What are the knowledge gaps that need to be filled before one can approve generic inhalation drugs on *in vitro* and PK studies alone?
Disclaimer

• The opinions expressed in this presentation are those of the speaker and not necessarily those of the University of Florida and Funding Agency.

• Consultant for pharmaceutical industry in inhalation space
Questions relevant for pulmonary equivalence?

• What is the deposited dose?
• What is the regional deposition?
• What is the pulmonary residence time?

What is FDA recommending?

• In vitro (cascade impactor, delivered dose)
• Pharmacokinetics (systemic safety)
• Clinical study

Hypothesis?

• In vitro tests and PK should be sufficient
Performed Work (HHSF223401610099C; Preliminary Results)

- Designed **three DPI formulations**:  
  - Differences in c/p ratio

- Assessed in vitro performance  
  - **Cascade impactor, anatomical throats**, inhalation profiles mirroring in vivo  
  - **Dissolution tests**

- PK Bioequivalence study  
  - **Non-compartmental Analysis** (NCA)  
  - **Compartmental Analysis** (NONMEM®)

- Are in vitro + PK studies able to identify differences in:  
  - **dose, pulmonary residence time, c/p ratio** (mucociliary clearance of central lung)
Cascade Impactor Studies

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Stage 1-3</th>
<th>Stage 4-7</th>
<th>MMAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (F17)</td>
<td>16</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>B (F16)</td>
<td>19</td>
<td>9.3</td>
<td>3.9</td>
</tr>
<tr>
<td>C (F15)</td>
<td>16</td>
<td>8.3</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Future work:
- What anatomical throats or combination of throats should be used to predict “deposited dose”
- Need for implementing **statistical tests** for profile comparison (User friendly App.....)
- Further work needs to relate differences in profiles to differences in geography of lung deposition (in vitro/in silico/PK)
In vitro methods: Dissolution rate and in vivo absorption rates

Potential Applications of Dissolution tests

• Dissolution profiles should be included in the array of in vitro tests

Further work:
• Which method (USP, Transwell®)?
• Research on which compounds should be performed (BCS)?
• Assess sensitivity of dissolution tests to predict differences in absorption profiles (ivic correlations)
• Which statistical test (f1/f2 test suitable?)
• Acceptance criteria (Calibrate acceptance criteria with PK: relate dissolution rate differences to differences in Cmax)
PK RESULTS

- PK is able to detect difference in pulmonary available **dose (AUC)**

- PK detected differences in \( C_{\text{max}} \) (differences in absorption rate, differences in c/p ratio?)

Normalized Mean (±SE)
PK Profiles by Formulation

![Graph showing PK profiles by formulation](image)

- Concentration (pg/ml)
- Time (h)
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
<table>
<thead>
<tr>
<th>Deposited Dose</th>
<th>Absorption Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose central (%)</td>
<td>$K_a$ central (h$^{-1}$)</td>
</tr>
<tr>
<td>A (F17) 5.4</td>
<td>A (F17) 0.08</td>
</tr>
<tr>
<td>B (F16) 5.4</td>
<td>B (F16) 0.10</td>
</tr>
<tr>
<td>C (F15) 5.0</td>
<td>C (F15) 0.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose peripheral (%)</th>
<th>$K_a$ peripheral (h$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (F17) 5.2</td>
<td>A (F17) 0.58</td>
</tr>
<tr>
<td>B (F16) 8.7</td>
<td>B (F16) 1.1</td>
</tr>
<tr>
<td>C (F15) 8.0</td>
<td>C (F15) 1.2</td>
</tr>
</tbody>
</table>

Population PK seems to be able to identify differences in c/p deposition within this study.
Summary

• In vitro + PK might holds promise to assess BE (for slowly dissolving inhalation drugs)

• Potential for more work:
  • Evaluation of ex throat/cascade impactor profiles
    • Develop easy to use validated statistical tool with suitable user interface for mCSRS test
    • Develop less complex statistical test with similar statistical behavior than mCSRS
    • Which throat/combination of throats should be used to provide a good estimate of lung dose for wide range of inhalation products. Research is proposed to design/identify such solutions
  • Dissolution tests
    • Identify best experimental approach (Transwell vs USP, sample preparation)
    • Evaluate whether f1/f2 statistical test is able to make discriminatory decisions. PBE approaches using alternative metrics (e.g. mean dissolution time, dissolution rate..)
    • Identify “confidence intervals”, e.g. through comparison with PK absorption behavior (Cmax, tmax), Identify for which class of compounds test is relevant (BCS system)
  • Evaluate PK Approaches to identify differences in pulmonary fate (c/p)
    • Use of compartmental methods to identify differences in c/p deposition seems very promising. More work is needed (PopPK, statistics)
  • Further Integration of in vitro/ in silico assessments into PopPK or PBPK models
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