Using PBPK to link systemic PK to local delivery in the lung

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In collaboration with
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Mike Hindle (VCU)
Disclaimer

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- **Views expressed in this presentation do not necessarily reflect the official policies of the U.S. Food and Drug Administration,**

- nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.
Topics related to Bioequivalence?

dose, regional deposition, time?

40 - 90 % Swallowed
(reduced by spacer or mouth rinsing)

Mouth and pharynx

10 - 60 %
Deposited in lung

Lung

Complete absorption from the lung

GI tract

Absorption from gut

Liver

Orally bioavailable fraction

First-pass inactivation

Systemic side effects

Systemic Circ.
Actual Question of this research Project

Can PK (NCA, PBPK/semi-mechanistic models) extract Information on:

• Dose
• Dissolution/Absorption
• Regional Deposition

\[ \text{Dose} \rightarrow \text{central} \rightarrow \text{peripheral} \]

\[ \text{Cl}_{\text{muc}} \rightarrow \text{Dose} \rightarrow \text{AUC?} \]

\[ k_a \rightarrow \text{Slow?} \rightarrow \text{fast?} \]
Study Outline

- Develop three DPI-FP formulations (R. Price/Jag Shur)
  - Same dose
  - Same dissolution rate
  - Difference in central to peripheral lung deposition.

- Characterize through in vitro experiments
  - Ex throat dose (Mike Hindle)
  - Cascade impactor profile
  - Dissolution rate

- Perform PK (4 way cross-over, repeat one formulation)
  - Inhalation profiles measured for each inhalation
  - Intra-subject variability
  - NCA, compartmental population PK modeling (PBPK)
### Cascade Impactor Data

<table>
<thead>
<tr>
<th>Mass deposition</th>
<th>Particle size (μm)</th>
<th>A - 4.5 μm</th>
<th>B - 3.8 μm</th>
<th>C - 3.7 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mass Median Aerodynamic Diameter</strong></td>
<td></td>
<td>4.50</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Larger Particles</td>
<td>2.8 - 8.1 μm</td>
<td>12.5</td>
<td>14.4</td>
<td>11.5</td>
</tr>
<tr>
<td>Smaller Particles(^p) (μg)</td>
<td>&lt; 2.8 μm</td>
<td>4.8</td>
<td>9.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Relative Ex Throat Dose</td>
<td></td>
<td>1</td>
<td>1.3</td>
<td>1.2</td>
</tr>
</tbody>
</table>

\(^c\) and \(^p\) presumable representing central and peripheral lung deposition, respectively

- Similar mass deposition on larger stages
- Mass deposition on smaller stages was substantially smaller for A-4.5μm
Do formulations provide same absorption rate?

In vitro dissolution and permeation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>MDT (h)</th>
<th>Relative surface area</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-4.5 µm</td>
<td>15.4</td>
<td>0.5</td>
</tr>
<tr>
<td>B-3.9 µm</td>
<td>13.3</td>
<td>0.7</td>
</tr>
<tr>
<td>C-3.7 µm</td>
<td>10.3</td>
<td>1</td>
</tr>
</tbody>
</table>
PK Study Design

- 4-way, cross-over, double blind
- 24 healthy volunteers
- Dose: 5 * 100 μg
- Record individual inhalation profiles
- Non-compartmental Analysis + Compartmental Analysis (population-PK)
- PBPK based evaluation of popPK results
Before dose normalization

![Graph](image)

- A-4.5 um
- B-3.8 um
- C-3.7 um
- C-3.7 um (Repeat)
Conclusion I: NCA/BE

Overall:

Before dose Normalization
• AUC and $C_{\text{max}}$: $A \# B = C$

After Dose Normalization
• AUC: $A = B = C$
• $C_{\text{max}}$/Dose: $A \# B = C$

AUC: c/p Differences could not be shown

$C_{\text{max}}$: c/p Differences ????
Population PK analysis.

Fc: absorbed dose fraction from the central region of the lungs

Fp: absorbed dose fraction from the central region of the lungs

First 6 h

Drug concentration (pg/mL)

Central lung

Periphe ral lung

Central CMT

Peripheral CMT

\( F_c \)

\( F_p \)

\( k_{a_c}^* \)

\( k_{a_P}^* \)

\( C \)

\( C_L \)

\( CL_D \)
<table>
<thead>
<tr>
<th>Parameters</th>
<th>A - 4.5 μm</th>
<th>B - 3.8 μm</th>
<th>C - 3.7 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption $t_{1/2}$ for central lung (h)</td>
<td>6.2</td>
<td>7.9</td>
<td>9.1</td>
</tr>
<tr>
<td>Absorption $t_{1 peripheral}$ lung (h)</td>
<td>0.241</td>
<td>0.114</td>
<td>0.096</td>
</tr>
<tr>
<td>Absorbed dose - central lung (%)</td>
<td>6.4 (18.2%)</td>
<td>4.4 (19.9%)</td>
<td>4.8 (15.1%)</td>
</tr>
<tr>
<td>Absorbed dose - peripheral lung (%)</td>
<td>5.1 (13%)</td>
<td>9.9 (17%)</td>
<td>9.9 (11%)</td>
</tr>
<tr>
<td>c/p ratio</td>
<td>1.25</td>
<td>0.44</td>
<td>0.48</td>
</tr>
</tbody>
</table>
Point estimate and 90% CI for geometric mean ratio

- B-3.8 µm and C-3.7 µm were bioequivalent for both Fc and Fp
- A-4.5 µm vs B-3.8 µm and A-4.5 µm vs. C-3.7 µm were not bioequivalent
Conclusion 2: Proposed New Methodology for PopPK BE testing

- **PK trial**: Perform PK study of Test (T) and Reference (R) Product
- **NCA**: Standard BE of $C_{\text{max}}$ and AUC
- **Perform PopPk analysis**: Determine absorbed dose in central and peripheral lung for every subject
- **Test BE**: Perform BE assessment for absorbed dose in **central** lung
  Perform BE assessment for absorbed dose in **peripheral** lung
Can we explain PopPK results by PBPK?

- We Know from PopPK
  - peripheral and central dose
  - central and peripheral $ka$

- PBPK Parameters
  - Deposited dose (in vitro)
  - c/p ratio (MMAD)
  - Dissolution (MMAD, GSD)
  - Permeability
    - caco-2-cells
    (isolated perfused lung)
PBPK Approach

Deposition:
- Subject related
  - Inhalation profile
- In vitro:
  - Ex-throat dose
  - Cascade impactor

In-silico Assessment:
- Deposition Modeling
  - c/p ratio
  - Regional doses

Dissolution:
- Subject related:
  - Healthy/Patient
- In vitro:
  - Solubility
  - Particle Size
  - Dissolution rates
- In-silico
  - Agglomeration factor
  - Noyes-Brunner

Output
- Dissolution rate

Diffusion:
- Subject related:
  - Surface Areas, Thickness
- In vitro:
  - Peff (caco-2)
- In-silico
  - Ficks-law (scaling)

Output
- Absorption rate

Input parameters:
- central
- peripheral
Absorption Profile: PopPK vs PBPK

 Peripheral

 Formulation C

 Central

 Formulation C

 Dose: 54 mcg, Preludium
 Surface area: 60.2 *10^4 cm^2
 Permeability Peff: 13.8*10^-3 cm/h (Eriksson)
 Fitted Parameter:
 Solubility: 0.73 µg/ml (Literature =0.5-1.4 µg/ml)

 Dose 25 mcg, Preludium
 Surface area: 1.00E+04 cm^2
 Solubility: 0.73 µg/ml
 Fitted Parameter:
 Permeability: 0.7*10^-3 cm/h
Drug Concentration in Lining Fluid

Peripheral Lung

Central Lung

Dissolved drug concentration (mcg/ml)

Time (hr)

Upper limit for sink condition

Upper limit for sink condition
Conclusion (Part 3)

• PBPK model appears to be able to describe central and peripheral absorption by considering dissolution and permeation.

• Slow central absorption due to lack of sink conditions and combined effects of dissolution and permeation.

• PBPK approach should be able to predict PK of formulations differing in regional deposition, dose and dissolution.

• Can PBPK support NCA approach?
Is $C_{\text{max}}$ sensitive to c/p ratio?

Differences in Dissolution Rate

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Integrate in PBPK Model

Nernst-Brunner

Ficks Law

$C_{\text{max}}$, if only dissolution differs

<table>
<thead>
<tr>
<th>$C_{\text{max}}$ ratio</th>
<th>Predicted</th>
<th>Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/A</td>
<td>1.15</td>
<td>1.8</td>
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Average % Dissolved

Time (h)

Concentration (ng/L)
Conclusions

• NCA Analysis are able to answer relevant questions related to BE assessment of Inhalation drugs (at least for lipophilic corticosteroids)
  – Dose
  – Residence time
  – Regional deposition

• Clinical studies might not be necessary

• Work underlines that PK may be able to provide supportive information important for pulmonary bioequivalence assessment
Study teams

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