PK/PD Modeling and Simulation for Efficacy and Safety of Corticosteroids in Asthma and Inflammation

Prof. Hartmut Derendorf

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DRUG DEVELOPMENT

New Estimate of Drug Development Costs Pegs Total at $1.5 Billion

Office of Health Economics suggest more flexibility and better alignment needed between stakeholders and innovators is needed.

DANIEL S. LEVINE

The Burrill Report

The cost of drug development has been a matter of controversy, particularly because the high cost and long time to bring a drug from discovery to market is used to justify high prices for innovative drugs. Now a new report that examines a wide range of previous studies pegs the total at $1.5 billion.

“The R&D costs identified in our study are driven by a combination...
Biomarker vs. Surrogate Endpoint

**Biomarker**

Drug- or disease-induced measurable change (physiological, pathophysiological, biochemical or other)

**Surrogate Endpoint**

Biomarker that has predictive value for therapeutic outcome
Pharmacokinetics
conc. vs time

Pharmacodynamics
conc. vs effect

PK/PD
effect vs time
Pharmacodynamic Potency

- Methylprednisolone
- Dexamethasone
- Triamcinolone Acetonide

RBA
Lymphocyte Trafficking Model

\[ N \ll N_{EVS} \]

\[
\frac{dN}{dt} = k_{in} \cdot \left( I - \frac{E_{max} \cdot C_f}{EC_{50} + C_f} \right) - k_{out} \cdot N
\]
Methylprednisolone and Lymphocytopenia
Pharmacokinetic Clearance

![Bar Graph]

- Methylprednisolone
- Dexamethasone
- Triamcinolone Acetonide

CL (l/h)
Lymphocytes

Methylprednisolone

Dexamethasone

Triamcinolone Acetonide
Correlation $1/\text{EC}_{50}$ vs. Relative Receptor Binding

$\text{EC}_{50}$ for modulation of lymphocytes

Mager et al. 2003
Systemic Equivalency Dose

$$DR_{50} = \frac{CL \cdot EC_{50}}{F \cdot f_u}$$
Pharmacodynamic vs. Therapeutic Potency

<table>
<thead>
<tr>
<th>Drug</th>
<th>RRB (DEX=100)</th>
<th>EC$_{50}$ [ng/ml]</th>
<th>CL [l/h]</th>
<th>F [%]</th>
<th>$f_u$</th>
<th>DR$_{50}$ [mg/day] (HC=1)</th>
<th>Rel.Pot. (HC=1)</th>
<th>Clin.Pot. (HC=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>55</td>
<td>2.7</td>
<td>12</td>
<td>72</td>
<td>0.36</td>
<td>3.1</td>
<td>21.9</td>
<td>25</td>
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<tr>
<td>Dexamethasone</td>
<td>100</td>
<td>1.7</td>
<td>16</td>
<td>83</td>
<td>0.32</td>
<td>2.4</td>
<td>28.6</td>
<td>25</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>233</td>
<td>0.8</td>
<td>37</td>
<td>23</td>
<td>0.29</td>
<td>10.6</td>
<td>6.3</td>
<td>6</td>
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<tr>
<td>Methylprednisolone</td>
<td>42</td>
<td>5.6</td>
<td>21</td>
<td>99</td>
<td>0.23</td>
<td>12.3</td>
<td>5.5</td>
<td>5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>16</td>
<td>13.4</td>
<td>14</td>
<td>81</td>
<td>0.25</td>
<td>22.3</td>
<td>3.0</td>
<td>4</td>
</tr>
<tr>
<td>Fluocortolone</td>
<td>82</td>
<td>6.3</td>
<td>30</td>
<td>84</td>
<td>0.10</td>
<td>52.0</td>
<td>1.3</td>
<td>5</td>
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<tr>
<td>Hydrocortisone</td>
<td>9</td>
<td>29.9</td>
<td>18</td>
<td>96</td>
<td>0.20</td>
<td>67.2</td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>Cloprednolone</td>
<td>41</td>
<td>7.7</td>
<td>17</td>
<td>100</td>
<td>0.17</td>
<td>18.5</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>21-Desacetyldeflazacort</td>
<td>29</td>
<td>3.1</td>
<td>114</td>
<td>92</td>
<td>0.60</td>
<td>15.3</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>
The Fate of Inhaled Corticosteroids

40 - 90% Swallowed (reduced by spacer or mouth rinsing)

10 - 60% Deposited in lung

Deposited in lung

Complete absorption from the lung

Orally bioavailable fraction

Absorption from gut

Liver

First-pass inactivation

Systemic side effects
Corticosteroids for Inhalation

- Triamcinolone acetonide
- Beclomethasone dipropionate
- Flunisolide
- Budesonide
- Fluticasone propionate
Corticosteroids for Inhalation

Mometasone Furoate

Ciclesonide

Fluticasone Furoate
Safety

Local Safety

• Linked to local exposure at site of administration

Systemic Safety

• Linked to systemic exposure (PK)
• Cortisol suppression serves as ‘common currency’ to compare different steroids
• All other systemic steroid effects (bone, eye, skin, growth etc. ) follow from systemic exposure
Receptor Binding

• All effects of corticosteroids are mediated through the same receptor types throughout the body
• A drug with high receptor affinity has both potential for significant efficacy as well as significant adverse effects
RRA=relative receptor binding affinity (relative to dexamethasone).
BMP=beclomethasone monopropionate; BUD=budesonide; FP=fluticasone propionate; des-CIC=ciclesonide-active principle; MF = mometasone furoate.

Pharmacokinetic Issues for Inhaled Corticosteroids

- Prodrug
- Bioavailability
- Clearance
- Half-life
- Protein binding
- Pulmonary residence time
- Lipid conjugation
Pro-Drugs and Local Safety
Bioactivation of ciclesonide

In Hansel TT, Barnes PJ, eds. New Drug for Asthma, Allergy and COPD. Basel, Karger.
Advantages of On-site Activation

- Activation in the lung
- Minimized oropharyngeal side effects
The deposition values of budesonide (BUD) and fluticasone propionate (FP) were used as references adjusted for the molar dose (100%).

Ciclesonide (CIC) – low deposition and minimal activation to des-CIC in the oropharynx

* The deposition values of budesonide (BUD) and fluticasone propionate (FP) were used as references adjusted for the molar dose (100%)

Incidence of Oropharyngeal AEs in Asthma Patients Treated With CIC vs. FP

Proportion of patients with oropharyngeal adverse events: Pooled analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ciclesonide-640 µg/d</th>
<th>Fluticasone propionate-880 µg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>0.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>2.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Pharyngitis*</td>
<td>4.1</td>
<td>5.4</td>
</tr>
</tbody>
</table>

* Placebo: 4.4

Poster ATS2004, R Engelstätter, D Banerji, VW Steinijans, W Wurst
Bioavailability

Pulmonary Bioavailability + Oral Bioavailability = Systemic Bioavailability
Oral Bioavailability

Clearance

Plasma Protein Binding

- Reversible vs irreversible
- Linear vs nonlinear
- Rapid equilibrium
- Only the free (unbound) fraction of the drug at the receptor site is available for pharmacologic activity
Plasma Protein Binding (cont’d)

Free Fraction

Derendorf H. Respir Med. 1997;91(suppl A):22-28;
Plasma Protein Binding (cont’d)

• High protein binding of a high-extraction drug after inhalation results in low systemic unbound concentrations
• Only the free, unbound drug is pharmacologically active
• High protein binding for an inhaled corticosteroid can dramatically improve its risk-benefit ratio
• Ciclesonide is an inhaled corticosteroid with very high protein binding
Cortisol Release Rate
determined by deconvolution of cortisol plasma levels
Cortisol Linear Release Model

Cortisol release

\[ R_c = \frac{R_{\text{max}}}{Vd \cdot (t_{\text{max}} - t_{\text{min}}) - 24} \cdot t - \frac{R_{\text{max}} \cdot t_{\text{min}}}{Vd \cdot (t_{\text{max}} - t_{\text{min}} - 24)} \]

\[ R_c = \frac{R_{\text{max}}}{Vd \cdot (t_{\text{max}} - t_{\text{min}})} \cdot t - \frac{R_{\text{max}} \cdot t_{\text{min}}}{Vd \cdot (t_{\text{max}} - t_{\text{min}})} \]

\( t_{\text{min}} \) (10:45 pm)

\( t_{\text{max}} \) (4:45 am)
Cortisol Linear Release Model

Cortisol plasma concentration

\[ \frac{dC_{\text{Cort}}}{dt} = R_C - k_e \cdot C_{\text{Cort}} \]

\( T_{\text{min}} \) (11:15 pm)

\( T_{\text{max}} \) (6:45 am)
Cortisol Baseline

Over one, two and three days
Cortisol Linear Release Model

Cortisol linear release / $E_{\text{max}}$ Model

\[
\frac{dC_{\text{Cort}}}{dt} = R_C \cdot \left( 1 - \frac{E_{\text{max}} \cdot C_f}{EC_{50} + C_f} \right) - k_e \cdot C_{\text{Cort}}
\]

- $R_c$: Cortisol Release Rate [conc/time]
- $C_{\text{Cort}}$: Cortisol Concentration
- $C_f$: Unbound Concentration of Exogenous Steroid
- $k_e$: Elimination Rate Constant of Cortisol
- $E_{\text{max}}$: Maximum Effect (=1)
- $EC_{50}$: $C_f$ for Half-Maximum Effect
Cortisol Linear Release Model
Cortisol plasma concentration
Cortisol Suppression
Triamcinolone Acetonide

- **intravenous administration (iv)**
  - 2 mg TCA phosphate
- **oral administration (po)**
  - 5 mg TCA in 100 ml ethanol (4 %)
- **pulmonary administration (inh)**
  - 2 mg TCA in 20 puffs over 5 minutes
Quantification of Cortisol Suppression

During Multiple Dosing

The graph shows cortisol concentration (ng/ml) over time (h) from 4 pm to 4 pm, illustrating the cortisol levels at 4 pm, 12 am, 8 am, and 4 pm. The shaded area represents the AUC_Supp, indicating the area under the curve for cortisol suppression.
### INPUT

<table>
<thead>
<tr>
<th>Situation</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs: FP, BUD, TA, FLU or ANY</td>
<td>FP</td>
<td>ANY</td>
</tr>
<tr>
<td>Enter dose (in micrograms)</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Enter time of dose (clock time)</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Device (MDI=1, DH=2, DSKS=3, TBH=4)</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

### OUTPUT

#### Cortisol suppression

<table>
<thead>
<tr>
<th>CCS (%)</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28.5</td>
<td>38.0</td>
</tr>
</tbody>
</table>

### Dynamics

- Baseline
- Situation A
- Situation B

### Kinetics

- Drug (ng/ml) over time (8 am to 8 pm)
Predicted and Measured Cortisol Suppression: Multiple Dose
Current Labeling for ICSs

Class Labeling for Intranasal and Orally Inhaled Corticosteroid Containing Drug Products
Regarding the Potential for Growth Suppression in Children
Division of Pulmonary Drug Products

November 9, 1998

PRECAUTIONS:

**General:** Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use section).
Growth Assessment

- **Length (first 2 years)**
- **Height**
  - Stadiometry during childhood
    - Long-term growth (>3 years)
    - Intermediate-term growth (>12 months)
  - Predicted adult height and final adult height
- **Low leg length (Knemometry)**
  - Short-term growth
  - Poor reproducibility
Fluticasone propionate

FP Effect on Cortisol

FP Long-Term Effect on Growth

ICS and Growth Retardation

• Total 33 references were located with available information, and total 53 study records were created accordingly.
• Each ICS, including BDP, BUD, FP, CIC, MF, TAA, FLU, has at least one clinical study, which was conducted for growth effects.
Results (Growth Velocity – CCS%)
Results (Individual)
Results (NONMEM®)
Results (Simulations)
### Prediction of Change of GV

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Age of Patients</th>
<th>Dosing Regimen</th>
<th>Estimated CCS %</th>
<th>Predicted ΔGV (cm/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP</td>
<td>QVAR®</td>
<td>5-11 years</td>
<td>40 μg BID</td>
<td>2.80%</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80 μg BID</td>
<td>5.40%</td>
<td>0.32</td>
</tr>
<tr>
<td>BUD</td>
<td>PULMICORT® FLEXHALER®</td>
<td>6-17 years</td>
<td>180 μg BID</td>
<td>10.70%</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>PULMICORT® RESPULES®</td>
<td>1-8 years</td>
<td>360 μg BID</td>
<td>18.00%</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500 μg QD</td>
<td>12.50%</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250 μg BID</td>
<td>10.30%</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1000 μg QD</td>
<td>19.10%</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500 μg BID</td>
<td>17.40%</td>
<td>1.04</td>
</tr>
<tr>
<td>CIC</td>
<td>ALCESCO®</td>
<td>&gt;12 years</td>
<td>80 μg QD</td>
<td>0.07%</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>160 μg QD</td>
<td>0.15%</td>
<td>0.009</td>
</tr>
<tr>
<td>FLU</td>
<td>AEROBID® FLOVENT® DISKUS®</td>
<td>6-15 years</td>
<td>500 μg BID</td>
<td>26.90%</td>
<td>1.61</td>
</tr>
<tr>
<td>FP</td>
<td></td>
<td>4-11 years</td>
<td>50 μg BID</td>
<td>6.30%</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100 μg BID</td>
<td>11.70%</td>
<td>0.70</td>
</tr>
<tr>
<td>MF</td>
<td>ASMANEX® TWISTHALER®</td>
<td>4-11 years</td>
<td>110 μg QD</td>
<td>3.10%</td>
<td>0.19</td>
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<tr>
<td>TAA</td>
<td>AZMACORT®</td>
<td>6-12 years</td>
<td>75 μg TID</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>150 μg BID</td>
<td>11.70%</td>
<td>0.70</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>300 μg BID</td>
<td>20.20%</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>150 μg QID</td>
<td>16.00%</td>
<td>0.96</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>300 μg TID</td>
<td>30.70%</td>
<td>1.84</td>
</tr>
</tbody>
</table>

*a*: Drug abbreviations; *o*: From product inserts

*p*: CCS%: cumulative cortisol suppression within 24 hr at steady state; estimated with the published algorithm

*q*: ΔGV: change of growth velocity compared to the placebo, or run-in period, or active control, or baseline; predicted with population estimates in the final model
Ciclesonide

<table>
<thead>
<tr>
<th>Month of Study</th>
<th>Placebo</th>
<th>CIC 40 µg/day*</th>
<th>CIC 160 µg/day</th>
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</thead>
<tbody>
<tr>
<td>Run-in Period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-blind Treatment Period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up Period</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pediatric dose TBD.

Skoner D. Poster presented at: American Academy of Allergy, Asthma & Immunology.
Miami Beach, Florida; 2006.
Efficacy

• Linked to local exposure at the target site (intracellular steroid receptors in the lung)

• How much drug gets into the lung and where in the lung is it deposited?
  – (Deposition)

• How long does the drug stay in the lung?
  – (Residence time)
Pulmonary Deposition: Factors Relevant for Pulmonary Deposition

- Inhaled particles (size, shape, density, hygroscopy, charge, velocity)
- Device (principle and design features such as DPI/MDI/nebulizer, spacer vs nonspacer, HFA/CFC devices, etc.)
- Patient (lung anatomy, breathing pattern, disease state, technique, mucociliary transport)
## Pulmonary Deposition

<table>
<thead>
<tr>
<th>Device</th>
<th>Deposition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI</td>
<td>10%–15%</td>
</tr>
<tr>
<td>Diskus® DPI</td>
<td>14%–20%</td>
</tr>
<tr>
<td>Diskhaler®</td>
<td>10%–15%</td>
</tr>
<tr>
<td>MDI with spacer</td>
<td>15%–25%</td>
</tr>
<tr>
<td>Turbuhaler®</td>
<td>20%–30%</td>
</tr>
<tr>
<td>QVAR®</td>
<td>60%</td>
</tr>
<tr>
<td>Respimat®</td>
<td>40%</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>50%</td>
</tr>
</tbody>
</table>

Diskus® and Diskhaler® are registered trademarks of the GlaxoWellcome group of companies. QVAR® is a registered trademark of IVAX Laboratories, Inc. Respimat® is a registered trademark of the Boehringer Ingelheim group of companies. Turbuhaler® is a registered trademark of the AstraZeneca group.

BDP: HFA vs CFC

Result:
- Smaller particle size (1-2 mm vs 2-5 mm)
- Higher pulmonary deposition
- More peripheral deposition

3M website.
Gamma Scintigraphy

BDP: CFC vs HFA

CFC-BDP

HFA-BDP

3M information.
Lung Deposition of Inhaled Corticosteroids

Dose to the Lungs
Ciclesonide

<table>
<thead>
<tr>
<th>Drug</th>
<th>%</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone DPI</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Fluticasone CFC-MDI</td>
<td>12–20</td>
<td></td>
</tr>
<tr>
<td>Budesonide CFC-MDI</td>
<td>15–18</td>
<td></td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>15–28, 32–42</td>
<td></td>
</tr>
<tr>
<td>Mometasone HFA-MDI</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>BDP HFA-MDI</td>
<td>53–60</td>
<td></td>
</tr>
<tr>
<td>BDP CFC-MDI</td>
<td>4–7</td>
<td></td>
</tr>
<tr>
<td>BDP DPI</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Deposition characteristics of $^{99m}$Tc-labeled CIC (ex-actuator)

Pulmonary Residence Time
Absorption Profiles of Inhaled Corticosteroids

Lipid Conjugation

• Corticosteroids with a hydroxyl group in C-21 can form esters with fatty acids in the lung
• These lipid conjugates increase the pulmonary residence time of the corticosteroids and provide a local depot for their slow release

In Vivo Kinetics of Fatty Esters

Central and Peripheral Lung – 6 patients undergoing lung lobe resection

Thorsson et al. 1998.
Effect of Disease

Area under the curve for plasma fluticasone propionate concentration after inhalation
Effect of Disease

Figure 1 Mean (SE) plasma concentrations of (A) fluticasone propionate and (B) budesonide in healthy subjects and subjects with moderately severe asthma.
Adherence

Reznik, Ozua, J.of Allergy (2012)
Vestbo et al, Thorax (2009)
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
- No active metabolites
- High plasma protein binding
- Negligible systemic effects
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High potency/efficacy

Negligible oropharyngeal effects

Negligible systemic effects
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- No active metabolites
- High plasma protein binding

- High potency/efficacy

- Negligible oropharyngeal effects

- Negligible systemic effects
Pharmacokinetics of Modified-Release Prednisone Tablets in Healthy Subjects and Patients With Rheumatoid Arthritis

Hartmut Derendorf, PhD¹, Klaus Ruebsamen, PhD², Lynsey Clarke, MBBS³, Achim Schaeffler, PhD², and John R. Kirwan, BSc, MD³
Delayed Release Prednisone

Figure 1. Absorption of prednisone after a single oral dose of conventional prednisone 5 mg and modified-release prednisone 5 mg.

Figure 2. Mean concentration of prednisone in plasma after a single oral dose of conventional prednisone 5 mg and modified-release prednisone 5 mg (key study KSI).
Bioequivalence Studies for Orally Inhaled and Nasal Drugs: An FDA Perspective

Wallace P. Adams, Ph.D.
OPS/CDER/US FDA

ACCP 32nd Annual Meeting
Palm Harbor (Tampa), FL
21 September 2003

This presentation represents the personal opinions of the speaker and does not necessarily represent the views or policies of the US FDA.
Locally Acting Drug Products (OINDP)*

The Bioequivalence Problem:

In general, pharmacokinetic studies are by themselves insufficient to establish BE

*Orally inhaled and nasal drug products (OINDP)
Bioequivalence of Inhaled Corticosteroids

Bioequivalence – FDA Definition

21 CFR 320.1

“Absence of a significant difference in the rate and extent to which the active ingredient or active moiety in *pharmaceutical equivalents* or *pharmaceutical alternatives* becomes *available at the site of drug action* when administered at the same molar dose under similar conditions in an appropriately designed study”
BE Criteria on the Dose Scale: Theory

Response resulting from the test product (Observed)

Dose-response curve for reference product

Reference product dose-response data

Dose of reference product that would result in a response equal to that resulting from the test product (Estimated)

Reference Product Dose
Clinical Studies

- Pulmonary Function (FEV₁)
- Exhaled NO
Mean change in FEV1

Litres

Study week

FP 50mcg bid
FP 100mcg bid
Placebo

Larsen et al, 1994
FEV₁ as % of predicted value

Randomized treatment

Run in on high dose budenoside

% 90 85 80 75

Months

-1 0 1 2 3 6 9 12

BUD800
BUD200

Pauwels et al, 1997
Time-series morning and evening fractional exhaled NO (FeNO) values after inhalation of either 100 (50 mcg bid) or 500 (250 mcg bid) mcg fluticasone propionate.

Two Dry Powder Inhalers

**RPID**
Multiple dose dry powder inhaler, containing a reservoir drug lactose blend from which unit doses are metered.

**DISKUS**
Multiple dose dry powder inhaler, containing unit doses of drug lactose blend in a peelable foil strip.

Both devices
Carrier: Lactose mono hydrate.
API / strength: micronised salmeterol 50 mcg and fluticasone propionate 250mcg.
Unit dose weight: 13mg.
Airflow resistance: 2.5KPa @ 60 L/min.
Performance: similar for range of flow rates.
Similar polymer composition.
RPID salmeterol/fluticasone propionate development

1. In-vitro assessment of emitted fine particle mass profiles by ACI for RPID versus Diskus.

2. Pharmacokinetic/pharmacodynamic study in adult asthmatics to determine in vivo drug delivery & systemic exposure for RPID versus Diskus.

3. Clinical efficacy/safety studies in adult, adolescent and paediatric asthmatics to assess clinical equivalence.

In-Vitro Test - RPID /Diskus ACI Profile

![Graph showing drug deposition across cascade impactor stages](graph_image)

- **Y-axis**: Mean Drug Deposited (µg/dose)
- **X-axis**: Cascade Impactor Stage
- **Legend**:
  - RPID FP
  - RPID Salmeterol
  - Diskus FP
  - Diskus Salmeterol

**ACI @ 60l/min**

[GlaxoSmithKline logo]
Results fluticasone propionate PK

Fluticasone

Plasma conc. (pg/mL)

0 1 2 3 4 5 6 7 8 9 10 11 12

Time (h)

Device RPID Diskus
Results salmeterol PK

Salmeterol

Plasma conc. (ng/mL)

Time (h)

Device  RPID  Diskus
Change in mean morning PEFR wks 1-12

FP/SALM (250/50) via RPID and Diskus in children 4-14yrs
Conclusions

• Based on *in vitro* particle size profiling and clinical efficacy endpoints the two inhalers were deemed equivalent.

• Based on PK data the two inhalers were not equivalent.
  • There was a surprising and unpredictable lack of correlation between *in vitro* particle size profiles, *in vivo* drug delivery and systemic exposure.

• For this example, there was no evidence that PK data were a suitable surrogate to assess the bioequivalence of a topically acting orally inhaled drugs.

• PK data still have a role in evaluating systemic safety and *in vivo* inhaler performance.
Bioequivalence Assessment of Fluticasone Propionate / Salmeterol Xinafoate Dry Powder Inhalers (FDA 2013)

In Vitro Studies

- Single actuation dose content (SAC)
- Aerodynamic particle size distribution (APSD)

Pharmacokinetic (PK) BE Study

- All strengths, single-dose, two-way crossover
- Normal healthy males and non-pregnant females
- 90% CI within 80-125% of Reference
Bioequivalence Assessment of Fluticasone Propionate / Salmeterol Xinafoate Dry Powder Inhalers (FDA 2013)

Clinical Endpoint Study

- Lowest strength only
- Randomized, multiple-dose, placebo-controlled, parallel group design with 2 week run-in followed by a 4-week treatment period of Placebo, Test (T) or Reference (R)
- Dose: 100/50 (FP/SX), twice daily
- Males & non-pregnant females with asthma ≥75% compliance
- T & R statistically significantly superior to placebo
Clinical Study Endpoints

- $AUC_{0-12h}$ for serial FEV$_1$ on the first day (10 time points)
- FEV$_1$ measured in the morning prior to dosing on the last day of a 4-week treatment
- Baseline adjusted (change from pre-dose FEV$_1$)
- 90% CIs for the T/R ratios within 80-125%
Pharmacokinetics – So much more than just for Systemic Safety
Pharmacokinetics – So much more than just for Systemic Safety
Effect of C/P-Deposition Ratio on PK

Simulations: AUC affected by C/P ratio

Drug is slowly dissolving, such as FP

<table>
<thead>
<tr>
<th>200 Simulations (same Dose)</th>
<th>Brand</th>
<th>Generic</th>
<th>Generic</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/P Ratio</td>
<td>45/55</td>
<td>45/55</td>
<td>63/37</td>
<td>22/78</td>
</tr>
<tr>
<td>Variability</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>N</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Bioequivalent Trials*</td>
<td>82%</td>
<td>6%</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

* % Trials with CI within 80-125%

- **AUC is sensitive to C/P ratio**

Hochhaus (2012)
21. Evaluation of orally inhaled medicinal products: NEW

1. The extent to which plasma levels reflect bio-availability in the lung

PKWP Response:

In the EU, PK bioequivalence studies are considered an acceptable methodology to compare the lung deposition of two inhalation products containing the same active substance. In cases where the oral bioavailability of swallowed drug is negligible, or in case it is made negligible by active charcoal blockade, the plasma concentration time curve reflects both the extent of and the pattern of deposition within the lungs.

To conclude equivalent efficacy, both the amount of drug reaching the lungs and the deposition pattern of drug particles within the lung needs to be equivalent.

The area under the plasma concentration-time curve (or AUC) reflects the amount of drug that has reached the lungs. As the rate of absorption from the inhaled particles is different at different areas of the lung, the deposition pattern within the lung is mirrored by the shape of the plasma concentration-time curve during the absorption phase, i.e. Cmax and tmax.

In the case where intestinal absorption is not prevented, i.e. in a study without charcoal blockade, and thus absorption is the sum of the absorption via the lungs and intestinal absorption, as for other modes of administration, equivalent systemic safety can be concluded if two products give rise to equivalent systemic exposure (AUC and Cmax).

Pharmacokinetic endpoints may be more discriminative than PD or clinical endpoints, in particular the efficacy endpoints available for inhaled corticosteroids.
Widening of the acceptance range

Widening of the conventional 20% acceptance range based on high variability is only possible for Cmax according to the CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) (up to 69.84 – 143.19%) if a replicate design is conducted.

To support safety, it should be demonstrated that the systemic exposure is not higher for the test product than for the reference product, i.e. the upper limit of the 90% confidence interval should not exceed the upper bioequivalence acceptance limit 125.00.

Between-batch variability of the reference product and intra-batch variability over time

Variability in particle-size distribution between batches of the reference product or within a single batch of a reference product through their storage period can be significant. There may even be situations where it may be difficult to demonstrate PK bioequivalence between batches of the same reference product. Therefore, before the in vivo comparison, several batches of both test and reference products could be tested to identify representative batches (within ±15% of the corresponding median fine particle dose (or APSD)) of test and reference, respectively. In case of fixed combinations this may imply, if pre-specified in the protocol, the use of different batches for each component.

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.

Another approach that might be acceptable is to show that the side batches (batches in the tails of the distribution) representing the test product specifications are not superior and not inferior to the side batches of the reference product obtained from the market.
Proposal

• Pharmaceutical Properties equivalent (goalposts to be established)
• Systemic PK equivalent (charcoal if oral absorption)
• Cortisol and Growth Studies not needed
• Clinical Studies not sensitive enough and not needed
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