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# IN-VITRO PERFORMANCE OF ALBUTEROL HFA FORMULATION IN TWO VALVED HOLDING CHAMBERS AT LOW INSPIRATORY FLOW RATES AND EXTENDED DELAY TIMES

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## ABSTRACT

**RATIONALE:** Valved Holding Chambers (VHCs) are an important adjunct in delivery of medication particularly to infants and young children.

**METHODS:** This *in-vitro* study evaluated the effect of two different VHCs (**AeroChamber Plus**<sup>®</sup> and **AeroChamber Plus**<sup>®</sup> Z-STAT<sup>™</sup>, Monaghan Medical Corp.) each with either a small or medium facemask on delivery of albuterol (Ventolin<sup>†</sup> HFA, GlaxoSmithKline) to an oral-breathing face model. Flow rates of 4.9, 8.0 and 12.0 L/min were examined in combination with delay times of zero, 2, 5 and 10 seconds. These conditions were considered to be representative of children 6–12 months, 2 – 5 years and > 5 years old. Aerodynamic particle size distributions were determined by low-flow Marple-Miller impactor.

**RESULTS:** Although the delivered dose of albuterol through the VHCs/facemasks was reduced under all conditions compared to label claim (90 µg), fine particle fraction was increased as a percentage of delivered dose consistent with deposition of the coarser fraction in the VHC. At the lowest flow rate and longest delay time, mean delivered dose was 14.6 – 17.1 µg, while fine particle fraction (0.77 to 4.7 µm) was close to 70% of the delivered dose. In contrast, fine particle fraction (1.1 to 4.7 µm) without VHC typically represents 35 – 45% of the delivered dose measured at the standard flow rate of 28.3 L/min.

**CONCLUSIONS:** The findings from this *in-vitro* study on Ventolin<sup>†</sup> HFA have shown that even at low flow rates and extended delay times, potentially experienced in real-world situations with young children, drug remains available at the patient interface from either VHC/facemask combination.

- Evaluated with a short-acting beta-2 adrenergic agonist:
  - Ventolin<sup>†</sup> HFA (GSK Inc.)
  - 90 µg/actuation albuterol ex actuator
- Delivered Dose (DD):
  - Filter collection of aerosol at mouthpiece of model face (oral breather)
  - 2-actuations/measurement
  - n = 5 VHCs/group
- Aerodynamic Particle Size Distribution for fine particle fraction (FPF):
  - Low flow Marple-Miller impactor
  - 5-actuations/measurement
  - n = 3 VHCs/group

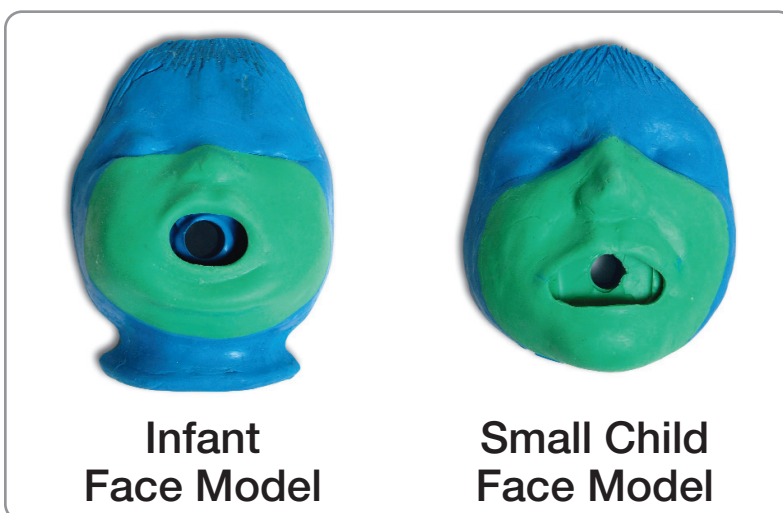
## STUDY DESIGN

| VHC Type  | AeroChamber Plus <sup>®</sup> VHC                      |        | AeroChamber Plus <sup>®</sup> with Z-STAT <sup>™</sup> VHC |        |
|-----------|--------------------------------------------------------|--------|------------------------------------------------------------|--------|
| Delay (s) | Small                                                  | Medium | Small                                                      | Medium |
| 0         | Each device tested at 4.9, 8.0,* and 12.0 L/min for DD |        |                                                            |        |
| 2         |                                                        |        |                                                            |        |
| 5*        |                                                        |        |                                                            |        |
| 10        |                                                        |        |                                                            |        |

\* Omitted for the APSD measurements

• All APSD measurements with the small mask performed only at 4.9 L/min and with the medium mask only at 12.0 L/min

## MODEL FACES



\*\* Patent pending

- The soft tissues surrounding the oral cavity were simulated\*\* so that the facemask dead volume is realistic when applied to the face with a clinically appropriate force of 1.6 kg<sup>3</sup>

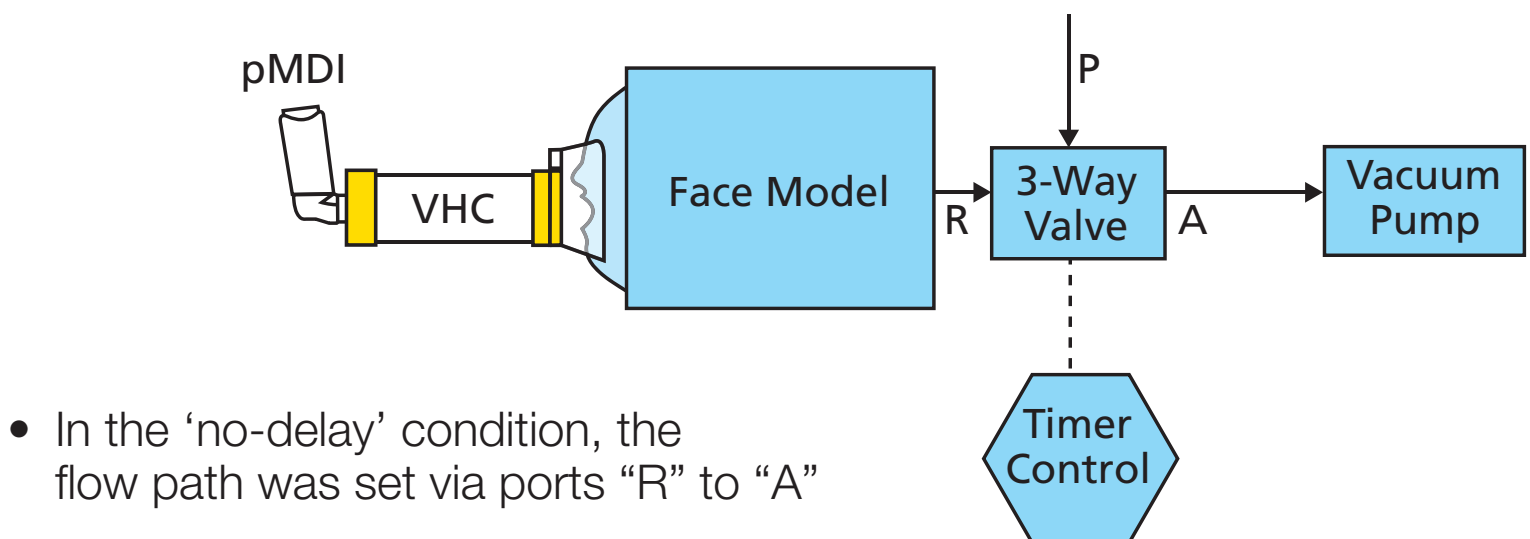
## VHC SUPPORT CRADLE

- The VHC/facemask was retained in a purpose-built\*\* cradle during each measurement, so that the positioning and sealing of the facemask on the face could be accurately reproduced, as an effective seal is critical for effective delivery of medication<sup>4</sup>



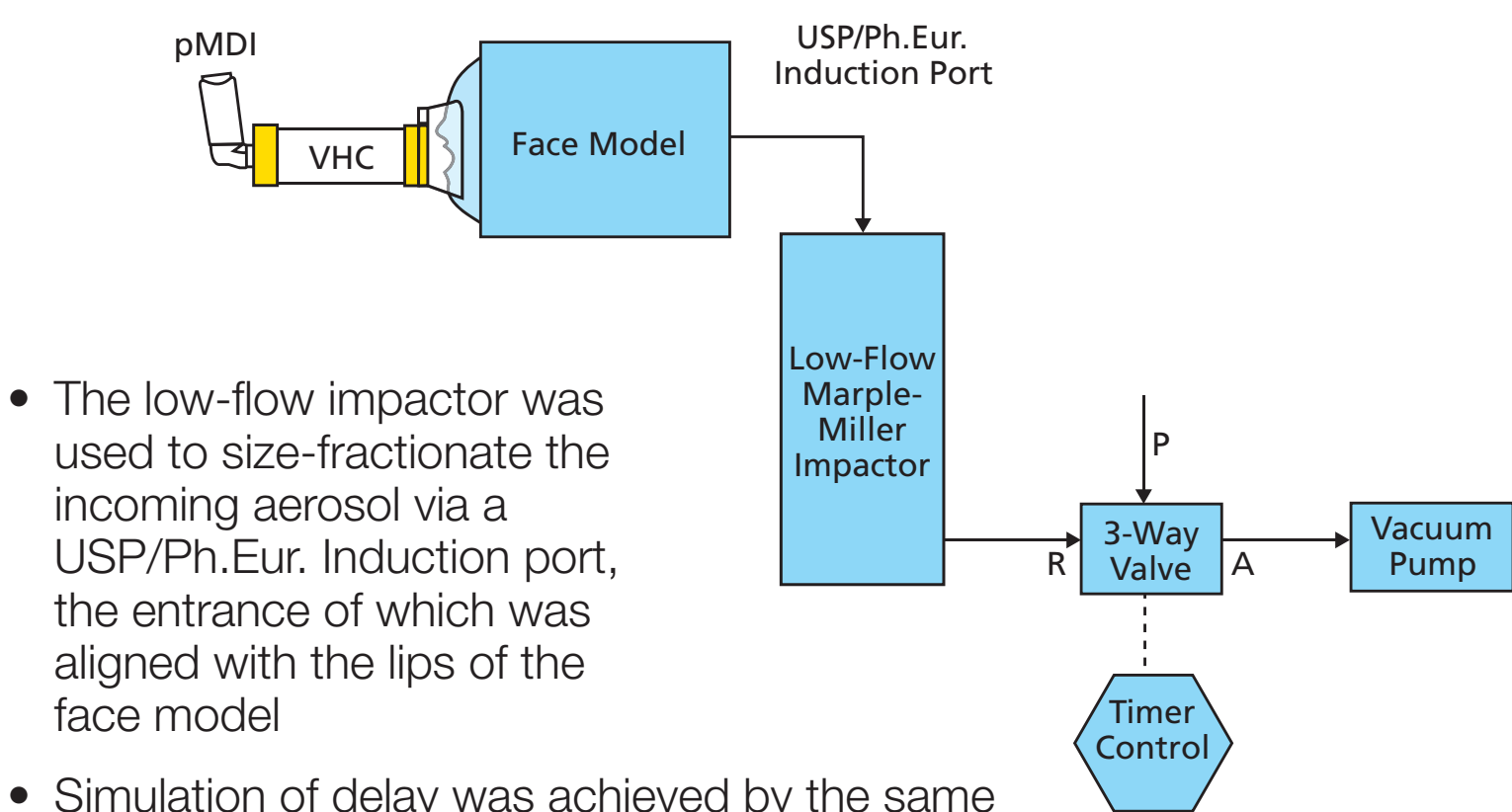
\*\* Patent pending

## MEASUREMENT OF DD



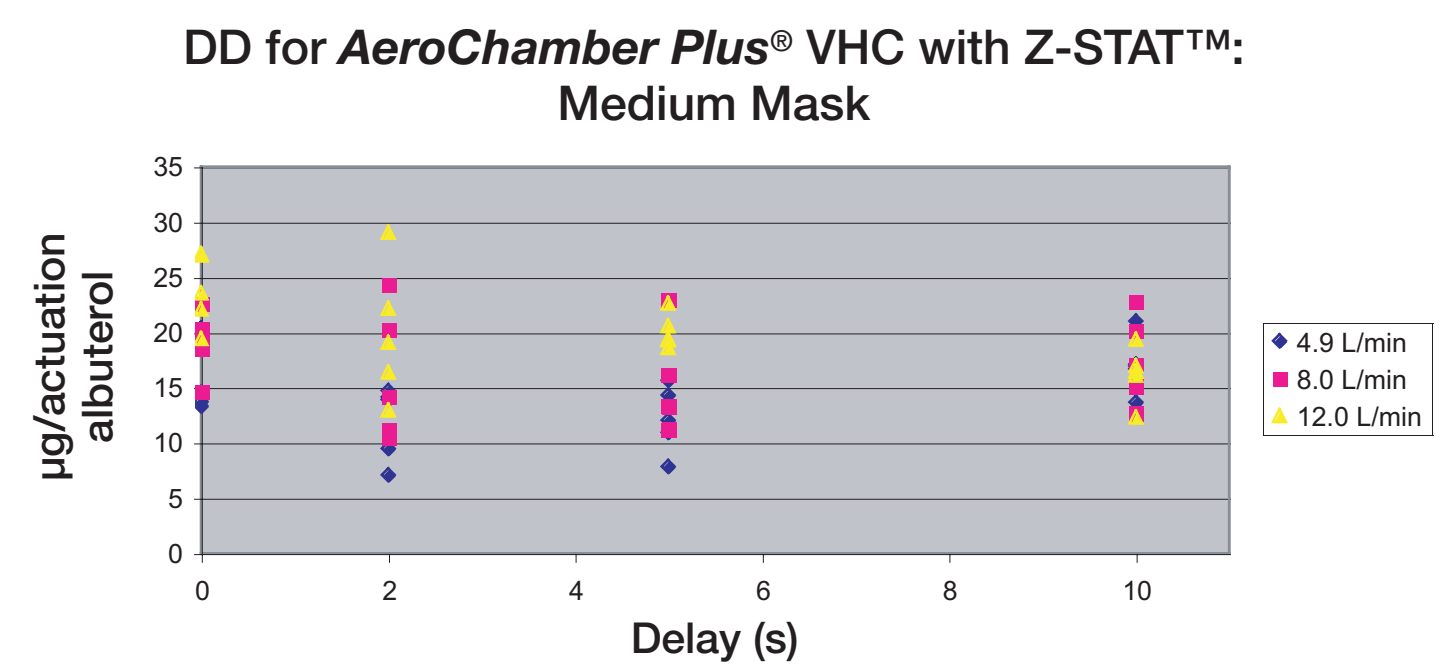
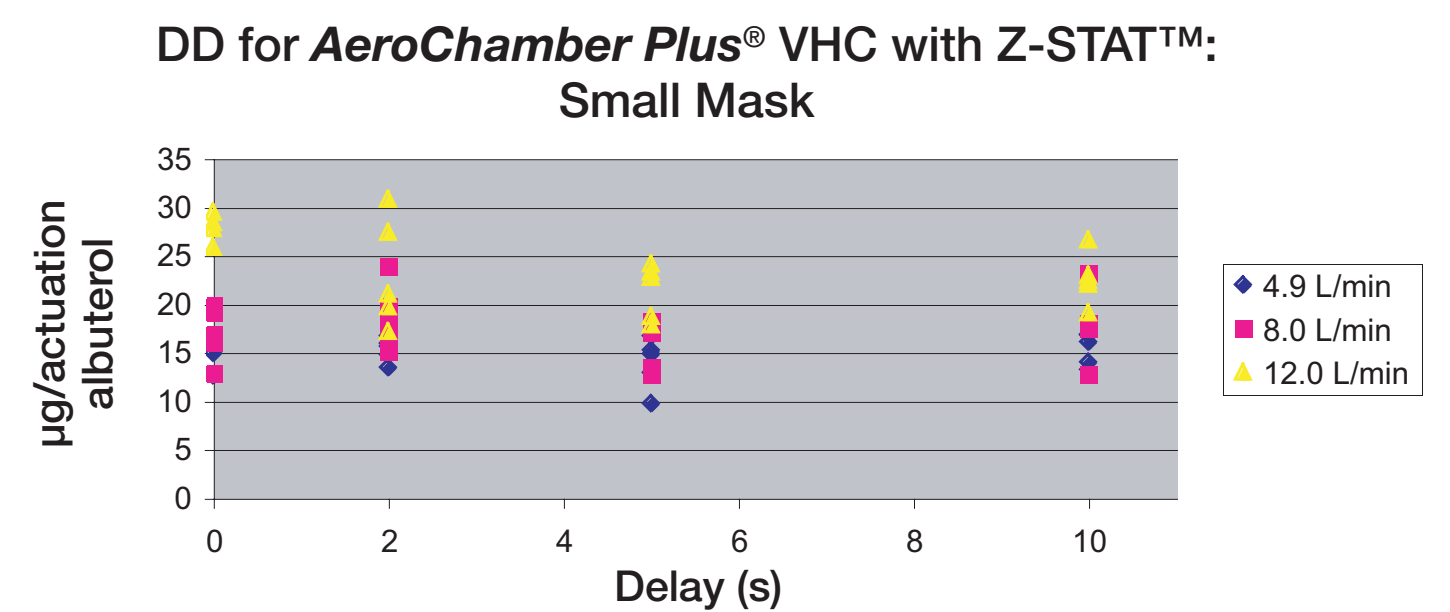
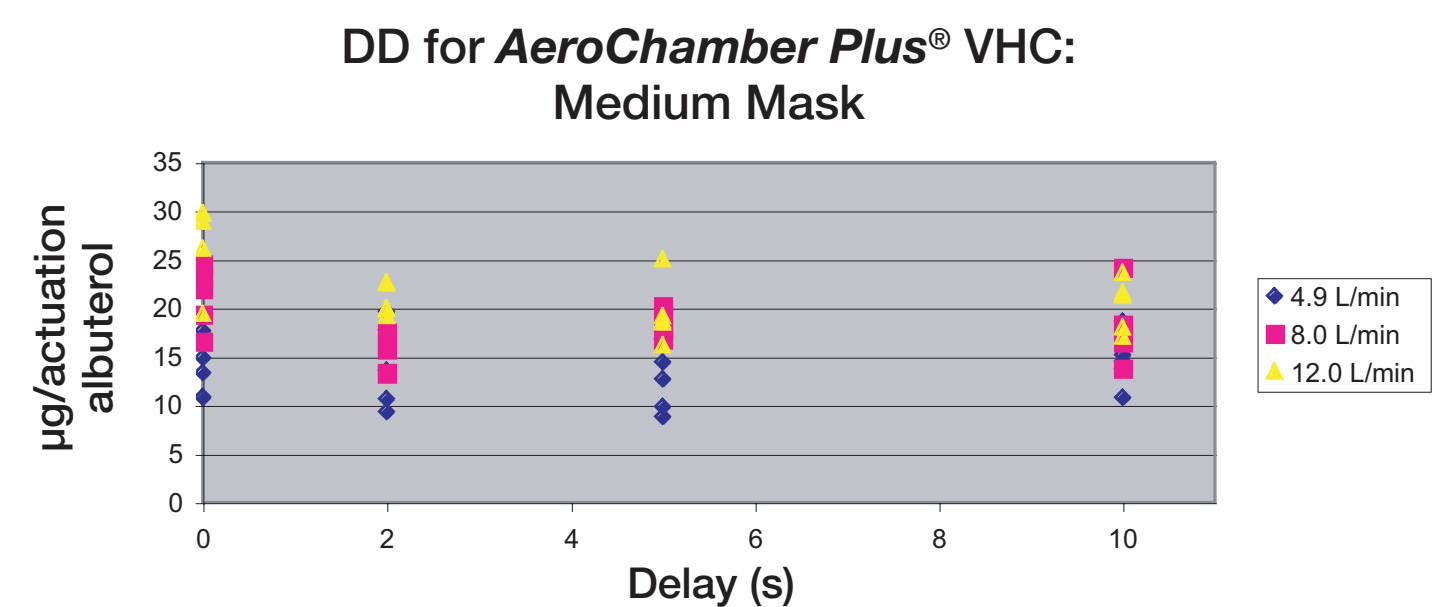
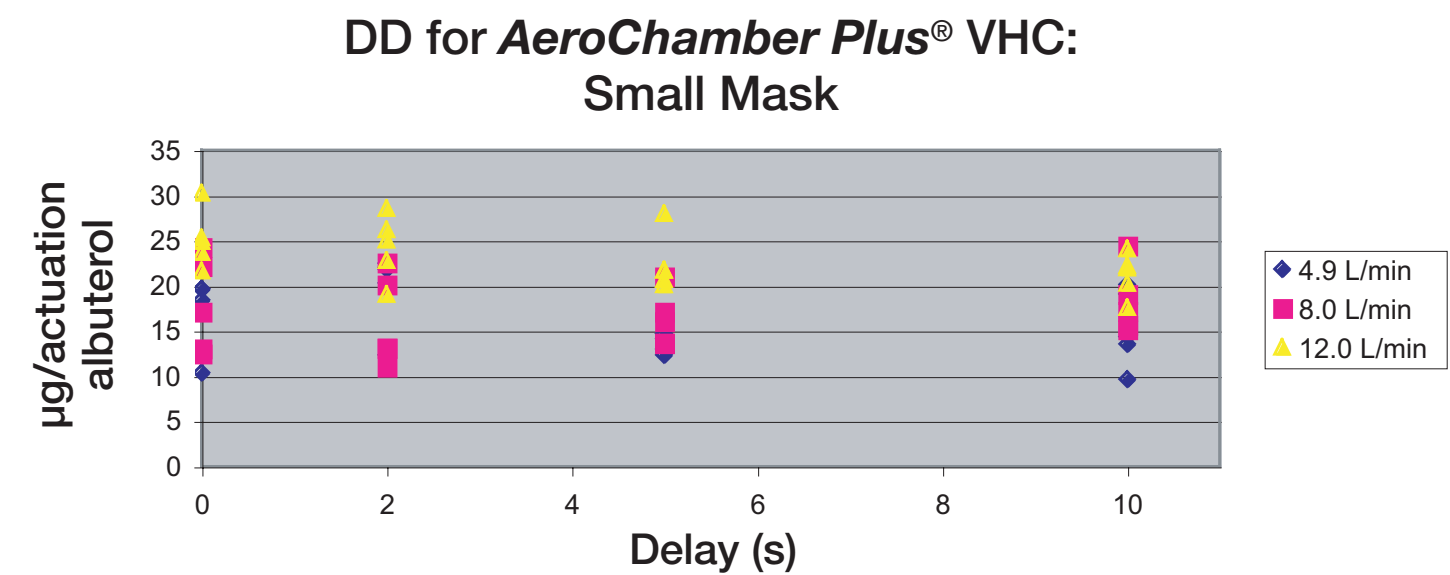
- In the 'no-delay' condition, the flow path was set via ports "R" to "A"
- When delay was required, the flow was initially set via ports "P" to "A", then after the prescribed interval the solenoid actuated to switch flow via ports "R" to "A"

## MEASUREMENT OF APSD



- The low-flow impactor was used to size-fractionate the incoming aerosol via a USP/Ph.Eur. Induction port, the entrance of which was aligned with the lips of the face model
- Simulation of delay was achieved by the same method as used for the DD measurements

## RESULTS – INDIVIDUAL DD VALUES



## RESULTS – MEAN FPF (%)

| VHC Type  | AeroChamber Plus <sup>®</sup> VHC |        | AeroChamber Plus <sup>®</sup> with Z-STAT <sup>™</sup> VHC |        |
|-----------|-----------------------------------|--------|------------------------------------------------------------|--------|
| Delay (s) | Small                             | Medium | Small                                                      | Medium |
| 0         | 67.1                              | 69.1   | 64.4                                                       | 67.1   |
| 2         | 65.2                              | 71.6   | 65.0                                                       | 68.0   |
| 10        | 69.1                              | 72.1   | 68.0                                                       | 73.2   |

## SUMMARY – APSD DATA

- Mean values for both measures were close to 70% for each type of VHC, irrespective of delay interval:
  - FPF<sub>0.77-4.7 µm</sub> - measurements at 4.9 L/min
  - FPF<sub>0.44-4.7 µm</sub> - measurements at 12 L/min
- FPF was increased compared with pMDI alone (typically 35 – 45% of DD), consistent with deposition of the coarser particles in the VHC

## CONCLUSIONS

- Although the mean DD is reduced under all test conditions compared to label claim, even under the lowest flow rate (4.9 L/min) and longest delay time (10-s), which were deemed to represent the worse case in terms of VHC delivery, the mean DD remained between 14.6 – 17.1 µg for both VHCs fitted with the small mask
- Under all conditions the FPF (70%) was increased compared to pMDI alone (35 – 45%)
- The findings from this *in-vitro* study on Ventolin<sup>†</sup> HFA have shown that even at low flow rates and extended delay times, potentially experienced in real-world situations with young children, drug remains available at the patient interface from either VHC/facemask combination

## REFERENCES

- Global Initiative for Asthma (GINA), Global Strategy for Asthma Management and Prevention, November 2006, NIH Publication 02-3659, available at: www.ginasthma.org
- both VHC types manufactured by Monaghan Medical Corp. Plattsburgh, NY
- Shah, S.A., Berlinski A.B. and Rubin B.K. Respir. Care. 2006;51:140-144
- Esposito-Festen, J.E. et al. J. Aerosol Med., 2004;17(1):1-6

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