Challenges in Meeting International Requirements for Clinical Bioequivalence of Inhaled Drug Products

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TEVA Pharmaceuticals
Presentation Topics

- Review of clinical requirements for orally inhaled drug products by various regulatory authorities
  - The need to demonstrate dose-response
- Study designs for determining clinical bioequivalence (BE)
  - Beta agonists (BA)
  - Inhaled corticosteroids (ICS)
- Implications of shallow dose-response for evaluating bioequivalence
- Alternative options?
## Status of Current Guidelines/Guidances For *In Vitro*/*In Vivo* BE of Orally Inhaled Products

<table>
<thead>
<tr>
<th>Country</th>
<th>Guideline/Guidance</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMEA</td>
<td>Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Treatment of Asthma in Children and Adolescents</td>
<td>Guideline, January, 2009</td>
</tr>
<tr>
<td>USA</td>
<td>Informal Only for Inhalation Products – Presentations given at Regulatory and Scientific Conferences. FDA seeking proposals.</td>
<td></td>
</tr>
</tbody>
</table>
Summary of EMEA Guideline

A stepwise approach to demonstrating BE has been proposed

- If BE is shown via *in vitro* comparison → STOP
- If *in vitro* data do not support BE, perform PK and deposition studies (PK with charcoal or imaging studies)
- If PK and deposition studies support BE → STOP
- If PK and deposition studies do not support BE, perform pharmacodynamic studies
Summary of EMEA Guideline: Pharmacodynamic Studies

- Bronchodilation or bronchoprotection may be used for efficacy studies.
- Study design must be sensitive enough to discern treatment differences:
  - Relative potency approach is recommended or statistically significant dose separation.
  - More than one dose of the test and reference product.
  - Use dose at the low end of recommended range.
  - 90% (?) confidence interval (CI) must be entirely within 67 to 150% if relative potency is used.
- For safety comparisons use high dose and include PK, PD measures and AE:
  - 90% CI must be entirely within 80 to 125% for PK.
  - Test product cannot be worse than reference product for any safety measure.
Summary of Canadian Guideline for Second Entry SABA

- **In vitro** comparison between test and reference products

- **Efficacy Study**
  - Two doses of test and reference using either bronchodilation or bronchoprovocation
  - Relative potency including 90% CI must be entirely between 80 – 125%.

- **Safety**
  - Maybe obtained from efficacy studies or separate studies
  - Monitor acute AEs (heart rate, tremor, serum potassium, etc)
  - Standard dose and higher dose
  - Safety of test product cannot be worse than reference product

- **PK ???**
Summary of Canadian Draft Guidance for Second Entry Market ICS

- *In vitro* comparison between test and reference
- A systemic exposure study (PK)
- A clinical study based on evaluating anti-inflammatory markers as primary endpoints
Canada Draft Guidance for ICS: Clinical Study

- **Study Population:** ICS naïve with stable asthma and > 3% sputum eosinophils.
  - Use of other anti-inflammatory measure needs to be pre-agreed
- **Study Duration:** Parallel design > 3 wks.
- **Choice of Dose:** Lowest dose of Test and Reference products vs Placebo.
- **Efficacy Endpoints:** Sputum eosinophils and pre-bronchodilator FEV₁
  - At least 50% change in sputum eosinophil counts and 10% predicted change in mean FEV₁ between active and placebo treatments are considered clinically significant.
- **Therapeutic Equivalence Criteria:** 90% CI of the ratio of mean eosinophil count and FEV₁ should be within 80-125%.
Summary of Likely FDA Expectations

From Dr. Chowdhury RDD 2008 (“US Perspectives on the Equivalence of ICS”)

- **In vitro**
  - Q1 and Q2 (same ingredients and all within 5% of reference)
  - Equal performance in applicable in-vitro testing (i.e., emitted dose, metered dose, APSD, general shape, appearance)
  - Similar instructions
  - Basically a “direct copy” of the reference

- **Safety:** Equivalent systemic effect (PK) at relevant dose or pharmacodynamic effect (PD) (i.e., HPA axis suppression if blood level comparisons not practical)

- **Efficacy:** Sensitive and relevant endpoints (dose-response)
  - SABA – bronchodilation or bronchoprotection models acceptable
  - ICS – no established clinical models capable of showing dose-response (candidates may include allergen challenge, sputum eosinophilia, exhaled nitric oxide and an “asthma stability model)
The Need to Demonstrate Dose-response?

- Scientific rationale for dose-response as a method for establishing dose equivalence
  - Study validity – assay sensitivity
  - Establishment of relative potency between Test and Reference
Dose-response Relationship

% Maximum Response

Dose
More Severe Disease Can Shift Dose-response Relationship to the Right

More severe disease
Most Current Respiratory Drugs Are Dosed at Flat Part of Dose-response Relationship

Currently available dose strengths of BA and ICS
Finney Bioassay (Parallel Line) Is Commonly Used to Establish the Relative Potency Ratio for Two Treatments

- The following hypotheses are tested:
  - The dose-response is LINEAR
  - The dose-response has a significant SLOPE
  - Dose response curves are PARALLEL

- The results demonstrate:
  - Dose independent RELATIVE POTENCY RATIO
  - Proof of a DOSE RESPONSE

Note: Data must overlap on the Response (y-axis) to use parallel-line assay
Effect of Slope on CI Using the Finney Bioassay

- With a shallow dose-response curve, the CI will be wider as compared with a dose-response curve that is steep.
Ideal Clinical Study Design/Efficacy Measure For Assessing Dose-response

- Sensitive for demonstrating dose-separation
  - Able to distinguish a doubling dose?
  - Steep dose-response slope

- Reproducible

- Low inter- and intra-subject variability

- Narrow CI for determining bioequivalence
  - Achieved with manageable patient numbers
Clinical Study Designs for BA – Formoterol and Albuterol

- Bronchoprotection
  - \( PC_{20} \) or \( PD_{20} \) to methacholine

- Bronchodilation
  - \( FEV_1 \) AUC
# Formoterol Dose-response Studies - Bronchoprotection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Key Endpoint</th>
<th>Design</th>
<th>Doses</th>
<th>Key Outcome</th>
<th>Estimated Dose Response Slope, per log dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becker and Simons, 1990</td>
<td>$PC_{20}$ at 6hr</td>
<td>Single dose Cross-over</td>
<td>Formoterol 12 and 24 mcg</td>
<td>Numerical dose-response</td>
<td>0.66 / log dose</td>
</tr>
<tr>
<td></td>
<td>$PC_{20}$ at 12hr</td>
<td>N=16 Ages 7-12</td>
<td></td>
<td></td>
<td>0.42 / log dose</td>
</tr>
<tr>
<td><strong>Single and Repeat Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipworth et al., 1999</td>
<td>Single dose-$PD_{20}$ 1 hr after first dose</td>
<td>Repeat dose Parallel N=38 Ages 18-45</td>
<td>Formoterol 6, 12 and 24 mcg</td>
<td>Numerical dose-response</td>
<td>1.0 / log dose</td>
</tr>
<tr>
<td></td>
<td>Repeat dose $PD_{20}$ 1 hr after last (2 wk) dose</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0 / log dose</td>
</tr>
</tbody>
</table>
Single Dose Formoterol Dose-response Studies – FEV\textsubscript{1}

<table>
<thead>
<tr>
<th>Reference</th>
<th>Key Endpoint</th>
<th>Design</th>
<th>Doses</th>
<th>Key Outcome</th>
<th>Estimated Dose Response Slope per log dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringdal et al, 1998</td>
<td>Max FEV\textsubscript{1}</td>
<td>N = 31 Ages 18-65</td>
<td>Formoterol 6, 12, 24 and 48 mcg</td>
<td>Significant dose-separation for 48 vs 6, 12, 24 mcg</td>
<td>0.16 L /log dose</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.15 L /log dose</td>
</tr>
<tr>
<td>Maesen et al, 1992</td>
<td>12 Average FEV\textsubscript{1}, FEV\textsubscript{1} AUC</td>
<td>N = 30 Ages 18-65</td>
<td>Formoterol 12, 24 and 48 mcg</td>
<td>Significant dose-separation for 12 and 48 mcg</td>
<td>0.09 L /log dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08 L /log dose</td>
</tr>
<tr>
<td>Palmqvist et al, 1997</td>
<td>12h Average FEV\textsubscript{1}</td>
<td>N=28 Ages 20-69</td>
<td>Formoterol 6, 12 and 24 mcg</td>
<td>Numerical dose-response</td>
<td>0.07 L /log dose</td>
</tr>
<tr>
<td>Bousquet et al, 2005</td>
<td>12h Average FEV\textsubscript{1}</td>
<td>N=51 Ages 18-70</td>
<td>Formoterol 12 and 24 mcg</td>
<td>Significant dose-separation</td>
<td>0.20 L /log dose</td>
</tr>
<tr>
<td>Pohunek et al, 2004</td>
<td>12h Average FEV\textsubscript{1}, FEV\textsubscript{1} at 12h</td>
<td>N=68 Ages 7-17</td>
<td>Formoterol 6, 12, 24 and 48 mcg</td>
<td>Significant dose-separation for 6 vs 24 and 48 mcg</td>
<td>0.08 L /log dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.09 L /log dose</td>
</tr>
</tbody>
</table>
Simulation Examining Power as a Function of Total Sample Size and Slope of Log Dose-response Relationship

- The sample size required to achieve reasonable study power was examined as a function of:
  - The slope of the dose-response curve
  - The confidence interval limits required to declare bioequivalency

- Intra-subject variability was estimated from the literature
## Sample Size for Methacholine Challenge

### 80% Power

<table>
<thead>
<tr>
<th>Slope</th>
<th>CI 0.8-1.25</th>
<th>CI 0.75-1.33</th>
<th>CI 0.67-1.5</th>
<th>CI 0.5-2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>70</td>
<td>45</td>
<td>20</td>
<td>&lt;10</td>
</tr>
<tr>
<td>0.9</td>
<td>90</td>
<td>50</td>
<td>30</td>
<td>&lt;10</td>
</tr>
<tr>
<td>0.8</td>
<td>120</td>
<td>65</td>
<td>40</td>
<td>&lt;10</td>
</tr>
<tr>
<td>0.7</td>
<td>145</td>
<td>85</td>
<td>45</td>
<td>&lt;10</td>
</tr>
<tr>
<td>0.6</td>
<td>195</td>
<td>115</td>
<td>60</td>
<td>25</td>
</tr>
</tbody>
</table>

### 90% Power

<table>
<thead>
<tr>
<th>Slope</th>
<th>CI 0.8-1.25</th>
<th>CI 0.75-1.33</th>
<th>CI 0.67-1.5</th>
<th>CI 0.5-2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>100</td>
<td>55</td>
<td>40</td>
<td>&lt;10</td>
</tr>
<tr>
<td>0.9</td>
<td>130</td>
<td>70</td>
<td>45</td>
<td>&lt;10</td>
</tr>
<tr>
<td>0.8</td>
<td>145</td>
<td>90</td>
<td>50</td>
<td>&lt;10</td>
</tr>
<tr>
<td>0.7</td>
<td>195</td>
<td>115</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>0.6</td>
<td>250</td>
<td>150</td>
<td>85</td>
<td>40</td>
</tr>
</tbody>
</table>

Based on assumed true relative potency of 0.95
Sample Point Estimates for Relative Potency Are Acceptable Even with Wider CIs

Range of sample point estimates of relative potency yielding 90% CIs that satisfy the given thresholds assuming 50 subjects and the same variances as used for the simulations

<table>
<thead>
<tr>
<th>Slope</th>
<th>CI 0.8-1.25</th>
<th>CI 0.75-1.33</th>
<th>CI 0.67-1.5</th>
<th>CI 0.5-2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacholine Challenge</td>
<td>1.0 – 1.1</td>
<td>0.9 – 1.2</td>
<td>0.8 – 1.3</td>
<td>0.7 – 1.6</td>
</tr>
<tr>
<td>(slope 0.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methacholine Challenge</td>
<td>0.9 – 1.1</td>
<td>0.9 – 1.2</td>
<td>0.8 – 1.3</td>
<td>0.7 – 1.7</td>
</tr>
<tr>
<td>(slope 0.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serial FEV₁</td>
<td>0.9 – 1.1</td>
<td>0.8 – 1.2</td>
<td>0.8 – 1.2</td>
<td>0.7 – 1.6</td>
</tr>
<tr>
<td>(slope 0.15)</td>
<td></td>
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</tbody>
</table>
# Summary of Albuterol Relative Potency and CI’s

<table>
<thead>
<tr>
<th>Citation</th>
<th># of Subjects</th>
<th>Dose (mcg) Albuterol</th>
<th>Treatment</th>
<th>Relative Dose Potency</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahrens et al. (1999)</td>
<td>24</td>
<td>90, 270</td>
<td>DPI Albuterol</td>
<td>1.12</td>
<td>0.68-1.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CFC MDI Ventolin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parmesewaran et al. (1999)</td>
<td>18</td>
<td>100, 200, 400</td>
<td>HFA MDI Proventil</td>
<td>1.08</td>
<td>0.81-1.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CFC MDI Ventolin</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stewart et al. (2000)</td>
<td>24</td>
<td>90, 360</td>
<td>CFC MDI Albuterol</td>
<td>1.01</td>
<td>0.69-1.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CFC MDI MDI Ventolin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Challenges Associated with Demonstrating Bioequivalence for BA

- Bronchoprotection and bronchodilator endpoints can be utilized

- Dose-response trends are observed with single dose studies
  - Slopes are generally flat (greater with methacholine challenge vs FEV$_1$)
  - CI needs to be wider than standard bioequivalence limit (0.8 to 1.25) in order for studies to be feasible
  - CI as wide as 0.67 to 1.5 still yields acceptable point estimates for dose potency when manageable patient numbers are utilized
Overview of Dose-response Data for Inhaled Corticosteroids (ICS) in Asthma

- A range of doses are approved based on studies investigating different doses in distinct populations (ICS naïve, ICS treated, OCS sparing)
  - Dose-response rarely demonstrated on traditional efficacy measures such as FEV$_1$, symptoms, rescue albuterol use, exacerbations, methacholine challenge

- The reproducibility of the occasional study design that have been able to discriminate ICS doses is unknown at present
# Dose Response Studies Where ICS Dose-response Was Observed

<table>
<thead>
<tr>
<th>Reference</th>
<th>Primary Endpoint</th>
<th>Design</th>
<th>ICS Doses</th>
<th>Key Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pauwels et al [NEJM 1997]</td>
<td>Exacerbations</td>
<td>210-215 patients/arm</td>
<td>BUD 100 and 400 mcg BD</td>
<td>Dose-response for Exacerbation Rate</td>
<td>No Dose Response for FEV$_1$, Sx or SABA use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1600 mcg bud</td>
<td>BUD 100 and 400 mcg BD + Formoterol 12 mcg BD</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>1 year study</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Parallel group</td>
<td></td>
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</tr>
<tr>
<td>Busse et al [JACI 1999]</td>
<td>FEV$_1$, %Predicted</td>
<td>Severe Asthma (FEV$_1$ 51-53%)</td>
<td>BDP CFC 100, 400 and 800 mcg/day</td>
<td>Dose-potency Ratio established</td>
<td>FEV$_1$ differences between adjacent doses was very small</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-59 patients/arm</td>
<td>BDP HFA 100, 400 and 800 mcg/day</td>
<td>2.6 (95%CI: 1.1-11.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 week study</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Parallel group</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ahrens et al [AJRCCM 2001]</td>
<td>Asthma Stability following OCS</td>
<td>12 patients on 800-2000 mcg ICS</td>
<td>BDP 100 and 800 mcg day</td>
<td>Dose-response established for FEV$<em>1$, PEF, FEF$</em>{25-75}$</td>
<td>Pilot study, CI 0.5-2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X-over</td>
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<tr>
<td></td>
<td></td>
<td>3 wks treatment</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>4-7 days wash-in</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>with 40mg bid OCS</td>
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</tr>
</tbody>
</table>
# Dose-response Using FeNO

<table>
<thead>
<tr>
<th>Reference</th>
<th>Primary Endpoint</th>
<th>Design</th>
<th>ICS Doses Daily</th>
<th>Key Outcome</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Silkoff et al [Chest, 2001] | FeNO             | 2 Studies (15 and 12 pts)  
Dose Escalation | Budesonide 100, 400 and 800 mcg | Dose-response between 100 and 800 mcg doses | FENO superior to FEV₁ and PC₂₀ in establishing dose-response |
| Jatakanon et al [Thorax, 1999]  | FeNO             | 21 pts  
4-week study  
Parallel Group | Budesonide 100, 400 mcg in QD or BID doses | Decrease in FeNO in a dose-dependent manner | Plateau after 400 mcg of BUD |
| Jones et al [ERJ, 2002]  | FeNO             | 65 pts on ICS, ICS withdrawn  
8-week study  
Parallel Group | Beclomethasone 50, 100, 200, and 500 mcg | Linear relationship between ICS dose and % change FeNO | Large drop-out rate  
Prednisone use |
| Kelly et al [JACI, 2006]  | FeNO, Sputum Eos. | 14 patients, ICS naive  
6-week, sequential, single-blind | Fluticasone 50, 100, 200, and 400 mcg | Linear dose-response relationship demonstrated | FeNO at screening was ~25 ppb. |
| Kharitonov et al [Thorax, 2002]  | FeNO (rate)      | 28 patients  
No controllers  
Parallel Group | Budesonide 100, 400 mcg | Onset of action was dose-dependent | Baseline FeNO 14-20 ppb. |
FeNO Studies – Silkoff et al

- FeNO difference was statistically significant from placebo at all ICS doses
- A significant dose-separation was demonstrated only between doses 100 and 800 mcg/d
- Must interpret with caution as this was a cumulative dose study

Adapted from Silkoff et al, Chest/119/5/May, 2001

FIGURE 1. Dose-response study: the change in FENO at each visit corresponding to baseline, placebo treatment, and then increasing doses of iBDP. The FENO trend for all the subjects (n = 15) is shown together with separate trends for high-baseline (n = 6) and low-baseline (n = 9) FENO groups. FENO at all doses of iBDP was significantly different from placebo treatment, but only FENO levels with 100 μg/d and 800 μg/d of iBDP were significantly different.
Summary of Dose-response Data With ICS

- Dose-response is difficult to demonstrate using traditional designs and efficacy measures.

- Study designs that may allow for dose-response to be shown include:
  - FeNO
  - Asthma stability using OCS wash-in

- Studies have limitations in design and have yet to be replicated.

- Even if successful, these studies will require 4-8 fold dose separation and a wider CI to succeed.
Challenges in Meeting Regulatory Requirements

- Limited guidances currently
  - All have different approaches and expectations
    - Almost all require dose-response to establish study validity

- Dose-response will be a challenge to demonstrate
  - Study designs which may succeed for BA and ICS have been reported
  - Additional confirmation still needed
  - Will require CI wider than current expectations
  - May require 4-8 fold dose separation
Additional Challenges

- Lowest strength available may be on flat part of dose-response relationship
- How to handle multiple strengths
- Availability of placebo devices to perform double-blind studies
- How to handle ICS/BA combinations
Alternative Approaches to Pursue if Dose-response Not Able to Be Shown

- Greater emphasis on *in vitro* equivalence
- EU approach of using PK with and without charcoal
- Canadian approach for ICS
  - Dose-response not necessary
- Clinical comparison using traditional measures
  - More pragmatic and clinically relevant especially for ICS
  - Compare Test product vs Reference product and placebo for each strength based on asthma severity
  - Inclusion of placebo arm provides study validity