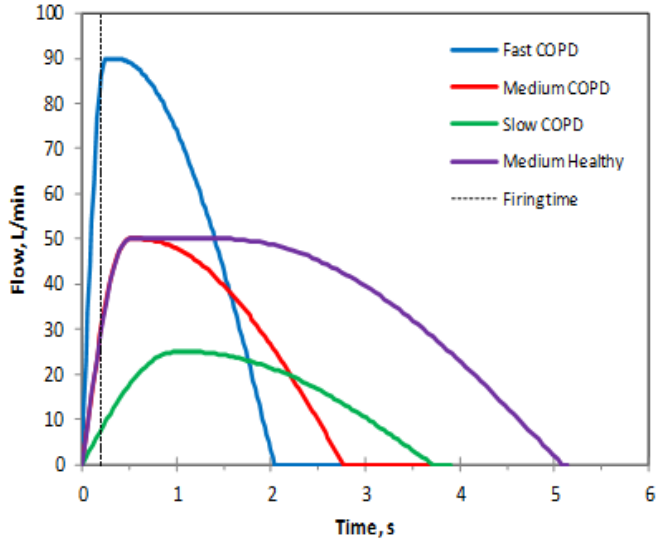


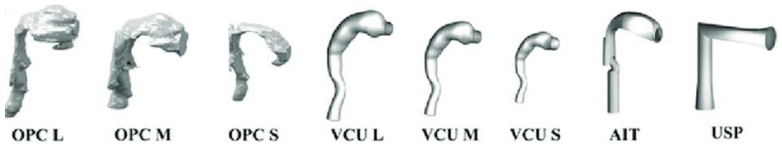
PD or Clinical Endpoint Efficacy Equivalence

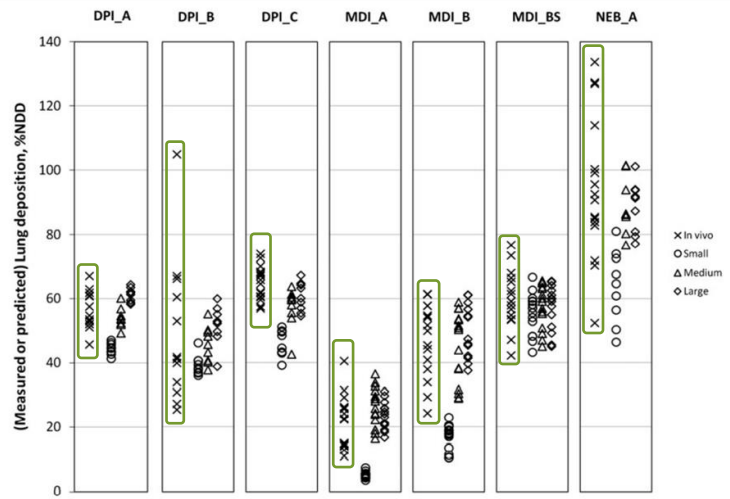
"effect at the local sites of action within the lung"

rAPSD to simulate patient cohort

- Breath profiles from review COPD patients and technical limitations of NGI apparatus
  - 4 profiles; fast, medium, slow COPD and healthy
- Throat geometries selected from correlation to *in vivo* data (DPI, pMDI and SMI)
  - 3 throats; OPC_S, OPC_M and OPC_L and standard USP
    - OPC derived from 90 MRI images of throat geometries

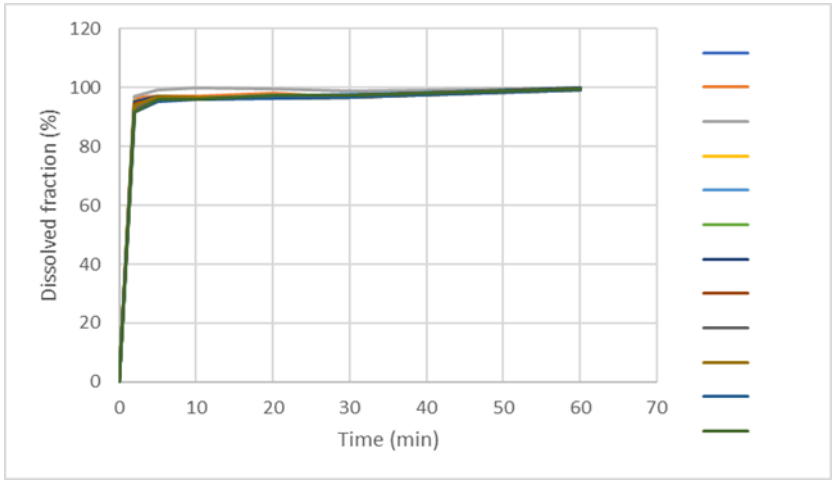


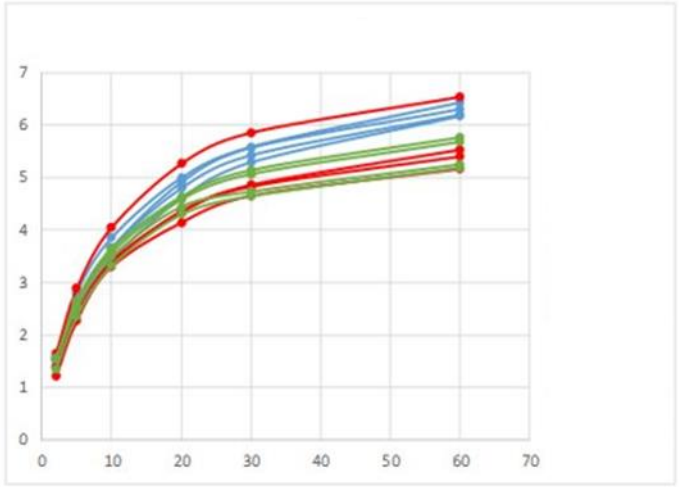




Dissolution

- Modified USP paddle over disk method
  - Sink conditions equivalent to dose expected *in vivo* (1 dose / 10 ML of epithelial lining fluid)
- ≥92% API dissolved at the first time point (2 minutes)
- *Unlikely that dissolution is a CQA*



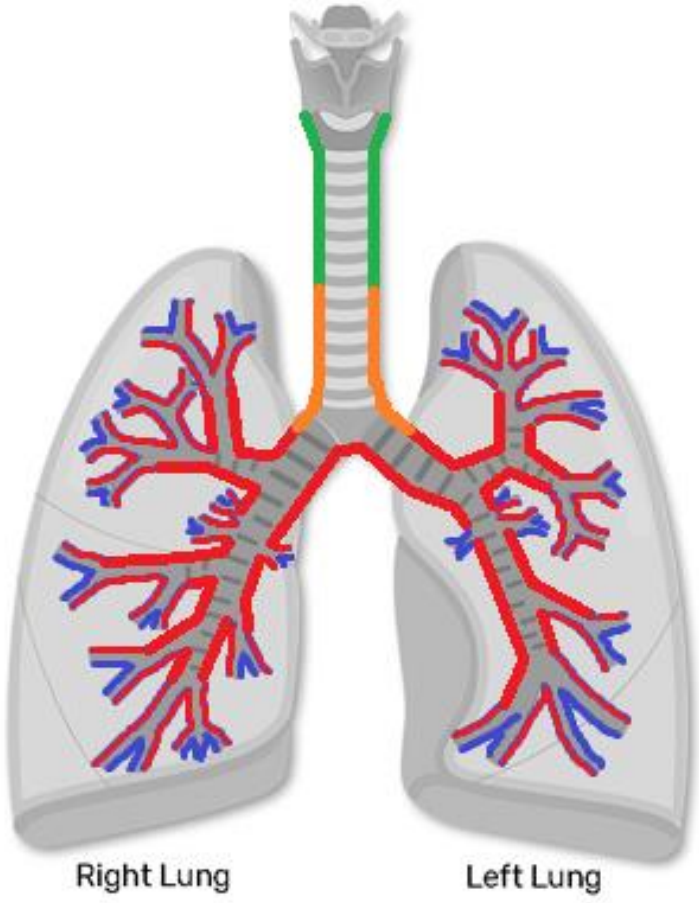


Deposition model

- Preludium encompasses lung, ventilation, transport and deposition models to derive regional deposition

- Output as % deposition in the extra-thoracic (ET), tracheobronchial (BB), bronchiolar (bb) alveolar interstitial (AI) regions and exhaled fraction

- Model leverages rAPSD source data (4 breath profiles, 4 throat geometries)



ET: Mouth-Throat BB: Tracheobronchial
Bb: Bronchiolar AI: Alveolar Interstitial

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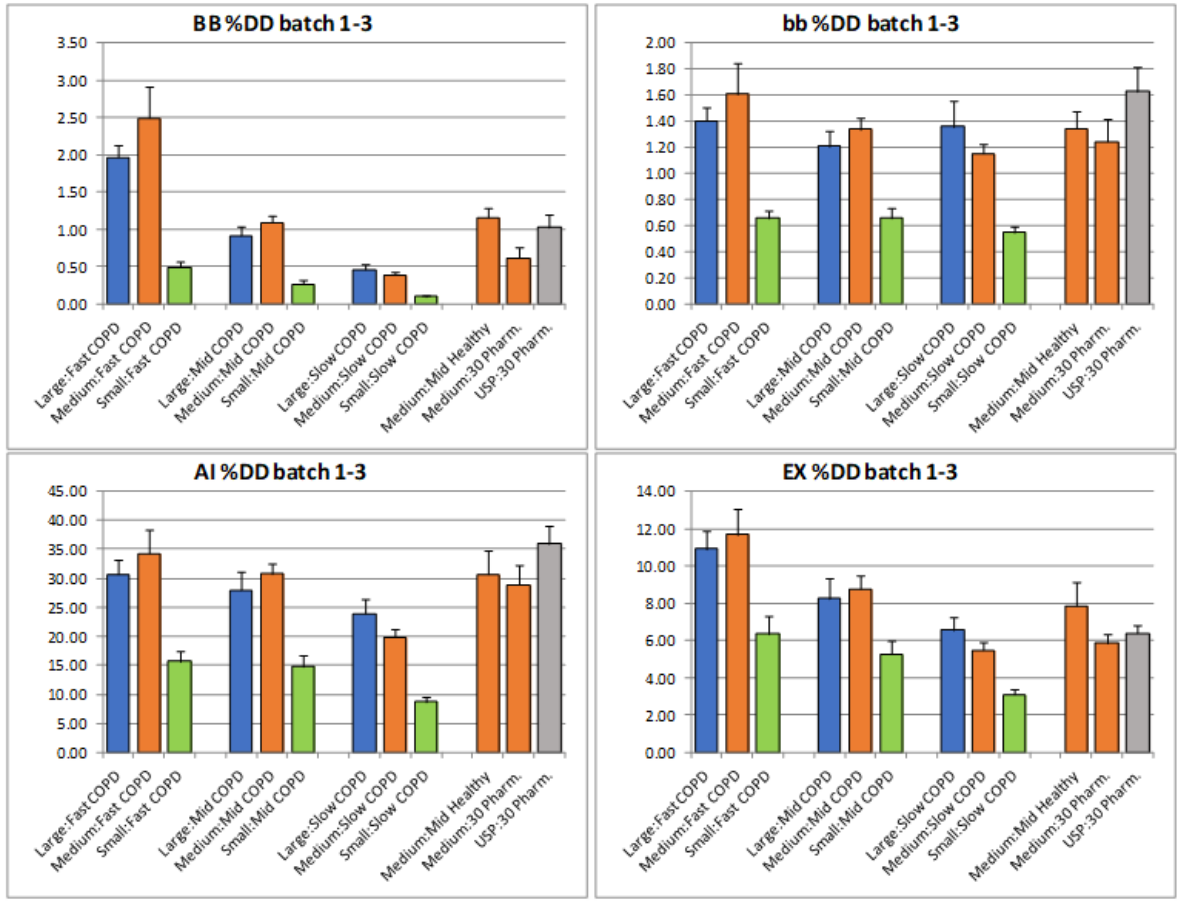
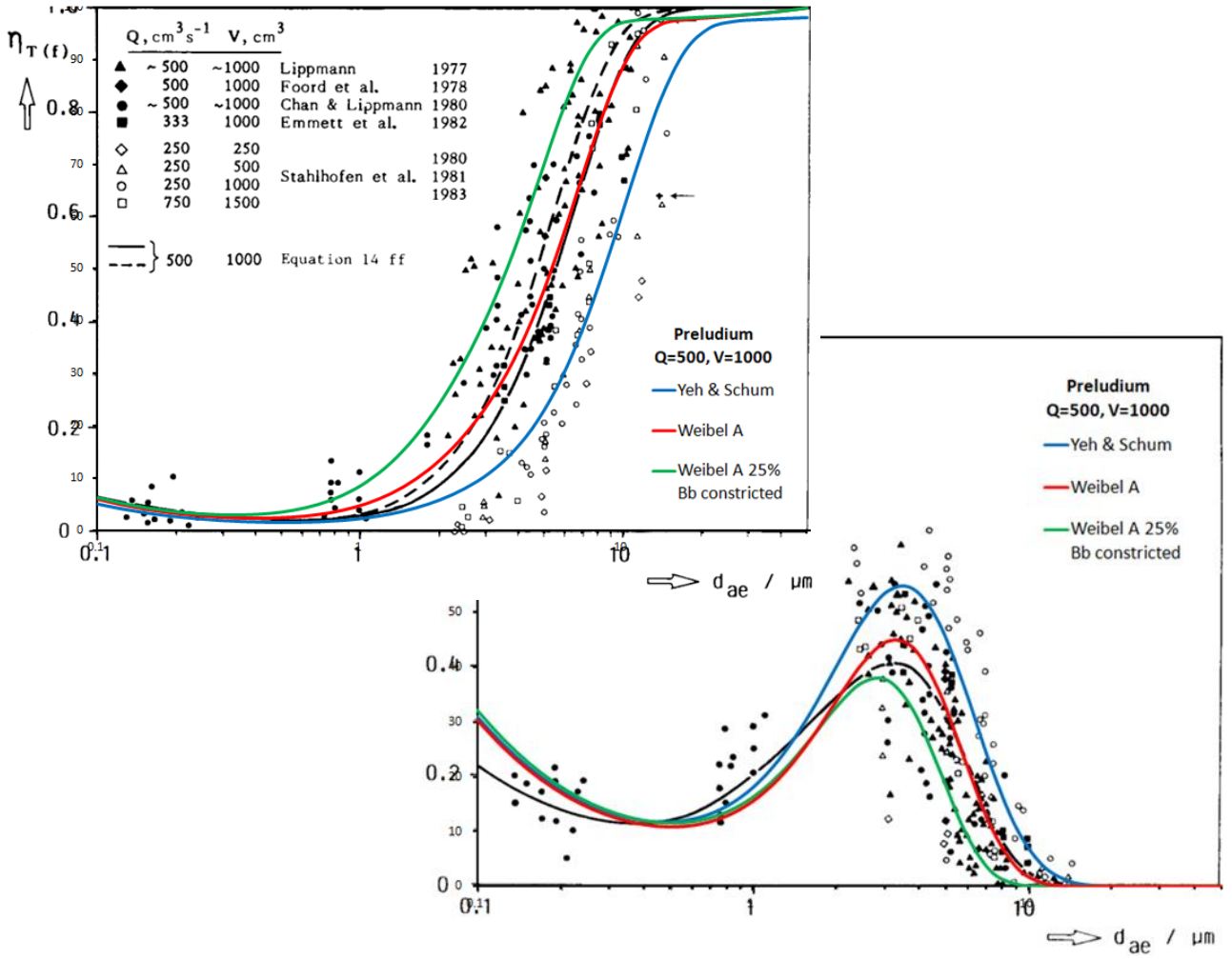


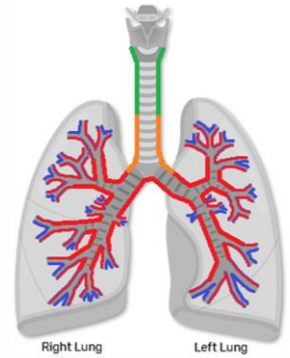
120 RLD NGIs deposition modelled

Verification of deposition model

- Deposition model compared with scintigraphy of radiolabelled insoluble particles (Stahlhofen1989)
  - 3 lung models assessed
  - Model covers clinical data well

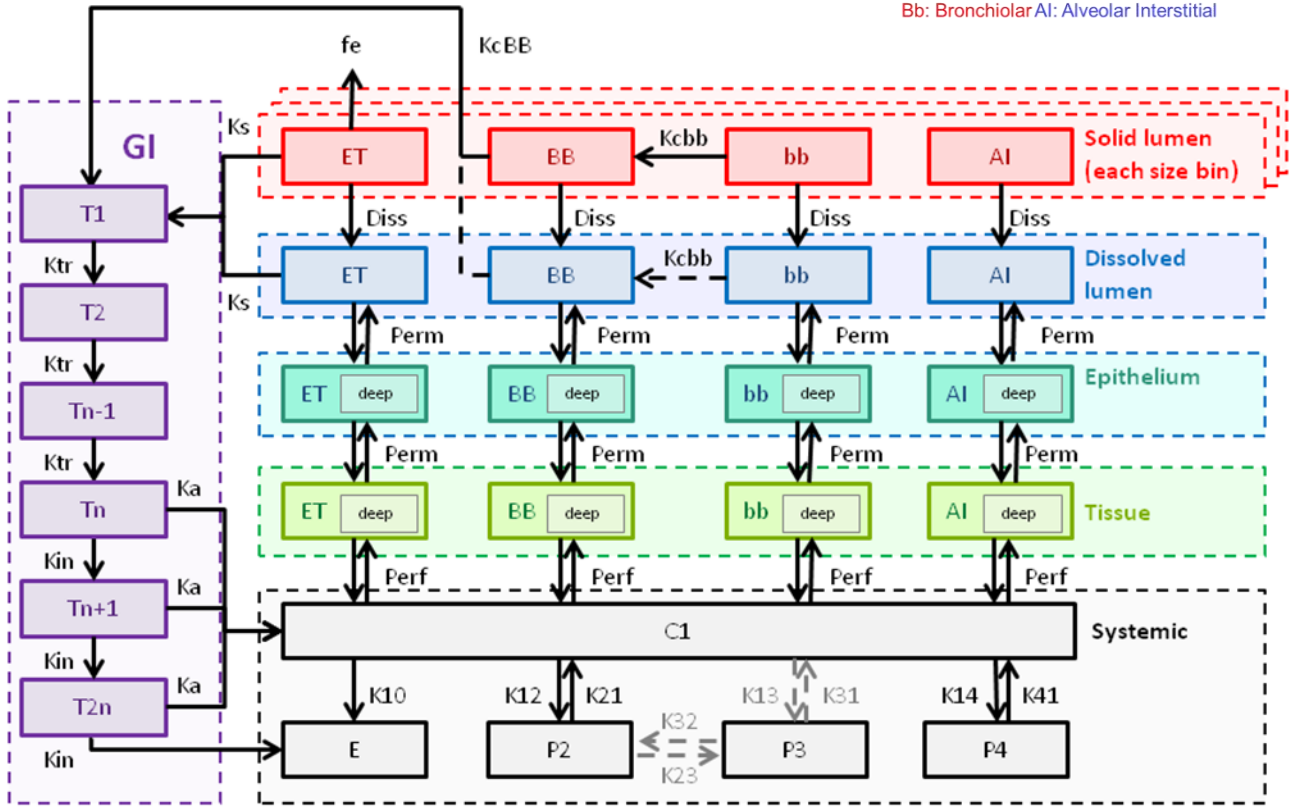


Compartmentalised PK simulation overview



- Simulation of rate and extent of pulmonary absorption = AUC_t and C_{max}

- Informed by:
  1. drug independent parameters (lung physiology)
  2. drug dependent parameters (drug molecular properties)
  3. product performance attributes



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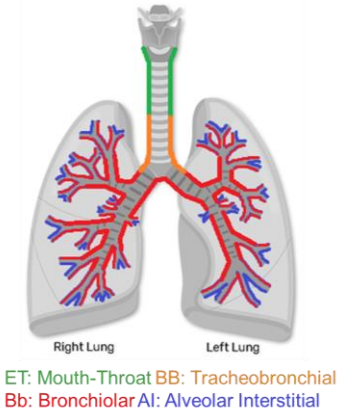

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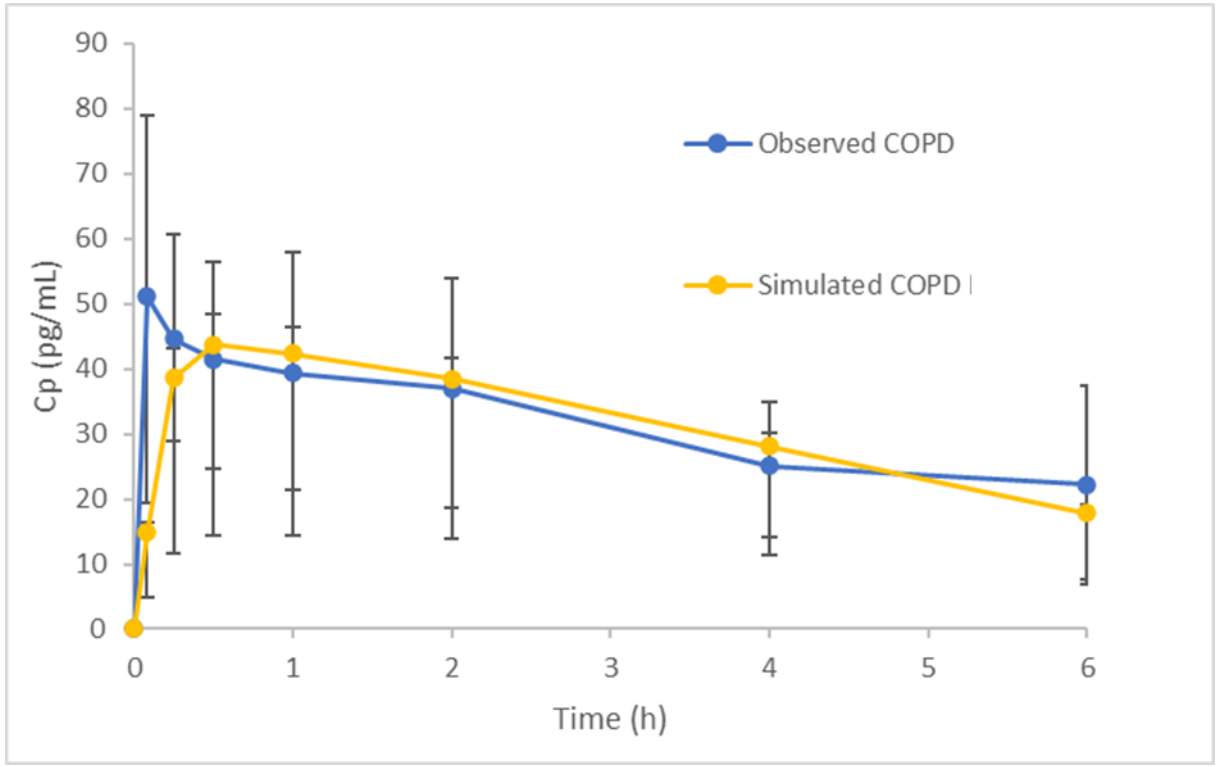
Parameter	Value
Diffusivity (D)	3.9E-4 cm^2/min
ELF solubility (C_s)	>90 mg/mL
Crystal Density	1.3 g/mL
logP	0.380
Physiological Charge	+1
Unbound conc	12.9 mL/g
Tissue to plasma partition co-efficient	12.3 mL/g

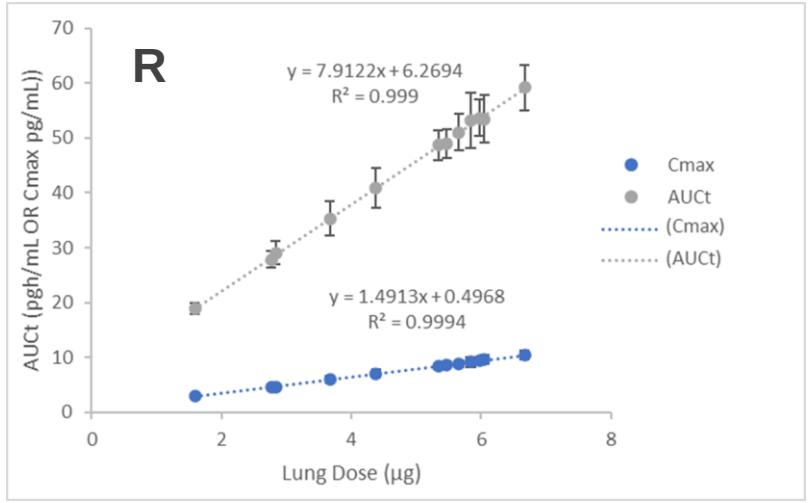
PK simulation well aligned with observed clinical data

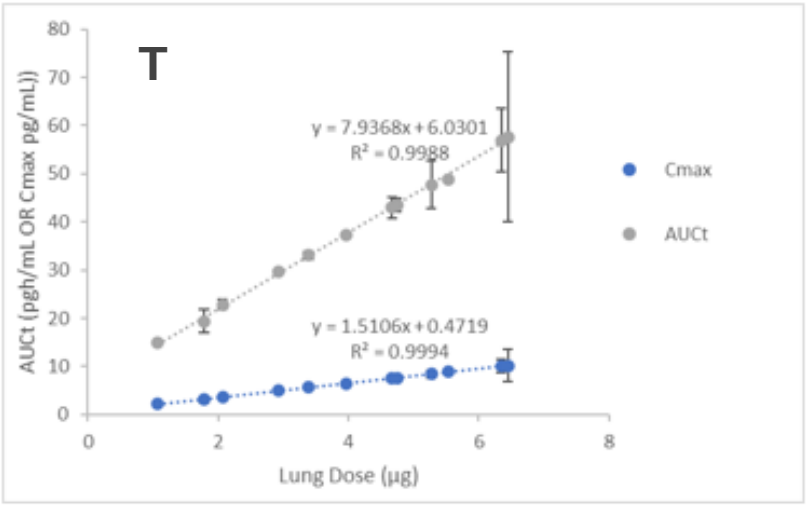
- Model shows good alignment for AUC but underestimates initial uptake
- This could be factor of disease state (model utilises “healthy” lung) but rapid uptake for this API is observed in both COPD and healthy patient cohorts
- Mode is insensitive to physical status of API given high solubility
  - No difference between assuming physical of solute deposition



Lung dose should be predictive of PK

- 12 combinations of flow and mouth-throat models for Test and RLD (240 NGIs, 144 simulations)
- Model is sensitive to changes in lung dose
  - Simulated C_{max} and AUC_t well correlated to *in vitro* lung dose
  - Test and Reference aligned
- Dose and dose deposition are likely CQAs

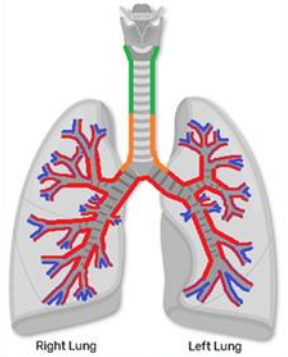




What's next

- Validation of literature/model-based correlations by PK
- Varying volatile component concentration to yield defined differences in lung dose (equivalent total dose, variable FPD)
- Confirm model accuracy
  - PK is affected by changes in regional deposition therefore PK parameters can inform equivalence in local drug delivery to the lung

System Exposure (PK) Equivalence



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Conclusions and Key Questions

1. Mechanistic modelling can be used to probe the impact of formulation changes on systemic absorption
2. Regional lung deposition appears sensitive to changes in *in vitro* performance and PK is sensitive to changes in regional lung deposition
3. Preludium can be used to understand the sensitivity of *in vivo* PK profiles to variations in *in vitro* product attributes

Key questions:

1. How do we efficiently model diseased lung state?
2. Additional computation is needed to establish that regional deposition can serve as a surrogate for regional absorption (scintigraphy)?
3. Is dissolution method sufficiently discriminatory?

End

Many thanks