

Equivalence Evaluation of Valved Holding Chambers with Albuterol Pressurized Metered Dose Inhaler

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INTRODUCTION

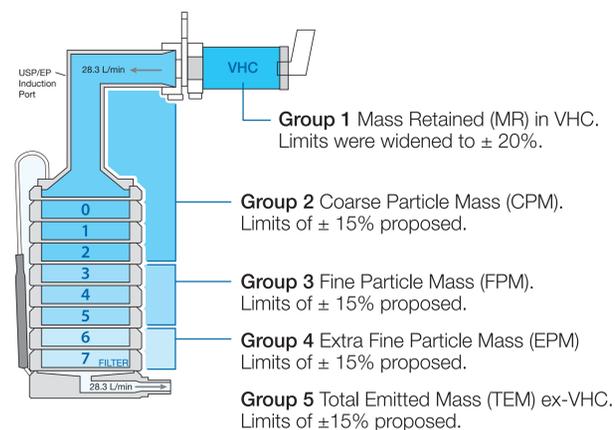
- Valved Holding Chambers (VHCs) are recommended by International Asthma and COPD guidelines^{1,2} to be used with pressurized metered dose inhalers (pMDI) as a delivery system. VHCs are designed to improve medication delivery, reduce oropharyngeal deposition of medication by substantially changing the aerodynamic particle size distribution (APSD). This may influence the therapeutically beneficial fine particles mass (< ca. 5 µm aerodynamic diameter) that reaches the airways of the lungs.³
- 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 1 named VHC.⁴ 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, i.e. delay between pMDI actuation and sampling.

Statistical Approach to Demonstrate VHC Equivalence

- A simple and widely used approach to test for statistical equivalence is the two one-sided test (TOST).⁵ A traditional t-test is inappropriate in this instance because it tests a hypothesis of difference/no difference rather than a hypothesis of equivalence/non-equivalence. Confirmation that two products are not significantly different does not necessarily mean that they are equivalent.
- Unlike the traditional t-test, TOST appropriately penalizes poor precision and/or small n-values and places the burden on the analyst to prove that the data sets are equivalent.⁶ Additionally, the use of subjective terms such as “comparable” or “similar” are sometimes used in relation to equivalence, which are unfounded from a scientific or statistical perspective.
- The EMA guideline⁴ proposed acceptance criteria are that the 90% confidence intervals of the observed differences between TEST and REFERENCE mean values must fall within the specified maximum allowable limits. The EMA states that, for example, limits of ± 15% may be justifiable.

Anderson Cascade Impactor Stage Groupings and Limits Justification

- The EMA Guideline⁴ requires the comparison to be performed by justified groupings of stages and recommends at least 4 groups based upon within-group similarity of regional deposition pattern (e.g., mouth/throat area, upper and lower parts of the lung).



MATERIALS AND METHODS

- The following VHCs, each with mouthpiece as patient interface (n=20 devices/group) were evaluated:

Reference VHC

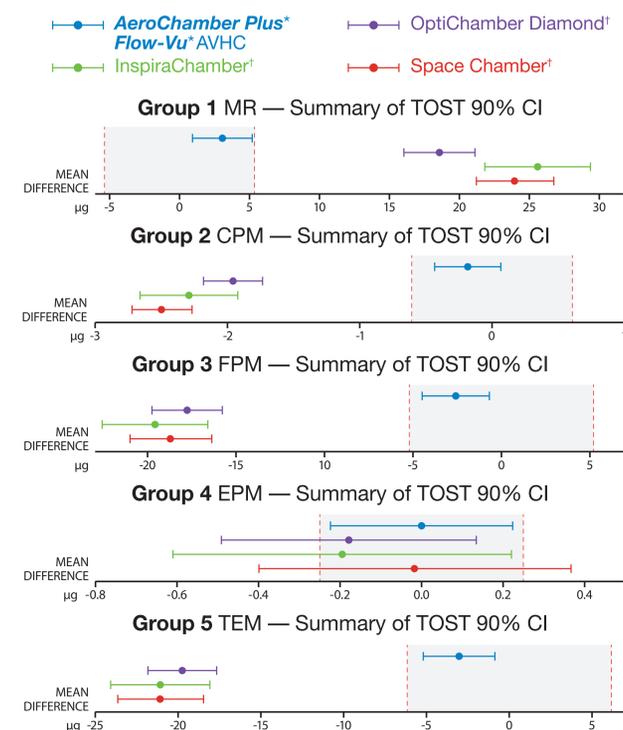


Test VHCs



- Pre-treatment for test VHC: Soaked device in lukewarm water/liquid detergent solution as per manufacturer instructions.
- Pre-treatment for all test VHCs not required; tested out-of-package as per manufacturer instructions.
- A randomized testing matrix for all VHCs (n=100 in total) was created to determine the testing order and each VHC paired with a randomly chosen pMDI (Ventolin¹-HFA, single Lot) and each canister primed before use in accordance with patient instructions.
- For each test, 5 actuations of medication were delivered to the VHC on test and APSD measurements made by Andersen 8-stage cascade impactor with a 2-s delay interval between actuation and sampling.
- Statistical equivalence was determined using a two-one sided test (TOST) approach and a 90% confidence interval and Minitab® 17.1.0 (Minitab, State College PA, USA) software was employed for statistical analysis

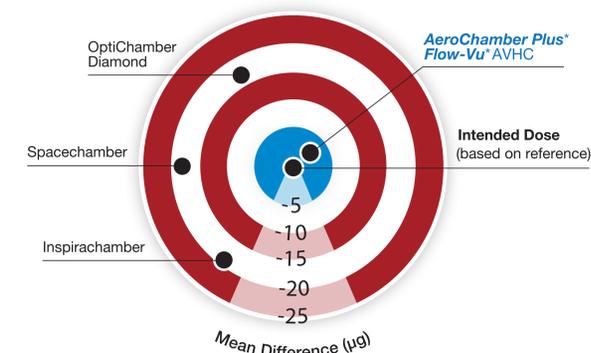
RESULTS



CONCLUSIONS

- The interchanging of VHCs has both safety and efficacy implications unless otherwise proven as equivalent through *in vitro* and/or *in vivo* data.⁷
- 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** VHC as the REFERENCE VHC, results showed that only one TEST VHC, the **AeroChamber Plus Flow-Vu** AVHC, was statistically equivalent to it.
- All other test VHCs did not meet the acceptance criteria for equivalence 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.
- This study highlights 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.

Mean Difference in Fine Particle Mass (1.1 µm - 4.7 µm)



REFERENCES

- Global Initiative for Asthma (GINA): Global strategy for asthma management and prevention. Available at: <http://www.ginasthma.org>. Accessed December 22, 2016.
- Global Strategy for the Diagnosis, Management and Prevention of COPD: Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available at: <http://goldcopd.org>. Accessed December 22, 2016.
- Mitchell J, Dolovich MB: Clinically relevant test methods to establish in vitro equivalence for spacers and valved holding chambers used with pressurized metered dose inhalers (pMDIs). *J Aerosol Med Pulm Drug Deliv* 2012; 25(4): 217-42.
- European Medicines Agency (EMA): Guidelines on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents. London, UK: 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/08/WC500003054.pdf. Accessed December 6, 2016.
- Walker E, Nowacki AS: Understanding equivalence and noninferiority testing. *J Gen Int Med* 2011; 26(2): 192-96.
- Liberant GB, Ringo MC, Ye F, Benquitt ML, McCloskey ED: Beyond the t-test: Statistical equivalence testing. *Anal Chem* 2005; 77(1): 251-56.
- Disseaux S: Application of the EU guidelines for pharmacokinetic studies of locally acting orally inhaled drug products. In *Respiratory Drug Delivery* 2010. Volume 1. Edited by Dabry FN, Byron PR, Peart J, Suman JD, Farr SJ, Young PM. DPH Publishing: River Grove, IL; 2010: 293-304.

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