Expert Opinion

The rejuvenated pressurised metered dose inhaler

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The pressurised metered-dose inhaler (pMDI) has now been available for 50 years. Once regarded as an inefficient and difficult-to-use device, the technology has evolved significantly over the last few years, particularly since the introduction of novel formulations containing hydrofluoroalkane (HFA) propellants. Many modern HFA pMDIs deposit drug more efficiently in the lungs, impact less forcefully on the back of the throat and feel less cold than their chlorofluorocarbon pMDI counterparts. An improved understanding of technical factors makes it possible to design HFA pMDIs to have specific spray properties, particularly in terms of fine particle dose and spray velocity. Device technology has also progressed with the introduction of compact and convenient breath-actuated, breath-coordinated and velocity-modifying devices, which help patients to achieve a reliable lung dose. Although it faces competition from dry powder inhalers and possibly from novel soft-mist inhalers containing liquid formulations, the rejuvenated HFA pMDI is a device with a significant future for asthma, chronic obstructive pulmonary disease and wider treatment indications.

Keywords: breath-actuated inhaler, dry powder inhaler, pressurised metered dose inhaler, spacer device

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1. Introduction

Until the second half of the 20th century, hand-held squeeze-bulb nebulisers were used to deliver inhaled drugs for the treatment of asthma and chronic obstructive pulmonary disease (COPD) [1]. These inhalers were unsatisfactory for several reasons. They were generally made of glass, and hence were easily broken. Additionally, drug delivery was inconsistent, as the dose could vary according to the amount of pressure applied to the squeeze-bulb.

By the mid 1950s, proprietary aerosols delivering cosmetics and insecticides were available as pressure packs [2], and this prompted Riker Laboratories (now 3M Pharmaceuticals) to undertake development of the first pressurised metered dose inhaler (pMDI). One of the pioneers, Charles Thiel, has described the early development process, including the part played by Susie Maison, the asthmatic daughter of the president of Riker Laboratories, who kept breaking her glass inhaler, and who asked her father why it was not possible to provide an inhaler in a pressurised container, like a hair spray [3]. The pMDI was quickly developed, providing a reliable dose in a robust, convenient and multi-dose presentation. Fortunately, at that time, metering valves capable of delivering at least 100 precise spray doses had just become available. The first pMDIs containing either isoprenaline (Medihaler-Iso™; 3M Pharmaceuticals) or adrenaline (Medihaler-Epi™; 3M Pharmaceuticals) were developed, tested and approved in early 1956 with a speed that seems remarkable by today's standards [4]. Sprays from pMDIs are self-propelled, the pressure of propellants inside the canister being used to force the spray out of the device via a narrow nozzle in the plastic actuator (Figure 1). Initially these inhalers were given the acronym 'MDI' but the term 'pMDI' is preferable in order to distinguish them from other types of

Figure 1. A basic press-and-breathe pressurised metered-dose inhaler.

(non-pressurised) inhaler that are also available in a multi-dose format.

Before long, the pMDI became the most important device for delivering inhaled drugs, and it has maintained that position for 50 years. Over 500 million pMDIs are produced annually [5], and it has been estimated that ~ 10^{12} pMDI doses have now been inhaled by patients.

The pMDI was once described as the most complex dosage form in medicine [6]. It now faces competition from dry powder inhalers (DPIs) [7] and perhaps from novel soft-mist inhalers containing aqueous or ethanolic formulations [8], some of which may be even more complex. It is against this background that the place of the pMDI in the clinic of the 21st century needs to be re-evaluated. This paper reviews pMDI technology, highlighting how device and formulation have evolved to provide an inhaler fit for the modern era.

2. Chlorofluorocarbon pressurised metered-dose inhalers and dry powder inhalers

2.1 The chlorofluorocarbon pressurised metered-dose inhaler

Propellants in pMDIs must be non-toxic, non-flammable, compatible with drug formulations and device hardware, have appropriate boiling points and densities, and have acceptable taste and smell [9]. Several chlorofluorocarbons (CFCs), which were developed initially as refrigerants in the 1930s, met the required criteria. These substances are liquefied compressed gases, being in the gaseous phase at atmospheric pressure and normal ambient temperatures, but forming liquids when cooled or compressed. In a closed container, a dynamic equilibrium is formed between liquid and saturated vapour phases, such that the vapour pressure at a given temperature remains constant, irrespective of whether the container is full or nearly empty [10].

Until the mid-1990s, pMDIs contained mixtures of the highly volatile CFC-12 (dichlorodifluoromethane) together with one or both of CFC-11 (trichlorofluoromethane) or CFC-114 (dichlorotetrafluoroethane). CFC-11 and CFC-114 have higher boiling points than CFC-12, and hence they are less volatile. They may be used more readily to prepare the formulation in the laboratory [11], after which CFC-12 is added, either by cold-filling (at low temperature before the metering valve is crimped in place) or by pressure-filling (via the metering valve after crimping). The vapour pressure inside a typical CFC pMDI is 300 – 500 kPa (3 – 5 atmospheres), but the pressure varies according to the propellant mixture, the concentration of other excipients and the ambient temperature [12].

The drug is present in CFC pMDIs either as a suspension of micronised particles, or as a solution. Suspension formulations in CFCs also include low concentrations of one of three surfactants (oleic acid, sorbitan trioleate or lecithin) to reduce particle aggregation and to lubricate the valve (Table 1). Solution formulations in CFCs may require a co-solvent, such as ethanol, together with antioxidants and flavouring agents [13]. Many early CFC pMDIs comprised solution formulations, but they tended to have low fine particle doses owing to high concentrations of non-volatile excipients [14]. Suspension formulations became preferred because many drugs have low solubility in CFC propellants, leading to good chemical stability. Suspension formulations need to be shaken regularly in order to disperse the drug uniformly in the propellants, and hence to ensure reproducible dosing. The metering valve in CFC pMDIs usually has a volume ranging 25 – 63 µl, so that typically 100 – 200 metered doses (occasionally up to 400) are available from a single canister. The quantity of drug contained in a pMDI dose is usually 50 – 250 µg, but has ranged from < 10 µg to 5 mg in approved products.

The way in which the pMDI spray is formed has been described in detail elsewhere [15,16], with a recent update provided by Versteeg and Hargrave [17]. Spray formation involves fragmentation of the propellants into droplets during passage through a narrow orifice in the plastic actuator (typical diameter 0.6 mm in CFC pMDIs). The spray from a CFC pMDI is rapid moving, of short duration (0.1 – 0.2 s), and comprises large propellant droplets. Early measurements involving hair sprays showed that pressurised aerosol plumes made from CFCs may have

Table 1. Formulation of some chlorofluorocarbon and hydrofluoroalkane pressurised metered-dose inhaler products.

Product	Company	Drug	Formulation	Propellants	Surfactant	Other excipients
Ventolin®	GlaxoSmithKline	Salbutamol	Suspension	CFC-11/12	Oleic acid	(None)
Becotide®	GlaxoSmithKline	Beclometasone dipropionate	Suspension	CFC-11/12	Oleic acid	(None)
Flixotide®	GlaxoSmithKline	Fluticasone propionate	Suspension	CFC-11/12	(None)	(None)
Maxair™	3M Pharmaceuticals	Pirbuterol	Suspension	CFC-11/12	Sorbitan trioleate	(None)
Proventil®	Schering-Plough	Salbutamol	Suspension	CFC-11/12	Oleic acid	(None)
Berotec®	Boehringer Ingelheim	Fenoterol	Suspension	CFC-11/12/114	Sorbitan trioleate	(None)
Ventolin® Evohaler®	GlaxoSmithKline	Salbutamol	Suspension	HFA-134a	(None)	(None)
Flixotide® Evohaler®	GlaxoSmithKline	Fluticasone propionate	Suspension	HFA-134a	(None)	(None)
Proventil®	Schering-Plough, via agreement with 3M Pharmaceuticals	Salbutamol	Suspension	HFA-134a	Oleic acid	Ethanol
Airomir®	Ivax, via agreement with 3M Pharmaceuticals	Salbutamol	Suspension	HFA-134a	Oleic acid	Ethanol
QVAR®	Ivax, via agreement with 3M Pharmaceuticals	Beclometasone dipropionate	Solution	HFA-134a	(None)	Ethanol
Alvesco®	Altana	Ciclesonide	Solution	HFA-134a	(None)	Ethanol
Intal®	sanofi-aventis	Sodium cromoglicate	Suspension	HFA-227	(None)	(None)
Tilade®	sanofi-aventis	Nedocromil sodium	Suspension	HFA-227	(None)	(None)

a velocity > 30 m/s at distance of 2 cm from the actuator nozzle, falling to < 5 m/s at a distance of 20 cm from the nozzle [18]. This finding was largely confirmed for CFC pMDI aerosols by Clark [15], who also showed that the initial droplet mass median diameter (MMD) typically exceeds 20 µm. The droplet size decreases rapidly owing to evaporation as the spray moves away from the canister, one set of data showing a fall from MMD 36 µm at the nozzle to MMD 12 µm at a distance of 25 cm [13]. Sprays from CFC pMDIs exhibit a high impaction force, and feel cold on the back of the throat owing to propellant evaporation. The maximum impact force at a distance of 5 cm from the end of the actuator is 75 – 125 mN, and the minimum spray temperature is between -20 and -30 °C [19].

The combination of large droplet size and high spray velocity explains why only 10 – 20% of the dose from a CFC pMDI is deposited in the lungs, with the majority of the dose being deposited in the oropharynx [20-22]. Lung deposition from CFC pMDIs has been shown to vary according to inhalation technique [22,23] or according to physicochemical aspects of the formulation [24], and to be zero or close to zero when severe forms of poor inhaler technique are present [25].

In the last 10 – 15 years, a huge change has occurred in pMDI formulation and development. This change can be traced back to 1974 [26], when a visionary paper in the journal *Nature* prophesised that the chlorine liberated by degradation of CFCs would damage the ozone layer in the stratosphere. The veracity of this prediction was demonstrated in the 1980s, when an ozone hole was detected over Antarctica [27]. The international community moved with commendable speed to ban CFCs under a number of agreements, the best known being the Montreal Protocol of 1987 [28]. The benefits resulting from replacement of CFCs in pMDIs are described later in this paper.

2.2 Correct and incorrect pressurised metered-dose inhaler use

A reasonable consensus exists about what constitutes correct pMDI technique, and much of this knowledge has been used to standardise manufacturers' instruction leaflets. Correct or optimal pMDI technique is generally considered to involve actuating the pMDI while taking a slow deep breath, continuing to inhale after the pMDI has been actuated, and then holding the breath for up to 10 s [22,23,29].

Early studies recommended actuating the pMDI early in the breath [30], but other studies reported better broncho-dilatation if the pMDI was actuated late in the breath [31]. Patients are usually instructed to exhale to residual volume before beginning to inhale from a pMDI, although one study suggested that inhaling from functional residual capacity was equally effective [29]. Some of these more detailed aspects of inhaler technique may be unnecessarily complicated, and in order to increase the likelihood that an inhaler is used correctly, the ideal set of instructions should be simple.

The most important error in pMDI technique is usually considered to be poor coordination [32], (i.e., not actuating the pMDI at the same time as inhaling). This problem can occur in any patient, and may be especially prevalent in young children, the elderly and patients undergoing severe exacerbations of their asthma or COPD. It is useful to distinguish between crucial and non-crucial errors when using an inhaler [33]. Crucial errors (e.g., actuating the pMDI at or after the end of inhalation) results in zero lung dose, whereas non-crucial errors (e.g., actuating the pMDI before the start of inhalation, or inhaling too quickly) may result in a lower lung dose compared with that from optimal inhaler technique.

Another crucial error occurs when a patient stops inhaling at the moment the spray is released, or continues to inhale but through the nose [32]. This phenomenon came to be termed the 'cold Freon' effect. There are few quantitative data about the incidence of this effect, and it is possible that its incidence is reduced by the introduction of hydrofluoroalkane (HFA) pMDIs. The rapidly moving, cold and short-duration CFC pMDI spray seems to be a major factor contributing to crucial errors in inhaler technique.

Errors in pMDI technique are clinically relevant [34]. One recent study [35] involving almost 4000 asthmatic patients calculated an asthma instability score based on symptoms and the use of rescue medication. It was concluded that the asthma instability score was higher in patients with poor inhaler technique than in those with good technique. It was especially high in patients unable to coordinate actuating the pMDI with inhalation, for whom the use of inhalers not requiring coordination, including breath-actuated pMDIs (Section 6.2) and DPIs (Section 2.3), was recommended.

2.3 Dry powder inhalers

The present major alternative to the pMDI is the DPI. The first significant device in this class was the Spinhaler introduced by Fisons in the late 1960s, utilising a unit dose of dry powder contained in a standard size two hard gelatine capsule [36]. Each dose comprised 20 mg sodium cromoglicate together with an equal weight of coarse lactose as an excipient, to provide appropriate powder flow properties. The inhaler design challenge was to provide mechanisms to pierce exit holes in the capsule, and then to shake the powder out into the inhaled air stream. This device was followed into the clinic by the Rotahaler® (GlaxoSmithKline) using broadly similar technology [37], and there was a spate of other unit-dose DPIs, some of which progressed as far as moulding and evaluation stages, but many of which existed only in the patent literature.

The appearance in 1987 of the Turbuhaler® DPI from AstraZeneca was a significant step forward [38]. The Turbuhaler is a multi-dose reservoir device with a self-metering mechanism, utilising pure drug. The success achieved by this device set a new standard for DPI device design, the development of which accelerated in the last decade of the twentieth century, driven by the need to eliminate CFC propellants. By 2007, around 20 different DPIs have reached the market, and many more have been described in the patent literature [7,39]. Most multi-dose devices contain powder reservoirs, but the Diskus® (or Accuhaler®) and Diskhaler® DPIs (GlaxoSmithKline) contain individual doses that have been factory-metered into blisters [40]. With one exception, all of the available DPIs are breath-actuated, as the patient's inhalation operates the device, and they do not suffer from the coordination problems seen with pMDIs. A manually actuated DPI that uses compressed air to disperse a powder dose containing insulin (Nektar Therapeutics, Inc.) was recently approved.

It is generally accepted that drug particles with an aerodynamic size of < 5 µm are required for successful pulmonary therapy [41] and this requirement dictates that active drug substances must be milled or size-reduced to this particle size range for use in DPIs [42]. This process produces very fine powders that exhibit strong cohesive and adhesive properties [43]. This creates problems not only in processing the final dosage form, but also in ensuring that the patient's inhalation through the DPI is able to disperse the powder sufficiently well to achieve an adequate fine particle dose.

In practice, the powder is only partially dispersed by the patient's inhalation, and the powder cloud inevitably contains a wide spectrum of sizes, ranging from single particles of diameter < 5 µm to drug particle agglomerates and drug/lactose complexes. Particles of different sizes deposit in the airways according to their aerodynamic behaviour: the large ones mainly in the upper respiratory tract, but some particles < 5 µm diameter penetrate into the lungs [44]. The feel of the powder on the back of the throat is often considered to provide the patient with reassurance that a dose has been delivered, but may carry the risk of inducing reflex coughing.

The lung dose for most DPIs is optimised by maximal inspiratory effort [45]. In clinical practice, inspiratory effort may change from breath to breath, leading inevitably to lung dose

variation from DPIs. For this reason, DPIs used to deliver drugs with narrow therapeutic windows that require precise lung doses (e.g., for systemic applications) are designed to generate the aerosol independently of patient effort [46].

2.4 Pressurised metered-dose inhalers and dry powder inhalers: relative ease of use

The number and complexity of DPIs is growing, and each DPI device is different, thus requiring a specific set of skills to be taught to each patient [47]. This situation contrasts with that for pMDIs, where the same handling and inhalation technique seems to apply to all pMDIs. The need to teach a specific correct inhaler technique for each DPI is potentially confusing to patients, and may consume significant amounts of healthcare professionals' time. Although all pMDIs have a similar low resistance to airflow, the resistances of DPIs vary considerably from product to product [45].

Variations between DPIs, such as those described above, have led to concerns about the growing number of different designs of DPIs in the clinic. A recent paper discussed the potential interchangeability of DPIs [48], and concluded that owing to differences in pharmaceutical performance, patient behaviour and clinical outcomes, patients should not be switched from one DPI to another without appropriate training and physician involvement.

The widespread belief that pMDIs are inevitably much more difficult to use correctly than DPIs is not borne out by the evidence. In a study involving the assessment of inhaler techniques of almost 4000 patients [33], approximately one patient in three using pMDIs made crucial errors in technique (mainly poor coordination between actuating and inhaling), and a similar proportion of patients made crucial errors using the Turbuhaler DPI (mainly failure to hold the inhaler upright while loading a dose, and exhaling into the device). However, only ~ 1 patient in 10 made crucial errors when using the Diskus DPI.

Unfortunately, incorrect use or poor understanding of inhalers (both pMDIs and DPIs) is not confined to patients, and is also to be found among healthcare workers, including physicians, nurses and pharmacists [47,49,50]. Incorrect inhaler technique is really an aspect of poor adherence to inhalation therapy [51]. These observations highlight not only the need for improved education about inhaler devices and their use, but also the potential advantages of serious efforts to minimize the number of different devices any patient is prescribed, so as to avoid the confusion sometimes termed 'device delirium' or 'device dementia' [47].

3. Transition to hydrofluoroalkanes in pressurised metered-dose inhalers

3.1 Reformulation challenges

The elimination of CFCs has necessitated finding new propellants for use in pMDIs. Suitable alternatives with appropriate thermodynamic properties proved to be two HFAs (tetrafluoroethane, HFA-134a and heptafluoropropane, HFA-227), and the pharmaceutical industry collaborated via the International Pharmaceutical Aerosol Consortia for Toxicology in order to demonstrate the safety of these substances when administered to man [52]. The first non-CFC pMDI (Airomir®; Ivax under licence from 3M Pharmaceuticals) reached the market in 1994, but the transition to non-CFC propellants is ongoing, and will not be complete for several more years [53].

The reformulation process is complex and time consuming for several reasons [54]. It is not possible simply to replace CFC propellants with non-CFC propellants. HFA-134a and HFA-227 both have similar boiling points to CFC-12, and most companies have chosen HFA-134a as the replacement for CFC-12 in the first instance. However, neither of these chemicals replaces CFC-11 or CFC-114. A further problem is that the surfactants regularly used in CFC formulations each show < 0.02% solubility in either HFA-134a or HFA-227 [55]. In addition, the elastomeric components in existing metering valves often proved to be incompatible with HFA propellants [56]. As well as addressing these major technical challenges, it was also necessary to conduct clinical trials demonstrating safety and efficacy of new drug formulations [52]. Examples of some HFA pMDI formulations are shown in Table 1.

In the 1990s an extensive search began for alternative surfactants or other excipients which would assist the development of new HFA pMDI products [57,58]. The ideal surfactant would be chemically inert, biologically compatible, commercially available and would enhance both formulation stability and drug delivery. Several classes of compound have been suggested to meet these criteria, including oligolactic acids, acyl amide acids and mono-functionalised polyethylene glycols [57,58]. Polyvinyl alcohol and polyvinyl pyrollidone have shown some promise as stabilisers and form the basis of present patent applications [201]. In general the search for new excipients has proved challenging and is ongoing.

3.2 Reformulation approaches

3.2.1 Propellant alone without surfactant

Scientists in the laboratories of GlaxoSmithKline developed formulations of salbutamol, salmeterol and fluticasone propionate using propellant HFA-134a alone, without any excipients [59,60]. The drug is present as a particulate suspension, as in CFC pMDIs. This was a difficult technology, and measures were required to inhibit adhesion of drug particles to the canister walls which could cause unacceptable dose variations [202]. This approach has formed the basis of several successful HFA pMDI products (Ventolin®, Serevent® and Flixotide® Evohalers®; GlaxoSmithKline; Table 1).

3.2.2 The use of solvents to solubilise surfactants

An alternative strategy is the use of ethanol to increase the solubility of the classical surfactants sufficiently to permit their use. A formulation of salbutamol from Schering-Plough

(Proventil®) contains HFA-134a together with oleic acid and ethanol (Table 1). A recent patent [203] describes a process of introducing alcohol to increase the solubility of oleic acid in order to produce stable suspensions of mometasone furoate. The manufacture of a concentrate of ethanol, active pharmaceutical ingredient and oleic acid, with later addition of propellant in a two-stage process, was stated to result in particle size growth of the drug while the concentrate was being filled, whereas use of a single-stage process was claimed to prevent this effect.

3.2.3 *Solution formulations*

It was quickly realised that some inhaled corticosteroids, notably beclometasone dipropionate (BDP), were soluble in HFA-134a using ethanol as a co-solvent (Table 1). This allowed immediate progression to formulations that required no shaking by the patient such as is required to redisperse suspension products, and the solutions also provided very accurate metering of the dose. Furthermore, the aerosol generated by one such formulation (QVAR®, Ivax under licence from 3M Pharmaceuticals) was significantly finer than that from CFC pMDIs [61]. The approach is not without problems as drugs in solution may be exposed to greater risk of chemical degradation, for example by moisture. Ganderton *et al.* [62] further modified this approach by the inclusion of small quantities of low vapour pressure liquids such as glycerol and polyethylene glycol, which inhibited the evaporation of the propellant, providing aerosols of similar particle size distributions to the CFC products which they were replacing.

It has been known for many years that the physicochemical properties of the pMDI formulation and design of the actuator influence the spray characteristics [63]. A combination of formulation and actuator dimension changes permits solution formulations from pMDIs to be designed with required characteristics. The actuator nozzle diameter for use with suspension CFC pMDI products is typically 0.6 mm, but is usually smaller for solution HFA pMDIs. As the nozzle diameter is reduced, the size of the emitted aerosol also decreases. Aerodynamic particle size from solution pMDIs is influenced not only by nozzle diameter but also by the depth of the expansion chamber in the actuator and by nozzle length [55,64].

Lewis *et al.* [65] have described a series of empirical equations which allow the fine particle fraction (FPF) of HFA-134a solution formulations to be predicted. One of these equations predicts that the FPF of a solution formulation containing HFA-134a and ethanol may be expressed as a function of actuator nozzle diameter (mm), metered dose size (µl) and HFA-134a content (%). Fairly modest changes in these parameters can be used to make profound changes in the FPF, and it is possible to design HFA pMDIs either to have characteristics similar to those of a CFC pMDI that is to be replaced, or to have 'improved' characteristics, including a higher FPF. This concept is the basis of the Modulite formulation [66], which has been commercialised by Chiesi.

In further studies [67], experimental actuators with nozzles ranging in diameter from 0.12 – 0.3 mm have been tested, as well as actuators with multiple nozzles, and nozzles with non-circular shapes. In these studies, the FPF of a solution formulation containing HFA-134a and ethanol was inversely proportional to orifice diameter, with an FPF up to 80% of the ex-valve dose possible for the smallest nozzle diameter. Using a very small nozzle, FPFs > 40% could be obtained even with formulations containing 30% ethanol, allowing the possibility of increasing drug loading for poorly soluble molecules by using relatively high concentration of co-solvent. Nozzle size also affects the aerodynamic size of aerosols delivered from pMDIs formulated as suspensions [68].

3.3 Progress with the hydrofluoroalkane transition

By the end of 2006, only 10 HFA pMDI products had been marketed in the UK (5 bronchodilators, 4 corticosteroids and one bronchodilator/corticosteroid combination). In recognition of the time required to develop HFA pMDIs, and of the importance of the health benefits that pMDIs provide, an essential-use exemption has been granted to allow continued availability of CFC pMDIs [69]. The FDA has stated that it will not withdraw CFC pMDIs containing salbutamol until the end of 2008, at which point sufficient alternative products are expected to be available. Looking further ahead, HFAs are recognized as greenhouse gases and although it is estimated that they will account for only 0.02% of worldwide greenhouse gas emissions by 2010 [70], it is not inconceivable that restrictions could be placed on their use at some future date [28]. It is to be hoped that the importance of the pMDI in clinical practice will be seen to outweigh their insignificant contribution to environmental problems.

4. Improving the performance of the new hydrofluoroalkane pressurised metered-dose inhaler

4.1 Softer and warmer sprays

Although most CFC pMDI sprays have essentially similar characteristics, HFA pMDI sprays vary to a much greater extent from product to product. Hochrainer *et al.* [71] compared the spray velocities and plume durations of several commercially available CFC and HFA drug products. For each of four CFC pMDIs and for two of five HFA pMDIs, the mean velocities at a distance of 10 cm from the nozzle were 5.1 – 8.4 m/s, and the plume durations were 0.15 – 0.16 s. The three remaining HFA pMDIs were much 'softer' sprays, with mean velocities at 10 cm from the nozzle being 2.0 – 2.7 m/s, and with plume durations of 0.21 – 0.36 s.

As described earlier, CFC pMDI sprays have a high impaction force, and a plume temperature < 0 ºC [19]. Impaction force and cold feel are reduced in many HFA pMDIs, and data for several products show a maximum impact force of ~ 25 mN, which is only one-fifth to one-third

of that from a typical CFC pMDI, together with a minimum plume temperature > 0°C. However, as with the spray velocity and plume duration, these parameters are product specific. The lower impact force of many HFA pMDIs seems to result mainly from the use of narrower actuator nozzles compared with those commonly used in CFC pMDIs [19].

4.2 Drug targeting

In some HFA pMDIs utilising solution formulations, drug is targeted to the lungs much more efficiently than in CFC pMDIs. Early indications that significantly higher lung deposition was achievable with pMDIs than the traditional 10 – 20% of the dose came from the studies of Ashworth *et al.* [72], using a propellant-soluble radiolabel. The solution formulation of BDP in HFA-134a developed by 3M Pharmaceuticals (QVAR™) has a smaller droplet size (MMD of 1 µm) than CFC BDP (MMD of 4 µm), together with a lower spray velocity. Hence it achieves lung deposition > 50% of the dose [73] and, compared with CFC BDP, it results in asthma control from a smaller daily drug dose [74,75]. Fears that the small aerosol droplets from the QVAR pMDI would increase systemic side effects via alveolar absorption have not been realised [76], and indeed QVAR has been suggested as a useful aerosol for targeting the small peripheral airways in the lungs of asthma patients [77]. Despite these potential benefits, QVAR does not seem to be widely used.

Subsequently, lung deposition ~ 50% of the dose, and peripheral drug distribution within the lungs, was also shown for other HFA pMDI corticosteroid formulations, containing flunisolide [78] and ciclesonide [79]. Lung deposition in children is generally less than in adults, but even children of 5 – 7 years of age have been shown to achieve lung deposition averaging 37% of the dose with the QVAR pMDI [80].

Although targeting drug efficiently to the lungs represents a good pharmacological principle, it is not critical for drugs used to treat asthma and COPD. Low and variable lung deposition is tolerated for drugs used to treat asthma and COPD, which tend to have wide therapeutic windows, and for which patients can take extra doses as needed. However, high lung deposition would be a future requirement if other drugs, such as inhaled peptides, were to be delivered by a pMDI. Recent data show that there is an inverse correlation between mean lung deposition and the variability of lung deposition [81], so that pMDI products that target drug efficiently to the lungs would also be likely to result in a less variable lung dose.

4.3 Reduced need for priming

In order to achieve reproducible dosing, a pMDI may require priming (i.e., firing several doses to waste before use). The emitted dose from CFC pMDIs can vary according to when the device was last primed and also upon the orientation of the pMDI during storage [82]. Recent improvements in valve design from several companies including 3M Pharmaceuticals and Bespak may reduce these problems [83]. The number of priming doses required, and the time since last use after which priming is needed, probably varies from product to product. One review suggested that a CFC pMDI should be reprimed by the patient if not used for 24 – 48 h, and an HFA pMDI should be reprimed if not used for 4 – 7 days [4]. Truly prime-free valves are in development [83].

4.4 Sharper 'tail-off'

A pMDI is designed to deliver a reproducible quantity of drug over the number of doses stated on the label. In some CFC pMDIs, 20 – 30 subsequent doses may be delivered, but these are highly erratic and variable, owing to inconsistent filling of the metering valve. The decrease in delivered dose at the end of canister life is called 'tail-off'. Improvements in valve design for one HFA pMDI resulted in the amount of delivered drug falling relatively smoothly to zero in only a small number of doses, giving a sharper tail-off [84].

4.5 Reduced dependence on ambient temperature

The ability of a pMDI to perform in a similar way irrespective of the ambient temperature would be an obvious advantage. The fine particle mass of one CFC pMDI formulation of salbutamol was shown to decrease dramatically as the ambient temperature was reduced from +20 to -10 °C, but the fine particle fraction of one HFA pMDI formulation of salbutamol was virtually independent of ambient temperature over this range, falling significantly only once the ambient temperature dropped below -10 °C [84]. It is not known whether this result can be extrapolated to other HFA pMDIs. The vapour pressures of HFA-134a and CFC blends both fall with decreasing temperature [301], but at 0 °C, HFA-134a has a vapour pressure approximately twice that of a 40:60 CFC-11:12 blend [301], so that HFA-134a might be more able to disperse the formulation at this temperature. The humid environment of the lungs could also affect spray characteristics, although recent data have suggested that the evaporation of HFA-227 is unchanged in the presence of high levels of humidity [85].

5. Advantages and disadvantages of the pressurised metered-dose inhaler

5.1 Advantages

The pMDI has both advantages and disadvantages which will be discussed below, and which are listed in Box 1. A more detailed comparison of the advantages and disadvantages of other types of inhaler is presented elsewhere [86].

Compared to unit-dose nebulisers, pMDIs have many practical advantages that explain their popularity over half a century. pMDIs are compact, portable, robust, convenient and unobtrusive. Treatment times are much shorter than for nebulisers. pMDIs are much easier to prepare for treatment than nebulisers, and use much lower drug doses.

Box 1. Advantages and disadvantages of the pressurised metered-dose inhaler.

Advantages

Versus nebuliser

- Compact, portable, robust, convenient, unobtrusive
- Multi-dose
- Shorter treatment time
- Easier to prepare for treatment
- Lower drug dose required
- Relatively inexpensive

Versus dry powder inhaler

- Aerosol formation independent of inhalation effort
- Often better dose content uniformity
- Average regulatory review time shorter
- Pressurised contents give better protection against ingress of moisture and pathogens
- Performance independent of ambient humidity
- More familiar and consistent format
- Same handling and inhalation technique for all pressurised metered-dose inhalers
- Relatively inexpensive

Disadvantages

- Usually no breath actuation
- Usually no dose counter
- Low lung deposition and high oropharyngeal deposition for many formulations
- Ex-valve dose usually limited to < 1 mg
- Formulation may be challenging
- Performance may depend on ambient temperature
- Present models need priming
- Contains propellants (hydrofluoroalkanes have a small global warming potential)
- Mid-twentieth century technology

pMDIs also have several advantages over DPIs. An important inherent advantage of the pMDI is that aerosol formation is independent of the patient's inspiratory effort. This contrasts with DPIs, where achieving satisfactory particle de-agglomeration and an adequate lung dose may depend upon how hard the patient inhales through the device [7]. Dose content uniformity seems to be better in pMDIs than in many DPIs [87], and the average regulatory review time is shorter [88]. The seals and high pressure inside the pMDI provide resistance against the ingress of moisture and pathogens independent of dessicants or packaging, and the performance of the pMDI is likely to be independent of ambient humidity.

As mentioned earlier, evidence suggests that all pMDIs can be used with essentially the same handling and inhaler technique. By contrast, the correct technique for preparing and using each DPI is potentially different, and may involve loading a capsule, piercing a blister, moving a lever, or holding the device in a specific orientation [47].

A key feature of pMDIs is that the basic components (canisters, valves, actuators and propellants) are well specified and available from alternative suppliers. Commercial competition ensures that these components are not only relatively inexpensive but of very high quality. Low cost may prove to be a significant future advantage of pMDI over other types of inhaler, especially in developing countries, or in developed countries for patients inadequately covered by health insurance.

5.2 Disadvantages

The pMDIs also have some disadvantages. The conventional 'press-and-breathe' pMDI lacks breath actuation, and many patients cannot use it correctly, consequently receiving either zero lung dose or a highly variable lung dose [86]. This problem may be less severe for HFA pMDIs, and can be further minimised using auxiliary pMDI hardware, including breath-actuated pMDIs, spacer devices and holding chambers, which will be described below. Most pMDIs lack dose counters – a surprising deficiency which is only now being properly addressed.

Even with correct inhaler technique, all CFC pMDIs and many HFA pMDIs disperse drug relatively inefficiently into the fine particle range, and consequently deliver only a small fraction of the dose to the lungs.

Present pMDIs are unsuitable for delivery of high drug doses. Both the amount of drug that can be delivered per shot from a pMDI, and the fine particle dose, are limited by particle aggregation and valve clogging in suspension pMDIs, and by drug solubility in solution pMDIs. There have been few marketed pMDI products with ex-valve doses of $\geq$ 1 mg. Increasing the ex-valve dose is to some extent counter-productive, as the fine particle fraction for suspension pMDIs has been shown to fall with increasing ex-valve dose [89]. However, recent data have shown that complexing agents in a solution formulation may be used to increase drug solubility in propellants, allowing fine particle doses per shot of 1.0 – 1.5 mg to be obtained [90].

Propellant vapour pressure, and hence pMDI spray characteristics, are likely to vary according to ambient temperature, and all present pMDIs require priming before use. All pMDIs contain propellants, and even HFAs have a minor environmentally damaging aspect.

Some of the disadvantages of the pMDI have sometimes caused it to be regarded as an outdated mid-twentieth century technology. However, it is clear that many of these disadvantages have been, or are being, addressed successfully by device hardware improvements coinciding with the propellant transition process, as is now described.

6. Improving the pressurised metered-dose inhaler via device hardware

6.1 Dose counters

As modern pMDIs almost invariably comprise opaque aluminium canisters, it is not possible for patients to see when the canister becomes empty [91,92], and they may try to use the

Figure 2. Some dose counters in pressurised metered-dose inhalers, either marketed or in development.

pMDI beyond its recommended number of doses. One way of assessing the emptiness of a pMDI canister is to try floating it in water, but this is totally unreliable [93], and water in the valve stem or in the actuator expansion chamber and nozzle may affect the function of the device.

The FDA issued guidance in 2003 to the effect that new pMDIs must be equipped with a dose counter that indicates the number of doses remaining [94]. This guidance and that issued in Europe [95] have spurred industry to develop dose-counting systems for pMDIs, as shown in Figure 2. In addition to the dose counters shown in Figure 2, Trudell Medical supply several designs. A comprehensive review of the topic has been given by Bradshaw [96] who noted that the primary purpose of a dose counter is patient safety. Although the requirements of the regulatory authorities (including count reliability and a clear display method) are laudable, access to counters is inhibited by extensive patent coverage stretching back over decades. Dose counters can be either direct (relying on an active event of firing such as sound, temperature or pressure change) or indirect (relying on canister movement/thumb pressure). The field for the first type seems to be relatively patent-free, but is very crowded for counters of the second type. The available indirect counters consist of two types, pressure operated (utilising the 'press' employed to operate the canister) or displacement operated (using the canister movement to work a mechanism; Table 2).

Direct counters may be the least likely to fail, being linked to the actual delivery of a dose, but are technically more difficult to achieve. Indirect counters are simpler to devise, and all

Table 2. Dose counters for pressurised metered-dose inhalers.

Organisation	Ref.
GlaxoSmithKline*	[97]
Bang & Olufsen Medicom	[99,302]
42 Technology	[303]
RPC-Formatec	[204]
Valois	[304]
Cambridge Consultants	[306]
Clinical Designs (Helix™)	info@clinicaldesigns.com
Bespak	[100,305]
3M Drug Delivery Systems	[101]
Trudell	[307]

*Marketed device

Table 3. Breath-actuated pressurised metered-dose inhalers.

Device	Company	Ref.
Autohaler®*	3M Pharmaceuticals	[102]
Easi-Breathe®*	Teva (Ivax)	[103]
SmartMist®	Aradigm	[104]
Xcelovent®	Pfizer (Meridica)	[308]
K-Haler®	Clinical Designs	[105]
Tempo™	Map Pharmaceuticals	[106]
Breath-actuated Inhaler	Abbott (Kos)	[309]
Insulair®	Bang and Olufsen Medicom	[107]
MD Turbo®*	Respirics/Inyx	[310]
Breath-operated inhaler	SHL Medical	[205]

*Marketed device

available dose counters are of this type. At time of writing, only one organisation has introduced a counter to the market [97,98], but it can be expected that they will become a standard item.

6.2 Breath-actuated pressurised metered-dose inhalers

6.2.1 *Concept*

The most important error in pMDI technique is considered to be poor coordination, which is failure or inability of the user to actuate the pMDI at the same time as inhaling [32]. Breath-actuated pMDIs (Figure 3) are novel actuators designed to sense the patient's inhalation, and to actuate the pMDI automatically as the patient inhales. There are two major devices already in use, recently joined by a third, and several others are in development (Table 3). There is evidence of significant clinical benefits associated with the use of breath-actuated pMDIs. One study claimed that the use of these inhalers required fewer prescriptions for asthma medications, and placed fewer demands on healthcare services [108]. The marketing of more pMDIs as breath-actuated devices has been predicted [109].

Several studies have reported that patients find it easier to use a breath-actuated pMDI correctly, compared with a press-and-breathe pMDI and also that they prefer the former [110,111]. However, breath-actuated pMDIs do not solve the 'cold Freon' problems encountered particularly with CFC pMDIs [112]. In common with DPIs, they are usually considered unsuitable for children younger than 5 years of age [113].

6.2.2 *Autohaler®*

The first model of the Autohaler breath-actuated device (3M Pharmaceuticals) was developed in the early 1970s [114], and was even launched with a combination pMDI formulation (Duohaler®) containing isoprenaline and phenylephrine. This innovative breath-actuated device proved not to be user-friendly because it needed a high inhaled flow rate to trigger it, and the triggering mechanism was noisy. These problems have been addressed in a more user-friendly version of the device introduced in the late 1980s. To use it, the patient raises a lever on the top of the device, and inhalation through the mouthpiece then triggers a vane mechanism which causes the pMDI canister to be fired. Triggering is virtually silent, and occurs at a flow rate averaging 30 l/min [102,115]. In the UK, the Autohaler is available with products containing both salbutamol and beclometasone dipropionate, but in the US, it is only available with a little-used bronchodilator (pirbuterol). The Autohaler has recently been acquired by Ivax Corporation (now Teva).

In a scintigraphic study, patients with poor coordination achieving negligible lung deposition with a press-and-breathe pMDI were able to deposit ~ 20% of the dose in the lungs using an Autohaler [25], and there was a corresponding increase in bronchodilator response to inhaled salbutamol. In another study [116], lung deposition of QVAR aerosol via Autohaler was identical to that from a correctly used press-and-breathe pMDI. Lung deposition was reduced from a mean of 60% of the dose for Autohaler or 59% for a correctly used press-and-breathe pMDI to a mean of 37% when patients actuated a press-and-breathe QVAR pMDI just before starting to inhale.

6.2.3 *Easi-Breathe®*

Easi-Breathe [206] (Ivax Corporation, now Teva) is the most widely used breath-actuated device, and is simpler to use than the Autohaler. Opening the mouthpiece automatically prepares the device for inhalation. It is available with a short tube spacer for use with appropriate medications [207], and it is readily used as a standard press and breathe device if need arises (e.g., for use with a large

Figure 3. Breath-actuated pressurised metered-dose inhalers, either marketed or in development.
BAI: Breath-actuated inhaler; BOI: Breath-operated inhaler.

volume holding chamber for a child). Easi-Breathe operates using a unique pneumatic system, which restrains the operating mechanism [103].

6.2.4 *MD Turbo®*

MD Turbo (developed by Respirics) is the most recently introduced breath-actuated inhaler, and is now available on prescription in the US. The device operates with a vane movement triggered by the inhaled air stream, which releases a spring to actuate the canister. The spring is preloaded prior to each use by pressing a lever. The whole of the pMDI, including its actuator, is inserted in the body of the MD Turbo, which is sufficiently large to accept a range of products. It also includes a dose counter.

6.2.5 *K-Haler®*

The K-Haler (Clinical Designs Ltd) is a device which performs the same function as the Autohaler and the EasiBreathe devices, but is simpler in construction and can be used in a number of formats. It is based on the K-valve™ (Figure 4) – a kinked plastic tube – into which the metered dose is discharged from the standard metering valve of a conventional pMDI. The dose is then released by straightening of the tube during inhalation [208]. It is anticipated to enter the European market in 2007, and is also available combined with a dose-counter (Helix™, Clinical Designs Ltd). The design and introduction of low-cost devices such as the K-valve could facilitate the widespread replacement of the traditional 'press-and-breathe' pMDI with modern breath-actuated inhalers.

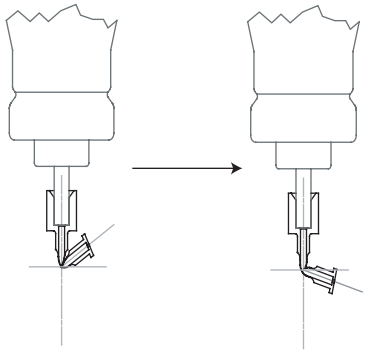

Figure 4. A simple breath-actuated pressurised metered-dose inhalers (K-Haler®; Clinical Designs Ltd). The metered dose is discharged into a kinked tube (K-valve™), and is released by straightening of the tube during inhalation.

6.2.6 *Smartmist®*

Another breath-actuated pMDI (Smartmist; Aradigm Corporation) incorporates a small microprocessor that records the patient's inhalation, and only actuates the pMDI providing that a preprogrammed combination of inhaled volume and inhaled flow rate has been achieved [104]. This device is relatively bulky, complex and expensive, but could be useful in a variety of situations, including controlling patient inhaler technique during clinical trials.

6.2.7 *Correct use of breath-actuated pressurised metered-dose inhalers*

It is possible to misuse any inhaler [117]. Although breath-actuated pMDIs are not exempt from this possibility, the potential for crucial errors is very much reduced. The Autohaler may be prepared incorrectly for inhalation (e.g., not raising the priming lever). If the patient's inhalation is not sufficient, then the pMDI will not be actuated, although the low inhaled flow rates needed to trigger presently marketed breath-actuated pMDIs are easy to achieve. Regulators often require that data on inhaled flow rates achieved by the target population are provided in the Product Licence Application.

6.3 Breath-coordinated pressurised metered-dose inhalers

Breath-coordinated devices are distinct from breath-actuated devices because they do not actuate the pMDI but help patients to achieve coordination. These devices typically function by opening inhalation channels when the patient manually actuates the device, so that reduction in airflow resistance encourages the patient to inhale. A marketed inhaler (Optihaler®; Respironics) [118] and two non-marketed inhalers (Easidose®; Bespak [119], and BCI™; Kos Pharmaceuticals [120]) are examples of these devices. There is a lack of published clinical data to support the use of breath-coordinated inhalers.

6.4 Velocity modifying devices

The high plume velocity of many CFC pMDI formulations creates several potential problems. It may result in high oropharyngeal deposition, can prevent coordination, and may lead to the cold Freon effect and hence to cessation of inhalation. A device capable of reducing the spray velocity from a pMDI could, thus, be useful.

The Spacehaler™ (Celltech Medeva, also known as Gentlehaler™ [Schering-Plough] and as Neohaler™ [Cipla]) is a compact low-velocity pMDI device, 7.5 cm in length, with a long and complex history. The actuator nozzle produces a rapidly spinning spray vortex that removes much of the forward momentum of the spray, and reduces the spray velocity by an order of magnitude compared with a conventional actuator [121]. In man, one scintigraphic study [122] and a pharmacokinetic study [123] indicated higher lung deposition compared with a conventional pMDI, and another scintigraphic study [124] found similar lung deposition to a conventional pMDI. Oropharyngeal deposition was markedly reduced by the device, but up to 50% of the dose was deposited on the actuator, presumably where the spinning vortex meets the mouthpiece walls. Although this device was launched in the UK market, it did not seem to prove very popular.

Another compact velocity modifying device (Tempo™) is currently in development by Map Pharmaceuticals (formerly Sheffield Pharmaceuticals). This device contains a novel vortexing flow control chamber to reduce the forward momentum of the pMDI spray, some of the inhaled air being entrained to blow in the opposite direction to the spray plume [106]. It also contains a breath-actuation facility, and hence is listed on Table 3. Compared with a conventional actuator, lung deposition of a fluticasone propionate pMDI was more than doubled, whereas oropharyngeal deposition was markedly reduced. In another study, plasma levels of ergotamine were comparable to those from a 16-fold larger dose delivered by a conventional press-and-breathe pMDI [125]. A further velocity-modifying device (Vortex Nozzle Actuator™; Kos Pharmaceuticals) was recently described [126].

It is difficult to predict the likely future success of velocity-modifying devices. They may help patients by producing a 'softer' and more efficiently delivered pMDI spray, but with the increasing availability of HFA pMDI sprays that already possess these characteristics, the requirement for velocity-modifying devices may not be as great as it once was.

6.5 Spacer devices and holding chambers

Spacer devices and holding chambers are sometimes known as 'add-on' devices because they are attachments to the mouthpiece of the press-and-breathe pMDI [127]. Spacer devices are usually simple tube-shaped mouthpiece extensions,

and arguably include the 8 cm-long mouthpieces of the first pMDIs from 1956 [3]. Successful holding chambers vary in volume from between ~ 150 ml (e.g., AeroChamber®; Trudell Medical) to 750 ml (e.g., Volumatic®; GlaxoSmithKline and Nebuhaler®; AstraZeneca), and generally have a one-way valve in the mouthpiece, which prevents the patient exhaling into the device. In a third category of device, sometimes called 'reverse-flow' devices, the pMDI is actuated in the opposite direction to the mouth, for example into a collapsible bag [128]. A reverse-flow device (Watchhaler®; Activaero) designed as a toy for use by children was recently described [129]. All these devices reduce oropharyngeal deposition because some of the deposition that would occur in the oropharynx with a pMDI occurs on the walls of the spacer or holding chamber instead. At the same time, lung deposition may be increased [130].

Holding chambers make pMDIs easier to use because the pMDI can be actuated into the chamber and the contents inhaled after a short time delay, without the need to coordinate actuation and inhalation [131]. It is also possible to fire several doses from a pMDI into a holding chamber and inhale them in a single breath or by a number of tidal breaths [132]. However, firing multiple doses and delays between actuation and inhalation, reduce the delivered dose compared with coordinated inhalations of single doses [133]. When fitted with a facemask, holding chambers are probably the devices of choice for inhalation therapy in infants and young children [131].

Most spacer devices are made of plastic, and most of these accumulate static charge on their walls which attracts suspended aerosol and reduces the delivered dose [134]. Plastic devices made of static-free plastic or of lightweight metal are now available [135], and washing and handling instructions for specific devices should be followed to minimise static charge build-up [136].

Spacers and holding chambers are reliable drug delivery devices, and are considered to be at least as effective as nebulisers for delivering inhaled β-agonists to patients with stable chronic asthma or severe acute asthma [137]. However, the increased bulk and inconvenience they add to the pMDI is a significant limitation to their use as portable inhalers. Some patients prescribed a spacer or holding chamber apparently decide not to use it [138]; hence there is considerable interest in developing the more portable auxiliary drug delivery devices for pMDIs described above.

7. Conclusions

The pMDI is now > 50 years old, and its practicality and convenience have made it very popular. Replacement of CFC propellants has provided opportunities to formulate products with a wide range of delivery efficiencies, spray velocities and plume durations, but all probably require the same handling and inhalation technique. The main limitation of the pMDI is the variable lung dose that arises from inadequate inhalation technique, most notably poor coordination between firing the inhaler and breathing in. Patients unable to use a press-and-breathe pMDI may benefit from additional hardware, including breath-actuated pMDIs, spacer devices and holding chambers. Dose counters for pMDIs are now considered essential, and enable the patient to keep track of whether the inhaler is full or nearly empty.

8. Expert opinion

The pMDI celebrated its 50th birthday in 2006, and remains the most widely used inhaler device in clinical practice. How will the pMDI fare in the future, and will it maintain its pre-eminent position in the therapy of asthma and COPD? What is the likelihood that other metered-dose inhalers (DPIs and soft mist inhalers) will ultimately replace the pMDI?

It is possible to view the pMDI in different ways. In the early 1990s, it was seen as a mostly inefficient, difficult to use, and environmentally unfriendly technology. However, the pMDI is popular, inexpensive, durable and adaptable and it continues to fulfil a vital role in inhalation therapy. The relatively low cost of manufacturing pMDIs in bulk, together with humidity problems in DPIs, and dependence of DPI lung dose on the patient's inspiratory effort, have been suggested as reasons why DPIs will not entirely replace pMDIs [4]. The annual cost of replacing salbutamol pMDIs with DPIs has been estimated as $1.5 billion [139]. Although HFA propellants are greenhouse gases, their contribution to global warming is estimated to be negligible compared with carbon dioxide and methane [70], and it should be noted that no inhaler is environmentally neutral, as they all use raw materials and require energy to manufacture [28].

An increasingly wide range of portable inhaler technologies is becoming available for inhalation therapy. However, Smyth [140] has commented that the market for pulmonary drug delivery is at a bottleneck, reflected by an increasing number of HFA pMDIs, and the expanding DPI market, and the development of many new aqueous-based systems. The survivors will be those inhalers that successfully navigate past a variety of obstructions, including market consolidation, regulatory influences and health economics.

The pMDI is usually considered to be a device restricted to asthma and COPD formulations, but a surprising number of other drugs for both local and systemic therapy have been either formulated or proposed. These include amiloride [141], fentanyl [142], leuprolide [143], other peptides and proteins [144], ciclosporin [145] and gene therapy products [146]. A pMDI containing ergotamine for treatment of migraine (Medihaler-ergotamine™, Riker Laboratories) was marketed for several decades. Recently, a call was made for novel antitussive drugs [147], which could usefully be given by inhalation. Technical issues that have restricted the range of drugs for which pMDIs are suitable have been addressed, ranging from steps to make the lung dose higher and less variable, to development of novel packaging systems that contain fewer than the standard 100 – 200 doses, and which

would be more appropriate for expensive drug molecules [148]. Even single dose pMDI systems are a future possibility [149].

The incorrect use of inhalers and poor adherence to treatment are continuing causes for concern, and many patients are still treated suboptimally [51]. These problems are not limited to pMDIs, and they must be addressed aggressively via education of patients and healthcare workers [47,150,151].

A major literature review concluded that the different types of inhaler are able to be equally effective if used with correct technique [152]. Selection of an inhaler for a particular patient should take into the likelihood that the patient will be able to use the inhaler correctly [117]. Patients may be confused by the various instructions for using different inhalers and, therefore, it is useful if a patient can take all his or her medications from the same type of device. Unfortunately, this possibility is limited by the varying range of drug/device combinations that are marketed in different countries. Products containing both a bronchodilator and a corticosteroid in the same formulation are already either marketed or approved, and others are in development. By delivering 'reliever' and 'preventer' medications simultaneously, these pMDI products could help to address problems of poor adherence to therapy in asthma and COPD patients [153,154].

One factor likely to contribute to the future success of the pMDI is the availability of breath-actuated inhalers. These devices can help patients with severe 'press-and-breathe' problems to benefit fully from pMDI therapy, and they have the potential to eliminate the most important crucial error that patients make when using pMDIs. Breath-coordinated devices and velocity-modifying devices may also help poor coordinators. It is claimed that many modern HFA pMDIs with softer spray characteristics create fewer coordination problems for patients and although that seems a reasonable hypothesis, there seems to be no published clinical evidence to support it. Spacer devices and holding chambers can eliminate coordination problems that patients experience using pMDIs, but they do so at the cost of significantly increasing the bulk and inconvenience of the inhaler system. Although some breath-actuated pMDIs may be more expensive than press-and-breathe pMDIs, the former have been shown to reduce healthcare costs [101], which suggests that they are probably more cost-effective. Although patients with asthma or COPD can take additional pMDI doses as required, this strategy will not work if a patient's coordination of a press-and-breathe pMDI is so poor that negligible drug is inhaled into the lungs. The use of breath-actuated devices will be increasingly useful as the range of pMDI products becomes widened beyond traditional asthma and COPD therapies.

The pMDI was once regarded as a 1950s device that had changed little since its invention, but this is no longer an accurate assessment. Spurred on by the shift from CFC to HFA propellants, the pMDI has evolved significantly over the last few years, and this evolution process is set to continue. The pMDI is not inevitably an inefficient and difficult-to-use device because both of these problems have been addressed via hardware and formulation changes. The rejuvenated HFA pMDI is a device with a significant future for asthma, COPD and wider treatment indications. With the improvements described in this paper, the pMDI could well survive to celebrate its 100th birthday in 2056.

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