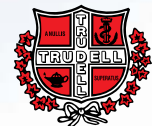


AeroChamber[®]

Plus^{*} with *Flow-Vu*^{*}
Valved Holding Chamber

Product Monograph



Trudell Medical International[®]

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1 Introduction

Valved Holding Chambers (VHCs), also commonly referred to as “spacers,” are designed to improve medication delivery, reduce oropharyngeal deposition of medication and help patients to overcome difficulties in the co-ordination between actuation of a pressurized metered dose inhaler (pMDI) and inhalation. For these types of patients, VHCs may offer the potential for better clinical outcomes over using their pMDI alone.

VHCs are commonly described as small or large volume according to the size of the holding chamber: **AeroChamber Plus*** VHC with **Flow-Vu*** Inspiratory Flow Indicator (IFI) is typically referred to as a small volume spacer (149ml).



AeroChamber Plus* VHCs with **Flow-Vu*** IFI are manufactured in clean room conditions (ISO Class 8 Standards) by Trudell Medical International (TMI) at its facilities in London, Ontario, Canada. **AeroChamber Plus*** VHCs with **Flow-Vu*** IFI are CE marked, in accordance with the European Medical Devices Directive 93/42/EEC for this Class 1 Medical Device. Trudell Medical International operates a quality system approved to ISO 13485:2003.

2 The Role of Valved Holding Chambers (VHCs)

VHCs such as the **AeroChamber Plus*** VHC with **Flow-Vu*** IFI have an important clinical role to play in the management of respiratory disease. They are designed to improve medication delivery, reduce oropharyngeal deposition of medication and help patients to overcome difficulties in the co-ordination between actuation of a pressurized metered dose inhaler (pMDI) and inhalation. The addition of the **Flow-Vu*** Inspiratory Flow Indicator (IFI) provides visual confirmation to the caregiver that inhalation is being performed properly, providing reassurance that may help improve patient compliance and control [Crompton, 2006].

National and international guidelines for the management of asthma and COPD all recommend the inhaled route as the preferred method of delivery for medications to treat asthma and COPD [GINA, 2006; BTS/SIGN, 2004; GINA, 2003; Gold, 2003; NIH, 2002]. Experts are calling for devices to be as easy to use as possible and incorporate multiple feedback mechanisms which reassure the caregiver that medication has been delivered and allow compliance checks to be made [Barnes, 2005]. Crompton et al. also comment that devices which provide reassurance that inhalation is performed correctly should help to improve patient compliance and control [Crompton, 2006]. For asthma, the GINA guidelines draw attention to the requirement for co-ordination of actuation of the pMDI with inhalation and recommend that a spacer device be used where appropriate, particularly in children. In infants and pre-school children, in whom active co-operation cannot be expected, a pMDI used with a spacer and facemask is recommended as the device of choice for maintenance treatment. As co-operation improves, often around the age of 4 to 6 years, it further recommends that the child is encouraged to use a mouthpiece rather than facemask attachment to the spacer [GINA 2006; GINA, 2003].

The GINA guidelines (2006) state:

“Spacers retain large drug particles that would normally be deposited in the oropharynx, reducing oral and gastrointestinal absorption and thus systemic availability of the inhaled drug. This is mainly important when inhaled glucocorticosteroids with first-pass metabolism (beclomethasone dipropionate, flunisolide, triamcinolone, and budesonide) are given via pressurized MDI.

Use of a spacer also reduces oropharyngeal side effects. During acute asthma attacks, an MDI should always be used with a spacer, as in this situation a child may be unable to correctly coordinate inhalation with actuation of the MDI. Commercially produced spacers with well-characterized drug output characteristics are preferable.”

Valved Holding Chambers are widely used for the delivery of inhaled maintenance treatment for asthma and COPD and also as an alternative therapy in the management of acute asthma.

3 Factors That Affect Aerosol Delivery From VHCs

Three main factors affect aerosol delivery via a VHC: VHC characteristics, pMDI characteristics and the characteristics of the patient who uses the VHC.

3.1 VHC Characteristics

Some VHC devices incorporate heavy plastic one-way valves to prevent exhalation back into the chamber. Patients with small lung volumes, such as infants, may not generate sufficient inspiratory flow rates to open these valves correctly [Kraemer, 1991; Barry, 1996b]. Modern small volume VHCs such as *AeroChamber Plus** VHC with *Flow-Vu** IFI with low resistance inspiratory valves may therefore be more appropriate for use in infants and small children.

The first truly portable, patient-friendly VHC was the *AeroChamber** VHC which was developed at McMaster University, Canada. It was designed to deliver the same lower respiratory tract dose of medication as the MDI alone when used under optimal conditions [Corr, 1982]. Since then new technologies and materials have become available and have been incorporated into the design of the *AeroChamber** VHC product line. The *AeroChamber Plus** VHC with *Flow-Vu** IFI provides feedback mechanisms that virtually eliminate the guesswork associated with pressurized metered dose inhaler aerosol drug delivery. The new *Flow-Vu** Inspiratory Flow Indicator has been designed expressly for the feedback process and does not alter aerosol characteristics from the inhaled medication. This feature allows caregivers to count patient breaths, ensure a satisfactory seal, and coordinate actuation with inhalation. The *EZ Flow* exhalation valve and the *FlowSignal** Whistle also ensure appropriate inhalation patterns through the device. The *ComfortSeal** Mask is composed of medical grade silicone, is anatomically designed to fit all faces comfortably, and minimizes dead space which results in consistent aerosol delivery.

In the case of *AeroChamber Plus** VHC with *Flow-Vu** IFI with facemask, the ability to ensure that a proper seal has been achieved between facemask and face is critical. Imperfect sealing between facemask and face can lead to almost complete loss of medication [Esposito-Festen, 2004], due to the ingress of non-aerosol containing ambient air when the patient inhales [Shah, 2006; Amirav, 2001].

3.2 pMDI Characteristics

When a VHC is used in conjunction with a pMDI, it is important that the respirable mass of aerosol (i.e. the amount of the actuated dose that comprises particles small enough (<5 microns in diameter) to reach the airways during inhalation), is not significantly affected by the addition of the VHC [Corr, 1982; Cripps, 2000]. In many cases, the reformulation of chlorofluorocarbon (CFC) pMDIs with hydrofluoroalkane (HFA) propellants has not affected the particle size distribution of the drug in the aerosol. However the characteristics of the aerosol plume, in terms of its size and velocity, have been shown to differ from the conventional CFC pMDI. In many HFA products the velocity of aerosol released from the pMDI is lower than that of the corresponding CFC product. Barry [Barry, 1996c] reported that the aerosol delivered from the HFA salbutamol pMDI, Airomir[®], is both slower and contained within a smaller volume than the corresponding CFC product. For these reasons small volume VHCs may be better suited to HFA pMDIs than the older large volume VHC devices such as Volumatic[†], which were designed for use with CFC pMDI formulations.

Electrostatic charge is generated when the aerosol is discharged, which can influence deposition in the VHC. The magnitude of this charge is influenced by the nature of the formulation eg. CFC and HFA. HFA pMDIs tend to be more susceptible to static charge on the chamber than the CFC MDIs they have replaced.

Early VHC devices were supplied for use in conjunction with company-specific pMDIs and only the actuators of the specified products fit into the opening of the VHC. If patients were prescribed a combination of different pMDIs from different manufacturers, more than one VHC was required. Newer spacers such as *AeroChamber Plus** VHC with *Flow-Vu** IFI have been designed with flexible, universal adapters to accommodate a wide range of actuator mouthpiece designs. This way, the same VHC can be used in conjunction with different pMDIs without affecting the metering performance of the pMDIs used [Berlinski, 2001]. All pMDIs compatible with the Volumatic[†] are also mechanically compatible with the *AeroChamber Plus** VHC with *Flow-Vu** IFI range. It is not recommended that patients switch between spacer devices as this may result in changes in the dose delivered to the lungs.

3.3 Patient Characteristics

Large volume VHC devices have been found to be cumbersome and obtrusive, particularly for elderly patients [Jones, 1999]. Studies have shown that patients prefer smaller, more discreet and portable devices [Chapman, 1995; Gunawardena, 1997]. A research study by NOP Healthcare UK in 2000 found that many asthma patients, or parents of children with asthma, do not have a VHC available when at work or school, or when going out socially [data on file, Trudell Medical International]. Patients and parents identified size and ease of use as the most important factors in achieving acceptability of their device. When compared with large volume chambers, the *AeroChamber Plus** VHC with *Flow-Vu** IFI may lead to improvements in adherence to treatment, due to improved patient acceptability of the device. Crompton *et al* also comment that devices which provide reassurance that inhalation is performed correctly should help improve patient compliance and control.

The use of VHCs in conjunction with pMDIs is advocated across the spectrum of patient populations, from infants to the elderly. Consequently there is considerable inter-subject variability in inhalation techniques, inspiratory flow rates, tidal volumes, breathing frequencies and airways calibre, in addition to variations in other factors such as patient dexterity and ability to self-administer the dose.

Even within an individual patient there is considerable variability on a day-to-day basis in aerosol delivery. In a randomised, cross over, real-life study in children with stable asthma, the mean coefficient of variation of filter dose in children 5-8 years using the Volumatic[†] was 34% versus 23% for AstraZeneca's antistatic Nebuchamber[†] device (p=0.003) [Janssens, 1999].

Patient handling characteristics are therefore of major importance. This may be of greater significance than the small differences seen in pharmaceutical performance between VHCs.

4 *AeroChamber Plus** VHC with *Flow-Vu** IFI – Patient Benefits

4.1 All *AeroChamber Plus** VHCs with *Flow-Vu** IFI Products

- Patented chamber design maximizes suspension time for aerosol medications, enhancing fine particle delivery to the lungs
- Caregiver feedback mechanisms that encourage proper technique, virtually eliminating the guesswork associated with aerosol drug delivery
- *Flow-Vu** Inspiratory Flow Indicator allows caregivers to count patient breaths, ensure a satisfactory seal and coordinate actuation with inhalation
- 149 ml holding chamber is manufactured from a shatter-resistant, clear, polymer blend, making it easy to carry and ensure no foreign bodies are in the chamber before use
- Universal pMDI adapter mechanically fits all commonly prescribed inhalers from major manufacturers
- Universal pMDI adapter is easily removed and replaced to facilitate cleaning inside the chamber
- Devices are supplied ready to use after first wash – no assembly required
- No latex or phthalates are used in the manufacture of *AeroChamber Plus** with *Flow-Vu** IFI devices



4.2 *AeroChamber Plus** VHC with *Flow-Vu** IFI – Infant and Child Mask

- Pictographic, child-friendly *AEROBEAR** instructions permanently printed onto the chamber
- Latex-free Infant (orange colour: 0-18 months approx.) and Child (yellow colour: 1 to 5 years approx.) *ComfortSeal** mask minimizes dead space and provides a secure, comfortable fit
- One-way, low resistance inhalation valve opens easily at low inspiratory flow rates and features a protective design to help ensure a long life
- *EZ Flow* exhalation valve offers low resistance to exhaled flow making device suitable for tidal breathing, and directs exhaled medication away from the patient's face and eyes

4.3 *AeroChamber Plus** VHC with *Flow-Vu** IFI – Mouthpiece and Large Mask

- Mouthpiece device designed for patients 5 years and over
- Mouthpiece device features an integrated inhalation/exhalation valve system to permit tidal breathing and direct exhaled medication away from the patient's face and eyes
- *FlowSignal** Whistle alerts patient if they inhale too rapidly, encouraging proper inhalation technique
- One-way, low resistance inhalation valve opens easily at low inspiratory flow rates and features a protective design to help ensure a long life
- *ComfortSeal** Large Mask features an *EZ Flow* exhalation valve offering low resistance to exhaled flow making the device suitable for tidal breathing, and directs exhaled medication away from the patient's face and eyes

4.4 Key Features of *AeroChamber Plus** VHC with *Flow-Vu** IFI

Feature	<i>AeroChamber Plus</i> * VHC with <i>Flow-Vu</i> * IFI
Manufacturer	Trudell Medical International
Transparent Chamber	Polymer blend
Visual Feedback Mechanism	<i>Flow-Vu</i> * Inspiratory Flow Indicator clearly indicates when a patient is inhaling
Flow Rate Alarm	<i>FlowSignal</i> * Whistle alerts patient to excessive inspiratory flow rates (on Mouthpiece and Large Mask products)
Permanent Instructions on unit	<ul style="list-style-type: none"> • Pictographic instructions printed on the products • Fun and child friendly <i>AeroBear</i>* instructional graphics on Infant and Child mask devices
Compatible with most pMDIs	Mechanically compatible with all commonly prescribed pMDIs
Recommended replacement	Replace after 12 months
Mask	Three different sizes of latex free, <i>ComfortSeal</i> * Mask – Infant, Child and Large, all with " <i>EZ Flow</i> " exhalation valve
Internal Volume	149 mL

5 Review of Scientific Data

5.1 *In Vitro* Data

This section presents published data from *in vitro* drug delivery studies of the use of pMDIs in conjunction with currently available VHC devices.

Summary

- *In vitro* data demonstrates *AeroChamber Plus** VHC and *AeroChamber Plus** VHC with *Flow-Vu** IFI offer the same aerosol performance with the added benefit of patient feedback mechanisms
- *In vitro* data on a wide range of pMDIs shows acceptable medication delivery performance with *AeroChamber Plus** VHC with *Flow-Vu** IFI.
- Clinical data demonstrate that:
 - *AeroChamber Plus** VHC with *Flow-Vu** IFI performs as expected for a spacer increasing drug delivery versus pMDI alone.
 - The increased drug exposure from *AeroChamber Plus** VHC with *Flow-Vu** IFI is within the range of exposure where cortisol is unlikely to be affected.

Summary continued...

- **AeroChamber Plus*** VHC with **Flow-Vu*** IFI is an effective alternative to nebuliser therapy in the beta₂ agonist management of acute asthma in children and adults.
- **AeroChamber Plus*** VHC with **Flow-Vu*** IFI is effective with tidal breathing.

5.1.1 Methodology

In vitro studies performed under controlled laboratory conditions are widely accepted as important in the evaluation of VHCs, by measuring the effect of the VHC on the fine particle fraction delivered by the pressurized metered dose inhaler (pMDI). Recent *in vitro* studies of **AeroChamber Plus*** VHC with **Flow-Vu*** IFI by TMI's aerosol laboratory have directly compared the *in vitro* performance of the **AeroChamber Plus*** VHC with **AeroChamber Plus*** VHC with **Flow-Vu*** IFI using the Andersen Cascade Impactor (ACI).

The ACI provides both a measure of the aerodynamic particle size distribution of the drug particles in the discharged aerosol and also a measure of the fraction of the delivered dose which is within a size range suitable for deposition in the lungs. This fraction is defined as the fine particle mass and corresponds to the summed deposition of drug on stages 3, 4 and 5 of the impactor. Under the flow rate conditions of 28.3 litres/minute, this deposition corresponds to material with an aerodynamic particle size range of 1.1 to 4.7 µm.

The performance of each VHC was evaluated by assessing the effect of the VHC on both the particle size distribution of drug in the aerosol and the fine particle mass. Each VHC was washed in accordance with the patient instructions, prior to testing in order to minimize the effects of electrostatic charge.

5.1.2 Evaluation of **AeroChamber Plus*** VHC and **AeroChamber Plus*** VHC with **Flow-Vu*** IFI with Commonly Prescribed Aerosol Medications

The data [data on file, TMI] demonstrates that the addition of the **Flow-Vu*** Inspiratory Flow Indicator (IFI) has no significant effect on aerosol performance between **AeroChamber Plus*** VHC with **Flow-Vu*** IFI when compared to **AeroChamber Plus*** VHC using commonly prescribed aerosol medications. Both Total Emitted Mass and Fine Particle Mass showed comparable results. This study demonstrates that **AeroChamber Plus*** VHC with **Flow-Vu*** IFI has equivalent performance to **AeroChamber Plus*** VHC.

An *in vitro* study of the performance of the **AeroChamber Plus*** VHC and **AeroChamber Plus*** VHC with **Flow-Vu*** IFI with six commonly prescribed aerosol medications was conducted to study the Fine Particle Mass (FPM) and Total Emitted Mass (TEM) of each of the chambers to determine whether the aerosol properties were affected by the addition of the **Flow-Vu*** IFI feature. Each of the chambers were tested in accordance with the manufacturers' instructions.

AeroChamber Plus* VHC – Wash No Rinse (n=3) and
AeroChamber Plus* VHC with **Flow-Vu*** IFI – Wash No Rinse (n=3)

A series of measurements were made using the Andersen Mark II cascade impactor (ACI) operated at 28.3 L/min ± 5% and equipped with USP/Ph. Eur. induction port in accordance with <601> of the US Pharmacopeia, and the procedure for testing spacers and holding chambers in ALP 017A (2003).

The data [data on file, TMI] demonstrate that for both the CFC and HFA products, the **Flow-Vu*** Inspiratory Flow Indicator (IFI) has no significant effect on the particle size distribution of the drug in the aerosol, with the fine particle fraction consistently deposited on stages 3, 4 and 5 of the cascade impactor. The data demonstrates that the Valved Holding Chamber gives an increase in the fine particle mass (FPM) compared to the pMDI alone.

5.2 Clinical Data

5.2.1 Clinical Relevance of *AeroChamber Plus** VHC with *Flow-Vu** IFI

Summary

As we look to the future, new reversible airways disease therapies are being developed, but most experts agree that established inhaled medications namely corticosteroids and β_2 -antagonists will still play a strong role in treatment over the next 10-15 years. [Barnes, 2005] As a result, the need for valved holding chambers will remain strong in the years to come. Experts are calling for devices to be as easy to use as possible and to incorporate multiple feedback mechanisms which reassure the patient that medication have been delivered and allow compliance checks to be made. [Barnes, 2005]

Crompton et al. also comment that devices which provide reassurance that inhalation is performed correctly should help to improve patient compliance and control.[Crompton, 2006]

The addition of the new *Flow-Vu** IFI has been designed expressly for the feedback process and does not alter aerosol characteristics from the inhaled medication. This is especially important in light of recent finding of the Global Asthma Physician and Patient (GAPP) study that indicated that parents of children diagnosed with asthma (n=1,017) responded that 69% of the time, physicians do not discuss correct inhaler technique. The GAPP survey is the first ever global quantitative survey to uncover asthma attitudes and treatment practices among patients and physicians. The pediatric findings of the GAPP survey also confirm what most physicians already know: Asthma medication compliance is low; patients with poor compliance experience more symptoms; and side effects lead patients to switch or drop medications.

In the case of *AeroChamber Plus** VHC with *Flow-Vu** IFI with facemask, the ability to verify movement of inhalation and exhalation valves is critical to ensure that a proper seal has been achieved between facemask and face. Imperfect sealing between facemask and face can lead to almost complete loss of medication [Esposito-Festen, 2004], due to the ingress of non-aerosol containing ambient air when the patient inhales [Shah, 2006; Amirav, 2001].

5.2.2 Management of Acute Asthma in Children and Adults – VHC versus Nebuliser

Cates *et al* [2005] performed a systematic review of large and small volume holding chambers versus nebulisers for β_2 agonist treatment of acute asthma. The review included 28 clinical studies. Of the studies included 18 involved children and the devices investigated were *AeroChamber** VHC (5), Nebuhaler[†] (3), Volumatic[†] (5), unspecified (2) Babyhaler[†] (1), ACE[†] spacer (1) and M/S Cipla (1). The 5 *AeroChamber** VHC studies included 443 children (age 1-16 years) [Chou, 1995; Leversha, 2000; Lin, 1995; Parkin, 1995; Williams, 1996]. The review concluded that pMDI with holding chamber produced outcomes that were at least equivalent to nebuliser delivery, although pulse rate was significantly lower when a VHC was used in children (possibly due to a lower total dose of beta₂ agonist). The authors also state that holding chambers may have some advantages compared to nebulisers for children with acute asthma.

5.2.3 Tidal Breathing

The *AeroChamber Plus** VHC device is suitable for use with tidal breathing [Mitchell 1996]. All four of the *AeroChamber Plus** VHC with *Flow-Vu** IFI devices are designed with a one-way, low resistance inhalation valve, which opens easily at low inspiratory flow rates. The *EZ Flow* exhalation valve on *AeroChamber Plus** VHC with *Flow-Vu** IFI products with facemask offers low resistance to exhaled flow making the device suitable for tidal breathing. The exhalation valve directs exhaled medication away from the patient's face and eyes.

Barry *et al* [1996] measured aerosol clearance from five different VHCs, two small volume (< 200ml); GlaxoSmithKline's (GSK) Babyhaler[†] and TMI's *AeroChamber** VHCs, and three large volume (>700ml); GSK's Volumatic[†], AstraZeneca's Nebuhaler[†] and Fisons' (now SanofiAventis) Fisonair[†] using a Pari Sinus Breath Simulator, to mimic tidal breathing. The study demonstrated more efficient clearance of aerosol from the Babyhaler[†] and *AeroChamber** VHCs at lower tidal volumes (<300ml), with aerosol still visible in the three larger chambers after 20 seconds (seven breaths). The study suggests that differences in VHC design and volume may affect clearance of aerosol from VHCs, and may mean that large volume VHCs are less efficient for use by patients with small tidal volumes.

5.2.4 Lung Deposition

Zar *et al* [2000] measured lung deposition of radio-labeled aerosol from the *AeroChamber** VHC and GSK's Babyhaler[†] in a study of 40 children with asthma (aged 3-7 years). Although the *AeroChamber** VHC is less than half the volume of the Babyhaler[†], equivalent aerosol deposition was obtained from both devices.

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