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Are valved holding chambers (VHCs) interchangeable? An in vitro evaluation of VHC equivalence

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ABSTRACT

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 + FV]; Compact Space Chamber Plus [CSC+]; InspiraChamber [IC]; OptiChamber Diamond™ [OCD]) were tested "out-of-packet". 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.

1. Introduction

Valved holding chambers (VHCs) used in conjunction with pressurised metered dose inhalers (pMDIs) allow deceleration and capture of the aerosol plume and largely obviate the need for coordination of actuation and inhalation [1]. The use of VHCs may therefore increase pulmonary drug deposition compared to pMDIs used alone [2–4], especially in patients who experience difficulty in coordinating pMDIs [5], and has, as a result, been associated with improved clinical outcomes including reduced airways hyperresponsiveness [6], improved lung function [7–10] and asthma control [11], and a reduction in the requirement for oral corticosteroids [12]. In view of the above, virtually all national and international clinical management guidelines for obstructive lung disease advocate the use of spacers/VHCs in patient subgroups prone to pMDI handling errors [13–21].

Whilst the potential benefits of VHCs are clear, it is also evident that performance differences exist between VHCs. Thus, chamber shape [22], volume [23,24] and length [25], the use of charge-dissipative versus non-conducting materials [25–27], inhalation valve function [28], and facemask design [29,30] have all been variously implicated in performance differences between different spacers/VHCs. In view of the substantial body of literature attesting to such differences, European Medicines Agency (EMA) guidelines on inhaled product development explicitly require that data for pMDIs should be generated with a '*specific named spacer*' [31,32]: implying that different VHCs should not automatically be considered to be interchangeable. Guidance on the requisite data to establish the interchangeability of VHCs is available from the EMA's Orally Inhaled Product (OIP) guideline. The latter

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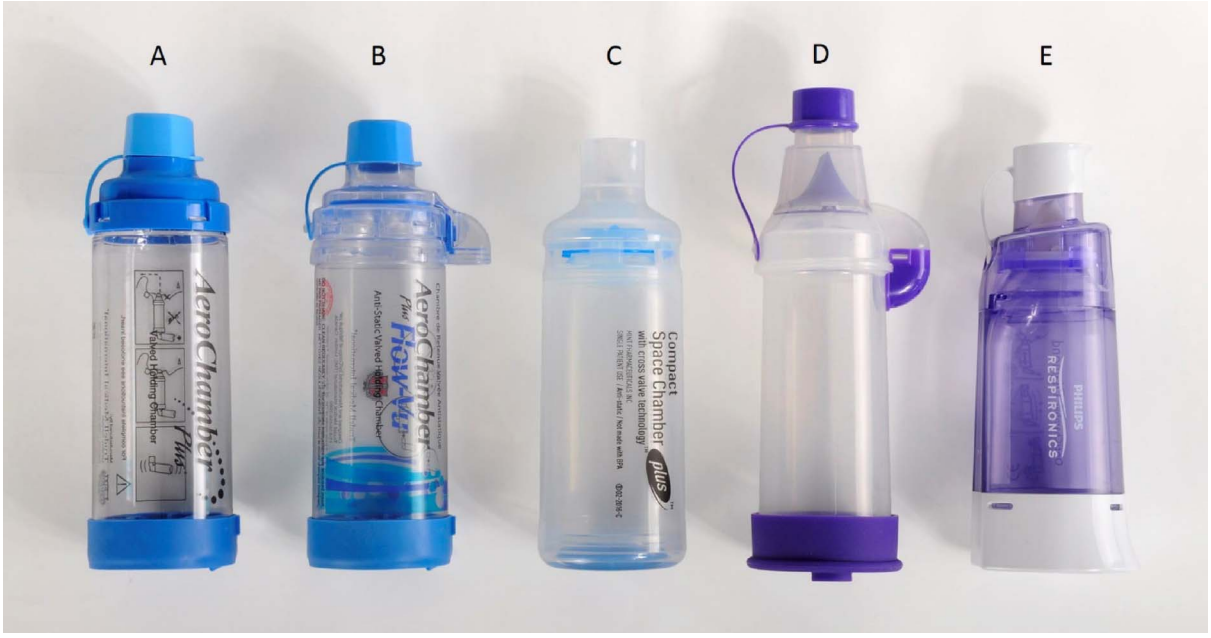

Fig. 1. The reference AeroChamber Plus™ VHC (A) and test antistatic devices: the AeroChamber Plus™ Flow-Vu™ aVHC (B), Compact Space Chamber Plus™ aVHC (C), InspiraChamber™ aVHC (D) and OptiChamber Diamond™ aVHC (E).

details a stepwise framework progressing from in vitro (step 1), to pharmacokinetic (step 2), to pharmacodynamic (step 3) testing; with the demonstration of product equivalence at either the first or second step in the algorithm precluding the need to ascend further up the investigative ladder. Prominent amongst the requisite step 1 in vitro tests is the evaluation of aerosol particle size distribution (APSD) in a validated multistage impactor. Per the OIP guideline where the mass deposited via a "test" VHC in each individual impactor stage, or in each of at least four "groups" of impactor stages, is within ± 15% of that deposited via a "reference" VHC, then two VHCs may be deemed equivalent [31].

The present study was performed to evaluate the performance of four "test" anti-static VHCs, in the context of the OIP guideline's APSD requirement, in comparison to the non-conducting AeroChamber Plus™ (AC+) VHC (Trudell Medical International). The latter is currently the most widely referenced VHC in pMDI monographs and summaries of product characteristics (SmPCs).

2. Methods and materials

All five VHCs tested had a mouthpiece patient interface (Fig. 1).

The reference (non-conducting) device, the AC + VHC, was prepared by soaking for 15 min in a lukewarm detergent solution followed by gentle shaking and allowing the VHC to drip-dry in air. This preparation is in accordance with the manufacturer's instructions and affords the VHC a temporary anti-static coating. No such preparation was required (or is advocated by the respective manufacturers) for the four anti-static VHCs which were evaluated once removed from their packaging. The four test VHCs were the:

- AeroChamber Plus™ Flow-Vu™ Anti-static VHC (AC + FV aVHC; Trudell Medical International)
- Compact Space Chamber Plus™ Anti-Static VHC (CSC + aVHC; Medical Developments)
- InspiraChamber™ Anti-Static VHC (IC aVHC; Lupin Pharmaceuticals, Inc.)
- OptiChamber Diamond™ Anti-Static VHC (OCD aVHC; Philips Respironics Inc.)

As can be seen from Fig. 1, all the test VHCs were of similar length, shape and volume. However differences did exist in the geometries of the chamber and the design of valves incorporated. It would also be likely, although not possible to confirm from the literature, that the anti-static nature of the chambers would vary.

APSD was determined using an Andersen Cascade Impactor (ACI) operated at a constant flow rate of 28.3 L/min with a 2-s delay between actuation and sampling. Five puffs of salbutamol (Ventolin® HFA, GlaxoSmithKline) from a primed pMDI were actuated into the VHC for each test. Salbutamol recovered from the ACI and from within the VHC was assayed using high performance liquid chromatography. The process was repeated for twenty devices of each VHC type (100 VHCs in total) each in conjunction with a randomly chosen pMDI (all from a single Ventolin Evohaler batch), with the pairing of VHC-pMDI units and the order of their testing determined by a randomization matrix.

2.1. Grouped stages

Per the OIP guideline comparative APSD testing should either incorporate evaluation of drug deposition in individual impactor stages, or deposition in at least 4 "groups" of stages, with these groups based upon anticipated regional pulmonary deposition patterns. Equivalent deposition may be inferred where the 90% confidence interval of the test/reference mass ratio for each stage or group of stages is contained within 85–118% [31].

In accordance with these requirements, deposition in four grouped stages was assessed:

ACI Group 1 (comprising Stages 0 + 1): Particles > 5.8–10 μm
ACI Group 2 (comprising Stages 2 + 3): Particles > 3.3–5.8 μm
ACI Group 3 (comprising Stages 4 + 5): Particles > 1.1–3.3 μm
ACI Group 4 (comprising Stages 6 + 7 + filter): Particles ≤1.1 μm

Group 1 represents large particles which are predominantly deposited in the oropharynx. A small degree of pulmonary deposition may be seen with the smaller particles within this size range, with such deposition being largely bronchial in nature [33–35].

Group 2 is a key respirable drug fraction. Particles of this approximate size range are expected to exhibit substantial bronchial and

alveolar deposition with high deposition efficiency (i.e. only a low percentage are exhaled prior to deposition on the respiratory epithelium) [33,35], and elicit optimal bronchodilatory effects [36,37].

Group 3 is the second key respirable drug fraction. Particles within this range exhibit a predominantly alveolar deposition pattern [33–35]. However, their bronchodilatory effects are still substantial [36,37]. The deposition efficiency of the particles within this size range is moderate but diminishes rapidly below 2 μm in diameter [33,35].

Group 4 represents principally submicron-sized particles which are highly prone to exhalation before they can settle on the respiratory epithelium by gravitational sedimentation [33–35]. Particles of this size that do successfully deposit, do so in the alveoli [33,34].

2.2. Statistics

No formal sample size calculation was performed. On the basis of previous studies [23,28] it was anticipated that testing 20 devices of each VHC type would allow estimation of test/reference ratios for the grouped stages with a high degree of precision.

The test/reference ratios for the four grouped stages and their 90% confidence interval were calculated using the delta method, a procedure based on the Taylor approximation that gives estimations for the means and variances of the ratios with the assumption that data are normally distributed. The software Stata version 14 (Stata Corp. College Station, Texas, USA) was used for the analysis. Test/reference ratios and associated 90% confidence intervals were also generated for the mass retained within the VHC to help explain differences in ACI grouped stage deposition. The OIP guideline does not however advocate inferential comparison of this retained mass fraction which has no direct clinical consequence.

3. Results

ACI group comparisons for the test VHC versus the four reference VHCs are presented in Fig. 2 and Table 1.

The mass retained within the AC + VHC and AC + FV aVHC was similar. By contrast the retained mass in the CSC+, IC and OCD was 70–96% greater than that within the reference chamber.

Salbutamol deposition in all ACI groups with the AC + FV aVHC was equivalent to that with the reference AC + VHC (evidenced by all 90% confidence intervals for the test/reference ratios lying within 0.85–1.18).

By contrast, salbutamol deposition in ACI Groups 1 to 3 with the CSC+, IC and OCD aVHCs was confirmed as being inequivalent to that with the reference VHC: the 90% CIs in all cases lying entirely outside 0.85–1.18. Deposition in Groups 1 to 3 with these three test aVHCs was approximately one half that achieved with the AC + VHC. Equivalence versus the reference VHC was also not shown for these three aVHCs for salbutamol deposition in ACI Group 4. However, this was related to the very small salbutamol mass in ACI Group 4 (mean approximately 1.5 μg), allied to high variability around the mean estimate.

Variability of performance between the 20 devices of each VHC-type tested was lowest for the AC + VHC (between-device coefficient of variation [CV] ranging from 10.2% to 24.1% for Groups 1 to 4) and AC + FV aVHC (9.3%–25.7%). This compared to between-device CVs for the CSC+ in Groups 1 to 4 ranging from 28.1% to 55.8%, for the IC from 41.6% to 68.7% and for the OCD from 17.5% to 47.7%.

4. Discussion

The AC + FV aVHC is the latest VHC from the AeroChamber™ VHC family. A major reason for the development of the AC + FV aVHC was to remove the requirement to pre-treat the VHC before first use, and hence improve ease of use and adherence. It was designed to mimic the performance of the non-conducting AC + VHC, where the latter is afforded an anti-static coating via appropriate pre-treatment with a detergent solution. The present study confirmed that the performance of these two AeroChamber™ variants is essentially similar, per the exacting criteria defined by the EMA [31]. An earlier in vitro study which performed a less granular assessment of the total emitted mass (TEM) and fine particle dose (FPD) for eight marketed pMDI products delivered via these two AeroChamber™ devices, employing either no delay or a 2-s sampling delay, arrived at the same conclusion [38]. These findings suggest that the substantial clinical literature that exists for the AC + VHC, which incorporates data for virtually all innovator pMDIs currently approved in the US and EU, can reasonably be extrapolated to the newer anti-static AeroChamber™ variant.

In contrast to the AC + FV aVHC, salbutamol delivery from the other aVHCs tested (the CSC+, IC and OCD) was inequivalent to that from the AC + VHC for ACI Groups 1 to 3; whilst equivalence between these aVHCs and the reference device could not be confirmed for ACI Group 4 (given the high degree of variability for these test aVHCs). Although the regulatory perspective on equivalence (or otherwise) is clear, it is also important to interpret these data in the appropriate clinical context. As previously stated, particles in ACI Group 1 (> 5.8–10 μm) largely deposit in the oropharynx and as such inequivalence between test and reference VHCs for this stage has negligible implications for the pulmonary effects of salbutamol. With respect to ACI Group 4 (particles ≤1.1 μm), mass deposition in this stage represents only about 5–10% of the total respirable particle mass (≤5.8 μm in diameter) for all the five VHCs tested whilst particles in this size range are also highly prone to exhalation before they can sediment upon the respiratory epithelium [33–35]. Thus, small differences in ACI Group 4 mass between the reference device versus the CSC+, IC and OCD aVHCs and/or greater variability for the latter are unlikely to be clinically meaningful.

Mismatches in ACI Groups 2 and 3 between the AC + VHC versus the CSC+, IC and OCD are however more concerning clinically. The

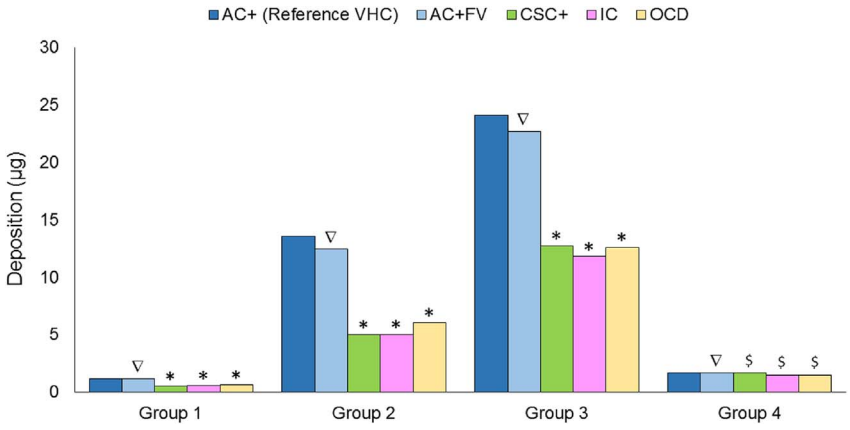

Fig. 2. Mass per ACI grouped stage for test and reference VHCs.
[∇]Equivalent to Reference (90% CI for test/reference ratio lies within 85–118%).
*Inequivalent to Reference (90% CI for test/reference ratio lies entirely outside 85–118%).
[$]Equivalence to Reference not proven (90% CI for test/reference ratio includes 100% but not entirely contained within 85–118%).

Table 1
Mass retained in VHC and mass per ACI grouped stage for test and reference VHCs.

	Reference VHC	Test aVHCs			
	AeroChamber Plus™	AeroChamber Plus™ Flow-Vu™	Compact Space Chamber Plus™	InspiraChamber™	OptiChamber Diamond™
Mean mass (SD) retained in VHC, μg	26.81 (3.78)	29.92 (4.20)	50.80 (6.33)	52.48 (9.04)	45.44 (5.52)
TEST/REF Ratio (90% CIs)	–	1.12 (1.04,1.19)	1.89 (1.74,2.05)	1.96 (1.80,2.11)	1.69 (1.59,1.80)
Group 1 mean mass (SD), μg	1.15 (0.19)	1.16 (0.19)	0.51 (0.15)	0.57 (0.35)	0.63 (0.11)
TEST/REF Ratio (90% CIs)	–	1.01 (0.92,1.10)	*0.45 (0.38,0.51)*	*0.50 (0.38,0.62)*	*0.55 (0.51,0.58)*
Group 2 mean mass (SD), μg	13.53 (2.04)	12.43 (2.19)	4.97 (1.42)	5.00 (2.40)	6.04 (1.59)
TEST/REF Ratio (90% CIs)	–	0.92 (0.85,0.99)	*0.37 (0.32,0.41)*	*0.37 (0.30,0.44)*	*0.45 (0.40,0.50)*
Group 3 mean mass (SD), μg	24.09 (2.45)	22.68 (2.11)	12.72 (3.58)	11.79 (4.91)	12.59 (2.33)
TEST/REF Ratio (90% CIs)	–	0.94 (0.90,0.98)	*0.53 (0.46,0.59)*	*0.49 (0.41,0.57)*	*0.52 (0.48,0.56)*
Group 4 mean mass (SD), μg	1.66 (0.40)	1.67 (0.43)	1.65 (0.92)	1.47 (1.01)	1.49 (0.71)
TEST/REF Ratio (90% CIs)	–	1.00 (0.89,1.11)	*0.99 (0.78,1.21)*	*0.88 (0.64,1.12)*	*0.89 (0.71,1.08)*

VHC - valved holding chamber; aVHC - anti-static valved holding chamber, SD - standard deviation; italized cells denote failure to satisfy EMA in vitro equivalence criteria.

drug mass in ACI Groups 2 and 3 with the CSC+, IC and OCD was only about half that attained with the AC + VHC. These two grouped stages, comprising particles from > 1.1 to 5.8 μm, are critical to clinical effect [36,37,39,40]. For example, Usmani and co-workers reported FEV1 increases ranging from approximately 350 mL–550 mL in mild to moderate asthmatics in response to single 30 μg doses of salbutamol monodisperse aerosols ranging from 1.5 to 6 μm in diameter [37]. Other authors have reported similar results for monodisperse salbutamol [36] and ipratropium aerosols [36,40]. A further recent study demonstrated that fluticasone monodisperse aerosols of 1.5 or 3 μm in diameter exert prominent anti-inflammatory effects in both the central lung and peripheral airways/alveoli [39]. The mismatches between the AC + VHC versus the CSC+, IC and OCD in ACI Groups 2 and 3 are thus important, especially since 90–95% of the respirable drug mass for the salbutamol formulation evaluated is present in these stages.

The results of the present study may be surprising to many clinicians given the broadly similar appearances and dimensions of the five VHCs tested. However, the abundant VHC literature would suggest that these results are not unexpected. For example, an earlier study which compared two of the devices evaluated in the present study, the AC + FV aVHC and the OCD aVHC, showed significant differences in their respective delivery of a fluticasone pMDI (Flovent® HFA).

It is not readily possible to ascertain which design differences between the VHCs tested in present study are principally implicated in the performance differences observed; as individual design elements of the respective VHCs cannot be evaluated in isolation. However, the single most likely candidate is the material used in the construction of the respective VHC bodies and inhalation valves. It is plausible that the anti-static polymers of the CSC+, IC and OCD dissipate charge less efficiently than the AC + FV aVHC or the detergent-washed AC + VHC and, as a result, interact with charged aerosol particles to a greater extent than the latter. A greater susceptibility to charge acquisition, e.g., through VHC handling during the course of the study, may also explain the approximately two-to three-fold greater between-device variability observed for the CSC+, IC and OCD aVHCs versus the AeroChamber™ devices. Unfortunately, resistivity testing to confirm this hypothesis in accordance with accepted standards requires flat plaques of VHC material for evaluation [41], which are not readily available.

Aside from each VHC's constituent materials, another putative contributor to the greater retained mass within the CSC+, IC and OCD versus the AeroChamber™ VHCs is the difference in the shape and surface area of the respective inhalation valves; with overt differences in valve shape evident between some of the VHCs included in the present study. The shape of an inhalation valve determines the drag it experiences and also the extent of recirculation vortices at the VHC exit which in turn determine the degree of particle trapping within the device itself [42]. A large valve surface area can also increase the potential for particle collisions at the VHC exit and hence again reduce drug delivery from the device [42]. Notwithstanding the above, inhalation valve function is perhaps more prominent a contributor to VHC performance with a tidal breathing pattern rather than a single deep inhalation (the latter being more analogous to the constant flow sampling condition employed in the present in vitro study).

Chamber shape may also contribute to differences in device performance with abrupt changes in wall direction implicated in the creation of airflow recirculation zones (and hence particle deposition within the VHC) [42]. However, the relative similarity of the contours of the five VHCs tested in the present study suggests that major differences in their airflow recirculation patterns are unlikely.

The in vitro data from the present study imply that in vivo differences in pulmonary salbutamol deposition are inevitable where Ventolin HFA™ is used with the CSC+, IC or OCD versus the reference device (or the AC + FV aVHC). Although the exact correlation between in vitro and in vivo data is difficult to predict, previous studies [43–45] suggest that the two-fold difference in respirable drug mass in vitro would equate to a broadly similar difference in vivo. In interpreting the clinical sequelae of such differences it is important to acknowledge that, on a population-wide basis, dose-response to β2-agonists [46,47], and other classes of OIPs [48,49], is shallow. Thus, group mean differences in clinical outcomes with a two-fold dose difference are likely to be modest. However, substantial interindividual variability in response to β2-agonists [47,50,51] (and other classes of OIPs [51,52]) is well described. Thus, effectively halving the respirable salbutamol dose will in some patients lead to a clinically relevant attenuation of bronchodilator response. A rightwards shift of the dose-response curve may have similar implications for patients who would normally tolerate a halving of bronchodilator dose without consequence. Perhaps the most broadly applicable context in which this may occur is acute severe asthma during which airway levels of pro-inflammatory cytokines are increased [53,54] which impair the smooth muscle relaxant effects of β2-agonists [55,56]. A further relevant example is in patients with nocturnal asthma: the nocturnal influx of eosinophils into the alveoli in these patients [57] leads to a rightwards shift of the dose-response curve at night with a corresponding dramatic increase in bronchodilator requirements [58]. Overall therefore, whilst halving the respirable salbutamol dose may have few consequences on a population-wide basis in stable asthma, there are situations in which it may have deleterious consequences.

The implications of performance variability between individual devices of a given VHC type are also of interest. The greatest inter-device variability was seen with the IC. The observed variance for the IC

indicates that for approximately one third of individual VHCs the emitted drug mass within Groups 2 and 3 (i.e. the key respirable drug mass for the salbutamol formulation evaluated) differed from the mean estimate by at least + or −43%. This magnitude of performance variability implies the potential for clinically relevant differences in effect when salbutamol is administered via different IC VHCs. By contrast inter-device variability was lowest with the two AeroChamber™ VHCs. In both cases the spread of observed data indicated that for the "outlying" one third of individual VHCs, the emitted drug mass within Groups 2 and 3 differed from the mean estimate by at least + or −10% only. This low variability in emitted drug dose implies that differences in clinical effect between different AeroChamber™ devices are, in contrast to the IC, very unlikely.

In view of the potential clinical sequalae of large mismatches in respirable dose between different VHC types, and differences in inter-device variability for different VHCs, the regional discordance between regulatory authority requirements is surprising. The EMA stands alone in requiring data for a "*specific named spacer*" to support pMDI approval. By contrast the US Food and Drug Administration (FDA) [59,60], Health Canada [61,62] and Japan's Pharmaceuticals and Medical Devices Agency are silent on this issue – implying that pMDIs may be used in conjunction with a variety of essentially substitutable VHCs. The FDA's position is perhaps the most surprising in view the agency's zealous approach to dose selection for novel inhaled products [49,63,64]; and stringent "weight of evidence" approach for generic inhalers which requires the demonstration of in vitro, pharmacokinetic *and* clinical equivalence between test and reference devices to support generic product approval [59,65,66]. In this context ignoring a two-fold difference in respirable dose between VHCs as in the present study, or even greater between-VHC differences [23,28], is difficult to rationalise. Harmonisation of regulatory guidelines across regions would seem desirable.

Finally, the principal limitation of the present study is that it compared salbutamol deposition in the ACI under a single set of sampling conditions. From a clinical perspective, testing in additional conditions (e.g. with no sampling delay or with a longer sampling delay) would be instructive. The consistency of performance between the AC + VHC and AC + FV aVHC in the present study, and in an earlier study which evaluated TEM and FPD from eight different marketed pMDIs (comprising 10 active substances) [38] suggests similar performances are likely with these devices under other conditions. However, this remains to be definitively ascertained. With regards to the other aVHCs tested, it is difficult to envisage any testing scenarios under which their respective performances could mimic those of the reference VHC given the magnitude of differences observed in this study.

5. Conclusion

The performance of the test AC + FV aVHC was equivalent to that of the pre-treated reference AC + VHC in an ACI operated at 28.3 L/min with a 2-s sampling delay. By contrast the CSC+, IC and OCD were all inequivalent to the reference device: the respirable dose emitted from these aVHCs was approximately half that of the reference device, with a corresponding doubling of the mass retained in the VHC in each case. Between-device variability (for the 20 devices of each VHC type) was approximately two to three-fold greater with the CSC+, IC, OCD aVHCs compared to the two AeroChamber™ devices. Overall, these data illustrate large performance differences, with potential clinical sequelae, between VHCs which are superficially visually similar. These data confirm that VHCs should not automatically be considered interchangeable.

AeroChamber™, Aerochamber Plus™ and Flow-Vu™ are trade marks and registered trade marks of Trudell Medical International.

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