Bioequivalence of Orally Inhaled Drug Products (OIDP)

Gustavo Mendes Lima Santos
Coordinator of Therapeutic Equivalence
General Office of Medicines

IV Simposium SINDUSFARMA – IPS/FIP – ANVISA
June 22, 2015
Why discuss OIDPs?

• Asthma: over 300 million affected in the world;

• In Brazil it is estimated that 10% of the population has asthma;

• OIDPs were included in the programme *Farmácia Popular*;

• Farmácia Popular budget in 2012 was approximately USD 3 billion;

• Number of diseases treated by OIDPs has increased.
Orally Inhaled Drug Products

- Intended for drug delivery to the sites of action in the lung;

- Lower Doses $\rightarrow$ Greater Effect;

- Limiting factors: Pulmonary Deposition and Drug Delivery From Device;
Pulmonary Deposition

- Influence the amount of drug available in the site of action;

Pulmonary Deposition

Aerosol particle size determine lung deposition

- > 5 μm impaction deposited into oropharynx and swallowed
- 1-5 μm sedimentation Optimal for delivery to the lower airways and parenchyma
- < 0.8 μm likely to be exhaled by tidal breathing

Pulmonary Deposition

Figure 10.2 Mechanisms for particle deposition in lung airways

Lippmann, M. Respiratory System. ILO Encyclopaedia: http://www.ilocis.org/documents/chpt10e.htm#JD_Ch10_19
Drug Delivery From Device

- Influence the amount of drug delivered;

- Most Common Delivery Systems:
  - Pressurized Metered Dose Inhalers (pMDI);
  - Nebulizers;
  - Dry Powder Inhalers (DPI)
Pressurized Metered Dose Inhalers (pMDI)
Pressurized Metered Dose Inhalers (pMDI)

Pressurized Metered Dose Inhalers (pMDI)

• Advantages:
  – Cost;
  – Transportation;
  – Conservation.

• Disadvantages:
  – Coordination of the inhalation movement;
  – Only 10% to 20% of the dose is delivered in the site of action (due to the particle size and speed);
Nebulizers
Nebulizers

Source: https://en.wikipedia.org/wiki/Nebulizer#
Nebulizers

• Jet and Ultrasonic Nebulizers;

• Advantages:
  – Formulations without conservants (single dose flasks);
  – Breath sync not required;
  – Patients with handling problems (children, arthritis).

• Disadvantages:
  – Price;
  – Transportation (power supply required);
  – Variability of particle size: only 4.2% of labeled dose is available for inhalation (Hickey and Evan, 1996);
Dry Powder Inhalers
Dry Powder Inhalers

- Single Unity Dose Devices (Inhaled Capsules):

Source: https://www.imgbusddy.com
Dry Powder Inhalers

• Multi-Dose Devices (Diskus):

(Source: http://www.wikihow.com/Use-an-Inhaler#)
Dry Powder Inhalers

- Multi-Dose Devices (Diskus):

Source: www.admit-online.info

Source: www.mims.com
Dry Powder Inhalers

• Advantages:
  – Transportation;
  – Conservation;
  – Drug Characteristics for Formulation.

• Disadvantages:
  – Capacity to deliver the drug (particle size and device related);
Therapeutic Equivalence for OIDPs
Challenges for Demonstration of Therapeutic Equivalence for OIDPs

• Classical bioequivalence approach is considered inadequate;

• Unharmonized regulatory requirements among countries;

• Devices Similarity;

• Acceptance criteria for *In vitro* comparability tests;

• Adequate *in vivo* models to demonstrate efficacy and safety.
# Regulatory Requirements for Therapeutic Equivalence of OIDPs in US and EU

<table>
<thead>
<tr>
<th>STEP</th>
<th>SYSTEMICALLY ACTING DRUGS</th>
<th>LOCALLY ACTING DRUGS (EMA)</th>
<th>WEIGHT OF EVIDENCE APPROACH (FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Blowaivers based on BCS or dosage forms in solution</td>
<td>In vitro comparison OR</td>
<td>In vitro comparison AND</td>
</tr>
<tr>
<td>Step 2</td>
<td>Conventional PK BE Surrogate of PD</td>
<td>PK BE for safety and lung deposition OR</td>
<td>PK for systemic safety AND</td>
</tr>
<tr>
<td>Step 3</td>
<td>PD / Clinical endpoints (Therapeutic equivalence)</td>
<td>Relative potency PD / Clinical endpoints for efficacy or safety</td>
<td>Relative potency PD / Clinical endpoints for efficacy</td>
</tr>
</tbody>
</table>

*Lee et al.* Regulatory Considerations for Approval of Generic Inhalation Drug Products in the US, EU, Brazil, China, and India. *The AAPS Journal.* 2015 May 23.
Regulatory Requirements for Therapeutic Equivalence of OIDPs in Brazil

• Resolution RDC nº 37, August 3rd 2011:
  – Solutions → *in vitro* tests only
  – Suspensions and Powders → *in vitro and in vivo* tests

• Specific guidance not issued: Technical Note nº 01/2013, 25 March 2013 (only for *in vitro* tests);

• Case-by-case analysis;

• Theme included in Anvisa’s Regulatory Agenda 2015-2016.
Regulatory Requirements for Therapeutic Equivalence of OIDPs in Brazil

• **Device Comparability:**
  
  – Does the operation mechanism of the device exacerbate differences in patients’ efforts and handling?
  
  – Does the shape and dimension of the device exacerbate differences in patients’ efforts and handling?
  
  – Evidence of similarities could be demonstrated in patient handling studies
Regulatory Requirements for Therapeutic Equivalence of OIDPs in Brazil

• In vitro Comparability:

Table 1. Comparative Performance Tests that Must be Part of an Oral pMDI or DPI Pharmaceutical Equivalence (PE) Submission in Brazil

<table>
<thead>
<tr>
<th>Performance tests</th>
<th>Oral pMDIs</th>
<th>Oral DPIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug appearance</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>Priming and repriming</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Content of an operation over</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>the total content of the device</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerodynamic particle size</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>distribution by cascade impaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Particle / droplet size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>distribution by laser diffraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emitted dose mass</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>Number of doses per device</td>
<td>X</td>
<td>X (for reservoir DPIs)</td>
</tr>
<tr>
<td>Spray pattern</td>
<td>X</td>
<td>-</td>
</tr>
</tbody>
</table>

Lee et al. Regulatory Considerations for Approval of Generic Inhalation Drug Products in the US, EU, Brazil, China, and India. The AAPS Journal. 2015 May 23.
Regulatory Requirements for Therapeutic Equivalence of OIDPs in Brazil

- Aerodynamic Particle Size Distribution:

Source: [http://www.pharmacopeia.cn/v29240/usp29nf24s0_c601_viewall.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_c601_viewall.html)
Aerodynamic Particle Size Distribution (APSD)

Source:
http://fy.chalmers.se/OLDUSERS/molnar/lectures/Measurement%20Methods%20II.htm
Aerodynamic Particle Size Distribution (APSD)

• **Challenges:**
  
  – Statistical Approaches (modified chi-square, population bioequivalence);
  
  – Acceptance Criteria;
Regulatory Requirements for Therapeutic Equivalence of OIDPs in Brazil

• *In vivo* comparability:
  
  – Efficacy related to pulmonary deposition;
    • crossover PK studies, with inhibition of absorption from the gastrointestinal tract through administration of activated charcoal (if necessary);

  – Safety related to total quantity of drug available systemically;
    • crossover PK studies, without inhibition of absorption from the gastrointestinal tract through administration of activated charcoal;
Pharmacokinetic Studies

• Challenges:

– Are PK studies correlated to the amount of drug available in the lung?

– Are PK studies correlated to the region of deposition of the drug in lung (central/peripheral)?

– Are PK studies correlated to the amount of time that the drug stays in the lung?

– Goyal and Hochhaus, 2010: Simulations results correlating AUC to pulmonary deposition and $C_{\text{max}}$ to residence time in lung.
Regulatory Requirements for Therapeutic Equivalence of OIDPs in Brazil

• If pharmacokinetic studies are not feasible, pharmacodynamic studies would be acceptable:

  – Proposed Endpoints:

    • Sputum eosinophilia
    • Exhaled nitric oxide (eNO)
    • Bronchoconstriction challenges
    • Spirometry
Pharmacodynamic Studies

- **Challenges:**
  - Sensitivity to differentiate products;
  - Dose-response relation;
  - High variability of the biomarker.
Final Considerations

• Important to discuss international harmonization of regulatory criteria;
  – PQRI and IPAC-RS

• Stimulation of Research of more biorelevant techniques;

• Anvisa come to a guidance for industry for registration of OIDPs.
References

References

Thank you!