Equivalence Evaluation of Valved Holding Chambers (VHCs) with Albuterol Pressurized Metered Dose Inhaler (pMDI)

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INTRODUCTION

Valved holding chambers (VHCs) are medical devices that are recommended by International Asthma and Chronic Obstructive Pulmonary Disease (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) of the inhaled aerosol, and help patients to overcome difficulties in the coordination between actuation of a pMDI and inhalation. 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 one 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 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.

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 guideline [4] 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. EMA states that for example limits of ± 15% may be justifiable.

ACI STAGE GROUPINGS AND LIMITS JUSTIFICATION FOR THIS EVALUATION

Comparisons between two orally inhaled producs are commonly made using inertial impaction methods (Andersen cascade impactor (ACI) or the next generation pharmaceutical impactor (NGI)). The EMA Guideline [4] 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).

Group 1 (Mass retained in VHC, MR)

Although not part of the ACI, the VHC reduces the amount of coarse particle mass that would otherwise be delivered to the upper airway as compared to a situation where the inhaler has been used alone without a VHC present. Therefore, this grouping has relevance to the potential efficacy and safety of the medicinal product *in vivo*. The EMA guideline [4] requests that the maximum allowable *in vitro* difference should be indicated and justified. Due to the potential difficulty in reproducibly recovering active pharmaceutical ingredient (API) from the various surfaces of the VHC, and the fact that it would not relate to patient delivered drug, limits were widened to ± 20%.

Group 2 (CPM)

Mass of API retained by the induction port and on stages 0 to 2 (coarse particle mass >4.7μm). Use of a VHC results in the near elimination of the coarse component of the dose emitted from the pMDI, however this group is an important attribute where there is concern about local and systemic safety effects arising from throat deposition of some formulations. Limits of ± 15% proposed.

Group 3 (FPM)

Mass of API collected on stages 3 to 5 – equivalent to the fine particle mass (1.1-4.7 μm) and therefore, likely to be physiologically beneficial. Limits of ± 15% proposed.

Group 4 (EPM)

Mass of API collected on stages 6 and 7 and the filter – equivalent to the extra-fine particle mass. Equating to mass <1.1 μm. Particles of this size are more likely to be exhaled than deposited during inhalation. Limits of ± 15% proposed.

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);

In the case of the REFERENCE VHC, preparation involved soaking the device for 15 minutes in lukewarm water with liquid detergent, followed by gentle agitation, removal from the wash and drip-drying in air as per manufacturer's instruction. In contrast, each of the four anti-static (TEST) VHCs were tested after removal from their package, as these devices do not require pre-treatment to eliminate surface electrostatic charges.

Before beginning the study, 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. A relatively common albuterol formulation (Ventolin®-HFA, single Lot) was chosen for this study and each canister primed before use in accordance with patient instructions. Measurements of APSD were made by ACI operated at 28.3 L/min ± 5% and the delay interval between actuation and sampling was set to 2 seconds.

For each test, five actuations of medication were delivered. Assays for albuterol recovered from all portions of the ACI and delivery system were undertaken by high performance liquic chromotography. Statistical equivalence was determined using a TOST approach and a 90% confidence interval and Minitab® 17.1.0 (Minitab, State College, PA) software was employed for statistical analysis.

RESULTS

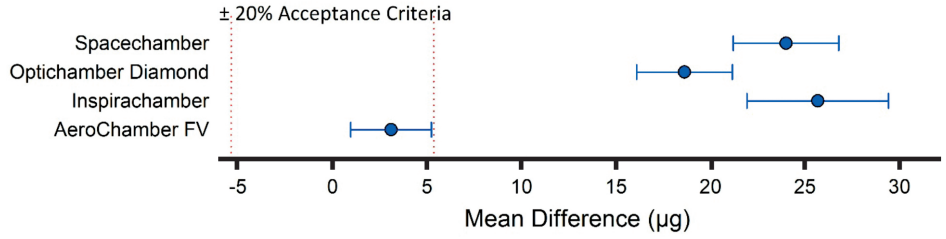

Figure 1. **Group 1, mass retained by VHC (MR): Mean difference (4 TESTs vs. REFERENCE) with 90% CIs.**

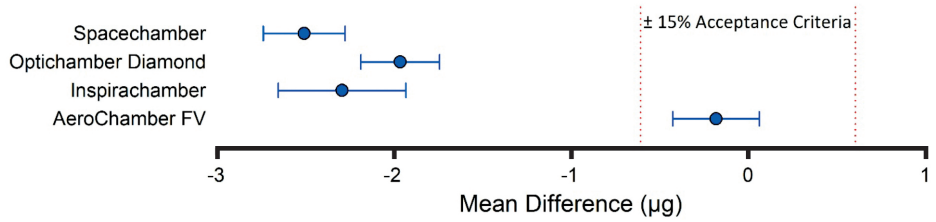

Figure 2. **Group 2, mass API on IP – stage 2 (>4.7 µm) (CPM): Mean difference (4 TESTs vs. REFERENCE) with 90% CIs.**

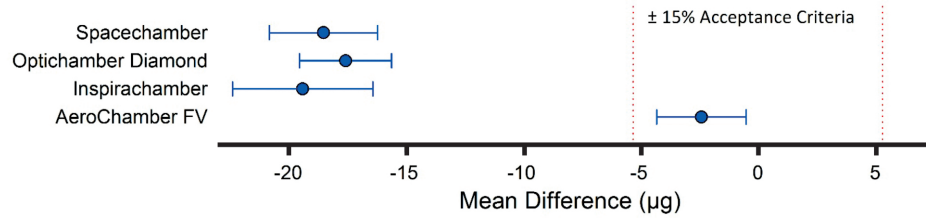

Figure 3. **Group 3, mass API on stages 3-5 (1.1 µm-4.7 µm) (FPM): Mean difference (4 TESTs vs. REFERENCE) with 90% CIs.**

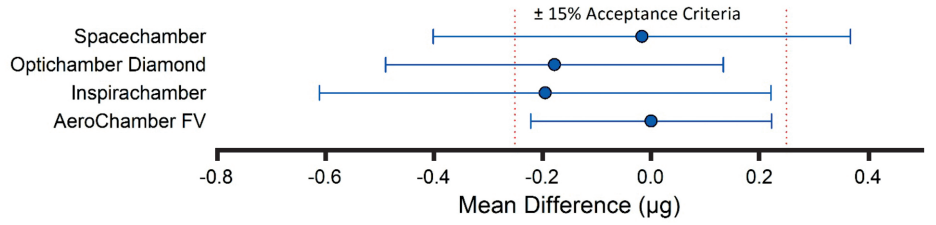

Figure 4. **Group 4, mass API on stages 6 and 7 and filter (<1.1 µm) (EPM): Mean difference (4 TESTs vs. REFERENCE) with 90% CIs.**

DISCUSSION AND CONCLUSIONS

Since the union of a particular pMDI and given VHC is considered a specific delivery system, during the pMDI development and registration process, supporting data is generated using a chosen VHC. 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 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.

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