

**AeroChamber®**  
**Brand of Valved Holding Chambers**

Study Summary

Updated: August 2022

## FOREWORD

Monaghan Medical and its affiliate company Trudell Medical have an enviable history of strong leadership in creating innovative medical devices that enhance the quality of life for people of all ages. We focus our efforts on the well-being of our employees and customers, and provide safe, valuable and easy to use devices for a global market.

The following variants of **AeroChamber Plus**<sup>®</sup> Valved Holding Chamber (VHC) are available:

- **AeroChamber Plus**<sup>®</sup> **Flow-Vu**<sup>®</sup> Anti-Static VHC
- **AeroChamber Plus**<sup>®</sup> **Z STAT**<sup>®</sup> Anti-Static Valved Holding Chamber (aVHC)

Both of the variants provide comparable fine particle delivery to the MDI alone. *In vitro* performance is not affected by the addition of the product enhancements (anti-static chamber, **Flow-Vu**<sup>®</sup> Indicator). The enhancements were made to increase ease of use for patients and their caregivers. The **Flow-Vu**<sup>®</sup> Inhalation Indicator is a feedback tool that helps provide assurance that inhalation is performed correctly and allows caregivers to: ensure a proper seal, coordinate actuation with inhalation and count patient breaths. The anti-static chamber provides consistent medication availability and can be used right out of package with no pre-treatment required.

The aerosol drug delivery performance of **AeroChamber**<sup>®</sup> Brand of VHC is supported by hundreds of peer-reviewed scientific studies. This study summary includes some of the more recent and relevant studies.

The following sections are included within the Study Summary:

1. Guidelines recommending Valved Holding Chambers
  - National and International Guidelines recommending the use of VHCs with MDIs
2. Importance of Valved Holding Chambers
  - VHCs help improve medication delivery, reduce oropharyngeal deposition and assist patients overcome difficulties in the co-ordination of actuation of the MDI with inhalation
3. Most Recommended - **AeroChamber**<sup>®</sup> Brand of Chambers
  - Confidence in Aerosol Drug Delivery
  - List of recommendations from MDI companies
4. Equivalency data
  - *In vitro* data showing comparable fine particle delivery of **AeroChamber Plus**<sup>®</sup> VHC variants compared to MDI alone
5. Importance of **Flow-Vu**<sup>®</sup> Inhalation Indicator
  - Researchers highlight the importance of the **Flow-Vu**<sup>®</sup> Inhalation Indicator in providing assurance of correct use for medication delivery
6. Influence of anti-static chambers
  - Anti-Static chambers, provide consistent medication availability and improved ease of use
7. Importance of Facemask Seal
  - Facemask seal is one of the most important factors in aerosol drug delivery to infants and children
8. Performance with different Metered Dose Inhaler formulations
  - Divided by drug formulation, the studies are listed in chronological order with the most recent studies appearing first
9. Large versus Small Volume VHCs
  - Comparable performance between large and small volume VHCs
10. Metered Dose Inhalers and VHCs versus Nebulizers
  - Advantages of MDI/VHC versus Nebulizer
11. Metered Dose Inhalers and VHCs Versus Dry Powder Inhalers
  - Advantages of MDI/VHC versus DPIs

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## Guidelines Recommending Valved Holding Chambers

The Metered Dose Inhaler (MDI) is the most commonly prescribed aerosol medication system. Valved Holding Chambers are designed to improve medication delivery, reduce oropharyngeal deposition of medication and help patients overcome difficulties in the co-ordination between actuation with an MDI and inhalation. Incorrect inhaler technique is prevalent and is a major issue associated with poor Asthma control.

### **American Association of Respiratory Care (AARC)** ([www.aarc.org](http://www.aarc.org)) – Neonatal and Pediatric Patients 2007

- A spacer/holding chamber should be used with an MDI
- A spacer/holding chamber with facemask is appropriate for patients (usually < 3 years) unable to use a mouthpiece

### **American College of Chest Physicians (ACCP)/American College of Allergy, Asthma & Immunology**

([www.chestnet.org](http://www.chestnet.org)) 2005

- For patients who have trouble coordinating inhalation with device actuation, the use of a spacer (with a valve) may obviate this difficulty
- The use of spacers is mandatory for infants and young children

### **British Thoracic Society/Scottish Intercollegiate Guidelines Network, UK (BTS / SIGN)** ([www.sign.ac.uk](http://www.sign.ac.uk)) 2014

- Children and adults with mild and moderate exacerbations of Asthma should be treated by bronchodilators given from a pMDI + Spacer/Holding Chamber with doses titrated according to clinical response
- In children aged 0-5, pMDI + spacer are the preferred method of delivery of  $\beta_2$  agonists or inhaled steroids
- The spacer should be compatible with the pMDI being used
- A spacer should be used at high doses of inhaled corticosteroid
- Standard MDI when used in isolation (without spacer) is rarely appropriate for elderly patients

### **Canadian Pediatric Asthma Consensus Guidelines** ([www.cmaj.ca/cgi/content/full/173/6\\_suppl/S12](http://www.cmaj.ca/cgi/content/full/173/6_suppl/S12)) 2005

- The use of a holding chamber with pMDI is strongly recommended for children

### **Canadian Thoracic Society – 2010 Consensus Summary for children six years of age and over, and adults**

The addition of a holding chamber with mouthpiece is helpful in overcoming poor hand-mouth coordination and reducing side effects, with increased drug delivery and lung deposition

- Holding chambers with facemask attachments are useful for the elderly, who can use four to six tidal breaths for each actuation of the medicine

### **Global Strategy for Asthma Management and Prevention 2017 (Global Initiative on Asthma)** ([www.ginasthma.com](http://www.ginasthma.com))

- pMDI + dedicated Spacer/Holding Chamber with facemask is the preferred delivery system for children less than 4 years of age
- pMDI + dedicated Spacer/Holding Chamber with mouthpiece is the preferred delivery system for children between 4 and 6 years of age
- Use of a spacer device improves delivery and (with inhaled corticosteroids) reduces the potential for side-effects
- The spacer device should have documented efficacy in young children
- The dose delivered may vary considerably between spacers, so consider this if changing from one spacer to another
- Delay between actuating the pMDI into the spacer and inhalation may reduce the amount of drug available. This varies between spacers, but to maximize drug delivery, inhalation should start as soon as possible after actuation.
- Ensure that the valve is moving while the child is breathing through the spacer.
- Static charge may accumulate on some plastic spacers, attracting drug particles and reducing lung delivery. This charge can be reduced by washing the spacer with detergent (without rinsing) and allowing it to air dry, but it may re-accumulate over time. Spacers made of anti-static materials or metals are less subject to this problem.

### **Global Initiative for Chronic Obstructive Lung Disease (GOLD)** ([www.goldcopd.com](http://www.goldcopd.com)) 2015

- For the MDI, the addition of a large or small volume spacer often overcomes coordination problems, and improves lower airway deposition and clinical benefit

**International Primary Care Respiratory Group (IPCRG)** ([www.theipcrg.org](http://www.theipcrg.org)) 2006

- The preferred device for administering inhaled asthma medication for infants and young children is a pressurized MDI with a spacer and face mask
- As the child's ability to co-operate improves (often around the age of 4-6 years), a spacer with a mouthpiece can be used rather than a face mask

**National Heart, Lung, and Blood Institute (NHLBI)** ([www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)) 2007

- All patients taking inhaled steroids should use a Spacer/Holding Chamber
- Patients under 5 years should use a Spacer/Holding Chamber with Facemask for inhaled steroids

**National Institute for Clinical Excellence, UK (NICE)** ([www.nice.org.uk](http://www.nice.org.uk)) 2010

- Spacer/Holding Chamber recommended with a facemask where necessary for both corticosteroids and bronchodilators (Children under 5)
- A press and breathe pMDI used with an appropriate Spacer/Holding Chamber is first choice for corticosteroids (Children aged 5-15 years)
- COPD - pMDI alone is rarely suitable for use with the elderly
- The spacer should be compatible with the patient's metered-dose inhaler

**Netherlands - Nederlands Huisartsen Genootschap (NGH)**

- Non breath-controlled MDIs are to always be used with a VHC unless the patient can adequately use the device themselves

**Spain - Guía Española Para el Manejo del asma**

- Inhalation is the choice for the treatment of asthma. The use of VHCs avoids the problem of coordination between the inspiration pulsation and improves the distribution and amount of drug that reaches the bronchial tree
- In the treatment of mild to moderate disease it is recommended to use pMDI with a VHC

## Importance of Valved Holding Chambers

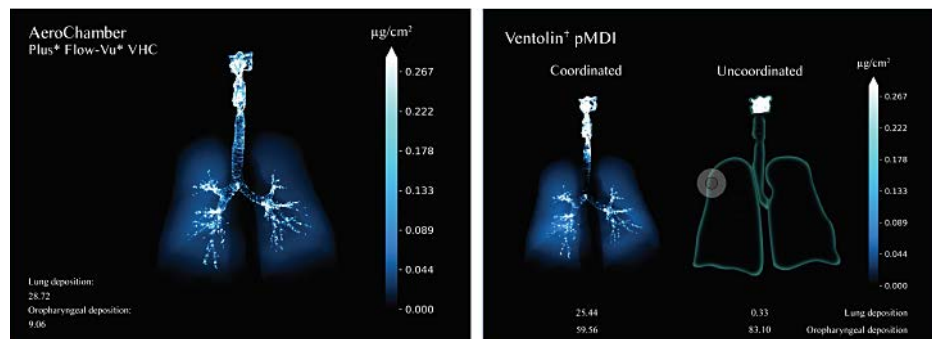
The majority of patients are not able to use pMDIs properly.

- A review of 2,123 asthma patients by the National Services for Health Improvement found that without training, 86% failed to properly use their inhaler. (Hardwell A. *et al. Technique training does not improve the ability of most patients to use pressurized metered-dose inhalers*. Prim Care Respir J 2011; 20(1):92-6)
- Studies show that only 30% of people prescribed puffer aerosol medications use them correctly, and that number may begin to slip as early as two months after the medication is prescribed. (*Inhaled Respiratory Medicines: Optimising use in COPD. Therapeutic Brief*, Government of Australia, Version 3. North Melbourne Therapeutic Guidelines Ltd. 2005)
- The majority (71%) of adult asthmatic patients are unable to use their inhaler devices effectively, and this misuse was shown to result in decreased control of asthma symptoms. (Giraud V *et al. Misuse of corticosteroid metered-dose inhaler is associated with decreased Asthma stability*, Eur Respir J 2002; 19:246-51)
- Unless they have been trained, only one in five patients is able to use the spray correctly. After being trained, however, this statistic is still only one in two. (Lenny J *et al. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices*. Respir Med 2000; 94:496-500)
- 3 out of 4 patients do not use their inhaler properly resulting in poor delivery of aerosol medication to the lungs. (Goodman DE *et al. The influence of age, diagnosis and gender on proper use of metered-dose inhalers*. Am. J Respiratory and Critical Care Med 1994;150:1256-1261)
- Up to 91% of Asthma patients use their metered-dose inhalers improperly. (Plaza V. *et al. Medical personnel and patient skill in the use of metered dose inhalers; a multicentre study*. Respiration 1998;65:195-198)
- Numerous studies have identified sub-optimal inhaler technique as a common problem in patients with respiratory disease. (Epstein SW *et al. Survey of the clinical use of pressurized aerosol inhalers*. Can Med Assoc J 1979;120:813-816)
- Only 1 out of 10 patients with a metered dose inhaler performs all essential steps correctly. (Restrepo RD *et al. Medication adherence issues in patients treated for COPD*. Int J Chron Obstruct Pulmon Dis. 2008; Sep;3(3):371-384)
- When a pMDI is used, more than 50% of subjects may perform  $\leq 5$  out of 9 steps correctly and only about 11% of the subjects could perform all steps correctly. Luk H *et al. Teaching chronic obstructive airway disease patients using a metered dose inhaler*. Chin Med J. 2006;119:1669-72

### THE IMPACT OF INHALATION DELAY ON LUNG DRUG DELIVERY: USING FUNCTIONAL RESPIRATORY IMAGING (FRI) TO COMPARE METERED DOSE INHALER (MDI) AND MDI/VALVED HOLDING CHAMBER (VHC) SYSTEMS.

Suggett J, Kushnarev V, Van Holsbeke C, Van Steen S, Mignot B. *Am J Respir Crit Care Med* 2020;201:A5689

**Rationale:** Evaluations of inhaler use have demonstrated that mishandling of MDIs is commonplace. One of the most common errors is the failure to coordinate inhalation with actuation of the inhaler. One of the reasons why VHCs are often prescribed, is to reduce the severity of this error. This FRI based study assessed the likely severity of a short inhalation delay (from actuation) with an MDI alone and how it contrasted to the use with a VHC. **Methods:** Three dimensional geometries of airways and lobes were extracted from a CT scan of a 67 year old male COPD Stage III patient. Drug delivery and airway deposition of MDI-delivered albuterol (Ventolin -HFA, 100mcg) was modelled using FRI with measured particle and plume characteristics with and without an AeroChamber Plus® Flow-Vu® VHC. For the MDI alone, in addition to the 'perfect' 0-seconds delay, a short inhalation delay of 0.5 seconds was evaluated. For the MDI/VHC system, a typical 2 second delay was evaluated. **Results:** See table below.



To view the FRI results video, visit:  
<https://www.trudellmed.com/fri-results-videos>.

**Conclusion:** The FRI Deposition profiles highlight the significant negative impact on lung deposition of even a relatively short 0.5 second delay between actuation and inhalation when an MDI is used alone. The intrathoracic delivery decreased from 25.4 mcg to 0.3 mcg. Extra thoracic delivery (related to oropharyngeal deposition) was consequently even higher. The MDI + AeroChamber Plus® Flow-Vu® VHC system with a 2 second delay delivered 28.7 mcg to the intrathoracic region with a greater central lung delivery the MDI alone (perfect coordination) which might be suggestive of greater delivery to beta adrenoreceptors. These results further the message that the use of an appropriate VHC should be considered as general practice for all people using MDIs other than those with a highly proficient inhaler technique.

## **OPTIMIZING THE DELIVERY OF INHALED MEDICATION FOR RESPIRATORY PATIENTS: THE ROLE OF VALVED HOLDING CHAMBERS.**

*McIvor RA, Devlin HM, Kaplan A. Canadian Respiratory Journal. Volume 2018, Article ID 5076259, 8 pages.*

Valved holding chambers (VHCs) have been used with pressurized metered-dose inhalers since the early 1980s. They have been shown to increase fine particle delivery to the lungs, decrease oropharyngeal deposition, and reduce side effects such as throat irritation, dysphonia, and oral candidiasis that are common with use of pressurized metered-dose inhalers (pMDIs) alone. VHCs act as aerosol reservoirs, allowing the user to actuate the pMDI device and then inhale the medication in a two-step process that helps users overcome challenges in coordinating pMDI actuation with inhalation. The design of VHC devices can have an impact on performance. Features such as antistatic properties, effective face-to-facemask seal, feedback whistles indicating correct inhalation speed, and inhalation indicators all help improve function and performance, and have been demonstrated to improve asthma control, reduce the rate of exacerbations, and improve quality of life. Not all VHCs are the same, and they are not interchangeable. Each pairing of a pMDI device plus VHC should be considered as a unique delivery system.

## **SPACER DEVICES FOR INHALER THERAPY: WHY USE THEM, AND HOW?**

*Vincken W, Levy ML, Scullion J, Usmani O, Dekhuijzen R, Corrigan C. ERJ Open Res 2018;4: 00065-2018.*

We present an extensive review of the literature to date pertaining to the rationale for using a spacer/valved holding chamber (VHC) to deliver inhaled therapy from a pressurized, metered-dose inhaler, a discussion of how the properties of individual devices may vary according to their physical characteristics and materials of manufacture, the potential risks and benefits of ancillaries such as valves, and the evidence that they contribute tangibly to the delivery of therapy. We also reiterate practical recommendations for the correct usage and maintenance of spacers/VHCs, which we trust offer practical help and advice to patients and healthcare professionals alike.

## **SYSTEMATIC REVIEW OF ERRORS IN INHALER USE. HAS PATIENT TECHNIQUE IMPROVED OVER TIME?**

*Sanchis J, Gich I, Pedersen S on behalf of the ADMIT group. Chest 2016; 150(2):394-406.*

**Background:** Problems with the use of inhalers by patients were noted shortly after the launch of the metered-dose inhaler (MDI) and persist today. We aimed to assess the most common errors in inhaler use over the past 40 years in patients treated with MDIs or dry powder inhalers (DPIs). **Methods:** A systematic search for articles reporting direct observation of inhaler technique by trained personnel covered the period from 1975 to 2014. Outcomes were the nature and frequencies of the three most common errors; the percentage of patients demonstrating correct, acceptable, or poor technique; and variations in these outcomes over these 40 years and when partitioned into years 1 to 20 and years 21 to 40. Analyses were conducted in accordance with recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Strengthening the Reporting of Observational Studies in Epidemiology. **Results:** Data were extracted from 144 articles reporting on a total number of 54,354 subjects performing 59,584 observed tests of technique. The most frequent MDI errors were in coordination (45%; 95% CI, 41%-49%), speed and/or depth of inspiration (44%; 40%-47%), and no postinhalation breath-hold (46%; 42%-49%). Frequent DPI errors were incorrect preparation in 29% (26%-33%), no full expiration before inhalation in 46% (42%-50%), and no postinhalation breath-hold in 37% (33%-40%). The overall prevalence of correct technique was 31% (28%-35%); of acceptable, 41% (36%-47%); and of poor, 31% (27%-36%). There were no significant differences between the first and second 20-year periods of scrutiny. **Conclusions:** Incorrect inhaler technique is unacceptably frequent and has not improved over the past 40 years, pointing to an urgent need for new approaches to education and drug delivery.

## INHALER MISUSE IN AN OLDER ADULT POPULATION

Vanderman AJ, Moss JM, Bailey JC, Melnyk SD, Brown JN. *Consult Pharm* 2015;30(2):92-100.

**Objective:** To determine the prevalence of inhaler misuse in an older adult population. **Design:** Prospective observational study. **Setting:** Two primary care outpatient clinics in a Veterans Affairs Medical Center in North Carolina. **Participants:** Male veterans 65 years of age and older ( $n = 24$ ) prescribed a pressurized metered dose inhaler (pMDI) or a dry powder inhaler (DPI). **Measurements:** Inhaler technique was evaluated using placebo inhaler devices and a standardized technique assessment form that included critical steps. Potential risk factors for misuse were obtained from the medical record, and the time for technique evaluation was collected. **Main Results:** Study participants yielded 44 unique device observations. Patients were male with an average age of 82 years. All patients made at least one error, with a mean error rate of 2.5 errors/patient/inhaler, while 20 of 24 (83%) patients made at least one critical error with a mean error rate of 1.2 critical errors/patient/inhaler. Assessment of inhaler technique required 2.3 minutes/inhaler. Critical errors were made during 15 of 19 (79%) pMDI observations and 22 of 25 (88%) DPI observations. Patients with multiple inhalers or a history of stroke committed errors more often, although no risk factors demonstrated meaningful differences in error rates. **Conclusions:** Inhaler misuse in older adults is common, including committing critical errors that have been shown to reduce drug delivery. The time necessary for technique evaluation is relatively small. The high rate of misuse observed should serve as motivation for increased vigilance, individualized technique education, and routine re-assessment in the highly heterogeneous older adult population.

## ASTHMA PATIENTS' INABILITY TO USE A PRESSURIZED METERED-DOSE INHALER (PMDI) CORRECTLY CORRELATES WITH POOR ASTHMA CONTROL AS DEFINED BY THE GLOBAL INITIATIVE FOR ASTHMA (GINA) STRATEGY: A RETROSPECTIVE ANALYSIS

Levy ML, Hardwell A, McKnight E, Holmes J. *Prim Care Respir J* 2013;22(4):406-11.

**Background:** In practice it is logical that inhalers are prescribed only after patients have received training and demonstrated their ability to use the device. However, many patients are unable to use their pressurized metered-dose inhaler devices (pMDIs) correctly. We assessed the relationship between asthma control and patients' ability to use their prescribed pMDIs. **Methods:** Evaluation of 3,981 (46% male) primary care asthma patient reviews, which included inhaler technique and asthma control, by specialist nurses in primary care in 2009. The paper focuses on people currently prescribed pMDI devices. **Results:** Accurate data on reliever and preventer inhaler prescriptions were available for 3,686 and 2,887 patients, respectively. In patients prescribed reliever inhalers, 2,375 (64%) and 525 (14%) were on pMDI alone or pMDI plus spacer, respectively. For those prescribed preventers, 1,976 (68%) and 171 (6%) were using a pMDI without and with a spacer, respectively. Asthma was controlled in 50% of patients reviewed. The majority of patients (60% of 3,686) were using reliever pMDIs, 13% with spacers. Incorrect pMDI use was associated with poor asthma control ( $p < 0.0001$ ) and more short burst systemic steroid prescriptions in the last year ( $p = 0.038$ ). Of patients using beclometasone (the most frequently prescribed preventer drug in our sample), significantly more of those using a breath-actuated pMDI device ( $p < 0.0001$ ) and a spacer ( $p < 0.0001$ ) were controlled compared with those on pMDIs alone. **Conclusions:** Patients who are able to use pMDIs correctly have better asthma control as defined by the GINA strategy document. Beclometasone via a spacer or breath-actuated device resulted in better asthma control than via a pMDI alone. Patients prescribed pMDIs should be carefully instructed in technique and have their ability to use these devices tested; those unable to use the device should be prescribed a spacer or an alternative device such as one that is breath-actuated.

## INHALER COMPETENCE IN ASTHMA: COMMON ERRORS, BARRIERS TO USE AND RECOMMENDED SOLUTIONS

The Inhaler Error Steering Committee, Price D, Bosnic-Anticevich S, Briggs A, Chrystyn H, Rand C, Scheuch G, Bousquet J. *Respiratory Medicine* 2013;107(1):37-46.

Whilst the inhaled route is the first line administration method in the management of asthma, it is well documented that patients can have problems adopting the correct inhaler technique and thus receiving adequate medication. This applies equally to metered dose inhalers and dry powder inhalers and leads to poor disease control and increased healthcare costs. Reviews have highlighted these problems and the recent European Consensus Statement developed a call to action to seek solutions. This review takes forward the challenge of inhaler competence by highlighting the issues and suggesting potential solutions to these problems. The opportunity for technological innovation and educational interventions to reduce errors is highlighted, as well as the specific challenges faced by children. This



review is intended as a policy document, as most issues faced by patients have not changed for half a century, and this situation should not be allowed to continue any longer. Future direction with respect to research, policy needs and practice, together with education requirements in inhaler technique are described.

#### **THE ADMIT SERIES - ISSUES IN INHALATION THERAPY. 5) INHALER SELECTION IN CHILDREN WITH ASTHMA**

*Broeders ME, Pedersen S, Dubus JC, Crompton G; ADMIT Working Group. Primary Care Respiratory Journal 2010;19 (3): 209-216.*

Many children with asthma do not use their inhalers correctly and consequently gain little or no therapeutic benefit from the treatment. The focus of inhalation therapy should be on those inhalers which are easiest to use correctly by various groups of children and the amount of tuition and training required to obtain a correct technique. It is recommended that clinicians focus on a limited number of inhalers. Most children can be taught effective inhalation therapy by using a pMDI, a pMDI with a spacer, or a DPI. Most preschool children can be taught effective use of a pMDI and spacer with a valve system and a face mask. Therefore, this is the preferred mode of delivery in these age groups. When the child is capable of using the spacer without a face mask this administration technique should be adopted. In older children pMDIs are more difficult to use correctly than a pMDI with a spacer, a DPI, or a breath-actuated pMDI. Because DPIs and breath-actuated pMDIs are more convenient to use these devices are normally considered the preferred inhalation devices in these age groups except for administration of beclometasone dipropionate, which for safety reasons should be delivered by a spacer.

#### **THE ADMIT SERIES - ISSUES IN INHALATION THERAPY. 2) IMPROVING TECHNIQUE AND CLINICAL EFFECTIVENESS.**

*Broeders ME, Sanchis J, Levy ML, Crompton GK, Dekhuijzen PN; ADMIT Working Group. Primary Care Respiratory Journal 2009;18(2):76-82.*

Aerosol inhalation is considered the optimal route for administering the majority of drugs for the treatment of obstructive airways diseases. A number of Pressurized Metered-Dose and Dry Powder Inhalers are available for this purpose. However, inhalation of therapeutic aerosols is not without difficulty; it requires precise instructions on the inhalation maneuverer, which is different from spontaneous normal breathing. Also, the characteristics of the inhaler device have to be suitable for the user. Available data indicate a frequent lack of knowledge demonstrated by health professionals and patients on the inhalation maneuverer and handling of inhalers, resulting in a reduction of therapeutic benefit. This paper reviews the literature concerning the fundamental aspects of inhaler devices, inhalation maneuverer and device selection, in an attempt to increase the knowledge of, and to optimize the clinical use of, therapeutic inhalers.

#### **TARGETING DRUGS TO THE AIRWAYS: THE ROLE OF SPACER DEVICES**

*Lavorini F, Fontana GA. Expert Opin Drug Deliv 2009;6(1):91-102.*

**Aim:** Spacer devices are inhalation aids of varying dimension and complexity, specifically designed to overcome problems with the use of pressured metered dose inhalers (pMDIs). The aim of this review is to examine the current understanding about these inhalation devices and discuss their advantages and disadvantages. **Methods:** The pertinent literature concerning the characteristics and effects of spacers on delivery and lung deposition of inhaled medications, as well as their clinical efficacy in patients with reversible airway obstruction, is examined. **Results:** Spacers minimize problems of poor inhalation technique with pMDI, reduce oropharyngeal deposition and increase lung deposition. Spacers improve the clinical effect of inhaled medications, especially in patients unable to use a pMDI properly. Compared to both pMDIs and dry-powder inhalers, spacers may increase the response to beta-adrenergic bronchodilators, even in patients with correct inhalation technique. A pMDI plus spacer has proven to be viable lower cost alternative to the use of a nebulizer for delivering large bronchodilator doses in patients with severe acute asthma or chronic obstructive pulmonary disease. The use of large-volume spacers is recommended for delivering high doses of inhaled corticosteroids, and may permit a lower maintenance dose to be used. **Conclusion:** pMDIs may be routinely fitted with a spacer, especially in situations where correct pMDI use is unlikely.

## CHARACTERISTICS OF SPACER DEVICE USE BY PATIENTS WITH ASTHMA AND COPD

Guss D, Barash IA, Castillo EM. *The Journal of Emergency Medicine* 2008; 35(4):357-361.

**Objective:** Spacer devices (SD) in conjunction with metered dose inhalers (MDI) have been shown to be as effective as saline nebulizers for the delivery of beta-agonists. A preliminary study suggests that SDs are not consistently used. The purpose of this study was to investigate patterns of SD ownership and use to identify potential targets for future educational efforts to increase ownership and use of SD. **Methods:** Cross-sectional convenience sample survey of patients presenting to an academic Emergency Department (ED) with a history of asthma/COPD (chronic obstructive pulmonary disease). Informed consent was obtained. Survey data included demographics, association with a primary care physician (PCP), SD ownership, patterns of use, opinions of efficacy about SD and disease severity assessed by duration of asthma/COPD, prior ED visits, hospitalizations, and history of prior intubation. Patterns of use are described and univariate and multivariate analyses were used to identify factors associated with SD ownership. **Results:** Of the 313 patients, 55.9% were female, the mean age was 46.0 years (standard deviation 14.7), 54.3% were white, and 143 patients (45.7%) reported owning a SD. A total of 36.4% reported a prior hospitalization for their condition and 24% reported a history of being intubated. Less than half of patients presenting with asthma or COPD exacerbation that reported owning a SD used it the day of presentation to the ED. Logistic regression identified having a PCP and a history of prior hospitalization for asthma/COPD as factors independently associated with SD ownership (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.1-2.7 and OR 2.2, CI 1.3-3.5, respectively). **Conclusion:** A majority of patients with asthma/COPD do not own a SD. These data suggest that there is significant opportunity for educational efforts directed at a broad range of asthma/COPD patients in hopes of increasing ownership and use of SD.

## THE NEED TO IMPROVE INHALATION TECHNIQUE IN EUROPE: A REPORT FROM THE AEROSOL DRUG MANAGEMENT IMPROVEMENT TEAM

Crompton GK, Barnes PJ, Broeders M, Corrigan C, Corbetta L, Dekhuijzen R, Dubus JC, Magnan A, Massone F, Sanchis J, Viejo JL and Voshaar T. *Respir Med* 2006;100:1479-1494.

Although the principles of asthma management are well established in Europe, the available data indicate that asthma in patients is not well controlled. Many patients derive incomplete benefit from their inhaled medication because they do not use inhaler devices correctly and this may compromise asthma control. The Aerosol Drug Management Improvement Team (ADMIT), incorporating clinicians from the UK, Germany, France, Italy, Spain and The Netherlands, reviewed published evidence to examine ways to improve the treatment of reversible airways disease in Europe. Data indicate that there is a clear need for specific training of patients in correct inhalation technique for the various devices currently available, and this should be repeated frequently to maintain correct inhalation technique. Devices which provide reassurance to patients and their physicians that inhalation is performed correctly should help to improve patient compliance and asthma control. Educational efforts should also focus on primary prescribers of inhaler devices. ADMIT recommends dissemination of information on the correct inhalation technique for each model of device by the use of an accessible dedicated literature base or website which would enable to match the appropriate inhaler to the individual patient. There is also a need for standardization of prescribing practices throughout Europe. Regular checking of inhalation technique by prescribers is crucial as correct inhalation is one of the keystones of successful asthma management.

## REGIMEN AND DEVICE COMPLIANCE: KEY FACTORS IN DETERMINING THERAPEUTIC OUTCOMES

Everard ML. *J Aerosol Med* 2006;19(1):67-73.

The two most important differences between inhaled and oral therapy are (1) the lungs have evolved to exclude foreign material while the gut has evolved to take in large amounts of foreign material, and (2) even if patients adhere to a treatment regimen (regimen compliance or adherence), they may fail to derive any benefit from using an inhaler due to failure of drug delivery (poor device compliance). In other words: True compliance = regimen compliance x device compliance. Aerosol scientists, building on the observations of those working in the field of industrial hygiene, have developed devices that largely address the challenge of bypassing the lung's defenses, in that current devices generate aerosols that contain a significant proportion of particles in the range of 1-5 microm. These have a relatively high probability of entering the lungs and depositing through impaction and/or sedimentation. The development of delivery systems for systemically acting drugs has led to further refinement. The second issue, that of patient

behavior, has, until very recently, received very little attention from those developing devices. Regimen compliance involves taking the medication at the suggested times. Device compliance (using the device optimally) is dependent on competence and contrivance. A patient taking a tablet before rather than after a meal is likely to receive some therapeutic benefit even if the effect is suboptimal. A patient whose device compliance is poor because either they are not competent to use the device or contrive to use it in an ineffective manner may derive little or no benefit even if they are scrupulously adhering to their treatment regimen. Lack of precision in the use of the terms “compliance” and “adherence” has contributed to the failure to build in features that may help address issues relating to patient behavior. The resurgence of interest in developing devices that can be used to deliver potent systemically acting drugs has, out of necessity, led to the development of systems that help minimize the impact of poor competence or contrivance on drug delivery. There are suggestions, that need to be confirmed, that regimen compliance (adherence) can be influenced by providing feedback. In the absence of formal studies, comparison of the high-tech and low-tech approaches to improving device compliance incorporated into novel devices might provide valuable insights into what aspects of feedback are important in the clinical setting.

## **RECENT ADVANCES IN AEROSOL THERAPY FOR CHILDREN WITH ASTHMA.**

*Devadason SG. Journal of Aerosol Medicine 2006;19(1):61-66.*

Inhalational drug delivery is the primary mode of asthma therapy in children and is the main focus on this article. Pressurized metered dose inhalers (pMDIs) are now the method of choice in infants and children under 5 years old, when used in combination with an appropriate valved holding chamber or spacer. Spacers are particularly important for steroid inhalation to maximize lung deposition and minimize unwanted oropharyngeal deposition. Optimal inhalation technique with a pMDI-spacer in infants is to inhale the drug by breathing tidally through the spacer. Drug delivery to the lungs using pMDIs can vary greatly, depending on the formulation used and the age of the child. Dry powder inhalers (DPIs) are driven by the peak inspiratory flow of the patient and are usually not appropriate for children under 5 or 6 years of age. Nebulizers continue to play a role in the treatment of acute asthma where high doses of bronchodilator are required, though multiple doses via pMDI spacer may suffice. Important drug delivery issues specific to children include compliance, use of mask versus mouthpiece, lower tidal volumes and inspiratory flows, determination of appropriate dosages, and minimization of adverse local and systemic effects.

**Conclusion:** In recent times, pMDI-spacers have become the most commonly used approach to aerosol therapy in children. They can be used for all ages, and can be used both for long-term preventative therapy and for short-term treatment of acute exacerbations. One of the main advantages of pMDI-spacer use is that normal tidal breathing can be used during aerosol administration, which makes them ideal for infants and younger children. However, there are many newer and more innovative devices available that offer therapeutic advantages in terms of increased efficacy, convenience, and compliance, particularly for older children and adolescents. The ability of a child to utilize an inhaler device and to perform the required inhalation technique consistently must be evaluated when making the choice of an appropriate delivery system for children of different ages.

## **SKILLS AMONGST PARENTS OF CHILDREN WITH ASTHMA: A PILOT INTERVENTIONAL STUDY IN PRIMARY CARE SETTING**

*Aziz NA, Norzila MZ, Hamid MZ, Noorlaili MT. Med J Malaysia 2006 Dec;61(5):534-9.*

The increasing prevalence of childhood asthma has become a concern among health practitioners. Effective management emphasizes long-term management and inhaled therapy has become the mainstay home management for children. However, proper utilization of medication is pertinent in improving control. Proper asthma education is mandatory in improving skills and confidence amongst parents. To assess the skills of using the metered-dose inhaler (MDI) with a spacer among asthmatic children before and after educational intervention and to analyze any difficulties which may occur amongst the participants in executing the assessment steps. A cross-sectional clinic based study involving 85 parents and children with asthma. A standardized metered-dose inhaler-spacer checklist of eight steps of medication usage and five steps of cleaning the spacer were used as the assessment tools for pre and post intervention. The performance on using the inhaler-spacer and spacer cleaning knowledge pre and two months post intervention was evaluated. One point was given for each correct step and zero points for incorrect answers/steps. The mean score for skills of inhaler technique improved significantly after educational intervention (3.51 to 6.01,  $p < 0.0001$ ) as did the mean score for parental knowledge of spacer cleaning technique (1.35 to 3.16,

*p* 0.001). Analysis showed only a limited improvement even after an educational session in three steps of inhalation technique: step 5 (23.5%/69.4%), step 6 (28.2%/68.2%) and step 7 (25.9%/61.2%). Parents with asthmatic children had poor skills in utilizing their children's medication. A short-term educational intervention was able to improve overall knowledge and skill but certain skills need more emphasizing and training.

### **ASTHMA MANAGEMENT: IMPORTANT ISSUES**

Barnes P, Virchow JC, Sanchis J, Welte T and Pedersen S. *Eur Respir Rev* 2005;14(97): 147-151.

Although most attention has been focused on the drugs used to control asthma, it is increasingly recognized that effective delivery of these drugs to the lungs is just as important. The most effective drugs,  $\beta_2$ -agonists and corticosteroids, are given by inhalation so there has been a search for more efficient inhaler devices that are easier for patients to use. A symposium at the European Respiratory Society Annual Meeting in 2005 discussed some of the important issues in inhaler therapy in adults and children. This article summarizes the major points of discussion that arose out of this symposium. New more effective inhaler devices are now becoming available and are likely to have an important impact on asthma management.

### **PEDIATRIC PULMONARY DRUG DELIVERY: CONSIDERATIONS IN ASTHMA TREATMENT**

Berger, William E. *Expert Opin Drug Deliv* 2005;2(6):965-980.

Aerosol therapy, the preferred route of administration for glucocorticosteroids and short-acting  $\beta_2$ -adrenergic agonists in the treatment of pediatric asthma, may be given via nebulizers, metered-dose inhalers and dry powder inhalers. For glucocorticosteroids, therapy with aerosolized medication results in higher concentrations of drug at the target organ with minimal systemic side effects compared with oral treatments. The dose of drug that reaches the airways in children with asthma is dependent on both the delivery device and patient-related factors. Factors that affect aerosol drug delivery are reviewed briefly. Advantages and disadvantages of each device and device-specific factors that influence patient preferences are examined. Although age-based device recommendations have been made, the optimal choice for drug delivery is the one that the patient or caregiver prefers to use, can use correctly and is most likely to use consistently.

### **DO PEDIATRIC HEALTHCARE PROVIDERS KNOW HOW TO USE METERED DOSE INHALER PLUS SPACER DEVICES?**

Iheagwara K, Sharif I, Ozuah PO. *Prim Care Respir J* 2005;14(3):172-3.

We tested whether health practitioners correctly used MDI-spacer devices. Of 122 subjects, 89% had instructed a patient on using a spacer. Whilst performance with the AeroChamber® was the best, only 3% correctly demonstrated all the steps for that device.

### **HOW CAN WE IMPROVE ASTHMA MANAGEMENT?**

Barnes PJ. *Curr Med Res Opin* 2005;21 Suppl 4:S1-3.

Asthma remains a poorly controlled disease both in Europe and the USA despite the availability of effective asthma treatments. Patient noncompliance, incorrect use of inhaler devices, insufficient treatment of peripheral airway inflammation as well as limitations of the asthma management guidelines themselves may all contribute to this poor control. Asthma control may be improved by improving the consultation process during the visit at the doctor. The ideal consultation would involve critical listening to the patient, accurate assessment of asthma symptoms as indicators for asthma control and prescribing the appropriate medication and dose for the individual patient according to the degree of severity of asthma. In addition, correctness of inhalation technique as performed by the patient should be regularly checked; patients should be educated and trained how to manage their personal condition and should be offered convenient follow-up options. Choosing the right inhaler for the patient may improve patient compliance. Inhaler choice should be based on an evidence-based rationale rather than on an empirical basis. The preference of the patient should also be taken into consideration, as it is the patient who has to use the inhaler daily over a long period of time. The ideal inhaler should demonstrate sufficient drug delivery to the lower airways as well as good drug distribution to both the central and peripheral airways. It should ensure consistency of the emitted dose, be easy to teach and use, be small in size and convenient to handle. It should also be multi-dose, require a

low inspiratory airflow for activation, provide feedback to the patient on correct inhalation technique, be re-usable/refillable, have an appealing design, and have a reliable dose counter.

### **MISUSE OF CORTICOSTEROID METERED-DOSE INHALER IS ASSOCIATED WITH DECREASED ASTHMA STABILITY**

*Giraud V, Roche N. Eur Respir J 2002;19:246-51.*

This study assessed whether the improper use of pressurized metered-dose inhalers (pMDIs) is associated with decreased asthma control in asthmatics treated by inhaled corticosteroids (ICS). General practitioners (GPs) included consecutive asthmatic outpatients treated by pMDI-administered ICS and on-demand, short-acting beta2-agonists. They measured an asthma instability score (AIS) based on daytime and nocturnal symptoms, exercise-induced dyspnea, beta2-agonist usage, emergency-care visits and global perception of asthma control within the preceding month; the inhalation technique of the patient also was assessed. GPs ( $n=915$ ) included 4,078 adult asthmatics; 3,955 questionnaires were evaluable. pMDI was misused by 71% of patients, of which 47% was due to poor coordination. Asthma was less stable in pMDI misusers than in good users (AIS: 3.93 versus 2.86,  $p<0.001$ ). Among misusers, asthma was less stable in poor coordinators (AIS: 4.38 versus 3.56 in good coordinators,  $p<0.001$ ). To conclude, misuse of pressurized metered-dose inhalers, which is mainly due to poor coordination, is frequent and associated with poorer asthma control in inhaled corticosteroid-treated asthmatics. This study highlights the importance of evaluating inhalation technique and providing appropriate education in all patients, especially before increasing inhaled corticosteroid dosage or adding other agents. The use of devices which alleviate coordination problems should be reinforced in pressurized metered-dose inhaler misusers.

### **POOR INHALATION TECHNIQUE, EVEN AFTER INHALATION INSTRUCTIONS, IN CHILDREN WITH ASTHMA**

*Kamps AWA, van Ewijk B, Roorda RJ et al. Pediatr Pulmonol 2002;29:39-42.*

The aim of this study was to evaluate the effect of instructions to children with asthma (given by general practitioners or by pharmacy assistants) on how to inhale from metered dose inhalers with spacers (MDI/s) or dry powder inhalers (DPI). We scored inhalation technique of asthmatic children according to criteria defined by the Netherlands Asthma Foundation, and related the performance to the inhalation instructions given. For each inhaler, a number of steps were considered essential for reliable drug delivery. Patients newly referred for asthma were asked to demonstrate their inhalation technique and to fill out a questionnaire on the inhalation instruction received prior to referral. Children participating in a clinical trial, who had received repeated comprehensive inhalation instructions, served as a control group. Sixty-six newly referred patients (1-14 years of age, median age 5 years; 37 boys) and 29 control patients (5-10 years of age, median age 7 years; 21 boys) completed the study. Sixty patients (91%) had received inhalation instruction prior to referral. Only 29% of these patients, using a dry powder inhaler, performed all essential steps correctly, compared to 67% of children using a metered dose inhaler/spacer combination ( $p<0.01$ ). Children who had received comprehensive inhalation instructions with repeated checks of proper inhalation technique at the pharmacy or in the clinical trial setting were more likely to perform all essential steps correctly (79% and 93%, respectively) than children who had received a single instruction by a general practitioner (39%,  $p<0.01$ ). Many asthmatic children use their inhalers devices too poorly to result in reliable drug delivery, even after inhalation instruction. Comprehensive inhalation instruction and repeated check-ups are needed to assure reliable inhalation technique.

### **DETERMINANTS OF CORRECT INHALATION TECHNIQUE IN CHILDREN ATTENDING A HOSPITAL-BASED ASTHMA CLINIC**

*Kamps AWA, Brand PLP, Roorda RJ. Acta Paediatr 2002;91:159-63.*

Many children with asthma use their inhaler device incorrectly even after comprehensive inhalation instruction. The aim of this study was to identify factors associated with correct inhalation technique. Two hundred children with asthma demonstrated their inhalation technique. Patient characteristics and the components of inhalation instructions they had received were compared for children demonstrating a correct or incorrect inhalation technique. In addition, the inhalation technique of 47 newly referred patients was followed-up prospectively after repeated comprehensive instruction sessions. Seventy-eight percent of all patients demonstrated a correct inhalation technique. Patients who had received repeated instruction sessions and patients who had previously been asked to

demonstrate the use of their inhaler during an instruction session were more likely than other children to demonstrate a correct inhalation technique ( $p < 0.001$  and  $p = 0.03$ , respectively). Multiple logistic regression analysis showed that repetition of instructions was significantly associated with a correct inhalation technique (odds ratio (OR) 8.2, 95% CI 3.2-21.5;  $p < 0.0001$ ) irrespective of type of inhaler used. Demonstration of the inhaler use by the patient was significantly associated with a correct inhalation technique for patients using a metered dose inhaler plus spacer device (OR 3.5, 95% CI 1.0-12.6;  $p = 0.05$ ), but not for patients using a dry powder inhaler (OR 1.6, 95% CI 0.4-6.4;  $p = 0.54$ ). The number of newly referred patients demonstrating a correct inhalation technique improved from 57.4% to 97.9% after three comprehensive instruction sessions. **Conclusion:** Inhalation instruction should be given repeatedly to achieve and maintain correct inhalation technique in asthmatic children.

## MEDICAL PERSONNEL AND PATIENT SKILL IN THE USE OF METERED DOSE INHALERS: A MULTICENTRIC STUDY

Plaza V, Sanchis J. *Respiration* 1998;65:195-8.

The objective was to evaluate the correctness of the inhalation technique in a nationwide sample of patients and medical personnel, in order to define targeted educational goals. A total of 1,640 volunteers (746 patients, 466 nurses and 428 physicians) were evaluated. Only 9% of patients, 15% of nurses and 28% of physicians showed a correct inhalation technique. Physicians performed significantly better (mean score 77 +/- 23) than nurses (71 +/- 22) and patients (62 +/- 26). Scores in general practitioners and pediatricians were significantly lower than those of chest physicians and allergists. In conclusion, proper use of metered dose inhalers (MDI) in patients and medical personnel is still faulty. Despite the physician's awareness of the importance of a correct inhalation technique in the use of MDI, this study shows severe deficiencies, showing the need for substantial changes in educational efforts, and particularly addressed to general practitioners.

## Most Recommended: AeroChamber® Brand of VHC

### Chambers Are Not Interchangeable:

"The dose delivered may vary considerably between spacers, so consider this if changing from one spacer to another"  
*Global Initiative for Asthma Management 2020.*

"There is published evidence that the union of a particular pMDI and a given spacer/VHC is considered a specific inhaled medication delivery system. Therefore, we recommend physicians to focus on selecting the most appropriate spacer/VHC for the patient and their pMDI(s), given the weight of clinical evidence available. Furthermore, we believe that pharmacists need to appreciate that spacers/VHCs may deliver different amounts of drug from the pMDI and therefore substitution of a different device from that prescribed by the physician may have an impact on the patient. Finally, regulatory authorities need to be aware of the risks inherent in the current approval process of spacer VHCs through CE mark registration and look for improvements to, at the very least, restrict the ability of devices with serious design/quality flaws to be approved and used by patients."

*Spacers and Valved Holding Chambers—The Risk of Switching to Different Chambers. Lavorini F et al. J Allergy Clin Immun Pract. 2020 May;8(5):1569-1573*

"Substitution of one type of spacer or VHC with another may have both safety and clinical implications unless otherwise proven as equivalent through in vitro and/or in vivo studies"

*Spacers and Valved Holding Chambers—The Risk of Switching to Different Chambers. Lavorini F et al. J Allergy Clin Immun Pract. 2020 May;8(5):1569-1573*

"Even small changes in VHC size and geometries, as well as different designs of valves, will likely result in differences in critical performance attributes - if it looks similar, it does not mean its performance is equivalent." *Suggett et al. Statistical Performance Evaluation of Similar Looking Valved Holding Chambers: If it looks the same, does it perform the same? Respiratory Drug Delivery 2016.*

"Different VHCs may provide varying amounts of the same medication to a patient. The medication delivery from the VHC can be affected by a number of factors, including size, shape, valve functionality and materials. *Mitchell JP et al. The attributes of an ideal universal valved holding chamber for use with pressurized metered dose inhalers. Respiratory Drug Deliver 2015.*

"The use of different spacer devices may result in variable effects on drug delivery." *Flovent HFA Product Monograph, Canada 2014.*

“VHCs are not interchangeable ... Parents, clinicians and pharmacists should be educated not to interchange VHCs once a child is stable on a particular ICS dose and VHC combination. Moreover, the initial prescription for a VHC should include language (e.g. “Do not substitute” or “Medically necessary”) to prevent the pharmacist from substituting a different VHC. We suggest that each VHC should be evaluated for relative lung bioavailability prior to their routine use with a particular ICS” *Blake K et al. Bioavailability of inhaled fluticasone propionate via chambers/masks in young children. Eur Respir J 2012;39:1.*

“Commercially produced spacers with well-characterized drug output characteristics are preferable, although spacer devices or face masks differ in their drug delivery and therefore may not be interchangeable” *GINA – Global Strategy for Asthma Management and Prevention. Updated 2012*

“Spacers come in different designs and, since the dose received may vary considerably from one device to another, a spacer device that has documented efficacy in young children is recommended.” *GINA – Global Strategy for the Diagnosis and Management of Asthma in Children 5 Years and Younger, 2010.*

“Spacers should not be regarded as interchangeable: patients who use a spacer with their inhaler should use the spacer device named in the Summary of Product Characteristics (where specified by name). Patients whose asthma is well controlled and who are using a spacer should always use the same type of spacer and not switch between spacers. Different spacers may deliver different amounts of inhaled corticosteroid, which may have implications for both safety and efficacy.” *Drug Safety Update – Inhaled products that contain corticosteroids, July, 2008. Medicines and Healthcare Products Regulatory Agency (MHRA).*

“Only spacer devices specifically identified as suitable for a particular CFC-free inhaler should be used – they are not interchangeable.” *PJ Practice Checklist – CFC-Free Inhalers. Produced by the Pharmaceutical Journal, February, 1999, Updated January 2001. Moffat T. Royal Pharmaceutical Society of Great Britain. Pharmacists – the scientists in the high street. 2002.*

## **AeroChamber® Brand of VHC Is Recommended for Use with the Following Metered Dose Inhalers:**

### **Spacers and Valved Holding Chambers – The Risk of Switching to Different Chambers**

*Lavorini F, Barreto C, van Boven J, Carroll W, Conway J, Costello RW, Hellqvist Dahl B, Dekhuijzen R, Holmes S, Levy M, Molimard M, Roche N, Román-Rodríguez M, Scichilone N, Scullion J, and Usmani O. J Allergy Clin Immun Pract. 2020 May;8(5):1569-1573.*

Spacers are pressurized metered-dose inhaler (pMDI) accessory devices developed to reduce problems of poor inhaler technique with pMDIs. Spacers that feature a 1-way inspiratory valve are termed valved holding chambers (VHCs); they act as aerosol reservoirs, allowing the user to actuate the pMDI device and then inhale the medication in a 2-step process that helps users overcome challenges in coordinating pMDI actuation with inhalation. Both spacers and VHCs have been shown to increase fine particle delivery to the lungs, decrease oropharyngeal deposition, and reduce corticosteroid-related side effects such as throat irritation, dysphonia, and oral candidiasis commonly seen with the use of pMDIs alone. Spacers and VHCs are not all the same, and also are not interchangeable: the performance may vary according to their size, shape, material of manufacture and propensity to become electrostatically charged, their mode of interface with the patient, and the presence or otherwise of valves and feedback devices. Thus, pairing of a pMDI plus a spacer or a VHC should be considered as a unique delivery system. In this Rostrum we discuss the risk potential for a patient getting switched to a spacer or VHC that delivers a reduced dose medication.

### **AirFluSal® MDI 25 microgram/125 microgram per actuation pressurised inhalation, suspension – Summary of Product Characteristics, UK**

If you find it difficult to use the inhaler, either your doctor or other healthcare provider may recommend using a spacer device such as the Volumatic<sup>+</sup> or AeroChamber Plus® (depending on National Guidance) with your inhaler. Patients should continue to use the same make of spacer device, either the Volumatic spacer device or the AeroChamber Plus® spacer device, as switching between spacer devices can result in changes in the dose delivered to the lungs. It is important that if you are using a spacer device with your inhaler that you do not stop using it without talking to your doctor first. It is also important that you do not change the type of spacer device that you use without talking to your doctor. If you stop using a spacer device or change the type of spacer device that you use your doctor may need to change the dose of medicine required to control your asthma.

### **Airomir<sup>†</sup> – Patient Instruction Leaflet, UK**

Some people find it difficult to press their inhaler and breathe in at the same time. A spacer device helps to overcome this problem. The spacer that fits AIROMIR Inhaler is called the AeroChamber Plus<sup>®</sup> spacer device. If you use the AeroChamber Plus<sup>®</sup> spacer device please follow the instructions provided with it. Your doctor, nurse or pharmacist will be able to advise you about the AeroChamber Plus<sup>®</sup> device.

### **Airomir<sup>†</sup> – Summary of Product Characteristics, UK**

For patients requiring a spacer device, the AeroChamber Plus<sup>®</sup> has been shown to be compatible with Airomir Inhaler.

### **AirSalb<sup>†</sup> CFC-free Inhaler 100 ug/dose, Summary of Product Characteristics, EU**

Salbutamol may be used with a Vortex<sup>†</sup> or AeroChamber Plus<sup>®</sup> spacer device by children and patients who find it difficult to synchronise aerosol actuation with inspiration.

### **AirSalb<sup>†</sup> CFC-free Inhaler 100 ug/dose, Package Leaflet, EU**

Some people find it difficult to release a puff of medicine just after they start to breathe in. In this case, as well as for children, the Vortex<sup>†</sup> or AeroChamber Plus<sup>®</sup> spacer device can be used. Please refer to the product information of the spacer device for its correct handling.

### **Alvesco<sup>†</sup> 160/80 Summary of Product Characteristics, EU**

To address specific patient needs, such as finding it difficult to press the inhaler and breathe in at the same time, Alvesco<sup>†</sup> Takeda can be used with the AeroChamber Plus<sup>®</sup> spacer device.

### **Alvesco<sup>†</sup> 100/200 Product Monograph, Canada**

In patients who find co-ordination of a pressurized metered dose inhaler difficult, a spacer device (AeroChamber Plus<sup>®</sup>) may be used with Alvesco<sup>†</sup>.

### **Alvesco<sup>†</sup> 40, 80 and 160 Patient Instruction Leaflet, UK**

If you find it difficult to use the inhaler, your doctor may recommend the use of a spacer. The spacer that fits the Alvesco inhaler is called AeroChamber Plus<sup>®</sup>. If you use the AeroChamber Plus<sup>®</sup> device, please follow the instructions provided with it. Your doctor or pharmacist will be able to advise you about the device.

### **Atrovent<sup>†</sup> Inhaler CFC-Free 20 Summary of Product Characteristics, EU**

The inhaler can be used with the AeroChamber Plus<sup>®</sup> spacer device. This may be useful for patients, e.g., children, who find it difficult to synchronize breathing in and inhaler actuation.

### **Atrovent<sup>†</sup> Inhaler CFC-Free 20 Patient Instruction Leaflet, UK**

If you find breathing in and pressing the inhaler at the same time (step 3) difficult you should talk to your doctor or pharmacist, as you could use a spacer device (AeroChamber Plus<sup>®</sup>) with your inhaler. A spacer is a device designed to make step 3 easier. A spacer is generally a plastic container with a mouthpiece at one end and a hole for inserting the mouthpiece of the inhaler at the other end. The puff of medicine from your inhaler is sprayed into the spacer and the puff of medicine stays there, inside the spacer, until you breathe in through your mouth from the spacer with the spacer mouthpiece in your mouth and with your lips closed around it. This means that you do not have to worry about breathing in and pressing the inhaler at the same time.

### **Bevespi<sup>†</sup> Aerosphere<sup>†</sup>, SmPC, EU**

Patients who find it difficult to co-ordinate actuation with inspiration of breath may use Bevespi<sup>†</sup> Aerosphere<sup>†</sup> with a spacer to ensure proper administration of the product. Compatibility with the AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> spacer device has been demonstrated.

### **Combisal<sup>†</sup> metered dose pressurized suspension, Summary of Product Characteristics, UK**

Use of an AeroChamber Plus<sup>®</sup> spacer device with Combisal<sup>†</sup> is recommended in patients who have, or are likely to have, difficulties in coordinating actuation with inspiration (e.g. Children < 12 years old). Only the AeroChamber Plus<sup>®</sup> spacer device should be used with Combisal<sup>†</sup>. Other spacing devices should not be used with Combisal and patients should not switch from one spacer device to another.



### **Combisal<sup>†</sup> metered dose pressurized suspension, Patient Instruction Leaflet, UK**

If you or your child find it difficult to use the inhaler, either your doctor or other healthcare provider may recommend using an AeroChamber Plus<sup>®</sup> spacer device with your inhaler. Other spacer devices are not recommended for use with Combisal<sup>†</sup> and you should not switch from the AeroChamber Plus<sup>®</sup> device to another. It is also important that you do not change or stop using the spacer without talking to your doctor, they will know how to modify the therapy.

### **Flutiform<sup>†</sup> pressurized inhalation suspension, Summary of Product Characteristics, EU**

Use of a spacer device with *Flutiform* inhaler is recommended in patients who find it difficult to synchronize aerosol actuation with inspiration of breath. The AeroChamber Plus<sup>®</sup> is the only spacer device recommended for use with *Flutiform* inhaler.

### **Flutiform<sup>†</sup> pressurized inhalation suspension, Patient Instruction Leaflet, EU**

If you have difficulty using your inhaler your doctor or asthma nurse may give you a device called an AeroChamber Plus<sup>®</sup> spacing device, to help you to breathe your medicine into your lungs properly.

### **Fostair<sup>†</sup> 100/6 Inhalation Aerosol – Summary of Product Characteristics, EU**

Patients who find it difficult to synchronize aerosol actuation with inspiration of breath, may use the AeroChamber Plus<sup>®</sup> spacer device.

### **Fostair<sup>†</sup> 100/6 Inhalation Aerosol – Patient Instruction Leaflet, EU**

If you find it difficult to operate the inhaler while starting to breathe in you may use the AeroChamber Plus<sup>®</sup> spacer device. Ask your doctor, pharmacist or nurse about this device.

### **Ipravent<sup>†</sup>-20 Inhalation Aerosol – Summary of Product Characteristics, EU**

The inhaler can be used with the AeroChamber Plus<sup>®</sup> spacer device. This may be useful for patients, e.g. adult, who find it difficult to synchronise breathing in and inhaler actuation.

### **Ipravent<sup>†</sup>-20 Inhalation Aerosol – Patient Instruction Leaflet, EU**

The inhaler can be used with a device called AeroChamber Plus<sup>®</sup> spacer. This may be useful for people who find it difficult to synchronise breathing in and inhaler actuation.

### **Kelhale<sup>†</sup> 100 – Patient Instruction Leaflet, UK**

The inhaler can be used with a device called AeroChamber Plus<sup>®</sup> spacer. This may be useful for people who find it difficult to synchronise breathing in and inhaler actuation.

### **Kelhale<sup>†</sup> 100 – Summary of Product Characteristics, UK**

Where a spacer is considered necessary for specific patient needs, beclometasone dipropionate aerosol can be used with AeroChamber Plus<sup>®</sup> holding chamber, as the extrafine particle fraction is maintained.

### **Qvar<sup>†</sup> 50/100 Product Monograph, Canada**

Where a spacer is considered necessary the AeroChamber<sup>®</sup> is a suitable device for use with QVAR<sup>†</sup> MDI as the extrafine particle fraction is maintained.

### **Qvar<sup>†</sup> 50/100 Summary of Product Characteristics, UK**

Where a spacer is considered necessary for specific patient needs, Qvar aerosol can be used with AeroChamber Plus<sup>®</sup> holding chamber, as the extrafine particle fraction is maintained.

### **Qvar<sup>†</sup> 50/100 Patient Instruction Leaflet, UK**

The spacer that fits Qvar aerosol is called the AeroChamber Plus<sup>®</sup> spacer device.

### **Respimat<sup>†</sup> Soft Mist<sup>†</sup> Inhaler – Kamin *et al.*, 2011**

To ensure standardized dosing, the use of the Respimat<sup>†</sup> inhaler with spacer (AeroChamber Plus<sup>®</sup>) is recommended for all children below 5 years of age.

### **Sereflo<sup>†</sup> 25/250 Summary of Product Characteristics, UK**

Either the Volumatic spacer or the AeroChamber Plus<sup>®</sup> spacer device can be used (depending on National Guidance).

### **Sereflo<sup>†</sup> 25/250 Patient Instruction Leaflet, UK**

If you find it difficult to use the inhaler, either your doctor or other healthcare provider may recommend using a spacer device such as the Volumatic<sup>®</sup> or AeroChamber Plus<sup>®</sup> with your inhaler.

### **Seretide<sup>†</sup> Evohaler<sup>†</sup> 50/125/250 – Summary of Product Characteristics, EU**

Use of a spacer device with Seretide inhaler is recommended in patients who have, or are likely to have difficulties to coordinate actuation with inspiration. Either the Volumatic<sup>†</sup> or AeroChamber Plus<sup>®</sup> spacer device can be used (depending on National Guidance).

### **Seretide<sup>†</sup> Evohaler<sup>†</sup> 50/125/250 - Patient Instruction Leaflet, EU**

If you or your child find it difficult to use the Evohaler, either your doctor or other healthcare provider may recommend using a spacer device such as the Volumatic<sup>†</sup> or AeroChamber Plus<sup>®</sup> with your inhaler. It is important that you do not change the type of spacer device that you use without talking to your doctor.

### **Sirdupla<sup>†</sup> Inhaler 25/125 and 25/250 – Patient Instruction Leaflet & Summary of Product Characteristics, UK**

Only the AeroChamber Plus<sup>®</sup> spacer device should be used with Sirdupla<sup>†</sup>. Other spacing devices should not be used with Sirdupla and you should not switch from one spacer device to another.

### **Symbicort<sup>†</sup> pMDI, Patient Instruction Leaflet, UK**

Your doctor, nurse or pharmacist may suggest that you use a spacer device (e.g., AeroChamber Plus<sup>®</sup> Flow Vu<sup>®</sup> or AeroChamber Plus<sup>®</sup>). Follow the instructions in the leaflet that is packed with the spacer device.

### **Symbicort<sup>†</sup> pMDI, Summary of Product Characteristics, UK**

Use of a spacer device (e.g. AeroChamber Plus<sup>®</sup> Flow Vu<sup>®</sup> or AeroChamber Plus<sup>®</sup>) with Symbicort (pressurised inhalation, suspension) is usually recommended, especially in patients who have, or are likely to have difficulties to coordinate actuation with inhalation.

### **Trimbow<sup>†</sup>, Summary of Product Characteristics, EU**

Patients who find it difficult to synchronise aerosol actuation with inspiration of breath may use the AeroChamber Plus<sup>®</sup> spacer device, properly cleaned as described in the relevant leaflet.

### **Trimbow<sup>†</sup>, Patient Instruction Leaflet, EU**

If you find it difficult to use the inhaler while starting to breathe in, you may use the AeroChamber Plus<sup>®</sup> spacer device. Ask your doctor or pharmacist about this device.

### **Zenhale<sup>†</sup> Product Monograph, Merck Canada Inc.**

Use of the AeroChamber Plus<sup>®</sup> Anti-Static valved holding chamber is recommended with ZENHALE<sup>†</sup>, in patients who find it difficult to synchronize aerosol actuation with inspiration of breath.

### **Clinical Data with AeroChamber<sup>®</sup> Brand of VHC Included in the Following Product Monographs:**

#### **Advair<sup>†</sup> Product Monograph, Canada, May 2011**

50 / 125 / 250 mcg

#### **Flovent<sup>†</sup> HFA Inhalation Aerosol Product Monograph, USA, 2014**

44 / 110 / 220 mcg

#### **Flovent<sup>†</sup> HFA Inhalation Aerosol Product Monograph, Canada, 2014**

50 / 125 / 250 mcg

#### **Ventolin<sup>†</sup> HFA Inhalation Aerosol Product Monograph, USA, 2014**

90mcg

## Confidence in Aerosol Delivery

### Most studied brand of VHC

Supported by hundreds of *in vitro* and *in vivo* studies

### Winner of Top Ten Innovations in Technology Award (2013)

**AeroChamber Plus® Flow-Vu®** Chamber has won an award for being one of the top 10 innovations in technology. The award was given by the nonprofit group - Allergy & Asthma Network Mothers of Asthmatics. A panel of editors, board members, families, and volunteers reviewed innovations and technologies that have changed the world, narrowing it down to the top 10 within the last 25 years. The award was given to products and services that have improved the quality of life for people with asthma and allergy conditions.

### Free of Bisphenol A, Phthalates, Latex, Lead and PVC



There continues to be new studies regarding the potential health risks associated with BPA. Since the medications taken with our products are critical to the health of those that need them, it is our responsibility to lead in the development of consumer friendly products that are manufactured from materials that do not contain BPA.

### Manufactured to the Highest Quality Standards

**AeroChamber Plus® Flow-Vu®** Chambers are manufactured in a registered facility. MMC is registered to ISO 13485, which is specific for medical device manufacturers.

REGISTERED  
**ISO 13485**  
QUALITY SYSTEM

## Equivalency Data – AeroChamber® Brand of VHCs

### ARE VALVED HOLDING CHAMBERS (VHCS) INTERCHANGEABLE? AN *IN VITRO* EVALUATION OF VHC EQUIVALENCE.

Dissanayake S, Nagel M, Falaschetti E, Suggett J. *Pulm Pharmacol Ther.* 2018 Feb;48:179-184. doi:10.1016/j.pupt.2017.10.005. Epub 2017 Oct 10

**Introduction:** The European Medicines Agency (EMA) requires that a specific valved holding chamber (VHC) is designated for use with a given pressurised metered dose inhaler (pMDI). No other regulatory authorities impose similar requirements, implying that VHCs are interchangeable. This *in vitro* study, employing EMA assessment criteria, assessed the equivalence of four antistatic VHCs (aVHCs) versus the non-conducting VHC most widely referenced in pMDI monographs, the AeroChamber Plus™ (AC+) VHC. **Materials & Methods:** The “reference” AC + VHC was prepared by soaking in detergent solution. The four test aVHCs (AeroChamber Plus™ Flow-Vu™ [AC + FV]; Compact Space Chamber Plus [CSC+]; InspiraChamber [IC]; OptiChamber Diamond™ [OCD]) were tested “out-of-pocket”. Twenty devices of each type were evaluated. A salbutamol pMDI was actuated into each VHC with a 2-s delay between actuation and Andersen Cascade Impactor (ACI) sampling. Drug deposition in four ACI particle size groups was assessed: Group 1, >5.8-10 µm; Group 2, >3.3-5.8 µm; Group 3, >1.1-3.3 µm; Group 4, ≤1.1 µm. Equivalence versus the reference VHC was demonstrated where the 90% confidence interval for the test/reference mass ratio was within 85-118%. **Results:** The mass retained within the VHC was similar for the AC + VHC and AC + FV aVHC, but was approximately twice as great for the other aVHCs. Salbutamol deposition in all ACI groups with the AC + FV aVHC was equivalent to the reference AC + VHC. By contrast, deposition in ACI groups 1 to 3 with the CSC+, IC and OCD aVHCs was inequivalent to (approximately half that of) the reference VHC. Inter-device variability for each VHC type was greatest for the IC and least for the AC + VHC and AC + FV aVHC. **Conclusions:** The performance of VHCs that superficially resemble one another may differ markedly. Thus, as implied by EMA guidelines, VHCs should not automatically be considered to be interchangeable.

### A REVIEW OF THE *IN VITRO* AND *IN VIVO* VALVED HOLDING CHAMBER (VHC) LITERATURE WITH A FOCUS ON THE AEROCHAMBER PLUS FLOW-VU ANTI-STATIC VHC.

Dissanayake S, Suggett J. *Ther Adv Respir Dis.* 2018, Vol. 12: 1-14

Valved holding chambers (VHCs) reduce the need for inhalation-actuation coordination with pressurized metered dose inhalers (pMDIs), reduce oropharyngeal drug deposition and may improve lung deposition and clinical outcomes compared to pMDIs used alone. While VHCs are thus widely advocated for use in vulnerable patient groups within clinical and regulatory guidelines, there is less consensus as to whether the performance differences between different VHCs have clinical implications. This review evaluates the VHC literature, in particular the data pertaining to large- versus small-volume chambers, aerosol performance with a VHC adjunct versus a pMDI alone, charge dissipative/conducting versus non-conducting VHCs, and facemasks, to ascertain whether potentially meaningful differences between VHCs exist. Inconsistencies in the literature are examined and explained, and relationships between *in vitro* and *in vivo* data are discussed. A particular focus of this review is the AeroChamber Plus® Flow-Vu® Anti-static VHC, the most recent iteration of the AeroChamber® VHC family.

### NEW EQUIVALENCE EVALUATION OF VALVED HOLDING CHAMBERS (VHCS) WITH ALBUTEROL PRESSURIZED METERED DOSE INHALER (PMDI).

Nagel M, Suggett J, Kushnarev V, McIvor RA. *CSACI Annual Scientific Meeting, October 2017.*

**Background:** VHCs are medical devices that are recommended by Asthma and COPD guidelines to be used with pMDI as a delivery system. VHCs improve medication delivery and reduce oropharyngeal deposition of medication; this is reflected in the fine particles mass (FPM, 1.1-4.7µm) that reaches the airways of the lungs. The significant role of the VHC in drug delivery was acknowledged by the European Medicines Agency (EMA) in their recommendation that pMDI manufacturers should nominate at least 1 named VHC during clinical safety and efficacy studies. It also recommends if a VHC is to be substituted by an alternative VHC, that appropriate *in vitro* methods be employed to demonstrate equivalence. **Methods:** Particle size measurements from the Inspirachamber, Optichamber Diamond®, Space Chamber®, Vortex® and Life Brand VHCs (test devices) were compared to the AeroChamber Plus® Flow-Vu® Antistatic VHC (reference device) and made with an Andersen 8-stage cascade impactor operated at 28.3 L/min

with Ventolin®-HFA pMDIs. The EMA guideline requires comparisons to be performed by justified groupings of stages and recommends at least 4 groups based on physiological relevance. Since a traditional t-test is inappropriate to demonstrate true equivalence a two one-sided test (TOST) was used. **Results:** The values for each of the 5 test devices at each of the 4 particle size groupings were outside acceptance criteria for equivalence, thus clearly demonstrating non-equivalence to the reference device. **Conclusions:** The drug delivery performance from AeroChamber Plus® Flow-Vu® AVHC was significantly different to all test VHCs, none of which passed a test for equivalence. Interchanging of such VHCs with the reference VHC may therefore result in safety and/or efficacy implications unless otherwise proven via *in vivo* studies.

## **EQUIVALENCE EVALUATION OF VALVED HOLDING CHAMBERS (VHCS) WITH ALBUTEROL PRESSURIZED METERED DOSE INHALER (PMDI).**

*Nagel M, Suggett J. Respiratory Drug Delivery Europe 2017.*

**Introduction:** In 2009, the significant role of the VHC in drug delivery was acknowledged when the European Medicines Agency (EMA) recommended that development of a pMDI should include the testing of at least one named VHC. It was also recommended that if a VHC was to be substituted by an alternative VHC, appropriate pharmacopeial *in vitro* methods must be presented that take into account clinically relevant factors such as time delays between pMDI actuation and sampling. If these experiments could not demonstrate equivalence, then a determination of equivalency via clinical development would be required. This article presents an experimental demonstration of an equivalency evaluation between several commercially available VHCs. **Materials and Methods:** The following VHCs, each with mouthpiece as patient interface ( $n=20$  devices/group) were evaluated: AeroChamber Plus® VHC (Trudell Medical International) (REFERENCE); AeroChamber Plus® Flow-Vu® Anti-static VHC (Trudell Medical International); OptiChamber Diamond<sup>†</sup> Anti-Static VHC (Philips Respironics Inc.); InspiraChamber<sup>†</sup> Anti-Static VHC (Lupin Pharmaceuticals, Inc.); Compact Space Chamber Plus<sup>†</sup> Anti-Static VHC (Medical Developments). **Discussion and Conclusion:** This *in vitro* equivalence study was performed using a recognized analytical test methodology and an appropriate statistical test for equivalence, as opposed to incorrectly testing a hypothesis of difference/no difference or making non-statistically-based subjective judgments. When using the AeroChamber Plus® as the REFERENCE VHC, results showed that only one TEST VHC, the AeroChamber Plus® FV, was statistically equivalent to it. All other test VHCs did not meet the acceptance criteria in any of the four defined groupings. This finding may not be so surprising, given that the two equivalent chambers are of the same size and design, other than anti-static properties out of package. However, it does highlight the impact of differences in VHC design (size, shape, valves, etc.) upon drug delivery, and therefore the potential risk of interchanging VHCs without understanding the impact of doing so.

## **EQUIVALENT ASTHMA CONTROL WHEN INFANTS WITH ASTHMA USE TWO DIFFERENT VERSIONS OF THE AEROCHAMBER PLUS® SPACER**

*Chrystyn H, Ammari WG, Chetcuti P, Toor S. Am J Respir Crit Care Med 2013; 187:A4574.*

The AeroChamber Plus® Spacer (Trudell Medical International, Canada) [AC] has recently been adapted to include a visual indicator that confirms the inhalation phase during use (AeroChamber Plus® Flow-Vu®; Trudell Medical International, Canada) [FV]. Movement of the indicator also confirms the required seal between the mask and the user's face. The asthma control of infants with asthma, aged <5 years, during routine use of these spacers has been compared and patient preference has been obtained. Ethical approval was obtained and all infants and their parents gave signed informed consent. All infants entered a 2 week run-in period using the AC. At visit 2 they were randomized to the AC or FV for the 12 week duration of this study. They returned after 6 and 12 weeks (visits 3 and 4). All infants were trained to use a gentle tidal breathing routine with their spacer. At each visit their asthma quality of life (ACQ; Juniper *et al*, *Eur Respir J*, 1996) was obtained by questioning each parent and their inhalation flow (IFR) was measured using the IN-Check Dial (Clement Clark International, UK). At visit 4 each FV parent was asked to rate their preference for the FV using a 5 point Likert scale (5=much better to 1=much worse). The FV was demonstrated to all AC parents and they were then asked the same preference rating. At visit 1 the mean (SD) age of the AC ( $n=38$ ) and FV ( $n=38$ ) infants was 3.3 (1.1) and 2.8 (0.9) years, respectively. A summary of the ACQ and IFR is presented in Table 1.

**Table 1. Mean (SD) ACQ and IFR data**

Visit	ACQ		IFR (L/min)	
	AC	FV	AC	FV
1	1.83 (0.88)	1.85 (0.91)	40.1 (16.4)	39.1 (11.0)
2	1.56 (0.91)	1.81 (0.87)	40.6 (14.8)	37.5 (11.6)
3	1.77 (1.16)	1.54 (1.07)	41.1 (15.7)	38.8 (10.8)
4	1.29 (0.90)	1.62 (0.92)	40.1 (16.0)	28.9 (10.8)

Two-way analysis of variance revealed no difference in the ACQ or the IFR between the visits and the two groups. Patient preference is shown in Table 2.

**Table 2. Parent preference for FV (5 = much better, 1 = much worse)**

	Likert Scale Rating				
	5	4	3	2	1
FV	21	11	6	0	0
AC	24	10	4	0	0

There was no difference in asthma control and IFR between the two groups suggesting that the Flow-Vu® did not affect drug delivery, therefore demonstrating clinical equivalency. Overall the IFR values were the required slow flows suggesting that the infants and their parents had retained the clinic training about the use of the spacer. This reflects the lack of any difference in asthma control between the two groups. Despite correct use of the AC in this group all parents preferred FV because it provides them with the reassurance that the correct inhalation procedure is performed and that their child has received their inhaled medication.

#### **FLO-VU® INDICATOR IN VALVED HOLDING CHAMBER FOR PEDIATRIC ASTHMA.**

*Baig M, Smith D, Kasmani S, Lichenstein R. American Academy of Pediatrics National Conference. Oct 26-29, 2013. Orlando, FL.*

**Purpose:** We sought to determine parent preferences and patient outcomes to chronic pediatric asthmatics using either valved holding chamber (VHC): Aerochamber Plus® (AC) or AC with Flow Vu® indicator (ACF) regarding preference and outcomes of Emergency Department (ED) visits and hospitalizations. **Methods:** This is a pilot prospective randomized controlled trial of chronic pediatric asthmatics on inhaled corticosteroids that were assigned and educated on AC or ACF. Parents were instructed by nurses and interviewed by research assistants blinded on device assignment. Parents were contacted at day 3-5, 30 and 90 and were questioned on preference using a modification of the Patient Satisfaction and Preference Questionnaire (PASPQ) using the domains of overall performance and satisfaction, the Asthma Control Test (ACT) at 30, 60, and 90 days and an overall open ended question of preference ranked from 0-100. ED visits and hospitalizations were also reviewed during the study period. The ACF was compared to the AC at day 0 and day 90 for ACT score, preference score and PASPQ score using student's t test (two tailed, unpaired). The day 0 to day 90 scores (for PASPQ and ACT) were compared within the ACF and AC groups using student's t test (two tailed, paired). ACT scores were adjusted to a % that just took into account the patient's age. Demographics of the AC and ACF groups were compared using students t test. **Results:** There were 48 patients who were assigned to ACF and 38 to AC. The mean age overall was 6.8 years, 61% of the study population was male, and there were no differences between age, sex race, ED visits and hospitalizations in the 2 groups. Both the ACF and AC group had PASPQ scores that improved significantly over the course of the study. There was no difference between spacer type PASPQ scores at either time point. Both the ACF and AC group had preference scores that were significantly higher over time. The ACF spacer had a higher preference score than the AC spacer. Both the ACF and AC group had asthma control scores that improved significantly over time. At day 0, the ACF group had worse control than the AC group. This difference was gone by day 90. **Conclusion:** VHCs are important adjuncts in pediatric asthma therapy that are well accepted. Both types of VHC were associated with good asthma control over time. A visual indicator for inhalation was associated with improved patient satisfaction, which may have implications for compliance.

## DEVELOPING A “UNIVERSAL” VALVED HOLDING CHAMBER (VHC) PLATFORM WITH ADDED PATIENT BENEFITS WHILST MAINTAINING CONSISTENT *IN VITRO* PERFORMANCE.

Mitchell JP, Nagel MW, MacKay HA, Avvakoumova VA, Malpass J. *Respiratory Drug Delivery-Europe 2009, Eds., R.N. Dalby, P.R. Byron, J. Peart, J.D. Suman and P.M. Young, Davis Healthcare International Publishing LLC, River Grove, Illinois, USA: 2009, 383-386.*

**Introduction:** Crompton et al. recently observed that inhalers which provide reassurance to patients and their health care providers that inhalation is performed correctly should help improve patient compliance and control (1). As a result of such concerns, more attention is being paid the incorporation of attributes into inhalers that assist the user in achieving both optimum compliance and consistent medication delivery (2,3). A progression of such changes with the AeroChamber Plus® (AC-Plus) VHC with mouthpiece (Trudell Medical International, London, Canada), has resulted in three variants being available depending on market needs and the local regulatory environment. These are: 1. the non-conducting AC-Plus, 2. the non-conducting AC-Plus with Flow-Vu® Inspiratory Flow Indicator (IFI) 3. the anti-static (charge dissipative) AC-Plus with IFI. The present study was undertaken to provide users with indicative *in vitro* performance data based on 8 different hydrofluoroalkane-based formulations that are currently available and which may be prescribed for use with these VHCs. **Materials and Methods:** All measurements ( $n=5$  VHCs/group) were made using an Andersen 8-stage cascade impactor equipped with USP/Ph.Eur. induction port and operated at 28.3 L/min  $\pm$  5%. The non-conducting variants were pre-treated in accordance with manufacturer instructions, thus ensuring that electrostatic charge was not a confounding factor. The anti-static VHCs were evaluated out-of-package, also to instructions. Measurements were made with no delay between pMDI actuation and the onset of sampling, and repeated with new devices, introducing a 2-s delay by means of a proprietary apparatus (4). The latter condition simulated use by an uncoordinated patient (5) in accordance with the Canadian standard for spacers and VHCs (6). The formulations evaluated are listed in Table 1. Recovery and assay for collected API was in each case undertaken by validated HPLC-UV spectrophotometric or fluorescence-based techniques.

Trade Name, manufacturer	Active Pharmaceutical Ingredient (API)	Label claim mass/actuation ex metering valve (ug)
Advair <sup>†</sup> , (GSK)	fluticasone propionate (FP)	50
	salmeterol xinafoate (SX)	25
Alvesco <sup>†</sup> , Nycomed	ciclesonide	100
Atrovent <sup>†</sup> , Boehringer Ingelheim	ipratropium bromide	20
Clenil <sup>†</sup> , Trinity Chiesi	beclomethasone dipropionate	100
Flovent HFA <sup>†</sup> , GSK	fluticasone propionate	125
Qvar <sup>†</sup> , TEVA	beclomethasone dipropionate	100
Symbicort <sup>†</sup> , AstraZeneca	budesonide (BUD)	80
	formoterol fumarate (FF)	4.5
Ventolin HFA <sup>†</sup> , GSK	salbutamol (base equivalent)	100

**Results:** Values of total emitted mass/actuation (TEM) and fine particle mass < 4.7  $\mu$ m aerodynamic diameter/actuation (FPD<4.7 $\mu$ m), are summarized in Tables 2 and 3 respectively. FPD<4.7 $\mu$ m was selected as the metric most appropriate to define the portion of TEM likely to deposit beyond the oropharynx. Equivalent values determined in parallel experiments for the pMDI alone (no delay) are provided as benchmark data. The addition of any of the VHC variants resulted in a large reduction in TEM compared with the pMDI alone, as the result of the removal of most of the coarse fraction. The three AC-Plus VHC variants provided substantially equivalent values of TEM and FPM<4.7 $\mu$ m at each delay condition. This outcome was anticipated as the IFI is an external visual feedback aid and does not interfere with the aerosol pathway within the VHC. FPM<4.7 $\mu$ m value(s) ex VHC with 2-s delay were within  $\pm$ 25% of the equivalent benchmark data from the pMDI alone.

**Total emitted mass / actuation (mean ± SD) for pMDI with and without AC-PLUS VHC variants**

	pMDI alone	Non conducting AeroChamber Plus® VHC		Non conducting AeroChamber Plus® VHC with Flow-Vu® Indicator		Anti-Static AeroChamber Plus® VHC with Flow-Vu® Indicator	
		0	2	0	2	0	2
Delay (s)	0	0	2	0	2	0	2
Advair (FP)	36.0 ± 1.9	29.6 ± 1.6	21.7 ± 2.3	25.7 ± 1.9	19.2 ± 2.3	26.6 ± 1.4	19.2 ± 1.2
Advair (SX)	17.9 ± 1.4	15.3 ± 0.9	12.0 ± 1.1	13.9 ± 0.7	10.2 ± 0.9	15.0 ± 1.0	10.4 ± 0.6
Alvesco	68.2 ± 2.6	68.2 ± 2.7	56.6 ± 2.6	64.9 ± 3.1	50.3 ± 3.0	68.3 ± 1.8	51.5 ± 3.9
Atrovent	15.8 ± 0.7	10.7 ± 0.2	8.2 ± 0.8	10.7 ± 0.7	8.3 ± 0.5	9.3 ± 0.3	8.1 ± 0.4
Clenil	94.0 ± 1.7	53.5 ± 3.4	40.2 ± 2.6	54.4 ± 1.6	42.0 ± 1.5	54.6 ± 1.8	39.1 ± 3.1
Flovent HFA	107.4 ± 3.4	72.3 ± 2.7	51.5 ± 1.5	67.0 ± 3.2	61.2 ± 5.4	68.3 ± 3.1	41.0 ± 1.8
Qvar	78.0 ± 3.1	69.4 ± 4.8	44.5 ± 6.8	73.6 ± 3.2	52.2 ± 3.8	65.4 ± 4.5	44.4 ± 4.5
Symbicort (BUD)	78.8 ± 1.4	61.6 ± 2.9	53.4 ± 2.5	62.2 ± 3.1	52.0 ± 1.9	61.3 ± 2.7	48.5 ± 1.3
Symbicort (FF)	4.0 ± 0.1	3.5 ± 0.2	3.0 ± 0.2	3.3 ± 0.1	2.8 ± 0.1	3.6 ± 0.3	2.8 ± 0.1
Ventolin HFA	76.8 ± 1.8	53.6 ± 5.0	38.8 ± 2.1	46.8 ± 4.0	32.6 ± 2.3	55.2 ± 3.8	35.3 ± 3.9

**FPM<4.7µm (mean ± SD) for pMDI with and without AC-PLUS VHC variants**

	pMDI alone	Non conducting AeroChamber Plus® VHC		Non conducting AeroChamber Plus® VHC with Flow-Vu® Indicator		Anti-Static AeroChamber Plus® VHC with Flow-Vu® Indicator	
		0	2	0	2	0	2
Delay (s)	0	0	2	0	2	0	2
Advair (FP)	17.4 ± 2.1	26.6 ± 1.4	20.4 ± 1.8	23.0 ± 1.9	18.2 ± 2.3	23.7 ± 1.4	18.1 ± 1.3
Advair (SX)	8.9 ± 1.3	13.9 ± 0.9	11.1 ± 1.0	12.2 ± 0.8	9.6 ± 0.9	13.7 ± 1.0	9.9 ± 0.6
Alvesco	42.4 ± 3.8	68.1 ± 2.8	56.5 ± 2.6	64.5 ± 3.1	50.3 ± 3.0	68.2 ± 1.8	51.5 ± 3.9
Atrovent	6.7 ± 0.4	10.0 ± 0.2	8.1 ± 0.8	9.8 ± 0.8	8.2 ± 0.5	9.2 ± 0.3	8.0 ± 0.4
Clenil	30.9 ± 1.6	45.0 ± 2.3	33.2 ± 1.0	46.1 ± 1.7	35.4 ± 0.7	45.0 ± 1.9	33.7 ± 1.6
Flovent HFA	46.2 ± 2.1	64.6 ± 3.0	47.3 ± 1.5	59.9 ± 2.5	56.9 ± 4.9	62.1 ± 3.8	38.8 ± 1.7
Qvar	41.9 ± 2.2	67.2 ± 5.8	44.4 ± 6.9	71.6 ± 3.5	52.0 ± 3.7	63.1 ± 6.0	44.4 ± 4.5
Symbicort (BUD)	43.2 ± 1.8	48.6 ± 2.2	42.0 ± 2.4	48.2 ± 2.9	39.9 ± 1.1	50.6 ± 2.3	41.1 ± 0.9
Symbicort (FF)	2.7 ± 0.2	3.1 ± 0.2	2.6 ± 0.2	3.0 ± 0.1	2.5 ± 0.1	3.2 ± 0.2	2.5 ± 0.1
Ventolin HFA	34.8 ± 1.4	48.6 ± 4.6	36.3 ± 1.8	42.3 ± 3.4	30.9 ± 2.9	49.5 ± 3.0	33.2 ± 3.3

**Conclusions:** Two recent improvements made to the AC-Plus VHC to mitigate electrostatic charge and provide visual feedback to users have not affected *in vitro* performance compared with the original device. These devices also provide comparable delivery of fine particles to the pMDI alone in the likelihood that the user delays inhalation after actuating their inhaler.



## Importance of Flow-Vu® Inhalation Indicator

### **The Flow-Vu® Inhalation Indicator is a valuable feedback tool**

Parents stated that with the **Flow-Vu®** Inhalation Indicator they could tell that their children were actually taking their puff. The novel **Flow-Vu®** Indicator provided visual feedback to the parents, reassuring them of sufficient therapy inhaled by their infants. Moreover, the indicator's movement enabled the parents to count the number of breaths taken by their children as per their healthcare providers' recommendation. The visual drug delivery reassurance, might justify the significant improvement in the quality of life of the parents. (Ammari et al. *Evaluation of asthma control, parents' quality of life and preference between AeroChamber Plus® and AeroChamber Plus® Flow-Vu® spacers in young children with asthma*. Journal of Asthma October 2014)

A visual indicator for inhalation was associated with improved patient satisfaction, which may have implications for compliance. (Baig M et al. *Flow-Vu Indicator in Valved Holding Chamber for Pediatric Asthma*. American Academy of Pediatrics Conference 2013)

The **Flow-Vu®** Indicator prevents the potential for large losses of medication due to facemask-to-face leakage, by guiding the caregiver or patient to seat the facemask on the face correctly - and at the same time, it indicates the optimum timing for inhaler actuation. (Michell JP et al. *Letter to the Editors: Improving the odds that patients and caregivers will use inhalers correctly: a manufacturer's response*. Prim Care Respir J 2011; 20(2):219-220)

### **A number of researchers highlight the importance of a feedback mechanism on aerosol delivery devices.**

Practical technology for patients to self-assess technique would be of value (e.g. a feedback mechanism built into the inhaler device to confirm correct inhalation). (Papi A et al. *Inhaler devices for asthma: a call for action in a neglected field*. Eur Respir J 2011;37:982-985)

It is important that feedback be provided to the patient or caregiver to confirm they are operating each device correctly. Steps critical to successful drug delivery should be a particular focus, such as ensuring a facemask seal to the face during use of a pMDI-valved holding chamber. (Mitchell JP et al. *Developing Patient-Friendly Devices for Inhalation Therapy*. Respiratory Drug Delivery Europe 2011:463-467)

Providing devices that are quick and easy to use effectively is a basic requirement for future devices, while some form of feedback does appear to have an impact on both regimen compliance and device delivery. (Everard ML. *Playing the Game: Designing Inhalers for Pediatric Use*. Respiratory Drug Delivery Europe 2007: 71-78)

Devices which provide reassurance to patients and their physicians that inhalation is performed correctly should help to improve patient compliance and asthma control. (Crompton GK et al. *The need to improve inhalation technique in Europe: A report from the Aerosol Drug Management Improvement Team*. Respiratory Medicine 2006;100:1479-1494)

Devices should be easy to use and incorporate multiple feedback mechanisms which reassure the patient that medication has been delivered. (Barnes P et al. *Asthma Management: important issues*. European Respiratory Review 2005;14,(97)147-151)

## **EVALUATION OF ASTHMA CONTROL, PARENTS' QUALITY OF LIFE AND PREFERENCE BETWEEN AEROCHAMBER PLUS® AND AEROCHAMBER PLUS® FLOW-VU® SPACERS IN YOUNG CHILDREN WITH ASTHMA.**

Ammari WG, Toor S, Chetcuti P, Stephenson J, Chrystyn H. *Journal of Asthma Vol 52;3,2015.*

**Objective:** The AeroChamber Plus® (AC) valved holding chamber has been enhanced to include the Flow-Vu (FV) inspiratory flow indicator that provides visual inhalation feedback during use. We have investigated if FV alters asthma control and whether parents accept it. **Methods:** At visit 1, children with asthma, age 1-5 years, used an AC with their pressurized metered dose inhaler and 2 weeks later (visit 2) they were randomized to use either AC or FV. Subjects returned 6 (visit 3) and 12 (visit 4) weeks later. The Asthma Control (ACQ) and Pediatric Asthma

Caregiver's Quality of Life (PACQLQ) questionnaires were scored at each visit, and their peak inhalation flow (PIF) when they used their spacer was measured. **Results:** Forty participants in each group completed the study. There was no difference in the ACQ scores from visits 2 to 4 between the two groups. The improvements in the PACQLQ scores were greater in the FV group ( $p=0.029$ ). The mean difference (95% confidence interval) for the change from visits 2 to 4 between FV and AC groups was 0.05 (-0.33, 0.43) and 0.39 (0.035, 0.737) for the ACQ and PACQLQ, respectively. Most parents preferred the FV ( $p<0.001$ ). There was no difference in the PIF rates at each visit and between the two spacers. **Conclusions:** There was no change in asthma control of the young children but that of their parents improved. Parents preferred the FV and this could be related to their improved perception of their children's asthma control by better PACQLQ scores.

#### **FLOW-VU® INDICATOR IN VALVED HOLDING CHAMBER FOR PEDIATRIC ASTHMA.**

Baig M, Smith D, Kasmani S, Lichenstein R. *American Academy of Pediatrics National Conference. Oct 26-29, 2013. Orlando, FL.*

**Purpose:** We sought to determine parent preferences and patient outcomes to chronic pediatric asthmatics using either valved holding chamber (VHC): AeroChamber Plus® (AC) or AC with Flow Vu® indicator (ACF) regarding preference and outcomes of Emergency Department (ED) visits and hospitalizations. **Methods:** This is a pilot prospective randomized controlled trial of chronic pediatric asthmatics on inhaled corticosteroids that were assigned and educated on AC or ACF. Parents were instructed by nurses and interviewed by research assistants blinded on device assignment. Parents were contacted at day 3-5, 30 and 90 and were questioned on preference using a modification of the Patient Satisfaction and Preference Questionnaire (PASPQ) using the domains of overall performance and satisfaction, the Asthma Control Test (ACT) at 30, 60, and 90 days and an overall open ended question of preference ranked from 0-100. ED visits and hospitalizations were also reviewed during the study period. The ACF was compared to the AC at day 0 and day 90 for ACT score, preference score and PASPQ score using student's t test (two tailed, unpaired). The day 0 to day 90 scores (for PASPQ and ACT) were compared within the ACF and AC groups using student's t test (two tailed, paired). ACT scores were adjusted to a % that just took into account the patient's age. Demographics of the AC and ACF groups were compared using students t test. **Results:** There were 48 patients who were assigned to ACF and 38 to AC. The mean age overall was 6.8 years, 61% of the study population was male, and there were no differences between age, sex race, ED visits and hospitalizations in the 2 groups. Both the ACF and AC group had PASPQ scores that improved significantly over the course of the study. There was no difference between spacer type PASPQ scores at either time point. Both the ACF and AC group had preference scores that were significantly higher over time. The ACF spacer had a higher preference score than the AC spacer. Both the ACF and AC group had asthma control scores that improved significantly over time. At day 0, the ACF group had worse control than the AC group. This difference was gone by day 90. **Conclusion:** VHCs are important adjuncts in pediatric asthma therapy that are well accepted. Both types of VHC were associated with good asthma control over time. A visual indicator for inhalation was associated with improved patient satisfaction, which may have implications for compliance.

#### **IMPORTANCE OF PATIENT-FRIENDLY FEATURES TO ADDRESS LACK OF INHALER COMPLIANCE: A LABORATORY EVALUATION OF AN INSPIRATORY FLOW INDICATOR AS A FEEDBACK AID FOR A VALVED HOLDING CHAMBER.**

Mitchell J, Nagel M, Malpass J. *Journal of Aerosol Medicine and Pulmonary Drug Delivery 2011; 24(3):46(P-075).*

**Purpose:** Poor inhaler compliance is recognized as needing to be addressed. The Flow-Vu® Inspiratory Flow Indicator (IFI) is a feedback aid for those using the AeroChamber Plus® Flow-Vu® Anti-Static VHC (Trudell Medical Inc., London, Ontario). Regulators require that the modification does not affect delivery of the therapeutically beneficial fine particle dose  $< 4.7 \mu\text{m}$  diameter from the inhaler. **Methods:** Measurements ( $n=5$  VHCs/group) of fine particle mass for salbutamol (100  $\mu\text{g}$ /actuation) were made using an Andersen 8-stage impactor equipped with Ph.Eur. induction port and operated at 28.3 L/min. Data were obtained for the pMDI alone and for the pMDI +VHC (2-second delay), simulating poor coordination. The movement of the IFI monitored airflow through the VHC and a proper seal of the mouthpiece in the apparatus. The VHCs were tested out-of package in accordance with instructions. Recovery and assay for salbutamol was undertaken by HPLC-UV spectrophotometry. **Results:** Fine particle mass/actuation ( $\text{FPM}_{2.5}$ ) for pMDI alone (mean $\pm$ SD) was  $34.8 \pm 1.4 \mu\text{g}$ , compared with  $33.2 \pm 3.3 \mu\text{g}$ /actuation for the pMDI +VHC group. The IFI moved from the inhalation valve closed to open position immediately upon initiation of sampling. **Conclusions:**

The IFI provided feedback on the delivery of this widely prescribed 'rescue' medication and did not interfere with the new VHC, delivering substantially comparable FPM<sub>25</sub> to that from the pMDI alone. It should therefore aid patient compliance.

**COMPARISON OF THE AEROCHAMBER PLUS® PLUS SPACER TO THE AEROCHAMBER PLUS® WITH FLOW-VU® SPACER IN CHILDREN WITH ASTHMA AGED < 5 YEARS.**

Chrystyn H, Ammari W, Chetcuti P, Lee T. Proc. 20<sup>th</sup> ERS Annual Congress, Barcelona, Spain, in *Eur Respir J* 2010;36S54:P2024.

The AeroChamber Plus® with Flow-Vu® (FV) is a new version of the AeroChamber Plus® Spacer (AC). The only difference is that FV has a caregiver feedback mechanism that provides a visual indicator whose movement confirms correct inhalation technique and a secure seal between the facemask and the face. The latter is a critical factor in aerosol drug delivery to infants and children (Amirav *et al.*, 2008). After a run-in period of 2 weeks children <5 years with uncontrolled or partially controlled asthma (GINA Guidelines) were randomized to receive their medication using either AC (n=9) or FV (n=10). Ethical approval was obtained and all children and their parents gave signed consent. Each parent completed the first 6 questions of the asthma control questionnaire (Juniper *et al.*, 1999) on behalf of their child and the Pediatric Asthma Caregiver's Quality of Life Questionnaire (Juniper *et al.*, 1996) at 0, 6 and 12 weeks. The use of either AC or FV, with proper training, resulted in good asthma control. At the end of the study the FV group parents were asked to rank their preference compared to the AC whilst the FV was demonstrated to the AC group and the parents were asked about the 2 spacers. There was a clear preference among both groups for the FV device.

Group	FV Preference				
	Much Better	Better	No Difference	Worse	Much Worse
FV	5	3	2	0	0
AC	6	2	2	0	0

The FV and AC provide similar asthma control but the Flow-Vu® feature was preferred by parents. Devices which provide reassurance to patients and their physicians that inhalation is performed correctly should help to improve patient compliance and asthma control (Crompton *et al.*, 2006).

**A VISUAL INDICATOR FOR INHALATION FROM A VALVED HOLDING CHAMBER IS AN AID IN DELIVERY OF INHALED MEDICATION TO INFANTS AND SMALL CHILDREN VIA FACEMASK.**

Mitchell JP, Doyle C, Ali R, Avvakoumova V, Nagel M, Sharpe R. *Eur Respir J* 2009;34(S53)P2044.

Delivery of inhaled medication to infants/small children by VHC-facemask can be difficult to verify. An external visual aid (Flow-Vu®) is available with the AeroChamber Plus® (Trudell Medical International) VHCs as an inspiratory flow indicator (IFI) to aid compliance with instructions for use. We report an *in vitro* study in which delivery of salbutamol (Ventolin®; 100µg/actuation, GSK plc) was measured using infant and child models (ADAM-II), in which the soft facial tissues are modeled where the facemask makes contact. The facemask was applied with an appropriate force of 1.6 kg, and tidal breathing was simulated (tidal volume (V<sub>T</sub>) 50 ml, 30 bpm, 25% duty cycle -VHC-infant facemask; V<sub>T</sub> = 155 ml; 25 bpm, 33% duty cycle - VHC-child facemask (n=5 devices/group)). Total emitted mass (TEM) of salbutamol was collected by filter located behind the lips after 1, 2, 3, 4 and 5 inhalations.

**TEM (mean SD; µg) for AeroChamber Plus® VHCs with Flow-Vu® IFI**

Number of Inhalations	1	2	3	4	5
Infant	5.8 ± 2.2	13.0 ± 4.0	13.8 ± 3.8	14.5 ± 3.2	15.6 ± 3.6
Child	15.9 ± 3.7	17.6 ± 4.6	20.1 ± 3.5	20.8 ± 2.9	22.6 ± 4.2

At least two inhalations were required to achieve consistent medication delivery from the VHC-infant facemask. The first inhalation was sufficient to achieve similar consistency with the VHC-child facemask. However, these tests were undertaken with a well-fitting facemask and no leakage. Manufacturer instructions indicate 5-inhalations be

taken as a precaution. The IFI validates an effective seal between facemask-face as well as confirms the number of inhalations, assisting in compliance with instructions.

### **A VISUAL INDICATOR FOR INHALATION FROM A VALVED HOLDING CHAMBER (VHC) IS AN IMPORTANT ATTRIBUTE WHEN DELIVERING INHALED MEDICATION TO INFANTS.**

*Mitchell JP, Avakoumova V, Mackay H, Ali R and Nagel M. J Aerosol Med Pulm Deliv 2009;22(3):289.*

Delivery of inhaled medication to infants by valved holding chamber (VHC) with facemask may require more than one inhalation to empty the VHC because tidal volumes are typically smaller than chamber capacity. This study investigated the correlation between movement of an integrated inspiratory flow indicator (IFI) as a caregiver feedback aid for a VHC-facemask, number of inhalations and mass of medication, simulating use by a 6-9 month infant (tidal volume ( $V_T$ ) = 50-ml; duty cycle = 25%; 30 cycles/min). Anti-static AeroChamber Plus® VHCs incorporating the IFI feature, with infant facemask ( $n=5$ /group, 3 replicates/device; Trudell Medical International, London, Canada) were coupled to a breathing simulator (ASL5000 test lung, IngMar Medical, Pittsburgh, PA, USA). The VHCs were prepared as per manufacturer instructions and the facemask of the device on test was fitted to the ADAM-II flexible infant face model with a clinically appropriate force of 1.6 kg. Aerosol capture took place using an electret filter positioned behind the lips of the face model. Delivery of medication was evaluated from two different pressurized metered dose inhaler formulations likely to be used with pediatric patients (Flovent HFA<sup>†</sup> 44; 44 µg fluticasone propionate (FP) delivered ex-actuator and Ventolin HFA<sup>†</sup>; 90 µg salbutamol base equivalent (SAL) delivered ex-actuator, both from GSK plc. One actuation was delivered to the VHC at the onset of inhalation, and the filter removed after 1 complete breathing cycle, observing the movement of the IFI to confirm inhalation valve opening. This procedure was subsequently repeated by removing the filter after 2, 3, 4, 5 and 6 breathing cycles. Assay for FP or SAL was undertaken by HPLC-UV spectrophotometry. During these measurements, the IFI of each device was observed to move in synchrony with valve opening on all occasions, confirming that the facemask sealed onto the face model without leakage of ambient air into the mask during the inspiratory phase of each breathing cycle. Emitted mass after the first breathing cycle (EM1) was  $2.1 \pm 0.7$  µg (FP) and  $5.8 \pm 2.2$  µg (SAL); substantially lower than the corresponding values after 6 cycles (EM6), being  $9.0 \pm 2.1$  µg (FP), and  $15.9 \pm 3.1$  µg (SAL) [paired ttest for each formulation;  $p < 0.001$ ]. After 2 breathing cycles, values of EM2 ( $6.9 \pm 2.0$  (FP) and  $13.0 \pm 4.0$  µg (SAL)), though significantly greater than their corresponding EM1 values [ $p \leq 0.002$ ], were still noticeably lower than the corresponding EM6 value for FP ( $p = 0.028$ ), and barely statistically insignificant for SAL ( $p = 0.063$ ). After 3 inhalations, EM3 increased further to  $7.6 \pm 2.0$  µg (FP) and  $13.8 \pm 3.8$  µg (SAL), and thereafter were close to the corresponding EM6 values, indicating emptying of the VHC had taken place. We conclude that at least two successive inhalations are required to achieve optimum medication delivery for the 'infant' condition under optimum conditions with a well fitted facemask with no leakage. The IFI is an important feature which validates that the facemask is properly sealed to the infant's face and also confirms the number of inhalations that take place, thereby optimizing the therapeutic dose. Clinical studies are recommended to evaluate the benefit of this aid for the delivery of inhaled medication by VHC to this age group.

## Influence of Anti-Static Chambers

### A COMPARATIVE ANALYSIS OF CHANGES IN PMDI DRUG DOSE DELIVERY BEFORE AND AFTER DETERGENT COATING USING FIVE ANTISTATIC VALVED HOLDING CHAMBERS.

Hagedoorn P, Wasiq Bawary, Frijlink HW, Grasmeyer F. *The Journal of Allergy and Clinical Immunology: In Practice*. Available online 5 October 2019.

Pressurized metered dose inhalers (pMDIs) are preferably to be used in combination with a spacer or valved holding chamber (VHC). Most notably, this reduces the impact of actuation-inhalation (“hand-lung”) coordination problems, and it lowers oropharyngeal deposition as smaller particles are presented to the patient at a lower velocity.<sup>1,2</sup> Spacers and VHCs may therefore improve compliance and reduce the chance of local and systemic side effects with the use of pMDIs. Although the use of spacers and VHCs is warranted by the advantages they offer, they also retain a notable fraction of the drug and hence lower the dose from a pMDI that is delivered to the patient. Moreover, not only differences in the size, shape, or construction material, but also differences in the cleaning and use of spacers and VHCs may greatly affect the delivered doses from these devices and limit their interchangeability.<sup>1</sup> This was recently illustrated in a comparison of 4 antistatic VHCs (aVHCs) by Dissanayake *et al.*<sup>3</sup> They showed that the fine particle dose from a salbutamol pMDI (Ventolin) may differ by up to a factor 2, even for VHCs that are comparable in size, shape, and (claimed) antistatic properties. Such significant performance differences between similar aVHCs complicate the drafting of generally applicable guidelines for their choice and use. For example, nonconducting spacers and VHCs can be made “antistatic” with a detergent coating (i.e., “primed”) by soaking them in a household detergent solution followed by drying to the air, also known as “drip-drying.”<sup>4</sup> This lowers drug retention in the VHCs caused by electrostatic attraction. Understandably, drip-drying is only advocated for nonconducting VHCs, whereas it is deemed unnecessary for aVHCs.<sup>2</sup> However, if the great performance differences between aVHCs are caused by differences in their antistatic properties, drip-drying may be advisable for some of these devices too. Furthermore, the performance differences may then depend on the type of drug or the PMDI being used, as drugs and their formulations may differ in their sensitivity to electrostatic charging. To test the supposition that all aVHCs are equally antistatic and do not need to be coated with a detergent by drip-drying, we determined the delivered doses of salbutamol (Ventolin 100 mg/dose label claim) and beclomethasone dipropionate (Qvar 100 mg/dose label claim) from the Aerochamber Plus® Flow-Vu® (AC+FV), the Compact Space Chamber Plus (CSCp), the InspiraChamber (IC), the OptiChamber Diamond (OCD), and the Vortex (Vortex); see Figures E1 and E2, and Table E1 (available in this article’s Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). These aVHCs were cleaned in a mild detergent solution and either rinsed with water (to test their intrinsic antistatic properties) or “drip-dried” (to test standardized antistatic properties) before every measurement. The “rinsing” method is the cleaning method advocated by aVHC manufacturers. More methodological details about the experiment are available in this article’s Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org). The “rinsing” method causes a difference in the delivered dose between the aVHCs of up to a factor 2, with the Vortex and AC+FV performing significantly better than the CSCp, IC, and OCD (Figure 1). Drip-drying particularly increases the delivered doses from the CSCp and the IC ( $.0003 < P < .06$ , Figure 1), which indicates that their antistatic properties are suboptimal. On the contrary, the antistatic properties of the AC+FV, OCD, and Vortex are optimal, as their delivered doses are minimally affected by drip-drying. The consistently lower delivered dose from the OCD than from the AC+FV and Vortex therefore must be the result of differences other than their antistatic properties, such as their size, shape, or valve functioning. It follows from these results that differences in antistatic properties are an important cause of the large performance differences between aVHCs. Therefore, the assumption that aVHCs do not require drip-drying to improve drug delivery does not hold true for all of these devices. Furthermore, drip-drying may greatly improve the interchangeability of aVHCs, as no significant differences in delivered dose between 4 of 5 aVHCs tested (AC+FV, CSCp, IC, and Vortex) were measured after drip-drying, whereas only 2 (AC+FV and Vortex, or CSCp and IC) performed similarly after rinsing. Therefore, as a general guideline, it seems appropriate to recommend drip-drying, even for aVHCs, or to at least discourage the switching between them. It should be noted that a similar delivered dose in this study may not equal full *in vitro* equivalence of the devices. For that, also the particle size distributions of the delivered doses have to be identical. It is worth pointing out in this regard that the Vortex does not result in a finer aerosol of beclomethasone than the pMDI alone, contrary to the other aVHCs (see Table E2, available in this article’s Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). This may result in a different deposition pattern. Patient factors will also affect the deposition pattern, and therefore, the clinical implications of the observed differences can only be determined by *in vivo* studies. Nevertheless, a lower delivered dose with an aVHC compared with a pMDI alone does not necessarily result in a

lower bioavailability,<sup>5,6</sup> as the lung deposition fraction may increase. The approximate 2-fold difference in delivered dose between salbutamol and beclomethasone when used with an aVHC can be explained by their different aerosol characteristics. The salbutamol pMDI has a higher plume velocity<sup>7</sup> and a larger median particle size of the aerosol than the beclomethasone pMDI (see Figure E3 and Table E2, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Both factors likely increase salbutamol particle deposition in the aVHCs by inertial impaction and sedimentation. The qualitative similarity of the results obtained with the different drugs (salbutamol and beclomethasone) from different pMDI types suggests that the findings from this study are generally applicable to other pMDIs. Despite differences in particle size distribution and aerosol plume velocity between salbutamol and beclomethasone, performance differences between the individual aVHCs remain largely the same. Also a different charging behavior of both drug products<sup>8</sup> does not affect the aVHC performance differences. The clinical benefit of spacers and VHCs is extensively discussed by others. Rather than doubting this benefit, health care workers should be aware of the far-reaching noninterchangeability of VHCs, including their antistatic counterparts. Although this noninterchangeability of VHCs is well recognized,<sup>1,2</sup> aVHCs are often considered a homogeneous, interchangeable group of devices. However, this study shows that the antistatic properties of some aVHCs, such as the CSCp and IC, are suboptimal to such an extent that they are rather to be used as ordinary nonconducting VHCs instead, and that switching between aVHCs should be discouraged.

## ARE VALVED HOLDING CHAMBERS (VHCS) INTERCHANGEABLE? AN IN VITRO EVALUATION OF VHC EQUIVALENCE

S Dissanayake, M Nagel, E Falaschetti, J Suggett. *Pulmonary Pharmacology & Therapeutics* 2018;48:179-184.

**Introduction:** The European Medicines Agency (EMA) requires that a specific valved holding chamber (VHC) is designated for use with a given pressurised metered dose inhaler (pMDI). No other regulatory authorities impose similar requirements, implying that VHCs are interchangeable. This *in vitro* study, employing EMA assessment criteria, assessed the equivalence of four anti-static VHCs (aVHCs) versus the non-conducting VHC most widely referenced in pMDI monographs, the AeroChamber Plus™ (AC+) VHC. **Material & Methods:** The “reference” AC + VHC was prepared by soaking in detergent solution. The four test aVHCs (AeroChamber Plus™ Flow-Vu™ [AC+V]; Compact Space Chamber Plus [CSC+]; InspiraChamber [IC]; OptiChamber Diamond™ [OCD]) were tested “out-of-pocket”. Twenty devices of each type were evaluated. A salbutamol pMDI was actuated into each VHC with a 2-s delay between actuation and Andersen Cascade Impactor (ACI) sampling. Drug deposition in four ACI particle size groups was assessed: Group 1, >5.8–10 µm; Group 2, >3.3–5.8 µm; Group 3, >1.1–3.3 µm; Group 4, ≤1.1 µm. Equivalence versus the reference VHC was demonstrated where the 90% confidence interval for the test/reference mass ratio was within 85–118%. **Results:** The mass retained within the VHC was similar for the AC + VHC and AC + FV aVHC, but was approximately twice as great for the other aVHCs. Salbutamol deposition in all ACI groups with the AC + FV aVHC was equivalent to the reference AC + VHC. By contrast, deposition in ACI groups 1 to 3 with the CSC+, IC and OCD aVHCs was inequivalent to (approximately half that of) the reference VHC. Inter-device variability for each VHC type was greatest for the IC and least for the AC + VHC and AC + FV aVHC. **Conclusions:** The performance of VHCs that superficially resemble one another may differ markedly. Thus, as implied by EMA guidelines, VHCs should not automatically be considered to be interchangeable.

## A REVIEW OF THE *IN VITRO* AND *IN VIVO* VALVED HOLDING CHAMBER (VHC) LITERATURE WITH A FOCUS ON THE AEROCHAMBER PLUS FLOW-VU ANTI-STATIC VHC

S Dissanayake, J Suggett. *Therapeutic Advances in Respiratory Disease* 2018;12:1-14.

**Abstract:** Valved holding chambers (VHCs) reduce the need for inhalation-actuation coordination with pressurized metered dose inhalers (pMDIs), reduce oropharyngeal drug deposition and may improve lung deposition and clinical outcomes compared to pMDIs used alone. While VHCs are thus widely advocated for use in vulnerable patient groups within clinical and regulatory guidelines, there is less consensus as to whether the performance differences between different VHCs have clinical implications. This review evaluates the VHC literature, in particular the data pertaining to large- versus small-volume chambers, aerosol performance with a VHC adjunct versus a pMDI alone, charge dissipative/conducting versus non-conducting VHCs, and facemasks, to ascertain whether potentially meaningful differences between VHCs exist. Inconsistencies in the literature are examined and explained, and relationships between *in vitro* and *in vivo* data are discussed. A particular focus of this review is the AeroChamber Plus® Flow-Vu® Anti-static VHC, the most recent iteration of the AeroChamber VHC family.

## A RETROSPECTIVE STUDY OF THE EFFECTIVENESS OF THE AEROCHAMBER PLUS® FLOW-VU® ANTISTATIC VALVED HOLDING CHAMBER FOR ASTHMA CONTROL.

Burudpakdee C, Kushnarev V, Coppolo D, Suggett J. *Pulm Ther* (2017). <https://doi.org/10.1007/s41030-017-0047-1>.

**Introduction:** Electrostatic charge in valved holding chambers (VHCs) may lead to inconsistent metered-dose inhaler (MDI) asthma drug delivery. We compared the AeroChamber Plus® Flow Vu® Antistatic Valved Holding Chamber (AC+FV AVHC) with non-antistatic control VHCs in terms of asthma exacerbations, resource use, and cost in an asthma population. **Methods:** Patients included in an adjudicated claims database with AC+FV AVHC or non-antistatic VHC (control VHC) use between 1/2010 and 8/2015 (index) who were treated with an inhaled corticosteroid (ICS) or a combination of an ICS and a long-acting  $\beta$ 2 agonist MDI within 60 days before or after the index date, were diagnosed with asthma, and had  $\geq 12$  months of pre- and  $\geq 30$  days of post-index health plan enrollment were included. Cohorts were matched 1:1 using propensity scores. We compared incidence rates (IR) of exacerbation, time to first exacerbation using Kaplan-Meier survival analysis, occurrence of exacerbations, and healthcare resource use and costs using generalized linear models. **Results:** 9325 patients in each cohort were identified. The IR of exacerbations per 100 person-days (95% CI) was significantly higher in the control VHC cohort than the AC+FV AVHC cohort [0.161 (0.150–0.172) vs. 0.137 (0.128–0.147)]. A higher proportion of exacerbation-free patients was observed in the AC+FV AVHC cohort. Among the 4293 patients in each cohort with  $\geq 12$  months of follow-up, AC+FV AVHC patients were found to be 10–12% less likely than control VHC patients to experience an exacerbation throughout the study period. A lower proportion of the AC+FV AVHC patients had an ED visit compared to the control VHC patients (10.8% vs. 12.4%). Exacerbation-related costs for the AC+FV AVHC cohort were 23%, 25%, 20%, and 12% lower than those for the control VHC cohort at 1, 6, 9, and 12 months, respectively. **Conclusions:** The AC+FV AVHC was associated with lower exacerbation rates, delayed time to first exacerbation, and lower exacerbation-related costs when compared to control non-antistatic VHCs.

## PREPARATION OF VALVED HOLDING CHAMBERS BEFORE USE CAN HAVE A SIGNIFICANT INFLUENCE ON SUBSEQUENT MEDICATION DELIVERY EFFICIENCY: A STUDY WITH PRESSURIZED METERED DOSE INHALER DELIVERED FLUTICASONE PROPIONATE.

Suggett J, Nagel M, Mitchell J. *Respiratory Drug Delivery*, 2017, pp 319-323.

**Introduction:** The present study set out to test the hypothesis that priming is not as effective as either pre-washing, or better yet, the use of anti-static materials in the design of a VHC to avoid the need for device preparation altogether. The following VHC types ( $n=5$  devices/group) were evaluated (Table 1).

Table 1.

AeroChamber Plus® Flow-Vu® Inspiratory Flow Indicator	AC Plus-AS	Anti-static (charge dissipative)	Trudell Medical International, London Canada
AeroChamber Plus® Volumatic†	AC Plus-NC VOL-NC	Non-conducting Non-conducting	GlaxoSmithKline, Uxbridge, UK
Able Spacer 2	ABL2-NC	Non-conducting	Clement Clarke International, Harlow, Essex, UK

**Conclusion:** EMFP at each of the 4 stages of the test protocol differed widely between devices, suggesting that more than one process was responsible for the observed outcomes: 1) The use of charge dissipative materials in VHC construction avoided the need either for priming or for pre-washing with detergent before use; 2) Where devices were manufactured from non-conducting materials, washing with detergent followed by drip-drying was more effective than priming with particles of medication from three actuations of the pMDI-delivered drug product. For some, but not all VHC types, such pre-treatment could provide comparable medication delivery performance to that achievable from anti-static/charge dissipative VHC group; 3) Priming provided inconsistent results across all the NC device groups evaluated, especially with the VOL-NC VHCs; this outcome is consistent with the findings of Barry [9]; 4) Cleaning of VHCs with detergent followed by drip-drying before use was more effective at charge mitigation than when a rinse with clean water was undertaken as a final step. Clinicians should be aware that priming of VHCs

is wasteful of medication, results in inconsistent medication delivery, and is unnecessary if an anti-static device is prescribed or if a non-conducting device is washed in mild detergent followed by drip-drying instead of a rinse.

## EVALUATION OF PERFORMANCE OF VALVED HOLDING CHAMBERS (VHCs) USED OUT-OF-PACKAGING FOR SPEED OF MEDICATION DELIVERY: CAREFUL SELECTION OF THE VHC IS REQUIRED.

Suggett J, Nagel M, Schneider H, Avvakoumova V, Ali R, Mitchell JP. *American Journal of Critical Care Medicine* 2015;191:A4257.

The Electrostatic charging of non-conducting VHCs is known to be associated with loss of aerosolized medication delivered by pressurized metered-dose inhaler (pMDI) to patients who are prescribed these devices to aid poor coordination. In the hospital setting and potentially also in the home, time-to-treat pressures may encourage the use of such single-patient devices immediately from the packaging. This laboratory study was undertaken to test the hypothesis that pre-treatment of such devices is essential if significant loss of medication is to be avoided. Three different non-conducting (NC) VHCs with mouthpiece ( $n=3$ /group were evaluated (Breath-a-Tech<sup>†</sup>; Able Spacer<sup>†</sup> Universal; SpaceChamber Plus<sup>†</sup>) and compared with the AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> Anti-Static Valved Holding Chamber (aVHC) with mouthpiece) as the reference device. 5-actuations of fluticasone propionate (110 µg FP/actuation; GSK Inc.) were delivered at 30-s intervals to devices removed from their packaging without pre-washing to mitigate charging. 2, 5 and 10s delay intervals were simulated using a proprietary apparatus following pMDI actuation to mimic uncoordinated use. The emitted dose of FP was sampled at 28.3 L/min ± 5% into an abbreviated Andersen cascade impactor. FP was subsequently recovered and assayed by HPLC-UV spectrophotometry. Measures of total emitted mass (TEM) and fine particle mass < 4.7 µm (FPM<4.7 µm) per actuation are summarized in Table 1.

**Table 1:**  
**Comparative Values of TEM and FPM<4.7 µm FP (mean ± SD) from NC and AS VHCs Used without Pre-Washing**

VHC Name	Type	Delay (s)	TEM ( µg/actuation)	FPM<4.7 µm (µg/actuation)
Breath-a-Tech <sup>†</sup>	NC	2	9.7 ± 1.5	8.9 ± 1.1
	NC	5	4.4 ± 1.4	4.2 ± 1.4
	NC	10	3.6 ± 0.9	3.3 ± 0.8
Able Spacer <sup>†</sup> Universal	NC	2	5.6 ± 1.8	5.2 ± 1.7
	NC	v5	2.1 ± 1.1	2.0 ± 1.0
	NC	10	1.4 ± 0.7	1.3 ± 1.1
SpaceChamber Plus <sup>†</sup>	NC	2	1.5 ± 0.6	1.5 ± 0.6
	NC	5	0.5 ± 0.1	0.5 ± 0.1
	NC	10	0.5 ± 0.3	0.5 ± 0.3
AeroChamber Plus <sup>®</sup> Flow-Vu <sup>®</sup> aVHC	AS	2	44.9 ± 3.8	44.2 ± 3.1
	AS	5	43.1 ± 4.7	40.9 ± 3.4
	AS	10	38.3 ± 2.5	35.7 ± 2.0

FP delivery as total mass or as fine particles via the antistatic AeroChamber Plus<sup>®</sup> VHC were largely unaffected by delay interval magnitude, and for delay intervals of 2 and 5 s were within ±15% of FPM<4.7 µm observed in a previous study for the pMDI alone, fully coordinated use, without VHC (46.2 ± 2.1 µg/actuation). On the other hand, all the non-conducting VHCs delivered almost no FP regardless of delay interval. Clinicians need to be aware that use of non-conducting VHCs without pre-washing could result in significant under-dosing of the patient.

## RESPONSE TO ALBUTEROL MDI DELIVERED THROUGH AN ANTI-STATIC CHAMBER DURING NOCTURNAL BRONCHOSPASM.

Prabhakaran S, Shuster J, Chesrown S, Hendeles L. *Respir Care* 2012;57(8):1291-1296.

**Background:** Decreasing electrostatic charge on valved-holding chambers increases the amount of drug delivered. However, there are no data demonstrating that this increases bronchodilatation. The objective of this study was to investigate the influence of reducing electrostatic charge on the bronchodilator response to albuterol inhaler during nocturnal bronchospasm. **Methods:** This randomized, double-blind, double-dummy, crossover study included subjects 18-40 years with nocturnal bronchospasm (20% overnight decrease in peak flow on 3 of 7 nights during run-in), FEV<sub>1</sub> 60-80% predicted during the day, and ≥ 12% increase after albuterol. Subjects slept in the Clinical Research



Center up to 3 nights for each treatment. FEV<sub>1</sub> and heart rate were measured upon awakening spontaneously or at 4 am, and 15 minutes after each dose of 1, 2 and 4 cumulative puffs of albuterol MDI. The drug was administered through an anti-static valved holding chamber (AeroChamber Plus® Z-Stat®) or a conventional valved holding chamber containing a static charge (AeroChamber Plus®). **Results:** Of 88 consented subjects, 11 were randomized and 7 completed the study. Most exclusions were due to lack of objective evidence of nocturnal bronchospasm. Upon awakening, FEV<sub>1</sub> was 44±9% predicted before the anti-static chamber and 48±7% predicted before the static chamber. The mean (±SD) % increase in FEV<sub>1</sub> after 1, 2 and 4 cumulative puffs using anti-static vs static chambers, respectively, were 52%±26% vs 30%±19%, 73%±28% vs 48%±26% and 90%±34% vs 64%±35%. The point estimates for the difference (95% CI) between devices (antistatic-static) were 21% (4-38) [*p*=0.026], 23% (6-41) [*p*=0.018] and 25% (7-42) [*p*=0.013] for 1, 2, and 4 cumulative puffs, respectively. There was no significant difference in heart rate between treatments. **Conclusion:** Delivery of albuterol through an anti-static chamber provides a clinically relevant improvement in bronchodilator response during acute, reversible bronchospasm, such as nocturnal bronchospasm.

## Importance of Facemask Seal

### ASSESSING DIFFERENT VALVED HOLDING CHAMBERS (VHC) WITH FACEMASK FOR DELIVERED MASS TO CARINA WITH INHALED CORTICOSTEROID BY PRESSURIZED METERED-DOSE INHALER (PMDI).

Bracey A, Suggett J, Nagel M, Mitchell JP. *British Thoracic Society Annual Meeting, December 2017.*

**Introduction and Objectives:** Laboratory evaluation of VHC-facemask add-ons is ideally undertaken simulating conditions of use. We report a study in which such devices for small child use were evaluated using an anatomical face-model and upper airway commensurate with that of a 4 year old child. **Methods:** A number of VHCs with facemask ( $n=3$  devices/group) were evaluated using an anatomical face-model and upper airway commensurate with that of a 4 year old child. Each VHC was prepared to manufacturer instructions, then evaluated by breathing simulator (ASL5000), mimicking a short coordination delay of 2 s followed by tidal breathing (tidal volume ( $V_T$ )=155-mL, I:E ratio = 1:2, rate=25 cycles). The facemask was attached to ADAM-III small child model. The airway was coupled directly to the breathing simulator via a filter below its exit to capture drug particles that would penetrate as far as the carina in a real patient. 5-actuations of fluticasone propionate (50 $\mu$ g, FP) were delivered at 30-s intervals. FP recovered from various locations in the aerosol pathway was subsequently assayed by HPLC-UV spectrophotometry. **Results:** The distribution of recovered FP from each type of VHC is summarized in Table 1.

**Table 1: FP (mean  $\mu$ g  $\pm$ SD) recovered from VHCs indicated for small child use, simulating a 2 s coordination delay followed by tidal breathing**

Retention Location	AeroChamber Plus® Flow-Vu®	Pocket-Chamber®	Vortex®	Compact SpaceChamber Anti-Static	A2A Spacer®	Volumatic®	Optichamber Diamond*
VHC	17.5 $\pm$ 1.6	36.6 $\pm$ 0.2	39.7 $\pm$ 6.7	36.1 $\pm$ 3.6	28.3 $\pm$ 2.8	33.6 $\pm$ 1.9	22.7 $\pm$ 2.7
Facemask	1.4 $\pm$ 0.2	1.9 $\pm$ 0.8	1.2 $\pm$ 0.2	0.5 $\pm$ 0.3	0.2 $\pm$ 0.1	0.1 $\pm$ 0.1	3.4 $\pm$ 0.8
Airway	1.1 $\pm$ 0.2	0.4 $\pm$ 0.2	0.6 $\pm$ 0.3	0.1 $\pm$ 0.1	0.4 $\pm$ 0.1	0.0 $\pm$ 0.0	0.7 $\pm$ 0.1
Filter at 'Carina'	10.1 $\pm$ 1.0	4.0 $\pm$ 1.7	2.7 $\pm$ 1.5	1.5 $\pm$ 0.9	4.1 $\pm$ 0.9	1.5 $\pm$ 0.8	5.1 $\pm$ 0.9

**Conclusions:** Significantly more FP was delivered to the model 'carina' from the AC Plus VHC with child mask ( $p < 0.001$ ), the increased mass counterbalanced by decreased retention of medication within the VHC. It is important that clinicians are aware that large differences in delivery efficiency may exist when a facemask is present.

### CLINICALLY APPROPRIATE TESTING OF DIFFERENT VALVED HOLDING CHAMBER (VHC)-FACEMASK COMBINATIONS INVESTIGATING DELIVERED MASS TO CARINA FOR A WIDELY PRESCRIBED INHALED CORTICOSTEROID DELIVERED BY PRESSURIZED METERED-DOSE INHALER (PMDI).

Suggett J, Nagel M, Schneider H, Mitchell JP. *Proc ERS Annual Congress, Amsterdam, Netherlands in Eur. Respir. J., 2015.*

**Rationale:** Laboratory evaluation of VHC-facemask add-ons is ideally undertaken simulating conditions of use. We report a study in which such devices for small child use ( $n=3$ /group) (AeroChamber Plus® Flow-Vu® Anti-Static Valved Holding Chamber (aAC+); PocketChamber® (POC); Vortex® (VOR); L'Espace® (ESP); SpaceChamber Plus® (SP); A2A Spacer® (A2A)) were evaluated using an anatomical face-model and upper airway commensurate with that of a 4 year old child. **Methods:** Each VHC was prepared to manufacturer instructions, then evaluated by breathing simulator (ASL5000), mimicking a short coordination delay of 2 s followed by tidal breathing (tidal volume ( $V_T$ ) = 155-mL, inspiratory: expiratory (I:E) ratio = 1:2, rate/min (Rmin) = 25 cycles). The facemask was attached to the Aerosol Delivery to Anatomic Model (ADAM-III) small child face equipped with oropharynx. The airway was coupled directly to the breathing simulator via a filter below its exit to capture drug particles that would penetrate as far as the carina in a real patient. 5-actuations of fluticasone propionate (44  $\mu$ g FP/actuation ex actuator; GSK Inc.) were delivered at 30-s intervals. FP recovered from various locations in the aerosol pathway was subsequently assayed by HPLC-UV spectrophotometry. **Results:** The distribution of recovered FP from each type of VHC is summarized in Table 1.

**Table 1: FP (mean  $\mu\text{g} \pm \text{SD}$ ) recovered from VHCs indicated for small child use, simulating a 2 s coordination delay followed by tidal breathing.**

Location	aAC+	POC	VOR	ESP	SP	A2A
Retained by VHC	17.5 $\pm$ 1.6	36.6 $\pm$ 0.2	36.2 $\pm$ 3.8	42.3 $\pm$ 1.4	30.3 $\pm$ 12.7	28.3 $\pm$ 2.8
Deposited Inside Facemask	1.4 $\pm$ 0.2	1.9 $\pm$ 0.8	0.5 $\pm$ 0.7	0.4 $\pm$ 0.1	1.5 $\pm$ 1.0	0.2 $\pm$ 0.1
Deposited in Airway	1.1 $\pm$ 0.2	0.4 $\pm$ 0.2	0.3 $\pm$ 0.1	0.2 $\pm$ 0.0	0.5 $\pm$ 0.2	0.4 $\pm$ 0.1
Filter at 'Carina'	10.1 $\pm$ 1.0	4.0 $\pm$ 1.7	0.7 $\pm$ 1.1	0.8 $\pm$ 0.3	4.5 $\pm$ 2.6	4.1 $\pm$ 0.9

**Conclusions:** Significantly more FP was delivered to the model 'carina' from the aAC+ VHC with child mask ( $p < 0.001$ ), the increased mass counterbalanced by decreased retention of medication within the VHC. It is important that clinicians are aware that large differences in delivery efficiency may exist when a facemask is present.

**CLINICALLY APPROPRIATE TESTING OF ANTISTATIC VALVED HOLDING CHAMBERS (VHCS) WITH FACEMASK INDICATES SUBSTANTIAL DIFFERENCE IN DELIVERED MASS TO CARINA FOR A WIDELY PRESCRIBED INHALED CORTICOSTEROID.**

*Suggett J, Nagel M, Schneider H, Mitchell JP. Am J Respir Crit Care Med 191;2015: A4153.*

**Rationale:** Laboratory evaluation of VHCs used with pressurized metered-dose inhalers (pMDIs) is ideally undertaken under conditions of use. We hypothesize that this approach is likely to be important when a facemask is the patient interface and the product is indicated for pediatric use. We report a study in which two anti-static VHCs ( $n=5$ /group) for small child use (AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> Anti-Static Valved Holding Chamber (aVHC) with child mask; OptiChamber<sup>†</sup> Diamond<sup>†</sup> with medium mask) were evaluated using the ADAM III anatomical face and upper airway model replica of a 4 year old child. **Methods:** Each VHC was evaluated by breathing simulator (ASL5000, IngMar Medical, Pittsburgh, PA), mimicking a short coordination delay of 2 s before starting to inhale, followed by tidal breathing (tidal volume ( $V_t$ ) = 155-mL, inspiratory: expiratory (I:E) ratio = 1:2, rate/min (Rmin) = 25 cycles). The facemask of the VHC-on-test was attached to the Aerosol Delivery to Anatomic Model (ADAM-III) of a small child face equipped with oropharynx. The airway was coupled directly to the breathing simulator via an electret filter located immediately below the exit to capture drug particles that would penetrate as far as the carina in a patient. 5-actuations of fluticasone propionate (44 ug FP/actuation ex pMDI actuator; GSK Inc.) were delivered at 30-s intervals. FP recovered from specific locations in the aerosol pathway was subsequently assayed by HPLC-UV spectrophotometry. **Results:** The distribution of recovered FP from each type of VHC is summarized in Table 1.

**Table 1: FP (mean  $\mu\text{g} \pm \text{SD}$ /actuation) Recovered from AntiStatic VHCs Indicated for Small Child Use, Simulating a 2 s Coordination Delay Followed by Tidal Breathing**

Location	AeroChamber Plus <sup>®</sup> Flow-Vu <sup>®</sup> (aVHC) with child mask	OptiChamber <sup>†</sup> Diamond <sup>†</sup> with medium mask
Retained by VHC	17.5 $\pm$ 1.6	22.7 $\pm$ 2.7
Deposited Inside Facemask	1.4 $\pm$ 0.2	3.4 $\pm$ 0.8
Deposited on Face	0.6 $\pm$ 0.4	0.5 $\pm$ 0.3
Deposited in Airway	1.1 $\pm$ 0.2	0.7 $\pm$ 0.1
Collected by Filter at 'Carina'	10.1 $\pm$ 1.0	5.1 $\pm$ 0.9

**Conclusions:** Significantly more FP was delivered to the Adam III model carina from the AeroChamber Plus<sup>®</sup> VHCs with child mask (un-paired t-test,  $p < 0.001$ ). Many factors could have accounted for this difference, such as chamber

shape and capacity as well as inhalation valve design, so it is important that clinicians are aware that even if the VHC is anti-static, large differences in delivery efficiency may exist.

### COMPARISON OF AEROSOL DRUG DELIVERY TO A NASO-PHARYNGEAL REPLICA VIA TWO VALVED HOLDING CHAMBERS (VHC) WITH FACEMASK VIA BREATH SIMULATION.

DiBlasi R, Coppolo DP, Mitchell JP, Wang V, Doyle C, Nagel MW. Presented at the AARC Congress Nov, 2013.

**Background:** In order to improve patient compliance, the use of charge dissipative materials in VHC construction is becoming the standard of care. A facemask is required as the interface between patient and VHC for young children who cannot breathe through a mouthpiece. Recent studies have emphasized that a well-fitting facemask is critical for optimal drug delivery. We report a laboratory based comparison of aerosol drug delivery between two 'antistatic' VHCs under simulated breathing conditions, using an anatomically correct infant face-upper airway model [ADAM-III, Trudell Medical International (TMI)]. **Methods:** Delivery of fluticasone propionate (FP; 44 µg/actuation GSK) as evaluated via anti-static AeroChamber Plus® VHC with Flow-Vu® IFI/infant mask (AC-Plus, MMC) and OptiChamber Diamond® VHC/LiteTouch® small-mask (OD, Philips) ( $n=5$  devices/group). Tidal-breathing (tidal-volume ( $V_t$ )= 155-mL, duty-cycle=33%, rate= 25-breaths/min) was simulated with an Ingmar ASL 500 test lung. Each facemask was applied to the face with the same clinically-appropriate force (1.6 kg). FP was recovered from the pMDI mouthpiece, VHC, facemask, face and airway of the model as well as the filter at the carinal exit of the model airway (equivalent to lung dose). Delivered mass of FP (DMFP) was quantified by HPLC. **Results:** DMFP (mean±SD) was significantly greater from AC-Plus (11.6±1.4µg) than OD (7.2±1.4µg) (unpaired t-test,  $p=0.002$ ). This difference was largely due to the FP lost on the facemask of the OD facemask (8.8±0.9 µg) compared to that of the AC-Plus (4.3±0.3 µg). **Conclusion:** While other factors such as facemask dead volume and device design are important factors in device performances, decreased aerosol delivery from the OD is explicable in terms of leakage between facemask and face, or choice of anti static materials, supported by higher deposition in its facemask. Clinicians should be aware that each VHC-pMDI combination is unique.

### DELIVERY OF AEROSOLIZED FLUTICASONE PROPIONATE VIA VALVED HOLDING CHAMBER WITH FACEMASK: BEWARE FACEMASK LEAKAGE.

Sharpe R, Nagel MW, Avvakoumova V, Schneider H, Ali R, Mitchell JP. Proc. 4<sup>th</sup> conference of the European Pediatric Formulation Initiative, Prague, Czech Republic, September 19-20, 2012.

**Background and Objectives:** Leakage between facemask-and-face may result in medication loss by valved holding chamber (VHC)-facemask (1). Our study evaluated how an inspiratory flow indicator (IFI) can be used to avoid leakage. **Methods:** An infant face with realistic soft-tissue modeling (ADAM-III, Trudell Medical International (TMI), London, Canada (2)) was used to evaluate delivery of fluticasone propionate (FP; 50 µg/actuation, GSK (Canada)) via anti-static AeroChamber Plus® VHC with Flow-Vu® IFI/infant mask (AC-Plus, TMI) or OptiChamber® Diamond® VHC/LiteTouch® small-mask (OD, Philips-Respironics, Parsipanny, NJ, USA) ( $n=5$  devices/group), simulating tidal-breathing (tidal-volume ( $V_t$ )=155-mL, duty-cycle=33%, rate= 25-breaths/min. Each facemask was applied to the face with the same clinically-appropriate force (1.6 kg). The IFI of the AC-Plus was observed to be moving. FP was recovered from the nasopharynx and base (lung dose) of the model, and delivered mass (DMFP) quantified by HPLC-spectrophotometry as % label claim (LC). **Findings:** DMFP (mean±S.D.) was significantly greater from AC-Plus (25.8±5.3%LC) than OD (17.0±3.7%LC) (unpaired t-test,  $p=0.019$ ). FP on the facemask of the AC-Plus (6.2±1.9% LC), was slightly smaller than that determined with the OD facemask (9.9±2.6%). **Discussion/Conclusion:**  $V_t$  was set larger than normal in order to detect facemask-to-face leakage more precisely. Leakage was eliminated with the AC-Plus, by observing IFI movement. However, inasmuch as the OD does not have an IFI, it was not possible to do more than ensure that its facemask was applied with the same force to the model. Decreased aerosol delivery from the OD is explainable in terms of leakage between facemask and face, supported by higher deposition in its facemask.

### EVALUATION OF TWO VALVED HOLDING CHAMBERS WITH FACEMASK USING A NEW INFANT FACE MODEL: IMPORTANCE OF AVOIDING LEAKAGE BETWEEN FACEMASK AND FACE.

Coppolo DP, Mitchell JP, Mackay HA, Avvakoumova VA, Nagel MW. Respiratory Care 2008;53(11):1522.

**Background:** Valved Holding Chambers (VHCs) with facemask as patient interface are an important adjunct in delivery of medication particularly to infants. Leakage between facemask and face can result in severe loss of medication

because there is no pressure source to drive the aerosol towards the patient once the inhaler has been actuated. Laboratory performance testing therefore needs to be undertaken with the facemask in place. **Methods:** We evaluated the effect of two different but similar-sized VHCs (AeroChamber Plus® with small mask - Monaghan Medical Corp.) and Vortex<sup>+</sup> with Babywhirl<sup>+</sup> mask - PARI Respiratory Equipment Inc., Midlothian, PA) on delivery of albuterol (2-actuations of Ventolin<sup>+</sup> HFA, GlaxoSmithKline) to an oral-breathing 9-12 month anatomical infant face model with simulated *in-vivo* facial surfaces where the mask was applied with a clinically relevant force of 1.6 kg. The VHCs were prepared in accordance with manufacturer instructions and evaluated at a flow rate of 4.9 L/min, sampling the aerosol by low-flow impactor to determine total emitted mass (TEM) and fine particle fraction (FPF) < 4.7 µm aerodynamic diameter. These conditions were considered to be representative of a 6-12 month old infant having a 50th percentile body weight range from 7.5 to 9.9 kg. Recovered albuterol was determined by HPLC-UV spectrophotometry. **Results:** TEM/kg (*n* = 5 devices, mean ± SD) from the AeroChamber Plus® VHCs was in the range 1.6 to 2.2 µg/kg, comparable with data provided in the Patient Information Leaflet for this formulation with infant users, and FPF was 73%. No leakage was detected between facemask and face (100% flow to the face via the VHC). In contrast, a perfect seal could not be achieved between the Vortex<sup>+</sup> VHCs and associated wider facemask with the model face (97% of the flow by-passed the VHC under best conditions achievable), so that TEM/kg from these devices ranged from 0.07 to 0.09 µg/kg, with FPF of 100%. **Conclusion:** The Aerosol-Delivery-to-Anatomical-Model (ADAM-II) face technique allows laboratory testing of VHC-facemask to be evaluated as a complete system. The data obtained confirm that no leakage between facemask and face must be achieved for reliable delivery of medication from these devices.

## DESIGN OF FACEMASKS FOR DELIVERY OF AEROSOL-BASED MEDICATION VIA PRESSURIZED METERED DOSE INHALER WITH VALVED HOLDING CHAMBER: KEY ISSUES THAT AFFECT PERFORMANCE.

Morton RW and Mitchell JP. *Journal of Aerosol Medicine* 2007;20(1):S29-45.

Valved holding chambers (VHCs) are widely prescribed for use with pressurized metered dose inhalers (pMDIs) for the treatment of respiratory disease by aerosol therapy. The facemask is the preferred patient interface for use by infants and small children, as well as by geriatric patients, due primarily to poor coordination skills. However, care is required in the design of the facemask-VHC system to optimize the delivery of medication. In particular, it is essential to achieve an effective mask-to-face seal and to minimize the volume of dead space. It is also important to ensure that the fit of the facemask is comfortable to the patient when applied with sufficient force to create a seal. We review each of these design principles and their application in the evolution of a range of VHCs from the same family of devices during the past fifteen years. We also examine the various methods available for evaluating VHC-facemasks as a system, recommending where future work might be directed.

## FORCE-DEPENDENT STATIC DEAD SPACE OF FACE MASKS USED WITH HOLDING CHAMBERS.

Shah SA, Berlinski AB, Rubin BK. *Respir Care* 2006;51(2):140-144.

**Background:** Pressurized metered-dose inhalers with valved holding chambers and masks are commonly used for aerosol delivery in children. Drug delivery can decrease when the dead-space volume (DSV) of the valved holding chamber is increased, but there are no published data evaluating force-dependent DSV among different masks. **Methods:** Seven masks were studied. Masks were sealed at the valved holding chamber end and filled with water to measure mask volume. To measure mask DSV we used a mannequin of 2-year-old-size face and we applied the mask with forces of 1.5, 3.5, and 7 pounds. Mask seal was determined by direct observation. Intra-brand analysis was done via analysis of variance. **Results:** At 3.5 pounds of force, the DSV ranged from 29mL to 100mL, with 3 masks having DSV of < 50mL. The remaining masks all had DSV > 60 mL. At 3.5 pounds of force, DSV percent of mask volume ranged from 33.7% (AeroChamber®, *p*<0.01 compared with other masks) to 100% (Pocket Chamber). DSV decreased with increasing force with most of the masks, and the slope of this line was inversely proportional to mask flexibility. Mask fit was 100% at 1.5 pounds of force only with the AeroChamber® and Optichamber. Mask fit was poorest with the Vortex, Pocket Chamber, and BreatheRite masks. **Conclusion:** Rigid masks with large DSV might not be suitable for use in children, especially if discomfort from the stiff mask makes its use less acceptable to the child.

## AEROSOL THERAPY WITH VALVED HOLDING CHAMBERS IN YOUNG CHILDREN: IMPORTANCE OF THE FACEMASK SEAL.

Amirav I, Newhouse MT. *Pediatrics* 2001;108:389-94.

**Objective:** Masks are an essential interface between valved holding chambers (VHCs), or spacers, and a small child's face for providing aerosol therapy. Clinical experience suggests that many young children do not cooperate with the VHC treatment or tolerate a mask of any kind. This might impair the mask-face seal and reduce the dose delivered to the child. The objective of this study was to evaluate the ability of parents to provide a good mask-face seal in infants and toddlers using 3 masks provided with commonly used pediatric VHCs and compare this with the seal obtained with the Hans Rudolph pediatric anesthesia mask. **Methods:** A preliminary *in vitro* filter study was conducted to validate the assumption that reduced ventilation as a result of increased facemask leak reduces the drug aerosol dose delivered to the mouth. Facemask leak then was studied *in vivo* for NebuChamber, AeroChamber®, BabyHaler, and Hans Rudolph masks by measuring ventilation with an in-line pneumotachograph while the facemask was held in place by experienced parents who were asked to demonstrate how they deliver medication to their children without any additional instruction. Thirty children (mean age: 3.2 +/- 1.4 years) performed 4 repeat studies with each mask. The first 10 patients performed the tests once again within 1 month. On the second occasion, the parents were coached continuously and encouraged to hold the mask tightly against the child's face. **Results:** The AeroChamber® and Hans Rudolph masks provided the best seal as reflected in the magnitude of the ventilation measured through them. The NebuChamber provided the poorest seal, with 45% less ventilation than the AeroChamber® and Hans Rudolph masks. There was considerable intraindividual variability for all masks (24% to 48%); however, the variability with the NebuChamber mask was 2-fold greater than the other masks. All ventilatory volumes during the coached session were significantly greater than during the uncoached session. Variability during the coached session was significantly less (except for the BabyHaler, which remained unchanged). **Conclusions:** VHCs with masks designed for use with small children may provide a poor seal with the face, leading to reduced or more variable dose delivery. The facemask seal is critical for efficient aerosol delivery to infants and young children, and this should be stressed to parents.

# AeroChamber Plus® VHC – Performance with Different MDI Formulations

**Alvesco<sup>®</sup> (Ciclesonide) Nycomed<sup>†</sup>**

## EFFICACY AND SAFETY OF THREE CICLESONIDE DOSES VS. PLACEBO IN CHILDREN WITH ASTHMA: THE RAINBOW STUDY.

*Pedersen S, Potter P, Dachev S, Bosheva M, Kaczmarek J, Springer E, Dunkel J, Engelstätter. Respiratory Medicine 2010;104(11):1618-1628.*

**Objective:** To evaluate the efficacy and safety of three doses of ciclesonide (with or without spacer) in children with persistent asthma. **Patients and methods:** This was a multicenter, double-blind, placebo-controlled, 12-week study of ciclesonide 40, 80 or 160 µg (once daily pm). Children (6–11 years) were randomized 1:1 to treatment via a metered dose inhaler (MDI) or MDI plus spacer (AeroChamber Plus®). The primary variable was change from baseline in mean morning peak expiratory flow (PEF). Secondary variables included: time to first lack of efficacy (LOE), asthma control, forced expiratory volume in 1 s (FEV<sub>1</sub>), asthma symptom score and quality of life (QoL). Safety assessments included: adverse events (AEs), urinary cortisol excretion and body height. **Results:** In total, 1073 children received treatment. At endpoint, mean morning PEF significantly improved with all doses of ciclesonide vs. placebo. There was no difference over placebo in time to first LOE, but ciclesonide was superior to placebo on asthma control, symptom score, FEV<sub>1</sub> and QoL. There were no differences between the spacer or non-spacer subgroups. The incidences of AEs were comparable between treatment groups (approximately 35%) and there were no between-group differences in body height or urinary cortisol. **Conclusions:** Ciclesonide 40–160 µg once daily is effective and well tolerated in children with persistent asthma; its efficacy and safety are unaffected by the use of a spacer.

## SIMILAR RESULTS IN CHILDREN WITH ASTHMA FOR STEADY STATE PHARMACOKINETIC PARAMETERS OF CICLESONIDE INHALED WITH OR WITHOUT SPACER.

*Boss H, Minic P, Nave R. Clinical Medicine Insights: Pediatrics 2010;4: 1-10.*

**Background:** Ciclesonide is an inhaled corticosteroid administered by a metered dose inhaler (MDI) to treat bronchial asthma. After inhalation, the inactive ciclesonide is converted by esterases in the airways to active metabolite desisobutyl-ciclesonide (des-CIC). **Aim:** To compare the pharmacokinetic (PK) parameters of des-CIC in children after administration of therapeutic dose of ciclesonide with and without spacer (AeroChamber Plus®). **Methods:** Open-label, 3 period, cross over, repeated dose, PK study in 37 children with mild to moderate stable asthma (age: 6–11 y; body weight: 20–53 kg). During each 7-day treatment period, ciclesonide was inhaled once in the morning: A) 160 µg MDI with spacer, B) 80 µg MDI with spacer, and C) 160 µg MDI without spacer. Serum PK parameters of ciclesonide and des-CIC were determined on Day 7 of each period. The primary PK parameters were the AUC<sub>0–24</sub> and C<sub>max</sub> for des-CIC. **Results:** Inhaling ciclesonide with spacer led to a dose proportional systemic exposure (AUC<sub>0–24</sub>) of des-CIC (0.316 µg\*h/L for 80 µg and 0.663 µg\*h/L for 160µg). The dose-normalized systemic exposure for des-CIC (based on AUC<sub>0–24</sub>) was 27% higher after inhalation of ciclesonide 80 µg or 160 µg with spacer than without spacer; the corresponding C<sub>max</sub> values for des-CIC were, respectively, 63% and 55% higher with spacer. No clinically relevant abnormalities or adverse drug reactions were observed. **Conclusions:** Inhalation of therapeutic ciclesonide dose with spacer led to a slight increase in the systemic exposure of des-CIC, which does not warrant dose adjustment.

## ONCE-DAILY CICLESONIDE VIA METERED-DOSE INHALER: SIMILAR EFFICACY AND SAFETY WITH OR WITHOUT A SPACER.

*Engelstätter R, Szlavik M, Gerber C, Beck E. Respir Med 2009;103(11):1643-50.*

Inhaled corticosteroids (ICS) are recommended as first-line treatment for adults and children with persistent asthma. The Global Initiative for Asthma recommends that patients taking medium- or high-dose ICS delivered by metered-dose inhalers (MDIs) should use a spacer device. This randomized, open-label, 12-week, non-inferiority study compared the efficacy and safety of ciclesonide 160 µg once daily delivered via hydrofluoroalkane-MDI alone (CIC160) or with a spacer (either an AeroChamber Plus® [CIC160P] or an AeroChamber MAX® [CIC160M]) in patients with persistent asthma. The primary efficacy variable was change in forced expiratory volume in 1 s (FEV<sub>1</sub>) from baseline to study end. Significant improvements in FEV<sub>1</sub> were observed from baseline to study end in each treatment group; least squares mean change from baseline ranged between 0.32 and 0.34L in the per-protocol (PP) analysis and similar results were observed for the intention-to-treat (ITT) analysis ( $p < 0.0001$  for all). Non-inferiority of CIC160P

and CIC160M to CIC160 was observed for both PP and ITT populations ( $p < 0.0001$  [one-sided]). In all groups, daily asthma symptom scores were reduced to 0 and significant reductions were observed in rescue medication use at study end ( $p < 0.0001$  versus baseline for all). Ciclesonide was well tolerated in all groups and no cases of oral candidiasis were reported. Morning serum cortisol levels significantly increased in all groups from baseline to study end ( $p \leq 0.0389$ ), with no significant between-treatment differences. In patients with persistent asthma, ciclesonide was shown to have similar efficacy and tolerability when administered via MDI alone or with a spacer.

#### **COMPARISON OF THE EFFICACY AND SAFETY OF CICLESONIDE 160 MICROG ONCE DAILY VS. BUDESONIDE 400 MICROG ONCE DAILY IN CHILDREN WITH ASTHMA.**

*Von Berg A, Engelstätter R, Minic P, Sréckovic M, Garcia ML, Latoś T, Vermeulen JH, Leichtl S, Hellbardt S, Bethke TD. *Pediatr Allergy Immunol* 2007 Aug;18(5):391-400.*

Ciclesonide is an onsite-activated inhaled corticosteroid (ICS) for the treatment of asthma. This study compared the efficacy, safety and effect on quality of life (QOL) of ciclesonide 160 microg (ex-actuator; nominal dose 200 microg) vs. budesonide 400 microg (nominal dose) in children with asthma. Six hundred and twenty-one children (aged 6-11 yr) with asthma were randomized to receive ciclesonide 160 microg (ex-actuator) once daily (via hydrofluoroalkane metered-dose inhaler and AeroChamber Plus® spacer) or budesonide 400 microg once daily (via Turbohaler® both given in the evening for 12 wk. The primary efficacy end-point was change in forced expiratory volume in 1 s (FEV<sub>1</sub>). Additional measurements included change in daily peak expiratory flow (PEF), change in asthma symptom score sum, change in use of rescue medication, pediatric and caregiver asthma QOL questionnaire [PAQLQ(S) and PACQLQ, respectively] scores, change in body height assessed by stadiometry, change in 24-h urinary cortisol adjusted for creatinine and adverse events. Both ciclesonide and budesonide increased FEV<sub>1</sub>, morning PEF and PAQLQ(S) and PACQLQ scores, and improved asthma symptom score sums and the need for rescue medication after 12 wk vs. baseline. The non-inferiority of ciclesonide vs. budesonide was demonstrated for the change in FEV<sub>1</sub> (95% confidence interval: -75, 10 ml,  $p = 0.0009$ , one-sided non-inferiority, per-protocol). In addition, ciclesonide and budesonide showed similar efficacy in improving asthma symptoms, morning PEF, use of rescue medication and QOL. Ciclesonide was superior to budesonide with regard to increases in body height ( $p = 0.003$ , two-sided). The effect on the hypothalamic-pituitary-adrenal axis was significantly different in favor of ciclesonide treatment ( $p < 0.001$ , one-sided). Both ciclesonide and budesonide were well tolerated. Ciclesonide 160 microg once daily and budesonide 400 microg once daily were effective in children with asthma. In addition, in children treated with ciclesonide there was significantly less reduction in body height and suppression of 24-h urinary cortisol excretion compared with children treated with budesonide after 12 wk.

#### **EQUIVALENT PHARMACOKINETICS OF THE ACTIVE METABOLITE OF CICLESONIDE WITH AND WITHOUT USE OF THE AEROCHAMBER PLUS® SPACER FOR INHALATION.**

*Drollmann A, Nave R, Steinijans VW, Baumgärtner E and Bethke TD. *Clin. Pharmacol Ther* 2006;45(7):729-736.*

**Background:** Ciclesonide is an inhaled corticosteroid that provides safe and effective control of patient asthma. Ciclesonide is administered as an aerosol solution in a metered-dose inhaler, using hydrofluoroalkane-134a as a propellant. It is activated in the lung to form its only active metabolite, desisobutryl-ciclesonide (des-CIC). A spacer may be used in combination with the hydrofluoroalkane metered-dose inhaler (HFA-MDI) to maintain inhaled corticosteroid delivery to the lung in patients with poor inhalation technique. **Objective:** To determine if the pharmacokinetics of des-CIC and ciclesonide are altered when a spacer is used for ciclesonide inhalation. **Methods:** A randomized, open-label, 2-period crossover, single-center pharmacokinetic study was conducted in 30 patients with asthma (forced expiratory volume in 1 second  $\geq 70\%$  predicted). A single dose of ciclesonide (320  $\mu\text{g}$  ex-actuator; equivalent to 400  $\mu\text{g}$  ex-valve) was administered via the HFA-MDI with and without an AeroChamber Plus® spacer (Trudell Medical International, London, ON, Canada). Serum concentrations of ciclesonide and des-CIC were measured before inhalation and at various intervals until 14 hours after treatment using high-performance liquid chromatography with tandem mass spectrometric detection. **Results:** The pharmacokinetic properties of the active metabolite, des-CIC, were equivalent after inhalation of ciclesonide with and without the AeroChamber Plus® spacer. Point estimates and 90% confidence intervals (CIs) for the ratio of des-CIC pharmacokinetic properties in the presence or absence of a spacer were within the conventional bioequivalence range of 0.80-1.25 (area under the serum concentration time curve from time zero to infinity 0.96 [0.85, 1.07]; peak serum concentration 1.05 [0.94, 1.18]; elimination half-life 1.04 [0.92, 1.18]). Furthermore, there was no relevant difference in the point estimate



and 90% CI of the difference of the time to reach peak serum concentration of des-CIC with or without a spacer. **Conclusion:** The AeroChamber Plus® spacer did not influence the pharmacokinetics of the pharmacologically active des-CIC. Thus, systemic exposure to the active metabolite is similar when ciclesonide is inhaled with or without a spacer.

### **Beclomethasone Dipropionate**

#### **THE EFFECTIVENESS OF LOCAL CORTICOSTEROIDS THERAPY IN THE MANAGEMENT OF MILD TO MODERATE VIRAL GROUP.**

*Eboriadou M, Chryssanthopoulou D, Stamoulis P, Damianidou L, Haidopoulou K. Minerva Pediatr 2010;62(1):23-8.*

**Aim:** The purpose of this study was to determine whether local anti-inflammatory therapy with inhaled beclomethasone dipropionate is effective in the outpatient management of acute viral croup. **Methods:** Children six months to five years of age, presenting to the Emergency Department (ED) with a croup score of at least 2 participated in the study. All children were assigned in a randomized double-blind fashion to receive either nebulized L-epinephrine (LE), a single intramuscular injection of dexamethasone (D) 0.6 mg/kg, or inhaled beclomethasone dipropionate (BD) 200 mg, via AeroChamber®. Croup score (CS), heart rate (HR), blood pressure, respiratory rate (RR) and oxygen saturation were recorded at study entry and at 15, 30, 60, 90 and 120 minutes after treatment. **Results:** Sixty-four patients were enrolled into the study. Significant improvement of the croup score was noticed at the end of observation time in all groups. The LE group showed significant improvements of CS, HR and RR in comparison to the other two groups. Inhaled BD was as effective as intramuscular D in the treatment of mild to moderate croup in the ED. **Conclusion:** The use of inhaled beclomethasone in the outpatient management of croup was associated with a significant reduction in the severity of illness within 24 h after treatment.

### **Bevespi<sup>®</sup> Aerosphere<sup>®</sup> (Glycopyrrolate/formoterol) AstraZeneca Pharmaceuticals**

#### **RANDOMIZED STUDY OF THE EFFECTS OF AEROCHAMBER PLUS<sup>®</sup> FLOW-VU<sup>®</sup> ON THE EFFICACY, PHARMACOKINETICS AND SAFETY OF GLYCOPYRRONIUM/FORMOTEROL FUMARATE DIHYDRATE METERED DOSE INHALER IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE.**

*Fakih F, Spangenthal S, Sigal B, Darken P, Maes A, Siddiqui S, Gillen M, Reisner C, Martin UJ. Respiratory Medicine 2018;138:74-80.*

**Objectives:** This study compared the efficacy, pharmacokinetics (PK), and safety of GFF MDI (Bevespi<sup>®</sup> Aerosphere<sup>®</sup>), a fixed-dose combination of glycopyrronium and formoterol fumarate dihydrate (14.4/10 µg) delivered by a metered dose inhaler (MDI) formulated using innovative co-suspension delivery technology, in patients with moderate-to-very severe chronic obstructive pulmonary disease (COPD) with and without the AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> valved holding chamber (VHC). **Methods:** In this multicenter, open-label, crossover, Phase III study (NCT02454959), patients were randomized to receive GFF MDI 14.4/10 µg (equivalent to glycopyrrolate/formoterol fumarate 18/9.6 µg) twice daily for 7 days with and without the VHC. The primary endpoint was forced expiratory volume in 1 s area under the curve from 0 to 12 h (FEV<sub>1</sub> AUC<sub>0-12</sub>) on Day 8. Steady state PK parameters for glycopyrronium and formoterol (AUC<sub>0-12</sub>, peak concentration [C<sub>max</sub>] and time to peak concentration [t<sub>max</sub>]) were estimated from 12-h plasma concentration time data on Day 8. Safety and tolerability were also assessed throughout. **Results:** Eighty patients were randomized. On Day 8, the ratio (90% confidence interval [CI]) of least squares mean (LSM) FEV<sub>1</sub> AUC<sub>0-12</sub> for GFF MDI with VHC (LSM = 1538 mL; n = 67) versus without VHC (LSM = 1516 mL; n = 68) was 101.4% (100.1, 102.7). PK parameters were comparable overall with a slightly higher exposure to glycopyrronium with the VHC. The AUC<sub>0-12</sub> geometric LSM ratio (90% CI) for GFF MDI with versus without VHC was 115.99% (99.74, 134.89) for glycopyrronium and 96.66% (86.69, 107.78) for formoterol. GFF MDI with and without VHC were well tolerated with a similar adverse event profile. **Conclusions:** The magnitude of bronchodilatory effect was similar with and without a VHC following GFF MDI treatment. This, together with the PK and safety profiles, supports the use of the VHC with GFF MDI for the maintenance treatment of COPD, which could be particularly useful for patients who have difficulty with the coordination of an MDI.

## EFFICACY, SAFETY AND PHARMACOKINETICS OF A LAMA/LABA GLYCOPYRROLATE/FORMOTEROL METERED DOSE INHALER (GFF MDI) WITH AND WITHOUT AEROCHAMBER PLUS® FLOW-VU® VALVED HOLDING CHAMBER IN PATIENTS WITH MODERATE-TO-VERY SEVERE COPD.

Fakih F, Spangenthal S, Sigal B, Orevillo C, Darken P, Maes A, Reisner C, Martin U. *American Journal of Respiratory and Critical Care Medicine* 2017;195:A5466.

**Rationale:** The addition of a valved holding chamber to a metered dose inhaler (MDI) can be useful for patients with difficulties coordinating simultaneous aerosol actuation and inspiration. Glycopyrrolate/formoterol fumarate (GFF) MDI is a long-acting muscarinic antagonist/long-acting B<sub>2</sub> agonist (LAMA/LABA) fixed-dose combination delivered by MDI using novel Co-Suspension<sup>†</sup> Delivery Technology. This study evaluated efficacy, safety and pharmacokinetics (PK) of GFF MDI with and without addition of an AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> valved holding chamber (VHC) in patients with chronic obstructive pulmonary disease (COPD). **Methods:** In this multicenter, open label, Phase III cross-over study (NCT02454959), patients with moderate-to-very severe COPD were randomized to receive GFF MDI (18/9.6 µg, equivalent to glycopyrronium/formoterol fumarate dihydrate 14.4/10 µg) twice daily with and without VHC in random order for each of two separate 7-day treatment periods. The primary efficacy endpoint was forced expiratory volume second area under the curve 0-12 hours (FEV<sub>1</sub> AUC<sub>0-12</sub>) on Day 8. Twelve-hour plasma PK profiles were obtained on Day 8, and steadystate parameters reported for glycopyrrolate and formoterol: AUC<sub>0-12</sub>) on Day 8. Twelve-hour plasma PK profiles were obtained on Day 8, and steadystate parameters reported for glycopyrrolate and formoterol: AUC<sub>0-12</sub>, peak concentration (C<sub>max</sub>) and time to peak concentration (T<sub>max</sub>). Safety and tolerability were monitored throughout. **Results:** All 80 patients randomized were included in the safety population (modified intent-to-treat {mITT} population, n=68; PK population, n=72). GFF MDI treatment with and without VHC resulted in similar FEV<sub>1</sub> improvements over a 7-day period (**Figure**). The ratio (90% confidence interval) of least square mean FEV<sub>1</sub> AUC<sub>0-12</sub> for GFF MDI with VHC (1538 mL) versus without VHC (1516 mL) was 101.4% (100.1,102.7; mITT population). Pharmacokinetics were also comparable: AUC<sup>0-12</sup> geometric least squares mean ratio (95% confidence interval) for GFF MDI with or without VHC was 116.0% (99.7, 134.9) for glycopyrrolate, and 96.7% (86.7, 107.8) for formoterol fumarate (PK population). GFF MDI with or without VHC were well tolerated with a similar adverse event profile. **Conclusion:** In this study, the benefits of GFF MDI using novel Co-Suspension delivery technology on lung function were maintained with addition of the VHC. Systemic exposure to formoterol over the dosing interval was similar with and without VHC, but for glycopyrrolate was slightly higher with the VHC than without. The safety and tolerability profile of GFF MDI was similar with and without the VHC. Overall, this study supports use of the VHC with GFF MDI for patients with moderate-to-very severe COPD if needed (e.g. in patients who find it difficult to coordinate simultaneous aerosol actuation and inspiration).

## Breztri<sup>†</sup> Aerosphere<sup>†</sup> (Budesonide / Glycopyrrolate / Formoterol) AstraZeneca Pharmaceuticals

### RELATIVE BIOAVAILABILITY OF BUDESONIDE/ GLYCOPYRROLATE/FORMOTEROL FUMARATE METERED DOSE INHALER ADMINISTERED WITH AND WITHOUT A SPACER: RESULTS OF A PHASE I, RANDOMIZED, CROSSOVER TRIAL IN HEALTHY ADULTS.

Dorinsky P et al. *Clinical Therapeutics* Vol 42;4,2020.

**Purpose:** The triple combination therapy budesonide/glycopyrrolate/formoterol fumarate in a metered dose inhaler (BGF MDI), formulated by using innovative cosuspension delivery technology, is a new inhaled corticosteroid/long-acting muscarinic antagonist/longacting b<sub>2</sub>-agonist fixed-dose combination for the maintenance treatment of COPD. For some patients, the use of an MDI may be optimized with a spacer. This Phase I study assessed the effect of a spacer on lung exposure, total systemic exposure, and safety of BGF MDI 320/36/9.6 mg in healthy subjects. **Methods:** This randomized, open-label, crossover study assessed the pharmacokinetic and safety profiles of BGF MDI in healthy adult subjects who received a single dose of BGF MDI 320/36/9.6 mg (administered as 2 inhalations with 160/18/4.8 mg per actuation) in 4 regimens: without spacer and no charcoal; with spacer and no charcoal; without spacer and with charcoal; and with spacer and with charcoal. Primary objectives were to assess total systemic exposure (without charcoal) and lung exposure (with charcoal) of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without a spacer. Safety was also assessed. **Findings:** In total, 56 subjects were randomized (mean age, 29.9 years; 60.7% male, 17.9% former smokers). For systemic exposure (without charcoal), the spacer/without spacer ratio, expressed as a percentage (intrasubject %CV) of C<sub>max</sub> and AUC<sub>0-tlast</sub>, respectively, was 152.0 (47.5) and 132.8 (43.6) for budesonide, 240.6 (80.2) and 154.7 (73.4) for glycopyrronium, and 165.6 (50.7) and 98.6 (53.8) for formoterol. For lung exposure (with charcoal), the spacer/without spacer ratio

percentage (%CV) of C<sub>max</sub> and AUC<sub>0-tlast</sub>, respectively, was 183.6 (65.9) and 198.4 (71.5) for budesonide, 262.0 (91.8) and 373.9 (120.7) for glycopyrronium, and 222.9 (56.3) and 385.2 (147.0) for formoterol. Subjects who were judged to have suboptimal inhalation technique without a spacer (those in the lowest drug exposure quartile based on AUC<sub>0-tlast</sub>) had the greatest increase in both total systemic and lung exposure when a spacer was used versus no spacer. Subjects in the highest quartile had a minimal change in both total systemic and lung exposure when the spacer was used. Treatment-emergent adverse events (TEAEs) (all mild/moderate) reported by >1 subject per regimen were headache, cough, and dizziness. One subject withdrew because of TEAEs of headache and presyncope (neither considered treatment-related). **Implications:** Drug delivery can be improved for subjects with suboptimal MDI inhalation technique when using a spacer device with BGF MDI triple.

## RELATIVE BIOAVAILABILITY OF BUDESONIDE/GLYCOPYRRONIUM/FORMOTEROL FUMARATE DIHYDRATE METERED DOSE INHALER (BGF MDI) ADMINISTERED WITH AND WITHOUT A SPACER IN HEALTHY ADULTS.

P, Depetrillo P, Deangelis K, Trivedi R, Mo M, Ballal S, Gillen M. *European Respiratory Journal* 2019 54: PA3376; DOI: 10.1183/13993003.congress-2019.PA3376.

**Objective:** To assess the effect of a spacer device on lung exposure, total systemic exposure and safety of BGF MDI, a triple fixed-dose ICS/LAMA/LABA combination formulated using co-suspension delivery technology. **Methods:** In this Phase I, randomized, open-label, single-centre, crossover study (NCT03311373), US healthy adults (N=56) received 4 single-dose regimens of BGF MDI 320/28.8/10µg (with or without an AeroChamber Plus® Flow-Vu® spacer and with or without concurrent oral activated charcoal) to estimate lung and total systemic exposure. **Results:** Administration of BGF MDI with a spacer increased total systemic exposure of budesonide and glycopyrronium and lung exposure of all three components (Table). Use of a spacer increased formoterol total systemic exposure as measured by C<sub>max</sub> but not AUC<sub>0-tlast</sub>. In a quartile analysis, subjects with the lowest drug exposure without a spacer (suggesting poor inhalation technique) had the greatest increases in exposure when using the spacer, but not exceeding the exposure observed in subjects who had the highest exposure without a spacer (suggesting good inhalation technique). All regimens of BGF MDI were well tolerated with no unexpected safety findings. **Conclusion:** Administration of BGF MDI 320/28.8/10µg with a spacer device may increase drug delivery in subjects with suboptimal inhalation technique.

**Table. Budesonide, glycopyrronium and formoterol PK parameters**

	Total systemic exposure (without charcoal)		Lung exposure (with charcoal)	
	Without spacer	With spacer	Without spacer	With spacer
<b>Budesonide</b>				
n	52	52	52	52
AUC <sub>0-tlast</sub> , h pg/mL	1452.8 (66.0)	1934.0 (54.9)	823.9 (121.2)	1618.5 (74.9)
C <sub>max</sub> , pg/mL	452.6 (74.6)	702.3 (46.4)	340.0 (117.1)	612.0 (74.0)
t <sub>max</sub> , hours	0.33 (0.10, 2.00)	0.33 (0.10, 1.00)	0.33 (0.10, 2.00)	0.33 (0.10, 1.00)
<b>Glycopyrronium</b>				
n	52	52	51	51
AUC <sub>0-tlast</sub> , h pg/mL	48.1 (122.4)	74.3 (96.4)	19.8 (325.0)	69.2 (85.2)
C <sub>max</sub> , pg/mL	19.0 (131.0)	47.7 (73.3)	17.1 (181.7)	42.1 (65.4)
t <sub>max</sub> , hours	0.03 (0.03, 4.00)	0.03 (0.03, 0.67)	0.03 (0.03, 0.67)	0.03 (0.03, 0.10)
<b>Fomoterol</b>				
n	52	52	51	51
AUC <sub>0-tlast</sub> , h pg/mL	37.0 (88.7)	35.9 (97.5)	8.9 (471.8)	33.1 (71.3)
C <sub>max</sub> , pg/mL	10.8 (66.30)	18.1 (58.4)	8.3 (98.6)	17.9 (48.1)
t <sub>max</sub> , hours	0.10 (0.03, 4.00)	0.10 (0.03, 0.67)	0.10 (0.03, 0.67)	0.10 (0.03, 0.33)

Data shown are geometric means (CV%) except for t<sub>max</sub> which is median (range).

AUC<sub>0-tlast</sub>, area under the plasma concentration-time curve from time 0 to the time of the last measureable plasma concentration; CV%, coefficient of variation expressed as a percentage; PK, pharmacokinetics; t<sub>max</sub>, time to C<sub>max</sub>.

**COMPARISON OF ADVERSE EVENTS ASSOCIATED WITH DIFFERENT SPACERS USED WITH NON-EXTRAFINE BECLOMETASONE DIPROPIONATE FOR ASTHMA.**

*Wan Yah Ming S, Haughney J, Ryan D, Patel S, Ochel M, Stagno d'Alcontres M, Thornhill S, Kocks JWH, Price D. NPJ Prim Care Respir Med. 2019 Feb 8;29(1):3.*

Co-prescription of AeroChamber<sup>®</sup> spacer with non-extrafine beclomethasone dipropionate (non-EF BDP) is common but unlicensed. We report a comparison of inhaled corticosteroid (ICS)-related adverse events between patients co-prescribed AeroChamber<sup>®</sup> compared to the licensed Volumatic<sup>®</sup> spacer. We utilised two historical cohorts: questionnaire-based and electronic medical record (EMR)-based, to assess patient-reported and EMR-recorded adverse events in patients with asthma prescribed non-EF BDP. Marginal effect estimate (MEE) was calculated to determine non-inferiority of AeroChamber<sup>®</sup> compared to Volumatic in terms of patient-reported oral thrush and hoarseness with margin of 0.13. Other patient-reported adverse events (sore throat, bruising, weight gain, and coughing), and EMR-recorded adverse events were also assessed. Rate of patient-reported oral adverse events were non-inferior in 385 patients prescribed AeroChamber<sup>®</sup> compared to 155 patients prescribed Volumatic (27.7 vs 29.9%; MEE, -0.043; 95% CI, -0.133 to 0.047). Total patient-reported adverse events did not differ significantly between AeroChamber<sup>®</sup> and Volumatic (53.3 vs 49.7% with  $\geq 1$  adverse event). The EMR-based study of 1471 matched pairs of subjects did not show significantly different number of EMR-recorded adverse events between AeroChamber<sup>®</sup> and Volumatic (12.5 vs 12.8% with  $\geq 1$  adverse events). Co-prescribing AeroChamber<sup>®</sup> with non-EF BDP does not increase the risk for patient-reported and EMR-recorded ICS-related adverse events compared to co-prescribing Volumatic.

**SYSTEMIC ACTIVITY OF INHALED BECLOMETHASONE DIPROPIONATE: A DOUBLE BLIND COMPARISON OF VOLUME SPACERS.**

*Wolthers OD, Sergio F. Acta Paediatr 2012;101(2):159-63.*

**Background:** To which extent volume spacers may influence systemic activity of inhaled beclomethasone dipropionate (BDP) has not been evaluated. **Aim:** To assess whether the AeroChamber Plus<sup>®</sup> spacer is equivalent to the Volumatic<sup>(<sup>®</sup>)</sup> spacer for administration of inhaled hydroflouroalkane 134a propelled BDP in terms of lower leg growth rate (LLGR). **Patients and Methods:** Prepubertal children with mild asthma ( $n=26$ , ages 6-14 years) were included in a 3-time periods of 2 weeks duration randomized double-blind cross-over study with a single-blind placebo run-in and 2 wash-out periods. LLGR was measured with the knemometer. Interventions were inhaled BDP hydroflouroalkane 134a pMDI 100  $\mu\text{g}$  and 200  $\mu\text{g}$  b.i.d. with the AeroChamber Plus<sup>®</sup> and 200  $\mu\text{g}$  b.i.d. with the Volumatic spacer. **Results:** BDP 200  $\mu\text{g}$  b.i.d. from the AeroChamber Plus<sup>®</sup> was non-inferior to BDP 200 b.i.d. from the Volumatic spacer as the lower margin of confidence interval of the difference between treatments (-0.18 to 0.13 mm/week) was greater than the pre-specified lower limit for non-inferiority (-0.20 mm/week). UFC/creatinine data showed no statistically significant variations. **Conclusion:** The systemic activity of BDP via the Volumatic<sup>(<sup>®</sup>)</sup> and AeroChamber Plus<sup>®</sup> spacers is similar. The AeroChamber Plus<sup>®</sup> spacer may be used in children without risk of increasing systemic activity of BDP.

**SHORT-TERM LOWER LEG GROWTH IN 5- TO 11-YEAR-OLD ASTHMATIC CHILDREN USING BECLOMETHASONE DIPROPIONATE INHALERS WITH CHLOROFLUOROCARBON OR HYDROFLUROALKANE PROPELLANTS: A 9-WEEK, OPEN-LABEL, RANDOMIZED, CROSSOVER, NONINFERIORITY STUDY.**

*Wolthers OD, Walters EG. Clinical Therapeutics 2011;33(8):1069-1076.*

**Background:** Beclomethasone dipropionate-hydroflouroalkane (BDP-HFA) is a non-chlorofluorocarbon (CFC)-propelled metered dose inhaler. Data is needed to support the registration of BDP-HFA in pediatric populations for countries in the European Union. **Objective:** The aim of the study was to assess short-term lower leg growth in children with asthma during treatment with BDP-HFA 100  $\mu\text{g}$  BID compared with BDP-CFC 200  $\mu\text{g}$  BID. **Methods:** Children with asthma were included in this open-label, randomized, crossover study with 2-week run-in, active treatment, and washout periods. Lower leg length was measured every second week. As a secondary outcome parameter, 24-hour urine was collected for assessment of free cortisol. Interventions were inhaled BDP-HFA 100  $\mu\text{g}$  BID with AeroChamber Plus<sup>®</sup> spacer and BDP-CFC 200  $\mu\text{g}$  BID with Volumatic spacer. **Results:** In 63 patients with asthma aged 5 to 11 years, BDP-HFA 100  $\mu\text{g}$  BID was noninferior to BDP-CFC 200  $\mu\text{g}$  BID, as the lower margin of CI

(-0.03 to 0.10 mm/wk) of the estimated difference (0.03 mm/wk) was greater than the prespecified lower limit for noninferiority of -0.12 mm/wk. Mean (SD) lower leg growth rate during run-in, BDP-HFA 100 µg BID, and BDP-CFC 200 µg BID was 0.36 (0.17), 0.27 (0.21), and 0.23 (0.18) mm/wk, respectively (BDP-HFA estimate of difference, -0.09 [95% CI, -0.16 to -0.03 mm/wk;  $p < 0.01$ ]; BDP-CFC estimate of difference, -0.13 [95% CI, -0.19 to -0.06 mm/wk;  $p < 0.001$ ]). No statistically significant differences were seen in urinary free cortisol assessments. Eight and 6 mild to moderate adverse events in 10 children were reported during treatment with BDP-HFA and BDP-CFC, respectively. One event in each group was judged to be probably related to the study medication; no others were judged to be related. **Conclusions:** No statistically significant differences were found in lower leg growth between BDP-HFA 100 µg BID with AeroChamber Plus® spacer and BDP-CFC 200 µg BID with Volumatic spacer during 2-week treatment. Evidence of differences in systemic activity between the treatments was not found.

## **EFFECTS OF AEROCHAMBER PLUS® AND VOLUMATIC® ADD-ON DEVICES ON BDP DELIVERY FROM HFA SOLUTION PMDIS.**

*Church T, Brambilla G, Lewis D, Meakin B. Respiratory Drug Delivery, Scottsdale, Arizona, 2008.*

**Introduction:** Factors affecting dose delivery from pMDIs fitted with add-on devices include formulation, device design (e.g., materials, size, incorporation of a non-return valve), cleaning procedures and use-mode. Spacer-mode involves a conventional press-and-breathe maneuver whilst inhaling through the mouthpiece of the pMDI-device assembly. The spacer creates a longer path-length, allowing more time for propellant evaporation and slowing the cloud to facilitate lung access. Use in holding-chamber mode requires the device to have a non-return valve and discharging the dose into the chamber where it is held for a period before being inhaled, eliminating the need for press-and-breathe co-ordination. This mode also permits the patient to carry out repeated inhalations from the same dose. We were interested in comparing the effects of different add-on devices and their mode of use because the large size of some holding chamber devices may deter user acceptability. This study compares the dose delivered when beclometasone dipropionate (BDP) HFA solution type pMDIs were used in conjunction with both small and large volume devices in the two modes. **Conclusions:** These *in vitro* results would imply that, when used by patients in association with AeroChamber Plus®, the drug delivery performance for Modulite-BDP pMDIs could be similar to that obtained with Volumatic up to holding times of at least 5s for all three product strengths and up to 10s for the 50µg and 100µg dose strengths.

## **Combivent® (Salbutamol and Ipratropium Bromide) Boehringer Ingelheim® Pharmaceuticals Inc.**

### **DELIVERY OF ALBUTEROL/IPRATROPIUM BROMIDE BY PRESSURIZED METERED DOSE INHALER VIA SMALL VOLUME HOLDING CHAMBERS (VHCS): A COMPARATIVE *IN-VITRO* ASSESSMENT.**

*Mitchell JP, Bates SL, Wiersema KJ, Nagel MW, Morton RW, Schmidt JN. Presented at Proc. Ann. Meet. Amer. College of Chest Physicians (ACCP), San Francisco, October 2000, in Chest 2000;118(4):99S.*

**Purpose:** To compare the performance of a new small volume VHC (AeroChamber Plus® - 149 ml - Monaghan Medical Corp, Plattsburgh, NY) with a larger VHC (OptiChamber® - 218 ml, Respironics, Cedar Grove, NJ) for the delivery of a combination b-agonist/anticholinergic formulation for the treatment of COPD (Combivent®: 103 µg/dose albuterol sulfate (SAL) + 18 µg/dose ipratropium bromide (IPR) ex actuator mouthpiece (Boehringer-Ingelheim Pharmaceuticals Inc). **Methods:** Fine particle dose (FPD, particles < 4.7 µm aerodynamic diameter) and total emitted dose (ED) were determined for each VHC ( $n = 5$  devices for each group) by Andersen 8-stage impactor, operating at  $28.3 \pm 0.5$  L/min. The quantities of SAL and IPR components collected in the impactor were determined by HPLC-UV spectrophotometry. Results: FPD and ED (% of label claim dose) were as follows. AeroChamber Plus® VHC: SAL -  $56.2 \pm 3.6\%$ ,  $59.7 \pm 4.1\%$ ; IPR -  $47.0 \pm 4.5\%$ ,  $51.0 \pm 5.0\%$ , OptiChamber® VHC: SAL -  $41.1 \pm 3.3\%$ ,  $43.5 \pm 3.1\%$ ; IPR -  $35.0 \pm 6.0\%$ ,  $38.0 \pm 7.0\%$ . The AeroChamber Plus® VHCs delivered significantly more of both components as either FPD or ED [un-paired t-test,  $p = 0.001$ ]. **Conclusions:** Increased chamber volume does not necessarily correlate with improved FPD or ED with this formulation. Other considerations, such as internal geometry and inhalation valve design contribute to performance by controlling internal aerosol losses. Clinical Implications: The differences observed with these specific devices may have significant clinical implications that require further study.

## Flovent<sup>®</sup> (Fluticasone Propionate) GSK<sup>®</sup> Inc.

### ASSESSING DIFFERENT VALVED HOLDING CHAMBERS (VHC) WITH FACEMASK FOR DELIVERED MASS TO CARINA WITH INHALED CORTICOSTEROID BY PRESSURIZED METERED-DOSE INHALER (PMDI).

Bracey A, Nagel M, Suggett J. *British Thoracic Society*, Dec 2018.

**Objective:** Laboratory evaluation of VHC-facemask add-ons is ideally undertaken simulating conditions of use. We report a study in which VHC-facemask add-on devices for infants and small children use were evaluated using anatomical models. **Methods:** 2 VHCs with facemask ( $n=3$  devices/group) were evaluated using anatomical models comprised of airway replicas commensurate with that of a 7 month old infant and 4 year old child. Each VHC was prepared to manufacturer instructions, then evaluated by breathing simulator (ASL5000), mimicking a short coordination delay of 2 s followed by age appropriate tidal breathing. The facemask was attached to ADAM-III infant and child anatomical models. The airways were coupled directly to the breathing simulator via a filter below its exit to capture drug particles that would penetrate as far as the carina in a real patient. 5-actuations of fluticasone propionate (50 $\mu$ g, FP) were delivered at 30-s intervals. FP recovered from various locations in the aerosol pathway was subsequently assayed by HPLC-UV spectrophotometry. **Results:** The distribution of recovered FP from each type of VHC is summarized in Table 1. **Conclusions:** Significantly more FP was delivered to the model 'carina' from the AC Plus<sup>®</sup> VHC ( $p < 0.001$ ), the increased mass counterbalanced by decreased retention of medication within the VHC. It is important that clinicians are aware that large differences in delivery efficiency may exist when a facemask is present and some VHCs may fail to deliver any medication in certain cases.

Table 1: FP (mean  $\mu$ g  $\pm$  SD) recovered from VHCs and Models following tidal breathing

Breathing Pattern	Child Pattern 155 ml, 25 bpm, 1:2 I:E		Infant Pattern 50 ml, 30 bpm, 1:3 I:E	
	Free Breathe	AeroChamber Plus <sup>®</sup> Flow-Vu <sup>®</sup>	Free Breathe	AeroChamber Plus <sup>®</sup> Flow-Vu <sup>®</sup>
VHC	34.2 $\pm$ 2.8	17.5 $\pm$ 1.6	40.5 $\pm$ 3.7	20.3 $\pm$ 1.8
Facemask	1.1 $\pm$ 0.6	1.4 $\pm$ 0.2	0.0 $\pm$ 0.0	1.4 $\pm$ 0.2
Airway	0.3 $\pm$ 0.2	1.1 $\pm$ 0.2	0.0 $\pm$ 0.0	0.5 $\pm$ 0.1
Filter at 'Carina'	5.5 $\pm$ 1.8	10.1 $\pm$ 1.0	0.0 $\pm$ 0.0	3.0 $\pm$ 0.9

### USEFULNESS OF NONVALVED SPACERS FOR ADMINISTRATION OF INHALED STEROIDS IN YOUNG CHILDREN WITH RECURRENT WHEEZING AND RISK FACTORS FOR ASTHMA.

Kofman C, Teper A. *Canadian Respiratory Journal*. Accepted 26 July 2018; Published 3 September 2018.

**Background.** *In vitro* and scintigraphic studies have suggested that effectiveness of metered-dose inhalers (MDI) with nonvalved spacers (NVS) is similar to that of MDI with valved holding chambers (VHC). Nevertheless, there are no clinical studies that compare these techniques in long-term treatment with inhaled steroids in young children with recurrent wheezing and risk factors for asthma. **Objective.** To compare the efficacy of a long-term treatment with Fluticasone Propionate administered by an MDI through both type of spacers, with and without valves, in young children with recurrent wheezing and risk factors for asthma. **Patients and Methods.** Outpatient children (6 to 20 months old) with recurrent wheezing and risk factors for asthma were randomized to receive a 6-month treatment with metered-dose inhaler (MDI) of Fluticasone Propionate 125 mcg BID through an NVS or through a VHC. Parents recorded daily their child's respiratory symptoms and rescue medication use. **Results.** 46 patients of 13.4  $\pm$  5 months old were studied. During the study period, the NVS group ( $n = 25$ ) experienced 3.9  $\pm$  2.4 obstructive exacerbations, and the VHC group ( $n = 21$ ) had 2.6  $\pm$  1.6 ( $p = 0.031$ ). \*e NVS group had 17.4  $\pm$  14% of days with respiratory symptoms, and the VHC group had 9.7  $\pm$  7% ( $p = 0.019$ ). \*e NVS group spent 29.8  $\pm$  22 days on albuterol while the VHC group spent 17.9  $\pm$  11 days ( $p = 0.022$ ). **Conclusion.** Long-term treatment with inhaled steroids administered by MDI and NVS is less effective than such treatment by MDI and VHC in infants with recurrent wheezing and risk factors for asthma.

**PREPARATION OF VALVED HOLDING CHAMBERS BEFORE USE CAN HAVE A SIGNIFICANT INFLUENCE ON SUBSEQUENT MEDICATION DELIVERY EFFICIENCY: A STUDY WITH PRESSURIZED METERED DOSE INHALER DELIVERED FLUTICASONE PROPIONATE.**

*Suggett J, Nagel M, Mitchell J. Respiratory Drug Delivery, 2017, pp 319-323.*

**Introduction:** The present study set out to test the hypothesis that priming is not as effective as either pre-washing, or better yet, the use of anti-static materials in the design of a VHC to avoid the need for device preparation altogether. The following VHC types (n=5 devices/group) were evaluated (Table 1).

**Table 1.**

AeroChamber Plus® Flow-Vu® Inspiratory Flow Indicator	<b>AC Plus-AS</b>	Anti-static (charge dissipative)	Trudell Medical International, London Canada
AeroChamber Plus® Volumatic†	<b>AC Plus-NC</b> <b>VOL-NC</b>	Non-conducting Non-conducting	GlaxoSmithKline, Uxbridge, UK
Able Spacer 2	<b>ABL2-NC</b>	Non-conducting	Clement Clarke International, Harlow, Essex, UK

**Conclusion:** EMFP at each of the 4 stages of the test protocol differed widely between devices, suggesting that more than one process was responsible for the observed outcomes: 1) The use of charge dissipative materials in VHC construction avoided the need either for priming or for pre-washing with detergent before use; 2) Where devices were manufactured from non-conducting materials, washing with detergent followed by drip-drying was more effective than priming with particles of medication from three actuations of the pMDI-delivered drug product. For some, but not all VHC types, such pre-treatment could provide comparable medication delivery performance to that achievable from anti-static/charge dissipative VHC group; 3) Priming provided inconsistent results across all the NC device groups evaluated, especially with the VOL-NC VHCs; this outcome is consistent with the findings of Barry [9]; 4) Cleaning of VHCs with detergent followed by drip-drying before use was more effective at charge mitigation than when a rinse with clean water was undertaken as a final step. Clinicians should be aware that priming of VHCs is wasteful of medication, results in inconsistent medication delivery, and is unnecessary if an anti-static device is prescribed or if a non-conducting device is washed in mild detergent followed by drip-drying instead of a rinse.

**CLINICALLY APPROPRIATE TESTING OF DIFFERENT VALVED HOLDING CHAMBER (VHC) FACEMASK COMBINATIONS INVESTIGATING DELIVERED MASS TO CARINA FOR A WIDELY PRESCRIBED INHALED CORTICOSTEROID DELIVERED BY PRESSURIZED METERED DOSE INHALER (PMDI).**

*Suggett J, Nagel M, Schneider H, Mitchell J. Drug Delivery to the Lungs 26, 2015.*

**Background:** Laboratory evaluation of VHC-facemask add-ons is ideally undertaken simulating conditions-of-use. We report a study in which VHCs for small child use (n=3/group) (AeroChamber Plus® Flow-Vu® anti-static/child mask (aAC+); PocketChamber† (POC); Vortex† (VOR); SpaceChamber Plus† (SP); A2A Spacer† (A2A); Able Spacer†-2 (AB2)) were evaluated using an anatomical face/ 4-year child oropharynx model (ADAM-III). **Materials and Methods:** Each VHC was evaluated out-of-package (OOP), but the non-anti-static devices were also washed with mild detergent / drip-drying (W). Performance was evaluated by breathing simulator (tidal volume = 155-mL, inspiratory: expiratory (I:E) ratio = 1:2, rate/min = 25 cycles). The facemask was attached to the model face following a 2-s coordination delay post pMDI actuation. The airway was coupled directly to the breathing simulator via an exit filter capturing fine particles that could theoretically penetrate as far as the carina in a patient (FPcarina). 5-actuations of fluticasone propionate (50 µg FP/actuation ex actuator) were delivered at 30-s intervals. Recovered FP was assayed by HPLC-UV spectrophotometry. **Results:** Values of FPcarina (µg/actuation; mean±SD) were 10.5±1.0 (aAC+/OOP); 4.0±1.7 (POC/OOP); 0.7±1.1 (VOR/OOP); 1.0±0.3 (SP/OOP); 5.0±1.4 (SP/W); 0.6±0.1 (A2A/OOP); 4.1±0.9 (A2A/W); 0.3 ± 0.1 (AB2/OOP); 4.8 ± 0.9 (AB2/W). **Conclusions:** Significantly more FP was delivered to the model ‘carina’ from the aAC+ VHC (1-way ANOVA; p < 0.001); associated primarily with decreased VHC retention of medication. Large differences in delivery efficiency may exist when using different VHC-facemask delivery systems. Some of the difference can be eliminated by pre-conditioning non-anti-static devices before first use, however even when this is performed significant differences still exist.

**CLINICALLY APPROPRIATE TESTING OF VALVED HOLDING CHAMBERS (VHCS) WITH FACEMASK INDICATES SUBSTANTIAL DIFFERENCE IN DELIVERED MASS TO CARINA FOR A WIDELY PRESCRIBED INHALED CORTICOSTEROID.**

Harkness H, Suggett, J, Nagel M. Canadian Network for Respiratory Care Conference November 2015.

*In-vitro* evaluation of VHCs used with pressurized metered-dose inhalers (pMDIs) is ideally undertaken under conditions of use. We report a study of two VHCs ( $n=5$ /group, AeroChamber Plus® Flow-Vu® Anti-Static Valved Holding Chamber (aVHC) with child mask; Tips-haler<sup>†</sup> with medium mask evaluated using the Aerosol Delivery to Anatomic Model (ADAM III) face and airway replica of a 4 year old child. The VHCs were tested out of package. Each VHC was evaluated by breathing simulator (ASL5000, IngMar Medical), mimicking tidal breathing (tidal volume (Vt) = 155-mL, inspiratory: expiratory (I:E) ratio = 1:2, rate/min (Rmin) = 25 cycles). The facemask of the VHC was coupled to the ADAM-III model face and the model airway attached directly to the breathing simulator via a filter located at the carinal region of the model. 5-actuations of fluticasone propionate (125 µg FP/actuation ex pMDI actuator) were delivered at 30-s intervals. FP recovered from specific locations in the aerosol pathway was subsequently assayed by HPLC. The distribution of recovered FP from each type of VHC is summarized in Table 1.

**Table 1: FP (mean µg ± SD/actuation) Recovered from VHCs Indicated for Small Child Use, following Tidal Breathing**

Location	AeroChamber Plus® Flow-Vu® (aVHC) with child mask	Tips-haler <sup>†</sup> with medium mask
Retained by VHC	48.4±5.9	53.7±2.5
Deposited Inside Facemask	5.8±0.6	3.4±0.7
Deposited on Face	1.1±0.2	1.4±0.7
Deposited in Airway	4.4±0.2	1.1±0.3
Collected by Filter at 'Carina'	27.3±2.5	13.7±2.6

Significantly more FP was delivered to the carinal region from the AeroChamber Plus® Flow-Vu® VHCs (un-paired t-test,  $p < 0.001$ ). Many factors could have accounted for this difference, such as mask shape as well as inhalation valve design. Therefore, it is important that clinicians are aware of potential patient under-dosing with certain VHCs.

**EVALUATION OF PERFORMANCE OF VALVED HOLDING CHAMBERS (VHCS) USED OUT-OF-PACKAGING FOR SPEED OF MEDICATION DELIVERY: CAREFUL SELECTION OF THE VHC IS REQUIRED.**

Suggett J, Nagel M, Schneider H, Avvakoumova V, Ali R, Mitchell JP. Am J Resp Crit Care Med 2015;191:A4257

Electrostatic charging of non-conducting VHCs is known to be associated with loss of aerosolized medication delivered by pressurized metered-dose inhaler (pMDI) to patients who are prescribed these devices to aid poor coordination. In the hospital setting and potentially also in the home, time-to-treat pressures may encourage the use of such single-patient devices immediately from the packaging. This laboratory study was undertaken to test the hypothesis that pre-treatment of such devices is essential if significant loss of medication is to be avoided. Three different non-conducting (NC) VHCs with mouthpiece ( $n=3$ /group were evaluated (Breath-a-Tech<sup>†</sup>; Able Spacer<sup>†</sup> Universal; SpaceChamber Plus<sup>†</sup>) and compared with the AeroChamber Plus® Flow-Vu® Anti-Static Valved Holding Chamber (aVHC) with mouthpiece) as the reference device. 5-actuations of fluticasone propionate (110 µg FP/actuation; GSK Inc.) were delivered at 30-s intervals to devices removed from their packaging without pre-washing to mitigate charging. 2, 5 and 10s delay intervals were simulated using a proprietary apparatus following pMDI actuation to mimic uncoordinated use. The emitted dose of FP was sampled at 28.3 L/min ± 5% into an abbreviated Andersen cascade impactor. FP was subsequently recovered and assayed by HPLC-UV spectrophotometry. Measures of total emitted mass (TEM) and fine particle mass < 4.7µm (FPM<4.7µm) per actuation are summarized in Table 1.



**Table 1: Comparative Values of TEM and FPM<4.7µm FP (mean ± SD) from NC and AS VHCs Used without Pre-Washing**

VHC Name	Type	Delay (s)	TEM (µg/actuation)	FPM<4.7µm (µg/actuation)
Breath-a-Tech <sup>†</sup>		2	9.7 ± 1.5	8.9 ± 1.1
		5	4.4 ± 1.4	4.2 ± 1.4
		10	3.6 ± 0.9	3.3 ± 0.8
Able Spacer <sup>†</sup> Universal	NC	2	5.6 ± 1.8	5.2 ± 1.7
		5	2.1 ± 1.1	2.0 ± 1.0
		10	1.4 ± 0.7	1.3 ± 0.7
SpaceChamber Plus <sup>†</sup>		2	1.5 ± 0.6	1.5 ± 0.6
		5	0.5 ± 0.1	0.5 ± 0.1
		10	0.5 ± 0.3	0.5 ± 0.3
AeroChamber Plus <sup>®</sup> Flow-Vu <sup>®</sup> aVHC	AS	2	44.9 ± 3.8	42.2 ± 3.1
		5	43.1 ± 4.7	40.9 ± 3.4
		10	38.3 ± 2.5	35.7 ± 2.0

FP delivery as total mass or as fine particles via the antistatic AeroChamber Plus<sup>®</sup> VHC were largely unaffected by delay interval magnitude, and for delay intervals of 2 and 5 s were within ±15% of FPM<sub><4.7µm</sub> observed in a previous study for the pMDI alone, fully coordinated use, without VHC (46.2 ± 2.1 µg/actuation). On the other hand, all the non-conducting VHCs delivered almost no FP regardless of delay interval. Clinicians need to be aware that use of non-conducting VHCs without pre-washing could result in significant under-dosing of the patient.

#### COMPARISON OF AEROSOL DRUG DELIVERY TO A NASO-PHARYNGEAL REPLICA VIA TWO VALVED HOLDING CHAMBERS (VHC) WITH FACEMASK VIA BREATH SIMULATION.

*DiBlasi R, Coppolo DP, Mitchell JP, Wang V, Doyle C, Nagel MW. American Association for Respiratory Care AARC Open Forum, Anaheim, CA, Nov 16-19, 2013.*

**Background:** In order to improve patient compliance, the use of charge dissipative materials in VHC construction is becoming the standard of care. A facemask is required as the interface between patient and VHC for young children who cannot breathe through a mouthpiece. Recent studies have emphasized that a well-fitting facemask is critical for optimal drug delivery. We report a laboratory based comparison of aerosol drug delivery between two ‘antistatic’ VHCs under simulated breathing conditions, using an anatomically correct infant face-upper airway model (ADAM-III, Trudell Medical International (TMI)). **Methods:** Delivery of fluticasone propionate (FP; 44 µg/actuation GSK) as evaluated via anti-static AeroChamber Plus<sup>®</sup> VHC with Flow-Vu<sup>®</sup> IFI/infant mask (AC-Plus, MMC) and OptiChamber Diamond<sup>†</sup> VHC/LiteTouch<sup>†</sup> small-mask (OD, Philips) (*n*=5 devices/group). Tidal-breathing (tidal-volume (V<sub>T</sub>)= 155-mL, duty-cycle=33%, rate= 25-breaths/min) was simulated with an Ingmar ASL 500 test lung. Each facemask was applied to the face with the same clinically-appropriate force (1.6 kg). FP was recovered from the pMDI mouthpiece, VHC, facemask, face and airway of the model as well as the filter at the carinal exit of the model airway (equivalent to lung dose). Delivered mass of FP (DMFP) was quantified by HPLC. **Results:** DMFP (mean±SD) was significantly greater from AC-Plus (11.6±1.4µg) than OD (7.2±1.4µg) (unpaired t-test, *p*=0.002). This difference was largely due to the FP lost on the facemask of the OD facemask (8.8±0.9µg) compared to that of the AC-Plus (4.3±0.3 µg). **Conclusion:** While other factors such as facemask dead volume and device design are important factors in device performances, decreased aerosol delivery from the OD is explicable in terms of leakage between facemask and face, or choice of anti static materials, supported by higher deposition in its facemask. Clinicians should be aware that each VHC-pMDI combination is unique.

#### ANTI-STATIC VALVED HOLDING CHAMBERS DO NOT NECESSARILY OFFER SIMILAR AEROSOL DELIVERY PERFORMANCE.

*Suggett J, Mitchell J, Doyle C, Wang V, Nagel M. Proc. 23<sup>rd</sup> ERS Annual Congress, Barcelona, Spain, in Eur. Respir J. 2013:41S.*

**Rationale:** Adoption of materials to mitigate medication losses due to electrostatic charge accumulation on VHCs has been associated with improved reliability of output. We investigated if this change has resulted in similar *in vitro* performance, simulating poor coordination of inhalation with inhaler actuation, for which VHCs are prescribed. **Methods:** Each VHC (*n*=5 devices/group) tested out-of-package. 5-actuations of fluticasone propionate (125 µg

FP/actuation; Flovent<sup>1</sup>-HFA, GSK plc) was delivered at 30-s intervals to the VHC on test, sampling via a cascade impactor (CI) after 2, 5 and 10-s delay intervals, using a proprietary “delay” apparatus. FP was recovered from the CI and assayed by HPLC-spectrophotometry. Fine particle mass <4.7 µm aerodynamic diameter (FPM<4.7µm) provided a measure of the therapeutically beneficial medication capable of reaching the lungs. **Results:** Values of FPM<4.7 µm (µg FP; mean ± SD) are summarized in the Table. FPM<4.7 µm for the pMDI alone (no delay) was 46.2 ± 2.1 µg.

#### Fine Particle Mass (µg/actuation) after Various Delay Intervals Following Inhaler Actuation

VHC/manufacturer	Delay Interval (s)		
	2	5	10
AeroChamber Plus <sup>®</sup> /Trudell Medical International	42.2 ± 3.1	39.7 ± 1.3	35.7 ± 2.0
Antistatic Pocket Chamber <sup>1</sup> /nSpire Health Inc.	24.1 ± 4.0	21.4 ± 1.8	20.9 ± 3.0
OptiChamber <sup>1</sup> Diamond <sup>1</sup> /Philips-Respironics Inc.	35.0 ± 3.2	29.2 ± 1.7	23.0 ± 2.8
Vortex <sup>1</sup> /PARI Respiratory Equipment Inc.	39.9 ± 2.9	29.1 ± 4.7	19.1 ± 4.8

**Conclusions:** Although antistatic materials enable VHCs to be used without pre-washing, there are still large differences in output. Regardless of delay length, the AeroChamber Plus<sup>®</sup> VHC most closely matched the benchmark FPM<sub>4.7µm</sub> for the pMDI without VHC.

#### NOT ALL ANTI-STATIC VALVED HOLDING CHAMBERS HAVE EQUIVALENT PERFORMANCE: AN EXAMPLE WHY EACH VALVED HOLDING CHAMBER-INHALER COMBINATION SHOULD BE CONSIDERED UNIQUE.

Malpass J, Nagel M, Avvakoumova V, Ali R, Schneider H, Mitchell JP. Proc. 22nd ERS Annual Congress, Vienna, Austria, in Eur. Respir. J., 2012, 40S56, 384S - Poster p. 2154.

**Rationale:** Electrostatic charge mitigation by the use of charge dissipative materials with VHCs is common, since initial pre-washing can be avoided. We compared ‘antistatic’ VHCs; Optichamber<sup>1</sup> Diamond<sup>1</sup> (OD), Phillips Healthcare with AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> (AC Flow-Vu) Trudell Medical International) (n=4 devices/group), to determine suitability for patients delaying inhalation post-actuation. **Methods:** An abbreviated Andersen impactor that determined fine particle mass < 4.7 µm at 28.3 L/min (FPM<4.7µm) was used with an apparatus simulating 2, 5 and 10 s delay intervals following pMDI actuation (Flovent<sup>1</sup>, GSK plc, 125 µg/actuation fluticasone propionate (FP)). This approach conforms to guidance from European authorities that testing of VHCs should simulate delayed inhalation. Assay for FP was undertaken by HPLC-UV spectrophotometry. Measurements without delay were undertaken to assess mass recovery for FP, validating the procedure. All values are mean±SD. **Results:** Mass recoveries (131.5±2.9 and 130.7±3.8 µg/actuation for the OD and ACPlus VHCs respectively) were close to label claim, validating system suitability. The variation of FPM<4.7µm with delay interval is shown in the Table.

#### Relative Depletion of FPM<4.7µm

	Delay (s)		
	2	5	10
AC Flo-Vu	42.2 ± 3.1	39.7 ± 1.3	35.7 ± 2.0
OD	35.0 ± 3.2	29.2 ± 1.7	23.0 ± 2.8

The ratio FPM<4.7µm-ACPlus/FPM<4.7µm-OD) increased from 1.2 (2-s) to 1.4 (5-s) and to 1.6 (10-s), demonstrating faster depletion of the therapeutically beneficial medication from the OD. **Conclusion:** Not all VHCs manufactured from anti-static materials provide optimum performance for patients who have poor coordination.

#### DELIVERY OF AEROSOLIZED FLUTICASONE PROPIONATE VIA VALVED HOLDING CHAMBER WITH FACEMASK: BEWARE FACEMASK LEAKAGE.

Sharpe R, Nagel MW, Avvakoumova V, Schneider H, Ali R, Mitchell JP. Proc. 4<sup>th</sup> conference of the European Pediatric Formulation Initiative, Prague, Czech Republic, September 19-20, 2012

**Background & Objectives:** Leakage between facemask-and-face may result in medication loss by valved holding chamber (VHC)-facemask (1). Our study evaluated how an inspiratory flow indicator (IFI) can be used to avoid leakage. Methods: An infant face with realistic soft-tissue modeling (ADAM-III, Trudell Medical International (TMI), London, Canada (2)) was used to evaluate delivery of fluticasone propionate (FP; 50 µg/actuation, GSK (Canada))

via anti-static AeroChamber Plus® VHC with Flow-Vu\* IFI/infant mask (AC-Plus, TMI) or OptiChamber<sup>†</sup> Diamond<sup>†</sup> VHC/LiteTouch<sup>†</sup> small-mask (OD, Philips-Respironics, Parsippany, NJ, USA) ( $n=5$  devices/group), simulating tidal-breathing (tidal-volume ( $V_t$ )=155-mL, duty-cycle=33%, rate= 25-breaths/min. Each facemask was applied to the face with the same clinically-appropriate force (1.6 kg). The IFI of the AC-Plus was observed to be moving. FP was recovered from the nasopharynx and base (lung dose) of the model, and delivered mass (DMFP) quantified by HPLC-spectrophotometry as % label claim (LC). **Findings:** DMFP (mean±S.D.) was significantly greater from AC-Plus (25.8±5.3%LC) than OD (17.0±3.7%LC) (unpaired t-test,  $p=0.019$ ). FP on the facemask of the AC-Plus (6.2±1.9% LC), was slightly smaller than that determined with the OD facemask (9.9±2.6%). **Discussion/Conclusion:**  $V_t$  was set larger than normal in order to detect facemask-to-face leakage more precisely. Leakage was eliminated with the AC-Plus, by observing IFI movement. However, inasmuch as the OD does not have an IFI, it was not possible to do more than ensure that its facemask was applied with the same force to the model. Decreased aerosol delivery from the OD is explainable in terms of leakage between facemask and face, supported by higher deposition in its facemask.

## **A VISUAL INDICATOR FOR INHALATION FROM A VALVED HOLDING CHAMBER (VHC) IS AN IMPORTANT ATTRIBUTE WHEN DELIVERING INHALED MEDICATION TO INFANTS.**

Mitchell JP, Avakoumova V, Mackay H, Ali R and Nagel M. Presented at Drug Delivery to the Lungs-XIX, Edinburgh, UK, December, 2008. Published as abstract in *J Aerosol Med Pulm Deliv* 2009;22(3):289.

Delivery of inhaled medication to infants by valved holding chamber (VHC) with facemask may require more than one inhalation to empty the VHC because tidal volumes are typically smaller than chamber capacity. This study investigated the correlation between movement of an integrated inspiratory flow indicator (IFI) as a caregiver feedback aid for a VHC-facemask, number of inhalations and mass of medication, simulating use by a 6-9 month infant (tidal volume ( $V_t$ ) = 50-ml; duty cycle = 25%; 30 cycles/min). Anti-static AeroChamber Plus® VHCs incorporating the IFI feature, with infant facemask ( $n=5$ /group, 3 replicates/device; Trudell Medical International, London, Canada) were coupled to a breathing simulator (ASL5000 test lung, IngMar Medical, Pittsburgh, PA, USA). The VHCs were prepared as per manufacturer instructions and the facemask of the device on test was fitted to the ADAM-II flexible infant face model with a clinically appropriate force of 1.6 kg. Aerosol capture took place using an electret filter positioned behind the lips of the face model. Delivery of medication was evaluated from two different pressurized metered dose inhaler formulations likely to be used with pediatric patients (Flovent HFA<sup>†</sup> 44; 44 µg fluticasone propionate (FP) delivered ex-actuator and Ventolin HFA<sup>†</sup>; 90 µg salbutamol base equivalent (SAL) delivered ex-actuator, both from GSK plc. One actuation was delivered to the VHC at the onset of inhalation, and the filter removed after 1 complete breathing cycle, observing the movement of the IFI to confirm inhalation valve opening. This procedure was subsequently repeated by removing the filter after 2, 3, 4, 5 and 6 breathing cycles. Assay for FP or SAL was undertaken by HPLC-UV spectrophotometry. During these measurements, the IFI of each device was observed to move in synchrony with valve opening on all occasions, confirming that the facemask sealed onto the face model without leakage of ambient air into the mask during the inspiratory phase of each breathing cycle. Emitted mass after the first breathing cycle (EM1) was  $2.1 \pm 0.7$  µg (FP) and  $5.8 \pm 2.2$  µg (SAL); substantially lower than the corresponding values after 6 cycles (EM6), being  $9.0 \pm 2.1$  µg (FP), and  $15.9 \pm 3.1$  µg (SAL) [paired ttest for each formulation;  $p < 0.001$ ]. After 2 breathing cycles, values of EM2 ( $6.9 \pm 2.0$  (FP) and  $13.0 \pm 4.0$  µg (SAL)), though significantly greater than their corresponding EM1 values [ $p \leq 0.002$ ], were still noticeably lower than the corresponding EM6 value for FP ( $p = 0.028$ ), and barely statistically insignificant for SAL ( $p = 0.063$ ). After 3 inhalations, EM3 increased further to  $7.6 \pm 2.0$  µg (FP) and  $13.8 \pm 3.8$  µg (SAL), and thereafter were close to the corresponding EM6 values, indicating emptying of the VHC had taken place. We conclude that at least two successive inhalations are required to achieve optimum medication delivery for the 'infant' condition under optimum conditions with a well fitted facemask with no leakage. The IFI is an important feature which validates that the facemask is properly sealed to the infant's face and also confirms the number of inhalations that take place, thereby optimizing the therapeutic dose. Clinical studies are recommended to evaluate the benefit of this aid for the delivery of inhaled medication by VHC to this age group.

## **EFFICACY AND SAFETY OF FLUTICASONE PROPIONATE HYDROFLUOROALKANE INHALATION AEROSOL IN PRE-SCHOOL-AGE CHILDREN WITH ASTHMA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY.**

*Qaqundah PY, Sugerman RW, Ceruti E, Maspero JF, Kleha JF, Scott CA, Wu W, Mehta R and Crim C. The Journal of Pediatrics May 2007;150(5):565.*

**Objective:** To evaluate the efficacy and tolerability of fluticasone propionate (FP) hydrofluoroalkane (HFA) in children age 1 to <4 years with asthma. **Study Design:** Children were assigned (2:1) to receive FP HFA 88 µg ( $n=239$ ) or placebo HFA ( $n=120$ ) twice daily through a metered-dose inhaler with a valved holding chamber and attached facemask (AeroChamber Plus® VHC) for 12 weeks. The primary efficacy measure was mean percent change from baseline to endpoint in 24-hour daily (composite of daytime and nighttime) asthma symptom scores. **Results:** The FP-treated children had significantly greater ( $p \leq .05$ ) reductions in 24-hour daily asthma symptom scores (-53.9% vs -44.1%) and nighttime symptom scores over the entire treatment period compared with the placebo group. Daytime asthma symptom scores and albuterol use were slightly more decreased with FP than with placebo; however, the differences were not statistically significant. Increases in the percentage of symptom-free days were comparable. The percentage of patients who experienced at least 1 adverse event was similar in the 2 groups. Baseline median urinary cortisol excretion values were comparable between the groups, and there was little change from baseline at endpoint. FP plasma concentrations demonstrated that systemic exposure was low. **Conclusions:** FP HFA 88 µg twice daily was effective and well tolerated in pre-school-age children with asthma.

## **SYSTEMIC EXPOSURE FOLLOWING FLUTICASONE PROPIONATE METERED DOSE INHALER USING HYDROFLUOROALKANE PROPELLANT WITH VALVED HOLDING CHAMBERS AND FACE-MASKS IN PRE-SCHOOL CHILDREN.**

*Blake K, Hendeles L, Spencer T, Mehta R, Beerah M, Daley-Yates P and Kunka R. Presented at the 2006 Annual Meeting of the American College of Clinical Pharmacy, St. Louis, Missouri, October 29, 2006.*

Valved holding chambers with masks are often used with metered-dose inhalers in children with asthma to deliver drug to the lungs. Differences in holding chamber design can influence the amount of drug delivered. Lung deposition of fluticasone propionate (FP) using hydrofluoroalkane (HFA) propellant was examined using the AeroChamber Plus® and Babyhaler valved holding chambers. Children 1 to <4 years old were randomized in an open-label, 2-way crossover design (no washout between treatments) to receive 88 µg (44 µg/actuation) twice daily (every 12 hours) for 7.5 days (15 doses) using the AeroChamber Plus® VHC and Babyhaler with face-masks (FAS10002). The first and last 4 doses were directly observed by study staff. To limit the amount of blood collected from any one patient, children were randomized to one of three groups for blood sampling: Group 1: pre-dose, and 0.5-1, 1.5-2, 2.5-3, 3.5-4 hours post-dose; Group 2: 2.5-3, 3.5-4, 4.5-5, 6.5-7, 7.5-8 hrs post-dose; Group 3: 7.5-8, 8.5-9, 9.5-10, 11.5-12, post-dose, 12.5-13 hrs (0.5-1 hrs hour post dose #16). FP systemic exposure as described by area under the curve (AUC) was determined by population pharmacokinetics. Seventeen and 18 children completed AeroChamber® and Babyhaler treatments, respectively: one child completed only the Babyhaler treatment. Population mean (95% confidence interval) for FP exposure following dosing with the AeroChamber Plus® VHC was 97pg\*h/ml (85, 113) and with the Babyhaler was 52pg\*h/ml (34, 64). Lung deposition of FP through the AeroChamber Plus® VHC was higher when compared to the Babyhaler. However, systemic exposure for both devices was well below the threshold observed for decreases in cortisol production. Thus, both devices provide safe delivery of FP HFA to young children.

## **FLUTICASONE PROPIONATE HFA IMPROVES ASTHMA CONTROL IN PRE-SCHOOL AGE CHILDREN WITH ASTHMA.**

*Sugerman RW, Teper AM, Girardi G, Scott CA, Clements DS, Wu W, Crim C. J Allergy Clin Immunol Feb 2005; 115(2):S4-S5.*

**Rationale:** To evaluate the efficacy of fluticasone propionate HFA 88mcg BID (FP) vs placebo HFA (PLA) via MDI with the AeroChamber Plus® spacer with attached facemask for 12 weeks in pre-school age children with asthma. **Methods:** One to <4 year-olds with  $\geq 2$  episodes of increased asthma symptoms requiring medical attention and pharmacotherapy  $\leq 12$  months prior to screening and a baseline 24-hr daily asthma symptom score (DASS; scale 0 = none to 3 = severe) of  $\geq 1.1$  were enrolled in this randomized (120 PLA: 239 FP), double-blind, parallel-group, placebo-controlled trial. Efficacy measures included: mean percent change from baseline to endpoint (last 28 days of treatment) in DASS (primary), mean change from baseline in nighttime asthma symptom scores over the entire treatment period (NASS), change from baseline to endpoint in daily rescue albuterol use (DRAB), and time to treatment failure (TF; i.e., time to first asthma exacerbation). **Results:** Baseline mean DASS and NASS were

comparable between groups (DASS=1.7 PLA, 1.8 FP; NASS = 1.2 PLA, 1.4 FP). At endpoint, FP-treated patients experienced a greater reduction (improvement) from baseline in DASS (54% FP, 44% PLA;  $p=0.036$ ) and NASS (-0.56 FP, -0.44 PLA;  $p=0.049$ ). Baseline DRAB use was comparable across groups (4 inhalations/day [IPD] PLA; 5 IPD FP). DRAB decreased by 2 and 3 IPD for the PLA and FP groups, respectively, at endpoint. More PLA patients (12%) discontinued due to TF compared with FP-treated patients (5%) ( $p=0.034$ ). **Conclusion:** Treatment with FP HFA 88 mcg BID for 12 weeks significantly improves asthma control in 1 to < 4 year-olds with asthma.

#### **SAFETY PROFILE OF FLUTICASONE PROPIONATE HFA IN PRE-SCHOOL AGE CHILDREN WITH ASTHMA.**

*Qaqundah PY, Maspero J, Ceruti E, Scott CA, Clements DS, Wu W, Crim C. J Allergy Clin Immunol Feb 2005;115(2):S211.*

**Rationale:** To evaluate the safety of fluticasone propionate HFA 88mcg BID (FP) vs placebo HFA (PLA) via MDI with the AeroChamber Plus® spacer with attached facemask for 12 weeks in pre-school age children with asthma. **Methods:** One to <4 year-olds with symptomatic asthma, receiving maintenance asthma medications (excluding systemic [SCS] or inhaled corticosteroids [ICS]) plus a short-acting beta-agonist (SABA) or SABA alone, were enrolled in this randomized (120 PLA: 239 FP), double-blind, parallel-group, placebo-controlled trial. Children receiving SCS within 10 weeks prior to randomization and/or ICS within 2 (low dose) or 8 (moderate-high dose) weeks prior to Screening were excluded. Safety assessments included: adverse events (AEs), clinical labs, oropharyngeal/nasal exams, asthma exacerbations, and 12-hour, overnight urinary cortisol excretion (U-Cortisol). **Results:** No deaths or treatment-related serious AEs were reported. The percentages and types of AEs were comparable between groups. Events most commonly reported were fever (PLA=24%, FP=28%), nasopharyngitis (PLA=14%, FP=16%) and URTI (PLA=11%, FP=13%), events common in this age-group. Clinical lab results were comparable between groups. Few (PLA=0, FP=2) patients had a negative to positive shift in the oropharyngeal/nasal exam. More PLA-treated patients experienced an asthma exacerbation (11%) compared with FP-treated patients (4%). Baseline median U-Cortisol values were similar between groups (PLA=2.3mcg; FP=2.8mcg); and, there was little change from baseline after 12 weeks (PLA = -0.1mcg; FP= -0.4mcg). **Conclusion:** 12-week treatment with FP HFA 88mcg BID was well tolerated in 1 to <4 year-olds with asthma. The safety profile was similar to PLA and there was no evidence of adrenal suppression.

#### **IN VITRO DEPOSITION OF FLUTICASONE AEROSOL FROM A METERED-DOSE INHALER WITH AND WITHOUT TWO COMMON VALVED HOLDING CHAMBERS.**

*Asmus MJ, Liang J, Coowanitwong I, Vafardari R, Hochhaus G. Annals of Allergy, Asthma & Immunology 2002;88:204-208.*

**Background:** Previous *in vitro* aerosol deposition experiments indicate that the corticosteroid respirable dose from a metered-dose inhaler (MDI) can vary by threefold depending on the specific valved holding chamber (VHC) MDI combination. **Objective:** We compared *in vitro* aerosol deposition from a fluticasone propionate MDI (Flovent, GlaxoSmithKline, Research Triangle Park, NC) to that of the same MDI used in combination with two VHCs (EasiVent, Dey, Napa, Ca; and AeroChamber Plus®, Monaghan Medical Corp., Plattsburgh, NY) to evaluate how these VHCs affect the respirable dose of fluticasone. **Methods:** The respirable dose (aerosol particles 1 to 5 microm in size) of fluticasone was determined by sampling 5 x 110-microg actuations from each configuration (MDI alone, MDI plus AeroChamber Plus®, and MDI plus EasiVent) in multiples of ten using a well established, *in vitro* cascade impactor method. Fluticasone aerosol was washed from individual impactor stages with 50% methanol and quantified via ultraviolet high-pressure liquid chromatography. Differences among outcomes were determined using analysis of variance. **Results:** Mean respirable dose from AeroChamber Plus® VHC (47.9 +/- 6.9 microg/actuation) was not different ( $p > 0.05$ ) from that produced by the MDI alone (50.3 +/- 2.2 microg/actuation). EasiVent respirable dose (27.0 +/- 3.6 microg/actuation) was less than that produced by either the AeroChamber Plus® VHC or the MDI alone ( $p < 0.001$ ). **Conclusions:** VHCs do not display equivalent *in vitro* performance with a fluticasone MDI. If a patient needs a VHC, clinicians should use available *in vitro* performance information to aid in selecting the best device.

#### **PERFORMANCE OF LARGE AND SMALL VOLUME VALVED HOLDING CHAMBERS (VHCS) AS A FUNCTION OF FLOW RATE.**

*Mitchell JP, Nagel MW, Wiersema KJ, Bates SL, Morton RW, Schmidt JN. J Aerosol Med 2001;14(1):122.*

It is useful from the standpoint of the health care provider, if the performance of add-on devices for use with pressurized metered dose inhalers is characterized within the range of flow rates likely to be achieved by users.

VHCs representing smaller (adult AeroChamber Plus®, 149-ml;  $n = 5$ ) and larger (Volumatic®, 750-ml;  $n = 5$ ) devices were compared with HFA-formulated fluticasone propionate (125 µg/dose ex metering chamber) at three flow rates, 28.3, 45 and 60 L/min. Measurements were made by Andersen 8-stage impactor. Fine particle fractions ( $< 4.7 \mu\text{m}$ ,  $< 4.6 \mu\text{m}$  and  $< 4.0 \mu\text{m}$  aerodynamic diameter at 28.3, 45 and 60 L/min respectively) from both VHCs were close to 90%, significantly greater than that from the pMDI alone. At 28.3 L/min, fine particle dose (FPD) from the smaller VHC ( $50.5 \pm 3.8 \mu\text{g}$ ) was comparable with that from the larger VHC ( $45.9 \pm 7.8 \mu\text{g}$ ) [ $p = 0.27$ ]. At the higher flow rates, FPD from the smaller VHC ( $65.5 \pm 2.6 \mu\text{g}$  (45 L/min) and  $65.2 \pm 6.2 \mu\text{g}$  (60 L/min)) exceeded equivalent values from the larger VHC ( $53.8 \pm 3.7 \mu\text{g}$  (45 L/min) and  $55.3 \pm 4.9 \mu\text{g}$  (60 L/min)) [ $p < 0.023$ ].

## PERFORMANCE CHARACTERIZATION OF PMDI-DELIVERED FLUTICASONE PROPIONATE FROM FOUR VALVED HOLDING CHAMBERS (VHCS).

Mitchell JP, Nagel MW, Wiersema KJ, Bates SL. Meeting of the ATS, San Francisco 2001.

**Rationale:** To compare the delivery of fluticasone propionate in terms of fine particle ( $< 4.7 \mu\text{m}$  aerodynamic diameter (FPD)) and total emitted dose (ED) from 4 VHCs. **Methods:** FPD and ED were determined for AeroChamber Plus® (Monaghan Medical Corp., Plattsburgh, NY, 149 ml), Optichamber® (Respironics, Cedar Grove, NJ, 218 ml), Pocket Chamber® (Ferraris Medical, Inc., Holland, NY, 90 ml) and ACE® (DHD Healthcare, Wampsville, NY, 150 ml) VHCs ( $n=5$  devices/group). Particle size measurements were made by Andersen cascade impactor (Graseby Andersen, USA) at  $28.3 \pm 0.5$  l/min. The VHCs were washed with a mild ionic detergent followed by air-drying before testing in order to minimize the influence of electrostatic effects. The mass of FP was assayed by HPLC-UV spectrophotometry. **Results:** Both FPD and ED unit doses, normalized to label claim, from the AeroChamber Plus® VHCs ( $60.2 \pm 3.8 \mu\text{g}$  (FPD);  $69.1 \pm 3.5 \mu\text{g}$  (ED)) significantly exceeded equivalent values from the Optichamber® VHCs ( $38.4 \pm 1.7 \mu\text{g}$  (FPD);  $43.7 \pm 1.2 \mu\text{g}$  (ED)), Pocket Chamber® ( $37.2 \pm 0.8 \mu\text{g}$  (FPD);  $41.1 \pm 0.8 \mu\text{g}$  (ED)) and ACE® ( $20.3 \pm 4.1 \mu\text{g}$  (FPD);  $22.0 \pm 4.5 \mu\text{g}$  (ED)) (1-way ANOVA,  $p < 0.001$ ). **Conclusion:** Chamber volume alone does not necessarily correlate with improved FPD or ED and other considerations, such as internal geometry and inhalation valve design are also important.

## PERFORMANCE OF AN IMPROVED SMALL VOLUME VALVED HOLDING CHAMBER (VHC).

Mitchell JP, Nagel MW, Schmidt JN, Morton RW. Presented at the ERS Annual Congress/World Congress on Lung Health, Florence, Italy, September 2000.

We report an *in vitro* investigation in which the performance of an improved small volume (149 ml) VHC (adult AeroChamber Plus®, Trudell Medical International, London, Canada;  $n = 5$  devices) was compared with a 218 ml VHC (OptiChamber®, Respironics, Cedar Grove, NJ, USA) for a corticosteroid (HFA-fluticasone propionate (HFA-FP) 125 µg/dose, GlaxoSmithKline plc, UK). Measurements of emitted dose (ED), together with fine particle fraction (FPF) and fine particle dose (FPD), were made by Andersen 8-stage impactor equipped with a USP induction port at  $28.3 \pm 0.5$  L/min. We observed the following (mean  $\pm$  S.D):

VHC	FPD* (mg)	FPF* (%)	ED (mg)
AeroChamber Plus®	$43.1 \pm 3.8$	$86.3 \pm 3.1$	$49.9 \pm 4.4$
OptiChamber®	$19.3 \pm 2.7$	$80.2 \pm 1.6$	$24.1 \pm 3.5$

\*particles  $< 4.7 \mu\text{m}$  aerodynamic diameter

In spite of its smaller volume, the AeroChamber Plus® VHCs delivered significantly more HFA-FP than the OptiChamber® VHCs, both in terms of FPD and ED (un-paired t-test,  $p < 0.001$ ). The size selectivity of the smaller VHC was also significantly better ( $p = 0.005$ ). The improved small volume VHC provides highly efficient delivery of particles of HFA-FP in sizes likely to penetrate to receptors in the lung, whilst minimizing the release of coarser particles that are likely to deposit in the oropharyngeal region.

## IN VITRO PERFORMANCE OF VALVED HOLDING CHAMBERS (VHCS) AT FLOW RATES APPROPRIATE FOR LOW FLOW RATE USERS.

Mitchell JP, Nagel MW, Coppola D. Journal of Allergy & Clinical Immunology January 2000;105(1):Sec 26 pS10.

The delivery of aerosolized medication from valved holding chambers (VHCs) used with pressurized metered dose inhalers (pMDIs) is dependent on the inspiratory flow rate of the patient. A study was undertaken to evaluate the

delivery of a corticosteroid (Flovent<sup>®</sup>: 110 µg/dose CFC-fluticasone propionate (FP)) through two VHCs (AeroChamber Plus<sup>®</sup>; Monaghan Medical Corp., Plattsburgh, NY and OptiChamber<sup>®</sup>; Respironics, Cedar Grove, NJ;  $n = 10$  devices/group) at  $5.0 \pm 0.5$  and  $12.0 \pm 0.5$  l/min, representative of low flow rate patients. A single dose of medication was delivered to a filter square (Filtrete<sup>®</sup>; 3M Corp., St. Paul, MN) located at the mouthpiece/mask adapter of each device to provide data indicative of optimum performance without 'dead volume'. The filter was removed 30 s after pMDI actuation and agitated in methanol to release collected medication quantitatively. The mass of FP collected was assayed by HPLC-UV spectrophotometry. The AeroChamber Plus<sup>®</sup> VHCs delivered total emitted doses of  $45 \pm 2$  and  $67 \pm 4$  µg FP at 5 and 12 l/min respectively, compared with  $23 \pm 6$  and  $49 \pm 2$  µg from the OptiChamber<sup>®</sup> VHCs at the equivalent conditions. The difference in emitted dose between VHC types was statistically significant at both flow rates (un-paired t-test,  $p < 0.001$ ). *In vitro* data based on measurements made at a flow rate of 28.3 l/min or higher should not be taken as predictive of performance with patients that can only achieve low inspiratory flow rates.

## THE PERFORMANCE OF THE ADULT AEROCHAMBER PLUS<sup>®</sup> VALVED HOLDING CHAMBER (VHC) WITH HFA FORMULATED FLUTICASONE PROPIONATE.

Schmidt JN, Morton RW, Mitchell JP, Nagel MW. *Drug Delivery to the Lungs-X, London, UK, 1999, J Aerosol Med 1999;13(1):63.*

From the standpoint of the health care provider, it is helpful if the therapeutically beneficial fine particle dose of a pMDI-delivered formulation such a corticosteroid is comparable with that delivered by the pMDI alone, irrespective of the choice of propellant in the formulation. The performance of an improved valved holding chamber (adult AeroChamber Plus<sup>®</sup> VHC;  $n = 5$ ) is reported with HFA-formulated fluticasone propionate (HFA - FP; 125 µg/dose ex metering chamber). As expected, the VHC greatly increased the proportion of the emitted dose (ED) delivered in particles finer than 4.7 µm aerodynamic diameter (FPF) from  $39.0 \pm 3.0\%$  to  $74.7 \pm 3.7\%$  (HFA-FP) [paired t-test  $p < 0.001$ ]. The fine particle dose (FPD) with the VHC ( $43.5 \pm 5.3$  µg) was comparable with that delivered by the pMDI alone ( $47.4 \pm 1.1$  µg) [ $p = 0.21$ ]. The portion of the dose contained in coarser particles that might otherwise deposit in the upper respiratory tract and be associated with unwanted side-effects, decreased substantially from  $74.5 \pm 7.5$  µg (pMDI alone) to  $14.7 \pm 2.2$  µg with the addition of the VHC [ $p < 0.001$ ].

## Flutiform<sup>®</sup> (Fluticasone / Formoterol ) SkyePharma AG

### SHORT-TERM GROWTH DURING TREATMENT WITH INHALED FLUTICASONE PROPIONATE/FORMOTEROL, FLUTICASONE AND BECLOMETHASONE TREATMENT.

Wolthers D, Moore A, Mersmann S, Dissanayake S. *Journal of Aerosol Medicine and Pulmonary Drug Delivery. May 2017, ahead of print.*

**Background:** Fluticasone propionate/formoterol (FP/FORM) is a pressurized metered-dose inhaler (pMDI; Flutiform<sup>®</sup>) approved for use in adolescents and adults and under development for pediatric use. **Objective:** To compare short-term growth in asthmatic children treated with FP/FORM, FP pMDI with valved holding chamber, and beclomethasone dipropionate (BDP) in a breath-actuated device. **Methods:** Children with persistent asthma ( $n = 48$ ; 5 to <12 years) participated in an assessor-blinded, randomized, three-way crossover trial with run in, wash out, and active treatment periods, each of 2 weeks duration. Interventions were FP/FORM 100/10 µg b.i.d. with an AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> Spacer, FP pMDI (Flixotide<sup>®</sup>) 100 µg b.i.d. with a Volumatic<sup>®</sup> spacer, and extra-fine BDP breath-actuated inhaler (Aerobec<sup>®</sup>/QVAR<sup>®</sup> Autohaler<sup>®</sup>) 100 µg b.i.d. Lower leg growth rate (LLGR) was measured by knemometry. **Results:** The least square (LS) mean difference in LLGR between FP/FORM and FP (per protocol population) was  $-0.006$  mm/week (95% CI:  $-0.095$  to  $0.084$ ;  $p < 0.001$  for noninferiority [noninferiority margin  $-0.200$  mm/week]). Both treatments elicited no change from baseline off-treatment growth rate. The LS mean treatment difference of FP/FORM versus BDP was  $0.116$  mm/week (95% CI:  $-0.004$  to  $0.235$ ;  $p = 0.057$ ) and of FP versus BDP  $0.163$  mm/week (95%CI:  $0.078$ - $0.249$ ;  $p < 0.001$ ). Results in the full analysis population were: FP/FORM versus FP  $-0.012$  mm/week (95% CI:  $-0.080$ - $0.056$ ;  $p < 0.001$ ); FP/FORM versus BDP  $0.143$  mm/week (95% CI:  $0.064$ - $0.222$ ;  $p < 0.001$ ); FP versus BDP  $0.163$  mm/week (95% CI:  $0.093$ - $0.233$ ;  $p < 0.001$ ). **Conclusions:** FP/FORM pMDI with AeroChamber and FP pMDI with Volumatic spacer did not affect lower leg growth, measured by knemometry, in asthmatic children. Conversely, extra-fine BDP from a breath-actuated inhaler resulted in short-term growth suppression.

## FLUTICASONE PROPIONATE/FORMOTEROL FUMARATE COMBINATION THERAPY IS EQUALLY EFFECTIVE AND WELL-TOLERATED WHEN ADMINISTERED WITH OR WITHOUT A SPACER DEVICE TO PATIENTS WITH ASTHMA.

Price D, Papi A, Kaiser K, Grothe B, Lomax M. Presented at the European Respiratory Conference in Amsterdam, September, 2011.

**Background:** Phase 3 studies involving a new asthma therapy combining fluticasone (FLUT) and formoterol (FORM) in a single aerosol inhaler (FLUT/FORM; flutiform<sup>®</sup>) either used a spacer or did not. This is the first comparison of the efficacy and tolerability of treatment with or without the use of a spacer device. **Methods:** Adults and adolescents with mild, moderate or moderate-severe asthma were treated with FLUT/FORM 100/10 $\mu$ g or 250/10 $\mu$ g b.i.d. delivered either with ( $n=195$ ) or without ( $n=532$ ) a spacer in 6 randomized, double-blind and open-label, parallel group studies. The endpoint was non-inferiority between spacer and non-spacer groups (concluded if the lower bound of the 95% CI was  $\geq -0.2L$ ) in terms of changes in morning pre-dose FEV<sub>1</sub> and morning pre-dose to 2h post-dose FEV<sub>1</sub> over 12 weeks. The incidence of adverse events (AEs) was analyzed over 8 weeks. **Results:** FLUT/FORM was consistently as effective when delivered with or without a spacer at all dose strengths and asthma severities. From baseline to end of study, the LS mean treatment difference in morning pre-dose FEV<sub>1</sub> was 0.067L greater without spacer (95% CI: -0.149, 0.015) and in morning pre-dose to 2h post-dose FEV<sub>1</sub> was 0.015L greater with spacer (95% CI: -0.051, 0.081). AEs were reported with similar frequency both with and without a spacer (nasopharyngitis: 14 (2.1%) vs 34 (3.2%); asthma: 12 (1.8%) vs 17 (1.6%) patients; cough: 4 (0.6%) vs 10 (0.9%); dysphonia: 5 (0.7%) vs 7 (0.7%)). **Conclusions:** Pooled analysis showed that fluticasone/formoterol may be given with or without a spacer device with both approaches providing similar efficacy and tolerability.

## DELIVERY FROM FLUTIFORM HFA PRESSURIZED METERED DOSE INHALER (PMDI) WITH AND WITHOUT VALVED HOLDING CHAMBER (VHC).

Mueller-Walz R, Fueg LM, Brindley A, Venthoye G. *Respiratory Drug Delivery Europe 2011*, pp431-434.

**Introduction:** Inhaled combination products are the mainstay of therapy in asthma and COPD. Three dosage strengths of Flutiform were developed to offer to the patient the novel combination of the well-established corticosteroid (ICS) fluticasone and the fast onset, long-acting beta-agonist (LABA) formoterol in a convenient pMDI presentation. Spacers or valved holding chambers (VHC) can be used coupled to pMDIs to address the common issues patients face with; (1) the co-ordination of inhalation and actuation, and (2) the mouth/throat deposition and/or swallowing of steroid drugs. The use of VHCs is intended to remove the larger particles from the emitted aerosol whilst maintaining the delivery of fine particles or lung dose to the patient. Regulatory guidance documents in Europe and the US require the product to be characterized *in vitro* with any spacer or VHC device recommended in the patient instructions (1,2). More recently, regulators specified that the same principals should be applied to *in vitro* spacer tests as were applied to comparative pMDI testing (3). **Methods:** Four different spacers and VHC were selected for *in vitro* characterization based on design and material considerations and market prevalence. Aerodynamic particle size distribution (APSD) was determined by Andersen Cascade Impactor (ACI. 28.3 L/min configuration) of medium strength Flutiform 125/5 delivered via spacer / VHC, with flutiform delivery without spacer as control. Further characterization of the product performance with the selected spacer was performed by evaluating dose delivery and APSD of flutiform strengths (50/5, 125/5, 250/10 ug/actuation) at various flow rates (28.3, 60 and 90 L/min) and different operating regimes (0 second time lag between actuation and inhalation and 2 and 5 second time lag to simulate poor coordination). **Results and Discussion:** In the first part of the study, APSD of flutiform delivery via four different spacers was evaluated for selecting the device providing the best match for further evaluation. As exemplified by Figure 1 and 2, a comparable *in vitro* APSD of the delivered drugs was found when the product was delivered via its proprietary press-and-breathe actuator with or without the use of the TMI AeroChamber Plus<sup>®</sup> VHC device, apart from a major proportion of large particles being kept in the spacer which other-wise would be deposited in the USP induction port ('throat') of the apparatus. Most importantly, the amount of drug deposited on stage 3 onwards of the ACI (28.3 L/min configuration) was very similar. Further studies were performed with all flutiform strengths to characterize the drug delivery from TMI AeroChamber Plus<sup>®</sup> VHC at various flow rates and operating regimes. The results showed no relevant impact of the time lag on the fluticasone deposited on grouped stages of the ACI, as exemplified by Figure 3 and 4 for low strength flutiform 50/5. It should be noted that the fine particle fraction (FPF) (stage 3 to filter, < 4.7  $\mu$ m) is around 40% of the delivered dose across all conditions. Comparable results were found for the delivery of formoterol and for the other flutiform strengths. **Conclusions:** The *in vitro* APSD profiles confirm the design intent for improved delivery to patients by showing that use of the TMI AeroChamber Plus<sup>®</sup> delivers the same estimated lung dose as the standard press and breathe actuator whilst effectively removing the larger particles from the emitted



aerosol which would be expected to impact in the patient's mouth/throat and/or be swallowed. The FPF (expressed as % of delivered dose) was shown to be consistent at around 40% for both drugs under all conditions tested. The TMI AeroChamber Plus® was confirmed as a suitable spacer for recommendation in the patient instructions for flutiform.

**Fostair<sup>®</sup> (Beclomethasone Dipropionate / Formoterol Fumarate)**  
**Chiesi Farmaceutici S.p.A**

**THE SYSTEMIC EXPOSURE TO INHALED BECLOMETASONE / FORMOTEROL PMDI WITH VALVED HOLDING CHAMBER IS INDEPENDENT OF AGE AND BODY SIZE.**

*Govoni M, Piccinno A, Lucci G, Poli G, Acerbi D, Baronio R, Singh D, Kuna P, Chawes B, Bisgaard H. Pulmonary Pharmacology & Therapeutics 2015;30:102-9.*

**Background:** Asthma guidelines recommend prescription of inhaled corticosteroids at a reduced dosage in children compared to older patients in order to minimize the systemic exposure and risk of unwanted side effects. In children, pressurized metered dose inhalers (pMDI) are recommended in combination with a valved holding chamber (VHC) to overcome the problem of coordinating inhalation with actuation. However, the influence of age and body size on the systemic exposure of drugs to be administered via a pMDI with VHC is still not fully elucidated. Therefore, we aimed to compare the systemic exposure to the active ingredients of a fixed combination of beclomethasone-dipropionate/formoterol-fumarate administered via pMDI with VHC in children, adolescents and adults. **Methods:** The pharmacokinetics of formoterol and beclomethasone-17-monopropionate (active metabolite of beclomethasone-dipropionate) was evaluated over 8 h from three studies, each performed in a different age and body size group. Children (7-11 years,  $n = 20$ ), adolescents (12-17 years,  $n = 29$ ) and adults ( $\geq 18$  years,  $n = 24$ ) received a single dose of beclomethasone/formoterol (children: 200 µg/24 µg, adolescents and adults: 400 µg/24 µg) via pMDI with AeroChamber Plus®. **Results:** The systemic exposure in children in comparison to adolescents was equivalent for formoterol while it was halved for beclomethasone-17-monopropionate in accordance with the halved dose of beclomethasone administered in children (90% CIs within 0.8-1.25 for formoterol and 0.4-0.625 for beclomethasone-17-monopropionate). The systemic exposure to beclomethasone-17-monopropionate and formoterol was equivalent between adolescents and adults. **Conclusions:** The systemic exposure to the active ingredients of a fixed dose combination of beclomethasone/formoterol administered via pMDI with AeroChamber Plus® correlates with the nominal dose independently of patient age and body size. Thus, dose reduction in relation to age when using a pMDI with VHC may be unnecessary for reducing the systemic exposure in children.

**EFFECT OF AEROCHAMBER PLUS® ON THE LUNG AND SYSTEMIC BIOAVAILABILITY OF BECLOMETASONE DIPROPIONATE/FORMOTEROL PMDI.**

*Singh D, Collarini S, Poli G, Acerbi D, Amadasi A, Rusca A. British Journal of Clinical Pharmacology 2011;72(6):932-9.*

**WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT** • Use of a spacer minimizes oropharyngeal deposition and optimizes drug targeting to the airways in subjects with coordination difficulties. However, the increase in pulmonary deposition often observed with spacer devices, could potentially lead to an increase in overall systemic exposure. • EMA guidelines recommend that the development of a pMDI should always include testing of at least one specific spacer for use with a particular pMDI. • The aim of this study was to examine the effect of AeroChamber Plus® VHC on the lung bioavailability and total systemic exposure of a HFA pMDI fixed combination of extrafine beclomethasone dipropionate /formoterol (100/6 µg) (Foster<sup>(®)</sup>). **WHAT THIS STUDY ADDS** • The use of AeroChamber Plus® VHC optimizes the lung delivery of beclomethasone and formoterol in subjects that find it difficult to synchronize aerosol actuation with the inspiration of breath. • The total systemic exposure of beclomethasone 17-monopropionate and formoterol was not significantly increased by the use of the AeroChamber Plus® spacer. • Use of the AeroChamber Plus® spacer device with the extrafine beclomethasone dipropionate/formoterol (100/6 µg) fixed combination pMDI can be a valuable option for certain patients groups, such as subjects with difficulties in achieving an adequate inhalation technique. Aim To assess the effect of AeroChamber Plus® on lung deposition and systemic exposure to extrafine beclomethasone dipropionate (BDP)/formoterol (100/6 µg) pMDI (Foster<sup>(®)</sup>). The lung deposition of the components of the combination given with the pMDI was also evaluated using the charcoal block technique. **Methods:** Twelve healthy male volunteers received 4 inhalations of extrafine BDP/formoterol (100/6 µg) using (1) pMDI alone, (2) pMDI and AeroChamber Plus® and (3) pMDI and charcoal ingestion. Results Compared with pMDI alone, use of AeroChamber Plus® increased the peak plasma concentrations ( $C_{max}$ ) of BDP ( $2822.3 \pm 1449.9$  vs  $5454.9$

$\pm 3197.1$  pg/ml), its active metabolite beclometasone 17-monopropionate (17-BMP) ( $771.6 \pm 288.7$  vs  $1138.9 \pm 495.6$  pg/ml) and formoterol ( $38.4 \pm 17.8$  vs  $54.7 \pm 20.0$  pg/ml). For 17-BMP and formoterol, the  $AUC_{0-30 \text{ min}}$ , indicative of lung deposition, was increased in the AeroChamber Plus<sup>®</sup> group by 41% and 45%, respectively. This increase was mainly observed in subjects with inadequate inhalation technique. However, use of AeroChamber Plus<sup>®</sup> did not increase the total systemic exposure to 17-BMP and formoterol. Results after ingestion of charcoal confirmed that  $AUC_{0-30 \text{ min}}$  can be taken as index of lung bioavailability and that more than 30% of the inhaled dose of extrafine BDP/Formoterol 100/6  $\mu\text{g}$  was delivered to the lung using the pMDI alone. **Conclusions:** The use of AeroChamber Plus<sup>®</sup> optimizes the delivery of BDP and formoterol to the lung in subjects with inadequate inhalation technique. The total systemic exposure was not increased, supporting the safety of extrafine BDP/formoterol pMDI with AeroChamber Plus<sup>®</sup>.

#### **PHARMACOKINETIC AND PHARMACODYNAMIC EFFECT OF AEROCHAMBER PLUS<sup>®</sup> SPACER ON THE EXTRAFINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL COMBINATION (200/6 $\mu\text{g}$ ).**

Collarini S, Mariotti F, Acerbi D, Vets E. Proc. 20<sup>th</sup> ERS Annual Congress, Barcelona, Spain, in Eur. Respir. J 2010; 36S54: P4536.

The effect of AeroChamber Plus<sup>®</sup> spacer on the systemic exposure to formoterol, BDP and B17MP (beclometasone-17-monopropionate, the main BDP metabolite) was evaluated in healthy male subjects after inhalation of a single 4-puff dose of the extrafine BDP/formoterol 200/6  $\mu\text{g}$  pMDI fixed combination (total inhaled dose 800/24  $\mu\text{g}$ ) following a randomized, cross-over design. The use of the spacer increased peak plasma concentration ( $C_{\text{max}}$ ) of B17MP (+12%) and formoterol (+39%). The area under the curve of plasma concentration versus time over the first 30 minutes post-dose ( $AUC_{0-0.5 \text{ h}}$ ), indicative of lung absorption, increased by 25% and 32% for B17MP and formoterol, respectively, in the spacer group. However, the use of AeroChamber Plus<sup>®</sup> did not increase the total systemic exposure to B17MP and formoterol, as it decreased the amount of drug swallowed and absorbed from the gastrointestinal tract. This result was in accordance with the higher Fine Particle Dose observed *in vitro* for both components when using the spacer, and with the results of a previous study evaluating the effect of AeroChamber Plus<sup>®</sup> on FOSTER<sup>®</sup> (extrafine BDP/formoterol 100/6  $\mu\text{g}$ ). Similar systemic exposure was confirmed by comparable pharmacodynamic effects observed after administration with and without spacer. No differences were found between AeroChamber Plus<sup>®</sup> spacer and the standard actuator in serum and urinary cortisol, both treatments showing a statistically significant decrease compared to placebo, with mean values which remained within the physiological range. Serum potassium, vital signs and QTcB parameters were also not affected by the use of the spacer device.

#### **Proventil<sup>®</sup> (Albuterol Sulfate) Key Pharmaceuticals Inc.**

#### **RESPONSE TO ALBUTEROL MDI DELIVERED THROUGH AN ANTI-STATIC CHAMBER DURING NOCTURNAL BRONCHOSPASM.**

Prabhakaran S, Shuster J, Chesrown S, Hendeles L. Respir Care 2012;57(8):1291-1296.

**Background:** Decreasing electrostatic charge on valved-holding chambers increases the amount of drug delivered. However, there are no data demonstrating that this increases bronchodilatation. The objective of this study was to investigate the influence of reducing electrostatic charge on the bronchodilator response to albuterol inhaler during nocturnal bronchospasm. **Methods:** This randomized, double-blind, double-dummy, crossover study included subjects 18-40 years with nocturnal bronchospasm (20% overnight decrease in peak flow on 3 of 7 nights during run-in),  $FEV_1$  60-80% predicted during the day, and  $\geq 12\%$  increase after albuterol. Subjects slept in the Clinical Research Center up to 3 nights for each treatment.  $FEV_1$  and heart rate were measured upon awakening spontaneously or at 4 am, and 15 minutes after each dose of 1, 2 and 4 cumulative puffs of albuterol MDI. The drug was administered through an anti-static valved holding chamber (AeroChamber Plus<sup>®</sup> Z-Stat<sup>®</sup>) or a conventional valved holding chamber containing a static charge (AeroChamber Plus<sup>®</sup>). **Results:** Of 88 consented subjects, 11 were randomized and 7 completed the study. Most exclusions were due to lack of objective evidence of nocturnal bronchospasm. Upon awakening,  $FEV_1$  was  $44 \pm 9\%$  predicted before the anti-static chamber and  $48 \pm 7\%$  predicted before the static chamber. The mean ( $\pm$ SD) % increase in  $FEV_1$  after 1, 2 and 4 cumulative puffs using anti-static vs static chambers, respectively, were  $52\% \pm 26\%$  vs  $30\% \pm 19\%$ ,  $73\% \pm 28\%$  vs  $48\% \pm 26\%$  and  $90\% \pm 34\%$  vs  $64\% \pm 35\%$ . The point estimates for the difference (95% CI) between devices (antistatic-static) were 21% (4-38) [ $p=0.026$ ], 23% (6-41) [ $p=0.018$ ] and 25% (7-42) [ $p=0.013$ ] for 1, 2, and 4 cumulative puffs, respectively. There was no significant difference in heart rate

between treatments. **Conclusion:** Delivery of albuterol through an anti-static chamber provides a clinically relevant improvement in bronchodilator response during acute, reversible bronchospasm, such as nocturnal bronchospasm.

### **COMPARATIVE PERFORMANCE OF SMALL VOLUME VALVED HOLDING CHAMBERS FOR THE DELIVERY OF HFA-FORMULATED BRONCHODILATOR.**

Mitchell JP, Schmidt JN, Morton RW, Wiersema KJ, Bates SL. *Am. J. Resp Crit Care Med* 2000;161(3):A34.

**Purpose:** To compare fine particle (FPD) and total emitted dose (ED) from 149 and 218 ml valved holding chambers (VHCs) with an HFA-formulated bronchodilator. Methods: FPD and ED were determined for 5 OptiChamber VHCs (volume = 218 ml; Respironics, Cedar Grove N.J.) and 5 AeroChamber Plus® VHCs with mouthpiece (149 ml; Monaghan Medical Corp., Plattsburgh, N.Y.) with Proventil®-HFA (108 µg albuterol sulfate ex actuator; Key Pharmaceuticals Inc.) by means of an Andersen 8-stage impactor, sampling at  $28.3 \pm 0.5$  l/min. Results: (ED) and ((FPD), particles finer than 4.7 µm aerodynamic diameter) were as follows: OptiChamber VHC: ED =  $52.1 \pm 3.2$  µg, FPD =  $50.4 \pm 2.5$  µg, AeroChamber Plus®: ED =  $68.9 \pm 5.2$  µg, FPD =  $65.8 \pm 5.8$  µg. The differences in both ED and FPD were statistically significant (unpaired t-test for each variable,  $p < 0.001$ ). Fine particle fraction (FPF) from either type of VHC (OptiChamber®:  $96.9 \pm 2.3\%$ , AeroChamber Plus® ( $95.5 \pm 1.8\%$ ) were insignificantly different ( $p = 0.30$ ). **Conclusion:** Increased chamber volume does not necessarily equate with improved FPD or ED. Other considerations, such as internal geometry and inhalation valve design contribute to performance by controlling the internal aerosol losses.

### **Pulmicort® (Budesonide) AstraZeneca®**

#### **IN VITRO COMPARISON OF OUTPUT AND PARTICLE SIZE DISTRIBUTION OF BUDESONIDE FROM METERED DOSE INHALER WITH THREE SPACER DEVICES DURING PEDIATRIC TIDAL BREATHING.**

Kamin W and Ehlich H. *Treat Respir Med* 2006;5(6):503-508.

**Objectives:** The aim of this *in vitro* study was to determine the delivered dose of budesonide 200µg via a chlorofluorocarbon-free pressurized metered dose inhaler (pMDI) when administered through different spacers in tidal breathing patterns of young children. Methods: Tidal breathing was simulated for toddlers and children. Spacers tested were Babyhaler®, AeroChamber Plus® VHC small and medium; the pMDI was Dudiair® 200µg. Output was measured after one actuation and five inhalations in primed and unprimed spacers. Cumulated output was evaluated after each of five simulated inhalations. Aerosol characteristics – i.e. particle size distribution of the output – were determined in primed spacers with a cascade impactor using high-performance liquid chromatography and UV detection. **Results:** Total output from primed spacers after five inhalations was determined between 37.9 µg and 40.9 µg with little differences between spacers and breathing patterns. About 58 – 79% of this total output was inhaled with the first breath from the AeroChamber Plus® and about 26% from the Babyhaler®. The fine particles <5µg ranged between 87% and 92% of the delivered dose for all three spacers. Discussion and Conclusion: The nominal dose (200µg) of the Budiair® 200µg inhaler is reduced to 40µg delivered dose or less by using Babyhaler® and AeroChamber Plus® spacers taking five breaths. With a single breath the delivered dose can be reduced further to a minimum of 10µg using the Babyhaler®. Clinical studies are warranted in the future for decisions on ‘clinical efficacy’, safety, and exact dose adjustment.

### **QVAR® (Beclomethasone Dipropionate), Graceway® Pharmaceuticals LLC**

#### **ASSESSMENT OF POTENTIAL MOUTH/THROAT DEPOSITION AND LUNG DELIVERY OF SUSPENSION-AND SOLUTION-FORMULATED INHALED CORTICOSTEROID FORMULATIONS DELIVERED BY PRESSURIZED METERED-DOSE INHALER WITHOUT AND WITH VALVED HOLDING CHAMBER USING AN ANATOMIC ADULT UPPER AIRWAY.**

Suggett J, Nagel M, Mitchell JP. *Drug Delivery to the Lungs* 2017.

Exerpt from extended abstract: VHCs are widely prescribed to assist patients receiving inhaled medications by avoiding losses caused by imperfect coordination of the inhalation manoeuvre with pMDI actuation and also to reduce oropharyngeal deposition [1]. The latter is particularly important when formulations containing an ICS are inhaled, as these medications have been associated with severe oral candidiasis [2]. The transition from chlorofluorocarbon to hydrofluoroalkane (HFA) propellants provided the opportunity to reformulate some pMDI-delivered ICSs as solutions (rather than suspensions), producing ultrafine aerosols with mass median aerodynamic diameter (MMAD)

close to 1.1- $\mu\text{m}$  [3] emitted from the inhaler mouthpiece at a slower velocity profile than previously [4]. The claim was made that by reducing oropharyngeal deposition, the use of VHCs might be unnecessary with such products [5]. However, Devadason *et al.*, amongst others, have pointed out that significant oropharyngeal deposition still occurs with such products [6]. Currently, both solution and suspension ICS HFA pMDIs (the suspension products having larger MMAD values close to 2.4- $\mu\text{m}$  [7]) are marketed [8]. The present laboratory study explored how insertion of a VHC in the pathway between pMDI and the mouth might affect the transfer of particles from inhaler mouthpiece to the airways of the lungs. The behaviour of a conventional suspension formulated ICS (fluticasone propionate (FP)) with mass median aerodynamic diameter (MMAD) close to 2.4- $\mu\text{m}$  was compared with that of a solution-formulated ICS (beclomethasone dipropionate (BDP)) producing ultrafine particles with MMAD close to 1.1- $\mu\text{m}$ . An anatomically correct adult oropharyngeal airway, developed as a member of the Aerosol Delivery to Anatomic Model (ADAM) series [9] was used in conjunction with simulation of patient respiration. This simulation provided a greater degree of realism than is possible with the methods for inhaler assessment in the pharmacopeial compendia, that are developed primarily to assess inhaler product quality [10]. When the VHC was absent, the FP (suspension) formulation was deposited in the oropharyngeal passageway at approximately double the extent to that observed with the BDP (solution) formulation (62% v 29%). Importantly, significant oropharyngeal airway deposition still occurred, even with the ultrafine HFA solution product, which was greatly reduced when the VHC was present (29% v 3%,  $p < 0.001$ ). Aerosol particle penetration beyond the airway to the filter is considered indicative of potential lung deposition using the employed methodology. As expected, the finer aerodynamic particle size distribution of the ultrafine QVAR<sup>†</sup> solution aerosol resulted in greater delivery to the filter compared with the coarser Flovent<sup>†</sup> suspension aerosol ( $p < 0.001$ ) when the VHC was absent, although the large degree of difference (7% v 36%) is potentially surprising. Filter deposition was increased for both pMDI products when the VHC was present ( $p < 0.001$ ). The increase was more pronounced with the suspension product; however, an increase was still evident even when used with the solution HFA pMDI. Given the findings for both oropharyngeal and filter deposition in the present study, the view that a VHC might not add value with the solution type of product for oropharyngeal deposition [5], therefore appears to be an overstatement of reality.

#### **A PILOT STUDY TO ASSESS LUNG DEPOSITION OF HFA-BECLOMETHASONE AND CFC-BECLOMETHASONE FROM A PRESSURIZED METERED DOSE INHALER WITH AND WITHOUT ADD-ON SPACERS AND USING VARYING BREATHHOLD TIMES.**

Leach CL, Collice GL. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 2010;23:1-7.

**Background:** The study objective of this pilot study was to determine the lung delivery of HFA-134a beclomethasone dipropionate (HFA-BDP; QVAR<sup>†</sup>) and CFC-beclomethasone dipropionate (CFC-BDP; Becloforte<sup>†</sup>) with and without the add-on spacers, AeroChamber<sup>\*</sup>, and Volumatic<sup>†</sup>. The smaller particles of HFA-BDP were presumed to produce greater lung deposition using spacers, with and without a delay [i.e. metered dose inhaler (MDI) actuation into the spacer and subsequent inhalation 0 and 2 sec later], compared with the larger particles of CFC-BDP. The study included a comparison of breathhold effects (i.e. 1 and 10-sec breathholds) on lung deposition. **Methods:** The study was an open-label design and utilized healthy subjects ( $n=12$  males). Each arm of the study contained three subjects; thus, outcomes were not powered to assess statistical significance. HFA-BDP and CFC-BDP were radiolabeled with technetium-99m and delivered to subjects. **Results:** Results showed that the small particle HFA-BDP lung deposition averaged 52% and was not affected by the use of AeroChamber<sup>®</sup> with or without a spacer delay. The oropharyngeal deposition of HFA-BDP was reduced from approximately 28% to 4% with the AeroChamber<sup>®</sup>. Lung deposition with the large particle CFC-BDP was 3-7% and generally decreased with AeroChamber<sup>®</sup> or Volumatic. A 2-sec time delay between actuation and breath plus the spacer reduced lung deposition slightly but reduced oropharyngeal deposition substantially (84% down to 3-20%) using the AeroChamber<sup>®</sup> or Volumatic with and without a spacer delay. HFA-BDP lung deposition was dependent on the breathhold. Lung deposition with HFA-BDP was reduced by 16% with a 1-sec versus 10-sec breathhold. The difference was measured in the increased exhaled fraction, confirming that smaller particles need time to deposit and are exhaled if there is a reduced breathhold. The large particle CFC-BDP lung deposition was not affected by breathhold. **Conclusions:** The use of AeroChamber<sup>®</sup> or Volumatic spacers with HFA-BDP did not alter lung deposition but it did reduce oropharyngeal deposition. However, HFA-BDP displayed reduced oropharyngeal deposition without a spacer.

## SPACER INHALATION TECHNIQUE AND DEPOSITION OF EXTRAFINE AEROSOL IN ASTHMATIC CHILDREN.

Roller CM, Zhang G, Troedson RG, Leach CL, Le Souëf PN and Devadason SG. *Eur Respir J* 2007;29:299-306.

The aim of the present study was to measure airway, oropharyngeal and gastrointestinal deposition of <sup>99m</sup>Tc-labelled hydrofluoroalkane-beclomethasone dipropionate after inhalation *via* a pressurized metered-dose inhaler and spacer (AeroChamber Plus® VHC) in asthmatic children. A group of 24 children (aged 5-17 yrs) with mild asthma inhaled the labeled drug. A total of 12 children took five tidal breaths after each actuation (tidal group). The other 12 children used a slow maximal inhalation followed by a 5-10-s breath-hold (breath-hold group). Simultaneous anterior and posterior planar  $\gamma$ -scintigraphic scans (120-s acquisition) were recorded. For the tidal group, mean  $\pm$ SD lung deposition (% ex-actuator, attenuation corrected) was 35.4 $\pm$ 18.3, 47.5 $\pm$ 13.0 and 54.9 $\pm$ 11.2 in patients aged 5-7 ( $n=4$ ), 8-10 ( $n=4$ ) and 11-17 yrs ( $n=4$ ), respectively. Oropharyngeal and gastrointestinal deposition was 24.0 $\pm$ 10.5, 10.3 $\pm$ 4.4 and 10.1 $\pm$ 6.2. With the breath-hold technique, lung deposition was 58.1 $\pm$ 6.7, 56.6 $\pm$ 5.2 and 58.4 $\pm$ 9.2. Oropharyngeal and gastrointestinal deposition was 12.9 $\pm$ 3.2, 20.1 $\pm$ 9.5 and 20.8 $\pm$ 8.8. Inhalation of the extrafine formulation with the breath-hold technique showed significantly improved lung deposition compared with tidal breathing across all ages. Oropharyngeal and gastrointestinal deposition was markedly decreased, regardless of which inhalation technique was applied, compared with a previous pediatric study using the same formulation delivered *via* a breath-actuated metered-dose inhaler.

## IN VITRO PERFORMANCE OF TWO COMMON VALVED HOLDING CHAMBERS WITH A CHLOROFLUOROCARBON-FREE BECLOMETHASONE METERED-DOSE INHALER.

Asmus MJ, Coowanitwong I, Kwon SH, Khorsand N, Hochhaus G. *Pharmacotherapy* 2003;23(12):1538-1544.

**Study Objective:** To compare *in vitro* aerosol deposition from a beclomethasone dipropionate metered-dose inhaler (MDI) containing hydrofluoroalkane propellant with that of the MDI in combination with two common valved holding chambers (VHCs) to evaluate how these VHCs affect the respirable dose of beclomethasone dipropionate. **Design:** *In vitro* aerosol deposition study. **Setting:** University research center. **Devices:** Beclomethasone dipropionate hydrofluoroalkane MDI alone, the MDI with OptiChamber<sup>+</sup> VHC, and the MDI with AeroChamber Plus<sup>®</sup> VHC. **Intervention:** The respirable dose (1-5-microm aerosol particles) of beclomethasone dipropionate was determined by sampling 10 80-microg actuations from five runs with each configuration (MDI alone, MDI with OptiChamber<sup>+</sup>, and MDI with AeroChamber Plus<sup>®</sup> VHC), using a well-established *in vitro* cascade impactor method. **Measurements and Main Results:** Beclomethasone dipropionate aerosol was washed from the impactor with 50% methanol and quantified by means of high-performance liquid chromatography. Differences among outcomes were determined by using analysis of variance. Mean beclomethasone dipropionate respirable dose from AeroChamber Plus<sup>®</sup> VHC (27.2  $\pm$  10.0 microg/actuation) was not significantly different ( $p>0.05$ ) from that of the MDI alone (29.0  $\pm$  7.0 microg/actuation). OptiChamber<sup>+</sup> respirable dose (12.8  $\pm$  6.0 microg/actuation) was less than half that produced by either the AeroChamber Plus<sup>®</sup> VHC or the MDI alone ( $p=0.013$ ). **Conclusions:** The OptiChamber<sup>+</sup> and AeroChamber Plus<sup>®</sup> VHCs do not demonstrate equivalent *in vitro* performance when used with a beclomethasone dipropionate MDI that contains hydrofluoroalkane propellant. The respirable dose of beclomethasone dipropionate aerosol from the hydrofluoroalkane MDI was decreased by only 6% when the MDI was mated to an AeroChamber Plus<sup>®</sup> VHC and by 56% when used with an OptiChamber<sup>+</sup> VHC.

## EVALUATION OF THE IN-VITRO DELIVERY OF AN HFA-STEROID SOLUTION FORMULATION DELIVERED FROM A VALVED HOLDING CHAMBER (VHC).

Wiersema KJ, Mitchell JP, Bates SL, Nagel MW. *Am J Resp Crit Care Med* 2001;163 (5):A442.

**Purpose:** To demonstrate the reduction in coarse component (particles  $>4.7$   $\mu$ m aerodynamic diameter) of pressurized metered dose inhaler (pMDI) delivered HFA-beclomethasone dipropionate (BDP) (QVAR100: 100  $\mu$ g/dose, 3M Pharmaceuticals Inc.), using a small volume VHC (AeroChamber Plus<sup>®</sup>, (Monaghan Medical Corp.)). **Methods:** 5 AeroChamber Plus<sup>®</sup> VHCs were washed with a mild ionic detergent followed by air-drying prior to testing in order to minimize the influence of electrostatic effects. Particle size measurements were made by Andersen cascade impactor (Graseby Andersen, USA) at 28.3  $\pm$  0.5 l/min and the mass of BDP assayed by HPLC-UV spectrophotometry. 5 doses of medication were delivered 30 s apart. **Results:** The AeroChamber Plus<sup>®</sup> VHCs delivered total unit doses of 62.0  $\pm$  3.4  $\mu$ g (94 %  $<$  4.7  $\mu$ m), whereas the pMDI alone provided 74.3  $\pm$  1.6  $\mu$ g (61%  $<$  4.7 $\mu$ m). The amount of BDP  $>$ 4.7  $\mu$ m was 28.9  $\pm$  3.0  $\mu$ g and 3.1  $\pm$  1.1  $\mu$ g for the pMDI alone and AeroChamber Plus<sup>®</sup> respectively. **Conclusion:** Based on these data a holding chamber still appears to be necessary to minimize deposition in the upper airway, even with the introduction of this CFC-free solution formulation.

**COMPARATIVE EVALUATION OF CARDBOARD VERSUS RIGID SMALL VOLUME VALVED HOLDING CHAMBERS (VHCs) FOR THE DELIVERY OF A BETA-2 AGONIST FORMULATION: DELIVERY TO THE UNCOORDINATED USER.**

*Coppolo DP, Mitchell JP, Wiersema KJ, Avvakoumova VA, Meyer AK, Limbrick MR, Nagel MW, MacIntrye NR. Presented at the American College of Chest Physicians Annual Conference, 2005.*

**Purpose:** VHCs are prescribed for patients that have difficulty coordinating pressurized metered-dose inhaler (pMDI) use, frequently resulting in delayed inhalation following inhaler actuation. Our study introduced a realistic 2-second delay, comparing delivery of a beta-2 agonist via VHCs of similar size ( $n=5/\text{group}$ ), one manufactured from cardboard (LiteAire<sup>†</sup>, Thayer Medical, Tucson, AZ - 160-ml) the other from rigid polymer (AeroChamber Plus<sup>®</sup> VHC, Monaghan Medical Corp., Syracuse, NY - 150-ml). **Methods:** The AeroChamber Plus<sup>®</sup> VHCs were pretreated by washing in water containing a mild ionic detergent, rinsed and drip-dried, as recommended prior to use. The LiteAire<sup>†</sup> VHCs were assembled and used in accordance with manufacturer's instructions. Each VHC was tested using an Andersen 8-stage impactor with USP Induction Port operated at  $28.3 \pm 0.5$  L/min, representative of flow rates seen with adult patients. A shutter that interfaced between the VHC mouthpiece and induction port entrance was used to simulate a 2-s delay interval between pMDI actuation and the onset of sampling. The shutter moved to allow flow from the VHC to the impactor only after the defined delay. 5-actuations of albuterol (Ratiopharm, Mississauga, Canada, 100 µg/dose albuterol base equivalent ex metering valve) were delivered from a pre-primed and shaken pMDI canister at 30-s intervals. The induction port and stages of the impactor were subsequently assayed for albuterol by HPLC-UV spectrophotometry. Benchmark measurements were also made with the pMDI alone. **Results:** Fine particle mass/actuation ((FPM) <4.7 µm aerodynamic diameter (mean (95% CI)) was 27.8 (4.2) µg (pMDI alone), 21.7 (5.0) µg (AeroChamber Plus<sup>®</sup> VHC) and 13.9 (4.2) µg (LiteAire<sup>†</sup> VHC). **Conclusion:** FPM pMDI-alone represents delivery with perfect inhaler technique. The AeroChamber Plus<sup>®</sup> VHC delivered nearly 80% FPM pMDI-alone with a 2-s delay, but the corresponding delivery via the LiteAire<sup>†</sup> VHC was only 50% FPM pMDI-alone. **Clinical Implication:** Dosing may have to be adjusted to take into account the poorer efficiency of the cardboard VHC, considering the likelihood of imperfect coordination.

**Respimat<sup>†</sup> Soft Mist<sup>†</sup> Inhaler, Boehringer Ingelheim**

**IN VITRO AND CLINICAL CHARACTERIZATION OF THE VALVED HOLDING CHAMBER AEROCHAMBER PLUS<sup>®</sup> FLOW-VU<sup>®</sup> FOR ADMINISTRATING TIOTROPIUM RESPIMAT<sup>®</sup> IN 1-5-YEAR-OLD CHILDREN WITH PERSISTENT ASTHMATIC SYMPTOMS.**

*Wachtel H, Nagel M, Engel M, El Azzi G, Sharma A, Suggett J. Respiratory Medicine 137 (2018) 181-190.*

**Background:** When characterizing inhalation products, a comprehensive assessment including *in vitro*, pharmacokinetic (PK), and clinical data is required. We conducted a characterization of tiotropium Respimat<sup>®</sup> when administered with AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> anti-static valved holding chamber (test VHC) with face mask in 1-5-year-olds with persistent asthmatic symptoms. **Methods:** *In vitro* tiotropium dose and particle size distribution delivered into a cascade impactor were evaluated under fixed paediatric and adult flow rates between actuation and samplings. The tiotropium mass likely to reach children's lungs was assessed by tidal breathing simulations and an ADAM-III Child Model. PK exposure to tiotropium in preschool children with persistent asthmatic symptoms (using test VHC) was compared with pooled data from nine Phase 2/3 trials in older children, adolescents, and adults with symptomatic persistent asthma not using test VHC. **Results:** At fixed inspiratory flow rates, emitted mass and fine particle dose decreased under lower flow conditions; dose reduction was observed when Respimat<sup>®</sup> was administered by test VHC at paediatric flow rates. In <5-year-old children, such a dose reduction is appropriate. In terms of dose per kg/body weight, *in vitro*-delivered dosing in children was comparable with adults. Transmission and aerosol holding properties of Respimat<sup>®</sup> when administered with test VHC were fully sufficient for aerosol delivery to patients. At zero delay, particles <5 µm (most relevant fraction) exhibited a transfer efficacy of  $\geq 60\%$ . The half-time was  $>10$  s, allowing multiple breaths. Standardized tidal inhalation resulted in an emitted mass from the test VHC of approximately one-third of labelled dose, independent of coordination and face mask use, indicating predictable tiotropium administration by test VHC with Respimat<sup>®</sup>. Tiotropium exposure in 1-5-year-old patients using the test VHC, when adjusted by height or body surface, was comparable with that in older age groups without VHCs; no overexposure was observed. Adverse events were less frequent with tiotropium (2.5 µg,  $n = 20$  [55.6%]; 5 µg,  $n = 18$  [58.1%]) than placebo ( $n = 25$  [73.5%]). **Conclusions:** Our findings provide good initial evidence to suggest

that tiotropium Respimat® may be administered with AeroChamber Plus® Flow-Vu® VHC in 1-5-year-old patients with persistent asthmatic symptoms. To confirm the clinical efficacy and safety in these patients, additional trials are required.

## A LABORATORY INVESTIGATION INTO THE PERFORMANCE OF A VALVED HOLDING CHAMBER WITH THE RESPIMAT® SOFT MIST INHALER, USING AN ADULT OROPHARYNX MODEL AND TIDAL BREATHING SIMULATION.

Suggett J, Nagel M, Avvakoumova V, Mitchell JP. *Respiratory Drug Delivery* 2018.

**Introduction:** The Respimat® SMI (Boehringer Ingelheim, Germany) delivers medication in the form of a standing cloud of micrometer-sized droplets following actuation [1]. If the patient closes their lips over the mouthpiece and inhales at the time of actuation, medication is delivered efficiently to the lungs [2]. However, as with pressurized metered dose inhalers (pMDIs), if there is poor coordination between actuation and inhalation (for example, if the patient exhales or delays inhalation for more than a second or two), the effectiveness of aerosol delivery can be compromised, even though the SMI has a longer discharge time than a typical propellant-driven pMDI. Valved holding chambers (VHCs) are widely prescribed for use with pMDIs as they conserve the aerosolized medication following actuation for subsequent inhalation by patients who have poor coordination of inhaler actuation with the onset of inhalation [4]. Both plume velocity and shape are different for pMDI-and SMI-generated aerosols, so there is interest in investigating whether the use of such an add-on device with a SMI is associated with comparable mass of medication available for delivery to the lungs. The present laboratory study, mimicking adult use, examined the hypothesis that adding a VHC to the mouthpiece of a Respimat SMI would result in a similar dose of medication available for lung deposition. The patient was assumed to be perfectly coordinated, operating the SMI in accordance with instructions in this baseline study. **Materials and Methods:** Spiriva®, Combivent®, and Inspiolto® Respimat SMIs ( $n = 5$  inhalers/group), labeled to deliver 2.5 mg tiotropium bromide (TI), 100 mg albuterol sulfate (ALB) and 20 mg ipratropium bromide (IPR), and 2.5 µg tiotropium bromide (TI) and 2.5 mg olodaterol hydrochloride (OLO), respectively per actuation, were evaluated with and without an antistatic AeroChamber Plus® Flow-Vu® VHC (AC-Plus), with the mouthpiece of the SMI-on-test inserted into the pMDI adapter port of the VHC. In the first part of the study, the mouthpiece of each SMI was directly connected to a breathing simulator (ASL 5000, IngMar Medical, Pittsburgh, PA) via an anatomically correct adult oropharyngeal model (Aerosol Delivery to Anatomic Model (ADAM), Trudell Medical International) [5]. An aerosol filter collected the medication at the exit from the model's upper airway, representing medication likely to penetrate beyond the carinal ridge to reach the lungs. Previous work with this model had confirmed that capture of the aerosol from this arrangement was quantitative [5]. A tidally breathing adult (tidal volume = 770 mL, rate/min = 12; inspiratory: expiratory ratio = 1:2) was mimicked. Five actuations were each delivered at the beginning of an inhalation, with a six-breathing cycle sampling period in between each actuation. In the second part, the measurements were repeated with the AC-Plus VHC downstream of the SMI-on-test. In both parts of the study, the mass of active pharmaceutical ingredient(s) recovered from each filter, including its housing, was determined by an internally validated high performance liquid chromatography (HPLC)-spectrophotometric procedure. **Results:** The measures of emitted mass per actuation are summarized in Table 1, together with the corresponding mass recovered from within the VHC and within the airway.

**Table 1: Mass of API (µg/actuation) recovered downstream of an oropharyngeal model into which three different Respimat® SMI products with and without antistatic AeroChamber Plus® VHC-mouthpiece were discharged under simulation of adult tidal breathing conditions.**

Respimat® API	Spiriva® SMI		Combivent® SMI				Inspiolto® SMI			
	TI		ALB		IPR		TI		OLO	
Location	Alone	VHC	Alone	VHC	Alone	VHC	Alone	VHC	Alone	VHC
Model	0.9 ±	0.4 ±	31.5 ±	12.2 ±	6.6 ±	2.1 ±	0.4 ±	0.4 ±	0.9 ±	0.4 ±
Oropharynx	0.2	0.1	3.7	1.9	0.8	0.4	0.5	0.1	0.0	0.2
In VHC	N/A	1.3 ±	N/A	32.9 ±	N/A	6.0 ±	N/A	0.9 ±	N/A	0.9 ±
On Filter ("carina")	1.7 ±	1.3 ±	46.6 ±	48.4 ±	9.7 ±	9.7 ±	1.7 ±	1.4 ±	1.6 ±	1.4 ±
	0.3	0.2	6.4	5.1	1.0	1.3	0.2	0.1	0.2	0.1
Total	2.7 ±	3.0 ±	78.1 ±	93.5 ±	16.3 ±	17.8 ±	2.0 ±	2.7 ±	2.6 ±	2.6 ±
	0.2	0.1	8.8	4.6	1.8	±1.1	0.5	0.1	0.2	0.1

The mean values of total drug mass recovered ex SMI mouthpiece were within  $\pm 20\%$  label claim for all three products. In general, the mass of each active pharmaceutical ingredient (API) deposited in the model oropharynx was significantly reduced when the VHC was present (paired t-test,  $p < 0.001$ ). The exception was the tiotropium bromide component of the Inspiolto product, where we saw no difference (a finding perhaps confounded because we were close to the limit of detection for TI). Significant deposition of all APIs within the VHC was evident. In general, this additional deposition was associated with an increase in the total mass recovered, the exception being the olodaterol component of the Inspiolto product where no change was observed. The mass of API recovered from the filter, which we believe may represent the portion of the inhaled dose with the potential to penetrate the oropharynx, and therefore available for delivery to the lungs, was similar with or without the VHC present for all three products. **Conclusions:** The laboratory study, modeling adult use, confirmed the hypothesis that the addition of the AC-Plus VHC to the three different Respimat SMI products did not appreciably affect delivery of the portion of each API penetrating the model oropharynx, and therefore available for lung deposition. The slight increase in total mass of APIs recovered from within the VHC in the majority of tests may have been associated with small amounts of drug transfer from coalesced droplets typically deposited inside the SMI mouthpiece [6].

### **BRONCHODILATOR EFFECT OF TIOTROPIUM VIA RESPIMAT® ADMINISTERED WITH A SPACER IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD).**

*Ogasawara T, Sakata J, Aoshima Y, Tanaka K, Yano T, Kasamatsu N. Internal Medicine 56: 2401-2406, 2017.*

**Objective:** Among elderly patients with chronic obstructive pulmonary disease (COPD), there are some patients who cannot inhale tiotropium via Respimat® due to poor hand-lung coordination. This study aimed to examine whether or not tiotropium inhalation therapy using Respimat® with a spacer increased the forced expiratory volume in 1 s (FEV<sub>1</sub>) in patients with COPD. **Methods:** A randomized, crossover, single-center study was conducted in 18 patients with stable COPD. Tiotropium (5 µg) via Respimat® with or without a spacer (AeroChamber®) was administered for 2 weeks. Following a 2-week washout period using a transdermal tulobuterol patch (2 mg per day), participants were then crossed over to the other inhalation therapy with respect to spacer use. The trough FEV<sub>1</sub> was measured at every visit using a spirometer. A questionnaire regarding inhalation therapy was administered to patients at the final visit. **Results:** The administration of tiotropium via Respimat® both with and without a spacer significantly increased the trough FEV<sub>1</sub> from baseline during each treatment period, with mean differences of 115.0±169.6 mL and 92.8±128.1 mL, respectively. There was no significant difference in the change in the trough FEV<sub>1</sub> between the 2 procedures ( $p=0.66$ ). A total of 86% of patients reported that inhalation using a spacer was not difficult, and more than half also rated both the usage and maintenance of the AeroChamber® as easy. **Conclusion:** Tiotropium inhalation therapy administered via Respimat® using a spacer exerted a bronchodilatory effect similar to that observed with tiotropium Respimat® alone.

### **DELIVERY OF RESPIMAT SOFT MIST INHALER (SMI) FROM A VALVED HOLDING CHAMBER (VHC).**

*Kushnarev V, Nagel M, Doyle C, Suggett J. European Respiratory Conference September 2017.*

**Rationale:** The SMI platform is used to deliver inhaled medications to treat different disease conditions and patient populations. VHCs are also used to treat the same patient populations and questions have arisen regarding the applicability of the SMI+VHC particularly in pediatric and geriatric patients. This laboratory investigation was undertaken to assist practitioners with information regarding potential drug delivery from the SMI+VHC. **Methods:** AeroChamber Plus® Flow-Vu® Anti-Static VHCs (AC+FV, Trudell Medical International, London, Canada) were evaluated with Spiriva®, Inspiolto® and Combivent® Respimat® SMI formulations. Measurements of fine particle mass (FPM, 0.54-3.99 µm aerodynamic diameter) were made by means of a chilled Next Generation Pharmaceutical impactor (NGI) equipped with USP inlet operated at 30 L/min. Assay for APIs recovered from components of the apparatus was undertaken by HPLC. **Results:** The measures of FPM (µg/actuation; mean  $\pm$  SD) are summarized in the Table.1.



**Table 1:** FPM (mean±sd, µg)

	Respimat SMI Alone	AC+FV Anti-Static VHC
Spiriva <sup>†</sup> Respimat <sup>†</sup> SMI (Tiotropium)	1.8 ± 0.1	1.4 ± 0.1
Inspirolo <sup>†</sup> Respimat <sup>†</sup> SMI (Tiotropium/Olodaterol)	2.0 ± 0.1 / 1.7 ± 0.3	2.0 ± 0.1 / 1.4 ± 0.2
Combivent <sup>†</sup> Respimat <sup>†</sup> SMI (Ipratropium bromide/Salbutamol)	11.4 ± 0.9 / 61.7 ± 2.5	11.7 ± 0.8 / 54.8 ± 5.0

**Conclusions:** The small differences in FPM between the SMI and SMI+ VHC were within the typical magnitude of method variability. Healthcare providers can have assurance that the use of the SMI with AC+FV VHC should deliver a similar FPM of API compared to the SMI alone.

### **IN VITRO DETERMINATION OF RESPIMAT DOSE DELIVERY IN CHILDREN: AN EVALUATION BASED ON INHALATION FLOW PROFILES AND MOUTH-THROAT MODELS.**

*Bickmann D, Kamin W, Sharma A, Wachtel H, Moroni-Zentgraf P, Zielen S. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2015; Vol 28:1-10.*

Aerosol therapy in young children can be difficult. A realistic model based on handling studies and *in vitro* investigations can complement clinical deposition studies and be used to enable dose-to-the-lung (DTL) predictions. Predictions on dose delivery to the lung were based on (1) representative inhalation flow profiles from children enrolled in a Respimat<sup>†</sup> handling study, (2) *in vitro* measurement of the fine-particle DTL using mouth-throat models derived from nuclear magnetic resonance/computed tomography (NMR/CT) scans of children, and (3) a mathematical model to predict the tiotropium DTL. Accuracy of the prediction was confirmed using pharmacokinetic (PK) data from children with cystic fibrosis enrolled in a phase 3 clinical trial of tiotropium Respimat with valved holding chamber (VHC). Representative inhalation flow profiles for each age group were obtained from 56 children who successfully inhaled a volume >0.15 L from the Respimat with VHC. Average dimensions of the mouth-throat region for 38 children aged 1-<2 years, 2-<3 years, 3-<4 years, and 4-<5 years were determined from NMR/CT scans. The DTL from the Respimat plus VHC were determined by *in vitro* measurement and were 5.1 ± 1.1%, 15.6% ± 1.4%, 17.9% ± 1.5%, and 37.1% ± 1.8% of the delivered dose for child models 0-<2 years, 2-<3 years, 3-<4 years, and 4-<5 years, respectively. This provides a 40 possible explanation for the age dependence of clinical PK data obtained from the phase 3 tiotropium trial. Calculated *in vitro* DTL per body mass (µg/kg [±SD]) were 0.031 ± 0.014, 0.066 ± 0.031, 0.058 ± 0.024, and 0.059 ± 0.029, respectively, compared to 0.046 in adults. Therefore, efficacy of the treatment was not negatively impacted in spite of the seemingly low percentages of the DTL. We conclude that the combination of real-life inhalation profiles with respective mouth-throat models and *in vitro* determination of delivered DTL is a good predictor of the drug delivery to children via the Respimat with VHC. The data provided can be used to support data from appropriate clinical trials.

### **A HANDLING STUDY TO ASSESS USE OF THE RESPIMAT<sup>†</sup> SOFT MIST<sup>†</sup> INHALER IN CHILDREN UNDER 5 YEARS OLD.**

*Kamin W, Frank M, Kattenbeck S, Moroni-Zentgraf P, Wachtel H, Zielen S. Accepted for publication in the Journal of Aerosol Medicine and Pulmonary Drug Delivery 2015.*

**Background:** Respimat<sup>†</sup> Soft Mist<sup>†</sup> Inhaler (SMI) is a hand-held device that generates an aerosol with a high, fine-particle fraction, enabling efficient lung deposition. The study objective was to assess inhalation success among children using Respimat SMI, and the requirement for assistance by the parent/caregiver and/or a valved holding chamber (VHC). **Methods:** This open-label study enrolled patients aged < 5 years with respiratory disease and history of coughing and/or recurrent wheezing. Patients inhaled from the Respimat SMI (air only; no aerosol) using a stepwise configuration: “1” (dose released by child); “2” (dose released by parent/caregiver), and “3”(Respimat SMI with VHC, facemask, and parent/caregiver help). Co-primary endpoints included the ability to perform successful inhalation as assessed by the investigators using a standardized handling questionnaire and evaluation of the reasons for success. Inhalation profile in the successful handling configuration was verified with a pneumotachograph. Patient satisfaction and preferences were investigated in a questionnaire. Results: Of the children aged 4 to < 5 years (n=27) and 3 to < 4 years (n=30), 55.6% and 30.0%, respectively, achieved success without a VHC or help; with assistance,

another 29.6% and 10.0%, respectively, achieved success, and the remaining children were successful with VHC. All children aged 2 to < 3 years ( $n=20$ ) achieved success with the Respimat SMI and VHC. Of those aged < 2 years ( $n=22$ ), 95.5% had successful handling of the Respimat SMI with VHC and parent/caregiver help. Inhalation flow profiles generally confirmed the outcome of the handling assessment by the investigators. Most parent/caregiver and/or child respondents were satisfied with operation, instructions for use, handling, and ease of holding the Respimat SMI with or without a VHC. **Conclusions:** The Respimat SMI is suitable for children aged < 5 years; however, children aged < 5 years are advised to add a VHC to complement its use.

#### **FLOW PROFILE DATA INDICATE THAT RESPIMAT WITH SPACER IS SUITABLE FOR INHALATION THERAPY OF PRE-SCHOOL CHILDREN.**

*Kamin W, Bannemer-Schult K, Klemmer A, Schwienhorst PS, Wachtel H, Zielen S. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2011;24(3):558(p-104).*

**Purpose:** In a non-invasive handling study the Respimat<sup>†</sup> inhaler was investigated, followed by flow profile recording of children ( $n=99$ ) below 5 years of age to find out whether inhalation therapy will be possible. **Methods:** Handling of the active Respimat<sup>†</sup> inhaler alone or with a spacer and facemask (AeroChamber Plus<sup>®</sup>) was assessed using a standardized handling questionnaire. Next the inhalation flow profiles were recorded and results summarized by descriptive statistics. Results: The most important flow profile parameter was volume inhaled after release (VA) within 10s using the spacer (acceptable holding time of spray in the spacer, ~ 5 breaths) and 1.5s using Respimat<sup>†</sup> alone (spray duration). The criterion for successful inhalation was a minimum volume inhaled of 0.15L which equals the spacer volume and is an acceptable value in accordance with the young age. This criterion was met in all age groups and handling configurations. With Respimat<sup>†</sup> a single breath resulted in median VA: 0.63L (3-<4yr) and 0.47L (4-<5yr). Using the spacer, median values of VA were: 0.34L (0-<2yr), 0.71L (2-<3yr), 1.12L (3-<4yr), 0.94L (4-<5yr) for ~5 breaths. The median peak flow with Respimat<sup>†</sup> alone reached 1L/s and with spacer it was below 0.7L/s in all age groups. **Conclusions:** These data suggest Respimat<sup>†</sup> is suitable for inhalation therapy in pre-school children. In order to ensure standardized dosing, the use of Respimat<sup>†</sup> inhaler with spacer in children below 5 years of age is recommended.

#### **CHILDREN BELOW FIVE YEARS OF AGE CAN HANDLE RESPIMAT<sup>†</sup> SOFT MIST<sup>†</sup> INHALER.**

*Kamin W, Bannemer-Schult K, Klemmer A, Schulze Schwienhorst P, Wachtel H, Zielen S. Am J Respir Crit Care Med 2010;181: A5254.*

**Rationale / Introduction:** Drug delivery by inhalation is the most effective non-invasive therapy available today. While patients older than 5 years are mostly able to perform correct inhalation, children below that age require special assistance. Respimat<sup>†</sup> Soft Mist<sup>†</sup> Inhaler is a novel, easy to use hand-held multidose propellant-free inhalation device that generates a fine, slow-moving cloud with high fine particle dose. Since spray generation is independent of the inspiratory flow it may offer opportunities to treat young children. The objective of this study was to establish the age at which children below 5 years can use Respimat<sup>†</sup> inhaler and which degree of help by parents or by using a spacer may be appropriate. **Methods:** Open two-center observational handling study. 99 pediatric patients (any respiratory disease) in five age groups were analyzed. Children <2 years started directly the inhalation with Respimat<sup>†</sup> and spacer (AeroChamber Plus<sup>®</sup> with facemask). Children 2 years and older started with the use of Respimat<sup>†</sup> without spacer, with or without help by their parents. If correct handling was not achieved, inhalation was repeated with Respimat<sup>†</sup> and spacer. Successful handling was defined as: (A) enclosure of the inhaler mouthpiece without covering the airvents, (B) coordination of dose release and inhalation, and for use with spacer (C) correct placement of the spacer followed by inhalation. The primary endpoint was the proportion of correct handling maneuvers. The inhalation profile in the successful handling configuration was verified with a pneumotachograph. Patient satisfaction and preferences were investigated in a questionnaire answered by the parents as one of the secondary endpoints. **Results:** All children below 3 years of age achieved correct handling of Respimat<sup>†</sup> with spacer (only one child refused cooperation). 40% (12/30) of the 3 to <4 year old children achieved correct handling of Respimat<sup>†</sup> without spacer. 85% (23/27) of the 4 to <5 year old children achieved correct handling without spacer. The percentage of correct handling maneuvers is lower without assistance by parents. In general the correct handling maneuvers were confirmed by the inhalation profile assessments. Analysis of satisfaction and preferences showed that most parents were fully satisfied with the handling of Respimat<sup>†</sup> and more than 90% stated that they were able to handle Respimat<sup>†</sup>. **Conclusion:** Children below 3 years of age should use Respimat<sup>†</sup> with spacer. The majority of 4 to <5 year old patients can handle Respimat<sup>†</sup> without spacer. Respimat<sup>†</sup> can be considered as suitable for inhalation therapy of young patients.

## **Salbutamol (Albuterol Sulfate)**

### **EFFECT OF INTERVAL BETWEEN ACTUATIONS OF ALBUTEROL HFA INHALERS ON THEIR AEROSOL CHARACTERISTICS.**

Berlinski A, Pennington D. *European Respiratory Journal* 2016 48:PA3363.

**Background:** Manufacturers of albuterol HFA recommend a 60s interval between actuations. A shorter interval will allow an increase in productivity in the hospital setting where large doses are used. The aim of the study was to compare the aerosol characteristics of albuterol HFA connected to a small volume non electrostatic valved holding chamber (VHC) when different intervals between actuations were used. **Methods:** Four units of 3 different albuterol HFA brands (Ventolin<sup>†</sup>, Proventil<sup>†</sup>, & Proair<sup>†</sup>) were tested connected to a VHC (AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup>). Ten actuations were fired into a VHC connected to a Next Generation Cascade Impactor operated at 30 L/min. The tested interval times between actuations were 60, 30, & 15s. All canisters were shaken 5s right before actuation. Albuterol was extracted from the impactor and tested with spectrophotometer (276 nm). Particle size characteristics were calculated with CITDAS V3.1 software. **Results:** Expressed as mean (SD) of 4 experiments. **Conclusions:** Decreasing the interval between actuations of albuterol HFA attached to a VHC from 60s to either 30s or 15s did not change their aerosol characteristics.

### **INHALED MEDICATION DELIVERY TO INFANTS VIA VALVED HOLDING CHAMBER WITH FACEMASK: NOT ALL VHCS PERFORM THE SAME.**

Sharpe R, Suggett JA, Nagel MW, Ali R, Avvakoumova V, Mitchell JP. *Proceedings of the 2014 European Respiratory Conference.*

**Rationale:** We report a study using an *in vitro* model (ADAM-III) in which the structure of a 7 month infant face together with an anatomically accurate nasopharynx have been simulated. This model was used to test two VHC-facemask products (antistatic AeroChamber Plus<sup>®</sup> with Flow-Vu<sup>®</sup> inspiratory flow indicator (aAC Plus/IFI), TMI; A2A Spacer, Clement Clarke International) with a beta2 adrenergic agonist pMDI. **Methods:** Each VHC ( $n=5$  devices/group) was tested out-of-package, and the A2A spacer group were also tested after pre-washing with detergent to mitigate electrostatic charge. A filter at the distal end of the nasopharynx model collected aerosol capable of reaching the lungs. Test conditions included a tidal volume of 50 mL, inspiratory/expiratory ratio of 1:3 and 30 breaths/min. 5-actuations of salbutamol sulfate (90 µg/actuation) were delivered at 30-s intervals, timing each actuation to coincide with (a) onset of inhalation (coordinated) and (b) the onset of exhalation (uncoordinated). The mass of salbutamol was recovered from the filter to determine delivered mass/actuation (DM). **Results:** DM ex aAC Plus/IFI VHC group was significantly greater than from the A2A spacer devices, even after pre-washing the latter devices (unpaired t-test,  $p < 0.001$ ). Additionally, DM ex A2A Spacer markedly decreased when pMDI actuation coincided with exhalation (paired t-test,  $p < 0.001$ ), whereas the corresponding values from the aAC Plus/IFI VHC group were unaffected ( $p = 0.75$ ). **Conclusions:** The delivered mass from the two VHCS differed significantly as did the relationship with onset of inhalation. Clinicians should be aware of these differences and their potential clinical impact.

### **EFFICIENCY EVALUATION OF VHC: A CFD COMPARISON STUDY AT CONSTANT FLOW.**

Oliveira RF, Teixeira SF, Marques HC, Teixeira JC. *Proceedings of the 2014 International Conference on Mechanics, Fluid Mechanics, Heat and Mass Transfer.*

**Background:** The objective of this work is to numerically evaluate several commercial Valved Holding Chamber (VHC) geometries, in terms of airflow behavior and wall deposition. Also, the Fine Particle Dose (FPD) and Mass Mean Aerodynamic Diameter (MMAD) of the drug dose reaching the lungs were evaluated. Downwards the VHC Mouthpiece, the USP Throat geometry was added. Major detail was included in the VHC components representation. **Methods:** Through the use of Computational Fluid Dynamics (CFD), the airflow velocity and turbulence fields were calculated for four geometries (i.e. A2A<sup>†</sup>, Aerochamber Plus<sup>®</sup> Flow-Vu<sup>®</sup>, NebuChamber<sup>†</sup> and Volumatic<sup>†</sup>). Using a constant flow of 30 L/min and several realistic spray inputs, the deposition was analyzed for three distinct particle size distributions. **Results:** The Volumatic<sup>†</sup> presents the higher recirculation in comparison to the other small volume VHC devices. Each VHC Valve and Mouthpiece design leads to different flows entering the Throat, where the NebuChamber<sup>®</sup> exhibits the higher air velocities (i.e. 34 m/s). The higher is the MMAD of the distribution injected, the greater will be the deposition in the upper walls. Therefore, the lower MMAD distribution results in higher dose available for the patient. Volumatic<sup>†</sup> showed the higher Body deposition, as well as, the NebuChamber<sup>®</sup> USP Throat.

Although the Aerochamber® valve presents the higher deposition, it provides the greater amount of drug for the patient lungs. On the other hand, the Volumatic® geometry while yielding the lower MMAD for the patient is far from providing the higher FPD. **Conclusions:** Based on the results, the VHC components design lead to very distinct airflow patterns. The sudden changes in particle trajectory result in higher deposition at those locations. The Aerochamber® delivers the higher FDM to the patient lungs, while the Volumatic® delivers the smaller MMAD distribution to the lungs.

### COMBINING TREATMENT WITH PRESSURIZED METERED DOSE INHALER-VALVED HOLDING CHAMBER WITH DOSIMETRIC THERAPY VIA A BREATH ACTUATED NEBULIZER IN PATIENT TITRATION FOR OBSTRUCTIVE LUNG DISEASES.

Mitchell JP, Nagel MW. *ATS International Conference, Philadelphia, PA, 2013, Abstract A4115; Am. J. Respir. Crit. Care Med. 2013;187:A-4115.*

**Rationale:** Clinical guidelines for asthma and COPD suggest health care providers titrate the patient to the least dose that is efficacious. In mild stable asthma or COPD, the dosing regimen will likely be pMDI+VHC. However, in an exacerbation, nebulizer treatment may be more appropriate. If a dosimetric BAN is used, it is possible to relate the drug mass delivered in a given time to the equivalent number of pMDI actuations. We report such data here for salbutamol, which can be delivered by either pMDI+VHC or nebulizer routes. **Methods:** Fine particle mass < 4.7 µm salbutamol ex-AeroChamber Plus® VHC; Trudell Medical International (TMI), London, Canada (FPM<4.7µm; n=5 devices) was determined by Andersen 8-stage cascade impactor following the pharmacopeial method, but simulating a 2-s delay between pMDI actuation and the onset of sampling to mimic the poorly coordinate patient for whom these devices are prescribed. In parallel studies, the fine particle delivery rate (FPM<4.7µm/min) of salbutamol solution (2.5 mg/3mL) from AeroEclipse® II BANs (n=5) with 1.5, 2.0, 2.5 and 3.0 mL fill volumes operated at 50 psig was determined with the mouthpiece of the nebulizer connected via a collection filter to a breathing simulator (ASL5000, Ingmar Medical, Pittsburgh, PA), used to generate adult breathing (tidal volume = 600-mL; duty cycle = 33%; rate = 10-cycles/min). Assay for salbutamol in both studies was by HPLC-UV spectrophotometry. **Results:** Preliminary studies had confirmed linearity of FPM<4.7µm ex-VHC between 2 and 10 actuations. FPM<4.7µm/min for the BAN was independent of volume fill and linear with time until sputter. The table illustrates the relationships between ex VHC and treatment time ex BAN to achieve the same FPM<4.7µm from pMDI+VHC. Mean values are reported as coefficients of variation were <10%.

**Table 1. Comparison of Dosing for Salbutamol by pMDI/VHC and BAN**

pMDI + VHC (salbutamol: 100 µg/actuation label claim) with 2 s delay		BAN (2.5 mg/3 mL salbutamol)
Number of actuations	FPM<4.7µm (µg)	Treatment time (min:sec)
2	70	0:53
4	140	1:45
6	210	2:38
8	280	3:30
10	350	4:20

\*values calculated based on measured FPM<4.7 µm of 33.2 ± 3.3 µg/actuation for 5-actuations

**Conclusions:** The ability to transition to and from pMDI + VHC to BAN offers the clinician new possibilities in titrating the adult tidal-breathing patient through exacerbations of broncho-constrictive diseases such as asthma or COPD, and easing the transition from hospital to the home environment.

### EFFICACY OF TWO DIFFERENT SPACE HOLDING CHAMBERS IN THAI CHILDREN WITH ASTHMA: A PILOT STUDY.

Kamalaporn H, Thongkum K, Preutthipan A. *Chest 2011;140:371A.*

**Purpose:** To compare the clinical efficacy of a newly-designed spacer, AeroHaler® (Aerocare, Thailand) to an established space holding chamber, Aerochamber® (Trudell Medical, Canada) in Thai children with asthma. **Methods:** A double-blinded, experimental study was conducted at the Pediatric Chest Clinic, Ramathibodi Hospital. We recruited known cases of asthma, aged 6-15 years with history of significant bronchodilator response by ATS criteria.

Patients were double-blinded randomized into 2 groups with blocked allocation. The pulmonary function tests were performed at baseline. 4 puffs of salbutamol MDI was used to test bronchial reversibility. The patients received bronchodilator through either Aerochamber® or AeroHaler† on the first day of study and through another on the next day. The pulmonary function tests were repeated at 15 and 30 minutes after bronchodilator given. Significant bronchodilator response is identified as >12% increment of force expiratory volume in 1 second (FEV<sub>1</sub>) from baseline. The mean FEV<sub>1</sub> increment which reflects the efficacy of each space holding chamber in delivering bronchodilator was compared by paired T test. **Results:** Twenty children with median age of 9.1 years (range 7.0-12.0) were enrolled. Thirteen children were male. The mean baseline FEV<sub>1</sub> in patients using Aerochamber® was 75.1±17.9% predicted and 77.6±16.8 % predicted in patients using AeroHaler† ( $p=0.07$ ). Using Aerochamber®, 10 children (50%) demonstrated bronchodilator response but only 4 of them (20%) showed bronchodilator response while using AeroHaler†. The FEV<sub>1</sub> increment in patients using Aerochamber® was greater than that of AeroHaler† at both time points, 15 and 30 minutes, which maximal value found at 30 minutes. The mean increments of FEV<sub>1</sub> using Aerochamber® and AeroHaler† were 9.97±9.36 % and 5.57±8.51 % respectively ( $p=0.02$ ). **Conclusions:** As assessment of FEV<sub>1</sub> increment to demonstrate bronchodilator response in Thai children with asthma, Aerochamber® is superior to AeroHaler†.

### **IMPORTANCE OF PATIENT-FRIENDLY FEATURES TO ADDRESS LACK OF INHALER COMPLIANCE: A LABORATORY EVALUATION OF AN INSPIRATORY FLOW INDICATOR AS A FEEDBACK AID FOR A VALVED HOLDING CHAMBER.**

Mitchell JP, Nagel MW, Malpass J. J. *Aerosol Med. Pulmon. Deliv.* 2011; 24 (3):46.

**Purpose:** Poor inhaler compliance is recognized as needing to be addressed. The Flow-Vu\* Inspiratory Flow Indicator (IFI) is a feedback aid for those using the AeroChamber Plus® Flow-Vu® Anti-Static VHC (Trudell Medical Inc., London, Ontario). Regulators require that the modification does not affect delivery of the therapeutically beneficial fine particle dose < 4.7 µm diameter from the inhaler. **Methods:** Measurements ( $n=5$  VHCs/group) of fine particle mass for salbutamol (100 µg/actuation) were made using an Andersen 8-stage impactor equipped with Ph.Eur. induction port and operated at 28.3 L/min. Data were obtained for the pMDI alone and for the pMDI +VHC (2-second delay), simulating poor coordination. The movement of the IFI monitored airflow through the VHC and a proper seal of the mouthpiece in the apparatus. The VHCs were tested out-of package in accordance with instructions. Recovery and assay for salbutamol was undertaken by HPLC-UV spectrophotometry. **Results:** Fine particle mass/actuation (FPM<sub>2.5</sub>) for pMDI alone (mean±SD) was 34.8 ± 1.4 µg, compared with 33.2 ± 3.3µg/actuation for the pMDI +VHC group. The IFI moved from the inhalation valve closed to open position immediately upon initiation of sampling. **Conclusions:** The IFI provided feedback on the delivery of this widely prescribed 'rescue' medication and did not interfere with the new VHC, delivering substantially comparable FPM<sub>2.5</sub> to that from the pMDI alone. It should therefore aid patient compliance.

### **SIMILAR LUNG AND SYSTEMIC DELIVERY CHARACTERISTICS OF SALBUTAMOL FROM AN AEROCHAMBER PLUS® VHC AND A VOLUMATIC.**

Mazhar SHR, Chrystyn H. Presented at the American Thoracic Society Conference, 2006.

We have shown that the amount of urinary salbutamol excreted in the first 30 minutes (USAL0.5) represents the relative lung deposition and the 24 hour salbutamol plus its metabolite excretion (USAL24) indicates the total systemic delivery following an inhalation (Hindle and Chrystyn. *Brit J Clin Pharmacol* 1992; 34: 311-5). We have used these *in-vivo* methods together with *in-vitro* characterization of the emitted dose using an Andersen Cascade Impactor (ACI) to compare the Volumatic (VOL) and AeroChamber Plus® (AERO). Spacers were attached to a salbutamol CFC free metered dose inhaler (MDI). 13 subjects, mean (SD) 31.2(7.6) years and 64.9 (10.9) Kg completed the *in-vivo* study.

The *in-vitro* and *in-vivo* results were:

Mean (SD) from two 100µg doses (µg except MMAD µm)

	MDI	MDI+VOL	MDI+AERO
ACI			
Spacer		74.9(6.1)	90.6(6.7)
TED	176.6(7.6)	94.9(4.6)	85.3(4.5)
Throat	93.6(7.4)	11.3(1.9)	11.7(1.2)
FDP	41.5(3.4)	41.8(2.3)	36.8(1.5)
MMAD	2.69(0.03)	2.76(0.07)	2.91(0.10)
Urinary salbutamol			
USAL0.5	5.71(1.9)	16.36(8.2)	14.4(7.6)
USAL24	100.2(16.7)	97.3(12.7)	84.6(25.8)

TED - total emitted dose; Throat - ACI throat+S0+S1; FDP - fine particle dose, ACI S2-filter; MMAD - mass median aerodynamic diameter. Statistical analysis of the USAL0.5 data revealed no difference between the two spacers (mean difference [95% confidence interval] of 1.9[-4.5,8.3]µg). USAL 0.5 VOL and AERO were each greater ( $p<0.001$ ) than MDI alone (mean difference [95%CI] of 10.6[4.2,17.1] and 8.7[2.3,15.1]µg, respectively). USAL24 amounts were all similar. The *in-vitro* characteristics suggest that slightly more salbutamol will be delivered to the lungs from a Volumatic than an AeroChamber Plus® VHC. The *in-vivo* data confirms this but the difference, as predicted by the *in-vitro* data, is only small. The results are consistent with the smaller size of the AeroChamber Plus®.

#### THE EFFECT OF INHALATION TECHNIQUE, SPACER VOLUME AND TRAINING ON AEROSOL DELIVERY FROM SPACERS IN CHILDREN.

Devadason SG, Walker SL, Owen J, Perth, Western Australia, Australia. Presented at the American Thoracic Society Conference, San Diego, CA, 2005.

**Rationale:** Variability in the clinical use of inhaler devices is high, particularly in children. Optimization of inhalation therapy should ensure more consistent dose delivery to the airways of young children. We assessed the effect of spacer volume, inhalation technique and training of the parent/child on drug delivery to children using pressurized inhalers. **Methods:** Albuterol was delivered via large (Volumatic; VOL) and small (AeroChamber Plus®; AC+) spacers to 21 children (2-14yrs). Children  $\geq$  5yrs either took 5 tidal breaths, or one slow maximal inhalation with 10 sec breath-hold. Children  $<$ 5yrs used tidal breathing only. Training sessions were scheduled  $\geq$  12wks apart. Drug delivery was assessed using a low resistance filter attached to the spacer mouthpiece. **Results:** Mean (SD) drug delivery (% nominal dose) to children of all ages using AC+ [51.5 (14.7)%] was significantly higher ( $p=0.04$ ) than using VOL [39.3 (10.1)%]. Mean (SD) drug delivery using the single maximal inhalation technique [45.4 (13.7)%] was significantly higher ( $p=0.01$ ) than that using tidal breathing [32.3 (13.9)]. The improvement in delivery using the single maximal inhalation was most marked in the 5-7yr age group. Training the parent/child to use the spacer correctly gave a small (3.9%) but significant increase ( $p=0.04$ ) in drug delivery. **Conclusions:** AC+ (small volume) delivered more drug than VOL (large volume). This is possibly due to the more efficient construction and design of the AeroChamber Plus® as delivery is normally improved when using large volume spacers. The single maximal inhalation technique increased drug delivery to patients compared to tidal breathing. However, it is easier for children  $<$ 5yrs to use the tidal breathing technique. Training of the parent/patient resulted in a smaller than expected (albeit significant) increase in drug delivery.

#### A COMPARISON OF THE BRONCHOPROTECTIVE EFFECT OF CFC-AND HFA-ALBUTEROL METERED-DOSE INHALERS (MDIS) USED IN COMBINATION WITH THE AEROCHAMBER PLUS®.

Ahrens RC., Teresi ME., Lux CR., Tan Y. Presented at the American Thoracic Society Conference, Seattle, Washington 2003.

Previous studies have documented equivalent clinical efficacy of directly inhaled CFC and HFA albuterol MDIs but not whether use of a holding chamber alters this relationship. We compared albuterol delivery to the lungs by an HFA MDI with that of a CFC MDI when used in combination with an AeroChamber Plus® valved-holding chamber (VHC) using a methacholine challenge based bioassay. Seventeen subjects completed this double-blind, randomized,

balanced cross-over study. Treatments were 1 or 2 actuations of albuterol CFC MDI (90 mcg/puff) or HFA MDI (100 mcg/puff). One of 4 treatments was administered during each study period with the AeroChamber Plus® VHC. A methacholine challenge (modified Juniper method) was initiated 15 minutes after albuterol administration. Results: (geometric mean PC<sub>20</sub>FEV<sub>1</sub>)

1 Puff CFC	2 Puffs CFC	1 Puff HFA	2 Puffs HFA
16.96	18.81	15.06	20.79

The dose-response relationship was significant ( $p=0.034$ ) and parallelism and preparation contrasts were not significant ( $p=0.93, 0.27$ , respectively). The relative potency estimated using Finney 2-by-2 bioassay statistics was 0.97 (90% confidence interval [CI] 0.41-2.14). The 90% bias-corrected and accelerated percentile bootstrap CI for this estimate was 0.58-1.75. Removing an outlier from the data, the estimated relative potency was 1.04 (90% CI 0.65-1.73). **Conclusion:** HFA-and CFC-MDIs deliver equivalent quantities of albuterol to the lung when used with the AeroChamber Plus® VHC.

### **Seretide<sup>®</sup> (Salmeterol & Fluticasone Propionate) GSK<sup>®</sup> Inc.**

#### **THE EFFICACY AND SAFETY OF FLUTICASONE/SALMETEROL COMPARED TO FLUTICASONE IN CHILDREN YOUNGER THAN FOUR YEARS OF AGE.**

*Yoshihara S, Tsubaki T, Ikeda M, Lenney W, Tomiak R, Hattori T, Hashimoto K, Soutome T, Kato S. Pediatr Allergy Immunol. 2019 Mar;30(2):195-203.*

**Background:** Fluticasone propionate 50 µg/salmeterol xinafoate 25 µg (FP/SAL) is widely used in adults and children with asthma, but there is sparse information on its use in very young children. **Methods:** This was a randomized, double-blind, multicentre, controlled trial conducted in children aged 8 months to 4 years. During a 2-week run-in period, they all received FP twice daily. At randomization, they commenced FP/SAL or FP twice daily for 8 weeks. All were then given FP/SAL only, in a 16-week open-label study continuation. Medications were inhaled through an AeroChamber Plus® with attached face mask. The primary end-point was mean change in total asthma symptom scores from baseline to the last 7 days of the double-blind period. Analyses were undertaken in all children randomized to treatment and who received at least one dose of study medication. **Results:** Three hundred children were randomized 1:1 to receive FP/SAL or FP. Mean change from baseline in total asthma symptom scores was -3.97 for FP/SAL and -3.01 with FP. The between-group difference was not statistically significant ( $P = 0.21$ ; 95% confidence interval: -2.47, 0.54). No new safety signals were seen with FP/SAL. **Conclusion:** This is the first randomized, double-blind study of this size to evaluate FP/SAL in very young children with asthma. FP/SAL did not show superior efficacy to FP; no clear add-on effect of SAL was demonstrated. No clinically significant differences in safety were noted with FP/SAL usage.

#### **COMPARISON OF THE CLINICAL EFFECTS OF COMBINED SALMETEROL/FLUTICASONE DELIVERED BY DRY POWDER OR PRESSURIZED METERED DOSE INHALER.**

*Hojo M, Shirai T, Hirashima J, Iikura M, Sugiyama H. Pulmonary Pharmacology & Therapeutics 2016; 37, 43-48.*

The salmeterol/fluticasone combination (SFC) inhaler is currently the most widely used maintenance drug for asthmatics worldwide. Although the effectiveness of SFC as either a dry powder inhaler (DPI) or a pressurized metered dose inhaler (pMDI) is well documented, there is limited data comparing the clinical efficacies of the two devices. To address this issue, we carried out a randomized crossover trial in which asthmatic patients ( $n = 47$ ; mean age,  $62.5 \pm 16.5$  years old) received a 12-week treatment of SFC DPI (50/250 µg twice daily) or SFC pMDI (four puffs of 25/125 µg daily). After a 4-week washout period, patients received another crossover treatment for 12 weeks. Respiratory resistance and reactance were measured by forced oscillation technique (MostGraph-01), spirometry, fractional exhaled nitric oxide (FeNO), and an asthma control test (ACT) every 4 weeks. The mean forced expiratory volume 1.0 at the baseline was  $2.16 \pm 0.86$  (L). Respiratory system resistance at 5 Hz (R5), the difference between R5 and R at 20 Hz (R5 - R20), and FeNO improved in both treatment groups, while reactance at 5 Hz (X5) and ACT score improved only in the pMDI group. In patients > 70 years old ( $n = 21$ ), R5, R5 - R20,  $\Delta X5$ , and FeNO improved only in the pMDI group. These results suggest that SFC by pMDI (with AeroChamber Plus\* Anti-Static VHC) produces a stronger anti-inflammatory and bronchodilatory effect even in patients whose asthma is well controlled by SFC delivered by DPI.

## USE OF VALVED HOLDING CHAMBERS WITHOUT PRE-CONDITIONING AND THE INFLUENCE OF ANTI-STATIC MATERIALS.

Suggett J, Nagel M, Doyle C, Schneider H, Mitchell J. *Drug Delivery to the Lungs 2014; published in J. Aerosol Med. Pulm. Deliv., 2014.*

**Background:** In recent years ‘anti-static’ Valved Holding Chambers (VHCs) have become more widely available. They enable use directly out of packet without pre-treatment, as pre-washing with detergent followed by drip-drying in air is time-consuming and not always followed. This laboratory study sought to investigate whether fine particle (<4.7 µm) drug delivery efficiency was similar from four commercially available VHCs, two of which were ‘anti-static’, the others being non-conducting, when pre-washing was not performed. **Materials and Methods:** Each VHC ( $n=3$  or  $5$ /group) was evaluated with Seretide<sup>†</sup> 250 pMDI (fluticasone propionate (FP)/25 salmeterol xinafoate (SX)), sampling the emitted aerosol at 28.3 L/min via an abbreviated Andersen impactor connected to a PhEur/USP induction port. A 5 s delayed inhalation was mimicked using a proprietary apparatus. Recovered FP and SX were assayed by validated HPLC-based methods. **Results:** The  $FPM_{<4.7\mu m}$  for the non-conducting devices (Compact SpaceChamber Plus<sup>†</sup> and A2A<sup>†</sup> Spacer) were greatly reduced compared with the anti-static devices with as low as 6% of the medication delivered in some cases compared to the best performing Anti-Static VHC. The two Anti-Static VHCs (AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> Anti-Static VHC and OptiChamber<sup>†</sup> Diamond<sup>†</sup>) delivered consistently more medication as therapeutically beneficial  $FPM_{<4.7\mu m}$ , however even for these two devices, the performance was not equivalent, with the former device exhibiting significantly higher values (1-way ANOVA,  $p < 0.001$ ). **Conclusions:** The results indicate that if pre-conditioning is not performed for non-conducting VHCs then there is likely to be greatly reduced medication delivered to the patient and therefore under-dosing until VHC conditioning occurs. The use of ‘anti-static’ VHCs improves the reliability of medication delivery from pMDI-VHC combinations, although there are still differences in performance, and other factors, such as chamber design can also affect the fine particle delivery. Care should be taken by prescribers in the selection of these devices.

## VALVED HOLDING CHAMBERS (VHCs) CAN HAVE DIFFERENT MEDICATION DELIVERY PERFORMANCE AS A FUNCTION OF DELAY INTERVAL FOLLOWING ACTUATION OF THE PRESSURIZED METERED DOSE INHALER (PMDI).

Suggett J, Nagel M, Doyle C, Schneider H, Mitchell J. *Proceedings of the 2014 European Respiratory Conference.*

**Rationale:** VHCs are prescribed for patients who cannot coordinate inhalation with actuation of a pMDI. Performance of these add-on devices as a function of delayed inhalation is therefore critical. The present study explored the *in vitro* performance of three different anti-static VHCs, simulating 5 s and 10 s delays. **Methods:** 5 actuations of Seretide<sup>†</sup> 250µg fluticasone propionate (FP)/25µg salmeterol xinafoate (SX)(GSK) were delivered to AeroChamber Plus<sup>\*</sup> Anti-Static VHC with Flow-Vu<sup>®</sup> IFI ((AC-Plus) Trudell Medical International), OptiChamber<sup>†</sup> Diamond<sup>†</sup> VHC ((OD) Philips Respironics) and Vortex<sup>†</sup> ((Vortex) PARI Respiratory Equipment) non electrostatic VHC ( $n=5$  devices / group). Each VHC was used out of package and connected to an Andersen Mk II cascade impactor operated at 28.3 L/min. A proprietary apparatus enabled the required delay interval to be simulated. Recovered FP and SX were assayed using HPLC-UV spectrophotometry. **Results:** Measures (mean ± SD) of therapeutically beneficial fine particle mass <4.7 µm aerodynamic diameter ( $FPM_{<4.7\mu m}$ ) are summarized in the table.

VHC type	Seretide <sup>†</sup> component	Delay(s)	$FPM_{<4.7\mu m}$ (µg/actuation)
AC Plus	FP	5	88.2 ± 5.6
		10	78.3 ± 6.7
	SX	5	8.6 ± 0.6
		10	7.3 ± 0.5
OD	FP	5	63.8 ± 7.8
		10	48.6 ± 9.3
	SX	5	6.2 ± 0.9
		10	4.7 ± 0.8
Vortex	FP	5	67.4 ± 9.7
		10	47.8 ± 8.1
	SX	5	7.0 ± 1.0
		10	4.7 ± 0.8



**Conclusions:** FPM was significantly greater using the AC-Plus VHC compared to the OD and Vortex VHCs for both components at both time delays (1-way ANOVA,  $p \leq 0.002$ ). The clinical impact of potential under-dosing with poorly coordinated patients should be considered when selecting a VHC.

**CONSISTENT MEDICATION DELIVERY IS POSSIBLE FROM A PRESSURIZED METERED-DOSE INHALER (PMDI) WITH VALVED HOLDING CHAMBER (VHC) MANUFACTURED FROM ELECTROSTATIC CHARGE-DISSIPATIVE MATERIALS.**

*Nagel M, Avvakoumova V, Doyle C, Ali R, Mitchell J. Presented at Drug Delivery to the Lungs-22, Edinburgh, UK, December 2011, 157-160.*

We report the results from a laboratory study, in which the effect of transitioning a small volume VHC (145-mL) from non-conducting to electrostatic charge-dissipative polymer construction was demonstrated by determining the delivery of a two-component pMDI oral inhaled product comprising a long-acting bronchodilator (LABA) with inhaled corticosteroid (ICS). Measurements of fine particle mass between 1.1 and 4.7  $\mu\text{m}$  aerodynamic diameter made by cascade impactor with 1s, 2s, and 5s delay between actuation of the inhaler and the onset of sampling have demonstrated substantially equivalent performance to that of the pMDI alone and with an earlier version of the VHC manufactured from non-conducting materials that required pre-washing after removal from its packaging in order to mitigate loss of medication due to electrostatic charge. The ability to use the new VHC without prewashing is intended to make the device easier to use, with the ultimate goal of improving patient compliance with the prescribing clinician's intent for therapy.

**PHARMACODYNAMIC AND PHARMACOKINETIC COMPARISONS AFTER ADVAIR DISKUS AND ADVAIR HFA ADMINISTRATION IN PEDIATRIC SUBJECTS.**

*Qaqundah P, Kerwin E, Mehta R, Saggi P, Vanderslice T, Cahn A, Hsu Y, Kunka R. American Thoracic Society Meeting, Toronto, ON, 2008.*

Thirty-one pediatric subjects (4-11 years) with asthma participated in an open-label, repeat dose, crossover study to compare serial concentrations of serum cortisol, fluticasone propionate (FP) and salmeterol (SAL) after three weeks of administration of Advair Diskus<sup>†</sup>, Advair<sup>†</sup> HFA, or Advair<sup>†</sup> HFA with the valved holding chamber (spacer), AeroChamber Plus<sup>\*</sup>. Following a baseline assessment of serum cortisol and SAL pharmacodynamic parameters, 28 subjects completed the study with each subject receiving two of the three treatments using a randomized incomplete block design. FP systemic exposure was low after all treatments resulting in geometric mean (95% CI) C<sub>max</sub> of 54pg/mL (33,89) for Advair Diskus, 16pg/mL (8, 29) for Advair HFA and 35pg/mL (20, 60) for Advair HFA with spacer.

**PERFORMANCE OF LARGE AND SMALL VOLUME VALVED HOLDING CHAMBERS WITH A NEW COMBINATION LONG-TERM BRONCHODILATOR / ANTI-INFLAMMATORY FORMULATION DELIVERED BY PRESSURIZED METERED DOSE INHALER.**

*Nagel MW, Wiersema KJ, Bates SL, Mitchell JP. Journal of Aerosol Medicine 2002;15(4):427-433.*

The treatment of both the bronchoconstriction and inflammatory aspects of asthma simultaneously by a single pressurized metered dose inhaler (pMDI) represents a significant advance in convenience to the patient. However, a valved holding chamber (VHC) may still be needed to reduce the coarse component of the dose that is likely to deposit in the oropharyngeal region, and a small sized device may offer significant advantages to the patient from the standpoint of compliance with therapy. VHCs representing small (adult AeroChamber Plus<sup>®</sup> with mouthpiece, 149-mL) and large (Volumatic<sup>†</sup>, 750-mL) devices have been compared in an *in vitro* evaluation with Seretide<sup>†</sup>/Advair<sup>†</sup> (hydro-fluoro alkane [HFA]-formulated fluticasone propionate [FP = 125  $\mu\text{g}/\text{dose}$ ] and salmeterol xinafoate [SX = 25  $\mu\text{g}/\text{dose}$ ]) by Andersen Mark-II eight-stage impactor operated at 28.3L/min following compendial methodology. Fine particle fraction, based on the size range from 1.1 to 4.7  $\mu\text{m}$  aerodynamic diameter, from either large or small VHCs with either component (69-79%) was similar [ $p \geq 0.08$ ], and significantly greater than that from the pMDI alone (approximately 40%) [ $p < 0.001$ ]. Fine particle dose emitted by the VHCs for SX (8.2  $\pm$  0.8  $\mu\text{g}$  for the AeroChamber Plus<sup>®</sup> and 7.7  $\pm$  0.5  $\mu\text{g}$  for the Volumatic<sup>†</sup>) were comparable, and also similar to the fine particle dose delivered by the pMDI when used without a VHC (7.6  $\pm$  0.6  $\mu\text{g}$ ). Fine particle doses for the FP component delivered by the two VHCs (46.4  $\pm$  3.4  $\mu\text{g}$  for the AeroChamber Plus<sup>®</sup> and 46.3  $\pm$  2.7  $\mu\text{g}$  for the Volumatic<sup>†</sup>) were equivalent, but were slightly greater than the corresponding fine particle dose from the pMDI alone (39.1  $\pm$  2.6  $\mu\text{g}$ ). However, this difference (approximately 20%) is close to the limit of resolution based on intermeasurement variability and is unlikely to have

clinical significance, given the interpatient variability seen with inhaled drug therapy. It is therefore concluded that either of these VHCs has equivalent *in vitro* performance with this combination formulation in terms of the portion of the dose emitted from the pMDI that is likely to reach the receptors in the lungs.

### **Serevent<sup>®</sup> (Salmeterol Xinafoate) GSK<sup>®</sup> Inc.**

#### **COMPARISON OF A LARGE AND A SMALL VOLUME HOLDING CHAMBER (VHC) FOR THE DELIVERY OF SALMETEROL XINAFOATE.**

*Mitchell JP, Nagel MW, Wiersema KJ, Bates SL, Morton RW, Schmidt JN. Presented at Ann Meet Amer College of Allergy, Asthma and Immunology (ACAAI), Seattle, 2000.*

Salmeterol xinafoate is a widely prescribed long-acting beta-adrenergic agonist. Valved holding chambers (VHCs) improve drug delivery from pressurized metered-dose inhalers (pMDI), particularly with patients having poor coordination. The present study compared a large volume VHC (Volumatic<sup>†</sup>, GlaxoSmithKline - 750-ml, *n*=5 devices) with a small volume VHC (AeroChamber Plus<sup>®</sup>, Monaghan Medical Corp. - 149-ml, *n*=5 devices) with salmeterol xinafoate (Serevent<sup>†</sup>: total dose 21 µg ex actuator, GlaxoSmithKline). Measurements were also made with the pMDI without VHC. Total emitted dose (TD), fine particle dose (FPD - particles < 4.7 µm aerodynamic diameter) and fine particle fraction (FPF) were determined by Andersen 8-stage impactor with USP Induction Port at 28.3 ± 0.5 L/min. Assays for salmeterol xinafoate were undertaken by HPLC-fluorescence spectrometry at excitation and emission wavelengths of 226 nm and 296 nm respectively. As expected, both types of VHC greatly reduced the coarse component of the dose from the pMDI (10.5 ± 1.2 µg - pMDI alone; 1.0 ± 0.6 µg - AeroChamber Plus<sup>®</sup> VHC; 0.9 ± 0.7 µg - Volumatic<sup>†</sup> VHC). Both FPD and TD from the AeroChamber Plus<sup>®</sup> (12.7 ± 1.3 µg and 13.6 ± 0.9 µg respectively) and from the Volumatic<sup>†</sup> (12.3 ± 1.7 µg and 13.2 ± 2.1 µg respectively) VHCs were comparable (un-paired t-test, *p* > 0.70). FPD from the pMDI alone was 10.6 ± 1.0 µg, slightly lower but still comparable with the FPD from either type of VHC. The small volume VHC appears to be as effective as the larger chamber for the delivery of this formulation. These data are consistent with the recommendation to use a VHC with this formulation for patients with poor coordination (Demirkan *et al.* (Chest 2000; 117, 1314-1318)).

#### **SALMETEROL ADMINISTRATION BY METERED-DOSE INHALER ALONE VS METERED-DOSE INHALER PLUS VALVED HOLDING CHAMBER.**

*Demirkan K, Tolley E, Mastin T, Soberman J, Burbeck J, Self T. Chest 2000 May; 117 (5):1314-8.*

**Study Objective:** To determine whether a spacer device designed as a valved holding chamber with a flow signal increases the efficacy of the long-acting beta(2)- agonist, salmeterol, in patients who use incorrect technique with metered-dose inhaler (MDI) alone. **Design:** Double-blind, randomized, placebo-controlled study. **Setting:** University hospital outpatient rooms. **Patients:** Twenty adult outpatients with stable persistent asthma, receiving a daily anti-inflammatory drug. **Interventions:** Patients were randomized to either salmeterol MDI (incorrect use: 1 s after actuating MDI, inhale rapidly) and placebo plus spacer (correct use: inhale slowly as MDI is actuated, continue to inhale slowly and deeply) or placebo MDI (incorrect use) and salmeterol plus spacer (correct use). The following week, patients received the opposite treatment. The dose was two puffs from each device on each treatment day; each puff was separated by 1 min. **Measurements and Results:** After baseline peak expiratory flow (PEF), salmeterol was administered and serial PEF determined (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h). Administration of salmeterol MDI plus spacer resulted in significantly greater increases in PEF from baseline vs MDI at 4 h (44 L/min vs 10 L/min; *p* < 0.01) and 6 h (49 L/min vs 24 L/min; *p* < 0.05). Both methods of administration were equally well tolerated. **Conclusion:** We conclude that patients who have poor timing and rapid inhalation with salmeterol MDI alone will have greater increases in PEF at 4 h and 6 h and no additional side effects if the dose is administered with a valved holding chamber that is used correctly. Further study is needed regarding other errors in MDI technique with salmeterol.

**EFFECT OF A SPACER ON TOTAL SYSTEMIC AND LUNG BIOAVAILABILITY IN HEALTHY VOLUNTEERS AND IN VITRO PERFORMANCE OF THE SYMBICORT<sup>®</sup> (BUDESONIDE/FORMOTEROL) PRESSURIZED METERED DOSE INHALER.**

*Gillen M, Forte P, Svensson JO, Lamarca R, Burke J, Rask K, Nilsson UK, Eckerwall G.*

Many patients with chronic obstructive pulmonary disease or asthma experience difficulties in coordinating inhalation with pressurized metered-dose inhaler (pMDI) actuation. The use of a spacer device can improve drug delivery in these patients. The aim of this study was to establish the relative bioavailability of single doses of Symbicort<sup>®</sup> (budesonide/formoterol) pMDI 160/4.5 µg/actuation (2 actuations) used with and without a spacer device. In addition, an *in vitro* study was conducted to characterize performance of the inhaler when used in conjunction with a spacer device. A Phase I, randomized, open-label, single-dose, single-center, crossover study in 50 healthy volunteers (NCT02934607) assessed the relative bioavailability of single-dose Symbicort<sup>®</sup> pMDI 160/4.5 µg/actuation (2 actuations) with and without a spacer (AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup>). Inhaled doses were administered without or with activated charcoal (taken orally) to estimate total systemic exposure and exposure through the lung, respectively. The *in vitro* study characterized the effect of the spacer with respect to delivered dose, fine particle dose, and dose during simulated breathing of budesonide and formoterol. In terms of total systemic exposure, use of the spacer increased the relative bioavailability determined by AUC(O-last) and C<sub>max</sub> by 68% (spacer:no spacer treatment ratio, 167.9%; 90% CI, 144.1 to 195.6) and 99% (ratio, 198.7%; 90% CI, 164.4 to 240.2) for budesonide, and 77% (ratio, 176.6%; 90% CI, 145.1 to 215.0) and 124% (ratio, 223.6%; 90% CI, 189.9 to 263.3) for formoterol, respectively, compared with pMDI alone. Similarly, the lung exposure of budesonide and formoterol increased (AUC(O-last) and C<sub>max</sub> by 146% [ratio, 246.0%; 90% CI, 200.7 to 301.6] and 127% [ratio, 226.5%; 90% CI, 186.4 to 275.4] for budesonide, and 173% [ratio, 272.8%; 90% CI, 202.5 to 367.4] and 136% [ratio, 236.2%; 90% CI, 192.6 to 289.6] for formoterol, respectively) when the pMDI was administered through the spacer. When assessed by AUC(O-last) quartile without spacer, subjects in the lowest exposure quartile (indicating poor inhalation technique) with Symbicort<sup>®</sup> pMDI 160/4.5 µg/actuation (2 actuations) had markedly increased total systemic and lung exposure when the same dose was administered with the spacer. In contrast, for subjects in the highest exposure quartile with pMDI alone, total systemic and lung exposure of formoterol and budesonide was similar with and without the spacer. In the *in vitro* study, the fine particle dose (<5 µm) of both budesonide and formoterol from the spacer at delay time (i.e., pause period after actuation) =0 60 seconds (instantaneous) after actuation was similar to the fine particle dose when not using the spacer. The delivered doses of budesonide and formoterol from the spacer were both lower compared with the doses administered without the spacer. There was also a decrease in delivered dose with increasing delay time. The clinical study demonstrated that in subjects with poor inhalation technique the use of the AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> spacer increased the bioavailability of Symbicort<sup>®</sup> pMDI to a level observed in subjects with good inhalation technique without a spacer. The findings from the *in vitro* study support the fine particle dose characteristics of Symbicort<sup>®</sup> pMDI with the AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> spacer.

**IN VITRO CHARACTERIZATION OF SYMBICORT PRESSURIZED METERED DOSE INHALERS IN COMBINATION WITH AEROCHAMBER PLUS<sup>®</sup> FLOW-VU<sup>®</sup> AND AEROCHAMBER PLUS<sup>®</sup> SPACERS.**

*Svensson JA. Respiratory Drug Delivery 2018.*

A significant relationship between proper inhaler technique and control of symptoms in patients with chronic obstructive pulmonary disease (COPD) and asthma has been established. Studies have identified that the most common critical handling errors with pressurized metered dose inhalers (pMDIs) are related to coordination of inhalation with inhaler actuation. It has been shown that the use of a spacer (also known as a valved holding chamber) can mitigate coordination difficulties and improve the efficiency of drug delivery. To characterize Symbicort pMDI 160/4.5 (AstraZeneca Sweden) in combination with two commercially available spacers, Aerochamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> and Aerochamber Plus<sup>®</sup> (Trudell Medical International, Canada), an *in vitro* study has been performed. The study was designed according to EMA requirements. Both spacer types demonstrated broadly similar performance when tested with Symbicort pMDI. The fine particle dose ex-spacer and its time dependency were almost identical for both spacer types. When the spacers were used according to the instructions (0 second delay time), the FPD ex-spacer was very similar to the FPD without a spacer.

## A VALVED HOLDING CHAMBER DOES NOT DECREASE THE BRONCHODILATOR ACTIVITY OF BUDESONIDE-FORMOTEROL COMBINATION METERED DOSE INHALER

Mansfield LE, Maynes R. *J Asthma* 2013;50(1):71-4.

**Objective:** Spacers and valved holding chambers (VHCs) were developed to facilitate using pressurized metered dose inhaler (pMDI) by patients who could not coordinate the actions required for successful pMDI use. There is little *in vivo* evidence about how VHC may affect the bronchodilation from combination drugs in pMDI. This study was to determine the effect, if any, of VHC on the bronchodilating actions of the pMDI budesonide/formoterol combination.

**Methods:** Sixteen adult asthmatic subjects with 15% or greater reversibility of forced expiratory volume in one second (FEV-1), 15 minutes after inhaling 180-360 µg of albuterol, participated. The study had a randomized crossover design with each subject using budesonide-formoterol pMDI as described in the product information one time and on a second occasion using the pMDI with a VHC. Spirometry and impedance oscillometry were measured at baseline and repeatedly over a 12-hour period. This study was approved by IntegReview Institutional Review Board, Austin, TX, USA. The clinical trial number for this study was NCT 009-15538 (<http://www.westernskymed.com>). **Results:** The area under the curve of FEV-1, the FEV-1, and the fraction FEV-1/FVC was similar over the 12-hour time frame with both methods. Resistance was not different at any time point. In both procedures, the onset of bronchodilation occurred rapidly within 3 to 5 minutes. **Conclusions:** In well-trained asthmatic subjects, both tested methods caused equivalent bronchodilation. This suggests a VHC itself has no deleterious effect on the bronchodilator activity in the combined drug. These results may not apply to patients who have coordination problems with the pMDI and further study is indicated.

## USE OF A VALVED HOLDING CHAMBER DOES NOT ADVERSELY AFFECT BRONCHODILATION FROM BUDESONIDE/FORMOTEROL PRESSURIZED METER DOSE INHALER (PMDI).

Mansfield LE, Cueto E, Maynes R, Romero E. *Journal of Allergy and Clinical Immunology* 2010;125(2):S1.

**Rationale:** PMDI are often used clinically with valved holding chambers to facilitate patient coordination and use. There is no available information about the effect of using the valved holding chamber on the bronchodilator activity of combination PMDI of formoterol and budesonide. This study addresses this issue. **Methods:** 16 adult asthmatics with demonstrated 15% or greater increase in FEV-1 after 2-4 inhalations of albuterol 90µg were studied in a randomized crossover design. Pulmonary functions were measured for 12 hours after using Symbicort<sup>®</sup> PMDI, 160/4.5 in usual fashion or with a valved holding chamber (AeroChamber Plus<sup>®</sup>). Subjects inhaled from valved holding chamber immediately after actuation of PMDI. 12 hour area under the curve was determined for FEV-1 in liters, and FEV-1/FVC and individual time points compared. **Results:** AUC FEV-1 PMDI 1937.1 Liters, PMDI plus chamber 1920.7 liters, AUC FEV<sub>1</sub>/FVC PMDI 58417%, PMDI plus chamber 57830%. There were no significant differences at any time point. **Conclusions:** Use of a valved holding chamber does not adversely affect the bronchodilating activity of formoterol in the budesonide/formoterol combined PMDI when used by adult asthmatics.

## COMPARATIVE *IN VITRO* PERFORMANCE OF VALVED HOLDING CHAMBERS WITH A BUDESONIDE/FORMOTEROL PRESSURIZED METERED-DOSE INHALER.

Chambers FE, Brown S, Ludzik AJ. *Allergy Asthma Proc* 2009;30(4):424-32.

A combination of budesonide and formoterol in a single pressurized metered-dose inhaler (pMDI) is available in the United States and elsewhere. This study was designed to evaluate the delivered dose and fine particle dose (FPD; mass of particles <4.7-micrometer diameter) using the pMDI with two valved holding chambers (VHCs), using sampling methods reflecting different patient techniques. FPD was measured using an Andersen Cascade Impactor and delivered dose was measured using a disposable filter. Two VHCs, AeroChamber Plus<sup>®</sup> and AeroChamber MAX<sup>®</sup> (Trudell Medical International, London, Ontario, Canada), were evaluated using three sampling methods: (1) immediate collection; (2) collection after up to a 5-second delay; (3) using simulated adult, child, and infant tidal breathing patterns (delivered dose). Decreases in delivered dose were observed using a VHC compared with the pMDI alone. FPD with both VHCs was similar to that with the pMDI alone with minimal delay between actuation and collection. With delays, the antistatic AeroChamber MAX<sup>®</sup> was more resistant than AeroChamber Plus<sup>®</sup> to dose losses. Delivered doses from adult and child profiles were comparable with those after a 1-second delay. The infant profile produced lower delivered doses, probably because more breath cycles are required to empty the VHC. Budesonide/formoterol pMDI can be used effectively with AeroChamber Plus<sup>®</sup> and the antistatic AeroChamber MAX<sup>®</sup>. With minimal delay

between actuation and collection, FPD with both VHCs was similar to that with the pMDI alone, giving physicians a choice of administration regimen and taking into account the needs and skills of the patient.

### **THE *IN VITRO* FINE PARTICLE DOSE WITH SYMBICORT RAPIHALER PMDI IS SIMILAR USING EITHER NEBUCHAMBER OR AEROCHAMBER PLUS® VALVED HOLDING CHAMBER SPACER DEVICES.**

*Chambers F, Berg E, Brown M, Svensson JO. 15<sup>th</sup> ERS Annual Congress, Copenhagen, Denmark, in Eur. Respir. J. 2005; 26S49: P3291.*

**Background:** Symbicort (budesonide/formoterol) Rapihaler<sup>†</sup> is a novel pressurised HFA metered dose inhaler. This study aimed to evaluate the *in vitro* delivery of budesonide and formoterol via Symbicort Rapihaler from 2 spacer devices: the NebuChamber<sup>†</sup> and the AeroChamber Plus<sup>®</sup> valved holding chamber. **Methods:** The particle size distribution was analyzed using Next Generation Impactor (NGI) at 30 L/min. The effect of different dose regimens on fine particle dose (FPD) was investigated. The following regimens using Symbicort 80/4.5 µg were assessed: single actuation (act) with a 2-s delay between act and collection (1 act, 2-s delay) and 2 acts with a 2-s delay between acts and collection (2 acts, 2-s delay). Six acts were collected/test. **Results:** The graph shows FPD (as a % of nominal dose) for budesonide. Similar results were observed for formoterol. **Conclusion:** This *in vitro* study shows that the fine particle dose from Symbicort Rapihaler pMDI is similar when using either NebuChamber or AeroChamber Plus<sup>®</sup>.

### **Trimbow<sup>†</sup> (Beclometasone dipropionate, Formoterol fumarate dihydrate, glycopyrronium) Chiesi Ltd.**

#### **EFFECT OF ANTISTATIC AEROCHAMBER PLUS® FLOW-VU® SPACER ON THE SYSTEMIC BIOAVAILABILITY OF CHF5993 A NOVEL TRIPLE PMDI.**

*Mariotti F, Collarini S, Vezzoli S, Acerbi D, Scuri M, Kuna P. European Respiratory Journal 2016 48: PA964.*

This study evaluated the effect of antistatic AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> spacer on the systemic exposure to extrafine CHF5993 pMDI, a new fixed dose combination of Beclometasone Dipropionate (BDP), Formoterol Fumarate (FF), and Glycopyrronium Bromide (GB), being developed as a twice-daily treatment in COPD and asthma. **Methods:** Randomised, open-label, placebo-controlled, single dose, 3-way crossover study in moderate/severe COPD patients. They received 4 inhalations of CHF5993 pMDI (BDP/FF/GB total dose 400/24/100 µg) with or without spacer. Thirty-five randomised patients completed the study. Compared with pMDI alone, the spacer increased GB C<sub>max</sub> and AUC<sub>0-30min</sub> by 60% and AUC<sub>0-t</sub> by 45%, reflecting higher lung deposition and the limited contribution of oral absorption to GB total systemic exposure. The spacer also increased B17MP and formoterol C<sub>max</sub> and AUC<sub>0-30min</sub> (by 20% for B17MP and by 55% for formoterol) and decreased AUC<sub>0-t</sub> by 37% and 24%, respectively, reflecting a higher lung deposition and prevention of oral absorption, counterbalancing increased lung absorption. The effect of the spacer was mainly observed in patients with inadequate inhalation technique due to poor coordination. CHF5993 pMDI showed a good and similar safety profile with and without spacer and in comparison with placebo. The observed changes in terms of total exposure and the observed safety profile support the use of the spacer with CHF5993 pMDI. These changes are not expected to have an impact on efficacy since as expected the spacer increases the lung deposition of all CHF5993 pMDI components.

### **Ventolin<sup>†</sup> (Salbutamol) GSK<sup>†</sup> Inc.**

#### **THE IMPACT OF DIFFERENT VALVED HOLDING CHAMBERS (VHCS) ON LUNG DRUG DELIVERY: USING FUNCTIONAL RESPIRATORY IMAGING (FRI) AND A SINGLE METERED DOSE INHALER (MDI) TYPE.**

*Suggett J, Kushnarev V, Van Holsbeke C, Van Steen S, Mignot B. Accepted to the European Respiratory Society Conference 2020.*

**Rationale:** One of the most common MDI use errors is the failure to coordinate inhalation with actuation of the inhaler. VHCs are often prescribed to reduce the severity of this error. This FRI based study assessed a few different VHCs, comparing their impact on modelled lung delivery, in addition to when the MDI was used alone. **Methods:** 3D geometries of airways and lobes were extracted from a CT scan of a 67 year old male COPD Stage III patient. Drug delivery and airway deposition of MDI delivered albuterol was modelled using FRI with measured particle and plume characteristics with and without three VHCs (AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup>, ACPlus<sup>®</sup>FV<sup>†</sup>; OptiChamber Diamond, OD; Compact Space Chamber Plus, CSCP). For the MDI alone, in addition to the 'perfect coordination' 0 second

delay, a short inhalation delay of 0.5 second was evaluated. For the MDI/VHC systems, a typical 2 second delay was evaluated. **Results:** The deposition profile results are shown in Table (mcg).

Deposition Zone	MDI alone (zero delay)	MDI alone (0.5s delay)	MDI/ACPlusFV (2.0s delay)	MDI/OD (2.0s delay)	MDI/CSCP (2.0s delay)
Extrathoracic	59.6	83.1	9.1	5.5	5.6
Intrathoracic	25.4	0.3	28.7	15.8	14.5
Central Lung	8.7	0.1	13.1	7.2	6.6
Peripheral Lung	16.7	0.3	15.7	8.5	7.9
C/P ratio	0.52	0.36	0.83	0.85	0.83

**Conclusions:** The FRI deposition profiles highlighted significant differences between the VHCs on test, with intrathoracic delivery for the AeroChamber Plus® Flow-Vu® VHC system being almost double that of the other two VHC systems and being similar to the MDI alone with perfect coordination. When a short 0.5 second inhalation delay with the MDI alone was modelled, the intrathoracic lung delivery decreased from 25.4mcg to 0.3mcg. These results highlight that the use of an appropriate VHC should be considered as general practice for all MDI patients other than those with a highly proficient inhaler technique and that VHCs should not be considered interchangeable.

### THE IMPACT OF INHALATION DELAY ON LUNG DRUG DELIVERY: USING FUNCTIONAL RESPIRATORY IMAGING (FRI) TO COMPARE METERED DOSE INHALER (MDI) AND MDI/VALVED HOLDING CHAMBER (VHC) SYSTEMS.

*Suggett J, Kushnarev V, Van Holsbeke C, Van Steen S, Mignot B. Am J Respir Crit Care Med 2020;201:A5689*

**Rationale:** Evaluations of inhaler use have demonstrated that mishandling of MDIs is commonplace. One of the most common errors is the failure to coordinate inhalation with actuation of the inhaler. One of the reasons why VHCs are often prescribed, is to reduce the severity of this error. This FRI based study assessed the likely severity of a short inhalation delay (from actuation) with an MDI alone and how it contrasted to the use with a VHC. **Methods:** Three dimensional geometries of airways and lobes were extracted from a CT scan of a 67 year old male COPD Stage III patient. Drug delivery and airway deposition of MDI-delivered albuterol (Ventolin-HFA, 100mcg) was modelled using FRI with measured particle and plume characteristics with and without an AeroChamber Plus® Flow-Vu® VHC. For the MDI alone, in addition to the ‘perfect’ 0-seconds delay, a short inhalation delay of 0.5 seconds was evaluated. For the MDI/VHC system, a typical 2 second delay was evaluated. **Results:** See table at bottom of page. **Conclusions:** The FRI deposition profiles highlight the significant negative impact on lung deposition of even a relatively short 0.5 second delay between actuation and inhalation when an MDI is used alone. The intrathoracic lung delivery decreased from 25.4mcg to 0.3mcg. Extrathoracic delivery (related to oropharyngeal deposition) was consequently even higher. The MDI / AeroChamber Plus® Flow-Vu® VHC system with a 2 second delay delivered 28.7 mcg to the intrathoracic region with a greater central lung delivery than the MDI alone (perfect coordination) which might be suggestive of greater delivery to beta adrenoreceptors. These results further the message that the use of an appropriate VHC should be considered as general practice for all patients other than those with a highly proficient inhaler technique.

### A COMPARATIVE ANALYSIS OF CHANGES IN PMDI DRUG DOSE DELIVERY BEFORE AND AFTER DETERGENT COATING USING FIVE ANTISTATIC VALVED HOLDING CHAMBERS.

*Hagedoorn P, Wasiq Bawary, Frijlink HW, Grasmeijer F. The Journal of Allergy and Clinical Immunology: In Practice. Available online 5 October 2019.*

Pressurized metered dose inhalers (pMDIs) are preferably to be used in combination with a spacer or valved holding chamber (VHC). Most notably, this reduces the impact of actuation-inhalation (“hand-lung”) coordination problems, and it lowers oropharyngeal deposition as smaller particles are presented to the patient at a lower velocity.<sup>1,2</sup> Spacers and VHCs may therefore improve compliance and reduce the chance of local and systemic side effects with the use of pMDIs. Although the use of spacers and VHCs is warranted by the advantages they offer, they also retain a notable fraction of the drug and hence lower the dose from a pMDI that is delivered to the patient. Moreover, not only differences in the size, shape, or construction material, but also differences in the cleaning and use of spacers and VHCs may greatly affect the delivered doses from these devices and limit their interchangeability.<sup>1</sup> This was recently illustrated in a comparison of 4 antistatic VHCs (aVHCs) by Dissanayake *et al.*<sup>3</sup> They showed that the fine particle dose from a salbutamol pMDI (Ventolin) may differ by up to a factor 2, even for VHCs that are comparable

in size, shape, and (claimed) antistatic properties. Such significant performance differences between similar aVHCs complicate the drafting of generally applicable guidelines for their choice and use. For example, nonconducting spacers and VHCs can be made “antistatic” with a detergent coating (i.e., “primed”) by soaking them in a household detergent solution followed by drying to the air, also known as “drip-drying.”<sup>4</sup> This lowers drug retention in the VHCs caused by electrostatic attraction. Understandably, drip-drying is only advocated for nonconducting VHCs, whereas it is deemed unnecessary for aVHCs.<sup>2</sup> However, if the great performance differences between aVHCs are caused by differences in their antistatic properties, drip-drying may be advisable for some of these devices too. Furthermore, the performance differences may then depend on the type of drug or the PMDI being used, as drugs and their formulations may differ in their sensitivity to electrostatic charging. To test the supposition that all aVHCs are equally antistatic and do not need to be coated with a detergent by drip-drying, we determined the delivered doses of salbutamol (Ventolin 100 mg/ dose label claim) and beclomethasone dipropionate (Qvar 100 mg/ dose label claim) from the Aerochamber Plus® Flow-Vu® (AC+FV), the Compact Space Chamber Plus (CSCp), the InspiraChamber (IC), the OptiChamber Diamond (OCD), and the Vortex (Vortex); see Figures E1 and E2, and Table E1 (available in this article’s Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). These aVHCs were cleaned in a mild detergent solution and either rinsed with water (to test their intrinsic antistatic properties) or “drip-dried” (to test standardized antistatic properties) before every measurement. The “rinsing” method is the cleaning method advocated by aVHC manufacturers. More methodological details about the experiment are available in this article’s Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org). The “rinsing” method causes a difference in the delivered dose between the aVHCs of up to a factor 2, with the Vortex and AC+FV performing significantly better than the CSCp, IC, and OCD (Figure 1). Drip-drying particularly increases the delivered doses from the CSCp and the IC ( $.0003 < P < .06$ , Figure 1), which indicates that their antistatic properties are suboptimal. On the contrary, the antistatic properties of the AC+FV, OCD, and Vortex are optimal, as their delivered doses are minimally affected by drip-drying. The consistently lower delivered dose from the OCD than from the AC+FV and Vortex therefore must be the result of differences other than their antistatic properties, such as their size, shape, or valve functioning. It follows from these results that differences in antistatic properties are an important cause of the large performance differences between aVHCs. Therefore, the assumption that aVHCs do not require drip-drying to improve drug delivery does not hold true for all of these devices. Furthermore, drip-drying may greatly improve the interchangeability of aVHCs, as no significant differences in delivered dose between 4 of 5 aVHCs tested (AC+FV, CSCp, IC, and Vortex) were measured after drip-drying, whereas only 2 (AC+FV and Vortex, or CSCp and IC) performed similarly after rinsing. Therefore, as a general guideline, it seems appropriate to recommend drip-drying, even for aVHCs, or to at least discourage the switching between them. It should be noted that a similar delivered dose in this study may not equal full *in vitro* equivalence of the devices. For that, also the particle size distributions of the delivered doses have to be identical. It is worth pointing out in this regard that the Vortex does not result in a finer aerosol of beclomethasone than the pMDI alone, contrary to the other aVHCs (see Table E2, available in this article’s Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). This may result in a different deposition pattern. Patient factors will also affect the deposition pattern, and therefore, the clinical implications of the observed differences can only be determined by *in vivo* studies. Nevertheless, a lower delivered dose with an aVHC compared with a pMDI alone does not necessarily result in a lower bioavailability,<sup>5,6</sup> as the lung deposition fraction may increase. The approximate 2-fold difference in delivered dose between salbutamol and beclomethasone when used with an aVHC can be explained by their different aerosol characteristics. The salbutamol pMDI has a higher plume velocity<sup>7</sup> and a larger median particle size of the aerosol than the beclomethasone pMDI (see Figure E3 and Table E2, available in this article’s Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Both factors likely increase salbutamol particle deposition in the aVHCs by inertial impaction and sedimentation. The qualitative similarity of the results obtained with the different drugs (salbutamol and beclomethasone) from different pMDI types suggests that the findings from this study are generally applicable to other pMDIs. Despite differences in particle size distribution and aerosol plume velocity between salbutamol and beclomethasone, performance differences between the individual aVHCs remain largely the same. Also a different charging behavior of both drug products<sup>8</sup> does not affect the aVHC performance differences. The clinical benefit of spacers and VHCs is extensively discussed by others. Rather than doubting this benefit, health care workers should be aware of the far-reaching noninterchangeability of VHCs, including their antistatic counterparts. Although this noninterchangeability of VHCs is wellrecognized,<sup>1,2</sup> aVHCs are often considered a homogeneous, interchangeable group of devices. However, this study shows that the antistatic properties of some aVHCs, such as the CSCp and IC, are suboptimal to such an extent that they are rather to be used as ordinary nonconducting VHCs instead, and that switching between aVHCs should be discouraged.

**A LABORATORY STUDY INVESTIGATING THE IMPACT OF DEVICE HANDLING ERRORS UPON INHALED MEDICATION DELIVERY FROM PRESSURIZED METERED DOSE INHALERS (PMDIS) USED WITH AND WITHOUT A VALVED HOLDING CHAMBER (VHC).**

*Suggett J, Nagel M, Mitchell J. Drug Delivery to the Lungs 2018.*

Evaluations of inhaler use have demonstrated that patient mishandling of pMDIs is commonplace. This study investigated the potential impact on medication delivery associated with three errors: (a) delayed inhalation, (b) over-forceful inhalation, and (c) exhalation instead of inhalation at the time of pMDI actuation. The large adult Aerosol Delivery to an Anatomic Model (ADAM) model oropharyngeal airway was used to determine the penetration of pMDI-delivered salbutamol (Ventolin®-HFA, 100-µg salbutamol base equivalent/actuation) to a distal filter representing potential lung delivery. AeroChamber Plus® Flow-Vu® antistatic devices with mouthpiece (c = 3 devices, 1 measurement per device) were used as the test VHC. Delaying inhalation by 1-s resulted in a decrease of 80% in the mass penetrating as far as the filter compared to optimal no delay for the pMDI alone. When the VHC was present, the mass of salbutamol reaching the filter after a 2-s delay was comparable with optimum delivery of medication from the pMDI alone and further delays up to even 15-s resulted in less than 40% reduction. When a forceful inhalation was simulated, filter-collection of salbutamol for the pMDI alone and pMDI with VHC were both reduced in the order of 20-30% compared to the slow inhalation condition with the same configuration. No medication was collected on the filter when exhalation took place upon pMDI actuation when used alone. Adding the VHC resulted in filter collection comparable to the mass delivered under normal inhalation with a 2-s delay.

**PRESSURIZED METERED DOSE INHALER (PMDI) DELIVERY TO INFANTS VIA VALVED HOLDING CHAMBER (VHC) WITH FACEMASK: NOT ALL VHCS PERFORM THE SAME.**

*Nagel M, Suggett J, Bracey A. European Respiratory Society Conference, Sept 2017.*

**Rationale:** Delivery of inhaled medication to an infant from a pMDI via VHC-facemask is dependent upon the interaction between facemask and face of the patient. Using an anatomically accurate nasopharynx (ADAM-III) infant model we report the findings of clinically appropriate testing from several VHC facemask products used to deliver Ventolin. **Methods:** Each VHC (n=5 devices/group) was used according to manufacturer’s instructions ensuring appropriate facemask application to the face model. Aerosol was collected at the carinal end of the model by a filter whilst being connected to a breathing simulator (ASL 5000) set to mimic tidal breathing with VOL=50mL, I:E ratio =1.3, 30 BPM). 5-doses of Ventolin was delivered, timing each actuation (a) to coincide with inhalation (INH, coordinated) and (b) exhalation (EXH uncoordinated). The mass of Ventolin was subsequently recovered from the filter and assayed by HPLC to determine delivered mass (DM). Results: Values of the therapeutically beneficial DM (µg) actuation; mean ± SD) are summarized in the Table.

VHC	Pre-treatment	pMDI actuation	DM (ug)
Compact Space Chamber Plus <sup>†</sup> Anti-Static	Out of Package	INH	0.3 ± 0.3
	Out of Package	EXH	0.4 ± 0.3
Volumatic <sup>†</sup>	Out of Package	INH	0.5 ± 0.1
	Out of Package	EXH	0.5 ± 0.1
BabyHALER <sup>†</sup>	Wash/Rinse	INH	0.0 ± 0.0
	Wash/Rinse	EXH	0.0 ± 0.0
Able Spacer 2	Wash/Rinse	INH	1.0 ± 0.6
	No Rinse	EXH	0.7 ± 0.3
AeroChamber Plus <sup>®</sup> Flow-Vu <sup>®</sup> Anti-Static	Out of Package	INH	4.5 ± 2.2
	Out of Package	EXH	4.5 ± 1.3

DM ex AeroChamber® Plus® Flow Vu® Anti-Static VHC group was significantly greater than the other VHC devices (unpaired t-test, p<0.001). **Conclusions:** The DM from VHCs can differ significantly which may have a clinical impact.



**VALVED HOLDING CHAMBER (VHC) ANGLE CAN AFFECT PRESSURIZED METERED-DOSE INHALER (PMDI) MEDICATION DELIVERY EFFICIENCY.**

*Suggett J, Nagel M, Avvakoumova V, Mitchell J. European Respiratory Journal 2018 52: PA5487.*

**Rationale:** This laboratory study evaluated 3 widely prescribed VHCs with their long axis inclined by 45° upwards and downwards, representing likely extremes in user orientation. **Methods:** The following VHCs were evaluated (n=5/group): AeroChamber Plus® Flow-Vu® (AC+FV); TipsHaler\*(TIPS); Volumatic\*(VOL). A filter was placed on the mouthpiece of the VHC to capture the emitted aerosol. The filter was coupled to a breathing simulator to mimic a tidally-breathing (a) small child (tidal volume (VT)=155mL, rate/min (Rmin)=25; I:E ratio=1:2), and (b) an adult (VT=500mL;Rmin=13;I:E=1:2). The long-axis of the VHC was orientated 45°upward from horizontal (inhaler raised) and 45°downward. 5-doses of salbutamol (ALB) pMDI were delivered at 30s intervals. Emitted mass ALB (EMALB) recovered from the filter was determined using HPLC. **Results:** EMALB from 45°-up to 45°-down orientations were insignificant with both AC+FV (-13%, paired t-test, p=0.07) and TIPS (-14%, p=0.51) VHCs, but the decrease for the VOL group was significant (-48%, p=0.004). No orientation effect in the adult simulation was observed with the AC+FV VHCs (-0.7% p=0.77), but EMALB changed significantly by +24% and -28% with the TIPS (p=0.004) and VOL (p=0.019) VHCs. **Conclusions:** Clinicians should be aware that the output from some VHCs is susceptible to changes in handling orientation, potentially due to the effect of gravity on less effective inhalation valves.

**EFFECT OF PATIENT INTERFACE ON POTENTIAL LUNG DELIVERY OF INHALED MEDICATION FROM A VALVED HOLDING CHAMBER (VHC) TO AN ANATOMIC OROPHARYNGEAL MODEL.**

*Suggett J, Nagel M, Ali R, Avvakoumova V. American Journal of Respiratory and Critical Care Medicine 2017; 195:A6324.*

VHC delivery can be administered by mouthpiece (MP) or facemask (FM) but evidence suggests that a MP is often more effective. However, for the elderly who cannot manage hand-held coordination or proper inhalation technique a mask is a potential alternative. This laboratory study using a model taken from a 43yr old male with soft tissue face modeling and anatomically correct oropharynx was undertaken to explore medication delivery differences achieved via different VHC interfaces. Using the AeroChamber Plus® Flow-Vu® Anti-Static Valved Holding Chamber (aVHC with mouthpiece) as the reference device. 10 aVHCs of both MP and FM variants were attached to the Aerosol Delivery to Anatomic Model (ADAM-III) adult upper airway model (Trudell Medical International, London, Canada), where an electret filter was located at the airway outlet, representing the carina. The filter was connected in turn to a breathing simulator (ASL 5000, IngMar Medical, Pittsburgh, PA) operated to simulate tidal breathing (tidal volume = 770 mL; 12 cycles/min inspiratory: expiratory ratio 1:2). 5 actuations from a Ventolin\* HFA pMDI were delivered to the aVHC on test and sampled for 6 breathing cycles, following which the model was disconnected from the test apparatus and the mass of albuterol assayed by HPLC-UV spectrophotometry. **Results:** Mass of albuterol per actuation deposited in the test apparatus are summarized in Table 1.

**Table 1: Comparative Values of Albuterol Recovered from that Oropharynx model from both MP and FM aVHC variants**

	VHC with Mouthpiece	VHC with Adult Mask
Model Face	n/a	2.8 ± 1.7
Model Airways	13.0 ± 1.7	3.7 ± 0.8
Filter (carina)	31.1 ± 3.0	27.9 ± 7.5
pMDI	18.6 ± 1.7	25.6 ± 3.2
aVHC	26.9 ± 2.9	30.9 ± 5.0
Mask	n/a	4.3 ± 1.5

**Conclusions:** Although albuterol mass was lost to the face and mask, delivery to the filter (carina) of the model is similar from either aVHC configuration. Clinicians should be aware that the use of a FM can provide a comfortable and effective alternative for those patients who experience difficulty with a MP.

**EQUIVALENCE EVALUATION OF VALVED HOLDING CHAMBERS (VHCS) WITH ALBUTEROL PRESSURIZED METERED DOSE INHALER (PMDI).**

*Nagel M, Suggett J. Respiratory Drug Delivery Europe 2017.*

**Introduction:** In 2009, the significant role of the VHC in drug delivery was acknowledged when the European Medicines Agency (EMA) recommended that development of a pMDI should include the testing of at least one

named VHC. It was also recommended that if a VHC was to be substituted by an alternative VHC, appropriate pharmacopeial *in vitro* methods must be presented that take into account clinically relevant factors such as time delays between pMDI actuation and sampling. If these experiments could not demonstrate equivalence, then a determination of equivalency via clinical development would be required. This article presents an experimental demonstration of an equivalency evaluation between several commercially available VHCs. **Materials and Methods:** The following VHCs, each with mouthpiece as patient interface ( $n=20$  devices/group) were evaluated: AeroChamber Plus® VHC (Trudell Medical International) (REFERENCE) ; AeroChamber Plus® Flow-Vu® Anti-static VHC (Trudell Medical International); OptiChamber Diamond® Anti-Static VHC (Philips Respironics Inc.); InspiraChamber® Anti-Static VHC (Lupin Pharmaceuticals, Inc.); Compact Space Chamber Plus® Anti-Static VHC (Medical Developments). **Discussion and Conclusion:** This *in vitro* equivalence study was performed using a recognized analytical test methodology and an appropriate statistical test for equivalence, as opposed to incorrectly testing a hypothesis of difference/no difference or making non-statistically-based subjective judgments. When using the AeroChamber Plus® as the REFERENCE VHC, results showed that only one TEST VHC, the AeroChamber Plus® FV, was statistically equivalent to it. All other test VHCs did not meet the acceptance criteria in any of the four defined groupings. This finding may not be so surprising, given that the two equivalent chambers are of the same size and design, other than anti-static properties out of package. However, it does highlight the impact of differences in VHC design (size, shape, valves, etc.) upon drug delivery, and therefore the potential risk of interchanging VHCs without understanding the impact of doing so.

### **TRANSITIONING TO A MORE PATIENT-FRIENDLY VERSION OF A VALVED HOLDING CHAMBER (VHC): MEETING THE CHALLENGE OF PROVIDING CONSISTENT *IN VITRO* PERFORMANCE FOR PATIENTS.**

*Nagel M, Avvakoumova V, Doyle C, Ali R, Mitchell J. Presented at Drug Delivery to the Lungs-22, Edinburgh, UK, December 2011, 153-156.*

The AeroChamber Plus® VHC (Trudell Medical International, London, Canada) is a widely prescribed add-on device for patients having poor coordination with their pressurized metered-dose inhaler (pMDI). Changes have been made to its design to make it more patient-friendly, so that compliance with prescribed inhaled medication can be improved. However, there may be concern that these developments may affect medication delivery performance, where the intent is to match as closely as possible the therapeutically important metrics, emitted extra-fine (EPM $<1.1\mu\text{m}$ ) and fine particle mass (FPM $<4.7\mu\text{m}$ ) ex VHC, with those from the pMDI alone. We report a laboratory study in which both measures were compared, simulating a 2-s delay between pMDI operation and the onset of sampling via each VHC. Published data for the pMDI alone (no delay), the original VHC (non conducting (NC) and non conducting with inspiratory flow indicator (NC-IFI) were compared with new data for the anti-static, take-apart with IFI (AS). Both non-conducting device groups were pre-washed in ionic detergent and drip-dried in accordance with manufacturer instructions to mitigate surface electrostatic charge, whereas the AS group was evaluated out-of-package without pretreatment. We evaluated these devices with Ventolin®, representing a formulation known to have a high degree of electrostatic charge. We found both measures of performance were consistent between VHCs (EPM $<1.1\mu\text{m}$  =  $4.7\pm 0.8\ \mu\text{g}$  (NC);  $3.1\pm 0.5\ \mu\text{g}$  (NCIFI);  $3.9\pm 2.1\ \mu\text{g}$  (AS); FPM $<4.7\mu\text{m}$  =  $36.3\pm 1.8\ \mu\text{g}$  (NC);  $30.9\pm 2.0\ \mu\text{g}$  (NC-IFI);  $33.4\pm 4.2\ \mu\text{g}$  (AS)). The more important FPM $<4.7\mu\text{m}$  was within  $\pm 15\%$  of the benchmark value for the pMDI alone (FPM $<4.7\mu\text{m}$  =  $34.8\pm 1.4\ \mu\text{g}$ ).

### **REPEAT DOSING OF ALBUTEROL VIA METERED-DOSE INHALER IN INFANTS WITH ACUTE OBSTRUCTIVE AIRWAY DISEASE - A RANDOMIZED CONTROLLED SAFETY TRIAL.**

*Kaashmiri M, Shepard J, Goodman B, Lincourt WR, Trivedi R, Ellsworth A, Davis AM. Pediatric Emergency Care 2010;26(3):197-202.*

**Background:** Airway obstruction and bronchial hyperactivity often times lead to emergency department visits in infants. Inhaled short-acting beta2-agonist bronchodilators have traditionally been dispensed to young children via nebulizers in the emergency department. Delivery of bronchodilators via metered-dose inhalers (MDIs) in conjunction with holding chambers (spacers) has been shown to be effective. **Study Objective:** Safety and efficacy evaluations of albuterol sulfate hydrofluoroalkane (HFA) inhalation aerosol in children younger than 2 years with acute wheezing caused by obstructive airway disease. **Methods:** A randomized, double-blind, parallel group, multicenter study of albuterol HFA 180 microg ( $n = 43$ ) or 360 microg ( $n = 44$ ) via an MDI with a valved holding chamber and face mask in an urgent-care setting. Assessments included adverse events, signs of adrenergic stimulation, electrocardiograms,

and blood glucose and potassium levels. Efficacy parameters included additional albuterol use and Modified Tal Asthma Symptoms Score ([MTASS] reduction in MTASS representing improvement). **Results:** Overall, adverse events occurred in 4 (9%) and 3 (7%) subjects in the 180-microg and 360-microg groups, respectively. Drug-related tachycardia (360 microg) and ventricular extrasystoles (180 microg) were reported in 1 patient each. Three additional instances of single ventricular ectopy were identified from Holter monitoring. No hypokalemia or drug-related QT or QTc prolongation was seen; glucose values and adrenergic stimulation did not significantly differ between treatment groups. In the 180-microg and 360-microg groups, mean change from baseline in MTASS during the treatment period was -2.8 (-49.8%) and -2.9 (-48.4%), and rescue albuterol use occurred in 4 (9%) and 3 (7%) subjects, respectively. **Conclusions:** Cumulative dosing with albuterol HFA 180 microg or 360 microg via MDI-spacer and face mask in children younger than 2 years did not result in any significant safety issues and improved MTASS by at least 48%.

### A VISUAL INDICATOR FOR INHALATION FROM A VALVED HOLDING CHAMBER IS AN AID IN DELIVERY OF INHALED MEDICATION TO INFANTS AND SMALL CHILDREN VIA FACEMASK.

Mitchell JP, Doyle C, Ali R, Avvakoumova V, Nagel M, Sharpe R. *Eur Respir J* 2009;34S53:P2044.

**Body:** Delivery of inhaled medication to infants/small children by VHC-facemask can be difficult to verify. An external visual aid (Flow-Vu\*) is available with the AeroChamber Plus® (Trudell Medical International) VHCs as an inspiratory flow indicator (IFI) to aid compliance with instructions for use. We report an *in vitro* study in which delivery of salbutamol (Ventolin®; 100µg/actuation, GSK plc) was measured using infant and child models (ADAM-II), in which the soft facial tissues are modeled where the facemask makes contact. The facemask was applied with an appropriate force of 1.6 kg, and tidal breathing was simulated (tidal volume ( $V_t$ ) 50 ml, 30 bpm, 25% duty cycle -VHC-infant facemask;  $V_t$  = 155 ml; 25 bpm, 33% duty cycle - VHC-child facemask ( $n=5$  devices/group)). Total emitted mass (TEM) of salbutamol was collected by filter located behind the lips after 1, 2, 3, 4 and 5 inhalations.

TEM (mean SD; ug) for AeroChamber Plus® VHCs with Flow-Vu® IFI

Number of Inhalations	1	2	3	4	5
Infant	5.8 ± 2.2	13.0 ± 4.0	13.8 ± 3.8	14.5 ± 3.2	15.6 ± 3.6
Child	15.9 ± 3.7	17.6 ± 4.6	20.1 ± 3.5	20.8 ± 2.9	22.6 ± 4.2

At least two inhalations were required to achieve consistent medication delivery from the VHC-infant facemask. The first inhalation was sufficient to achieve similar consistency with the VHC-child facemask. However, these tests were undertaken with a well-fitting facemask and no leakage. Manufacturer instructions indicate 5-inhalations be taken as a precaution. The IFI validates an effective seal between facemask-face as well as confirms the number of inhalations, assisting in compliance with instructions.

### SAFETY OF DAILY ALBUTEROL IN INFANTS WITH A HISTORY OF BRONCHOSPASM: A MULTI-CENTER PLACEBO CONTROLLED TRIAL.

Hedrick JA, Baker JW, Atlas AB, Naz AA, Lincourt WR, Trivedi R, Ellworth A, Davis AM. *Open Respir Med J*. 2009; 3: 100-106.

**Introduction:** Inhaled short-acting bronchodilators are recommended for the quick relief of bronchospasm symptoms in children including those less than five years of age. However, limited safety data is available in this young population. **Methods:** Safety data were analyzed from a randomized, double-blind, parallel group, placebo-controlled multicenter, study evaluating albuterol HFA 90µg or 180µg versus placebo three times a day for 4 weeks using a valved holding chamber, AeroChamber Plus® and facemask in children birth ≤ 24 months old with a history of bronchospasm. **Results:** The overall incidence of adverse events (AE) during treatment was: albuterol 90µg (59%), albuterol 180µg (76%) and placebo (71%). The most frequently reported AEs were pyrexia in 7 (24%), 2 (7%), and 3 (11%) subjects in the albuterol 180µg, albuterol 90µg, and placebo groups, respectively. Upper respiratory tract infection (URTI) occurred in 5 (17%) and 3 (11%) subjects in the albuterol 180µg and placebo groups, respectively. Sinus tachycardia occurred in 5 (17%), 2 (7%) and 2 (7%) subjects receiving albuterol 180µg, albuterol 90µg and placebo, respectively. One subject in each of the albuterol treatment groups experienced drug related agitation and/or restlessness or mild sinus arrhythmia. No drug-related QT prolongation or abnormal serum potassium and glucose

levels were reported in the albuterol treatment groups. **Conclusion:** This study provides additional albuterol HFA safety information for the treatment of children aged birth  $\leq$  24 months with a history of bronchospasm.

### **A NEW VALVED HOLDING CHAMBER (VHC) FOR YOUTH THAT IS MANUFACTURED FROM ELECTROSTATIC CHARGE-DISSIPATIVE MATERIALS PROVIDES EFFICIENT DELIVERY OF MEDICATION IF USED OUT OF THE PACKAGE**

*Harkness H., Mackay H., Avvakoumova V., Ali R., Mitchell JP., Nagel MW. Presented at the Canadian Society of Allergy and Clinical Immunology, Hamilton, Ontario, 2008.*

Children prescribed a VHC are often reluctant to take inhaled medication for asthma in front of their peers. A new line of equivalent anti-static VHCs (AC Girlz\* and AC Boyz\* holding chambers), based on the AeroChamber Plus® anti-static VHC with Flow-Vu\* Inspiratory Flow Indicator (IFI) (Trudell Medical International, London, Canada), has been developed with attractive youth-relevant markings to improve compliance. We report a study in which delivery of Ventolin<sup>†</sup>-HFA via these VHCs ( $n=3$ ), was compared with VHCs manufactured from nonconducting polymer (OptiChamber<sup>†</sup> Advantage, Respironics Inc., Cedar Grove, NJ, USA ( $n=5$  VHCs)) as benchmark devices. Both VHC groups were evaluated immediately after removal from their packaging to simulate use in an urgent care situation, but the OptiChamber<sup>†</sup> Advantage VHCs were also studied after pre-washing in mild detergent, rinsing and drip-drying in accordance with instructions to minimize electrostatic charge. A proprietary apparatus that interfaced between the VHC mouthpiece and induction port leading to an 8-stage Andersen cascade impactor was used to simulate a 2-s delay between pMDI actuation and the onset of sampling at 28.3 L/min, representing a typical uncoordinated user. Reference data were also obtained with no delay. Fine particle mass (FPM ( $\mu\text{g}/\text{actuation}$ ; mean  $\pm$  SD)), based on particles  $< 4.7 \mu\text{m}$  aerodynamic diameter, was  $52.7 \pm 5.5 \mu\text{g}$  and  $37.7 \pm 3.4 \mu\text{g}$  for the AC Girlz\*/AC Boyz\* Chambers without and with delay respectively. Equivalent values for the OptiChamber<sup>†</sup> Advantage VHCs were  $29.5 \pm 4.3 \mu\text{g}$  (no delay) and  $8.9 \pm 2.1 \mu\text{g}$  (delay) when tested out-of package and  $38.5 \pm 3.7 \mu\text{g}$  (no delay) and  $19.7 \pm 3.0 \mu\text{g}$  (delay) after pre-washing. The AC Girlz\*/AC Boyz\* Chambers significantly outperformed the OptiChamber<sup>†</sup> Advantage VHC group (un-paired t-test at each delay interval,  $p < 0.001$ ), even when pre-washed. This study indicates the advantage of charge dissipative materials to avoid electrostatic charge-related losses.

### **A VISUAL INDICATOR FOR INHALATION FROM A VALVED HOLDING CHAMBER (VHC) IS AN IMPORTANT ATTRIBUTE WHEN DELIVERING INHALED MEDICATION TO INFANTS.**

*Mitchell J, Avakoumova V, Mackay H, Ali R and Nagel M. Presented at Drug Delivery to the Lungs-XIX, Edinburgh, UK, 2008.*

Delivery of inhaled medication to infants by valved holding chamber (VHC) with facemask may require more than one inhalation to empty the VHC because tidal volumes are typically smaller than chamber capacity. This study investigated the correlation between movement of an integrated inspiratory flow indicator (IFI) as a caregiver feedback aid for a VHC-facemask, number of inhalations and mass of medication, simulating use by a 6-9 month infant (tidal volume ( $V_T$ ) = 50-ml; duty cycle = 25%; 30 cycles/min). Anti-static AeroChamber Plus® VHCs incorporating the IFI feature, with infant facemask ( $n=5/\text{group}$ , 3 replicates/device; Trudell Medical International, London, Canada) were coupled to a breathing simulator (ASL5000 test lung, IngMar Medical, Pittsburgh, PA, USA). The VHCs were prepared as per manufacturer instructions and the facemask of the device on test was fitted to the ADAM-II flexible infant face model with a clinically appropriate force of 1.6 kg. Aerosol capture took place using an electret filter positioned behind the lips of the face model. Delivery of medication was evaluated from two different pressurized metered dose inhaler formulations likely to be used with pediatric patients (Flovent<sup>†</sup> HFA 44; 44  $\mu\text{g}$  fluticasone propionate (FP) delivered ex-actuator and Ventolin<sup>†</sup> HFA; 90  $\mu\text{g}$  salbutamol base equivalent (SAL) delivered ex-actuator, both from GSK plc. One actuation was delivered to the VHC at the onset of inhalation, and the filter removed after 1 complete breathing cycle, observing the movement of the IFI to confirm inhalation valve opening. This procedure was subsequently repeated by removing the filter after 2, 3, 4, 5 and 6 breathing cycles. Assay for FP or SAL was undertaken by HPLC-UV spectrophotometry. During these measurements, the IFI of each device was observed to move in synchrony with valve opening on all occasions, confirming that the facemask sealed onto the face model without leakage of ambient air into the mask during the inspiratory phase of each breathing cycle. Emitted mass after the first breathing cycle (EM1) was  $2.1 \pm 0.7 \mu\text{g}$  (FP) and  $5.8 \pm 2.2 \mu\text{g}$  (SAL); substantially lower than the corresponding values after 6 cycles (EM6), being  $9.0 \pm 2.1 \mu\text{g}$  (FP), and  $15.9 \pm 3.1 \mu\text{g}$  (SAL) [paired ttest for each formulation;  $p < 0.001$ ]. After 2 breathing cycles, values of EM2 ( $6.9 \pm 2.0$  (FP) and  $13.0 \pm 4.0 \mu\text{g}$  (SAL)), though significantly

greater than their corresponding EM1 values [ $p \leq 0.002$ ], were still noticeably lower than the corresponding EM6 value for FP ( $p = 0.028$ ), and barely statistically insignificant for SAL ( $p = 0.063$ ). After 3 inhalations, EM3 increased further to  $7.6 \pm 2.0 \mu\text{g}$  (FP) and  $13.8 \pm 3.8 \mu\text{g}$  (SAL), and thereafter were close to the corresponding EM6 values, indicating emptying of the VHC had taken place. We conclude that at least two successive inhalations are required to achieve optimum medication delivery for the 'infant' condition under optimum conditions with a well fitted facemask with no leakage. The IFI is an important feature which validates that the facemask is properly sealed to the infant's face and also confirms the number of inhalations that take place, thereby optimizing the therapeutic dose. Clinical studies are recommended to evaluate the benefit of this aid for the delivery of inhaled medication by VHC to this age group.

#### **SALBUTAMOL RELATIVE LUNG AND SYSTEMIC BIOAVAILABILITY OF LARGE AND SMALL SPACERS.**

Mazhar SHR, Chrystyn H. *Journal of Pharmacy and Pharmacology* 2008;60:1609-1613.

Differences between the size and shape of spacers may affect the emitted dose and provide different effects when interchanged during routine use. Using a urinary pharmacokinetic method we have measured the relative lung and systemic bioavailability from urinary salbutamol excretion 30 min (USAL0.5) and 24 h (USAL24), respectively, after the inhalation of two 100-mg doses from a Ventolin Evohaler when used alone (MDI) and when attached to the Volumatic (VOL) or the AeroChamber Plus® (AERO) spacers. The *in-vitro* properties of the emitted dose were determined. The mean (s.d.) USAL0.5 values following MDI, VOL and AERO ( $n = 13$  volunteers) were 5.7 (1.9), 16.4 (8.2) and 14.8 (7.4) mg, respectively. VOL and AERO were significantly greater ( $p < 0.001$  and  $< 0.01$ , respectively) than MDI. Comparison of VOL and AERO was similar with a mean ratio (90% confidence interval) of 108.2 (84.5, 138.6)%. USAL24 values between the three inhalation methods were similar. The values for the mean (s.d.) fine particle dose of two 100-mg doses emitted from MDI, VOL and AERO were 83.0 (6.8), 83.6 (4.6) and 73.6 (2.9) mg and the mass median aerodynamic diameters were 2.7 (0.03), 2.8 (0.07) and 2.9 (0.10) mm, respectively. The results showed that during routine use the Volumatic and the AeroChamber Plus® spacers should provide similar lung and systemic delivery when attached to a Ventolin Evohaler.

#### **Zenhale<sup>†</sup> (Mometasone Furoate / Formoterol Fumarate) Merck Sharp**

#### **BRONCHODILATION WITH MOMETASONE FUROATE/FORMOTEROL FUMARATE ADMINISTERED BY METERED-DOSE INHALER WITH AND WITHOUT A SPACER IN CHILDREN WITH PERSISTENT ASTHMA.**

Berger W, Bensch G, Weinstein S, Skoner D, Prenner B, Shekar T, Gates D, Nolte H, Teper A. *Pediatr Pulmonol.* 2014 May; 49(5):441-50.

**Rationale:** The bronchodilatory effect of mometasone furoate/formoterol fumarate (MF/F) administered by metered-dose inhaler (MDI) with or without spacer has not been evaluated previously in children. **Methods:** This was a randomized, multicenter, placebo (PBO)-controlled, single-dose, 4-period crossover study. Children with persistent asthma aged 5-11 y participated in this study. Subjects used inhaled corticosteroids with/without long-acting  $\mu_2$ -agonists for  $\geq 12$  wk before enrollment and had  $\text{FEV}_1 \geq 70\%$  predicted at screening. Subjects received MF/F-MDI 100/10  $\mu\text{g}$  with/without spacer, F-dry powder inhaler (DPI) 10  $\mu\text{g}$ , and PBOMDI with/without spacer in separate treatment periods. The primary end point was  $\text{FEV}_1 \text{ AUC}_{0-12\text{h}}$  for the comparison of MF/F with spacer vs PBO. Secondary measurements included MF/F without spacer vs PBO as well as MF/F with spacer vs MF/F without spacer and F-DPI vs PBO. Analysis was performed with an ANCOVA model for a crossover study. **Results:** A total of 87 subjects completed treatment, and 79 subjects were in the per-protocol analysis set. MF/F with spacer demonstrated a larger change in mean  $\text{FEV}_1 \text{ AUC}_{0-12\text{h}}$  vs PBO (115 vs -9 mL), with a treatment difference of 124 mL (95% CI, 94 to 154;  $p < .001$ ). Similarly, MF/F without spacer vs PBO resulted in a 102 mL difference in mean adjusted  $\text{FEV}_1 \text{ AUC}_{0-12\text{h}}$  (95% CI, 73 to 131,  $p < .001$ ), whereas the difference between MF/F with spacer vs MF/F without spacer was 22 mL (95% CI, -8 to 52,  $p = .144$ ). The difference between F-DPI vs PBO was 106 mL (95% CI, 77 to 135,  $p < .001$ ). No unexpected adverse events were observed. **Conclusions:** In this trial, MF/F-MDI 100/10  $\mu\text{g}$  demonstrated significant bronchodilation in children aged 5-11 y regardless of the use of a spacer. Similar bronchodilatory profiles were observed for F delivered by DPI and by MDI in combination with MF.

# Large vs Small Volume Valved Holding Chambers

## HOW MANY INHALATIONS DOES IT TAKE TO EMPTY A VALVED HOLDING CHAMBER?

### AN EXPERIMENTAL INVESTIGATION

Suggett J, Nagel M, Avvakoumova V, Mitchell J. *Respiratory Drug Delivery* 2018.

Exerpt from extended abstract: **Introduction:** Valved holding chambers (VHCs) are widely prescribed for use with pressurized metered dose inhalers (pMDIs) for those patients who have poor coordination of inhaler actuation with the onset of inhalation. The Volumatic® VHC is a large volume (ca. 750 mL) device that is still prescribed for use by small children (as well as some adults) in countries such as the UK. However, it has been reported previously that the preferred size should be closer to 150 mL. The present laboratory study examined the hypotheses that emptying of a VHC closer in size to 150 mL would be faster for a small child with small tidal volumes, and similar for adult users whose tidal volumes are larger. **Materials and Methods:** In the first part of the study, mimicking small child use, the large and small volume VHCs ( $n = 3$  devices/group, 3-replicates per device) were the 750 mL Volumatic®-infant facemask (VOL-Mask, GSK plc, UK) and 149 mL antistatic AEROCHAMBER PLUS® FLOW-VU®-child facemask (ACPlus-Mask, TMI, London, Canada). Each VHC was connected to a breathing simulator (ASL 5000, Pittsburgh, PA, USA) mimicking a tidally breathing small child (tidal volume = 155 mL, rate/min = 25; inspiratory:expiratory ratio 1:2). An aerosol filter collected the medication delivered at the exit of the chamber-on-test. Previous work with this model had confirmed that capture of the aerosol from this arrangement was quantitative. One actuation of fluticasone propionate (FP, GSK Canada, 50 µg/actuation ex metering valve) was delivered to the chamber-on-test, and the mass of medication was collected on the filter after one complete breathing cycle. The entire procedure was repeated after 2, 3, 5, 8, and 10 breathing cycles. In the second part of the study, simulating adult use, the Volumatic (VOL-MP) and antistatic AEROCHAMBER PLUS® FLOW-VU® (ACPlus-MP) VHCs were each equipped with a mouthpiece ( $n = 3$  devices/group, 3 replicates per device). The same approach as for the first part was undertaken to evaluating the mass of medication (125 µg/actuation FP ex-metering valve) delivered to a filter after 1, 2, 3, 5, 8, and 10 breathing cycles, except that a standardized adult breathing pattern (tidal volume = 500 mL, rate/min = 13; inspiratory:expiratory ratio 1:2) was used. **Results:** The total mass of FP (mean ± SD) recovered from the filters for different numbers of breathing cycles is summarized in Table 1 for both parts of the study. Very little FP was delivered from the VOLMask for the first five breathing cycles of the small child simulation, and only  $2.0 \pm 0.6$  µg/actuation was obtained after 10 cycles. In contrast, even after the first breathing cycle,  $6.4 \pm 0.7$  µg/actuation was delivered by the smaller AC-Plus-Mask (unpaired t-test, comparing total mass FP after the first inhalation with that from the Volumatic,  $p < 0.001$ ), which plateaued at around 9 µg/actuation following three breathing cycles. The output from the ACPlus-MP after the first breathing cycle was  $51.2 \pm 4.5$  µg/actuation FP for the adult simulation and remained similar thereafter. In contrast, the larger VOL-MP group delivered significantly less FP after the initial breathing cycle ( $21.9 \pm 2.9$  µg/actuation, unpaired t-test,  $p < 0.001$ ), but thereafter, the emitted mass varied in an unpredictable manner, never exceeding  $34.8 \pm 3.9$  µg/actuation which was attained after 10 breathing cycles. Table 1 - Total mass (µg/actuation ± SD) of pMDI-delivered FP emitted at the patient interface of large and small volume VHCs after 1, 2, 3, 5, 8, and 10 complete breathing cycles mimicking tidal breathing either by a small child or by an adult. **Conclusions:** Maximum emitted mass from the anti-static AEROCHAMBER PLUS® VHC appeared to plateau after two inhalations and one inhalation for child and adult breathing pattern simulations, respectively. Facemask fit for part 1, and residual electrostatic charge associated with the non-conducting Volumatic VHCs in both parts of the study, might have contributed to the observed lower and variable drug delivery from this large volume VHC. However, clinicians should also be aware that the volume of a VHC has a marked effect on the delivery of medication. An effective VHC should be able to maintain the availability of medication for inhalation in cases where multiple inhalations (and therefore more time) may be required to empty, as is especially the case with infants and small children.

Number of Breathing Cycles	Part 1: Small Child Simulated Breathing		Part 2: Adult Simulated Breathing	
	AC Plus-Mask	VOL-Mask	AC Plus-Mask	VOL-Mask
1	6.4 ± 0.7	0.3 ± 0.2	51.2 ± 4.5	21.9 ± 2.9
2	7.7 ± 0.7	0.5 ± 0.2	53.5 ± 4.9	14.9 ± 4.4
3	8.7 ± 0.9	0.5 ± 0.2	58.9 ± 7.8	26.9 ± 2.8
5	8.2 ± 0.7	0.5 ± 0.3	58.8 ± 4.7	30.0 ± 4.2
8	9.1 ± 1.0	1.2 ± 0.4	54.1 ± 7.8	29.9 ± 5.6
10	9.1 ± 0.9	2.0 ± 0.6	52.6 ± 5.4	34.8 ± 3.9

## SYSTEMIC ACTIVITY OF INHALED BECLOMETHASONE DIPROPIONATE: A DOUBLE BLIND COMPARISON OF VOLUME SPACERS.

Wolthers OD, Sergio F. *Acta Paediatr.* 2012;101(2):159-63.

**Background:** To which extent volume spacers may influence systemic activity of inhaled beclomethasone dipropionate (BDP) has not been evaluated. **Aim:** To assess whether the AeroChamber Plus® spacer is equivalent to the Volumatic® spacer for administration of inhaled hydroflouroalkane 134a propelled BDP in terms of lower leg growth rate (LLGR). **Patients and Methods:** Prepubertal children with mild asthma ( $n=26$ , ages 6-14 years) were included in a 3-time periods of 2 weeks duration randomized double-blind cross-over study with a single-blind placebo run-in and 2 wash-out periods. LLGR was measured with the knemometer. Interventions were inhaled BDP hydroflouroalkane 134a pMDI 100 µg and 200 µg b.i.d. with the AeroChamber Plus® and 200 µg b.i.d. with the Volumatic® spacer. **Results:** BDP 200 µg b.i.d. from the AeroChamber Plus® was non-inferior to BDP 200 b.i.d. from the Volumatic® spacer as the lower margin of confidence interval of the difference between treatments (-0.18 to 0.13 mm/week) was greater than the pre-specified lower limit for non-inferiority (-0.20 mm/week). UFC/creatinine data showed no statistically significant variations. **Conclusion:** The systemic activity of BDP via the Volumatic®, and AeroChamber Plus® spacers is similar. The AeroChamber Plus® spacer may be used in children without risk of increasing systemic activity of BDP.

## A PILOT STUDY TO ASSESS LUNG DEPOSITION OF HFA-BECLOMETHASONE AND CFC-BECLOMETHASONE FROM A PRESSURIZED METERED DOSE INHALER WITH AND WITHOUT ADD-ON SPACERS AND USING VARYING BREATHHOLD TIMES.

Leach CL, Colice GL. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2010;23:1-7.

**Background:** The study objective of this pilot study was to determine the lung delivery of HFA-134abeclomethasone dipropionate (HFA-BDP; QVAR) and CFC-beclomethasone dipropionate (CFC-BDP; Becloforte) with and without the add-on spacers, AeroChamber®, and Volumatic®. The smaller particles of HFA-BDP were presumed to produce greater lung deposition using spacers, with and without a delay [i.e., metered dose inhaler (MDI) actuation into the spacer and subsequent inhalation 0 and 2 sec later], compared with the larger particles of CFC-BDP. The study included a comparison of breathhold effects (i.e., 1 and 10-sec breathholds) on lung deposition. **Methods:** The study was an open-label design and utilized healthy subjects ( $n=12$  males). Each arm of the study contained three subjects; thus, outcomes were not powered to assess statistical significance. HFA-BDP and CFCBDP were radiolabeled with technetium-99 m and delivered to subjects. **Results:** Results showed that the small particle HFA-BDP lung deposition averaged 52% and was not affected by the use of AeroChamber® with or without a spacer delay. The oropharyngeal deposition of HFA-BDP was reduced from approximately 28% to 4% with the AeroChamber®. Lung deposition with the large particle CFC-BDP was 3-7% and generally decreased with AeroChamber® or Volumatic. A 2-sec time delay between actuation and breath plus the spacer reduced lung deposition slightly but reduced oropharyngeal deposition substantially (84% down to 3-20%) using the AeroChamber® or Volumatic with and without a spacer delay. HFA-BDP lung deposition was dependent on the breathhold. Lung deposition with HFA-BDP was reduced by 16% with a 1-sec versus 10-sec breathhold. The difference was measured in the increased exhaled fraction, confirming that smaller particles need time to deposit and are exhaled if there is a reduced breathhold. The large particle CFC-BDP lung deposition was not affected by breathhold. **Conclusions:** The use of AeroChamber® or Volumatic spacers with HFA-BDP did not alter lung deposition but it did reduce oropharyngeal deposition. However, HFA-BDP displayed reduced oropharyngeal deposition without a spacer.

## SALBUTAMOL RELATIVE LUNG AND SYSTEMIC BIOAVAILABILITY OF LARGE AND SMALL SPACERS.

Mazhar SHR, Chrystyn H. *Journal of Pharmacy and Pharmacology* 2008;60:1609-1613.

Differences between the size and shape of spacers may affect the emitted dose and provide different effects when interchanged during routine use. Using a urinary pharmacokinetic method we have measured the relative lung and systemic bioavailability from urinary salbutamol excretion 30 min (USAL0.5) and 24 h (USAL24), respectively, after the inhalation of two 100-mg doses from a Ventolin Evohaler when used alone (MDI) and when attached to the Volumatic (VOL) or the AeroChamber Plus® (AERO) spacers. The *in-vitro* properties of the emitted dose were determined. The mean (s.d.) USAL0.5 values following MDI, VOL and AERO ( $n = 13$  volunteers) were 5.7 (1.9), 16.4 (8.2) and 14.8 (7.4) mg, respectively. VOL and AERO were significantly greater ( $p < 0.001$  and  $< 0.01$ , respectively) than MDI. Comparison of VOL and AERO was similar with a mean ratio (90% confidence interval) of 108.2 (84.5, 138.6)%. USAL24 values between the three inhalation methods were similar. The values for the mean (s.d.) fine

particle dose of two 100-mg doses emitted from MDI, VOL and AERO were 83.0 (6.8), 83.6 (4.6) and 73.6 (2.9) mg and the mass median aerodynamic diameters were 2.7 (0.03), 2.8 (0.07) and 2.9 (0.10) mm, respectively. The results showed that during routine use the Volumatic and the AeroChamber Plus® spacers should provide similar lung and systemic delivery when attached to a Ventolin Evohaler.

#### **EFFECTS OF AEROCHAMBER PLUS® AND VOLUMATIC® ADD-ON DEVICES ON BDP DELIVERY FROM HFA SOLUTION pMDIS.**

*Church T, Brambilla G, Lewis D, Meakin B. Respiratory Drug Delivery, Scottsdale, Arizona, 2008.*

**Introduction:** Factors affecting dose delivery from pMDIs fitted with add-on devices include formulation, device design (e.g., materials, size, incorporation of a non-return valve), cleaning procedures and use-mode. Spacer-mode involves a conventional press-and-breathe maneuver whilst inhaling through the mouthpiece of the pMDI-device assembly. The spacer creates a longer path-length, allowing more time for propellant evaporation and slowing the cloud to facilitate lung access. Use in holding-chamber mode requires the device to have a non-return valve and discharging the dose into the chamber where it is held for a period before being inhaled, eliminating the need for press-and breathe co-ordination. This mode also permits the patient to carry out repeated inhalations from the same dose. We were interested in comparing the effects of different add-on devices and their mode of use because the large size of some holding chamber devices may deter user acceptability. This study compares the dose delivered when beclometasone dipropionate (BDP) HFA solution type pMDIs were used in conjunction with both small and large volume devices in the two modes. **Conclusions:** These *in vitro* results would imply that, when used by patients in association with AeroChamber Plus®, the drug delivery performance for Modulite-BDP pMDIs could be similar to that obtained with Volumatic up to holding times of at least 5s for all three product strengths and up to 10s for the 50 µg and 100 µg dose strengths.

#### **THE EFFECT OF INHALATION TECHNIQUE, SPACER VOLUME AND TRAINING ON AEROSOL DELIVERY FROM SPACERS IN CHILDREN.**

*Devadason SG, Walker SL, Owen J. Presented at the American Thoracic Society Conference, May, 2005, San Diego, CA.*

**Rationale:** Variability in the clinical use of inhaler devices is high, particularly in children. Optimization of inhalation therapy should ensure more consistent dose delivery to the airways of young children. We assessed the effect of spacer volume, inhalation technique and training of the parent/child on drug delivery to children using pressurized inhalers. **Methods:** Albuterol was delivered via large (Volumatic; VOL) and small (AeroChamber Plus® VHC; AC+) spacers to 21 children (2-14yrs). Children ≥ 5yrs either took 5 tidal breaths, or one slow maximal inhalation with 10 sec breath-hold. Children <5yrs used tidal breathing only. Training sessions were scheduled ≥ 12wks apart. Drug delivery was assessed using a low resistance filter attached to the spacer mouthpiece. **Results:** Mean (SD) drug delivery (% nominal dose) to children of all ages using AC+ [51.5 (14.7)%] was significantly higher ( $p=0.04$ ) than using VOL [39.3 (10.1)%]. Mean (SD) drug delivery using the single maximal inhalation technique [45.4 (13.7)%] was significantly higher ( $p=0.01$ ) than that using tidal breathing [32.3 (13.9)]. The improvement in delivery using the single maximal inhalation was most marked in the 5-7yr age group. Training the parent/ child to use the spacer correctly gave a small (3.9%) but significant increase ( $p=0.04$ ) in drug delivery. **Conclusions:** AC+ (small volume) delivered more drug than VOL (large volume). This is possibly due to the more efficient construction and design of the AeroChamber Plus® as delivery is normally improved when using large volume spacers. The single maximal inhalation technique increased drug delivery to patients compared to tidal breathing. However, it is easier for children <5yrs to use the tidal breathing technique. Training of the parent/ patient resulted in a smaller than expected (albeit significant) increase in drug delivery.

#### **PERFORMANCE OF LARGE- AND SMALL-VOLUME VALVED HOLDING CHAMBERS WITH A NEW COMBINATION LONG-TERM Bronchodilator / Anti-inflammatory Formulation Delivered by Pressurized Metered Dose Inhaler.**

*Nagel MW, Wiersema KJ, Bates SL, Mitchell JP. Journal of Aerosol Medicine 2002;15(4):427-433.*

The treatment of both the bronchoconstriction and inflammatory aspects of asthma simultaneously by a single pressurized metered dose inhaler (pMDI) represents a significant advance in convenience to the patient. However, a valved holding chamber (VHC) may still be needed to reduce the coarse component of the dose that is likely to deposit in the oropharyngeal region, and a small sized device may offer significant advantages to the patient from



the standpoint of compliance with therapy. VHCs representing small (adult AeroChamber Plus® with mouthpiece, 149-mL) and large (Volumatic<sup>†</sup>, 750-mL) devices have been compared in an *in vitro* evaluation with Seretide<sup>†</sup>/Advair<sup>†</sup> (hydro-fluoro alkane [HFA]-formulated fluticasone propionate [FP = 125 µg/dose] and salmeterol xinafoate [SX = 25 µg/dose]) by Andersen Mark-II eight-stage impactor operated at 28.3L/min following compendial methodology. Fine particle fraction, based on the size range from 1.1 to 4.7 µm aerodynamic diameter, from either large or small VHCs with either component (69-79%) was similar [ $p \geq 0.08$ ], and significantly greater than that from the pMDI alone (approximately 40%) [ $p < 0.001$ ]. Fine particle dose emitted by the VHCs for SX ( $8.2 \pm 0.8$  µg for the AeroChamber Plus® and  $7.7 \pm 0.5$  µg for the Volumatic<sup>†</sup>) were comparable, and also similar to the fine particle dose delivered by the pMDI when used without a VHC ( $7.6 \pm 0.6$  µg). Fine particle doses for the FP component delivered by the two VHCs ( $46.4 \pm 3.4$  µg for the AeroChamber Plus® and  $46.3 \pm 2.7$  µg for the Volumatic<sup>†</sup>) were equivalent, but were slightly greater than the corresponding fine particle dose from the pMDI alone ( $39.1 \pm 2.6$  µg). However, this difference (approximately 20%) is close to the limit of resolution based on intermeasurement variability and is unlikely to have clinical significance, given the interpatient variability seen with inhaled drug therapy. It is therefore concluded that either of these VHCs has equivalent *in vitro* performance with this combination formulation in terms of the portion of the dose emitted from the pMDI that is likely to reach the receptors in the lungs.

### **RANDOMIZED CONTROLLED STUDY OF CLINICAL EFFICACY OF SPACER THERAPY IN ASTHMA WITH REGARD TO ELECTROSTATIC CHARGE.**

Dompeling E, Oudesluys-Murphy AM, Janssens HM, Hop W, Brinkman JG, Sukhai RN, de Jongste JC. *Arch. Dis. Child* 2001;84;178-82.

**Background:** Inhalation therapy using a pressured metered dose inhaler (pMDI) and a spacer is frequently used in the treatment of airway disease in children. Several laboratory studies found a clear negative influence of electrostatic charge (ESC) on plastic spacers on the delivery of aerosol. **Aims:** To investigate whether ESC on plastic spacers could diminish bronchodilating responses to salbutamol. **Methods:** Ninety asthmatic children (aged 4-8 years) were randomized into three groups: metal Nebuchamber, plastic Volumatic, and plastic AeroChamber®. The bronchodilating response was measured by the change in peak expiratory flow rate (PEF) after 100 microgram and 400 microgram salbutamol. Within the Volumatic and AeroChamber® groups, a crossover comparison was made between electrostatic and non-electrostatic spacers. **Results:** We found no significant effect of ESC on the bronchodilating response to salbutamol with any of the doses in the AeroChamber® and Volumatic groups. For the plastic spacers, the mean difference of the change in PEF after 100 microgram salbutamol between non-electrostatic and electrostatic spacers was only +1.7% (95% CI -1.3% to 4.7%). After 400 microgram salbutamol this was +1.9% (95% CI -1.4% to 5.1%). A comparable efficacy was found for the Nebuchamber, the AeroChamber®, and Volumatic with respect to the change in PEF after 100 and 400 microgram salbutamol. **Conclusion:** This study showed no negative influence of ESC on plastic spacers with regard to clinical efficacy of a beta(2) agonist (salbutamol) in children with asthma. The metal Nebuchamber, plastic AeroChamber®, and plastic Volumatic were equally effective.

### **PERFORMANCE OF LARGE AND SMALL VOLUME VALVED HOLDING CHAMBERS (VHCs) AS A FUNCTION OF FLOW RATE.**

Mitchell JP, Nagel MW, Wiersema KJ, Bates SL, Morton RW, Schmidt JN. *J Aerosol Med* 2001;14(1):122.

It is useful from the standpoint of the health care provider, if the performance of add-on devices for use with pressurized metered dose inhalers is characterized within the range of flow rates likely to be achieved by users. VHCs representing smaller (adult AeroChamber Plus®, 149-ml;  $n = 5$ ) and larger (Volumatic<sup>†</sup>, 750-ml;  $n = 5$ ) devices were compared with HFA-formulated fluticasone propionate (125 µg/dose ex metering chamber) at three flow rates, 28.3, 45 and 60 L/min. Measurements were made by Andersen 8-stage impactor. Fine particle fractions ( $< 4.7$  µm,  $< 4.6$  µm and  $< 4.0$  µm aerodynamic diameter at 28.3, 45 and 60 L/min respectively) from both VHCs were close to 90%, significantly greater than that from the pMDI alone. At 28.3 L/min, fine particle dose (FPD) from the smaller VHC ( $50.5 \pm 3.8$  µg) was comparable with that from the larger VHC ( $45.9 \pm 7.8$  µg) [ $p = 0.27$ ]. At the higher flow rates, FPD from the smaller VHC ( $65.5 \pm 2.6$  µg (45 L/min) and  $65.2 \pm 6.2$  µg (60 L/min)) exceeded equivalent values from the larger VHC ( $53.8 \pm 3.7$  µg (45 L/min) and  $55.3 \pm 4.9$  µg (60 L/min)) [ $p < 0.023$ ].

## COMPARISON OF A LARGE AND A SMALL VOLUME HOLDING CHAMBER (VHC) FOR THE DELIVERY OF SALMETEROL XINAFOATE.

Mitchell JP, Nagel MW, Wiersema KJ, Bates SL, Morton RW, Schmidt JN. Presented at Ann Meet Amer College of Allergy, Asthma and Immunology (ACAAI), Seattle, 2000.

Salmeterol xinafoate is a widely prescribed long-acting beta-adrenergic agonist. Valved holding chambers (VHCs) improve drug delivery from pressurized metered-dose inhalers (pMDI), particularly with patients having poor coordination. The present study compared a large volume VHC (Volumatic<sup>†</sup>, GlaxoSmithKline - 750-ml,  $n=5$  devices) with a small volume VHC (AeroChamber Plus<sup>®</sup>, Monaghan Medical Corp. - 149-ml,  $n=5$  devices) with salmeterol xinafoate (Serevent<sup>†</sup>: total dose 21  $\mu\text{g}$  ex actuator, GlaxoSmithKline). Measurements were also made with the pMDI without VHC. Total emitted dose (TD), fine particle dose (FPD - particles < 4.7  $\mu\text{m}$  aerodynamic diameter) and fine particle fraction (FPF) were determined by Andersen 8-stage impactor with USP Induction Port at  $28.3 \pm 0.5$  L/min. Assays for salmeterol xinafoate were undertaken by HPLC-fluorescence spectrometry at excitation and emission wavelengths of 226 nm and 296 nm respectively. As expected, both types of VHC greatly reduced the coarse component of the dose from the pMDI ( $10.5 \pm 1.2$   $\mu\text{g}$  - pMDI alone;  $1.0 \pm 0.6$   $\mu\text{g}$  - AeroChamber Plus<sup>®</sup> VHC;  $0.9 \pm 0.7$   $\mu\text{g}$  - Volumatic<sup>†</sup> VHC). Both FPD and TD from the AeroChamber Plus<sup>®</sup> ( $12.7 \pm 1.3$   $\mu\text{g}$  and  $13.6 \pm 0.9$   $\mu\text{g}$  respectively) and from the Volumatic<sup>†</sup> ( $12.3 \pm 1.7$   $\mu\text{g}$  and  $13.2 \pm 2.1$   $\mu\text{g}$  respectively) VHCs were comparable (un-paired t-test,  $p > 0.70$ ). FPD from the pMDI alone was  $10.6 \pm 1.0$   $\mu\text{g}$ , slightly lower but still comparable with the FPD from either type of VHC. The small volume VHC appears to be as effective as the larger chamber for the delivery of this formulation. These data are consistent with the recommendation to use a VHC with this formulation for patients with poor coordination (Demirkan *et al.* (Chest 2000; 117, 1314-1318)).

## RESPONSE TO BRONCHODILATOR ADMINISTERED DIRECTLY WITH SPRAY OR WITH SPACER

[Article in Italian]. Battistini A, Pisi G, Attanasi G. *Pediatr Med Chir.* 1997 Jul-Aug;19(4):237-42.

If we assume that the only function of a spacer is to facilitate the execution of a spray, its use is limited to small children who do not collaborate (below age 6-7 years). However, spacers seem to improve the effectiveness of drugs and reduce both directly and indirectly the side effects. To assess if these characteristics have a role in clinical practice, the response to 100 micrograms of salbutamol administered directly by Autohaler was compared to that obtained with the same dose administered with three different spacers, AeroChamber<sup>®</sup> VHC, Babyhaler, Volumatic. A series of 88 asthmatic subjects with a FEF 25-75 less than 70% of the predicted value was considered. Overall patients provided 118 responses to the bronchodilator: 17 using the Aerotec (Autohaler), 38 the AeroChamber<sup>®</sup> VHC, 33 the Babyhaler, 30 the Volumatic. The response was evaluated considering the parameters obtained by spirometry just before, 5 and 20 minutes after the inhalation of salbutamol. Heart rate was also measured at the same time points. Heart rate, but not spirometric parameter were increased by the use of the Autohaler, proving that the drug had been inhaled. All the spacers determined a significant increase in the parameters considered. No significant difference was detected among spacers, although the smallest (AeroChamber<sup>®</sup> VHC, Babyhaler) showed a trend to a better response, in particular before age 7 years. The complete ineffectiveness of direct inhalation and the excellent response to inhalation with spacers show the indispensability of the latter, independent of age. Although no substantial difference among spacers was detected, the trend to obtain a better response with smaller spacers inclines us to use them in particular between 4 and 7 years of age. The negative correlation between the increase in spirometric parameters and the age of the patient would allow to have doses aimed to age or to body weight.

## Metered Dose Inhalers and Valved Holding Chambers vs Nebulizers

### IMPROVING EFFICIENCY OF PEDIATRIC EMERGENCY ASTHMA TREATMENT BY USING METERED DOSE INHALER.

Abaya R et al. *Journal of Asthma* Vol 56, 2019 – Issue 10.

**Objective:** Evidence suggests using metered dose inhaler (MDI) to treat acute asthma in the Emergency Department reduces length of stay, though methods of implementation are lacking. We modified a treatment pathway to recommend use of MDI for mild-moderate asthma in a pediatric ED. **Methods:** A baseline review assessed discharged patients >2 years with an asthma diagnosis and non-emergent Emergency Severity Index triage assessment (3/4). Our multi-disciplinary team developed an intervention to increase MDI use instead of continuous albuterol (CA) using the following: (1) Redesign the asthma pathway and order set recommending MDI for ESI 3/4 patients. (2) Adding a conditional order for Respiratory Therapists to reassess and repeat MDI until patient reached mild assessment. The primary outcome was the percentage discharged within 3 hours, with a goal of a 10% increase compared to pre-intervention. Balancing measures included admission and revisit rates. **Results:** 7635 patients met eligibility before pathway change; 12,673 were seen in the subsequent 18 months. For target patients, the percentage discharged in <3 hours increased from 39% to 49%; reduction in median length of stay was 33 minutes. We identified special cause variation for reduction in CA use from 43% to 25%; Revisit rate and length of stay for higher-acuity patients did not change; overall asthma admissions decreased by 8%. Changes were sustained for 18 months. **Conclusion:** A change to an ED asthma pathway recommending MDI for mild-moderate asthma led to a rapid and sustained decrease in continuous albuterol use, length of stay, and admission rate.

### THE EFFECT OF BRONCHODILATORS ADMINISTERED VIA AEROCHAMBER® OR A NEBULIZER ON INSPIRATORY LUNG FUNCTION PARAMETERS.

Ramlal S, Visser F, Hop W, Dekhuijzen P, Heijdra Y. *Respiratory Medicine* 2013;107:1393-1399.

**Background:** In chronic obstructive pulmonary disease (COPD) the clinical efficacy of bronchodilator therapy delivered via a nebulizer versus an AeroChamber® on FEV<sub>1</sub> is controversial. No studies comparing changes in inspiratory pulmonary function parameters (ILPs) using these inhaler devices are currently available. This information might be of interest because due to dynamic bronchial compression, the relationship between the ILPs and dyspnea is more reliable than that between FEV<sub>1</sub> and dyspnea. Therefore, our study aimed to investigate whether changes in ILPs after use of these inhaler devices were similar to the changes in FEV<sub>1</sub> and correlate with VAS (Visual Analogue Scale). **Methods:** Forty-one stable COPD patients participated in a crossover trial. Spirometry was performed before and after two puffs Combivent (200 mcg salbutamol and 20 mcg ipratropium per puff) using an AeroChamber® or 2 mL of Combivent (2.5 mg salbutamol and 250 mcg ipratropium per mL) using a nebulizer. Differences in lung function parameters and changes in VAS were measured. **Results:** ILP values improved significantly from baseline after Combivent administration using both devices ( $p \leq 0.004$ ). With both devices, the mean percent changes were significantly greater for FEV<sub>1</sub> than the ILPs ( $p \leq 0.003$ ), except for IC ( $p = 0.19$ ). The mean VAS score did not differ significantly between the devices ( $p = 0.33$ ), but significant correlations were found between the VAS and forced inspiratory flow at 50% of the vital capacity (FIF(50)) and peak inspiratory flow (PIF) when a nebulizer was used. With an AeroChamber®, no significant correlations between lung function parameters and VAS were found. **Conclusions:** The present study demonstrates that ILPs improved significantly after using either device. Although significant correlations were found between the VAS and FIF(50) and PIF for the nebulizer, in stable COPD patients, the pMDI plus spacer is a better route of administration than a nebulizer.

### HOLDING CHAMBERS (SPACERS) VERSUS NEBULIZERS FOR BETA-AGONIST TREATMENT OF ACUTE ASTHMA (REVIEW).

Cates CS, Welsh EJ, Rowe BH. *The Cochrane Library* 2013, Issue 9.

**Background:** In acute asthma inhaled beta(2)-agonists are often administered by nebulizer to relieve bronchospasm, but some have argued that metered-dose inhalers with a holding chamber (spacer) can be equally effective. Nebulizers require a power source and need regular maintenance, and are more expensive in the community setting. **Objectives:** To assess the effects of holding chambers (spacers) compared to nebulizers for the delivery of beta(2)-agonists for acute asthma. **Search Methods:** We searched the Cochrane Airways Group Trial Register and reference

lists of articles. We contacted the authors of studies to identify additional trials. Date of last search: February 2013. **Selection Criteria:** Randomized trials in adults and children (from two years of age) with asthma, where spacer beta(2)-agonist delivery was compared with wet nebulization. **DATA Collection and Analysis:** Two review authors independently applied study inclusion criteria (one review author for the first version of the review), extracted the data and assessed risks of bias. Missing data were obtained from the authors or estimated. Results are reported with 95% confidence intervals (CIs). **Main Results:** This review includes a total of 1897 children and 729 adults in 39 trials. Thirty-three trials were conducted in the emergency room and equivalent community settings, and six trials were on inpatients with acute asthma (207 children and 28 adults). The method of delivery of beta(2)-agonist did not show a significant difference in hospital admission rates. In adults, the risk ratio (RR) of admission for spacer versus nebulizer was 0.94 (95% CI 0.61 to 1.43). The risk ratio for children was 0.71 (95% CI 0.47 to 1.08, moderate quality evidence). In children, length of stay in the emergency department was significantly shorter when the spacer was used. The mean duration in the emergency department for children given nebulized treatment was 103 minutes, and for children given treatment via spacers 33 minutes less (95% CI -43 to -24 minutes, moderate quality evidence). Length of stay in the emergency department for adults was similar for the two delivery methods. Peak flow and forced expiratory volume were also similar for the two delivery methods. Pulse rate was lower for spacer in children, mean difference -5% baseline (95% CI -8% to -2%, moderate quality evidence), as was the risk of developing tremor (RR 0.64; 95% CI 0.44 to 0.95, moderate quality evidence). **Author's Conclusions:** Nebulizer delivery produced outcomes that were not significantly better than metered-dose inhalers delivered by spacer in adults or children, in trials where treatments were repeated and titrated to the response of the participant. Spacers may have some advantages compared to nebulizers for children with acute asthma.

#### **COST-EFFECTIVENESS OF METERED-DOSE INHALERS FOR ASTHMA EXACERBATIONS IN THE PEDIATRIC EMERGENCY DEPARTMENT.**

*Doan Q, Shefrin A, Johnson D. Pediatrics 2011;127(5): E1105-1111.*

**Objective:** To compare the incremental cost and effects (averted admission) of using a metered-dose inhaler (MDI) against wet nebulization to deliver bronchodilators for the treatment of mild to moderately severe asthma in pediatric emergency departments (EDs). **Methods:** We measured the incremental cost-effectiveness from the perspective of the hospital, by creating a model using outcome characteristics from a Cochrane systematic review comparing the efficacy of using MDIs versus nebulizers for the delivery of albuterol to children presenting to the ED with asthma. Cost data were obtained from hospitals and regional authorities. We determined the incremental cost-effectiveness ratio and performed probabilistic sensitivity analyses using Monte Carlo simulations. **Results:** Using MDIs in the ED instead of wet nebulization may result in net savings of Can \$154.95 per patient. Our model revealed that using MDIs in the ED is a dominant strategy, one that is more effective and less costly than wet nebulization. Probabilistic sensitivity analyses revealed that 98% of the 10,000 iterations resulted in a negative incremental cost-effectiveness ratio. Sensitivity analyses around the costs revealed that MDI would remain a dominant strategy (90% of 10,000 iterations) even if the net cost of delivering bronchodilators by MDI was Can \$70 more expensive than that of nebulized bronchodilators. **Conclusions:** Use of MDIs with spacers in place of wet nebulizers to deliver albuterol to treat children with mild-to-moderate asthma exacerbations in the ED could yield significant cost savings for hospitals and, by extension, to both the health care system and families of children with asthma.

#### **REPEAT DOSING OF ALBUTEROL VIA METERED-DOSE INHALER IN INFANTS WITH ACUTE OBSTRUCTIVE AIRWAY DISEASE.**

*Kaashmiri M, Shepard J, Goodman B, Lincourt WR, Trivedi R, Ellsworth A, Davis AM. Pediatr Emer Care 2010;26: 197-202.*

**Background:** Airway obstruction and bronchial hyperactivity oftentimes lead to emergency department visits in infants. Inhaled short-acting  $\mu$ 2-agonist bronchodilators have traditionally been dispensed to young children via nebulizers in the emergency department. Delivery of bronchodilators via metered-dose inhalers (MDIs) in conjunction with holding chambers (spacers) has been shown to be effective. **Study Objective:** Safety and efficacy evaluations of albuterol sulfate hydrofluoroalkane (HFA) inhalation aerosol in children younger than 2 years with acute wheezing caused by obstructive airway disease. **Methods:** A randomized, double-blind, parallel group, multicenter study of albuterol HFA 180  $\mu$ g ( $n = 43$ ) or 360  $\mu$ g ( $n = 44$ ) via an MDI with a valved holding chamber and face mask in an urgent-care setting. Assessments included adverse events, signs of adrenergic stimulation, electrocardiograms, and

blood glucose and potassium levels. Efficacy parameters included additional albuterol use and Modified Tal Asthma Symptoms Score ([MTASS] reduction in MTASS representing improvement). **Results:** Overall, adverse events occurred in 4 (9%) and 3 (7%) subjects in the 180- $\mu$ g and 360- $\mu$ g groups, respectively. Drug-related tachycardia (360  $\mu$ g) and ventricular extrasystoles (180  $\mu$ g) were reported in 1 patient each. Three additional instances of single ventricular ectopy were identified from Holter monitoring. No hypokalemia or drug-related QT or QTc prolongation was seen; glucose values and adrenergic stimulation did not significantly differ between treatment groups. In the 180- $\mu$ g and 360- $\mu$ g groups, mean change from baseline in MTASS during the treatment period was -2.8 (-49.8%) and -2.9 (-48.4%), and rescue albuterol use occurred in 4 (9%) and 3 (7%) subjects, respectively. **Conclusions:** Cumulative dosing with albuterol HFA 180  $\mu$ g or 360  $\mu$ g via MDI-spacer and face mask in children younger than 2 years did not result in any significant safety issues and improved MTASS by at least 48%.

## **DOES PARENTAL INVOLVEMENT IN PEDIATRIC EMERGENCY DEPARTMENT ASTHMA TREATMENT AFFECT HOME MANAGEMENT?**

*Hussain-Rizvi A, Kunkov S, Crain EF. J Asthma 2009;46(8):792-5.*

To determine whether parents who deliver albuterol treatments in a pediatric emergency department with a metered dose inhaler with a spacer device (MDIS) report better adherence to MDIS use at home compared to parents whose children undergo standard nebulizer therapy. Children aged 1-5 years were randomized by day to usual treatment with nebulized albuterol (40 children) or to treatment by the parent with albuterol with an MDIS (46 children). All caregivers received standard discharge instructions, a spacer and an MDI. Two weeks following the visit, a trained research assistant blinded to the child's group status, administered a brief telephone questionnaire to each caretaker. At follow-up, children in the MDIS group were 7.5 times more likely to be using the MDIS for their albuterol treatments (95%CI 1.6-35.6). Involving parents in treatment of asthma exacerbations in the emergency department using an MDIS may improve adherence to MDIS use at home.

## **NEBULIZERS OR SPACERS FOR THE ADMINISTRATION OF BRONCHODILATORS TO THOSE WITH ASTHMA ATTENDING EMERGENCY DEPARTMENTS?**

*Mason N, Roberts N, Yard N, Partridge MR. Respiratory Medicine 2008;102: 993-998.*

**Background:** Systematic reviews and national guidelines conclude that the nebulized route of administration of bronchodilators has no advantage over the use of a spacer in moderately severe exacerbations of asthma. Whether this recommendation is implemented and whether it might affect use of staff time is unknown. **Objectives:** To determine the current method of administration of bronchodilators to those with non-life-threatening asthma attending emergency departments (ED) in London, UK and to monitor the implementation of a new policy to administer bronchodilators by spacers in one ED with a special reference to the time taken by nurses to administer the therapy by two different routes. **Methods:** Thirty-five EDs in Greater London were surveyed regarding their current practice. A time and motion study was then undertaken in one department observing nurses administering bronchodilators in the 3 weeks before and 3 weeks after a departmental policy change to favor the use of spacer devices rather than nebulizers. **Results:** The majority of EDs (94.3%) in Greater London were using the nebulized route of administering bronchodilators to the majority of their adult patients. Spacers were more commonly used for the treatment of children (60.3% of departments using spacers and nebulizers or spacers alone). Over half of the hospitals surveyed (51.4%) were unaware that the British Guidelines on Asthma Management suggested that outcomes were the same and that there were potential advantages in the use of a spacer for both adults and children. Time and motion studies showed that the use of a spacer took no more nursing time than administration of the bronchodilator via a nebulizer; in fact treatment and set-up time were considerably lower for spacers. **Conclusion:** Spacer administration of bronchodilators to those with asthma attending EDs utilizes less treatment time than use of a nebulizer. A survey of EDs in Greater London has shown that despite guideline conclusions there appears to be little evidence of reduction in use of nebulizers; a fear that use of alternatives might take nurses longer is not supported by this study.

## THE CONVERSION TO METERED-DOSE INHALER WITH VALVED HOLDING CHAMBER TO ADMINISTER INHALED ALBUTEROL: A PEDIATRIC HOSPITAL EXPERIENCE.

Salyer JW, DiBlasi, Crotwell DN, Cowan CA, Carter ER. *Respir Care* 2008;53(3):338-345.

**Background:** Metered-dose inhalers with valved holding chambers (MDI-VHCs) have been shown to be equivalent to small volume nebulizers (SVNs) for the delivery of bronchodilators in children. At Seattle Children's Hospital and Regional Medical Center we sought to implement the conversion from SVN to MDI-delivered albuterol in nonintubated patients receiving intermittent treatments. **Methods:** There were 4 distinct interventions used to plan and implement this conversion program: (1) literature review, (2) product selection, (3) policy and operational changes, and (4) staff training. Bronchodilator administration guidelines and clinical pathways for asthma and bronchiolitis were revised to recommend MDI-VHC use in lieu of SVNs. Computerized physician order sets were amended to indicate MDI-VHC as the preferred method of delivering inhaled albuterol in children with asthma and bronchiolitis. Data from administrative case mix files and computerized medication delivery systems were used to assess the impact of our program. **Results:** MDI-VHC utilization increased from 25% to 77% among all non-intensive-care patients receiving albuterol, and from 10% to 79% among patients with asthma ( $p < 0.001$ ). Duration of stay among patients with asthma was unchanged after conversion to MDI-VHC ( $p < 0.53$ ). **Conclusions:** Our program was very successful at promoting the use of MDI-VHC for the administration of albuterol in our pediatric hospital. Duration of stay among patients with asthma did not change during or since the implementation of this program.

## B-AGONISTS THROUGH METERED-DOSE INHALER WITH VALVED HOLDING CHAMBER VERSUS NEBULIZER FOR ACUTE EXACERBATION OF WHEEZING OR ASTHMA IN CHILDREN UNDER 5 YEARS OF AGE: A SYSTEMATIC REVIEW WITH META ANALYSIS.

Castro-Rodriguez JA, Rodrigo GJ. *J Pediatr* 2004;145:172-7.

**Objective:** To compare the efficacy of beta-agonists given by metered-dose inhaler with a valved holding chamber (MDI+VHC) or nebulizer in children under 5 years of age with acute exacerbations of wheezing or asthma in the emergency department setting. **Study Design:** Published (1966 to 2003) randomized, prospective, controlled trials were retrieved through several different databases. The primary outcome measure was hospital admission. **Results:** Six trials ( $n=491$ ) met criteria for inclusion. Patients who received beta-agonists by MDI+VHC showed a significant decrease in the admission rate compared with those by nebulizer (OR, 0.42; 95% CI, 0.24-0.72;  $p=0.002$ ); this decrease was even more significant among children with moderate to severe exacerbations (OR, 0.27; 95% CI, 0.13-0.54;  $p=0.0003$ ). Finally, measure of severity (eg, clinical score) significantly improved in the group who received beta-agonists by MDI+VHC in comparison to those who received nebulizer treatment (standardized mean difference, -0.44; 95% CI, -0.68 to -0.20;  $p=0.0003$ ). **Conclusions:** The use of an MDI+VHC was more effective in terms of decreasing hospitalization and improving clinical score than the use of a nebulizer in the delivery of beta agonists to children under 5 years of age with moderate to severe acute exacerbations of wheezing or asthma.

## DRUG DELIVERY AND ADHERENCE IN YOUNG CHILDREN.

Iqbal S, Ritson S, Prince I, Denyer J, Everard ML. *Pediatric Pulmonology* 2004;37:311-317.

The aim of this pilot study was to compare the HaloLite Pediatric Nebulizer (HPN) with a pressurized metered dose inhaler and valved holding chamber (pMDI VHC, AeroChamber®) in terms of drug delivery, adherence to treatment, compliance with device, true adherence, and acceptability. Fourteen children aged 11-36 months with asthma on regular treatment with inhaled corticosteroids were enrolled into an open, randomized, crossover trial. They received budesonide for 2 weeks with each delivery system. Both devices incorporated a datalogger which recorded information on how the device was used. The HPN was preprogrammed to deliver 25 microg of budesonide to the patient. A single actuation of budesonide 200 microg was used with the pMDI VHC. The median delivered dose of budesonide was 36 microg (range, 31-45 microg; CV, 15%) for the HPN and 53 microg (range, 17-85 microg; CV, 47%) for the pMDI VHC. The median adherence was 68% (range, 11-96%) with the HPN and 71% (range, 11-100%) with the pMDI VHC. The median device compliance was 30% and 51% and the median true adherence was 23% and 36%, respectively. The shape, size, and weight of the HaloLite Pediatric Nebulizer were generally less acceptable than the shape, size, and weight of the pMDI VHC with datalogger. These results indicate that reproducible quantities of drug can be delivered to very young children using AAD technology such as that incorporated into the HPN. Drug delivery with the pMDI VHC was more variable, but parents preferred this device.

## **HOLDING CHAMBERS VERSUS NEBULIZERS FOR BETA-AGONIST TREATMENT OF ACUTE ASTHMA (COCHRANE REVIEW).**

*Cates CJ, Bara A, Crilly JA, Rowe BH. The Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: 2003;2: CD000052.*

A substantive amendment to this systematic review was last made on 18 February 2003. Cochrane reviews are regularly checked and updated if necessary. **Background:** In acute asthma inhaled beta-2-agonists are often administered to relieve bronchospasm by wet nebulization, but some have argued that metered-dose inhalers with a holding chamber (spacer) can be equally effective. In the community setting nebulizers are more expensive, require a power source and need regular maintenance. **Objectives:** To assess the effects of holding chambers compared to nebulizers for the delivery of beta-2-agonists for acute asthma. **Search strategy:** We last searched the Cochrane Airways Group trials register in February 2004 and the Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 1, 2004). **Selection criteria:** Randomized trials in adults and children (from two years of age) with asthma, where holding chamber beta-2-agonist delivery was compared with wet nebulization. **Data collection and analysis:** Two reviewers independently applied study inclusion criteria (one reviewer for the first version of the review), extracted the data and assessed trial quality. Missing data were obtained from the authors or estimated. Results are reported with 95% confidence intervals (CI). **Main results:** This review has been updated in 2003 and has now analyzed 1076 children and 444 adults included in 22 trials from emergency room and community settings. In addition, five trials on in-patients with acute asthma (184 children and 28 adults) have been added to the review. Method of delivery of beta-2-agonist did not appear to affect hospital admission rates. In adults, the relative risk of admission for holding chamber versus nebulizer was 0.88 (95% CI 0.56 to 1.38). The relative risk for children was 0.65 (95% CI 0.4 to 1.06). In children, length of stay in the emergency department was significantly shorter when the holding chamber was used, with a weighted mean difference of -0.47 hours, (95% CI -0.58 to -0.37 hours). Length of stay in the emergency department for adults was similar for the two delivery methods. Peak flow and forced expiratory volume were also similar for the two delivery methods. Pulse rate was lower for holding chamber in children, weighted mean difference -7.6% baseline (95% CI -9.9 to -5.3% baseline). An update search in February 2004 did not identify any new studies. **Authors' conclusions:** Metered-dose inhalers with holding chamber produced outcomes that were at least equivalent to nebulizer delivery. Holding chambers may have some advantages compared to nebulizers for children with acute asthma.

## **NEBULIZERS VS METERED-DOSE INHALERS WITH SPACERS FOR BRONCHODILATOR THERAPY TO TREAT WHEEZING IN CHILDREN AGED 2 TO 24 MONTHS IN A PEDIATRIC EMERGENCY DEPARTMENT.**

*Delgado A, Chou KJ, Johnson Silver E, Crain EF. Arch Pediatr Adolesc Med 2003;157:76-80.*

**Objective:** To determine if administration of albuterol by a metered-dose inhaler with a spacer device (AeroChamber\*) is as efficacious as administration of albuterol by nebulizer to treat wheezing in children aged 2 years and younger. **Design:** Double-blind, randomized, placebo-controlled clinical trial. **Setting:** Pediatric emergency department. **Patients:** From a convenience sample of wheezing children aged 2 to 24 months, 85 patients were enrolled in the nebulizer group and 83 in the spacer group. **Interventions:** The nebulizer group received a placebo metered-dose inhaler with a spacer followed by nebulized albuterol. The spacer group received albuterol by a metered dose inhaler with a spacer followed by nebulized isotonic sodium chloride solution. Treatments were given every 20 minutes by a single investigator blinded to group assignment. **Main Outcome Measures:** The primary outcome was admission rate. Pulmonary Index score and oxygen saturation were measured initially and 10 minutes after each treatment. **Results:** The nebulizer group had a significantly higher mean (SD) initial Pulmonary Index score compared with the spacer group (7.6 [2.5] vs 6.6 [2.0];  $p = .002$ ). With the initial Pulmonary Index score controlled, children in the spacer group were admitted less (5% vs 20%;  $p = .05$ ). Analyses also revealed an interaction between group and initial Pulmonary Index score; lower admission rates in the spacer group were found primarily in children having a more severe asthma exacerbation. **Conclusion:** Our data suggest that metered-dose inhalers with spacers may be as efficacious as nebulizers for the emergency department treatment of wheezing in children aged 2 years or younger.

## A COMPARISON OF ALBUTEROL ADMINISTERED BY METERED-DOSE INHALER AND SPACER WITH ALBUTEROL BY NEBULIZER IN ADULTS PRESENTING TO AN URBAN EMERGENCY DEPARTMENT WITH ACUTE ASTHMA.

Newman KB, Milne S, Hamilton C, Hall K. *Chest* 2002;121:1036-41.

**Study Objectives:** To determine the efficacy of albuterol by metered-dose inhaler (MDI) and spacer (AeroChamber<sup>®</sup>) compared to a nebulizer. **Design:** A prospective, open-label study. **Setting:** Large urban emergency department (ED). **Patients:** All consecutive adult asthma patients over a 2.5-year period. **Interventions:** ED personnel used a standardized treatment algorithm, which included albuterol administered by nebulization, for patients presenting to the ED during the first 12 months of the study. The treatment algorithm then was switched to one that utilized albuterol administered by MDI/spacer as the primary mode of delivery for the following 18 months. As part of the conversion to MDI/spacer, ED staff counseled patients on self management and supplied patients with a peak flow meter, an MDI/spacer, and an inhaled steroid for home use. **Measurements:** Pulmonary function, clinical outcome, laboratory data, and financial data were assembled and analyzed from 2,342 ED visits and 1,420 patients. **Results:** While there was no significant difference in hospital admission rates between patients in the MDI/spacer group and the nebulizer group (13.2% and 14.6%, respectively), there was a statistically greater improvement in peak flow rates in the MDI/spacer group (126.8 vs 111.9 L/min, respectively;  $p = 0.002$ ). The MDI/spacer group also spent significantly less time in the ED (163.6 and 175 min, respectively;  $p = 0.007$ ), had a lower total albuterol dose (1,125 microg and 6,700 microg, respectively;  $p < 0.001$ ), and showed a greater improvement in arterial oxygen saturation ( $p = 0.043$ ). Relapse rates at 14 and 21 days were significantly lower ( $p < 0.01$  and  $p < 0.05$ , respectively) among patients treated with the MDI/spacer and were associated with asthma education and the provision of a peak flow meter, a spacer, and an inhaled corticosteroid for patients' home use. **Conclusions:** Albuterol administered by MDI/spacer is an efficacious and cost effective alternative to nebulization in adults with acute asthma who present at a large urban ED.

## COSTS AND EFFECTIVENESS OF SPACER VERSUS NEBULIZER IN YOUNG CHILDREN WITH MODERATE AND SEVERE ACUTE ASTHMA.

Lerversha AM, Campanella SG, Aickin RP, Asher MI. *J Pediatr* 2000;136(4):497-502.

**Objective:** To compare the costs and effectiveness of albuterol by metered dose inhaler (MDI) and spacer versus nebulizer in young children with moderate and severe acute asthma. **Design:** Randomized, double-blind, placebo controlled trial in an emergency department at a children's hospital. The participants were children 1 to 4 years of age with moderate to severe acute asthma. Patients assigned to the spacer group received albuterol (600 microg) by MDI by spacer (AeroChamber<sup>®</sup>) followed by placebo by nebulizer ( $n = 30$ ). The nebulizer group received placebo MDI by spacer followed by 2.5 mg albuterol by nebulizer ( $n = 30$ ). Treatments were repeated at 20-minute intervals until the patient was judged to need no further doses of bronchodilator, or a total of 6 treatments. **Results:** Clinical score, heart rate, respiratory rate, auscultatory findings, and oxygen saturation were recorded at baseline, after each treatment, and 60 minutes after the last treatment. Baseline characteristics and asthma severity were similar for the treatment groups. The spacer was as effective as the nebulizer for clinical score, respiratory rate, and oxygen saturation but produced a greater reduction in wheezing ( $p = 0.03$ ). Heart rate increased to a greater degree in the nebulizer group (11.0/min vs 0.17/min for spacer,  $p < 0.01$ ). Fewer children in the spacer group required admission (33% vs 60% in the nebulizer group,  $p = 0.04$ , adjusted for sex). No differences were seen in rates of tremor or hyperactivity. The mean cost of each emergency department presentation was NZ\$825 for the spacer group and NZ\$1282 for the nebulizer group ( $p = 0.03$ ); 86% of children and 85% of parents preferred the spacer. **Conclusion:** The MDI and spacer combination was a cost-effective alternative to a nebulizer in the delivery of albuterol to young children with moderate and severe acute asthma.

## CONSENSUS STATEMENT: AEROSOLS AND DELIVERY DEVICES.

*Respir Care* 2000;45(6):589-596.

Because the pMDI and DPI delivery system are the most convenient and produce the lowest cost/dose, they should be the first choice of clinicians. A valved holding chamber should be used with the pMDI whenever the patient cannot demonstrate acceptable hand breath coordination and whenever pharyngeal deposition is of clinical concern (e.g. inhaled steroids). In general, the valved holding chamber often with mask is almost always required in pediatric and geriatric populations. The nebulizer may be used if the drug is only available as a solution or if the pMDI/DPI cannot be used effectively.



## BRONCHODILATOR RESUSCITATION IN THE EMERGENCY DEPARTMENT PART 1 OF 2: DEVICE SELECTION.

Fink J, Dhand R. *Respir Care* 1999;44(11):1353-1374.

This paper reviews the impact of device selection on bronchodilator resuscitation in the emergency department. The pMDI/holding chamber is equivalent to nebulizer therapy for treatment of infants, children, and adults with moderate to severe asthma. There may be some advantage in reduced treatment time and reduced adverse systemic effects of children with pMDI/HC. For treatment of patients with moderate airway obstruction (secondary to acute asthma and COPD), the selection of aerosol device appears to be less of an issue in effecting clinical response than for patients with severe airway obstruction. In treating the most severe asthmatic (adult, child, or infant), the pMDI/HC has been demonstrated to be as effective as the nebulizer (or other available devices) in relief of airway obstruction, and appears to offer some advantage in fewer adverse effects. If the pMDI/HC works in the ED, with the sickest of patients, it should be equally effective in other settings as well. The evidence is abundant and clear: The debate on pMDI/HC versus nebulizer appears to no longer be a relevant issue.

## COMPARISON OF ALBUTEROL DELIVERED BY A METERED DOSE INHALER WITH SPACER VERSUS A NEBULIZER IN CHILDREN WITH MILD ACUTE ASTHMA.

Schuh S, Johnson DW, Stephens D, Callahan S, Winders P, Canny GJ. *J Pediatr* 1999;135:22-7.

**Objective:** In children with mild acute asthma, to compare treatment with a single dose of albuterol delivered by a metered dose inhaler (MDI) with a spacer in either a weight-adjusted high dose or a standard low-dose regimen with delivery by a nebulizer. **Study Design:** In this randomized double-blind trial set in an emergency department, 90 children between 5 and 17 years of age with a baseline forced expiratory volume in 1 second ( $FEV_1$ ) between 50% and 79% of predicted value were treated with a single dose of albuterol, either 6 to 10 puffs ( $n = 30$ ) or 2 puffs ( $n = 30$ ) with an MDI with spacer or 0.15 mg/kg with a nebulizer ( $n = 30$ ). **Results:** No significant differences were seen between treatment groups in the degree of improvement in percent predicted  $FEV_1$  ( $p=0.12$ ), clinical score, respiratory rate, or  $O_2$  saturation. However, the nebulizer group had a significantly greater change in heart rate ( $p = 0.0001$ ). Our study had 93% power to detect a mean difference in percent predicted  $FEV_1$  of 8 between the treatment groups. **Conclusion:** In children with mild acute asthma, treatment with 2 puffs of albuterol by an MDI with spacer is just as clinically beneficial as treatment with higher doses delivered by an MDI or by a nebulizer.

## EFFECTS OF SALBUTAMOL DELIVERY FROM A METERED DOSE INHALER VERSUS JET NEBULIZER ON DYNAMIC LUNG MECHANICS IN VERY PRETERM INFANTS WITH CHRONIC LUNG DISEASE.

Gappa M, Gartner M, Poets CF, von der Hardt H. *Pediatr Pulmonol* 1997;23(6):442-8.

Treatment of chronic lung disease of prematurity requires effective aerosol delivery of different therapeutic agents. Aerosols can be generated by a metered dose inhaler (MDI) or a jet nebulizer. An MDI combined with a spacer device is easier to use and avoids undesirable effects noted in conjunction with jet nebulization. We compared the clinical effectiveness of 200 micrograms (2 puffs) salbutamol delivered from an MDI in conjunction with a valved spacer device (AeroChamber®), and 600 micrograms given via jet nebulizer (PariBaby) on 2 consecutive days, the order being randomized. Thirteen spontaneously breathing very pre-term infants [mean (SD) gestational age 27.2 (1.8) weeks; birth weight 0.90 (0.34) kg] were studied at a corrected age of 37 (2.3) weeks. Mean (SD) study weight was 1.83 (0.38) kg. Dynamic lung compliance and resistance were determined from measurements of flows, volumes, and transpulmonary pressures, using a pneumotachometer and a small esophageal microtransducer catheter before and 20 min after salbutamol application. Baseline values before salbutamol administration were similar on both occasions: the mean (SD) compliance was 7.7 (3.0) mL.kPa<sup>-1</sup>.kg<sup>-1</sup> pre-MDI plus-spacer and 8.4 (3.1) pre-jet nebulizer; the resistance was 10.4 (4.0) kPa.L<sup>-1</sup>.s pre-MDI plus-spacer and 9.7 (3.4) pre-jet nebulizer. Following salbutamol, compliance did not change significantly with either MDI plus spacer or jet nebulizer. Resistance fall significantly with MDI plus spacer (mean -2.2; 99.9% CI -0.35, -4.35) and jet nebulizer (-2.4; 99% CI -0.39, -4.42). We conclude that even in small pre-term infants 200 micrograms salbutamol via MDI plus spacer improves dynamic resistance as effectively as 600 micrograms via jet nebulizer and may therefore be a preferable mode of aerosol administration.

## METERED-DOSE INHALERS WITH SPACERS VS NEBULIZERS FOR PEDIATRIC ASTHMA.

Chou KJ, Cunningham SJ, Crain EF. *Arch Pediatr Adolesc Med* 1995;149:201-5.

**Objective:** To determine whether the administration of  $\beta$ -agonists by metered-dose inhaler (MDI) with a spacer device is as effective as the administration of  $\beta$ -agonists by nebulizer for the treatment of acute asthma exacerbations in children. **Design:** Randomized trial with two arms. Setting: Urban pediatric emergency department (ED) in Bronx, NY. Patients: Convenience sample of 152 children 2 years and older with a history of at least two episodes of wheezing presenting to the ED with an acute asthma exacerbation. **Interventions:** Patients were randomly assigned to receive standard doses of an  $\beta$ -agonists (albuterol) by an MDI with spacer (AeroChamber<sup>®</sup>) or by a nebulizer. Dosing intervals and the use of other medications were determined by the treating physician. **Measurements/Main Results:** Baseline characteristics and asthma history were recorded. Asthma severity score, peak expiratory flow rate in children 5 years or older, and oxygen saturation were determined at presentation and before admission or discharge. The groups did not differ in age, sex, ethnicity, age of onset of asthma, or asthma severity score, and peak expiratory flow rate, oxygen saturation, number of treatments given, admission rate. Patients given MDIs with spacers required shorter treatment times in the ED (66 minutes vs. 103 minutes,  $p < 0.001$ ). Fewer patients in the spacer group had episodes of vomiting in the ED (9% vs. 20%,  $p < 0.04$ ), and patients in the nebulizer group had a significantly greater mean percent increase in heart rate from baseline to final disposition (15% vs. 5%,  $p < 0.001$ ). **Conclusions:** These data suggest that MDIs with spacers may be an effective alternative to nebulizers for the treatment of children with acute asthma exacerbations in the ED.

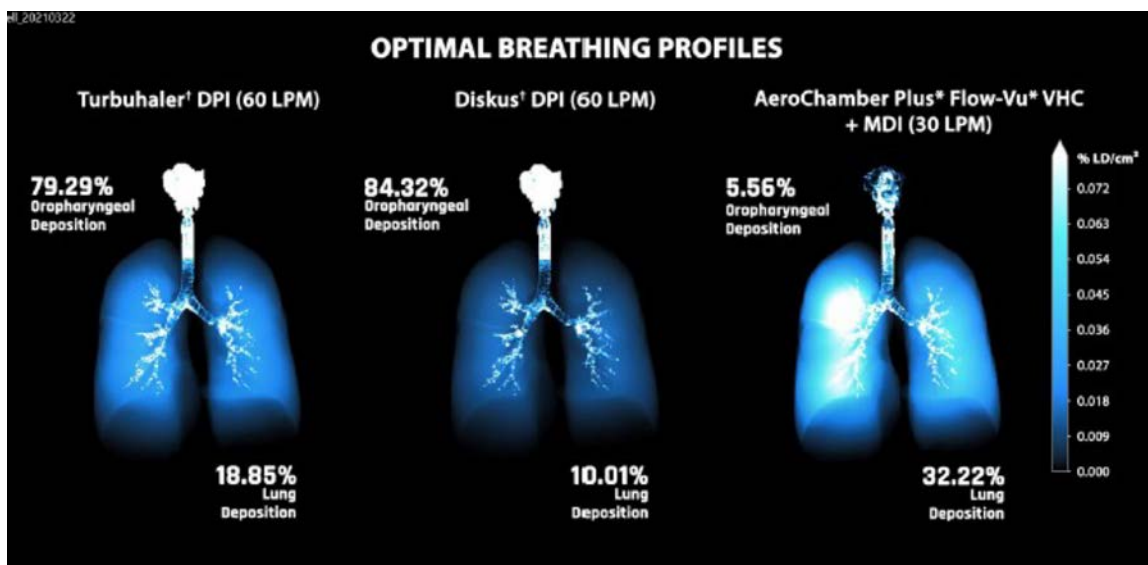
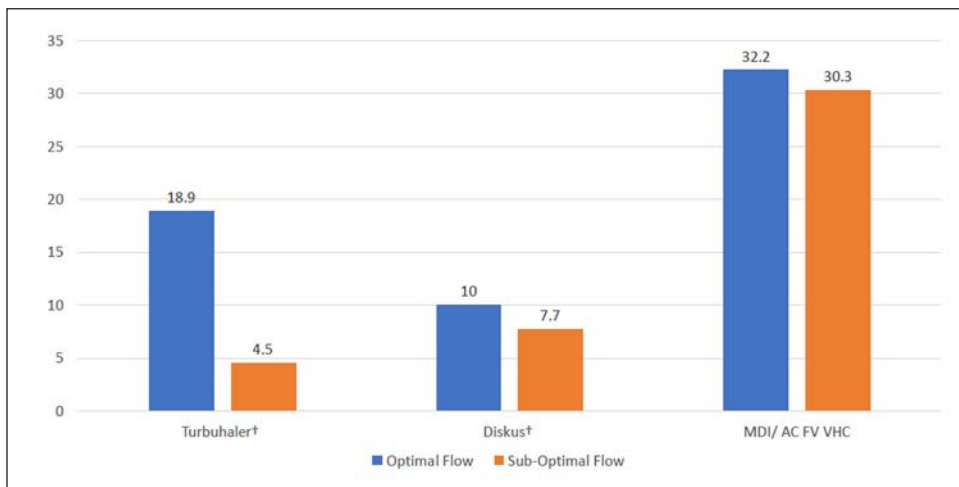
# Metered Dose Inhalers and Valved Holding Chambers vs Dry Powder Inhalers

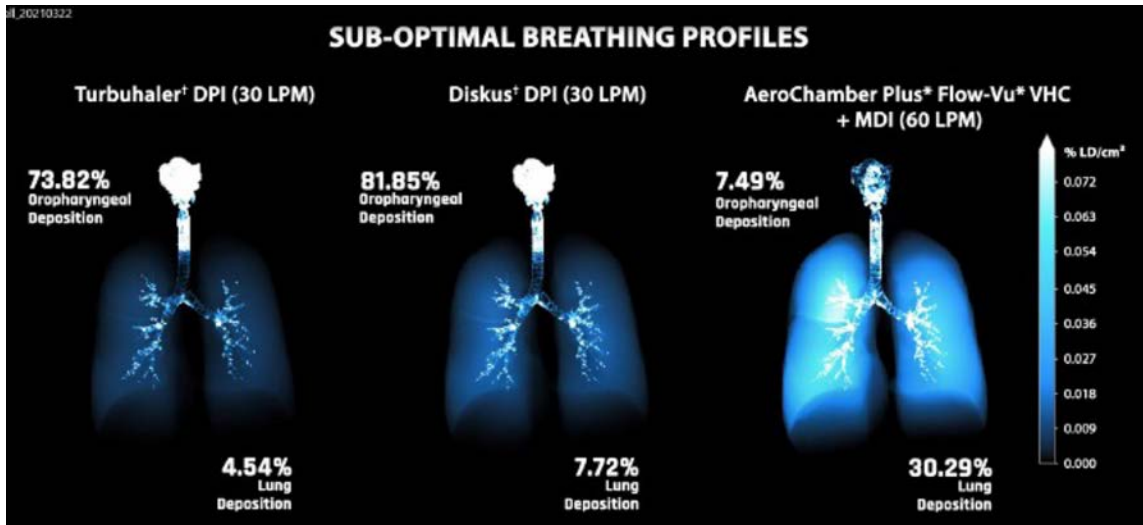
## METERED DOSE INHALER (MDI) WITH VALVED HOLDING CHAMBER (VHC) VS DRY POWDER INHALERS (DPIs): USING FUNCTIONAL RESPIRATORY IMAGING (FRI) TO ASSESS MODELLED LUNG DEPOSITION IN AN ASTHMATIC PATIENT.

Jason Suggett, V. Kushnarev, C. Van Holsbeke, S. Van Steen, B. Mignot; *Science and Technology, Am J Respir Crit Care Med* 2022;203:A4673.

**Rationale:** Both MDIs and DPIs can be used to deliver drugs to manage Asthma. VHCs can be used to help patients with inhalation coordination of their MDIs. Inspiratory flow rate is known to influence drug delivery. This FRI based study assessed the modelled airway drug delivery from an MDI/VHC system and two DPI systems at optimal and sub optimal flow rates. **Methods:** Three dimensional geometries of airways and lobes were extracted from a CT scan of a 21 year old male Asthma (moderate) patient. Drug delivery and airway deposition of MDI/VHC delivered albuterol (Ventolin® HFA) was modelled using FRI with measured particle and plume characteristics via an AeroChamber Plus® Flow-Vu® VHC. Symbicort® (budesonide/formoterol) Turbuhaler® and Seretide® (fluticasone/salmeterol) Diskus® DPIs were similarly modelled. Inhalation flow rates of 30 L/min (optimum for MDI/VHC, sub optimal for DPIs) and 60 L/min (optimum for DPIs, sub optimal for MDI/VHC) were assessed. **Results:** The modelled lung deposition results are shown in the chart, expressed as a percentage of label dose, using both optimal and sub-optimal inhalation flow rates. **Conclusions:** The FRI deposition profiles highlight that the MDI/AeroChamber Plus® Flow-Vu® VHC system delivered an appreciably greater percentage of drug to the lung region than either of the two DPIs. The influence of inhalation flow profile was less with the MDI/VHC system and differed between the two DPIs.

Percentage of Label Dose Delivered to Lungs





**EFFECT OF INHALATION PATTERNS ON THE DELIVERED DOSE OF SYMBICORT<sup>†</sup> FROM A DRY POWDER INHALER COMPARED TO A METERED DOSE INHALER PLUS VALVED HOLDING CHAMBER.**

M. Nagel, R. Ali, J. Suggett, C. Doyle; *Am J Respir Crit Care Med* 2020;201:A4763.

**Rationale:** The latest guidelines from the Global Initiative for Asthma (GINA) no longer recommends SABA-only treatment for Step 1 therapy. This is based on evidence that a SABA-only treatment increases the risk of severe exacerbations, and that adding any Inhaled Corticosteroid (ICS) significantly reduces that risk. Options for ICS delivery can be via Dry Powder Inhaler (DPI) or Metered Dose Inhaler (MDI), however, if delivering an ICS via MDI, a spacer should also be prescribed. This study evaluated the impact of inhalation maneuvers on medication delivery from either DPI or MDI Symbicort<sup>†</sup> 80/4.5 (80 µg budesonide / 4.5 µg formoterol furoate) with a spacer (AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> VHC). **Methods:** Inhalation waveforms were recorded from 5 DPI and MDI+VHC subjects and replayed via a breathing simulator attached to the adult Aerosol Delivery to an Anatomic Model (ADAM) oropharyngeal airway which was used to provide a clinically relevant laboratory determination of medication delivery of Symbicort<sup>†</sup>. DPI subjects inhaled as per their usual treatment regimen whereas VHC subjects were instructed to inhale via either i) slow deep inhalation or ii) following 2-3 inhalations as per VHC instructions. Following delivery of medication, all components of the apparatus were assayed for Active Pharmaceutical Ingredients (API) via HPLC-spectrophotometry.

**Results:**

Product	API	Delivered Dose µg (actuation)	
		Oropharyngeal Airway	Carina
Symbicort DPI	Budesonide	21.1±8.1	20.2±7.9
	FF	1.0±0.4	1.0±0.4
Symbicort MDI + VHC Deep Inhalation	Budesonide	7.1±3.9	35.9±4.0
	FF	0.3±0.2	2.1±0.2
Symbicort MDI + VHC Tidal Breathing	Budesonide	9.7±9.6	32.0±6.8
	FF	0.4±0.4	1.9±0.4

**Conclusion:** The widely differing inspiratory flow profiles from Turbuhaler<sup>†</sup> DPI contributed to greater variability in delivered dose to the carina. MDI delivery via the AeroChamber Plus<sup>®</sup> Flow-Vu<sup>®</sup> VHC resulted in significantly increased mass to the carinal region irrespective of inhalation maneuver as well as reduced oropharyngeal deposited mass which in vivo is likely to result in reduced throat irritation or thrush in the mouth and throat.

## COST EFFECTIVENESS COMPARISON OF A DRY POWDER INHALER TO A METERED DOSE INHALER PLUS VALVED HOLDING CHAMBER BASED ON AN IN-VITRO DRUG DELIVERY MODEL.

Nagel M, Suggett J, Ellery A. Accepted to the European Respiratory Society Conference 2020.

**Background:** In a previous study, healthy participants were asked to inhale from either a dry powder inhaler (DPI) or metered dose inhaler (MDI) + valved holding chamber (VHC). Results indicated that differing amounts of medication could be available to the lungs, depending on the delivery system used. **Objective:** To compare the relative cost of using a DPI and an MDI+VHC to deliver budesonide/formoterol (BUD/F; Symbicort®) in patients for whom low-dose ICS maintenance therapy is appropriate. **Methods:** Comparisons were based on BUD/F 200/6µg twice daily with yearly cost inputs of £336 for the DPI and £336+5.2 for the MDI + VHC obtained from a relevant source in the United Kingdom ([www.rightbreathe.com](http://www.rightbreathe.com)). Drug delivery data was taken from the aforementioned lab study. **Results:** The mass (µg) of FF and BUD delivered per £ are reported in the table.

Product	API	ug/£
Symbicort DPI	Budesonide	86.6
	FF	4.3
Symbicort MDI VHC Deep Inhalation	Budesonide	151.5
	FF	8.9

**Conclusion:** From a UK perspective, BUD/F delivered via an MDI + VHC offers an economic benefit for the treatment of patients with mild asthma. Further analysis is required to determine if there would be any quality-adjusted life-year (QALY) effects based on the chosen intervention.

## USE OF INSPIRATORY PROFILES FROM PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) TO INVESTIGATE DRUG DELIVERY FROM A PASSIVE DRY POWDER INHALER (DPI) COMPARED WITH A PRESSURIZED METERED DOSE INHALER WITH VALVED HOLDING CHAMBER (pMDI+VHC) – AN EXPERIMENTAL INVESTIGATION.

Nagel MW, Suggett J, Ali R, Doyle C, Mitchell JP. Respiratory Drug Delivery to the Lungs April 2020.

**Introduction:** COPD is a chronic and progressive disease that requires regular self-administration of inhaled medications. However, as the disease progresses, reduced respiratory muscle strength may prevent patients from generating sufficient inspiratory effort to effectively use dry-powder inhalers (DPIs) [1, 2]. In contrast, patients can inhale slowly or breathe tidally from a pMDI with VHC without the need to coordinate with inhaler actuation [3]. We compared the dose delivery characteristics using recorded inspiratory flow profiles generated by patients with varying severity of COPD. The participants were recorded when using a medium inspiratory flow resistance DPI compared with inhalation of the same active pharmaceutical ingredients (APIs) inhaled via a pMDI + VHC. **Materials and Methods:** A cohort of volunteer male patients ( $n = 10$ ) with varying COPD severity (aged 57–83) were asked to inhale from placebo versions of their prescribed medication. During patient visits, signed informed consent were obtained and their inhalation profiles recorded (SmartLab\* series 1140, Hans Rudolph Inc), using a purpose-constructed attachment to a pneumotachometer (SpiroQuant H flow sensor) [4]. Patients inhaled via either DPI ( $n= 5$ , designated A-E, Symbicort\* Turbuhaler, 100 mg budesonide (BUD) + 6 mg formoterol fumarate (FF) per actuation) or pMDI ( $n= 5$ , designated F-J) Vannair\* 80 mg BUD + 4.5 mg FF) with an antistatic adult AeroChamber Plus® Flow-Vu® (aAC-Plus) VHC (Trudell Medical). The inhalation profiles were subsequently recreated via a breathing simulator (ASL 5000, Ingmar Medical), coupled to the mouthpiece of the appropriate inhaler (DPI or pMDI + VHC) via the adult Aerosol Delivery to Anatomic Model (ADAM) [5]. The breathing simulator was located distal to a microbial collection filter, positioned at the exit of the oropharynx, to capture medication likely to have deposited at the carinal region and therefore potentially available for delivery to the lungs. **Results:** The mass of FF and BUD recovered from the model oropharynx (O-P) and filter (CARINA) from each simulation ( $n = 3$  replicate measurements), are summarized for the DPI (Figures 1A and 2A) and pMDI + VHC (Figures 1B and 2B) modalities. Example breathing profiles from DPI and MDI + VHC modalities are shown in Figure 3. **Discussion:** Reproducibility of the individual patient measurements made with either inhaler modality were within the expectations for the inhalers themselves as is apparent from Figures 1 and 2 [not shown here]. Less oropharyngeal deposition was also generally exhibited using the pMDI + VHC. It was notable that the corresponding mass of APIs recovered from the CARINA region when the pMDI + VHC modality was simulated, were generally and significantly greater than the outcomes obtained by simulating the DPI profiles ( $p \leq 0.03$ ). However, there were two inhalation profiles (Patients E - DPI and J - pMDI +

VHC) that contradict these observations. This might be expected, given the varying degrees of inhalation behavior reported from clinical studies. [6, 7]. Patient E (DPI) generated sufficient flow and volume that enabled similar quantities of API to be delivered to the filter/carina as found with most of the pMDI + VHC measurements. Patient J (pMDI + VHC) demonstrated an inhalation pattern with very high flow rates and reduced inhalation times which in turn resulted in increased deposition in the oropharynx and, consequently, reduced deposition at the filter/carina. These findings support the value of generating *in vitro* data of the kind presented from patient-derived, rather than standardized inhalation profiles that cannot by their nature provide insight into the real variability introduced by the patient-inhaler interaction process. **Conclusions:** These data provide support that the pMDI + VHC option can deliver more medication than the particular DPI evaluated to the carinal region and therefore, potentially available for lung delivery. These data also demonstrate a need for continued patient inhaler counseling and assessment to ensure that, as the patient's disease progresses, they are capable of generating the necessary inspiratory effort needed for sufficient drug delivery. This assessment is required not only in terms of peak inspiratory flow rate but also to ensure that their inspiratory volume is enough to empty the DPI dose. For those patients who can have difficulty performing the necessary maneuvers or cannot fully empty the DPI reservoir, the pMDI + VHC delivery should be considered. A larger investigation is required to confirm these results, however, if disease severity can be linked to delivered mass, then the implications are similar to those of Farkas in that severe COPD patients using DPIs are likely to receive a significantly lower lung dose [8]. Other DPI devices and disease states should also be evaluated to add more weight to these findings.

#### **ASSESSMENT OF NAÏVE INHALER USER INHALATION PROFILES AND THE IMPACT ON SUBSEQUENT AEROSOL PERFORMANCE : COMPARISON OF A DRY POWDER INHALER (DPI) AND A PRESSURIZED METERED DOSE INHALER (PMDI) WITH VALVED HOLDING CHAMBER (VHC) USING THE SAME ACTIVE PHARMACEUTICAL INGREDIENTS (APIS).**

*Suggett J, Nagel M, Mitchell J. Drug Delivery to the Lungs, Volume 30, 2019.*

The present scoping study was designed to determine the potential impact of variable inhalation technique on fine particle mass (FPM) emitted from the widely prescribed Diskus\* passive DPI (GSK) compared with inhalation of the same active pharmaceutical ingredients (APIs) via a pMDI with antistatic adult AeroChamber Plus® Flow-Vu® VHC either tidally breathing or taking a slow inhalation followed by a breath-hold. Inspiratory flow rate-elapsed time profiles were initially acquired with three volunteer adult participants, trained in the use of both inhalers, using a pneumotachometer with its own mouthpiece attached to the mouthpiece of the inhaler, which was rendered incapable of delivering medication. Subsequently, each inhalation waveform was re-played via an ASL5000 breathing simulator in order to actuate either an Advair\* Diskus\* DPI (250 µg/actuation fluticasone propionate (FP) + 50 µg/actuation salmeterol xinafoate (SX)) or an Advair\* Evohaler\* pMDI (250 µg/actuation FP + 25 µg/actuation SX with VHC). In each case, the emitted aerosol was sampled via a Next Generation Impactor (NGI) operated at either 60 L/min, or at 30 L/min alone for pMDI + VHC evaluations. Variation in breathing profile parameters was observed in both delivery platforms, however, FPM < 5.0 µm for either API delivered by pMDI with VHC was higher and more consistent across all breathing patterns from the three volunteers.

#### **COMPARISON OF THE CLINICAL EFFECTS OF COMBINED SALMETEROL/FLUTICASONE DELIVERED BY DRY POWDER OR PRESSURIZED METERED DOSE INHALER.**

*Hojo M, Shirai T, Hirashima J, Iikura M, Sugiyama H. Pulmonary Pharmacology & Therapeutics 2016; 37, 43-48.*

The salmeterol/fluticasone combination (SFC) inhaler is currently the most widely used maintenance drug for asthmatics worldwide. Although the effectiveness of SFC as either a dry powder inhaler (DPI) or a pressurized metered dose inhaler (pMDI) is well documented, there is limited data comparing the clinical efficacies of the two devices. To address this issue, we carried out a randomized crossover trial in which asthmatic patients ( $n = 47$ ; mean age,  $62.5 \pm 16.5$  years old) received a 12-week treatment of SFC DPI (50/250 µg twice daily) or SFC pMDI (four puffs of 25/125 µg daily). After a 4-week washout period, patients received another crossover treatment for 12 weeks. Respiratory resistance and reactance were measured by forced oscillation technique (MostGraph-01), spirometry, fractional exhaled nitric oxide (FeNO), and an asthma control test (ACT) every 4 weeks. The mean forced expiratory volume 1.0 at the baseline was  $2.16 \pm 0.86$  (L). Respiratory system resistance at 5 Hz (R5), the difference between R5 and R at 20 Hz (R5 - R20), and FeNO improved in both treatment groups, while reactance at 5 Hz (X5) and ACT

score improved only in the pMDI group. In patients > 70 years old ( $n = 21$ ), R5, R5 - R20,  $\Delta X_5$ , and FeNO improved only in the pMDI group. These results suggest that SFC by pMDI (with AeroChamber Plus\* Anti-Static VHC) produces a stronger anti-inflammatory and bronchodilatory effect even in patients whose asthma is well controlled by SFC delivered by DPI.

#### **EVALUATION OF INHALER TECHNIQUE, ADHERENCE TO THERAPY AND THEIR EFFECT ON DISEASE CONTROL AMONG CHILDREN WITH ASTHMA USING METERED DOSE OR DRY POWDER INHALERS.**

*Capanoglu M, Misirlioglu ED, Toyran M, Kocabas CN. Journal of Asthma 52(8) June 2015.*

To address the problems about correct use of inhaler devices, adherence to inhaler corticosteroid treatment and the effects of these problems on the control of asthma. Children with asthma were evaluated for the correct use of inhaler devices and adherence to therapy using a questionnaire. Effect of these on control of asthma was defined. A hundred and seventy-one patients and/or their families were interviewed. The mean age was  $8.29 \pm 4.65$  years (1-19) and 62.6% were male. Metered dose inhaler (MDI) with spacer was used by 119 (69.5%) patients and 52 (30.5%) used dry powder inhalers (DPIs). The devices were used correctly by 68.1% of patients using MDI and 34.6% of patients using DPI ( $p < 0.001$ ). The most common improper step was "breathe in from the spacer 5-6 times or 10 s" for MDI (24.4%) and "exhale to residual volume" for DPI (51.9%). Frequency of correct use was higher in patients trained 3 times ( $p < 0.001$ ). Asthma was controlled more frequently among correct users ( $p < 0.001$ ). Partial or poor adherence was showed 22.8% of patients. Patients with mothers who had lower educational status had higher frequency of incorrect use of inhaler device ( $p = 0.007$ ). It was found that asthma control was better among correct users. Repetitive training about using devices may contribute improving inhaler technique. Especially children whose mothers had low education level and patients using DPI should be evaluated more carefully.

#### **PHARMACODYNAMIC AND PHARMACOKINETIC COMPARISONS AFTER ADVAIR DISKUS AND ADVAIR HFA ADMINISTRATION IN PEDIATRIC SUBJECTS.**

*Qaqundah P, Kerwin E, Mehta R, Saggu P, Vanderslice T, Cahn A, Hsu Y, Kunka R. American Thoracic Society Meeting, Toronto, ON, 2008.*

Thirty-one pediatric subjects (4-11 years) with asthma participated in an open-label, repeat dose, crossover study to compare serial concentrations of serum cortisol, fluticasone propionate (FP) and salmeterol (SAL) after three weeks of administration of Advair Diskus®, Advair® HFA, or Advair® HFA with the valved holding chamber (spacer), AeroChamber Plus\*. Following a baseline assessment of serum cortisol and SAL pharmacodynamic parameters, 28 subjects completed the study with each subject receiving two of the three treatments using a randomized incomplete block design. FP systemic exposure was low after all treatments resulting in geometric mean (95% CI) C<sub>max</sub> of 54pg/mL (33,89) for Advair Diskus, 16pg/mL (8, 29) for Advair HFA and 35pg/mL (20, 60) for Advair HFA with spacer.

#### **COMPARISON OF THE EFFICACY AND SAFETY OF CICLESONIDE 160 MICROG ONCE DAILY VS. BUDESONIDE 400 MICROG ONCE DAILY IN CHILDREN WITH ASTHMA.**

*Von Berg A, Engelstätter R, Minic P, Sréckovic M, Garcia ML, Latoš T, Vermeulen JH, Leichtl S, Hellbardt S, Bethke TD. Pediatr Allergy Immunol 2007 Aug;18(5):391-400.*

Ciclesonide is an onsite-activated inhaled corticosteroid (ICS) for the treatment of asthma. This study compared the efficacy, safety and effect on quality of life (QOL) of ciclesonide 160 microg (ex-actuator; nominal dose 200 microg) vs. budesonide 400 microg (nominal dose) in children with asthma. Six hundred and twenty-one children (aged 6-11 yr) with asthma were randomized to receive ciclesonide 160 microg (ex-actuator) once daily (via hydrofluoroalkane metered-dose inhaler and AeroChamber Plus\* spacer) or budesonide 400 microg once daily (via Turbohaler® both given in the evening for 12 wk. The primary efficacy end-point was change in forced expiratory volume in 1 s (FEV<sub>1</sub>). Additional measurements included change in daily peak expiratory flow (PEF), change in asthma symptom score sum, change in use of rescue medication, paediatric and caregiver asthma QOL questionnaire [PAQLQ(S) and PACQLQ, respectively] scores, change in body height assessed by stadiometry, change in 24-h urinary cortisol adjusted for creatinine and adverse events. Both ciclesonide and budesonide increased FEV<sub>1</sub>, morning PEF and PAQLQ(S) and PACQLQ scores, and improved asthma symptom score sums and the need for rescue medication after 12 wk vs. baseline. The non-inferiority of ciclesonide vs. budesonide was demonstrated for the change in FEV<sub>1</sub> (95% confidence interval: -75, 10 ml,  $p = 0.0009$ , one-sided non-inferiority, per-protocol). In addition, ciclesonide

and budesonide showed similar efficacy in improving asthma symptoms, morning PEF, use of rescue medication and QOL. Ciclesonide was superior to budesonide with regard to increases in body height ( $p = 0.003$ , two-sided). The effect on the hypothalamic-pituitary-adrenal axis was significantly different in favor of ciclesonide treatment ( $p < 0.001$ , one-sided). Both ciclesonide and budesonide were well tolerated. Ciclesonide 160 microg once daily and budesonide 400 microg once daily were effective in children with asthma. In addition, in children treated with ciclesonide there was significantly less reduction in body height and suppression of 24-h urinary cortisol excretion compared with children treated with budesonide after 12 wk.

#### **COMPARISON OF EFFICACY AND SAFETY BETWEEN FLUNISOLIDE/AEROCHAMBER AND BUDESONIDE/TURBUHALER IN PATIENTS WITH MODERATE ASTHMA.**

*Newhouse M, Knight A, Wang S, Newman K. Annals of allergy, asthma & immunology. 84(3):313-319, Feb 2000.*

There is a limited body of evidence comparing the clinical effects of different inhaled corticosteroids in the treatment of asthma. This study compared the safety and efficacy of inhaled flunisolide and budesonide, both with unique delivery systems that may affect clinical response. This multicenter study was carried out to compare the efficacy and safety of flunisolide, administered via AeroChamber, with budesonide, administered via Turbuhaler, in the treatment of moderate asthma. Patients with moderate asthma, defined as an FEV<sub>1</sub> of 40% to 85% of predicted, underwent a 2-week run-in period during which beclomethasone, 750 µg twice daily by MDI, was administered, along with salbutamol prn. Patients ( $n = 176$ ) were then randomized into two groups. One group received flunisolide administered via AeroChamber, 750 µg (3 puffs), twice daily. The second group received budesonide administered via Turbuhaler, 600 µg (3 puffs), twice daily. All patients took salbutamol prn. At the end of the 6-week treatment period, there were no significant differences ( $p > 0.05$  for all comparisons) in efficacy between the groups as evaluated by any efficacy parameter. The treatment groups also did not differ significantly in the number of adverse events or in the incidence of oropharyngeal Candida infection. Flunisolide administered by AeroChamber and budesonide administered via Turbuhaler demonstrate similar efficacy and safety in the treatment of moderate asthma.