

# Principles of Metered-Dose Inhaler Design

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### **Summary**

The pressurized metered-dose inhaler (pMDI) was introduced to deliver asthma medications in a convenient and reliable multi-dose presentation. The key components of the pMDI device (propellants, formulation, metering valve, and actuator) all play roles in the formation of the spray, and in determining drug delivery to the lungs. Hence the opportunity exists to design a pMDI product by adjusting the formulation, metering-valve size, and actuator nozzle diameter in order to obtain the required spray characteristics and fine-particle dose. Breath-actuated pMDIs, breath-coordinated pMDIs, spray-velocity modifiers, and spacer devices may be useful for patients who cannot use a conventional press-and-breathe pMDI correctly. Modern pMDI devices, which contain non-ozone-depleting propellants, should allow inhalation therapy via pMDI to extend well into the 21st century for a variety of treatment indications. *Key words: metered-dose inhaler, MDI, asthma, chronic obstructive pulmonary disease, spacer, aerosol, drug delivery.* [Respir Care 2005;50(9):1177–1188.

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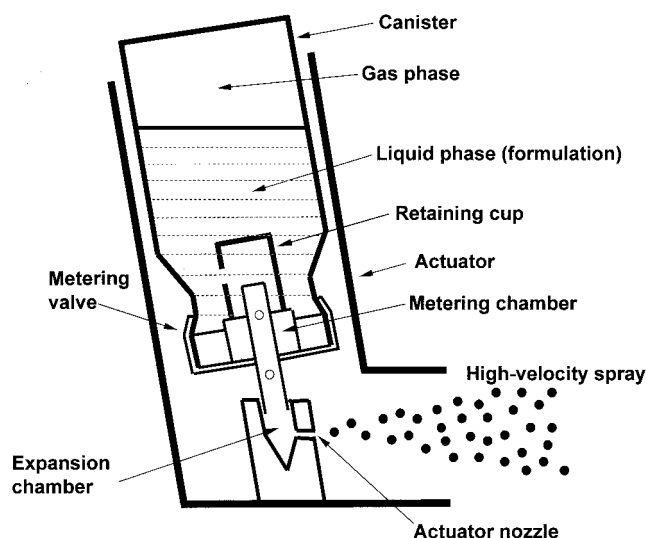


Fig. 1. Schematic of typical pressurized metered-dose inhaler.

### Introduction: Development of the Pressurized Metered-Dose Inhaler

In the first half of the 20th century, inhaled drugs for the treatment of asthma and chronic obstructive pulmonary disease (COPD) were mostly delivered via hand-held, squeeze-bulb nebulizers. These devices were fragile, and since the dose varied with hand pressure, they did not provide consistent drug delivery. As described in detail by Thiel,<sup>1</sup> Riker Laboratories set out in the mid-1950s to develop formulations of bronchodilator drugs in pressurized containers, providing greater convenience and a more reliable dose. This development followed the introduction of proprietary cosmetic aerosols as pressure-packs, and coincided with the invention of a metering valve capable of providing the patient with at least 100 precise doses.

The pressurized metered-dose inhaler (pMDI, Fig. 1) quickly became the most important device for delivering inhaled drugs, and today approximately 500 million are produced annually.<sup>2</sup> Initially, they were given the acronym

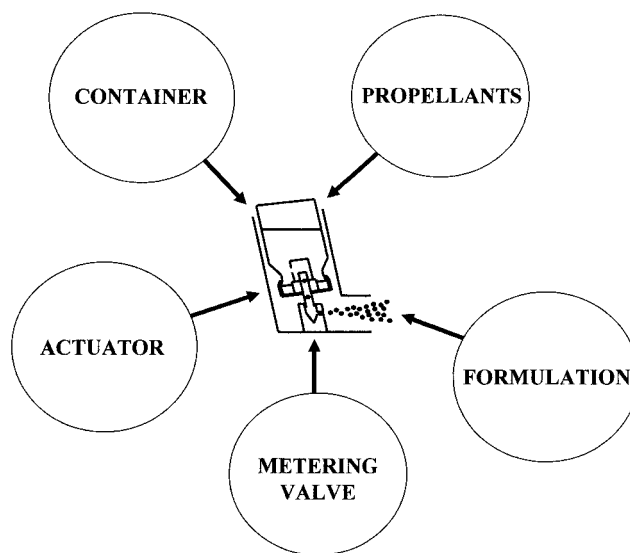


Fig. 2. The key component parts of the pressurized metered-dose inhaler.

“MDI,” but the term “pMDI” is preferable, in order to distinguish them from dry powder inhalers (DPIs) and other nonpressurized devices, some of which also have a multi-dose capability. The pMDI was once termed “the most complex dosage form used in medicine today,”<sup>3</sup> although with the development of increasingly sophisticated DPIs and microprocessor-controlled nebulizers, this may no longer be true.

### Component Parts of the pMDI

The pMDI comprises several components (Fig. 2), each of which is important to the success of the whole device. These components are container, propellants, drug formulation, metering valve, and actuator. It was demonstrated many years ago that the aerosol size from a pMDI could be influenced by a variety of factors associated with these components,<sup>4</sup> as listed in Table 1.

#### Container

The pMDI container must be able to withstand the high pressure generated by the propellant, it must be made of inert materials, and it must be sufficiently robust. The first prototype pMDI was formulated in a CocaCola bottle,<sup>1</sup> and smaller (10 mL) glass bottles were used in the earliest marketed pMDIs. Stainless steel has also been used as a pMDI container material. Aluminum is now preferred, since, compared to glass, it is lighter, more compact, less fragile, and light-proof. Coatings on the internal container surfaces may be useful to prevent adhesion of drug particles and chemical degradation of drug.<sup>5</sup>

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Table 1. Device and Formulation Variables That Influence Drug Delivery From Pressurized Metered-Dose Inhalers

Component	Details
Container	Internal coating
Propellants	Type and mixture
	Vapor pressure
Formulation	Ambient temperature
	Suspension versus solution
	Presence of surfactants
	Presence of ethanol and other excipients
	Drug concentration
Metering Valve	Drug particle size in suspension formulations
	Volume of metering chamber
	Valve design
	Elastomers
	Time since last actuation
Actuator	Orientation during storage
	Expansion chamber size and shape
	Nozzle diameter
	Nozzle path length
	Mouthpiece length and shape
	Breath-actuation/breath coordination
	Spray velocity modification
	Spacer attachments

## Propellants

Propellants in pMDIs are liquefied compressed gases that are in the gaseous phase at atmospheric pressure, but form liquids when compressed. They are required to be nontoxic, nonflammable, compatible with drugs formulated either as suspensions or solutions, and to have appropriate boiling points and densities.<sup>6</sup> To ensure consistent dosing, the vapor pressure must be constant throughout the product's life, and this rules out the use of compressed gases such as carbon dioxide, the pressure of which would decrease as doses were emitted.

Chlorofluorocarbons (CFCs) meet the required criteria, and pMDIs have traditionally been formulated with the highly volatile CFC-12 (dichlorodifluoromethane) as the major component. CFC-11 (trichlorofluoromethane) or CFC-114 (dichlorotetrafluoroethane), which have higher boiling points, may be used to modify the vapor pressure, and to facilitate preparation of the formulation. CFC-12 may be added to the container either at low temperature, before the metering valve is crimped in place (cold-filling), or via the metering valve after crimping (pressure-filling). A key property of CFCs is that within a closed container they form a 2-phase (liquid and saturated vapor) system, such that a dynamic equilibrium exists between liquid and vapor phases, giving a constant vapor pressure irrespective of whether the can is full or nearly empty. The vapor pressure inside a pMDI is typically 300–500 kPa

(3–5 atmospheres or 2,250–3,750 mm Hg), depending on the propellant mixture, the presence of other excipients (surfactants and other inactive components of the formulation), and ambient temperature.

Recently, the use of CFCs was banned under international agreement, because the release of chlorine during their degradation damages the ozone layer in the stratosphere.<sup>7</sup> Formulations containing one of 2 hydrofluoroalkanes (tetrafluoroethane [HFA-134a] and heptafluoropropane [HFA-227]) are now appearing on the market.<sup>8</sup> Reformulation of pMDIs with HFA propellants has led to many challenges, often involving the development of new excipients and metering valves.<sup>9,10</sup> HFA-134a and HFA-227 have broadly similar thermodynamic properties to CFC-12, but no HFA equivalent to CFC-11 or CFC-114 is available, so excipients with lower volatility may be required to modify the vapor pressure. This issue also influences the filling methods that are feasible for HFA products, and has led to the development of novel pressure-filling processes.<sup>11</sup> It has also been necessary to undertake extensive toxicity testing on the new propellants, and then to conduct clinical trials demonstrating safety and efficacy of new drug formulations. Taking into account the time required for reformulation, toxicity testing, and clinical testing, it has been estimated that development of a new HFA formulation of an inhaled drug takes about 10 years.<sup>8</sup> While CFC replacement continues, an essential-use exemption was granted for pulmonary inhalers, allowing the continued use of CFCs in recognition of the unique health benefits that pMDIs provide.<sup>12</sup>

HFAs are “greenhouse gases,”<sup>6</sup> which could lead to future restrictions on their use, although their contribution to global warming is likely to be very small.<sup>9</sup> Dimethyl ether, propane, or butane could be considered as propellants,<sup>5</sup> but propane and butane are likely to be ruled out because of their flammability.

## Drug Formulation

Drugs in pMDIs take the form of either particulate suspensions or solutions. Suspensions are formed by micronization, usually in a fluid-energy mill.<sup>13</sup> Suspensions have been widely used in pMDIs, because CFCs are nonpolar liquids in which many drugs have low solubility, and good chemical stability is achieved. Polar salts of drugs such as sulfates are sometimes used to further reduce solubility. Surfactants (usually sorbitan trioleate, oleic acid, or soya lecithin, in concentrations ranging from 0.1% to 2%) are used in CFC pMDIs to reduce particle aggregation and lubricate the valve mechanism. However, these surfactants are virtually insoluble in HFA-134a and HFA-227.<sup>10</sup> The use of ethanol as a low-volatility co-solvent in HFA formulations has become widespread, initially to solubilize the surfactants approved for use in CFC formulations, but

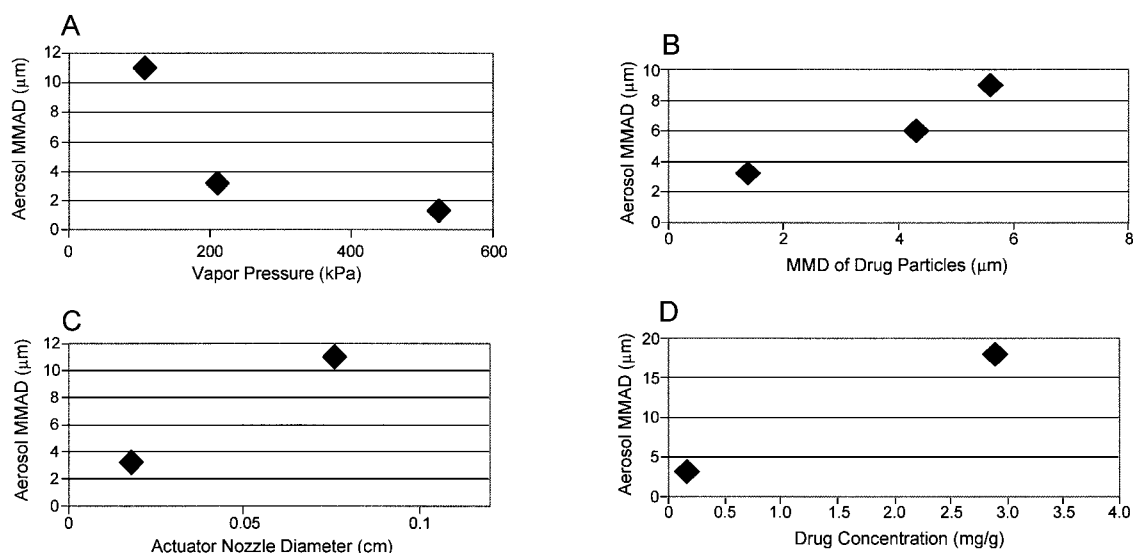


Fig. 3. Effect of changes in (A) propellant vapor pressure, (B) mass median aerodynamic diameter (MMAD) of suspended drug particles, (C) actuator nozzle diameter, and (D) drug concentration, on the MMAD of the emitted aerosol from experimental pressurized metered-dose inhalers. (Adapted from Reference 4.)

more recently to solubilize the drug itself.<sup>14</sup> Solution formulations were used in many early CFC bronchodilator aerosols in the 1960s and 1970s, with anti-oxidants and flavoring agents added as excipients.

The particle size distribution of a pMDI aerosol depends on the physicochemical properties of the formulation.<sup>5</sup> For instance, work undertaken over 35 years ago by Polli et al<sup>4</sup> showed that the aerosol size for suspension formulations may be reduced if the formulation has a high vapor pressure, a small drug particle size, or a low drug concentration (Fig. 3).

Some companies have chosen to develop HFA pMDI products bioequivalent to the CFC pMDIs they replace,<sup>15</sup> while other companies have taken the opportunity afforded by the CFC ban to develop HFA products with solution formulations, which have better lung deposition than their CFC counterparts<sup>16</sup> and which may be clinically effective in smaller doses.<sup>17</sup> Recent data suggest that delivered dose and fine-particle dose from HFA pMDIs may be less dependent on ambient temperature than are their CFC counterparts.<sup>18</sup>

A difference in density between the drug particles and the propellants will cause the drug particles either to rise to the liquid surface or to sink under the influence of gravity.<sup>13</sup> Patients are instructed to shake suspension-formulation pMDIs immediately prior to use, to ensure uniform dispersion of the drug particles in the propellants and, hence, that dosing is reproducible.<sup>19</sup> A suspension of hollow particles (PulmoSpheres, Nektar Therapeutics, San Carlos, California) was shown to form a homodispersion when mixed with propellant, which permeated the drug particles themselves, providing a more stable suspension.<sup>20</sup>

Most pMDIs deliver only 100–200 μg of drug per shot, partly because potential problems with valve clogging limits the quantity of drug that can be incorporated into a single dose of a suspension formulation.<sup>21</sup> However, recent work suggests that higher doses are possible with solution formulations. Complexing excipients may be used to increase drug solubility in propellants while minimizing the quantity of ethanol in the formulation, offering the possibility of obtaining fine-particle doses of 1.0–1.5 mg per shot with solution-formulation pMDIs.<sup>22</sup>

## Metering Valve

The metering valve crimped onto the container is the most critical component of the pMDI, and has a volume ranging from 25 μL to 100 μL. While there are many designs of metering valve, they all operate on the same basic principle.<sup>23</sup> Before firing, a channel between the body of the container and the metering chamber is open, but as the pMDI is fired, this channel closes, and another channel connecting the metering chamber to the atmosphere opens. The pressurized formulation is expelled rapidly into the valve stem, which, together with the actuator seating, forms an expansion chamber in which the propellant begins to boil (Fig. 4). The canister is used in the inverted position, with the valve below the container so that the valve will refill under gravity. Some valves are surrounded by a retaining cup that contains the next few doses of drug (see Fig. 1). Several other valve designs aimed at improving the precision of dosing were recently described.<sup>23,24</sup>

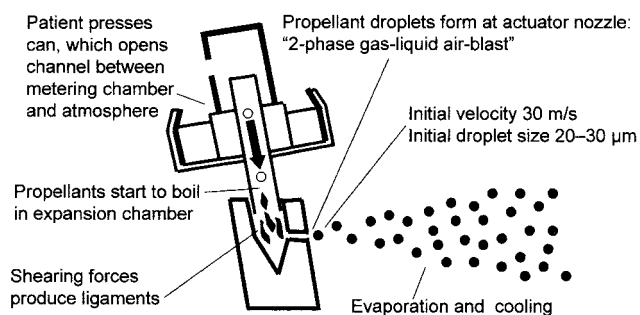


Fig. 4. How the spray from a pressurized metered-dose inhaler is formed.

It is important to ensure that the emitted dose is as reproducible as possible, irrespective of when the pMDI was last actuated, and irrespective of the orientation of the pMDI during storage.<sup>23</sup> When tested *in vitro*, pMDIs are usually “primed” by firing several times to waste, but this is seldom done in clinical practice. When CFC pMDIs are primed, stored valve-down for 3 hours, shaken, and then actuated, the drug content of the first dose may be erratic.<sup>25</sup> Improvements in valve design may have largely eliminated this problem, in addition to giving a more predictable dose at the end of the canister’s life span, when the pMDI is almost empty.<sup>18</sup>

Compatibility of the formulation with the valve components is essential. Elastomeric seals can swell because of solubility in CFCs, but this effect may be less marked in HFAs, so that the valve elastomers that function well with CFCs may not do so with HFAs. This has required the development of new elastomeric systems for use with HFAs. Valve elastomers must also be selected to ensure low concentrations of extractables and leachables into the formulation.<sup>26</sup> Many newly designed valves appear to function adequately without the need for surfactants to lubricate the valve stem.<sup>9</sup> For instance, one HFA formulation of albuterol (HFA Ventolin, GlaxoSmithKline, Research Triangle Park, North Carolina) contains drug and HFA-134a only, without the use of any surfactant,<sup>23</sup> while the equivalent CFC formulation also contains oleic acid as a surfactant (Table 2).

### Actuator

The complete pMDI canister is fitted into a plastic actuator for use by the patient. The design of the actuator is important, particularly because the aerosol particle size is determined partly by the nozzle diameter, which ranges between 0.14 mm and 0.6 mm.<sup>14</sup> Aerosol particle size varies directly with nozzle diameter,<sup>4,5</sup> and particle size influences lung deposition. For one solution formulation containing the bronchodilators fenoterol and ipratropium bromide (Fig. 5), mean lung deposition, measured via

Table 2. Comparison of the Albuterol Formulations\* in CFC and HFA Propellants

	CFC Ventolin	HFA Ventolin
Active ingredient	Albuterol sulfate	Albuterol sulfate
Formulation type	Suspension	Suspension
Excipient	Oleic acid	None
Propellants	CFC-11/12	HFA-134a

\*Ventolin, made by GlaxoSmithKline  
CFC = chlorofluorocarbon  
HFA = hydrofluoroalkane

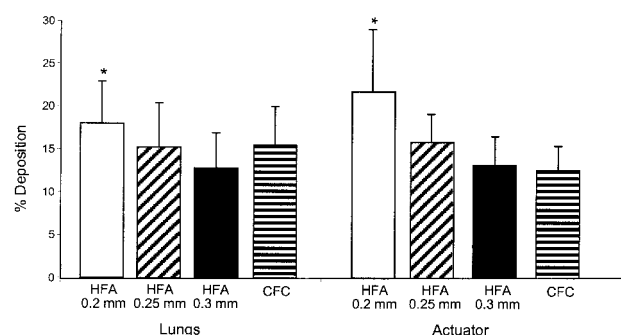


Fig. 5. Lung deposition and actuator retention with a hydrofluoroalkane (HFA) solution formulation of fenoterol and ipratropium bromide delivered through actuator nozzles with diameters of 0.2 mm, 0.25 mm, and 0.3 mm. The data are compared with values from a chlorofluorocarbon (CFC) formulation containing the same drugs. \* indicates a statistically significant difference compared with HFA 0.3 mm. (Adapted from Reference 27.)

gamma scintigraphy, increased step-wise, from 12.8% of the dose, to 15.2%, to 18.0%, as the actuator nozzle diameter was reduced from 0.3 mm to 0.25 mm to 0.2 mm.<sup>27</sup> However, the narrowest nozzle gave the greatest deposition on the mouthpiece of the actuator, probably because of a wider spray-cone angle, and this observation was confirmed by the results of another study.<sup>28</sup> Aerosol particle size can also be modified by changing the length of the actuator nozzle path.<sup>10</sup>

The actuator nozzle is critical to spray formation.<sup>29,30</sup> The final atomization process has been described as a 2-phase gas/liquid air-blast.<sup>23</sup> When the dose leaves the actuator nozzle, the liquid ligaments embedded in the propellant vapor are pulled apart by aerodynamic forces to form a dispersion of liquid droplets (see Fig. 4). Evaporation of propellant, both in the initial flashing and as the droplets move away from the nozzle, cools the droplets, so the spray usually feels cold on the back of the throat. However, as shown in Table 3, both spray force and temperature reduction appear to be less marked with some HFA formulations.<sup>2,31</sup> In one study, spray force was decreased by reducing the actuator nozzle diameter from



Table 3. Maximum Impact Force and Minimum Plume Temperature of CFC-Based and HFA-Based pMDI Products

Product	Manufacturer	Maximum Impact Force (mN)*	Minimum Plume Temperature (°C)*	Formulation
Qvar HFA	3M	34	+4	Beclomethasone dipropionate solution, HFA-134a, ethanol
Becotide CFC	GlaxoSmithKline	106	−32	Beclomethasone dipropionate suspension, oleic acid, CFC-11/12
Proventil HFA	Schering-Plough	29	+8	Albuterol suspension, oleic acid, HFA-134a, ethanol
Proventil CFC	Schering-Plough	82	−26	Albuterol suspension, oleic acid, CFC-11/12
Flixotide HFA	GlaxoSmithKline	117	−17	Fluticasone propionate suspension, HFA-134a
Flixotide CFC	GlaxoSmithKline	102	−21	Fluticasone propionate suspension, CFC-11/12
Ventolin CFC	GlaxoSmithKline	95	−29	Albuterol suspension, oleic acid, CFC-11/12
Maxair CFC	3M	94	−3	Pirbuterol suspension, sorbitan trioleate, CFC-11/12

CFC = chlorofluorocarbon

HFA = hydrofluoroalkane

pMDI = pressurized metered-dose inhaler

\*Measured a few centimeters from the actuator nozzle of various pressurized metered-dose inhaler (pMDI) products.

mN = milliNewton

(Adapted from Reference 31.)

0.48 mm to 0.32 mm.<sup>31</sup> For a CFC pMDI, the spray duration is typically 100–200 ms, plume velocity at the actuator nozzle is typically 30 m/s, and initial mean droplet diameter is 20–30  $\mu\text{m}$ .<sup>29,32</sup> The combination of large droplet size and high spray velocity cause high oropharyngeal deposition.<sup>27</sup> The spray may initially be very turbulent, which may increase deposition in the front part of the mouth.<sup>33</sup>

The first pMDI to reach the market, in 1956, had an elongated mouthpiece, about 8 cm in length,<sup>1</sup> but currently marketed pMDIs almost all have much shorter mouthpieces, only 2 to 3 cm, to improve convenience and portability.

Since the patient cannot usually see the contents of the pMDI, the patient has no way to gauge effectively the fullness or emptiness of the inhaler.<sup>34</sup> To overcome this problem, the Food and Drug Administration issued guidance to the effect that new pMDI actuators should be equipped with a dose counter that indicates the number of doses remaining.<sup>35</sup> This measure is intended to prevent the inhaler from being either discarded prematurely or used beyond the recommended number of doses.

### Designing pMDI products

As set out in Table 1, the actuator design, together with the properties of the formulation, determine the spray characteristics from HFA solution aerosols. Lewis et al<sup>14</sup> described a series of empirical equations that allow the fine-particle fraction of HFA-134a systems to be predicted from knowledge of variables that include the actuator nozzle diameter ( $A$ , in mm), the metered volume size ( $V$ , in  $\mu\text{L}$ ), and the HFA-134a content ( $C_{134}$ , in percent). One of these equations predicts that the fine-particle fraction of a solution formulation containing HFA-134a and ethanol can be expressed as follows:

fine-particle fraction (%) =

$$2.1 \times 10^{-5} \times A^{-1.5} \times V^{-0.25} \times C_{134}^3$$

This formula is really the modern embodiment of the pioneering work of Polli et al,<sup>4</sup> described earlier, and, importantly, it permits designing a pMDI with the desired spray characteristics and fine-particle dose by judicious selection of appropriate formulation and device variables.<sup>36</sup>

### Advantages and Limitations of the pMDI

pMDIs have been favored by patients for almost 50 years, because pMDIs combine the practical benefits of small size, portability, convenience, and unobtrusiveness, and are relatively inexpensive. The multi-dose capability means that a dose is immediately available when required to treat a wheezing attack. A dose can be delivered in a few seconds, unlike nebulizer therapy, which typically takes several minutes. Since the inhaler is pressurized, the contents are protected from the ingress of both moisture and pathogens. These factors provide powerful reasons why the pMDI has been successful for so long (Table 4).

Conversely, the limitations of pMDIs have also been recognized for decades. Drug delivery is highly dependent on the patient's inhaler technique. Reports of inhaler misuse are commonplace in the literature, and failure to coordinate or synchronize actuation with inhalation is said to be the most important problem patients have with pMDIs.<sup>37</sup> Some patients suffer the so-called cold-Freon effect (Freon is the registered trademark of CFCs from DuPont), in which the arrival of the cold propellant spray on the back of the throat causes the patient to stop inhaling.<sup>37</sup> The misuse of pMDIs can result in a suboptimal, or even zero, lung dep-

Table 4. Advantages and Disadvantages of Standard "Press and Breathe" pMDIs

Advantages	Disadvantages
Small size, portable, unobtrusive	Require propellants
Quick to use	Drug delivery highly dependent on good inhaler technique
Convenient	Possible to get no drug in lungs with very bad technique
More than 100 doses available	Most products have low lung deposition
Usually inexpensive	Most products have high oropharyngeal deposition
Pressurization of contents protects against moisture and bacteria	Difficult to deliver high doses

osition.<sup>38</sup> Misuse of corticosteroid pMDIs is associated with decreased asthma stability, especially when misuse involves poor coordination.<sup>39</sup>

Another problem with CFC pMDIs and some HFA pMDIs is that even with good inhaler technique they deposit only 10–20% of the dose in the lungs, with most of the dose being deposited in the oropharynx.<sup>38</sup> High oropharyngeal deposition of glucocorticosteroids can cause localized adverse effects (dysphonia and candidiasis) and systemic adverse effects. Poor lung deposition and high oropharyngeal deposition have been partly addressed by some recent HFA pMDI products that better target inhaled drugs to the lower respiratory tract.<sup>16,17</sup>

The drug-delivery characteristics of standard press-and-breathe pMDIs bear on the possible uses of pMDIs. Low lung deposition and dependence on inhaler technique can be accepted in the case of drugs for asthma and COPD, where the patient can simply take another dose as required. But those limitations may not be acceptable for targeted therapies that have narrow therapeutic windows, such as inhaled peptides for systemic action, where a very precise and reproducible dose may be needed.

Some device technologies aimed at improving the ease of use of pMDIs and/or improving the efficiency of drug delivery will now be reviewed.

### Breath-Actuated pMDIs

The concept of a breath-actuated pMDI is a good one, because it solves the problem of patient coordination of actuation with inhalation. Breath-actuated inhalers sense the patient's inhalation through the actuator and fire the inhaler automatically in synchrony.<sup>23</sup> Patients seem to find breath-actuated pMDIs easier to use than conventional pMDIs and may prefer them over other devices.<sup>40</sup> Some breath-actuated inhalers are described below, and several others are currently in development.

### Autohaler

An early model of the Autohaler breath-actuated device was described over 30 years ago,<sup>41</sup> but it operated noisily and some patients could not generate the necessary flow to trigger the device. The current Autohaler device (3M Pharmaceuticals, St Paul, Minnesota) overcomes these limitations, since it is quiet and can be triggered by a flow of only 30 L/min (Fig. 6). A lever on the top of the device is raised, and then inhalation triggers a vane mechanism, which results in the pMDI being actuated automatically by a spring. This device gave good lung deposition, even with patients who habitually exhaled immediately after firing a conventional pMDI.<sup>38</sup>

### Easibreathe

The Easibreathe is a pMDI actuator, originally developed by Norton Healthcare (London, United Kingdom).<sup>23</sup> In some ways it resembles the Autohaler, but is simpler to use because opening the mouthpiece automatically prepares the device for inhalation. The Easibreathe contains a pneumatic system, which restrains the operating spring. Actuation occurs in synchrony with inhalation at only 20 L/min.

### K-Haler

With the K-Haler breath-actuated device (Clinical Designs, Aldsworth, United Kingdom), the dose is actuated into a kinked tube, which is straightened by a breath-operated lever, which releases the dose.<sup>42</sup> Opening the device's dust cap kinks the tube and depresses the pMDI valve stem.

### MD Turbo

The MD Turbo (Respirics, Raleigh, North Carolina) is a breath-actuated inhaler that can accommodate various pMDI products. It incorporates "i-Point" technology, with which actuation only occurs at a pre-determined inspiratory flow.

### Xcelovent

Another breath-actuated pMDI device, the Xcelovent, designed by Meridica (Melbourn, United Kingdom), delivers an HFA formulation containing budesonide and formoterol. Xcelovent may in the future be developed by Pfizer (Sandwich, United Kingdom).

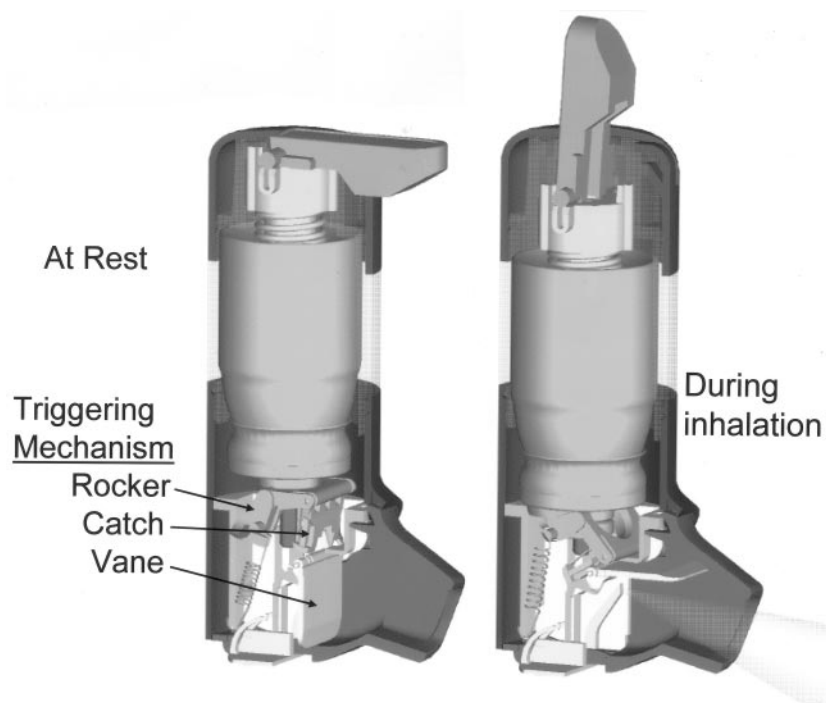


Fig. 6. Autohaler breath-actuated inhaler, at rest and during inhalation. The inhaler is primed by lifting the lever on the top of the device. (Courtesy 3M Pharmaceuticals, St Paul, Minnesota.)

## Smartmist

A sophisticated microprocessor-controlled pMDI actuator device, the Smartmist (Aradigm, Hayward, California),<sup>43</sup> accommodates a standard pMDI canister. A pneumotachograph reads the inhaled flow rate and volume, and a microprocessor actuates the pMDI only when a pre-programmed combination of flow and volume is achieved. While this device may be too complex and too expensive for routine pMDI use, it could provide a valuable function in controlled clinical trials by helping to ensure correct pMDI technique.

## Breath-Coordinated Devices

### Easidose

The Easidose (Bespak, Milton Keynes, United Kingdom) has been described as a breath-coordinated device, rather than a breath-actuated device.<sup>44</sup> Inhaled air can pass through it only when the pMDI is depressed, so the patient's inhalation should be coordinated with actuation.

### Breath Coordinated Inhaler

The Breath Coordinated Inhaler (Aeropharm, Edison, New Jersey)<sup>45</sup> is designed to coordinate the inspiration with the release of the dose. The device controls the in-

halation flow rate through the actuator, so the patient has more time to actuate the pMDI reliably during inhalation.

## Other Novel Devices

Breath-actuated inhalers and breath-coordinated inhalers do not attempt to solve the cold-Freon effect problem,<sup>37</sup> but devices with slower spray velocity are likely to help. At least one device is already marketed, and several others are in development. In 1989, Byron et al<sup>46</sup> reported that it is possible to reduce the nonrespirable fraction by placing baffles near the actuator nozzle, to intercept large, rapidly moving droplets. However, no devices based on this principle seem to be in development.

### Spacehaler

The Spacehaler (Celltech Medeva, Slough, United Kingdom), formerly known as the Gentlehaler (Schering-Plough, Kenilworth, New Jersey), is a compact, low-velocity-spray pMDI, 7.5 cm in length. The device produces a rapidly spinning vortex at the actuator nozzle, which reduces the initial spray velocity to approximately 2 m/s, which decreases oropharyngeal deposition and probably provides better lung deposition than a standard pMDI.<sup>47</sup>



## Tempo

The Tempo device, currently in development (Map Pharmaceuticals, Mountain View, California, formerly Sheffield Pharmaceuticals, St Louis, Missouri), contains a novel mechanism to manipulate the plume and reduce momentum of the spray. Some of the inhaled air is entrained to blow in the opposite direction to that of the spray plume.<sup>48</sup> Both *in vitro* and *in vivo* data show that the Tempo may be associated with less oropharyngeal deposition and better lung deposition than a standard pMDI. This device also includes a breath-actuated capability.

## BronchoAir

BronchoAir (BronchoAir Medizintechnik, Munich, Germany), a novel actuator, has a series of air jets that surround the valve-stem induction port, but the effect of this device on fine-particle dose seemed to vary between pMDI formulations.<sup>49</sup>

## Spacer Devices

### Spacer Design

Spacer devices are also known as add-on devices, accessory devices, extension devices, and holding chambers. They are attachments to pMDI actuators, with volumes ranging from 20 mL to 750 mL in commercially available models. Spacers perform several functions. By placing some distance (and, thus, time) between the point of aerosol generation and the patient's mouth, they reduce oropharyngeal deposition and increase lung deposition. Spacers make pMDIs easier to use by reducing or eliminating the need for coordination between actuation and inhalation, and reducing the cold Freon effect.<sup>50,51</sup> These benefits are achieved at the expense of making the pMDI system substantially larger and less convenient. Spacers can be grouped into 3 categories (Fig. 7): simple tube extensions to the actuator mouthpiece; holding chambers, which generally have a one-way valve in the mouthpiece to prevent the patient blowing the dose away; and reverse-flow devices, in which the spray is actuated away from the patient, into the spacer.

The 8-cm long actuator mouthpiece to the first pMDI, in 1956, was arguably the first tube spacer device, and 2 years later Franklin et al<sup>52</sup> described a 14-inch tube spacer for a hydrocortisone pMDI. At least 2 breath-actuated inhalers have been designed for use with short tube spacers to reduce oropharyngeal deposition.<sup>45,53</sup> One tube spacer, Synchroner (Aventis, Bridgewater, New Jersey), had an open section in its upper surface,<sup>54</sup> which served as a coordination aid, because the patient could see the spray emerging from the open section if actuation and inhalation were not



Fig. 7. Spacer devices used with pressurized metered-dose inhaler. Clockwise from top: InspirEase reverse-flow device, Azmacort tube spacer, Volumatic large-volume holding chamber, Aero-chamber.

correctly coordinated. This device was discontinued in January 2004.

Large-volume holding chambers include the Volumatic (GlaxoSmithKline) and Nebuhaler (AstraZeneca, Loughbrough, United Kingdom), and well as smaller devices such as Aerochamber (Trudell, London, Ontario, Canada) and Babyhaler (GlaxoSmithKline), which is specifically for use with infants. Both the Volumatic and Nebuhaler are pear-shaped, to match the shape of the expanding spray plume.<sup>50</sup> Holding chambers have proven to be a viable alternative to nebulizers for delivering large bronchodilator doses to patients with severe acute asthma or COPD.<sup>55</sup>

Drug delivery from spacer devices depends on the patient's inhalation technique, and in the case of plastic spacers it may be affected by static-charge build-up on the spacer walls.<sup>56</sup> At least one lightweight metal spacer is commercially available and is not affected by static charge.<sup>57</sup> Drug delivery from plastic spacers can be enhanced by antistatic linings on the internal walls and by appropriate washing techniques.<sup>58</sup> Recently a plastic spacer (Aerochamber Max) made from an "electrostatic dissipative" polymer was described.<sup>59</sup>

Some spacer devices have universal adaptors that allow them to be used with any pMDI actuator mouthpiece, while others have rigid adaptors that will only fit one shape of mouthpiece. These design features are sometimes reinforced by consideration of whether the spray from a particular pMDI matches the shape of the spacer, but may also be influenced by marketing considerations. Some spac-

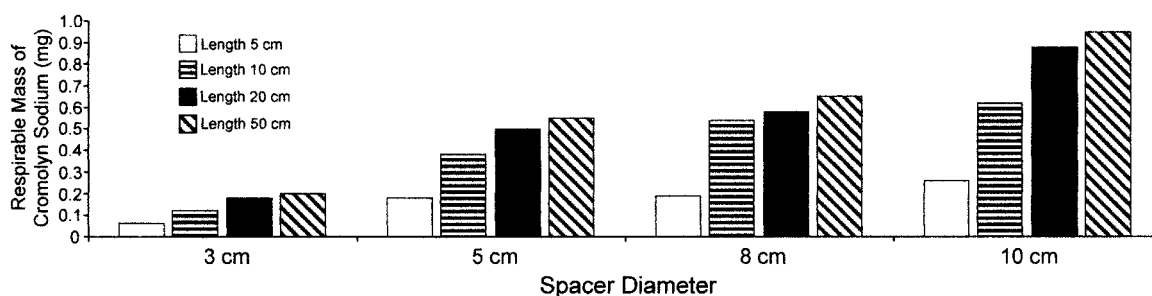


Fig. 8. Effect of spacer diameter and spacer length on availability of cromolyn sodium from a pressurized metered-dose inhaler. (Adapted from Reference 63.)

ers have a flow-rate signaling system that informs the patient if the inhalation is too fast.

One-way valves in large-volume holding chambers must be designed to operate effectively at all likely inhalation pressures encountered in clinical practice. The dead space in the mouthpiece or face mask should be minimized to ensure that as much of the suspended dose as possible is available to the patient.<sup>56</sup> Leaks of aerosol from either a mouthpiece or face mask should, obviously, be avoided.<sup>60</sup>

Reverse-flow devices involve either a bag into which the pMDI is actuated, and which collapses upon inhalation,<sup>61</sup> or a chamber with air vents that open during inhalation, allowing the dose to be inhaled in the entrained air.<sup>62</sup> The InspirEase (Schering-Plough, Kenilworth, New Jersey) and Optihaler (Respironics, Cedar Grove, New Jersey) are examples of reverse-flow devices based, respectively, on a collapsible bag and an air vent.

### Drug Delivery From Spacer Devices

As shown in Figure 8, the amount of drug available from a spacer device increases with both diameter and length.<sup>63</sup> Smaller spacers (< 200 mL) are convenient for patients, but particle deposition on the internal walls from high-velocity aerosol droplets is greater than with large-volume spacers (> 500 mL), with a consequent reduction in the dose available for inhalation.<sup>64</sup> The fine-particle dose with some large-volume (750 mL) spacers is higher than that from a pMDI alone, whereas some smaller spacers decrease the fine-particle dose.<sup>65</sup> However, increasing the spacer volume to > 1 L would probably be counterproductive, because the spacer would no longer be easily portable, and because it would be more difficult for the patient to inhale the complete contents.

The amount of deposition on the spacer walls, and thus the amount of drug available for inhalation, partly depends on the characteristics of the spray and the design of the spacer, so lung delivery from each pMDI/spacer combination is unique and difficult to predict.<sup>50</sup> There have been relatively few studies so far to assess drug delivery from

HFA pMDIs via different spacers. However, one study found that, while a large-volume holding chamber delivered a higher respirable dose than a small-volume holding chamber with a CFC-albuterol product, this difference was not apparent with an HFA-albuterol product.<sup>66</sup> Recent data suggest that not only the total dose emitted from a spacer device, but also the profile of that dose as a function of inhaled volume, should be considered.<sup>67</sup>

### Summary

pMDIs are sometimes regarded as old-fashioned inhalers that have changed little in half a century. However, this is only partly true. While the basic press-and-breathe pMDI is actually much the same as it was in the 1950s, apart from replacement of CFCs with HFA propellant formulations, there have been great strides in pMDI design relating to both devices and formulations. Device technology is available to assist patients with coordination and the cold-Freon effect problems and to adjust the characteristics of the spray plume. Careful design of both device and formulation can be used to achieve the desired aerosol size distribution, spray temperature, and spray impact force, as well as the mass of drug available per shot. These technologic improvements should mean that pMDI therapy can continue successfully well into the 21st century and provide many opportunities for inhalation therapy that are not confined to the traditional uses in the management of asthma and COPD.

### REFERENCES

1. Thiel CG. From Susie's question to CFC free: an inventor's perspective on forty years of MDI development and regulation. In: Dalby RN, Byron PR, Farr SJ, editors. *Respiratory drug delivery V*. Buffalo Grove: Interpharm Press; 1996:115–123.
2. Brown BAS. Dispelling the myths of MDIs. *Drug Delivery Technology* 2002;2(7):1–7.
3. Tansey IP. The challenges in the development of metered-dose inhalation aerosols using ozone-friendly propellants. *Proceedings of the First European Pharm Tech Conference, Dusseldorf*; 1993:182–187.

4. Polli GP, Grim WM, Bacher FA, Yunker MH. Influence of formulation on aerosol particle size. *J Pharm Sci* 1969;58(4):484–486.
5. Smyth HD. The influence of formulation variables on the performance of alternative propellant-driven metered dose inhalers. *Adv Drug Deliv Revs* 2003;55(7):807–828.
6. Noakes T. Medical aerosol propellants. *J Fluorine Chem* 2002;118(1–2):35–45.
7. Molina MJ, Rowlands FS. Stratospheric sink for chlorofluoromethanes: chlorine atomcatalysed destruction of ozone. *Nature* 1974;249:1810–1812.
8. Partridge MR, Woodcock AA. Propellants. In: Bisgaard H, O'Callaghan C, Smaldone GC, editors. *Drug delivery to the lung*. New York: Marcel Dekker; 2002:371–388.
9. McDonald KJ, Martin GP. Transition to CFC-free metered dose inhalers: into the new millenium. *Int J Pharm* 2000;201(1):89–107.
10. Vervaeke C, Byron PR. Drug-surfactant-propellant interactions in HFA-formulations. *Int J Pharm* 1999;186(1):13–20.
11. Smith IJ. The challenge of reformulation. *J Aerosol Med* 1995;8 Suppl 1:S19–S27.
12. Food and Drug Administration. Chlorofluorocarbon propellants in self-propelled containers; addition to list of essential uses. *Federal Register* 1993;58:6086–6088.
13. Hallworth GW. The formulation and evaluation of pressurised metered dose inhalers. In: Ganderton D, Jones T, editors. *Drug delivery to the respiratory tract*. Chichester, United Kingdom: Ellis Horwood; 1987:87–118.
14. Lewis DA, Ganderton D, Meakin BJ, Brambilla G. Theory and practice with solution systems. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, editors. *Respiratory drug delivery IX*. River Grove, Illinois: Davis Healthcare International; 2004:109–115.
15. Cripps A, Riebe M, Schulze M, Woodhouse R. Pharmaceutical transition to non-CFC pressurized metered dose inhalers. *Respir Med* 2000;94 Suppl B:S3–S9.
16. Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998;12(6):1346–1353.
17. Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999;104(6):1215–1222.
18. Ross DL, Gabrio BJ. Advances in metered dose inhaler technology with the development of a chlorofluorocarbon-free drug delivery system. *J Aerosol Med* 1999;12(3):151–160.
19. Berg E. In vitro properties of pressurised metered dose inhalers with and without spacer devices. *J Aerosol Med* 1995;8 Suppl 3:S3–S11.
20. Hirst PH, Pitcairn GR, Weers JG, Tarara TE, Clark AR, Dellamary LA, et al. In vivo lung deposition of hollow porous particles from a pressurized metered dose inhaler. *Pharm Res* 2002;19(3):258–264.
21. Gupta P, Adjei A. Therapeutic inhalation aerosols. In: Adjei A, Gupta P, editors. *Inhalation delivery of therapeutic peptides and proteins*. New York: Marcel Dekker; 1997:185–229.
22. Stein SW, Forsyth BR, Stefely JS, Christensen JD, Albani TD, Jinks PA. Expanding the dosing range of metered dose inhalers through formulation and hardware optimisation. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, editors. *Respiratory drug delivery IX*. River Grove, Illinois: Davis Healthcare International; 2004:125–133.
23. O'Callaghan C, Wright P. The metered-dose inhaler. In: Bisgaard H, O'Callaghan C, Smaldone GC, editors. *Drug delivery to the lung*. New York: Marcel Dekker; 2002:337–370.
24. Schultz RK, Dupont RL, Ledoux KA. Issues surrounding metered dose valve technology: past, present and future perspectives. In: Byron PR, Dalby RN, Farr SJ, editors. *Respiratory drug delivery IV*. Buffalo Grove, Illinois: Interpharm Press; 1994:211–219.
25. Cyr TD, Graham SJ, Lee KY, Lovering EG. Low first-spray drug content in albuterol metered dose inhalers. *Pharm Res* 1991;8(5):658–660.
26. Cummings RH. Pressurized metered dose inhalers: chlorofluorocarbon to hydrofluorocarbon transition-valve performance. *J Allergy Clin Immunol* 1999;104(6):S230–S235.
27. Newman S, Pitcairn G, Steed K, Harrison A, Nagel J. Deposition of fenoterol from pressurized metered dose inhalers containing hydrofluoroalkanes. *J Allergy Clin Immunol* 1999;104(6):S253–S257.
28. Warren SJ, Farr SJ. Formulation of solution metered dose inhalers and comparison with aerosols emitted from conventional suspension systems. *Int J Pharm* 1995;124(2):195–203.
29. Clark AR. MDIs: physics of aerosol formation. *J Aerosol Med* 1996;9(Suppl 1):S19–S26.
30. Versteeg HK, Hargrave GK, Wigley G. The physics of aerosol formulation by pMDI: an update. *Proceedings of Drug Delivery to the Lungs XIII*. Portishead: The Aerosol Society; 2002:60–66.
31. Gabrio BJ, Stein SW, Velasquez DJ. A new method to evaluate plume characteristics of hydrofluoroalkane and chlorofluorocarbon metered dose inhalers. *Int J Pharm* 1999;186(1):3–12.
32. Rance RW. Studies of the factors controlling the action of hair sprays. *J Soc Cosmet Chem* 1974;25:545–561.
33. Davies RJ, Lewis DA, Ganderton D, Meakin BJ, Brambilla G, Murphy SD, Nicholls TR. Velocity profiling of a new HFA budesonide pMDI. In: Dalby RN, Byron PR, Peart J, Farr SF, editors. *Respiratory drug delivery VIII*. Raleigh: Davis Horwood; 2002:759–762.
34. Rubin BK, Durotoye L. How do patients determine that their metered-dose inhaler is empty? *Chest* 2004;126(4):1134–1137.
35. Food and Drug Administration. Guidance for industry: integration of dose-counting mechanisms into MDI drug products: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 2001. <http://www.fda.gov/cder/guidance/index.htm>. Accessed June 21, 2005.
36. Brambilla G, Ganderton D, Garzia R, Lewis D, Meakin B, Ventura P. Modulation of aerosol clouds produced by pressurised inhalation aerosols. *Int J Pharm* 1999;186(1):53–61.
37. Crompton GK. Problems patients have using pressurised aerosol inhalers. *Eur J Respir Dis* 1982;63(Supplement 119):57–65.
38. Newman SP, Weisz AW, Talaei N, Clarke SW. Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax* 1991;46(10):712–716.
39. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J* 2002;19(2):246–251.
40. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices. *Respir Med* 2000;94(5):496–500.
41. Crompton GK. Breath-activated aerosol. *Br Med J* 1971;2(762):652–653.
42. Bacon RJ, McDermott I, Bell J. A new breath operated actuator. In: Dalby RN, Byron PR, Peart J, Farr SF, editors. *Respiratory drug delivery VIII*. Raleigh: Davis Horwood; 2002:403–406.
43. Farr SJ, Rowe AM, Rubsamen R, Taylor G. Aerosol deposition in the human lung following administration from a microprocessor controlled metered dose inhaler. *Thorax* 1995;50(6):639–644.
44. Howlett D. Devices to assist patient co-ordination with pMDIs: a review. *Proceedings of Drug Delivery to the Lungs IX*. Portishead: The Aerosol Society; 1998:184–187.
45. Zhang FL, Genova PA, Tanguay JF, Cronin J, Sexton F, Cutie AJ, Jewett W, Adjei AL. The breath coordinated inhaler (BCI): a new

- pulmonary drug delivery device for pressurized metered dose inhalers. In: Dalby RN, Byron PR, Farr SJ, Peart J, editors. *Respiratory drug delivery VII*. Raleigh: Serentec Press; 2000:323–326.
46. Byron PR, Dalby RN, Hickey AJ. Optimized inhalation aerosols. I. The effects of spherical baffle size and position upon the output characteristics of several pressurized non-aqueous suspension formulations. *Pharm Res* 1989;6(3):225–229.
  47. Newman SP, Steed KP, Hooper G, Jones JJ, Upchurch FC. Improved targeting of beclomethasone dipropionate (250 micrograms metered dose inhaler) to the lungs of asthmatics with the Spacehaler. *Respir Med* 1999;93(6):424–431.
  48. Mohsen N. pMDI aerosol momentum manipulation and biotargeted delivery. In: Dalby RN, Byron PR, Peart J, Farr SF, editors. *Respiratory drug delivery VIII*. Raleigh: Davis Horwood; 2002:593–597.
  49. Steckel H, Müller BW. Metered dose inhaler add-on devices: an in vitro evaluation of the BronchoAir inhaler and several spacer devices. *J Aerosol Med* 1998;11(3):133–142.
  50. Newman SP, Newhouse MT. Effect of add-on devices for aerosol drug delivery: deposition studies and clinical aspects. *J Aerosol Med* 1996;9(1):55–70.
  51. Newman SP. Spacer devices for metered dose inhalers. *Clin Pharmacokinetics* 2004;43(6):349–360.
  52. Franklin W, Lowell F, Michelson AL, Schiller I. Aerosolized steroids in bronchial asthma. *J Allergy* 1958;29(3):214–221.
  53. Hardy J, Jasuja A, Frier M, Perkins A. A small volume spacer for use with a breath-operated pressurized metered dose inhaler. *Int J Pharm* 1996;142(2):129–133.
  54. Newman SP, Clark AR, Talaei N, Clarke SW. Pressurized aerosol deposition in the human lung with and without an “open” spacer. *Thorax* 1989;44(9):706–710.
  55. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest* 2005;127(1):335–371.
  56. Bisgaard H, Anhoj J, Wildhaber JH. Spacer devices. In: Bisgaard H, O’Callaghan C, Smaldone GC, editors. *Drug delivery to the lung*. New York: Marcel Dekker; 2002:389–420.
  57. Kenyon CJ, Thorsson L, Borgström L, Newman SP. The effects of static charge in spacer devices on glucocorticosteroid aerosol deposition in asthmatic patients. *Eur Respir J* 1998;11(3):606–610.
  58. Wildhaber JH, Devadason SG, Eber E, Hayden MJ, Everard ML, Summers QA, Le Souëf PN. Effect of electrostatic charge, flow, delay and multiple actuations on the in vitro delivery of salbutamol from different small volume spacers for infants. *Thorax* 1996;51(10):985–988.
  59. Mitchell J, Morton R, Schmidt J, Snyder S, Doyle C, Nagel M. Overcoming electrostatic charge retention in a new valved holding chamber (VHC): in vitro performance comparison with current devices. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, editors. *Respiratory drug delivery IX*. River Grove, Illinois: Davis Healthcare International, 2004, 705–707.
  60. Esposito-Festen JE, Ates B, van Vliet FJ, Verbraak AF, de Jongste JC, Tiddens HA. Effect of a facemask leak on aerosol delivery from a pMDI-spacer system. *J Aerosol Med* 2004;17(1):1–6.
  61. Newman SP, Woodman G, Clarke SW, Sackner MA. Effect of InspirEase on the deposition of metered dose aerosols in the human respiratory tract. *Chest* 1986;89(4):551–556.
  62. Dolovich MB. In vitro measurements of delivery of medications from MDIs and spacer devices. *J Aerosol Med* 1996;9 Supplement 1:S49–S58.
  63. Barry PW, O’Callaghan C. The optimum size and shape of spacer devices for inhalational therapy. *J Aerosol Med* 1995;8:303–305.
  64. Zak M, Madsen J, Berg E, Bulow J, Bisgaard H. A mathematical model of aerosol holding chambers. *J Aerosol Med* 1999;12(3):187–196.
  65. Barry PW, O’Callaghan C. Inhalational drug delivery from seven different spacer devices. *Thorax* 1996;51(8):835–840.
  66. Mitchell JP, Nagel MW, Rau JL. Performance of large-volume versus small volume holding chambers with chlorofluorocarbon-albuterol and hydrofluoroalkane-albuterol sulphate. *Respir Care* 1999;44(1):38–44.
  67. Verbanck S, Vervaeke C, Schuermans D, Vincken W. Aerosol profile extracted from spacers as a determinant of actual dose. *Pharm Res* 2004;21:2213–2218.

## Discussion

**Atkins:** You said current use of HFA and CFC is about 800 million MDIs worldwide, but I think it’s probably more like 450–500 million.

**Newman:** I got that number out of the literature, and I think such figures simply get passed on—correct or incorrect—from publication to publication.

**Atkins:** Regarding the impact force, I think the actuator orifice size may play a role, but I think the valve size plays a role as well. There are differences in valve size between the various CFC and HFA MDI products.

**Newman:** I appreciate that. The difficulty of interpreting these data is that much seems to be empirical, and the reasons behind some of the observations are not well understood. Where they are well understood, a lot of the information is in-house and not in the public domain.

**Dhand:** One particular concern is crusting around the pin hole in the actuator stem. If this crusting occurs, it could change the characteristics of the aerosol produced by an MDI. Yet in clinical practice I have noted that aggregation of drug powder around the pin hole is very common. Clinicians need to emphasize the need for pa-

tients to take the canisters out from the plastic actuators and wash the plastic actuators to keep the pin hole patent and clean.

**Newman:** Yes, that’s a very important observation. MDI actuator nozzles eventually get caked with drug residue, so washing the actuator is very important. Having said that, you have to be very careful to get all the water out of the actuator, or moisture can create problems with the MDI’s functioning. Keeping the actuator clean and the nozzle free from residue is important. But you shouldn’t poke a needle into the actuator nozzle, or it could be damaged.



**Smaldone:** Would you comment about how important is a priming puff and whether that importance might be different with different devices?

**Newman:** Priming is important for CFC products, because it seems to take several puffs to get the inhaler going. That's something that people do in the laboratory when testing MDIs, but that patients might not do. There are some scary data indicating that if you don't prime the MDI and you store it in the wrong orientation, you may get a low dose on the first actuation or you may get a high dose on the next actuation.<sup>1</sup> The problem has been partly overcome by improved valve technologies with HFA products. I think we are learning how to overcome that and make it much less of an issue.

#### REFERENCE

1. Cyr TD, Graham SJ, Li KY, Lovering EG. Low first-spray drug content in albuterol metered-dose inhalers. *Pharm Res* 1991; 8(5):658-660.

**Nikander:\*** Do you know if HFA inhalers are quite sensitive to cold climate? If you kept it in your coat pocket or backpack in the winter, would it work?

**Newman:** I don't know. This seems to be a theoretical problem. People raise it as a potential problem, but is it something that patients really encounter with MDIs?

**Atkins:** Ross and Gabrio published some research<sup>1</sup> that showed that the HFA MDIs worked much better at lower temperatures than did the CFC MDIs.

#### REFERENCE

1. Ross DL, Gabrio BJ. Advances in metered dose inhaler technology with the development of a chlorofluorocarbon-free drug delivery system. *J Aerosol Med* 1999;12(3): 151-160.

\* Kurt Nikander, Respironics, Cedar Grove, New Jersey.

**Leach:** HFAs, especially those that contain ethanol, are not subject to cold temperatures. HFA albuterol doses are not different at temperatures as low as zero degrees Celsius, whereas CFC albuterol products deliver significantly less drug at lower temperature.

**Newman:** The data seem to show that the vapor pressure of the CFC products falls quite dramatically with reducing temperature. That effect seems to be much reduced or even totally absent for HFA products,<sup>1</sup> which I find surprising.

#### REFERENCE

1. Ross DL, Gabrio BJ. Advances in metered-dose inhaler technology with the development of a chlorofluorocarbon-free drug delivery system. *J Aerosol Med* 1999;12(3): 151-160.

**Leach:** The reason is the combination of the ethanol in the formulation and the valve design.

**Nikander:** CFCs deplete the ozone layer, but HFAs contribute to the global greenhouse effect. Will that diminish the application of HFAs?

**Newman:** The problem is different in that CFCs are the major cause of ozone depletion, so CFCs just have to go. HFAs are potent greenhouse gases, but their contribution to global warming is very small compared to carbon dioxide, methane, and other greenhouse gases, so the situation is not analogous. However, that's not to say that there won't be a move to ban HFAs in the future, because once the politicians wake up to the importance of global warming, HFAs could be tarred with the same brush as carbon dioxide and methane, and anything that is a greenhouse gas could be banned. If HFAs are banned, we might have to go through another reformulation exercise.

**Atkins:** I think that in Europe there is currently pending legislation to

phase out HFAs in refrigeration—mobile refrigeration in particular. That's the thin end of the wedge. The International Panel on Climate Change is going to publish a report that has been endorsed by some countries, which indicates that there are no known realistic short-term alternatives. So there is a viable lifetime for HFA MDIs, but new technology is coming, some of which could, in the next decade or so, change that view.

**Newman:** There would presumably be a temporary, essential-use exemption for HFAs, as was allowed for CFCs.

**Atkins:** The prediction for CFCs was that the essential-use exemption period would run for 3 or 4 years, but it has now been 10 years, so I think the politicians will not be easily persuaded to allow a similar exemption for HFAs. However, HFAs are a small contributor to global warming, whereas CFCs were the primary cause of ozone depletion.

**Leach:** The contribution of pharmaceutical-use HFA to global greenhouse gases is vanishingly small, so if science dictates policy, the HFAs will not be banned. To another point, I want to discuss the cost of drug delivery. With an MDI we can deliver albuterol and beclomethasone for about 1½ pennies a dose. Someone in our marketing group said that we need to keep the cost down because of third-world countries, where they don't have insurance. I have been told that every additional dollar of cost would take 100,000 patients off the rolls. No one ever seems to talk about it. I think DPIs can and should play a large role in inhalation therapy, but they are much more expensive than MDIs. Some people denigrate MDIs because they were invented a long time ago, but currently no DPI can match the manufacturing cost-per-dose of an MDI.



**Newman:** I think you're right. Cost is an extremely important issue, because if a device isn't affordable, then it's not going to get used, no matter how good it is. In the recent review by Dolovich et al<sup>1</sup> on clinical differences between various inhaler devices, one of the conclusions was that you can't see any clinical differences between inhalers but that the choice of device does matter. Two factors that have to be taken into account when choosing an inhaler are cost-effectiveness and reimbursement. Obviously it depends on the individual device, but MDIs are generally going to be cheaper than DPIs, which gives them an advantage. Would you agree with that? Is that the point you were trying to make?

#### REFERENCE

1. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest* 2005; 127(1):335-371.

**Leach:** Certainly, no currently marketed product can match MDIs with regard to cost. MDIs are as much as

10 times less expensive than DPIs. MDIs are cheap to manufacture.

**Fink:** With the CFC products the economics of the MDI starts changing as you no longer have use for the CFC in other commercial applications, and the production cost of the propellant dramatically increases. I assume that is going to happen to HFA as well. Even if you have an exemption for HFA, the availability will decrease and cost of the propellants will rise and affect the cost of an MDI.

**Atkins:** Chet [Leach] brought up an excellent point. During the process of the International Panel on Climate Change, one of the things we tried to do (I was part of the writing team) was analyze the cost for the salbutamol MDI phase-out. The conservative estimate to replace a salbutamol HFA MDI with a DPI is around \$1.5 billion a year, on a recurring basis. That's what the health-care systems around the world would have to pay to eliminate salbutamol MDI.

**Newman:** MDIs can't be used for all drugs. MDIs are not suitable for delivering large doses of antibiotics, for instance. So we must have a wider range of devices than just MDIs.

**Anderson:** Chet [Leach] commented that the United States is far behind other developed countries with regard to propellants and getting rid of CFCs, and is kind of a third-world country with regard to access to inhalers. We thought CFCs would be totally phased out within the next year, but the FDA's final ruling was that the CFC exemption will remain until the end of 2008. It's controversial, because if you take away cheap albuterol and you don't have cheap substitutes, there is the issue of patient access to bronchodilators, and so a lot of education has to happen in the United States. Also, the pharmaceutical companies are pledging that they are going to make suitable substitutes available at a reasonable price. It ought to be an interesting few years.