Bioequivalence of Inhaled Corticosteroids

-with emphasis on Pharmacokinetic Tools
Topics related to Bioequivalence

Mouth and pharynx

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

GI tract

Absorption from gut

10 - 60 % Deposited in lung

Complete absorption from the lung

Lung

Orally bioavailable fraction

Systemic Circ.

Systemic side effects

Liver

First-pass inactivation

Adapted from Meibohm, 2000
# BE of Inhalation Drugs

## LOCAL EFFECTS
- **How much is available to Lung?**
  - Considers mucociliary clearance
- **Where is drug deposited?**
  - (central / peripheral)
- **How long does drug stay in the lung?**
  - (residence time)

## SYSTEMIC SIDE EFFECTS
- **How much is absorbed?**
  - (Safety)

### BE of local effects:
- In-vitro tests, scintigraphy
- Pharmacokinetics
- Clinical studies
Clinical Studies

To show Differences in Therapeutic Outcome: Brand vs Generic

Use of meaningful clinical measures or biomarkers, able to show differences if dose, residence time, C/P ratio differs

- Steep dose-response curve
- Manageable study size
- Manageable cost
- Manageable Time frame
Comparative efficacy and safety of twice daily FP powder Vs Placebo in treatment of moderate asthma, Pearlman DS et al., A Annals of Allergy, Asthma and Immunology, 78, 356-362 (1997)

There were no statistically significant differences at endpoint among the three fluticasone propionate groups.”

Table 3. Mean Change (SEM) in Efficacy Variables from Baseline to Endpoint

<table>
<thead>
<tr>
<th>Efficacy Variable</th>
<th>Placebo</th>
<th>FP, 50 µg†</th>
<th>FP, 100 µg</th>
<th>FP, 250 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L*</td>
<td>-0.22 (0.06)</td>
<td>0.43 (0.06)</td>
<td>0.47 (0.07)</td>
<td>0.44 (0.06)</td>
</tr>
<tr>
<td>Morning PEF, L/min*</td>
<td>-24 (4)</td>
<td>20 (5)</td>
<td>16 (6)</td>
<td>27 (5)</td>
</tr>
<tr>
<td>Evening PEF, L/min*</td>
<td>-23</td>
<td>7</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Total daily asthma symptom score</td>
<td>0.21 (0.04)</td>
<td>-0.12 (0.03)</td>
<td>-0.17 (0.04)</td>
<td>-0.24 (0.05)</td>
</tr>
<tr>
<td>Albuterol use, puffs/day*</td>
<td>1.7 (0.3)</td>
<td>-0.9 (0.3)</td>
<td>-1.1 (0.3)</td>
<td>-1.2 (0.3)</td>
</tr>
<tr>
<td>Number of nighttime awakenings/wk*</td>
<td>0.21 (0.05)</td>
<td>0.03 (0.04)</td>
<td>-0.03 (0.02)</td>
<td>-0.03 (0.02)</td>
</tr>
</tbody>
</table>

* P < .001 based on comparisons versus placebo across all treatment groups within efficacy population.
† FP = fluticasone propionate.
SEM = standard error of the mean.

342 patients
Parallel group design

“to detect an increase in FEV1 of 20%—........—with a power of 80%, 630 patients would need to be randomized”
Clinical Alternatives

Ahrens (cross-over, about 30 patients, 10 weeks per patient)

Method awaits update through FDA sponsored study

80 mcg BDP/d 100 mcg FP/d 240 mcg BDP/d 300 mcg FP/d

LAST 7d TREATMENT 2.71 (0.087) 2.67 (0.086) 2.76 (0.086) 2.83 (0.086)

e-No ???
Clinical Studies

Clinical Differences between brand name and generics are likely to be smaller than detectable through “manageable” clinical methods.

More information on eNO, and other biomarkers are needed.
Alternative Approach

- In-vitro test
- How much is **deposited**? (Respirable Dose?)
- Where is it deposited?
  - Cascade impactor data?

- Pharmacokinetic tests
  - How much is **available** to the lung? (+/- charcoal)
  - Where is it deposited? (for slowly dissolving drugs)
  - How long does it stay in the lung?
    - AUC, $C_{\text{max}}$, or equivalent (MAT, MRT)
In-vivo/in-vitro Correlation

50 % Difference in RD

20% Difference in AUC and $C_{\text{max}}$

Asmus, Hendeles et al.

PK based AUC’s capture additional factors than just “respirable dose”
Goal of This Presentation

• Evaluate the role traditional PK Tools (AUC, $C_{\text{max}}$....) can play in BE of ICS
  • Slowly dissolving drugs
  • Fast dissolving drugs
  • Orally available drugs

• Assess whether traditional goal-post (CI within 80-125%) can be used
Trial Simulation

- Validate and Simulate Concentration-time profile for subjects within a trial considering variability across subjects
- Repeat simulation for 200 trials to assess variability across trials
- Perform Bioequivalence tests for 200 trials, report % trials showing equivalence.

**Variability**
- $\text{Cl}$ 10%
- $\text{Vd}$ 10%
- $K_a$ 30%
- $C/P$ ratio 40%
- $K_{\text{muc}}$ 20%
- Dose to lung 30%
- Residual 17-20%
Calculate: AUC, $C_{\text{max}}$, calculate ratios and 90% CI, Percent of independent trial showing bioequivalence.
AUC: What can it tell us? (for drugs with low oral bioavailability)

- **AUC**
  - ~ Systemic exposure (Safety)
  - ~ Quantifies: drug available to lung?

- **Drug available to Lung**
  - ~ Respirable dose – drug removed through mucociliary clearance

- **Drug removed via CL_{muc}**
  - ~ C/P ratio, Dissolution Rate

- **AUC**
  - ~ respirable Dose, C/P, dissolution rate
Orally available drugs

AUC ~ drug available through lung and GI tract
     ~ overall systemic load

AUC under GI charcoal ~ drug available to lung

Thorsson et al. (1994)
## Simulations: AUC affected by Dose

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>500 µg</td>
<td>500 µg</td>
</tr>
<tr>
<td><strong>Variability</strong></td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td><strong>Studies showing equivalence</strong></td>
<td>90%</td>
<td>3%</td>
</tr>
</tbody>
</table>

* % Trials with CI within 80-125%

- AUC is sensitive to Dose (respirable)
- for fast and slow dissolving drugs
AUC: Affected by C/P Ratio

slowly dissolving drugs

more central dose

more peripheral dose

CFC-BDP  HFA-BDP
Simulations: AUC affected by C/P ratio

drug is slowly dissolving, such as FP

200 Simulations (same Dose)

<table>
<thead>
<tr>
<th></th>
<th>Brand</th>
<th>Generic</th>
<th>Generic</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/P Ratio</td>
<td>45/55</td>
<td>45/55</td>
<td>63/37</td>
<td>22/78</td>
</tr>
<tr>
<td>Variability</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>N</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Bioequivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials*</td>
<td>82%</td>
<td>6%</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

* % Trials with CI within 80-125%

• AUC is sensitive to C/P ratio
Special Scenaria:

- AUC is affected by both respirable dose and C/P ratio
- Theoretically, differences might cancel out

Higher, more central dose

Lower, more peripheral dose

AUC is identical: Respirable Dose differs → Determine respirable dose, or PK in asthmatics …
What happens if one switches to asthmatics?

- Dose to lung is similar for Asthmatics and Healthy (Edsbaecker, 2008)
- C/P ratio has to differ to explain difference in AUC
  - 50/50 (typical value) in healthy to 90/10 in asthmatics
  - Deposition in asthmatics is central
  - If AUC in healthy is similar because differences in Dose and C/P cancels out
  - Shift to asthmatics with different C/P ratios will result in differences in AUC.

Harrison, Tattersfield, 2003
Actual PK Study in Healthy and Asthmatics

• Healthy volunteers:
  – AUC ‘s in formulation 1 and 2 were about the same
  – AUC’s of hydrophilic component were equivalent

• Asthmatics:
  – AUC of glucocorticoid in formulation 1 was significantly lower than in formulation 2
  – AUC’s of hydrophilic component were equivalent

• PK in Healthy and asthmatics can determine whether respirable dose and C/P ratio are similar
## P/C ratio \((50/50)_{\text{Brand}} \text{ vs } 30/70_{\text{Generic}}\) in Healthy

<table>
<thead>
<tr>
<th></th>
<th>Brand</th>
<th>Generic</th>
<th>Generic</th>
<th>Generic</th>
<th>Generic</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respirable Dose</strong></td>
<td>120 µg</td>
<td>100 µg</td>
<td>100 µg</td>
<td>100 µg</td>
<td>100 µg</td>
<td>100 µg</td>
</tr>
<tr>
<td><strong>C/P ratio</strong></td>
<td>90/10</td>
<td>50/50</td>
<td>65/35</td>
<td>70/30</td>
<td>75/25</td>
<td>90/10</td>
</tr>
<tr>
<td><strong>Variability (%)</strong></td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

**Bioequivalence**

| (%) of trials | 0%  | 1%  | 20% | 80% | 6%  |

Generic is very unlikely to show equivalent AUC in Asthmatics
How long does drug stay in the lung?

• Driven mainly by formulation
  – Solution
  – Suspension
  – DPI/MDI

• Important for pulmonary selectivity
How long does drug stay in the lung?

Differences in dissolution rate determine absorption rate differences.
How can PK assess Differences in Residence Time:

- **$C_{\text{max}}$:**
  - easy to determine

- **MRT:**
  - can be measured directly from Conc-Time profiles ($=\text{MAT} + \text{MRT}_{iv}$)

- **MAT:**
  - can be determined from inhalation and iv data ($\text{MRT}_{inh} - \text{MRT}_{iv}$)

- **Deconvolution**
### How long does drug stay in the lung?

200 Simulations

<table>
<thead>
<tr>
<th></th>
<th>Brand</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_a$ (h$^{-1}$)</td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td>Variability (%)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>$N$</td>
<td>36</td>
<td>36</td>
</tr>
</tbody>
</table>

#### Bioequivalence* (% of trials)

<table>
<thead>
<tr>
<th></th>
<th>Based on MRT</th>
<th>Based on MAT</th>
<th>Based on $C_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>22%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* $C_{\text{max}}$ is a sensitive parameter to evaluate differences in absorption rate.
Overall

• PK studies are able to detect differences in
  – How much drug is available (slow and fast dissolving drugs)
  – How long drug stays in lung (slow and fast dissolving drugs)
  – Where drug is deposited (slow dissolving drugs)
Cascade impacter profile was similar

PK (N=22;) differs by factor of 2 for both FP and Salmeterol

Clinical efficacy (N=270, randomized, parallel, peak expiratory flow) not different

Conclusion:
Pharmacokinetics should represent a main tool in BE of OID.
Potential Design

Perform PK of Brand and Generic in Healthy (evtl. with charcoal)

AUC Cmax similar?

No → Not equivalent

Yes

Avail. Dose, C/P, $k_a$

Available Dose, $k_a$
(special resp. Dose-C/P ratio)

either

Yes

Slowly Dissolving?

or

No → Respir. Dose, $k_a$

PK Asthmatics → Not equivalent

In-vitro: Respirable Dose

Equivalent?

No

Yes

Bioequivalent

In-vitro: P/C

Equivalent?

No → Not equivalent

Yes
Conclusion

• PK studies are suitable to make bioequivalence decisions
• How much, where, and for how long
• PK studies should be the cornerstone of any BE study for ICS
• Suitability should be studied

Acknowledgements:
Navin Goyal for developing and performing the trial simulations
Additional Slides
Deconvolution

How fast is absorption?

Fig. 4. Median cumulative bioavailability of systemically absorbed fluticasone propionate over a 12-hour period in healthy volunteers after inhalation of a 1000µg dose from 3 different devices. MDI = metered-dose inhaler.

Fig. 5. Amount of fluticasone propionate remaining to be absorbed from the lung, expressed as a fraction of the maximum amount, after inhalation of a 1000µg dose from 3 different devices in healthy volunteers. Values depicted on (a) linear and (b) logarithmic scales.

Charles Brindley, Christine Falcoz, Alison E. Mackie and Alan Bye
Lung function determines for most ICSs how much drug is available to the patient’s lung.

Mortimer et al., 2006
PK studies in Healthy and Asthmatics can solve Problem:

Brand, higher dose, more central (70/30; 100 µg)

Generic, lower dose, more peripheral (40/60, 80 µg)
EMEA

- EMEA: in-vitro might be sufficient for
  - Flow-rate dependent in-vitro data
  - Resistance to airflow
  - Dose delivered
  - Then: Scintigraphy or PK in Patients

- Canada:
  - in-vitro + clinical efficacy (sputum eosinophils or FEV1) + systemic exposure