Challenges in Equivalence and Bioequivalence of Orally Inhaled Products

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Developing and advancing dry powder inhalation towards enhanced therapeutics

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Disease prevalence
Chronic Obstructive Pulmonary Disease (COPD)

Fast growing segment in BRIC countries…

In China

Smokers: 57.4 % ♂ and 2.6 % ♀
Prevalence: 16.7 % (in people aged 50 years and older)

Datamonitor: Forecast insight Asthma/COPD (2010)
Age relationship of COPD

Prevalence of COPD among adults aged 18 and over, by age group and sex: United States, annual average 2007–2009
Chronic Obstructive Pulmonary Disease (COPD)

COPD remains undiagnosed even in the mature markets (data from USA 2000)
Asthma/chronic obstructive pulmonary disease (COPD) medication market is a fast growing market, especially in the emerging markets where drugs have not been launched due to high costs.

The market is divided into the following classes of drugs:
- (inhaled) Glucosteroids (ICS)
- β-Agonsits
- Cl-channel blockers
- Antileukotrienes
- Anticholinergics
- Combinations thereof

At least 14 NCE in late phase
### US INHALED MARKET

<table>
<thead>
<tr>
<th>Product</th>
<th>2010</th>
<th>2011</th>
<th>∆ 2011/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advair</td>
<td>4,026</td>
<td>3,980</td>
<td>-1%</td>
</tr>
<tr>
<td>Spiriva</td>
<td>1,781</td>
<td>1,822</td>
<td>2%</td>
</tr>
<tr>
<td>Combivent</td>
<td>833</td>
<td>847</td>
<td>2%</td>
</tr>
<tr>
<td>Symbicort (MDI)</td>
<td>721</td>
<td>846</td>
<td>17%</td>
</tr>
<tr>
<td>Flovent</td>
<td>666</td>
<td>720</td>
<td>8%</td>
</tr>
<tr>
<td>Budesonide Generic</td>
<td>550</td>
<td>696</td>
<td>27%</td>
</tr>
<tr>
<td>Xopenex</td>
<td>693</td>
<td>688</td>
<td>-1%</td>
</tr>
<tr>
<td>Pulmicort</td>
<td>676</td>
<td>592</td>
<td>-12%</td>
</tr>
<tr>
<td>ProAir</td>
<td>425</td>
<td>436</td>
<td>3%</td>
</tr>
<tr>
<td>Ventolin</td>
<td>275</td>
<td>370</td>
<td>35%</td>
</tr>
<tr>
<td>Proventil</td>
<td>321</td>
<td>337</td>
<td>5%</td>
</tr>
<tr>
<td>Dulera</td>
<td>25</td>
<td>71</td>
<td>184%</td>
</tr>
<tr>
<td><strong>TOTAL US INHALED M.</strong></td>
<td><strong>11,296</strong></td>
<td><strong>11,783</strong></td>
<td><strong>4%</strong></td>
</tr>
</tbody>
</table>

Data Source: IMS / Data Monitor; ∆2010 to 2011 = +8%; Based on 7 Major Regulated Markets only
Dry powder inhalation
Dry Powder inhaler (DPI)

Dry Powder Inhaler (DPI) consist of

1. Device
2. Powder container/primary packaging (capsule, blister, reservoir)
3. Interactive powder mixture (API, powder blend, porous particles)
Dry Powder Inhalation (DPI) Systems

Carrier-based formulations:
- adhesive active/excipient-mixture
- active: 1 µm – 5 µm, excipient: 50 µm – 200 µm

Carrier-free formulations:
- active-agglomerate or active/excipient-agglomerate
- active: 1 µm – 5 µm, excipient: 1 µm – 5 µm
Dry Powder Inhalation (DPI) Systems

detachment

dispersion
Computational fluid dynamics (CFD)

velocity magnitude

Particle trajectory

Aerolizer® - Novartis
Bioequivalence for DPI products
In vivo bioequivalence testing

- Bioequivalence testing for inhalation products is a challenge, because
  - regional and “topical” effect
  - low dose / differentiating dose
  - Variable administration capabilities / patient interface
  - Measurable parameter
    - PK profile
    - FEV value ( Forced expiratory volume )
- Bioequivalence versus therapeutic interchangeability
Basic clinical pharmacology

Measuring beyond plateau dose does not demonstrate interchangeability

Source: Lars Bergstrom, Istanbul 2012
Turbuhaler vs. pMDI

FEV₁ (% of baseline)

Hours since dose administration

TBH 0.50
TBH 0.25
pMDI 0.50
pMDI 0.25

Bioequivalent?

Turbuhaler vs. pMDI

	FEV₁ (% of baseline)


Not Bioequivalent
Patient selection: Terbutaline Smokers vs non-smokers

![Graph showing terbutaline concentration over time for smokers and non-smokers. The area under the curve (AUC) is the same for both groups, but the peak concentration (Cmax) is different.]
Drug safety evaluation

- Disease may influence the balance between absorption and mucociliary clearance differently for different drugs and different formulations.

- Potential impact of drug absorption on adverse drug reaction

In case bioequivalence is tested via plasma level, the orally absorbed fraction needs to be eliminated. Co-administration of a slurry of charcoal is swirled around in the oral cavity and swallowed. 

- 5 g
- 2 min

Inhalation

5 g
+ 2 min

10 g
1 h

10 g
2 h

10 g
3 h

10 g
4 h

Water ad lib

Special considerations for glucocorticoid DPI products
Pharmacokinetic Issues for Inhaled Corticosteroids

- Prodrug
- Bioavailability
- Clearance
- Half-life
- Protein binding
- Pulmonary residence time
- Lipid conjugation
PK/PD Features of the Ideal ICS

- High respirable fraction
- High receptor binding
- Lipid conjugation
- High potency/efficacy
- Small particle size
- Pro-drug moiety
- Negligible oropharyngeal effects
- Low oral bioavailability
- High systemic clearance
- Negligible systemic effects
- No active metabolites
- High plasma protein binding
- Derendorf, 3rd Open Forum Boston March 20, 2013
ICS are characterized by:

- High receptor affinity
- Low oral bioavailability
- High plasma protein binding
- Bioactivation in the lung
  (by endogenous esterases)

\[
\text{des-ciclesonide is 100x more effective than ciclesonide}
\]
Regulatory Bioequivalence considerations
European Guidelines

Inhaler class

Purpose

International Standards

National Standard

Pharmacopeia Monographs

Regulatory Guidances

pMDI

DPI

MLI

Nasal

Nebulizers inc.
mesh/membrane

ISO 20072

ISO 27427

CAN/CSA
Z264.1
Spacers/
Holding
Chambers

Ph. Eur. 2.9.18 – oral,
nasal preparations
(in progress)

Ph. Eur. 2.9.44
(preparations
for nebulisation)

Joint HC-EMEA Guidance:
Pharmaceutical Quality of Inhaled & Nasal Products
+ other EMEA draft guidance documents
EMA Guidelines on quality of OIP

Requirements for DPI

- Extractables and Leachables
- Delivered Dose Uniformity and FPM over lifetime of container
- Delivered Dose Uniformity and FPM over patient flow rate
- FPM with Spacer
- Particle Size Distribution
- Actuator and Mouthpiece deposition

- Shaking requirements
- Initial and Repriming Requirements
- Cleaning Requirements
- Low Temperature and Temperature cycling performance
- Effect of moisture
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 USE IN THE TREATMENT OF ASTHMA IN CHILDREN AND ADOLESCENTS

London, 22 January 2009
Doc. Ref. CPMP/EWP/4151/00 Rev. 1
Determination of equivalence

- complete individual stage particle size distribution profile
- in case of flow rate dependency, the comparative in vitro data should be obtained with a range of flow rates taking into account the intended patient population
- efficacy and safety will depend on the amount of active substance that reaches the lung and on the deposition site distribution
- safety will also be influenced by the rate and extent of systemic absorption from the gastrointestinal tract (i.e. the swallowed fraction)
- the in vitro comparison should be performed for the stages which are relevant to the efficacy and safety of the medicinal product in vivo
Determination of equivalence

- The comparison should be performed per impactor stage or justified group of stages. At least 4 groups of stages are expected. Justification should be based on the expected deposition sites in the lungs. The maximum allowable in vitro difference should be indicated and justified, e.g. +/- 15% may be justifiable.

Per impactor stage or justified group of stages the 90% confidence intervals for the observed in vitro differences must be calculated. Based on the pre-established maximum allowable differences, a decision regarding equivalence can be made.
In vitro similar?

Lung deposition similar?

PD similar?

Phase 3 similar?

Similar safety?

EMA OIP guideline to demonstrate “bioequivalence”

Equivalent

Not equivalent
FDA approach for demonstrating equivalence

Formulation and Device Design

Bioequivalence of Dry Powder inhalers

Comparative Systemic Exposure Studies

Pharmacodynamic or clinical Endpoint studies

Comparative In Vitro Tests

FDA requirements to demonstrate “bioequivalence”

..\Events\Seminar s\Turkey\2012\Literatur\FDA Guidance on MDI and DPI products 1998.pdf
3. In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2 (b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.

EWP comment March 2009: Orally inhaled products are definitely not “generics” but “hybrids”.

But there are many more guidelines…. 
Conclusions
Conclusions

- DPI products are a combination of 3 interacting and equally important components for the performance
- Patient interface is much more important than in oral products
- DPI products must be seen as a “targeted drug delivery” and the plasma concentration is not representative for performance
- Establishing equivalence between two different DPI products through in vitro testing (cascade impactor) is most unlikely
- In vivo “bioequivalence” testing much more complex than oral BE and quite specific for each product
- Regulatory Guidance on developing “generic” DPIs exist in Europe and to a certain extent in USA, however they are considered to be “hybrids” or “505(b)(2)” application
Acknowledgement

- Hartmut Derendorf
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Thank you for listening!

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