IPAC-RS/University of Florida
Orlando Inhalation Conference

In vitro and PK studies for generics based on European experience

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Outline

- European Approach for OIPs
  - 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.

- European experience on the approval of OIP based on
  - *In vitro* data only
  - PK data only
EU Step-wise Approach for Second-entry OIPs
Systemically acting drug products

- If drug levels are equivalent in plasma, drug levels will be equivalent in the site of action.

Evaluation of the *in vivo* performance → PK parameters → Clinical endpoints

- Solution → Intestinal wall → Blood → Site of action → Effect

Graphs:
- Dose vs. Dose
- Ln Dose vs. Ln Dose
Locally acting drug products

- Plasma concentrations reflect concentrations at the site of action better than clinical response because the D-R curve is flat
# THE STEP-WISE APPROACH

<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>Biowaivers 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>
DECISION TREE

IS IT SIMILAR IN VITRO?
- YES → R E G U L A T O R Y A P P R O V A L
- NO

IS IT SIMILAR IN PK LUNG DEPOSITION?
- NO

HAS IT SHOWN A SIMILAR RELATIVE POTENCY?
- NO → R E G U L A T O R Y R E F U S A L
- YES → IS IT SIMILAR IN SYSTEMIC EXPOSURE?

IS IT SIMILAR IN SYSTEMIC EXPOSURE?
- NO

IS IT SIMILAR IN SAFETY PD STUDY?
- NO

REGULATORY REFUSAL
In vitro tests for generics based on European experience
Solutions for nebulisation approved based on in vitro data

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>METHODOLOGY</th>
<th>PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol sulfate 1 &amp; 2 mg/ml Arrow Solution for nebulisation</td>
<td>In vitro</td>
<td>UK MRP 2005</td>
</tr>
<tr>
<td>Salbutamol sulfate 1 &amp; 2 mg/ml Teva Solution for nebulisation</td>
<td>In vitro</td>
<td>DE 2008</td>
</tr>
</tbody>
</table>
Solutions for nebulisation approved based on in vitro data

<table>
<thead>
<tr>
<th>PRODUCT.MONO FORM</th>
<th>METHODOLOGY</th>
<th>PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium 0.25 mg / Salbutamol 2.5 mg Teva Solution for nebulisation</td>
<td>In vitro</td>
<td>IE MRP 2006</td>
</tr>
<tr>
<td>Ipratropium 0.5 mg / Salbutamol 2.5 mg Arrow Solution for nebulisation</td>
<td>In vitro</td>
<td>PT 2007</td>
</tr>
<tr>
<td><a href="http://mri.medagencies.org/Human/Product/Details/9108">http://mri.medagencies.org/Human/Product/Details/9108</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium 0.5 mg / Salbutamol 2.5 mg Sandoz Solution for nebulisation</td>
<td>In vitro</td>
<td>NL 2012</td>
</tr>
</tbody>
</table>
Solutions for nebulisation approved based on in vitro data

<table>
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<th>PRODUCT</th>
<th>METHODOLOGY</th>
<th>PROCEDURE</th>
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<tbody>
<tr>
<td>Ipratropium Bromide 250 mcg/ml Solution for nebulisation</td>
<td>In vitro</td>
<td>NL DCP 2010</td>
</tr>
</tbody>
</table>

http://db.cbg-meb.nl/Pars/h27815.pdf

- If the composition is qualitatively and quantitatively identical, approval without in vitro testing
- If the composition is qualitatively or quantitatively different, in vitro testing is necessary.
  - In the nebuliser described in the SPC of the reference, if any
  - Droplet size distribution (hygroscopicity)
  - Nebuliser efficiency differs due to the presence of surfactants
  - Statistical methods in Europe based on Average Bioequivalence
Suspensions for nebulisation approved based on in vitro data

<table>
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<tr>
<th>PRODUCT</th>
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<th>PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide Breath 0.25 &amp; 0.5 mg/ml suspension for nebulisation</td>
<td>In vitro</td>
<td>DK MRP 2005</td>
</tr>
</tbody>
</table>

- In vitro testing is necessary:
  - Sameness in crystallographic analysis
  - Similar particle size distribution of the particles in suspension
    - Accepted as surrogate for in vivo dissolution
  - Similar aerodynamic particle size distribution of the nebulised droplets
pMDI in solution approved based on in vitro data

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<tbody>
<tr>
<td>Ipatropium Bromide 20 mcg/actuation pMDI</td>
<td>In vitro</td>
<td>ES National procedure 2010</td>
</tr>
</tbody>
</table>


- In vitro requirements described in the OIP guideline
  - Consider also the in vitro tests for nasal products described in the FDA draft guideline
  - Statistical methods in Europe based on Average Bioequivalence
  - 15% acceptance range

- pMDI in suspensions and DPIs have not been submitted / succeed based only on in vitro data as far as I know
Nasal Sprays in Suspension submitted based on in vitro data

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<tbody>
<tr>
<td>Mometasone Furoate Sandoz 50 mcg/actuation nasal spray, suspension</td>
<td>In vitro</td>
<td>2013</td>
</tr>
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</table>

- In vitro tests described in the FDA draft guideline
- Statistical methods in Europe based on ABE
  - Population Bioequivalence (FDA) is not acceptable
Additional comments

• Generics are approved based on *in vitro* data since they are considered a minor variation of the reference product

• Does *in vitro* testing need to mimic *in vivo* conditions?
  – The more *in vivo* relevant the better
    • Flow profiles, realistic inlet ports
  – But it is not essential
    • *In vitro* dissolution for solid dosage forms: 900mL, 50 rpm, buffer

• Do we need *in vitro – in vivo* correlation?
  – No, as long as *in vitro* is more discriminative

• Do we need to predict regional deposition?
  – No, as long as it is the same in T and R, whatever it is
Additional comments

- Variability in Reference (& Test): within & between batch
  - Increase sample size. No ethical problems
  - Two batches of the reference may fail a comparison because what we are comparing are the means, not individual batches.

- Do we need to know of a clinically relevant difference to define the acceptance range?
  - No, as long as it is very conservative
  - 15% is based in QC limit for DDU
  - Similarity factor f2>50 is used for dissolution and it lacks clinical meaning

- Absence of data to relate in vitro and PK?
  - Qvar: Finer APSD, more peripheral deposition, PK was different and Relative Potency was different
Current problems

- How to pool stages
- How to conclude that the flow rate dependency is the same between T and R devices in order to accept the use of HV
  - The flow rate can be different as long as the trend is the same
- How to conclude that different strengths exhibit the same flow rate dependency
- How to conclude that different strengths exhibit proportional APSD
A study in patients with low inspiratory capacity with the lowest strength seems necessary.
A study in patients with low inspiratory capacity with the lowest strength seems necessary.
Flow rate dependency in different strengths

A study in patients with low inspiratory capacity with the lowest strength seems necessary.
PK studies for generics based on European experience
Requirements

• PK for local efficacy
  – Distinguish lung absorption from gut absorption
  – Dose absorbed from the lungs (AUC) reflects the dose that has reached the lung, the site of action
    • If the drug is available to bind the receptors, it is available to be absorbed
  – Cmax differences reflect differences in distribution pattern within the lungs
    • Drug deposited in the periphery is absorbed more rapidly

• PK for systemic safety
  – Total systemic exposure: lung and gut absorption
Where and how to distinguish lung and gut absorption?

- **Drugs with no absorption in the gut:**
  - Ipatropium, tiotropium, chromoglycate, nedocromil
  - Only one PK study for efficacy and safety

- **Drugs with (almost) complete first pass effect:**
  - Beclometasone, fluticasone, ciclesonide
  - Only one PK study for efficacy and safety

- **Drugs with significant gut absorption, but delayed with respect to a very quick lung absorption (e.g. \( t_{\text{max}} = 5 \text{ min} \))**
  - Salbutamol / albuterol, salmeterol
  - Only one PK study, but AUC\(_{0-30}\) for efficacy and AUC\(_{0-t}\) for safety

- **Drugs with significant gut absorption**
  - Budesonide
  - A PK study with active charcoal to assess efficacy and a PK study without charcoal to assess safety
  - Charcoal blockade has to be validated
Salbutamol pMDI (suspension) approved based on PK data

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- A PK study without active charcoal is also valid for efficacy because lung absorption is much quicker than gut absorption
  - AUC\(_{0-30}\) for efficacy and AUC\(_{0-t}\) for safety
  - Cmax for efficacy and safety
Salmeterol pMDI (suspension) approved based on PK data

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<tr>
<th>PRODUCT</th>
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<tbody>
<tr>
<td>Neovent / Sereflo CFC-free inhaler</td>
<td>PK with charcoal</td>
<td>UK/3624/001/DC 2011 DE, IE, NL, PL</td>
</tr>
<tr>
<td>Salmeterol Neolab 25 µg pMDI</td>
<td>AUC: 99.58-128.35</td>
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<tr>
<td></td>
<td>Cmax: 99.33-122.71</td>
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<tr>
<td></td>
<td>PK w/o charcoal</td>
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<tr>
<td></td>
<td>AUC: 92.07-116.09</td>
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<tr>
<td></td>
<td>Cmax: 89.70-136.29</td>
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<tr>
<td></td>
<td>PK with spacer</td>
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<tr>
<td></td>
<td>AUC: 83.87-98.03</td>
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<tr>
<td></td>
<td>Cmax: 87.11-102.61</td>
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<td>PD safety: Relative potency</td>
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<td></td>
<td>7-way: HR, K⁺, glucose</td>
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- PK study with spacer is less discriminative
- Higher AUC with charcoal is a problem of higher efficacy, if any
- Higher Cmax without charcoal is a problem of worse safety
  - PD study to show equivalent safety.

http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con120337.pdf
Fluticasone pMDI (suspension) approved based on PK data

<table>
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</table>
| Fluticasone 125 and 250 mcg/actuation | PK w/o charcoal  
  AUC: 98.55-113.06  
  Cmax: 97.46-112.34  
  PK with spacer  
  AUC: 96.21-111.22  
  Cmax: 88.13-104.88 | DCP |

- A PK study with the highest strength is extrapolated based on in vitro data to the lowest strength
- Proportionality:
  - Assessed as FPD by Q assessors
  - Stage by stage dose-normalised (3 batches x 3 life cycle x 10 canisters):
    - Mean values within 15% acceptance range
    - 90% CI within 15% acceptance range for the test. Stage pooling for Ref.
Salmeterol / Fluticasone DPI approved based on PK data

<table>
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<tr>
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<tbody>
<tr>
<td>Relanio</td>
<td>50/500 mcg PK with charcoal</td>
<td>DCP</td>
</tr>
<tr>
<td>Flusanium</td>
<td></td>
<td>SE/H/972/01-02/DC</td>
</tr>
<tr>
<td>Salmeterol / Fluticasone PharOs</td>
<td></td>
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</tr>
</tbody>
</table>

https://docetp.mpa.se/LMF/Relanio%20inhalation%20powder,%20pre-dispensed%20ENG%20PAR.pdf

- Not accepted in Spain
Nasal Spray (suspension) approved based on PK data

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>METHODOLOGY</th>
<th>PROCEDURE</th>
</tr>
</thead>
</table>
| Mometasona Cipla 50 mcg/actuation nasal spray, suspension | PK with and without active charcoal 4 sprays into each nostril: 400 μg  
  PK with charcoal (n=52)  
  AUC: 90.45-109.63  
  Cmax: 93.57-110.89  
  PK w/o charcoal (n=47)  
  AUC: 96.17-115.87  
  Cmax: 85.61-103.17 | DCP (UK, 2012)                                                        |

http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con239398.pdf

- Budesonide can also be compared with PK methods:
Nasal Spray (suspension) approved based on PK data

<table>
<thead>
<tr>
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<th>METHODOLOGY</th>
<th>PROCEDURE</th>
</tr>
</thead>
</table>
| Mometasona Teva 50 mcg/actuation nasal spray, suspension | PK with and without active charcoal
2 sprays into each nostril: 200 μg
PK with charcoal (n=101)
AUC: 88.73-103.31
Cmax: 94.75-106.81
PK w/o charcoal (n=48)
AUC: 92.24-111.60
Cmax: 86.84-106.76 | DCP (UK, 2013) |

http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con355541.pdf

- Doses do not need to be supra-therapeutic

Orlando Inhalation Conference
Session: In vitro and PK: Generic
Lessons learned

• PK is not as variable as expected if correctly standardized: PK BE is easy for pMDI

• In vitro specifications are so wide that
  – Generally > ±20%. Side-batches are not BE
  – In some cases up to ±50% at shelf-life (50-150%)
    • Find a test batch and a reference batch sufficiently similar to show BE with PK is very difficult in some DPIs.

• In vitro characteristics (FPD) change in short time periods: between period 1 and 2 of a BE study
Inter-batch variability of the reference product
FPD changes quickly and unpredictably during the shelf-life
FPD changes quickly and unpredictably during the shelf-life
Lessons learned

• Batches should be representative of
  – the REFERENCE products in the market and
  – any TEST batches to be manufactured in the future
  – e.g. ±15% of the median value
  – A large number of batches have to be analyzed to describe the reference products in the market
Thank you very much for your attention

Any questions?
Additional slides
Question 1

- For FDC product, is it necessary to test both drugs in the same study?
- It is acceptable to test two different R batches for each drug
  - To select representative batches
  - To have greater probability of success
  - Predefined in the protocol:
    - Which batch for each drug
    - 3-way cross over design or two separate studies
Question 2

• Is it possible to widen the acceptance range for OIP, taking into account the large difference between R batches?
  – For lung deposition
    • Yes, as described in the BE guideline
    • AUC cannot be widened
    • Cmax can be widened based on CV
      – Up to CV=50% (approx. 70-143%)
      – Based on replicate design
  – For non-inferior safety, based on PK/PD
Question 3

• Is it possible to use healthy volunteers?
  – HV are more discriminative and reproducible
  – HV are easier to recruit

• HV are acceptable if the devices exhibit
  – A) No flow-rate dependency
  – B) Similar flow-rate dependency (30-90 L/min)

• Patients are necessary if
  – C) Flow-rate dependency differs
    • Patients with good and poor inspiratory capacity
Question 4

• Is it possible to correct the PK results by differences in FPD?
  – Only if a IVIVC (level C) has been established
  – IVIVC based on absolute values if tested in the same study
    • Specifically designed to establish an IVIVC
  – IVIVC based on ratios of FPD vs. ratios of AUC and Cmax if tested in different studies.
    • Combinations of studies where different test and reference batches have been tested at the same dose level
  – Useful to define specifications and justify apparently inconsistent results
Question 5

- How much GI contribution is negligible?
  - If after an oral dose AUC <5%
  - But 5% of what?
  - Not oral BA < 5%
  - But 5% of total (GI+lungs) exposure after inhalation, since lung deposition is low
  - Both fractions absorbed from the lungs and the gut need to be known

<table>
<thead>
<tr>
<th>Fraction</th>
<th>% of dose</th>
<th>BA</th>
<th>Contribution</th>
<th>Contribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallowed</td>
<td>80</td>
<td>2</td>
<td>1,6</td>
<td>7,41</td>
</tr>
<tr>
<td>Inhaled</td>
<td>20</td>
<td>100</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21,6</td>
<td>100</td>
</tr>
</tbody>
</table>
Question 6

- How effective does active charcoal need to be?
  - It does not need to be 95% efficient
  - Just able to make GI contribution negligible
  - So, it depends on the GI contribution without active charcoal
  - If GI is minor without active charcoal (e.g. 10%), charcoal blockade only needs to make it negligible (e.g. >50% efficiency)
Question 7

• What if the test is non-superior and non-inferior to the reference product?
  – When the reference is so variable
  – Simpler to show that the test is less variable
  – One 4x4 design or two 2x2 designs
  – Demonstrate that the worst batch of the test is better than the worst batch of the reference, but without being an outlier batch
  – Side-batches would be the product specifications