

# Performance of breath-actuated (Qvar) pressurize metered dose inhaler with different spacers: In-vitro study

Mohammed Almeziny<sup>1</sup>, Brian Clark<sup>2</sup>, Henry Chrystyn<sup>3</sup>

Correspondence:

Mohammed Almeziny  
Consultant Clinical Pharmacist,  
Prince Sultan Military Medical City  
(PSMMC), Riyadh, KSA  
Email: meziny@hotmail.com

1 Consultant Clinical Pharmacist,  
Prince Sultan Military Medical City  
(PSMMC), Riyadh, KSA

2 Institute of Pharmaceutical  
Innovation, School of Pharmacy,  
University of Bradford, UK

3 Inhalation Consultancy Ltd,  
Leeds, UK

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## Abstract

### Background

Spacers are commonly used especially for paediatric and elderly patients. However, there is a considerable discussion about their use and operation. The purpose of this study was to examine the performance of different types of spacers with Qvar breath actuated pressurize metered dose inhaler (pMDI) containing Beclometasone with fine particles.

### Methods

The dose evaluation method for pMDIs in the British Pharmacopoeia (BP) was used to find out the total emitted dose (TED) and particle size distribution of Qvar pMDI. The study looked at pMDI alone and with three different spacers (Optimizer, Aerochamber Plus, and Aerochamber MAX) at a flow of 28.3 L/min and 4 L inhalation volume to mimic adults. At different times, from the first to the last actuation, the average amount of drug in each pMDI alone and connected to the three different spacers was evaluated.

### Results

The pMDI by itself had the highest TED, which was significantly higher than all pMDI-spacer combinations ( $p < 0.05$ ). The spacers also had higher fine particle dose, and fine particle fraction ( $p < 5 \mu\text{g}$ ) than pMDI alone. No significant difference was observed in mass median aerodynamic diameter between the four tested combinations. No significant difference was observed between the three evaluated spacer.

### Conclusions

These results show that there are improving effects on aerodynamic characterisation and the amount of drug available for inhalation when spacers are used as inhalational aids to pMDI. That support the GINA recommendation regarding the use of spacer with all patients using pMDI even the breath actuated pMDIs.

**Keyword:** in-vitro; aerodynamic particle size distribution; Qvar pressurize metered dose inhaler; Optimizer; Aerochamber Plus; and Aerochamber MAX

### Introduction

Pressurize metered dose inhaler (pMDIs) are a convenient way of administering medication. <sup>1</sup> They emit an aerosol at high velocity and to be used properly they require co-ordination of inhalation and pMDI actuation. <sup>2-4</sup> But, even with an optimum technique, only  $< 15\%$  of the emitted dose regularly reaches the airways. <sup>5, 6</sup> Spacer devices were introduced to try to improve the efficacy of inhaled therapy with pMDIs by decreasing the need for coordination between actuation and inhalation and by allowing evaporation of propellant, so decreasing oropharyngeal deposition of therapy <sup>7</sup>. Global Initiative for Asthma (GINA) recommended the use of spacers to decrease oropharyngeal deposition that cause adverse effects and counter the common problem of poor inhaler technique. <sup>8, 9</sup>

Many different spacer devices are currently available, some designed to fit with one particular product, while others are intended for use with a variety of pMDIs.<sup>2, 10-13</sup> Material of spacer has a significant difference effect on dose delivery. Anti-static accessory devices delivered a higher amount of aerosol compared with non-antistatic accessory devices in terms of pharmacokinetics (urinary salbutamol).<sup>2, 14, 15</sup>

In addition, particle size is obviously a crucial factor in inhaled drugs, affecting both the lung dose and delivery location and therefore clinical efficacy. It has been proposed that the primary factor of drug deposition in the lung is its aerodynamic size.<sup>11, 12, 16</sup> In many formulations, the fraction of the cloud in sizes of 1 to 5  $\mu\text{m}$  is usually expressed as the fine particle dose (FPD), i.e. the fraction of the label claim  $< 5 \mu\text{m}$ .<sup>17</sup>

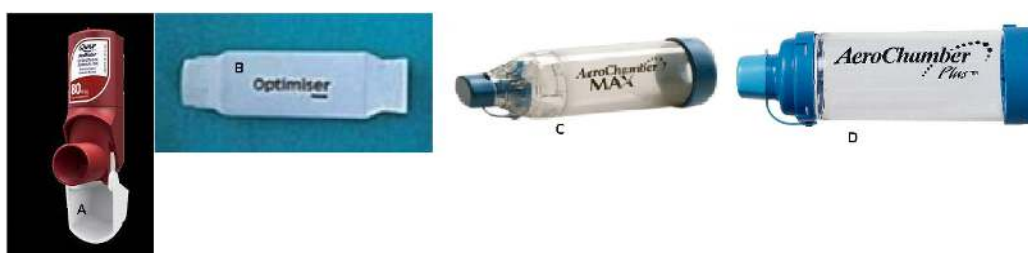
Local side effects of inhaled corticosteroids are considered minor problems. However, while not generally serious, they are clinically important, because they may hamper compliance with therapy. They include dysphonia, oropharyngeal candidiasis, thirst, cough, tongue hypertrophy and peri-oral dermatitis. In addition, the cold Freon effect, in which the cold high-velocity aerosol impacts on the back of the throat can cause patients to stop inhaling prematurely.<sup>11, 12, 16</sup> The use of a spacer may reduce these effects or eliminate them. However, the spacer may cause peri-oral dermatitis, especially when a mask is used.<sup>18</sup>

Qvar is a breath actuated pMDI designed for oral inhalation only (Figure 1A). Each unit contains a solution of beclomethasone dipropionate in 1,1,1,2 tetrafluoroethane (HFA-134a) propellant and ethanol.<sup>19</sup> Increased lung deposition of Qvar permits a decrease in dose relative to CFC-beclomethasone dipropionate. Clinical indication confirms that adult and elderly patients needed about half the dose of Qvar to achieve the same degree of asthma control as with CFC-beclomethasone dipropionate.<sup>20</sup> In long-term evaluations, patients taking CFC-beclomethasone dipropionate was shown to be easily switched to Qvar at half the daily dose without exacerbation of their asthma symptoms. Qvar was related to a low overall occurrence of side effects and, at the maximum recommended dose of 640  $\mu\text{g/day}$ , caused no more adrenal suppression than 672  $\mu\text{g/day}$  CFC-beclomethasone dipropionate.<sup>20</sup>

The Optimizer is an antistatic spacer specially used for Easi-Breath breath actuated pMDI with 50 mL volume (Figure 1 B). It comprises a plastic tube with a cross section of 2.5 x 3.5 cm. and has an overall length of 10 cm.<sup>21</sup>

AeroChamber MAX (AMAX) is an antistatic valve holding chamber (VHC). The volume of AMAX is 198 mL (Figure 1 C). It is manufactured from a shatter-resistant, clear, anti-static polymer blend. It incorporates a Flow-Vu™ the Inspiratory Flow Indicator to provide the caregiver with reassurance of medication delivery to the lungs. Also, it has a one-way, low resistance duckbill valve system.<sup>22</sup>

In contrast with the AMAX, the Aerochamber PLUS VHC (APLUS) is antistatic VHC and the volume is 149 mL (Figure 1 D). But it can be used with various pMDIs.<sup>23</sup>



**Figure 1.** A. Qvar is a breath actuated pMDI, B. Optimizer, C. Aerochamber MAX, and D. Aerochamber Plus

The aim of the study is to examine the effect of the spacers on pulmonary delivery to the patient. The objectives were to examine the effect of different type of spacers on the dose of beclometasone delivered to the lungs and the throat deposition and to measure the dose emitted from Qvar alone and attached to spacers; and to compare the in-vitro aerosol deposition characteristics from Qvar with three common spacers using mass median aerodynamic diameter (MMAD), FPD and fine particle fraction (FPF) as parameters.

## Methods

### Instrumentation used

A GAST 1023 Pump, 0-100L/min (GAST, Brook Hampton, Doncaster, UK). Electronic digital flow meter model DFM

(Copley Scientific Ltd, Nottingham UK); Andersen MKII cascade impactor (Copley Scientific Ltd.); Critical Flow Controller Model TPK. (Copley Scientific Ltd.); Sampling Apparatus for MDIs (Copley Scientific Ltd.); Copley Inhaler Testing Data Analysis Software (CITDAS) Copley Scientific Ltd); And A Qvar Easi-Breathe containing beclomethasone 100 µg/metered inhalation was obtained from (IVAX, Harlow, UK)

#### *Dose emission*

The dose emission method described in the British Pharmacopoeia (BP) for pMDIs was used. The flow control valve was adjusted to achieve a steady flow through the system at the required rate (28.3L/min ±5%) which was measured by an electronic digital flow meter (Model DFM). According to the pharmacopoeial method, 4 L of air was drawn through the inhaler for each determination and the absolute pressure ratio P3/P2 < 0.5 was confirmed.

Each pMDI/spacer was prepared according to the patient leaflet instructions. The inhalation time (8.4 sec ±5%) was calculated according to equation below.

$$T = \frac{60 \text{ sec} \times X}{Q}$$

Where T = Time duration consistent for withdrawal of X litres of air from the inhaler

Q = Flow rate required

X = Volume in litres to be drawn through inhaler

The mean content of drug per actuation was tested at different points between the first and final actuation. Determinations were made for each pMDI attached to each of the three different spacers and the emitted dose was washed from the collection tube/spacer into 50 mls of a washing solution (acetonitrile: water 70:30, v/v). Both the collecting tube and spacer content was reported separately. The amount of drug was determined by HPLC using the validated method.<sup>24</sup>

#### *Particle size analysis*

In order, to analyse the particle size the Andersen MKII cascade impactor (ACI) has been used. The procedure is identical to that above except that, the ACI was used and its stages were assembled as described in the manufactures manual. Each dose of five was separately discharged into the apparatus by opening the valve spacer and each ACI stage content is reported separately.

#### *Statistical analysis*

One-way ANOVA with Bonferroni effect test was used to compare the aerodynamic particle size characterization of the different flow using SPSS V15.0 (SPSS Inc., Chicago, USA).

#### *Fine particle analysis*

All the aerodynamic calculations were conducted using the Copley software (CITDAS version 2).

### **Results and discussion**

#### *Effect of spacers on delivered dose*

Table 1 shows the summary of performance of the spacers with Qvar. All the investigated spacers decrease the delivered dose compared to the pMDI alone. There are also statistical differences, which is  $p > 0.001$  in case of APLUS and  $p < 0.01$  with optimizer. Furthermore, there is no statistical differences in case of AMAX. Many studies show the same effect. Barry and co-workers examined inhalation drug delivery from seven different spacers and found that they reduced the total amount of drug delivered from spacers.<sup>25</sup>

Moreover, Nagel et al reported a reduction in the total delivered dose with Fluticasone and Salmeterol from 102.1 µg and 20 µg for pMDIs alone to 58.4 µg and 10.8 µg with APLUS respectively<sup>26</sup>. Hardy et al examined optimizer performance with three Easi-Breath Beclazone CFC formulations. Using the twin impinger they demonstrated that the spacer removed 27%-39% of the total dose. Also, their data showed a mean of 55% of the dose was deposited in the spacer, which was assayed using an imaging technique (gamma camera, transmission images with technetium-99m).<sup>21</sup> The major cause of the loss of part of the inhaled drug is impaction due to inertia, sedimentation due to reduced speed of the aerosol particles and adsorption due to electrical charge.<sup>27</sup> The loss by impaction occurs immediately after actuation, and loss due to sedimentation and adsorption is time-dependent.<sup>7</sup>

Electrostatic charge is created on discharging the aerosol, which can influence deposition in the spacer. Moreover, different spacers have different electrostatic properties. Non-electrostatic devices have been recommended for young children as these result in increased lung deposition.<sup>28</sup>

**Table 1.** Mean±SD of delivered dose percentage (% nominal dose) from different formulations of Qvar with different spacers; Mean difference (95% confidence interval) for delivered dose of pMDI alone compared to delivered dose of pMDI+spacers (Mean±SD).

Experiment (n=10)	Delivered dose (%)	Mean difference
Qvar 100 µg Easi-Breathe 1 dose	101.3±34.83	
Qvar 100 µg 1 dose Easi-Breathe AMAX	93.98±11.89	-7.4(-16.9- 2.2)
Qvar 100 µg 1 dose Easi-Breathe Optimizer	86.38±6.69	-15.0**(-24.5- -5.4)
Qvar 100 µg 1 dose Easi-Breathe APLUS	63.32±11.13	-23.1***(-32.6- -13.5)

\*  $p < 0.05$ , \*\*  $< 0.01$ , \*\*\* $< 0.001$ , otherwise no significant difference. SD= Standard Deviation

**Table 2.** The effect of type of spacer (95% confidence interval) on percent of delivered dose (% emitted dose) for Qvar.

Experiment (n=10)	Delivered dose (%)	Mean difference
Qvar 100 µg 1 dose Easi-Breathe AMAX	87.24±2.68	7.8 (-0.4- -16.0) <sup>a</sup>
		24.6*** (16.4-32.9) <sup>b</sup>
Qvar 100 µg 1 dose Easi-Breathe Optimizer	79.44±3.54	-7.8 (-16.0-0.4) <sup>c</sup>
		16.8*** (8.6-25.1) <sup>d</sup>
Qvar 100 µg 1 dose Easi-Breathe APLUS	62.62±10.20	-24.6*** (-32.9- -16.4) <sup>e</sup>
		-16.8*** (-25.1- -8.6) <sup>e</sup>

a AMAX vs. optimizer, b AMAX vs. APLUS, c optimizer vs. AMAX d optimizer vs. APLUS, e APLUS vs. AMAX, f APLUS vs. optimizer. \*  $p < 0.05$ , \*\*  $< 0.01$ , \*\*\* $< 0.001$ , compared to pMDI alone otherwise no significant difference.

Table 2 summarises the performance of the spacers with different Qvar. The data show statistically significant differences between spacer performances except with AMAX and Optimizer where the difference is not statistically significant. The AMAX spacers delivered the highest dose of all formulations, while the Optimizer performed better than APLUS. It is proposed that the half-life of the aerosol available for inhalation is reduced by electrostatic activity resulting in a reduction in the delivered dose.<sup>29</sup> Furthermore, the aerosol half-life is 10s with the plastic spacers, while it is 30s if the static charge is abolished.<sup>7</sup> This agrees with the work of Terzano who reported that antistatic spacers deliver a significantly higher lung dose than ordinary spacers.<sup>30</sup> In addition, Anhoj et al examined the effect of electrostatic charges *in-vivo* on the lung dose of Salbutamol in children. The plasma level of Salbutamol was measured before and 5, 10, 15 and 20 min after inhalation of four single doses of 100 µg salbutamol.  $C_{max}$  and  $C_{av}$  (5–20 min) were used as a reflection of lung deposition. The results show that the dose of Salbutamol had to be halved when an ordinary plastic spacer was used compared with the same spacer after antistatic priming.<sup>31</sup>

Geller and co-workers tested the lung delivery in infants of Flovent CFC-free inhaler (Fluticasone propionate) using the AMAX, Pari Vortex (antistatic coating), and OptiChamber Advantage (no antistatic treatment) as significantly AMAX delivered more Flovent than the other two chambers. Geller et al. suggested that the results could be due to the lower chamber static and better valve design for AMAX.<sup>32</sup> Hardy et al. measured the drug amount deposited in an optimizer spacer with Qvar 100 and 50 ug. Their result shows that the spacer deposition was 27% and 34% for 50 and 100 ug respectively.<sup>21</sup> Iula et al tested the performance of four different spacers coupled with Azmacort (Triamcinolone acetonide) and found up to a five-fold differences in the amount of drug delivered when using different spacers.<sup>33</sup> Barry et al. demonstrated large variations in the lung dose delivered from different spacers and variations in the performance of spacers to deliver different drug.<sup>25</sup>

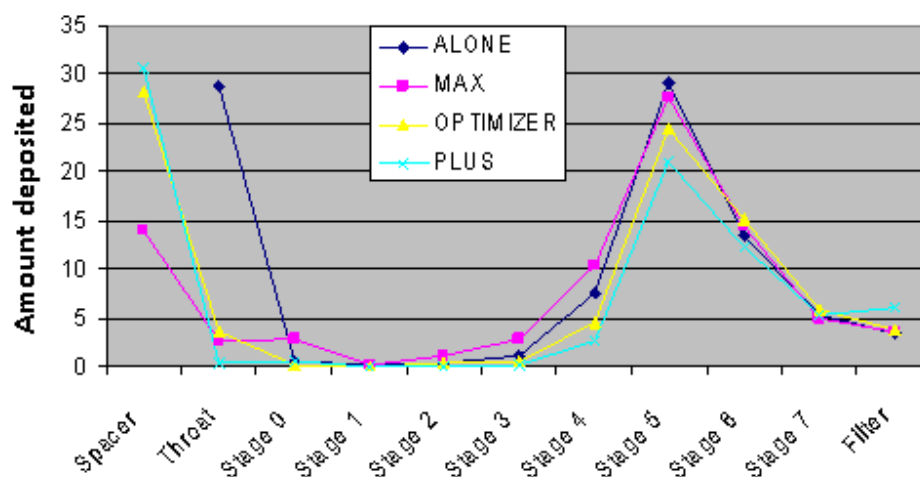
#### *Effect of spacer type on aerodynamic characterization*

Table 3 and Table 4 and Figures 2 and 3 summarised the aerodynamic results of Qvar with two spacers.<sup>34</sup>

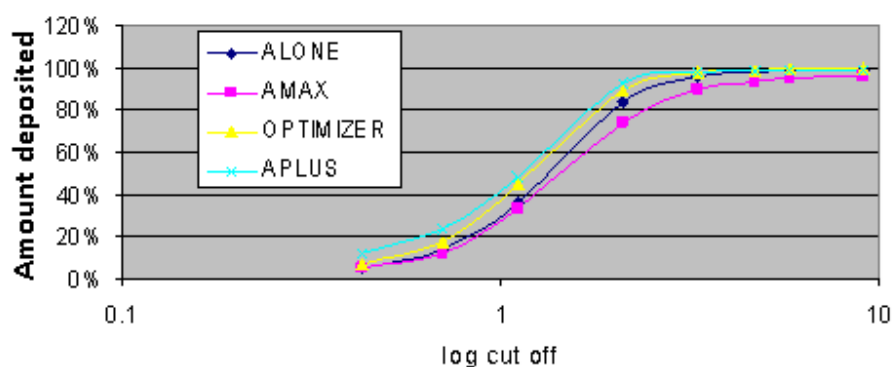
#### *Effect of spacer type on MMAD*

There were no statistically significant differences between the Qvar alone and Qvar with spacers. The results of this

study disagree with those reported by Barry and co-workers. Where they showed that, in most cases, a reduction in the size of drug particles delivered, which was demonstrated by the decrease in MMAD of the aerosol from pMDIs with spacers.<sup>25</sup> However, Rahmatalla et al. reported no significant difference ( $p = 0.1$ ) in MMAD after cascade impactor measurements at an inhalation flow of 28.3 L/min with and without a spacer.<sup>10</sup> Another study which compared many parameters including MMAD of Flovent CFC delivered via APLUS or Easivent spacers versus the pMDI alone has shown no difference in MMAD.<sup>35</sup> Also, Cripps et al. examined the effect of Volumatic and Babyhaler spacers on the particle size distributions for the corresponding HFA 134a and CFC Salbutamol and Fluticasone propionate pMDIs and found no significant effect on MMAD.<sup>36</sup>



**Figure 2.** Amount ( $\mu\text{g}$ ) of Beclomethasone deposited on each stage of the ACI from Qvar alone and with different spacers.



**Figure 3.** Cumulative mass percentage under size for Beclomethasone deposited on each stage of the ACI from Qvar alone and with different spacers.

#### Throat deposition

Table 3 illustrates the throat deposition for Qvar alone and with spacers. The differences between the pMDIs alone and pMDIs with spacers were statistically significant ( $p < 0.001$ ). Furthermore, the mean differences between spacer types. The differences were not statistically significant among spacers. These findings are consistent with previous studies. The average reduction caused by spacers is 26.47% (25.1%-28.3%). The amount of drug deposited in the throat in this study was similar to several experiments. Bisgaard et al reported the deposition with the pMDI alone ranged from 30% to 70% compared with 5% to 10% with spacers.<sup>7</sup> Rahmtalla et al. examined the effect of spacer on the mouth-throat deposition of Qvar and found that adding the spacer reduced drug deposition in the throat.<sup>10</sup> Asmus et al. tested the performance of spacers with a Fluticasone pMDI. Their results showed a

**Table 3.** Amounts ( $\mu\text{g}$ ) of beclomethasone using five doses, deposited on each stage of the ACI, from Qvar 100  $\mu\text{g}$  alone and with different spacers.

	ALONE	AMAX	OPTIMIZER	APLUS
Spacer	--	14.07 $\pm$ 3.52	28.15 $\pm$ 4.27	30.65 $\pm$ 5.99
Throat [ $\mu\text{g}$ ]	28.67 $\pm$ 5.84	2.72 $\pm$ 0.52	3.61 $\pm$ 0.09	0.33 $\pm$ 0.28
Stage 0 [ $\mu\text{g}$ ]	0.66 $\pm$ 0.26	2.85 $\pm$ 4.66	0.23 $\pm$ 0.20	0.64 $\pm$ 0.92
Stage 1 [ $\mu\text{g}$ ]	0.16 $\pm$ 0.19	0.13 $\pm$ 0.22	0.09 $\pm$ 0.08	0.05 $\pm$ 0.09
Stage 2 [ $\mu\text{g}$ ]	0.30 $\pm$ 0.12	1.17 $\pm$ 1.29	0.33 $\pm$ 0.28	0.07 $\pm$ 0.12
Stage 3 [ $\mu\text{g}$ ]	1.07 $\pm$ 0.33	2.78 $\pm$ 0.83	0.63 $\pm$ 0.40	0.26 $\pm$ 0.22
Stage 4 [ $\mu\text{g}$ ]	7.48 $\pm$ 1.66	10.46 $\pm$ 2.81	4.55 $\pm$ 1.87	2.65 $\pm$ 3.92
Stage 5 [ $\mu\text{g}$ ]	29.17 $\pm$ 3.29	27.66 $\pm$ 0.50	24.38 $\pm$ 2.70	20.97 $\pm$ 3.92
Stage 6 [ $\mu\text{g}$ ]	13.49 $\pm$ 2.33	14.39 $\pm$ 2.22	15.18 $\pm$ 3.70	12.21 $\pm$ 0.55
Stage 7 [ $\mu\text{g}$ ]	5.26 $\pm$ 0.12	4.97 $\pm$ 1.37	5.90 $\pm$ 1.09	5.30 $\pm$ 2.05
Filter	3.39 $\pm$ 0.72	3.54 $\pm$ 0.16	3.78 $\pm$ 0.90	6.07 $\pm$ 1.19
Ex-mouth dose [ $\mu\text{g}$ ]	89.63 $\pm$ 3.76	84.74 $\pm$ 7.49	86.83 $\pm$ 0.65	79.20 $\pm$ 3.09
Delivered Dose [ $\mu\text{g}$ ]	89.63 $\pm$ 3.76	70.67 $\pm$ 5.05	58.68 $\pm$ 4.75	48.55 $\pm$ 5.32
Fine Particle Dose [ $\mu\text{g}$ ]	59.60 $\pm$ 6.31	64.30 $\pm$ 5.19	53.97 $\pm$ 4.75	47.26 $\pm$ 4.80
Fine Particle Fraction [%]	66.49 $\pm$ 6.52	90.98 $\pm$ 5.22	91.97 $\pm$ 0.95	97.33 $\pm$ 1.36
MMAD [ $\mu\text{m}$ ]	1.31 $\pm$ 0.04	1.43 $\pm$ 0.07	1.17 $\pm$ 0.10	1.11 $\pm$ 0.06
GSD	1.62 $\pm$ 0.06	1.90 $\pm$ 0.28	1.60 $\pm$ 0.04	1.55 $\pm$ 0.06

**Table 4. Cumulative mass percentage under size for Qvar alone and with different spacers.**

Stage	ALONE	AMAX	OPTIMIZER	APLUS
Stage 0 [%]	100.0	100.0	100.0	100.0
Stage 1 [%]	98.92	95.81	99.58	98.67
Stage 2 [%]	98.66	95.62	99.41	98.56
Stage 3 [%]	98.16	93.90	98.81	98.41
Stage 4 [%]	96.41	89.81	97.67	97.87
Stage 5 [%]	84.14	74.42	89.41	92.38
Stage 6 [%]	36.30	33.71	45.15	48.89
Stage 7 [%]	14.18	12.53	17.58	23.57
Filter [%]	5.55	5.21	6.87	12.59

decrease in quantity of drug deposited in the throat so they suggested the use of spacers may diminish the risk of topical adverse effects.<sup>35</sup> Spacers reduce deposition in the mouth and throat, decreasing cough, and also may decrease oral candidiasis when oral inhaled corticosteroids are used. Furthermore, their use may decrease the systemic bioavailability and the risk of systemic side effects.<sup>37</sup> Also, radio-labelling data for Qvar showed an up to three time lower dose is deposited in the throat when the spacer is used.<sup>7</sup> In addition, Roland et al suggested the spacers use as a part of treatment to prevent local side effects recurring through reduction of throat deposition. However, another study found that the spacer may increase the incidence of cough.<sup>18</sup>

#### FPD

Table 3 illustrates the FPD results. The highest FPD was Qvar with AMAX (64%) while the lowest FPD was Qvar with APLUS. In addition, the effect of spacers, on the FPD depended on spacer type. The effect of APLUS on FPD was statistically significant, while the effect of the optimizer and AMAX were not statistically significant.<sup>38</sup>

Rahmatalla et al. showed a selective effect for spacers, reducing the throat deposition while slightly increasing the lung deposition. However there was no significant influence on the size distribution of FPD after examining the effect of a spacer on Qvar aerodynamic characterisation.<sup>10</sup> Also, Leach et al. found no significant differences in lung deposition when a spacer was tested *in-vivo*; however, there was a large variability in *in-vivo* results.<sup>39</sup> In addition, Bisgard et al. reported that the lung dose with intermediate and large volume spacers is about double the dose compared to pMDI alone; however, in other studies, the large and small volume spacers delivered a lung dose similar to pMDI alone.<sup>7</sup>

In contrast, Fink et al. compared the effect of several spacers on Salbutamol pMDI. They found a significant variation in FPD when compared to pMDI alone. FPD was similar for the Aerochamber, but there was a 33%, 35% and 55% reduction for Optihaler Ace and Inspirease, respectively.<sup>40</sup> Furthermore, another study compared Flovent CFC delivery with APLUS and Optichamber spacer to pMDI alone in terms of FPD and showed equivalent delivery.<sup>35</sup> Use of ethanol to reformulate Qvar resulted in a an increase in the FPD which led to a two-fold reduction in dosage with the Qvar compared with the CFC Beclometasone pMDI under certain conditions.<sup>36</sup>

The spacers allow more time for the propellant to evaporate; this promotes the formation of small aerosol particles (1-5  $\mu\text{m}$ ) which are more likely to be entrained by inspiration into small human airways.<sup>41</sup> In addition, the spacer acts as a settling chamber, allowing large particles to sediment or impact. Therefore the final size of drug particles depends on the time available for evaporation of propellant and distance from the actuator orifice.<sup>7</sup> Faarc et al studied a nonelectrostatic versus a non-conducting spacer using Xopenex (Levalbuterol) HFA Inhalation, the FPD difference between AMAX and APLUS was statistically significant in their study.<sup>42</sup> Furthermore, Rau et al reported that electrostatic charge is more prevalent with HFA formulations compared to CFC.<sup>43</sup> Moreover, the half-life of the aerosol inside the spacer is reduced by electrostatic activity of the spacer.<sup>7</sup> Terzano concluded that non-electrostatic spacers delivered a significantly higher dose than non-conducting; furthermore, a reduction in dose should be considered when CFC-free formulation is used with a spacer.<sup>30</sup>

#### FPF

Table 3 shows the FPF results. The FPF is calculated by the equation below. The highest FPF was Qvar with APLUS and the lowest was with Qvar alone. There were strong statistically significant differences between Qvar alone and with spacers ( $p > 0.001$ ). As the spacer retains large particles and passes the small.

$$FPF = \frac{R}{\sum A}$$

Where  $\sum A$  is delivered dose, R is FPD

Therefore the FPF result with spacer is higher since the delivered dose is smaller than pMDI alone.<sup>44</sup>

### Conclusion

The results support the GINA recommendation regarding the use of spacer with all patients using pMDI even the breath actuated pMDIs. The interaction of the aerosol particles with spacers could result in a change of the drug deposition within spacers. There are also many other factors which may affect drug deposition within spacers, which are spacer dependent, including electrostatic charge, volume and the shape of the spacer, incorporated valves and the materials used to build the spacer. In contrast with the pMDI alone, spacers, especially the APLUS, markedly reduce throat drug deposition. Therefore, a proportion of the particles that would have been deposited in the throat are shifted to the spacer itself and thereby diminish the risk of local adverse effects. In addition, compared with the pMDI alone, the FPD, and FPF was increased markedly by using spacers.

### Reference:

1. Saeed, H., Abdelrahim, M.E., Rabea, H., et al., *Evaluation of Disposable and Traditional Accessory Devices for Use With a Pressurized Metered-Dose Inhaler*. Respir Care, 2020. **65**(3): p. 320-325.
2. Saeed, H., Abdelrahim, M.E., Rabea, H., et al., *Evaluation of disposable and traditional accessory devices for use with a pressurized metered-dose inhaler*. Respiratory care, 2020. **65**(3): p. 320-325.
3. Nelson, H.S., *Inhalation devices, delivery systems, and patient technique*. Annals of Allergy, Asthma & Immunology, 2016. **117**(6): p. 606-612.
4. Cazzola, M., Rogliani, P., Anzueto, A., et al., *Inhaled medication: which device for which patient*. ERS Monogr, 2015. **69**: p. 213-223.
5. Steiropoulos, P., Bakakos, P., Hatziagorou, E., et al., *The present and future of inhalation therapy for the management of obstructive airway diseases: Emphasis on pressurized metered-dose inhalers*. Pneumon, 2021. **34**(4): p. 24.
6. Moraga-Espinoza, D.F., Brunaugh, A.D., Ferrati, S., et al., *Overview of the delivery technologies for inhalation aerosols*, in *Inhalation Aerosols*. 2019, CRC Press. p. 123-143.
7. Bisgaard, H., Smaledone, G.C., and O'Callaghan, C., *Drug Delivery to the Lung*. Vol. 162. 2002, New York Marcel Dekker. 511.
8. Asthma., G.I.f. *Global Strategy for Asthma Management and Prevention 2024*. 2024 October 31 2024.]; Available from: <https://ginasthma.org>.
9. Saeed, H., Ammari, W.G., Osama, H., et al., *Evaluation of a cardboard-based spacer for enhancing aerosol delivery from pressurized metered dose inhalers*. Journal of Asthma, 2025(just-accepted): p. 1-9.
10. Rahmatalla, M.F., Zuberbuhler, P.C., Lange, C.F., et al., *In Vitro Effect of a Holding Chamber on the Mouth-Throat Deposition of QVAR®(Hydrofluoroalkane-Beclomethasone Dipropionate)*. Journal of Aerosol Medicine, 2002. **15**(4): p. 379-385.
11. Anderson, G., Johnson, N., Mulgirigama, A., et al., *Use of spacers for patients treated with pressurized metered dose inhalers: focus on the VENTOLIN™ Mini Spacer*. Expert Opinion on Drug Delivery, 2018. **15**(4): p. 419-430.
12. Nikander, K., Nicholls, C., Denyer, J., et al., *The evolution of spacers and valved holding chambers*. Journal of aerosol medicine and pulmonary drug delivery, 2014. **27**(S1): p. S-4-S-23.
13. Lung, N.H. and Institute, B., *Expert panel report 3 (EPR3): guidelines for the diagnosis and management of asthma*. <http://www.nhlbi.nih.gov/guidelines/asthma/>, 2007.
14. Nicola, M., Hussein, R.R., Soliman, Y.M., et al., *Effect of different accessory devices on the dose delivered from pressurised metred-dose inhalers*. International Journal of Clinical Practice, 2021. **75**(6): p. e14157.
15. Nicola, M., Soliman, Y.M., Hussein, R., et al., *Comparison between traditional and nontraditional add-on devices used with pressurised metered-dose inhalers*. ERJ Open Research, 2020. **6**(4).
16. Saini, D., Biris, A., Srirama, P., et al., *Particle size and charge distribution analysis of pharmaceutical aerosols generated by inhalers*. Pharmaceutical development and technology, 2007. **12**(1): p. 35-41.



17. Ganderton, D., Lewis, D., Davies, R., et al., *Modulite®: a means of designing the aerosols generated by pressurized metered dose inhalers*. Respiratory Medicine, 2002. **96**(Supplement 4): p. S3-S8.
18. Roland, N.J., Bhalla, R.K., and Earis, J., *The Local Side Effects of Inhaled Corticosteroids\* Current Understanding and Review of the Literature*. Chest, 2004. **126**(1): p. 213-219.
19. Product-information, Qavr® product monograph 2006, 3M Drug Delivery Systems.
20. Burgt, J.A.V., Busse, W.W., Martin, R.J., et al., *Efficacy and safety overview of a new inhaled corticosteroid, QVAR (hydrofluoroalkane-beclomethasone extrafine inhalation aerosol), in asthma*. Journal of Allergy and Clinical Immunology, 2000. **106**(6): p. 1209-1226.
21. Hardy, J.G., Jasuja, A.K., Frier, M., et al., *A small volume spacer for use with a breath-operated pressurised metered dose inhaler*. International Journal of Pharmaceutics, 1996. **142**(1): p. 129-133.
22. Product-Monograph, Aerochamber Max Product monograph, 2006, Trudell Medical International (TMI).
23. Product-Monograph, Aerochamber Plus Product Monograph, 2005, Trudell Medical International (TMI).
24. Almeziny, M., *Performance of two different types of inhalers. Influence of flow and spacer on emitted dose and aerodynamic characterisation.*, 2009, University of Bradford.
25. Barry, P.W. and O'Callaghan, C., *Inhalational drug delivery from seven different spacer devices*. Thorax, 1996. **51**(8): p. 835.
26. Nagel, M.W., Wiersema, K.J., Bates, S.L., et al., *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*. Journal of Aerosol Medicine, 2002. **15**(4): p. 427-433.
27. Abdelfattah, A.M., Sarhan, R.M., Madney, Y.M., et al., *User-Friendliness Evaluation of Handling pMDI with Various Add-on Devices in Asthmatic Patients*. AAPS PharmSciTech, 2024. **25**(8): p. 274.
28. Devadason, S.G., *Recent Advances in Aerosol Therapy for Children with Asthma*. Journal of Aerosol Medicine, 2006. **19**(1): p. 61-66.
29. Saeed, H., G., A.W., Hasnaa, O., et al., *Evaluation of a cardboard-based spacer for enhancing aerosol delivery from pressurized metered dose inhalers*. Journal of Asthma, 2025: p. (in press).
30. Terzano, C., *Pressurized Metered Dose Inhalers and Add-on Devices*. Pulmonary Pharmacology & Therapeutics, 2001. **14**(5): p. 351-366.
31. Anhoj, J., Bisgaard, H., and Lipworth, B.J., *Effect of electrostatic charge in plastic spacers on the lung delivery of HFA-salbutamol in children*. British Journal of Clinical Pharmacology, 1999. **47**(3): p. 333.
32. Geller, D. and Kesser. *Effects of Pre-treatment of Static and Non-static Holding Chambers (HC) on the Delivery of Flovent 110-HFA (F) in an Infant Airway Model*. in *The American Thoracic Society Conference*. 2006. San Diego, USA.
33. Iula, A.K., Obetz, C.L., and Deluccia, F., *Comparative study of dose delivery from an Azmacort™ MDI paired with an Azmacort™ integrated actuator/spacer, an Aerochamber™, Inspirease™, and a Microspacer™*. Respir Drug Deliv, 1996: p. 352-353.
34. Nicola, M., Hussein, R.R.S., Soliman, Y.M.A., et al., *Effect of different accessory devices on the dose delivered from pressurised metered-dose inhalers*. International Journal of Clinical Practice, 2021. **75**(6): p. e14157.
35. Asmus, M.J., Liang, J., Coowanitwong, I., et al., *In vitro deposition of fluticasone aerosol from a metered-dose inhaler with and without two common valved holding chambers*. Annals of Allergy, Asthma and Immunology, 2002. **88**(2): p. 204-208.
36. Cripps, A., Riebe, M., Schulze, M., et al., *Pharmaceutical transition to non-CFC pressurized metered dose inhalers*. Respiratory Medicine, 2000. **94**(Supplement 2): p. S3-S9.
37. Rabe, K.F., Hurd, S., Anzueto, A., et al., *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary*. American Journal of Respiratory and Critical Care Medicine, 2007. **176**(6): p. 532.
38. Nicola, M., Soliman, Y.M.A., Hussein, R., et al., *Comparison between traditional and nontraditional add-on devices used with pressurised metered-dose inhalers*. ERJ Open Research, 2020. **6**(4): p. 00073-2020.
39. Leach, C.L., Davidson, P.J., Bredow, T.S., et al., *Patient factors influencing the deposition of HFA-beclomethasone dipropionate metered dose inhaler*. Eur Respir J, 1998. **12**: p. 66s.

40. Fink, J.B., Wilkes, W., Dhand, R., et al., *Do spacers and holding chambers influence respirable mass from a metered-dose inhaler*. Am J Respir Crit Care Med, 1998. **157**(3).
41. Asmus, M.J., Liang, J., Coowanitwong, I., et al., *In Vitro Performance Characteristics of Valved Holding Chamber and Spacer Devices with a Fluticasone Metered-Dose Inhaler*. Pharmacotherapy, 2004. **24**(2): p. 159-166.
42. Faarc, D., Csci, J., and Nagel, M.W., *Levalbuterol Aerosol Delivery With a Nonelectrostatic Versus a Nonconducting Valved Holding Chamber*. Respiratory Care, 2006. **51**(5): p. 511.
43. Rau, J.L., Coppolo, D.P., Nagel, M.W., et al., *The importance of nonelectrostatic materials in holding chambers for delivery of hydrofluoroalkane albuterol*. Respiratory care, 2006. **51**(5): p. 503-510.
44. Tony, S.M., A., A.M., Mogeda, A.E., et al., *Effect of using acoustic flo-tone training device and its smartphone application on enhancing inhalation technique from metered-dose inhaler with spacer in asthmatic children*. Experimental Lung Research, 2022. **48**(7-8): p. 224-238.