“Best Practices” Bioequivalence Testing for pMDIs with Spacer/VHC

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Discussion Points

• Rationale for demonstrating bioequivalence
  – Spacer/VHC impact on critical product characteristics
  – Potential effect of these dose changes on clinical outcomes

• Regulatory requirements
  – Overview of General Guidelines
  – Summary of Canadian Standard

• Recommendations for clinically relevant in-vitro testing
  – Suggestions for “realistic” testing parameters
INHALER LIFE CYCLE

IN VITRO/PK/PD

Tx Guidelines, Patient Education

Regulatory Agency

Safety & Efficacy

Product Performance & Use

Design & Manufacturing

Clinician

Pharmacist

Care-Giver

Patient
Why *In-Vitro* Testing?

- May be used to assess pharmaceutical product equivalence and consistency of drug delivery
  - In the context of the use of spacers and VHCs, quantifies impact of ‘add-on’ to pMDI performance
- Provides guidance to the clinician on likely performance
Limitations

• Cannot define results with every patient:
  – No account of *effect of disease on airway patency and therefore correlation with deposition of the aerosolized drug* is unknown

• Restricted to a limited number of representative conditions to keep scope of testing within realistic bounds:
  – Concept of ‘*characteristic performance*’ is central to the development of *in vitro* standards for these devices
Two Distinctly Different Purposes For *In Vitro* Testing

- **COMPENDIAL TESTING**
  - Product quality control
  - Regulatory compliance

- **CLINICAL USE SIMULATION**
  - Prediction of likely delivered drug dose
  - Prediction of clinical outcomes
  - Optimize instructions for use to patients
  - Guidance to health-care givers

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EMA/HC 2006 *In Vitro* Guidance

Real Use Test Parameters
Types of S/VHCs used with pressurized MDIs

S/VHC Devices for pMDIs

Function and Effect

• Overcome hand-lung missco-ordination
  – *Benefit for 30-50% of patients*
• Impaction of aerosol on valves and walls of chamber
  – *Selective removal of non-respirable particles*
• Enhance vaporization of propellant
  – *Decrease particle size*
• Slow aerosol jet
  – *Decrease aerosol forward velocity*
• Reduce oropharyngeal dose
  – *Decrease steroid side effects*
Design features affecting deposition of aerosolized drug delivered from S/VHCs

- Device design – S vs VHC vs RF
- Dimensions of device
- Volume of device
- Materials of manufacture (e.g., anti-static material or coating)
- Presence of inspiratory/expiratory valves
- Resistance of inspiratory/expiratory valves
- Designed with an integrated actuator
- Presence of flow indicator
- Mouthpiece design
- Facemask design, deadspace, fit to face
Changes to OIP with addition of VHC: Emitted Mass & Fine Particle Mass Ex-actuator, Ex-VHC

- **Figure A**:
  - Emitted Dose (µg)
  - Loss of OIP in VHC ➔ ED<LC
  - Data from M Dolovich DICE Study AJRCCM 2002

- **Figure B**:
  - Fine Particle Dose (µg)
  - Similarity in FPM from VHC to OIP FPM
Clinically Appropriate *In Vitro* Simulations: T vs R product ± S/VHC

- **Inlet geometry** used with impactor should be similar to human dimensions (adult, child)
- **Ventilatory test variables** (refer to CSA Spacer Standard Table)
  - age-appropriate inspiratory flow rate,
  - age-appropriate inspiratory volume
- **Delay between actuation and inhalation** when sampling aerosol from VHC
  - effect of variable delay on aerosol available from VHC
- **Facemask variables** on S/VHC
  - facemask deadspace
  - fit to (model) face (leakage)
- **Humidity, temperature** of ambient air drawn into impactor should mimic conditions in the lung
In Vitro Delivery of Airomir HFA pMDI + Spacers using Pari Breath Simulator

Drug Output (µg)

1 puff, 1 min tidal breathing
n=4-6

Simulated Breath Pattern

- BBH
- NES
- AC

<table>
<thead>
<tr>
<th>Simulated Breath</th>
<th>BBH</th>
<th>NES</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>50</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>2 yrs</td>
<td>100</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>12 yrs</td>
<td>200</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>500</td>
<td>800</td>
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</table>

Are VHCs interchangeable?

M Dolovich 2003
### TABLE 2 DEMOGRAPHIC CHARACTERISTICS

Demographic Characteristics of Study Population

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
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</thead>
<tbody>
<tr>
<td>All</td>
<td>Mean</td>
<td>2.3</td>
<td>93.50</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.79</td>
<td>6.89</td>
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<tr>
<td>N = 20</td>
<td>Range</td>
<td>1-3</td>
<td>82-106</td>
</tr>
</tbody>
</table>

45% Female, 55% Male, 40% African American, 55% Caucasian, 5% Other

<table>
<thead>
<tr>
<th>VHC</th>
<th>AC</th>
<th>BH</th>
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</thead>
<tbody>
<tr>
<td>Length - cm</td>
<td>14.9</td>
<td>39</td>
</tr>
<tr>
<td>Volume - cc</td>
<td>145</td>
<td>350</td>
</tr>
<tr>
<td>Facemask Dead Space - ml</td>
<td>24 - 46</td>
<td>117</td>
</tr>
<tr>
<td>Weight - g</td>
<td>71.7</td>
<td>190.7</td>
</tr>
</tbody>
</table>

Blake et al ERJ 2012

VHCs are not interchangeable

AUC Fluticasone Propionate

Blake et al ERJ 2012
Current European and Canadian Regulatory Practice Regarding VHCs

EMA and Health Canada

• advise that the manufacturer of an oral inhaled drug product (OIP) delivered by pressurized metered-dose inhaler (pMDI) identify a specific spacer (S) or valved holding chamber (VHC) to be used with the named product

• recognize that S/VHCs are widely prescribed for use with pMDIs, and that the aerosol physical properties may be changed by the addition of this type of add-on device, possibly requiring dose revision for the patient.
Regulatory Guidance: US

• The US position with respect to the use of spacers/VHCs is less clear as there is currently no mention of requirements related to these add-on devices in FDA (CDER) guidance.

• So-called ‘universal’ spacers/VHCs are tested in accordance with a 1993 Reviewer Guidance developed by CDRH that essentially allows for compendial testing methods to determine aerosol performance in terms of APSD.

Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators CDRH/ODE/DAGID/ARDB issued October 1993
Health Canada 2011 Revised ICS Draft Guidance

• The subsequent entry of inhaled corticosteroid (ICS) products into the marketplace, supports the testing of VHCs, through its recommendation:

“Since the drugs (ICS) are used in adults and children, evidence of compatibility with existing spacer devices or chambers is required for both adults and children.”

Three possibilities for BE testing for pMDI products with S/VHC add-on devices

- **REFERENCE PRODUCT (R)**
  - pMDI (R) alone
  - pMDI(R) + S/VHC

- **TEST PRODUCT (T)**
  - pMDI (T) alone
  - pMDI(T) + S/VHC

- **BE-1**
- **BE-2**
- **BE-3**
- **BE-4 if not identical add-on device**
REGULATORY AGENCIES:
increasing awareness of need for clinically relevant testing in EU

...but apart from need to test simulating delayed inhalation for VHCs, there is a lack of detail as to what needs to be done

“..... the in vitro testing should be carried out by preparing the spacer and setting up the apparatus in a clinically relevant manner which may influence the performance of the product...”

EMA 2009
EMA 2009 Guidance

• In 2010 UK Medicines and Healthcare Products Regulatory Agency (MHRA), interpreted the EMA 2009 guidance in the context of regulatory approval of a generic pMDI-based product as follows:

“..given that a generic and reference pMDI should be interchangeable and given the importance of spacer [VHC] use particularly in children, the failure to provide either in vitro or in vivo spacer [VHC] data confirming equivalence would generally preclude regulatory approval of the generic product.”
A Standard for S/HCs

- CANADIAN STANDARD (Z-264 series)
  - Referenced by ISO 20072:2009 Aerosol drug delivery device design verification — Requirements and test methods
- Compares performance with S/HC to pMDI without add-on device
  - Existing compendial methodology for particle size analysis (constant flow rate) but introduces a delay between inhaler actuation and onset of sampling
  - Additional testing for the effect of breathing asynchrony using breathing simulator
- First issued in 2002, and revised with minor improvements in 2008
Recommendations for clinically relevant \textit{in-vitro} testing

Modelling & Simulations in combination with APSD and ED measurements:

- Mass of API available at the mouth – \textit{in vitro/ex-vivo} measurement
- Simulation of age-dependent breathing patterns
  - IFR, $V_t$, I/E ratio, breath-hold, delay post-actuation
- Facemask deadspace & fit to face
- Hygroscopic growth
  - simulate high humidity/temperature conditions within the lung and/or delivery system
- Airway morphology in disease
  - Airway narrowing, turbulence & ventilation (CFD), mucus layer
Inhaled aerosol caught in absolute filter on inspiration; filter removed from housing and API assayed.
1.5 µm Inhaled $^{18}$F-FDG

When Models Meet Reality: Lung Deposition

ii. DEPOSITION VARIES BETWEEN INDIVIDUALS

iii. INFLUENCE OF AEROSOL SIZE AND IRF ON DEPOSITION

\[ \text{Lung Deposition (\% Ex-Actuator $^{99m}$Tc)} \]

\[ \begin{align*}
\text{BV} & \quad \text{QVAR} & \quad \text{Ratio} \\
0 & \quad 1 & \quad 2 \\
20 & \quad 3 & \quad 4 \\
40 & \quad 5 & \quad 6 \\
60 & \quad 7 & \quad 8 \\
80 & \quad 9 & \quad 10 \\
100 & \quad 11 & \quad 12
\end{align*} \]

\[ \text{MMAD: BV 3.2 µm; QVAR 1 µm} \]

\[ \text{Oro} + \text{Gut} \]

\[ \text{Oro} \]

\[ \text{Lung} \]

\[ \text{15 Lpm} \]

\[ \text{60 Lpm} \]

\[ \text{Lung} = -25.99 \times \log(d^2/Q) + 137.95, r^2 = 0.70 \]

\[ \text{Oropharynx} = 17.06 \times \log(d^2/Q) - 43.97, r^2 = 0.28 \]

\[ \text{Oropharynx + Gut} = 38.60 \times \log(d^2/Q) - 108.62, r^2 = 0.60 \]

M Dolovich JAMPDD 2001
In Summary

• Clinically relevant laboratory testing is becoming important as a means of evaluating OIPs as the patient might use them
• Various methodologies have been developed in recent years that provide ways to establish this type of information
• Such testing should not be viewed as an alternative to the existing standardized techniques for OIP quality evaluation