Implementing IVIVC in development of orally inhaled products

Vit Perlik
Content

• Understanding the requirements of inhalation drug development

• PK as a surrogate: Systemic exposure versus pulmonary deposition

• Practical solutions to establish IVIVC for inhalation products

• Cofounding factors
Epidemiology of Asthma, COPD

**Asthma world prevalence:** between 4-5 % (300 million patients).

- large inter-regional differences: prevalence exceeding 20 % in some countries (Sweden, Australia).

**COPD world prevalence:** 9 to 10% in adults aged >40 years.

- predicted to become the third leading cause of death by 2020 worldwide.

Partridge 2007; To et al. 2012; Halbert et al. 2006
### Products in development

<table>
<thead>
<tr>
<th>Condition</th>
<th>Developer</th>
<th>Product</th>
<th>API(s)</th>
<th>Phase</th>
<th>Type</th>
<th>Comments</th>
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<td>GSK-961081</td>
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<td>fluticasone/umeclidinium</td>
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<td>CHF 5993</td>
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<td>MDI</td>
<td>Triple combination</td>
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</table>

### Other

Current trend **shifts the focus to monoclonal antibodies** in the severe conditions (prevalently asthma): Anti IgE (Novartis, omalizumab), anti IL-5 (GSK, mepolizumab).

**In development**

anti IL4Ra (Sanofi, dupilumab), anti IL-13 (Novartis, QGE031; Roche lebrikizumab), toll-like receptor 7 agonist (GSK 2245035), CXCR2 antagonist (GSK, danirixin-COPD), p38 kinase inhibitor (GSK, losmapimod-COPD; Pfizer, PF-03715455), CRTh2 antagonist (Novartis, fevipiprant)...  

**Device improvements**
Treatment compliance

- Preferred route of administration is **oral inhalation** (high local therapeutic exposure, limited systemic exposure/side effects)
- Correct use of the inhalation device is key for achieving optimal efficacy

Main Inhaler Types

**Metered Dose Inhalers (MDIs)**
- Aerosol canister
- Drug dissolved or suspended in propellant

- Require hand-breath coordination, some patients may experience difficulties
- Suboptimal use of the device reported in the majority of patients (> 70 %)

**Dry-Powder Inhalers (DPIs)**
- Dry powder
- Breath actuated
- Capsule or multi-dose

Presumably easier to use than MDIs, but handling errors also commonly reported (more than 50%).

Giraud and Roche 2002; Khassawneh et al. 2008
Development considerations

Aerosol characteristics

- Size and shape of particles
- Particles size distribution, groupings
- Resistance of the device
Regulatory considerations

• **OIP guidance stepwise approach**  (CPMP/EWP/4151/00 Rev. 1, January 2009)

• **In vitro characterization**
  • Pharmaceutical equivalence/evaluation

• **In vivo characterization**
  • PK equivalence/evaluation
  • Therapeutic equivalence/evaluation (PD endpoints acceptable)
  • Generally independent program for children is required considering the approved/target indications
Pharmaceutical equivalence/evaluation

- Active substance in the same form (i.e. salt, ester, hydrate etc.) and in the solid state (powder, suspension)

- Identical pharmaceutical dosage form with similar handling
  - Device with the same resistance to airflow (within +/- 15%)
  - Inhaled volume through the device should be similar (within +/- 15%)
  - Qualitative and/or qualitative differences in excipients should not influence the product and its safety profile
Pharmaceutical equivalence/evaluation

- **In vitro multistage impactor characterization**
  - Complete particle size distribution profile
  - Target delivered dose, relevant stage distribution should be similar (within +/- 15%)
  - Similar flow rate dependency (justified with the use of 10th, 90th percentile and median of the target population)

<table>
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<th>Stage Number</th>
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<td>0.7</td>
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</table>
PK equivalence/evaluation

- **Pulmonary deposition - surrogate for efficacy**
  - Describing extent (AUC) and rate (Cmax) of absorption delivered via lungs
    - Achieved by charcoal block
  - Imaging studies possible however rather supportive
    - Requires labeling of active compound(s) – formulation and deposition impact
    - Difficult as a surrogate for equivalence evaluation

- **Systemic exposure - surrogate for safety**
  - Describing extent (AUC) and rate (Cmax) of absorption delivered via lungs and gastrointestinal tract
  - Healthy volunteers vs Patients

PK equivalence/evaluation

- 10%–60% deposited in lung
- Complete absorption from the lung
- Lung
- Systemic circulation
- Systemic side effects
- Liver
- First-pass inactivation
- Oral bioavailable fraction
- Absorption from gut
- GI tract
- Charcoal Block
- Mouth and pharynx
- 40%–90% swallowed (reduced by spacer or mouth rinsing)

Bioequivalence and Development Workshop
September 22nd – 23rd, 2016, Prague, CZ
ESTABLISHING IVIVC FOR INHALATION PRODUCTS
Pharmacokinetics of inhaled monodisperse beclomethasone as a function of particle size

J. E. Espósito-Posten, R. Zane, H. A. W. M. Tiddens, J. W. J. Lammers

Department of Pulmonology, Erasmus University Medical Center, Rotterdam-Sophia Children’s Hospital and Thorax, Lung Center, Erasmus University Medical Center, Rotterdam, the Netherlands

What is already known about this subject
• For asthmatic adults, bronchodilators with a mean diameters of 2.5 and 4.5 µm were shown to give the best improvement in lung function and the least systemic side-effects.
• It is not known, however, what is the most effective particle size for inhaled steroids in asthmatic adults. Clinical efficacy and systemic side-effects of inhaled steroids should be measured to define the optimal particle sizes.

Pharmacokinetics of Inhaled Monodisperse Beclomethasone: Establishing IVIVC for OIP

What this study adds
• Our study investigated the systemic absorption of inhaled steroids. We found that the particle size of 2.5 and 4.5 µm gave higher pulmonary absorption compared with the 4.5 µm inhomogeneous aerosol in adults with mild asthma and therefore were more likely to result in systemic adverse effects.

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**Keywords**
- Asthma
- Monodisperse aerosols
- Beclomethasone

**Received**
16 June 2006
**Accepted**
10 December 2006
**Published online**
15 April 2007

**Aims**
For optimal efficacy, antiasthmatic drugs should be delivered to the desired region in the lungs. To date, the optimal particle size for steroids in adults is not known. The aim of the study was to evaluate the pulmonary biodistribution and the steady-state beclomethasone dipropionate absorption (BSAB) across different particle sizes.

**Methods**
In a randomized, double-blind, crossover trial, 10 adult asthmatic patients inhaled monodisperse 100-µm aerosols with mass median aerodynamic diameters (MMADs) of 1.5, 2.5, and 4.5 µm. Pulmonary absorption was evaluated by ophthalmic clinical chiasmal plasma concentrations of 17β-hydroxysteroid dehydrogenase (17βHSD) were measured by liquid chromatography mass spectrometry.

**Results**
Aerosols with MMADs of 1.5, 2.5, and 4.5 µm gave mean maximum concentrations (Cmax) of 729 pmol/ml, 1283 pmol/ml, and 1132 pmol/ml, respectively. The area under the curve (AUC) values of 17βHSD for MMADs of 1.5, 2.5, and 4.5 µm were 2302 pg/ml*h, 2650 pg/ml*h, and 2276 pg/ml*h, respectively. The mean terminal halflife of 17βHSD for all three aerosol sizes was around 1.5 h.

**Conclusions**
Monodisperse BDP aerosols with a mean size of 4.5 µm gave mean AUC lower values for Cmax and AUC than those with MMADs of 3.0 and 4.5 µm.

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**Establishing IVIVC for OIP**

- **Literature search**
  - Beclomethasone (ICS)
  - Mass median aerodynamic diameters
    - 1.5; 2.5; 4.5 µm
  - Cmax and AUC
    - Cmax 475; 1300; 1161 pg/ml
    - AUC 825; 2629; 2276 pg/ml*h
  - 2.5 and/or 4.5 µm
Regional Lung Deposition and Bronchodilator Response as a Function of β₂-Agonist Particle Size

Dusan S. Usman, Martyn F. Bhide, and Peter J. Barnes
National Heart and Lung Institute, Imperial College London, Royal Brompton Hospital, London, United Kingdom

Regional drug delivery has the advantage of delivering drug to the lung at a site more likely to affect airway remodeling and inflammation, which is particularly important for therapies that can alter the natural progression of chronic obstructive pulmonary disease (COPD) (1, 2). Therefore, research is ongoing to establish the potential for regional delivery of inhaled and intrapulmonary drug formulations. Given the importance of targeting regional delivery of inhaled drug, the objective of the current study was to evaluate the regional delivery of inhaled albuterol (SABA) (3) by varying the lung deposition and pulmonary function.

**Methods**

Methods were adapted to explore the effects of modifying delivery of inhaled drug to the lung by altering the size of the drug particles. Albuterol was delivered via a metered-dose inhaler (MDI) to simulate a clinical scenario. Lung deposition and pulmonary function were measured using planar scanning and lung function tests, respectively. The primary outcome measure was the percentage of total drug delivered to the lung. The study used a randomized, controlled, double-blind, placebo-controlled design with the following groups:

1. Albuterol administered via an MDI
2. Albuterol administered via an MDI with a dry powder inhaler
3. Albuterol administered via an MDI with a dry powder inhaler and a nebulizer

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1. Albuterol administered via an MDI
2. Albuterol administered via an MDI with a dry powder inhaler
3. Albuterol administered via an MDI with a dry powder inhaler and a nebulizer

**Conclusions**

The results of the current study suggest that the size of the drug particles can significantly affect the regional delivery of inhaled drug. The study findings support the potential for regional delivery of inhaled drug and highlight the importance of further research to optimize delivery and efficacy.

**References**


**Bioequivalence and Development Workshop**

September 22nd – 23rd, 2016, Prague, CZ
Establishing IVIVC for OIP

- **Establishing IVIVC**
  - In vitro NGI particle size distribution (no dissolution available)
  - 1st and 2nd pilot study - 3 formulation/device adjusted prototypes tested in vivo
  - Level C correlation between particle size distribution grouping 1 - 5 µm with AUC\text{last} and C\text{max} (GeoMean vs in vitro mass)

- **Formulation adjusted based on IVIVC - pivotal study launched**
  - Randomized, open, single dose, 4-period cross over study with and without charcoal

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### Bioequivalence and Development Workshop

**September 22nd – 23rd, 2016, Prague, CZ**

<table>
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<table>
<thead>
<tr>
<th>Compound A (ICS)</th>
<th>Ratio</th>
<th>PE*</th>
<th>90 % CI**</th>
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<td>AUC0–T\text{last}</td>
<td>TC/RC</td>
<td>85.24</td>
<td>78.28 – 92.81</td>
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<td>C\text{max}</td>
<td>TC/RC</td>
<td>76.68</td>
<td>70.12 – 83.36</td>
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</table>
IVIVC optimization

• Established IVIVC (grouping 1-5 μm) had a good correlation however not good prediction

• Need of IVIVC adjustment combining pilot and pivotal evidence and indicating parameter /grouping with better prediction

• Data correction based on reference product (changing in vitro properties) not suitable due to its unknown in vitro correction parameter /grouping (1-5 μm 1-3 μm; <3 μm etc.?)

• T/R in vitro and in vivo ratios used instead of absolute data
IVIVC optimization

- Extended scope of in vitro groupings (in vitro T/R ratios used)
  - FPD < 0.5 up to FPD < 6 μm; groupings 1-1.5 up to 1-6 μm; 1.5-2 up to 1.5-6 μm etc. with the groupings according to the NGI stages (31 in vitro groupings tested)
  - In vivo AUC and Cmax ratios were used (outlying values removed)

**Compound A (ICS)**

<table>
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<th>Parameter</th>
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Establishing IVIVC for OIP - Conclusion

- Pharmaceutical Development Targets based on IVIVC
  - Optimized grouping for NGI identified
  - Optimized target for Test product set
  - Prediction of the study results a priori predefined

### Compound A (ICS)

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<td>AUC</td>
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## New BE data

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<td>Ratio</td>
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<td>90 % CI**</td>
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<td>82.96 – 90.26</td>
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<td>TC/RC</td>
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<td>69.86</td>
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<td>TC/RC</td>
<td>67.27</td>
<td>63.36 – 71.42</td>
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- **Bioequivalence not demonstrated between Test and Reference**
  - Prediction error has increased
    - AUC from 3% to 18%
    - C<sub>max</sub> from 9% to 33%

- **Root cause**
  - Compound A: Test increased as expected with new formulation however in parallel reference performance improved in vivo by 25%
Establishing IVIVC for OIP - Caveat

- Similar prediction error observed for other compounds
  - Compound B (ICS) - correlation of geometric mean and in vitro data

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<th>Test pilot</th>
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**Reference pivotal**

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**Test pivotal**

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<td>250.68</td>
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Evaluation of In Vitro and In Vivo Flow Rate Dependency of Budesonide/Formoterol Easyhaler®

L. Pekka Malmberg, MD, PhD,1 Mark L. Everard, MB, CHB, MD,2 Jussi Hakkarainen, MSc(Pharm),3 and Satu Lähdehiiden, MSc(Pharm)1

Abstract

Background: The Easyhaler® (EH) device-metered dry powder inhaler containing budesonide and formoterol is being developed for asthma and chronic obstructive pulmonary disease (COPD). As a part of product optimization, a series of in vitro and in vivo studies on flow rate dependency were carried out.

Methods: Inspiratory flow parameters via EH and Symbicort Turbuhaler® (TH) inhalers were evaluated in 187 patients with asthma and COPD. The 10th, 50th, and 90th percentile flow rates achieved by patients were utilized to study in vitro flow rate dependency of budesonide/formoterol EH and Symbicort TH. In addition, an exploratory pharmacokinetic study on pulmonary deposition of active substances for budesonide/formoterol EH in healthy volunteers was performed.

Results: Mean inspiratory flow rates through EH were 64 and 56 L/min in asthmatics and COPD patients, and through TH 79 and 72 L/min, respectively. Children with asthma had marginally lower PIF values than the adults. The inspiratory volumes were similar in all groups between the inhalers. Using weighted 10th, 50th, and 90th percentile flows of in vitro delivered doses (DDs) and fine particle doses (FPDs) for EH were rather independent of flow as 98% of the median flow DDs and 89%-90% of FPDs were delivered already at 10th percentile air flow. Using ±15% limits, EH and TH had similar flow rate dependency profiles at 10th and 90th percentile flows. The pharmacokinetic study with budesonide/formoterol EH in healthy subjects (n=16) revealed a trend for a flow-dependent increase in lung deposition for both budesonide and formoterol.

Conclusions: Comparable in vitro flow rate dependency between budesonide/formoterol EH and Symbicort TH was found using the range of clinically relevant flow rates. The results of the pharmacokinetic study were in accordance with the in vitro results showing only a trend of flow rate-dependent increase in lung deposition of active substances with EH.

Key words: dry powder inhalers, flow rate dependency, peak inspiratory flow, Easyhaler

Introduction

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are significant public health problems and cause substantial economic burdens on societies.1-6 In most countries, both diseases are increasing in prevalence, and are predicted to remain leading causes of morbidity and mortality worldwide.1-6 COPD is currently the fourth leading cause of death globally6 and it is projected to become the third leading cause by 2020.6

Inhalation is the preferred route for administration of drugs to patients with asthma and COPD as it facilitates direct exposure of the airways to the therapeutic agents. Inhalation also includes a clinical effect at considerably lower doses than used in oral treatments and thereby the risk of systemic side-effects is reduced. Corticosteroids and adrenergic β2 agonists bronchodilators are the two major classes of asthma drugs. Most of the agents within the classes have been successfully formulated for inhalation-alone or as a combination in a single inhaler. Inhaled anticholinergics

- PIF investigated in 187 asthma and COPD patients comparing EH and Turbuhaler
  - 10th, 50th, and 90th percentile flow rates used for in vitro characterization
- Exploratory PK study on pulmonary deposition (n=16) in healthy volunteers
Flow Dependency

Example 1

- In vitro DD and FPD of EH independent of flow
- Trend for a flow-dependent increase in lung deposition for both BUD and slightly higher for FOR without statistical significance

- Correlation demonstrated based on mean data
- Is this the missing factor in the IVIVC puzzle?

Data plotted from Malmberg et al, 2014
Flow Dependency

**Example 2**

**Conclusion**

- Correlation between PIF and AUCt not demonstrated based on individual study data
  - PIF recorded prior to the study
Conclusion

- No correlation demonstrated between AUC flow and AUCt
- No correlation found also for other parameters (not demonstrated)
  - Flow profiles recorded prior to the study
IVIVC – does it make sense?

Between- and intra-batch variability of the reference product

The development of an IVIVC may be useful to correct the results of the PK study to justified parts of the APSD of the typical marketed batch of the reference product and the corresponding typical test product batch according to the proposed specifications. The IVIC could also be used as scientific support of the in vitro specification of the test product.

Conclusion

- Valuable development toll
- Possible use of IVIVC for correction of the PK data
- Possible use of IVIVC to set the in vitro specification

Q and A PKWP, EMA/618604/2008 Rev. 11, 2015
Conclusion

Key factors

- Critical to understand data and study conditions
- IVIVC valuable tool for setting target formulation
- Multivariate conditions
- Other parameters to impact the study outcome
  - Selection of study population
  - Unknowns in reference product or clinical conditions
  - Direct control of the inspiration maneuver in individual volunteers

Outlook – painkillers or science?

- Case 1 (Compound A) – partly on the market
- Case 2 (Compound B) – positive results
- Case 3 (Example 2) – positive pilot results
- Case 4 (Example 3) – ongoing
Thank you for your attention

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