Challenges in the development of affordable orally inhaled products

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Overview

- Drivers and Barriers to developing affordable OIPs
- Challenges in choosing a Reference drug
- Study conduct challenges
- Key regulatory challenges
- Summary
Drivers and Barriers to developing affordable OIPs
Asthma Prevalence Versus Cost of Care in Developed and Emerging Markets

World Map of the Prevalence of Clinical Asthma

North America $18.2 bn*
EU $9.0 bn*
Rest of the world = $3.6 bn *

*asthma & COPD inhaled drugs

Proportion of population (%) *

Source:
GINA guidelines 2013
IMS Worldview

2.5-5.0
0-2.5
No standardised data available

10.1
7.6-10.0
5.1-7.5

[Map showing prevalence and cost of care]
The Changing Spectrum of COPD

3 million deaths every year
65% of all global COPD deaths occur in India and China

<table>
<thead>
<tr>
<th>Country</th>
<th>Avg number of Cigarettes smoked per capita</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russia</td>
<td>2786</td>
</tr>
<tr>
<td>Japan</td>
<td>1841</td>
</tr>
<tr>
<td>China</td>
<td>1711</td>
</tr>
<tr>
<td>Turkey</td>
<td>1399</td>
</tr>
<tr>
<td>US</td>
<td>1028</td>
</tr>
<tr>
<td>Brazil</td>
<td>504</td>
</tr>
</tbody>
</table>

COPD estimated deaths in 2002

Source: International Classification of Diseases-10 codes: J40-J44, World Lung Foundation, American Cancer Society
Drivers And Barriers for the development of affordable inhalation products

Drivers

- Government and Payer demands
- Rising healthcare costs
- Increasing prevalence of respiratory disease in developed and emerging markets
- Demand for cost effective OIPs
- Greater availability of OIP BE Guidances

Barriers

- Freedom to operate
- Balance of development costs and profitability
- Unharmonized and changing regulatory requirements
- Requirements for evaluation in children/adolescents
- Complex delivery devices
- Commercialization
Challenges in Choosing a Reference Product
Choosing a reference listed drug (RLD) for global development

- Regulatory authorities often require studies to be conducted with their national RLDs and may even require that the studies be conducted at certified centres in their respective countries.

- Reference product can suddenly be withdrawn from the market.

- Selection of a “representative” reference batch can be a major problem especially when limited RLD batches are available in the market.

- Batch to batch variation is observed for the same RLD by country/within a market.
RLD differences within a market/across markets

Source: Cipla, Data on file 2013

mo = months from date of manufacture; FPM = Fine particle mass

- Reference Batch 1 (Country A) - Age of sample 3 Month
- Reference Batch 3 (Country A) - Age of sample 6 Month
- Reference Batch 5 (Country A) - Age of sample 8 Month
- Reference Batch 2 (Country B) - Age of sample 9 Month
- Reference Batch 4 (Country B) - Age of sample 17 Month
- Reference Batch 2 (Country C) - 12 month
- Reference Batch 1 (Country D) - 5 month
- Reference Batch 3 (Country D) - 8 month

Source: Cipla, Data on file 2013
Study Conduct Challenges
Study Conduct Challenges

• Phase I centers with respiratory expertise

• Complex, skill-based analytical methods and testing.

• Country restrictions in the inclusion of vulnerable populations (e.g., children, adolescents, women of child bearing potential).

• RLD blinding

• Estimating sample size/designing dose response studies when limited data is available

• Assuring proper device training
Lung deposition changes with Inspiratory flow rate

Inhalation rate    SLOW (30 L min⁻¹)          FAST (60 L min⁻¹)

FEV₁ 55% predicted

% Lung Deposition

0  4  8  12  16

Inhalation rate    SLOW (30 L min⁻¹)          FAST (60 L min⁻¹)
Inhaler Technique: Critical Errors

- Risk of critical error increased ($p<0.001$) with age, lower schooling, lack of instruction provided for the inhaler.

- Critical errors associated with ($p<0.001$) ↑ hospitalisation risk, emergency room visits, oral corticosteroid, poor disease control.
Challenges in conducting paediatric PK BE studies

- EMA generally requires *in vivo* studies in children.
- PK studies in children are prohibited in many countries for ethical reasons.
- PK profiling has to be truncated due to blood loss limitations.
- Centers with the required expertise are limited.
- Prohibitive sample size requirements due to:
  - Training limitations.
  - Need to evaluate asthma patients.
  - Variability associated with tidal versus deep breathing through a spacer.
EMA OIP guidelines – A standard for most markets?

**EMA – OIP guidelines**

- **In vitro**
  - Required

- **PK**
  - Required

- **Clinical**
  - Is it required?
Key Regulatory Challenges
Demonstrating equivalence for Stages with Low Mcg Quantities May not be Possible

Figure 1: Mass collected on each component of an Andersen 8-stage cascade impactor.

- Test
- Reference

Low amount of drug deposition
Within reference batches may not pass within 15% at stages with low deposition.
Healthy volunteers vs patients – the debate continues

Figure 1: Fate of inhaled drug in normal (A) and constrained (B) lung.

Aerolized drug

A

Normal

GI tract

lung tissue

B

Constrained

Aerolized drug

GI tract

lung tissue

Initial lung deposition

Absorption and mucociliary clearance

Figure 2: Lung retention, attained by scintigraphy of 99m Technetum-labelled BDP liposomes delivered via Aerotech II nebuliser to patients with asthma.
Do *in vitro* and PK bioequivalence assure comparable safety & efficacy?
## PK/PD relationship - LABA

**Formoterol DPI**

<table>
<thead>
<tr>
<th>Dose (mcg)</th>
<th>12 mcg</th>
<th>24 mcg</th>
<th>48 mcg</th>
<th>96 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>69 (10)</td>
<td>71 (10)</td>
<td>72 (11)</td>
<td>77 (11)</td>
</tr>
<tr>
<td><strong>Serum potassium (mmol/L)</strong></td>
<td>3.6 (0.2)</td>
<td>3.5 (0.2)</td>
<td>3.5 (0.2)</td>
<td>3.2 (0.3)</td>
</tr>
<tr>
<td><strong>FEV1 (L)</strong></td>
<td>3.86 (0.63)</td>
<td>3.96 (0.65)</td>
<td>4.01 (0.72)</td>
<td>4.04 (0.70)</td>
</tr>
<tr>
<td><strong>QTc (ms)</strong></td>
<td>399.6 (25.1)</td>
<td>409.2 (20.7)</td>
<td>414.0 (24.8)</td>
<td>423.1 (24.3)</td>
</tr>
<tr>
<td><strong>Blood glucose (mmol/L)</strong></td>
<td>6.2 (1.0)</td>
<td>6.7 (1.3)</td>
<td>7.1 (1.1)</td>
<td>7.4 (0.9)</td>
</tr>
<tr>
<td><strong>AUC0-t (pg.hr/ml)</strong></td>
<td>95.39</td>
<td>170.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cmax (pg/ml)</strong></td>
<td>21.39</td>
<td>42.99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PK studies are designed to assess a defined 20% difference b/w two products which is a very conservative margin to confirm equivalence.

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PK/PD relationship – ICS

Table 1: Pharmacokinetic parameters (Geometric mean values) for fluticasone HFA pMDI

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax (pg/ml)</th>
<th>AUC infinity (pg.hr/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP 50 mcg</td>
<td>118.7</td>
<td>693.1</td>
</tr>
<tr>
<td>FP 125 mcg</td>
<td>237.7</td>
<td>1547.1</td>
</tr>
<tr>
<td>FP 250 mcg</td>
<td>506.8</td>
<td>3365.4</td>
</tr>
</tbody>
</table>

PK studies based on a conservative margin of 80-125% are adequate to assess the lung and systemic exposure between two inhaled formulations.

Figure 1: % Change from baseline in FEV1 predicted

Figure 2: Mean plasma cortisol suppression for single doses of budesonide 800 µg and FP 250 µg, 500 µg, 1000 µg, and following the last of 7 doses of FP 1000 µg twice daily. *P < 0.001.
**AUC\(_{0-30\text{min}}\) is a good predictor of lung deposition**

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol (Test)* 200 mcg</th>
<th>Salmeterol (Reference) * 200 mcg</th>
<th>T/R ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>*AUC(_{0-30}) (with charcoal) hr. pg/ml</td>
<td>223</td>
<td>199</td>
<td>1.12</td>
</tr>
<tr>
<td>*AUC(_{0-30}) (without charcoal) hr. pg/ml</td>
<td>222</td>
<td>215</td>
<td>1.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Beclomethasone (17 BMP-Test)* 2000 mcg</th>
<th>Beclomethasone (17-BMP Reference)* 2000 mcg</th>
<th>T/R ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>**AUC(_{0-30}) (with charcoal) hr. pg/ml</td>
<td>1190</td>
<td>1250</td>
<td>0.95</td>
</tr>
<tr>
<td>**AUC(_{0-30}) (without charcoal) hr. pg/ml</td>
<td>933</td>
<td>1026</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*Pharmacokinetic evaluations comparing AUC\(_{0-30\text{ min}}\) (and C\(_{\text{max}}\)) are important in understanding bioequivalence of inhaled drugs, and these estimates can provide reliable estimates of lung deposition*

Source: *ERS 2010; **Inhalation Asia 2013

*Geometric mean values
Summary

• Equivalence to be evaluated using the most sensitive methodology i.e. PK studies

• Population most sensitive to detect differences to be considered

Harmonization of BE guidances for OIP across countries (sharing best practices) and improve global availability and access to affordable OIPs

• Leveragability of data and BE programs across countries

• Engage Industry-Regulators communication to build best practices
Acknowledgements

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Thank You