Why Clinically Appropriate In Vitro Inhaler Testing? - Introducing the Patient Experience into the Picture

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Disclosures

• I am a former employee of Trudell Medical International (TMI), manufacturer of some of the devices I will be showing
• I continue to provide consultancy services to TMI
• The advice I will give represents my own view of the subject and not necessarily that of TMI
Key Messages

1. Clinically appropriate testing is not meant to replace the existing compendial methods for product quality assurance.
2. The principle of clinically meaningful testing is to mimic as closely as possible the conditions of patient use.
3. The goals of such testing are:
   a. Obtain improved *in vitro-in vivo* correlations for OIPs.
   b. Provide clinicians with laboratory-generated performance data that take into account patient ability to operate the inhaler.
   c. Assist the process of matching the inhaler to the patient, thereby (hopefully) improving compliance and clinical outcomes.
1. Two distinct pathways for *in vitro* performance testing
2. Realistic testing of inhalers as support to regulators and clinicians
3. Stakeholder acceptance
4. Summary of current position
Two Measurement Pathways in the Lab

Inhaler product quality control

- Regulatory compliance

EXISTING COMPENDIAL METHODS

Prediction of likely clinical effect

Guidance to health-care givers

METHODS THAT SIMULATE PATIENT USE/MISUSE
1: In Product Quality Assessment:

• **FOCUS IS ON METHOD ROBUSTNESS:**
  - *simplicity* as far as is possible
  - *high accuracy* and *precision*

• **Standardized Methods:**
  - formulation and inhaler development
    - regulatory submissions
  - batch release testing

*Goal is to minimize inter-operator and inter-laboratory variation*
2: In Clinically Appropriate Testing:

• FOCUS IS ON METHOD REALISM:
  • Likely to introduce *complexity*
  • Goal is to maintain as high accuracy and precision as is practical

• Specialized Methods:
  • Simulate correct use
  • Predict consequences of imperfect use
  • Potential to achieve improved *in vitro-in vivo* correlations/relationships than current compendial methods

Breathing simulation is a key component
SIMPLE TO EXECUTE, RAPID REPEATABLE, ROBUST METHODS

MORE COMPLEX MODELS SIMULATING PART/ALL RESPIRATORY TRACT WITH BREATH SIMULATION

CLINICAL REALITY PATIENT FACTORS SUCH AS COMPLIANCE CONTRIVANCE AND CAPABILITY

LARGE GAP
The Care Pathway

Data from clinically appropriate testing also supports the pharmacist and care-giver, who are closer to the user.
The High Cost of Patient Non-Adherence to Therapy

• Non adherence in US costs $300 bn. annually (2010) ¹:
  • COPD is among the conditions with lowest adherence ²

• Canadian hospital expenditures caused by non-adherence to controller therapy in asthma exceeded US$1.6 bn. (2004)³

¹Lareau SC and Yawn BP *Int. J. COPD*. 2010;5:401-406
Inhalers are Complex to use!

- The inhalation route requires the patient or caregiver to learn a relatively complex series of steps:
  1. Inhaler preparation:
  2. Preparation of add-on device and applying the facemask (if used) correctly
  3. Coordination of inhaler actuation with onset of inhalation
  4. Inhale forcefully if a DPI
  5. Inhale slowly if not a DPI
  6. Assurance that the dose has been given: Note, more than 1 actuation may be needed
  7. Clean-up after treatment – especially important with nebulizers
Potential Misuse of Laboratory Performance Data

• Re-use of regulatory submissions data in marketing context is widespread:
  • methods may be appropriate for quality control, but not necessarily predictive of actual use by patients
  • data are often of limited value to the clinician
  • little or no guidance given as to expectations with optimum use
Patient use and potential for misuse should be considered at all stages of the inhaler design process.
Regulatory Support is Also Key:

- Encourage 'Good' design:
  - Intuitive
  - Ergonomic
  - Portable
  - Clear instructions

Supported by:

- Laboratory performance data obtained by clinically appropriate means
- Clinical studies

The focus of good testing practices

MORE REALISTIC TEST METHODS
Mimicking Patient Use: How Far?

• Not just ideal inhaler technique:
  • Although ‘ideal’ performance measurements serve as a useful benchmark

• Also consider less than perfect scenarios:
  • poor coordination
  • use by the young or elderly patient
  • effect of disease on airways

FOUR KEY ELEMENTS ARE INVOLVED:
1. Introduce Breathing Simulation

- Relatively easy when determining total mass of API/actuation
- Tidal breathing or forced maneuver?
- User age appropriate parameters
- New methods for use when measuring APSD by cascade impactor
Tidal Breathing: Important Parameters

- Tidal volume ($V_t$) in mL
- Duty cycle
  - sometimes referred to as Inspiratory/Expiratory time ratio
- Respiration cycles per unit time
  - typically per minute
- Positive End Expiratory Pressure (PEEP) for mechanical ventilation

Tidal breathing with a **duty cycle** of 50% is the simplest waveform to simulate;
- However it does not accurately reproduce duty cycle, for a normal adult, typically 33%, falling to 25% for a small child
There is a myriad of different breathing patterns that have been used. The parameters in the Table are the nearest we have to standard settings.

<table>
<thead>
<tr>
<th>Breathing Parameter</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neonate</td>
<td>Infant</td>
</tr>
<tr>
<td><strong>Tidal Volume (mL)</strong></td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td><strong>Respiration rate (min⁻¹)</strong></td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td><strong>Inspiratory/Expiratory Ratio</strong></td>
<td>1:3</td>
<td>1:3</td>
</tr>
<tr>
<td><strong>Minute Volume (mL)</strong></td>
<td>1000</td>
<td>1500</td>
</tr>
</tbody>
</table>

*from CAN/CSA/Z264.1-02:2008*
Breath Simulation is Essential for Some Nebulizers

• Breath-enhanced (air entrainment) or actuated nebulizers:
  • Duty cycle can have large effect on API delivery
  • Ability to mimic infants and small children respiration important, given widespread use of nebulizers for treating these populations
Breath Simulation is needed for Holding Chambers

1. Valve function checked
2. Flow indicator(s), if equipped, can also be assessed
3. Tests assure effective medication transfer from the VHC via the patient interface
   - This aspect is critical when the interface is a facemask

Example taken from testing valved holding chambers marketed in Canada

DPIs Require a Different Approach to Tidal Breathing:

1. Mimic inhalation portion of the breathing cycle as closely as possible to reality:
   • Patient-Generated waveforms are even better

2. Flow resistance plays a key part in determining:
   • Time dependent flow profile
   • Powder release and aerosol formation kinetics

N.B. The compendial method does not do more than standardize the flow-rate time curve for a given DPI resistance
Forced Maneuvers: A Potential Enhancement

- Long, slow inhalation followed by a breath-hold is linked with improved peripheral lung deposition
  - Darquenne, C et al., *J. Appl. Physiol.* 2000;89:1787-1792

- Gravitational sedimentation enhances deposition during breath-hold

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**A**

<table>
<thead>
<tr>
<th>Deposition DE (%)</th>
<th>Breath hold (sec)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
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<tr>
<td></td>
<td>5</td>
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**B**

<table>
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<th>Deposition DE (%)</th>
<th>Breath hold (sec)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

- $V_p = 150$ ml
- $V_p = 500$ ml

- • microgravity
- • normal gravity

Darquenne C. et al.
2. Use an Anatomically Age-Appropriate Inlet

- Anatomically correct inlets have been used for several years in research, but:
  - Cadaver-prepared casts may not reflect airway geometry *in vivo*
  - Much variation can exist from one cast to another within the same age range
Consider Size of Inlet with Adults

Inlet configurations derived from research by Oropharyngeal Consortium

Courtesy: M Svensson, Emmace Consulting AB
‘Idealized’ inlets may be an alternative

- Idealized anatomic inlets capture the air flow characteristics of an anatomically correct naso- or oropharynx in a simplified geometry that can be manufactured.
- Finlay (University of Alberta) pioneered to development and verification of idealized upper airway models:
  - Fabricated like the Ph.Eur/USP induction port
  - Yet have similar aerosol transport properties to anatomic inlets

“Alberta” adult idealized inlet (AIT) courtesy: Copley Scientific Ltd.
Idealized Inlets: Performance is Different to USP/Ph.Eur. Induction Port

• Recent testing of the adult AIT with full resolution and abbreviated CIs:
  • A greater proportion of coarse mass fraction is collected by the AIT compared with the Ph.Eur./USP induction port
  • Agrees qualitatively with comparable measurements made with anatomic throats

Copley M et al. Inhalation 2011;5(4):12-16
An idealized child oropharyngeal inlet has also been developed:
- mimics the average deposition during oral inhalation among children aged 6–14 years old

An infant inlet is in development
- Nasopharynx
- Most infants are obligate nasal breathers

Golshahi, L and Finlay, WH. AS&T 2012;4 6: i -iv
3. Test the Patient Interface* Appropriately

* Mouthpiece or facemask

- A mouthpiece can be readily fitted to the inlet of the aerosol sampler by means of a short adapter connection
- A facemask is a different situation entirely:
  - Here it is necessary to re-create the conditions of use
Facemask-to-Face Seal can be Critical with VHCs

- There is no energy source to prevent ambient air ingress after pMDI propellant has vaporized:
  - Esposito-Festen et al., *J. Aerosol Med.*, 2004;17:1–6

- Testing requires a suitable face model in order to achieve clinically realistic facemask fit:
  1. Mimic an appropriate force that mask is applied to face:
    - Create an accurate dead-space
  2. Reproduce soft tissue and facemask response to applied force realistically
  3. Confirm absence of leakage between mask-and-face
Facemask Dead-Space is Also Important

- Dead-space in flexible facemasks is affected by force with which mask is applied to face.
- Soft tissues move in contact with facemask also affecting dead space.
- There is therefore a need to model all these processes simultaneously in the laboratory.

1.6 kg widely used in VHC testing
Face-Upper Airway Models are Important

• Focus on modeling:
  • Age-appropriate facial profiles
  • Underlying soft tissues and rigid bone structures
  • Upper airway:
    • nasal or oral depending upon age being simulated

SAINT infant model

ADAM-III infant model
Mitchell et al. RDD Europe-2011;457-461

VHC Testing: Breathing Simulator Linked to Model

- Simple to do when collecting total API mass by filter
Interplay Between Tidal Breathing Variables and Delivered Mass (DM) to Carina of an Infant Model

- **ADAM-III infant model:**
  - Anatomically correct naso-pharynx – 7 month infant
  - Soft tissue modeling
  - VHC-facemask applied with 1.6 kg force
    - Orientation of VHC-to-face adjusted simulating realistic use

Qualitative agreement with Tal *et al.*, *J Pediatr.*, 1996;128(4):479-84 for upper airway and lung deposition of radiolabeled salbutamol

Mitchell *et al.* *RDD Europe-2011;457-461*
Small Child ADAM-III Model

• 4-year old, 15.9 kg male:
  • Anatomy from MRI scan
  • Oral and nasal breather offering possibility of 3 separate options for breathing
    • obligate nasal
    • oral
    • oral and nasal
  • Software facial render underlying bony structures
  • Soft facial tissue modeling as for infant

Courtesy: Robarts Research Institute, London Ontario
4. Particle Sizing is More Complex

- Cascade impactors operate at a fixed and constant flow rate
  - Stage cut-point sizes ($d_{50}$) are determined by the operating volumetric flow rate ($Q$):

$$\sqrt{C_{c,50}d_{50}} = \left[ \frac{9\pi\mu n W^3}{4 \rho_0 Q} \right]^{1/2} \sqrt{St_{50}}$$

Basic Approach for Sizing with Delayed Inhalation

- Useful for pMDI-valved holding chamber combinations
- ‘Delay’ apparatus contains shutter between VHC and Induction port. Shutter opens to sample VHC contents after fixed delay following pMDI actuation

Induction port can be replaced with anatomic or idealized inlet to improve clinical ‘realism’

1. Microphone starts timer on pMDI actuation
2. VHC located upstream of shutter
3. Aerosol not sampled during delay interval
4. Shutter falls away after delay, allowing aerosol to be sampled

CAN/CSA/Z264.1-02:2008
Draft USP <1602>
Sizing with Variable Flow-Time Profiles at Inhaler

- Uses the Nephele-Miller mixing inlet

- Inhaler ‘sees’ breathing pattern
- Impactor operates at constant flow rate

Olsson B. et al. Respiratory Drug Delivery 2008: pp. 197-206
Olsson B. et al. Study: Methods/Results

- Multiple inhaler platforms
- Budesonide as common API
- Nephele Mixer/NGI
- Small/Medium/Large adult inlets
- Strong/medium/weak flow-time patterns
- Lung deposition from pharmacokinetic measurements
- Excellent IVIVCs across pMDI+VHC, DPI and nebulizer platforms

Table 2. Nominal Delivered Dose In Vitro (NDD) Scaled for the Same Number of Actuations Used During In Vivo Testing

<table>
<thead>
<tr>
<th>Device</th>
<th>Geometric mean (µg)</th>
<th>CV (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPI_A</td>
<td>505</td>
<td>6.3</td>
<td>27</td>
</tr>
<tr>
<td>DPI_B</td>
<td>714</td>
<td>7.7</td>
<td>27</td>
</tr>
<tr>
<td>DPI_C</td>
<td>663</td>
<td>6.6</td>
<td>27</td>
</tr>
<tr>
<td>MDI_A</td>
<td>756</td>
<td>7.3</td>
<td>24</td>
</tr>
<tr>
<td>MDI_B(\text{a})</td>
<td>601</td>
<td>4.1</td>
<td>48</td>
</tr>
<tr>
<td>NEB_A</td>
<td>434</td>
<td>8.0</td>
<td>27</td>
</tr>
</tbody>
</table>

\(\text{a}\)Including results for MDI_B during spacer experiments (MDI_BS).

Highly consistent measures of NDD across all inhaler platforms

Olsson et al: Improved IVIVCs were Obtained

Compendial Methods
Various API/inhaler formats

Nephele Mixer Method
budesonide/pMDI, DPI, nebulizer

Evidence of bias

Newman S P, Chan H-K.

Insignificant bias

The GSK ‘Electronic Lung’ is an Alternative Approach

- 2-step process useful particularly with DPIs
  - The inhaler aerosol is drawn into the sample chamber using an appropriate ‘inhalation’ maneuver
  - The cascade impactor samples from the base of the chamber at constant flow rate after the chamber is closed by the valves following inhalation

Hamilton M, Daniels G. *DDL22;2011*
• **EMA:** increasing awareness of need for clinically relevant testing

• ....but apart from need to test simulating delayed inhalation for pMDI-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...”
Pharmacopeia Acceptance: Europe

- The British Pharmacopeial Commission, in recently issued policy statement has called for the Ph.Eur. to consider developing a monograph following the lead set by the USP
- It is anticipated that both Ph.Eur. And USP activities will be harmonized from the start, as was done with Ph.Eur. Monograph 2.9.44 and <1601> covering preparations for nebulisation

BP Inhaled Products Working Party
Policy Document issued September 2012

Commission that a general monograph providing information for the testing of spacers, holding chambers and facemasks should be developed through the Pharmacopoeial Discussion Group (PDG) harmonization process
USP Acceptance

• **Normative chapters below 1000:** currently provide test methods optimized to evaluate OIP quality:
  • <5>
  • <601>
  • <602>
  • <603>
  • <604>

• More scope possible with informative chapters above 1000:
  • <1601> Products for Nebulization, established the precedent
  • <1602> Spacers/VHCs in development advocates clinically appropriate test methods for these devices*

*This chapter has just completed public review as an In Process Revision – Pharm. Forum 2014; 40(1)*
Concluding Remarks

1. Enhancing the patient/care-giver-inhaler experience is key to achieving adherence to prescribed inhalation therapy
2. The inhaler manufacturer, supported by regulatory agencies and the compendia, has a key role to play in providing ‘patient-friendly’ products
3. Part of the support to clinicians are data from clinically appropriate laboratory testing; this is the means of evaluating inhalers as the patient might use them
4. Various methodologies have been developed that provide ways to establish this type of information
5. Such testing should be viewed as an augmentation of the ways these products are evaluated, *by putting the patient in the picture*