Holding chamber valve technology: effectiveness at low flow rates.

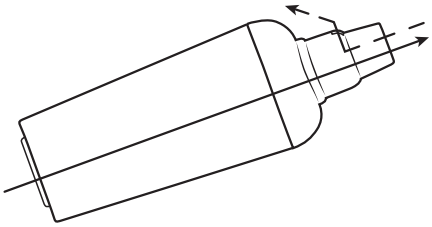
Mark Sanders[1] and Ronald Bruin[1], Cuong Tran[2]

Clement Clarke International Ltd, Edinburgh Way, Harlow, CM20 2TT, UK. [1]
i2c Pharmaceutical Services, Cardiff Medicentre, Cardiff, CF14 4UJ, UK. [2]

Introduction

- Valved holding chambers (VHCs) are valuable add-on devices for improving pMDI drug delivery [1].
- VHC valves open for inhalation and close for exhalation to facilitate tidal breathing and non-dilution of aerosol cloud.
- Typically, exhaled breath is diverted via a two-way valve and/or an exit port (**Figure 1**).
- VHC performance can be marred by several factors, including failure of the inhalation valve to open fully [1].
- This is more likely to occur at low inspiratory flow rates (IFRs), with young children [2].

Figure 1 - Example VHC (solid line = inhalation, dotted line = exhalation)

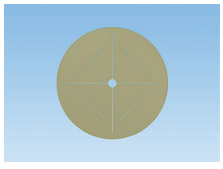


Background

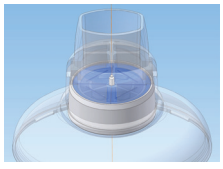
- The Able Spacer®-2 VHC (**Figure 2**) has a thin, low resistance silicone, circular valve (**2a**) supported between chamber top (**2b**) and mouthpiece (**2c**).

Figure 2

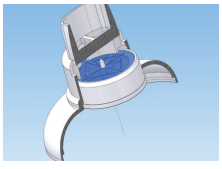
a



b



c



- Valve diagonal cross-cuts open/close during inhalation/exhalation.
- The current mouthpiece and valve effectively create permanently open exhalation ports that inevitably affect the valve-open inhalation flow rate.
- **Our challenge :**
  - to develop true two-way valve function
  - to develop 'valve-open' at low IFR, ensuring suitability for children

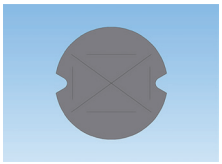
The funding source for this study was Clement Clarke International Ltd. The authors gratefully acknowledge the assistance of Janet Allan and David Spencer of Clement Clarke International Ltd.

Valve development

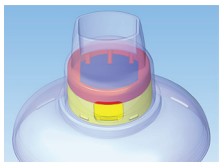
- Additional valve cut-geometry and shape (**3a**)
- Increase in exit port size (**3b**)
- Two-piece valve support that closes exhalation ports during inhalation (**3c**)

Figure 3

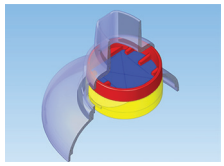
a



b



c



Deposition studies

- **Aerosol performance of Ventolin Evohaler®, 100µg salbutamol pMDI :**
  - Next Generation Impactor – standard flow of 30 L/min
  - DUSA – low flow of 10 L/min
- **Comparisons (n=5 per group):**
  - Able-Spacer 2 plus current valve (**A1**)
  - Able-Spacer 2 plus development valve assembly (**A2**)
  - Able-Spacer 2 plus alternative development valve assembly (**A3**)
  - pMDI alone
- **Standard instrumentation, sample preparation, chromatography and analysis.**

Table 1 – Similar key aerosol characteristics at 30 L/min (mean ± SD)

	Fine Particle Fraction (%<5µm)	Fine Particle Dose (µg<5µm)
pMDI only	47.9 ± 2.4	41.7 ± 4.4
+ A1	55.0 ± 2.0	55.8 ± 9.2
+ A2	51.8 ± 2.4	52.2 ± 9.9
+ A3	55.4 ± 2.5	53.1 ± 10.3

Table 2 – Similar DUSA recovery at 10 L/min (mean ± SD)

	µg recovered per actuation	% recovered of emitted dose
+ A1	43.6 ± 6.5	49.4 ± 6.3
+ A2	45.1 ± 2.8	56.6 ± 4.4
+ A3	52.7 ± 4.5	58.0 ± 2.1

(pMDI-only DUSA: 82.1 ± 5.8 µg recovered per actuation, representing 100% of emitted dose)

Discussion

- Mitchell & Nagel concluded from their research [2] "*In vitro measurements made at constant high flow rates in excess of 20 L/min do not reveal [these] differences in performance that are clinically significant, and may lead the physician to prescribe a device that under certain conditions may not deliver any drug to infants or small children.*"
- Our low IFR research has shown improved performance from the new valves at 10 L/min.
- **Current developments** :
  - anti-microbial additive research
  - use of mobile Apps with VHC facemask whistles

Conclusions

- The current data indicate that valve developments may increase drug availability at IFRs that are representative of paediatric or compromised lung function users.

References

1. Mitchell JP, Nagel MW. Valved holding chambers (VHCs) for use with pressurized metered-dose inhalers (pMDIs): a review of causes of inconsistent medication delivery. Prim Care Respir J 2007; 16: 207-214.
2. Mitchell JP, Nagel MW. In vitro performance testing of three small volume-holding chambers under conditions that correspond with use by infants and small children. J Aerosol Med 1997; 10: 341-349.