Abbreviated New Drug Application (ANDA) and Pre-ANDA experience with Orally Inhaled Drug Product (OIDP) modeling

Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

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OIDP Models Included in ANDA and Pre-ANDA Submissions

- Model Types
  - Semi-empirical regional deposition
  - Computational fluid dynamics (CFD)
  - Physiologically based pharmacokinetic (PBPK)
  - Population pharmacokinetics (PK)
- Model-related information has been provided for metered dose inhalers (MDIs), dry powder inhalers (DPIs) and soft mist inhalers (SMIs)
- Objective is typically to demonstrate that local drug delivery to the site of action is equivalent via:
  - Regional deposition predictions
  - PK metrics such as maximum plasma concentration (C_{max}) or area under the plasma concentration-time curve (AUC_{0-t})

Common Areas for Improvement

1. Validation and verification activities are commonly inadequate.
   a) Comparison with experimental data may be absent or demonstrate inability of model to capture key processes.
   b) Validation typically only includes comparison with data from one drug product.

Regional Deposition Validation

- Deposition should be predicted in all lung regions (especially, central and peripheral).
- Lung region definition should be supported by in vivo data and clinical understanding.
  - Complementary model may be needed for small airways if CFD is used for regional deposition predictions of upper airways.
- Preferred source of comparator data is in vivo imaging data via either gamma scintigraphy or single positron emission computed tomography (SPECT)/computed tomography (CT)

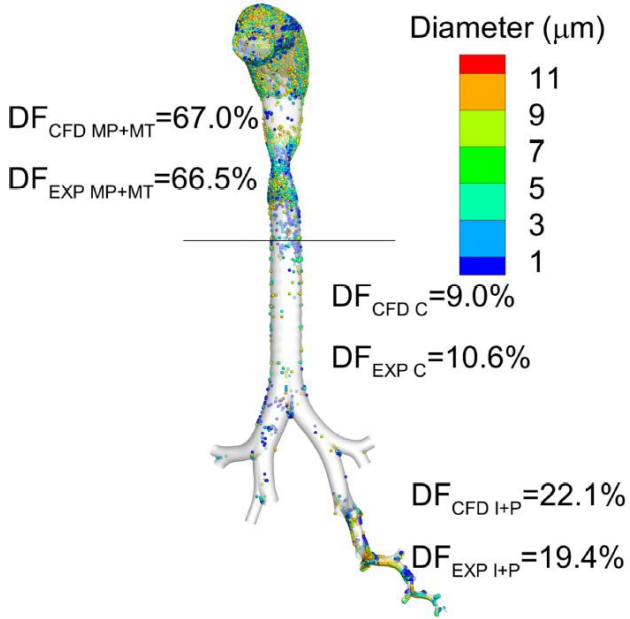

Figure 6 from Tian et al.[1] – Predictions of regional deposition fraction (DF) (mouthpiece (MP), mouth-throat (MT), central (C), intermediate (I), and peripheral(P)) for DPI, as compared with in vivo gamma scintigraphy data.[2]

In vivo Imaging Data Limitations

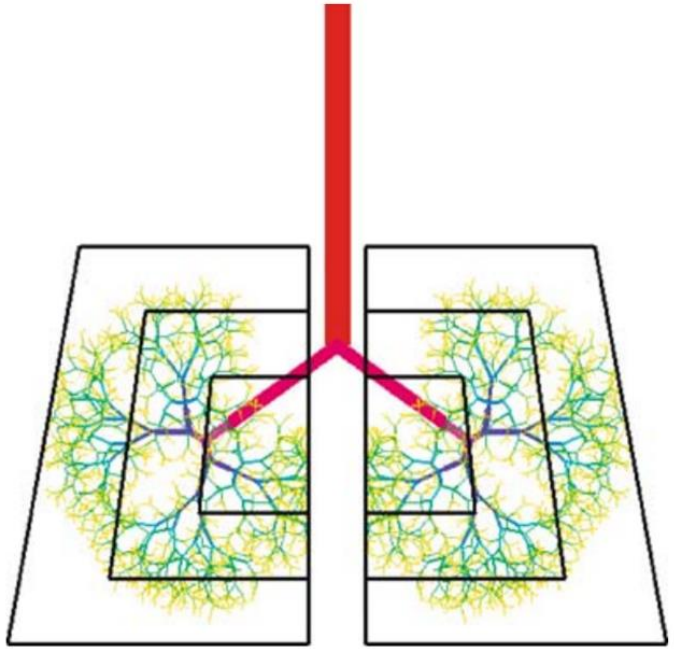

Figure 4 from Schroeter et al.[3] – 3D airway model overlaid with 2D central (inner), intermediate, and peripheral (outer) regional definitions

- In vivo imaging data are typically collected using a two-dimensional (2D) scheme divided into central, intermediate, and peripheral regions.
- There is a lack of precision when comparing three-dimensional (3D) regional deposition predictions with 2D data.
- If CT scan is taken in subject in addition to deposition data, the subject's lung may be mapped onto 2D regions.
- A small in vivo study may be considered to support model validation.

Common Areas for Improvement (cont'd)

2. Model structure may be lacking in precision.
   a) CFD models often truncate the central lung region at the limit of CT scan resolution.
3. Regional deposition models may not consider relevant physics such as evaporation for MDIs and SMIs or agglomeration/deagglomeration for DPIs.

Small Airway Definition

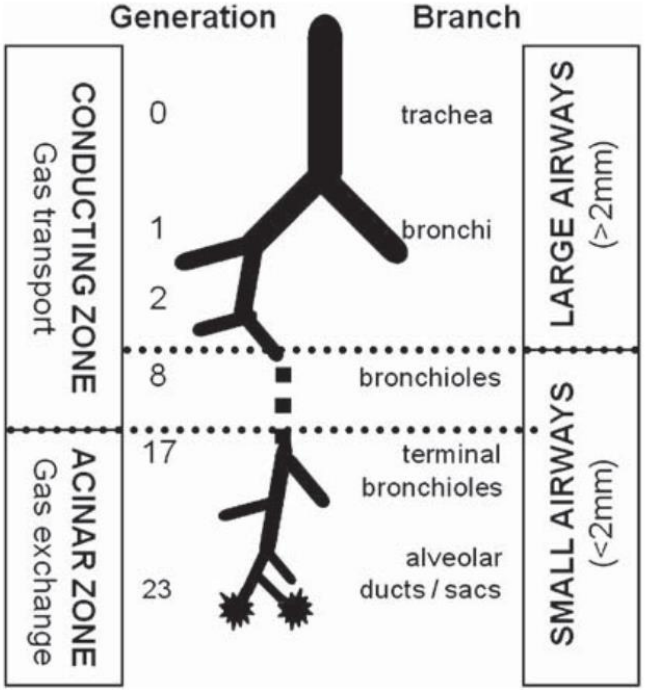

Diagram of lung regions (from Usmani and Barnes[4])

- Bronchi, bronchiole, alveolar regions
- Small airway cutoff
  - After bronchi[4]
  - Airways smaller than 2 mm in diameter[4]
  - Cutoff for 2 mm airways may be beyond bronchioles[5]

Solution-Based MDIs

- Internal research project (ongoing)
- Beclomethasone dipropionate metered aerosol (new drug application (NDA) 020911)
  - Solution-based product containing API, propellant, and co-solvent
- Use CFD to predict DF and droplet evaporation following actuation into United States Pharmacopeia (USP) induction port
- Is the active ingredient completely solubilized in the aerosol?

Initial Droplet Size (µm)	Initial Mass (µg)	Exit Mass (µg)	Exit Mass Dissolved (µg)
1.1	0.11	0.090	0.000024
1.6	0.36	0.298	0.000078
2.5	1.54	1.301	0.000342
4.0	4.65	3.967	0.001044
8.0	15.05	12.293	0.003236
12.0	11.00	8.385	0.002207
15.0	5.40	2.057	0.000542
18.0	3.71	1.485	0.000393
21.0	2.56	0.477	0.000255
25.0	2.27	0.241	0.017590
32.0	2.19	0.029	0.010102
40.0	1.17	0.000	0.000000
Total	50.0	30.62	0.03582

Table 1 from Walenga et al.[6]

Carrier-API Particle Interactions

- CFD typically considers particles as point masses
  - Cannot consider complex carrier-API particle interactions for DPIs
- Discrete element method (DEM) modeling can consider complex particle interactions
- May be paired with CFD

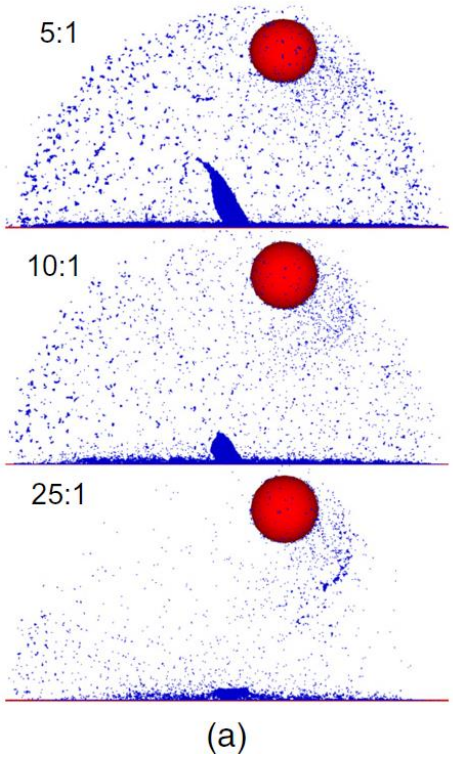

Figure 4a from Tong et al.[7]

Common Areas for Improvement (cont'd)

4. Compartmental PK models may be used to establish BE at the local site of action. However, these models often do not directly predict local lung tissue PK and may attempt to use systemic PK metrics as indicators of BE at the site of action without firmly establishing the connection.

PBPK Modeling for Understanding Role of Regional Deposition

- While regional deposition is an important component of delivery to the local site of action, it may not always be a surrogate for regional absorption.
- PBPK modeling may be used to understand impact of dissolution and permeation on relationship between regional deposition and regional absorption.

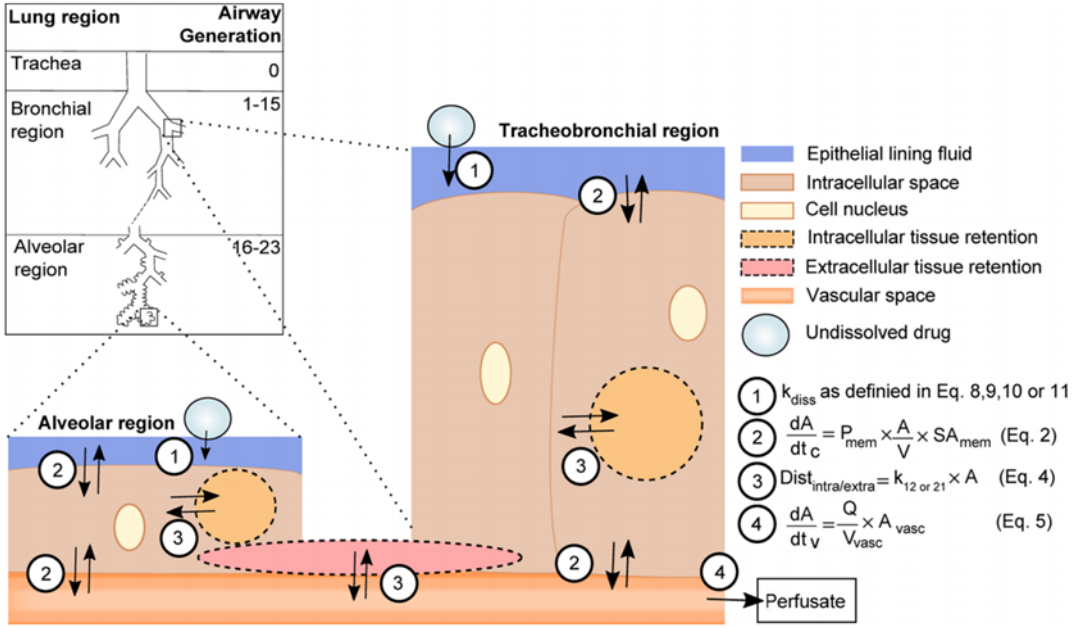

Figure 2 from Eriksson et al.[8] – Model structure for estimating dissolution rate constant (k_{diss}) for pulmonary drug delivery.

Common Areas for Improvement (cont'd)

5. Parallel models may produce contradicting predictions without an attempt to reconcile differences (e.g., two models that predict regional deposition).
6. Statistical plan is either absent or inappropriate.
7. There is often a lack of connection between in vitro data collected by firm and model inputs.

Statistical Approaches

5. Recommendation Related to the Population Bioequivalence (PBE) Statistical Analysis Procedure Used in Bioequivalence Determination of Budesonide Suspension Inhalation Product:

A. Step-wise Procedure of the PBE Computation:

Step 1. Establish population BE criterion:

Population BE criterion:

$$\frac{(\mu_T-\mu_R)^2+(\sigma_T^{\,2}-\sigma_R^{\,2})}{\sigma_R^{\,2}}\le\theta \quad \textbf{or} \quad \frac{(\mu_T-\mu_R)^2+(\sigma_T^{\,2}-\sigma_R^{\,2})}{\sigma_{T0}^{\,2}}\le\theta$$

Linerarized Criteria:

$$\eta_1=(\mu_T-\mu_R)^2+(\sigma_T^{\,2}-\sigma_R^{\,2})-\theta_p\bullet\sigma_R^{\,2}<0 \qquad \textbf{for } \sigma_R>\sigma_{T0}$$

$$\eta_2=(\mu_T-\mu_R)^2+(\sigma_T^{\,2}-\sigma_R^{\,2})-\theta_p\bullet\sigma_{T0}^{\,2}<0 \qquad \textbf{for } \sigma_R\le\sigma_{T0}$$

Where,

$\mu_T-\mu_R$: Mean difference of T (log scale) and R (log scale) products

$\sigma_T^{\,2},\sigma_R^{\,2}$: Total variance of T and R products

σ_{TO}: Regulatory constant (σ_{TO}= 0.1)

θ_p: Regulatory constant (θ_p= 2.0891) calculated as following:

$$\frac{[\ln(1.11)]^2+0.01}{0.1^2}=2.089$$

Excerpt from product specific guidance for budesonide inhalation suspension describing PBE procedure.[9]

- For models that use aerodynamic particle size distribution (APSD) results from realistic mouth-throat testing as inputs, population bioequivalence (PBE) may be useful if in vitro data are available from three lots.
- If model predictions are made on an individual basis, average bioequivalence may be appropriate.

Connections with In Vitro Data

- APSD results from realistic mouth-throat testing may used as direct inputs for semi-empirical regional deposition models or to validate CFD model predictions.
- Dissolution data may be used as inputs to assess biorelevance.
- Other relevant studies include plume geometry and spray velocity.
- Ensure that modeling assumptions or results are not in conflict with collected in vitro data.

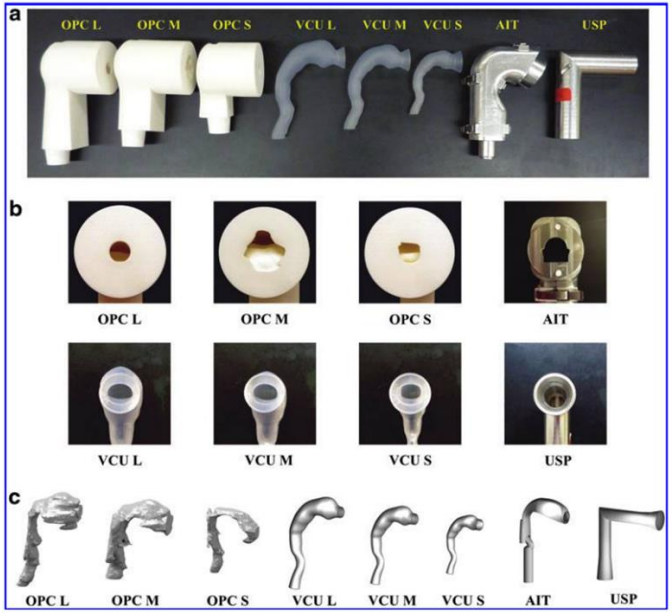

Figure 1 from Wei et al.[10] – Various realistic mouth-throat models include Oropharyngeal Consortium (OPC), Virginia Commonwealth University (VCU), Alberta Idealized Throat (AIT), and United States Pharmacopeia (USP).

Common Areas for Improvement (cont'd)

8. Details on modeling methods are often not sufficient.
   a) Justifications for assumptions may not be provided.
   b) Methods should be provided to the extent that the work could be replicated.
   c) Sources for parameterization may be unspecified or there may be identifiability issues.
   d) For further details, please see *Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry*.[11]

Conclusions

1. Mechanistic modeling is currently used to support ANDA submissions for OIDPs.

2. Several areas for improvement have been observed across several ANDA and Pre-ANDA submissions, including model validation.

3. Models may be used to elucidate the relationship between regional deposition and regional absorption as well as provide connections with in vitro data to predicted in vivo outcomes.

4. Successful models can be used to support alternative bioequivalence approaches for OIDPs based on sufficient verification and validation.

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