Expert Opinion

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Propellant-driven metered-dose inhalers for pulmonary drug delivery

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The current market for pulmonary drug delivery is at a bottleneck. The therapeutic advantages of inhalation aerosols, and the potential for the lungs as a route for systemically acting drugs, vaccines and gene therapeutic agents, have resulted in a rapid growth of the industry. Alongside this, the environment of inhaler design and formulation has changed markedly in recent years. Environmental concerns over propellants, the commercial success of dry powder inhalers, and the apparent lack of advancement of propellant-driven metered-dose inhalers (pMDIs) has led to a less clear future for these devices. This review critically assesses these pressures and also potential opportunities for the pMDI. It is proposed that the future role of pMDIs will be determined by several important forces that can be classified under 'technology development' or 'market climate' categories. Technology development forces will be strengthened by the ability of the industry to have a systematic understanding of mechanisms of spray formation, perform subsequent and continued device and formulation advances, and a focus on all patient groups: particularly paediatric and geriatric populations. The ability to succeed in these areas will be largely determined by the willingness to invest in fundamental research of pMDI technologies.

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1. Introduction

The current market for pulmonary drug delivery is at a bottleneck. A series of events in the past two decades are converging to direct the future of inhaler design and therapy. Most significantly and widely discussed is the potential for the lungs as a route for systemically acting drugs, vaccines and gene therapeutic agents [1]. Concurrently, the environment of inhaler design and formulation has changed markedly in recent years [2,3]. Concerns over ozone-depleting propellants and greenhouse gases cast doubt on the future of propellant-driven inhalers [4,5]. With the rise and commercial success of dry powder technologies [2], the future role of metered-dose inhalers (MDIs) has been less clear, at least in the eyes of practitioners and market analysts. However, as discussed in this review, there is little data to suggest that dry powder inhalers (DPIs), including those in late development, are superior in performance to the state-of-the-art propellant-driven metered-dose inhalers (pMDIs). Furthermore, a detailed look at environmental issues with alternative propellants reveals that hydrofluoroalkane (HFA) greenhouse gas contributions are likely to be insignificant, particularly with pharmaceutical systems. The future role of pMDIs will be determined by several important forces that can be classified under 'technology development' or 'market climate' categories. Technology development forces will be strengthened by the ability of the industry to have a systematic understanding of mechanisms of spray formation, to perform subsequent and continued device and formulation advances, and to focus on all patient groups, particularly paediatric. In addition, pharmaceutical marketing forces are intimately tied with research and the continued improvement of pulmonary drug delivery systems. Market forces will

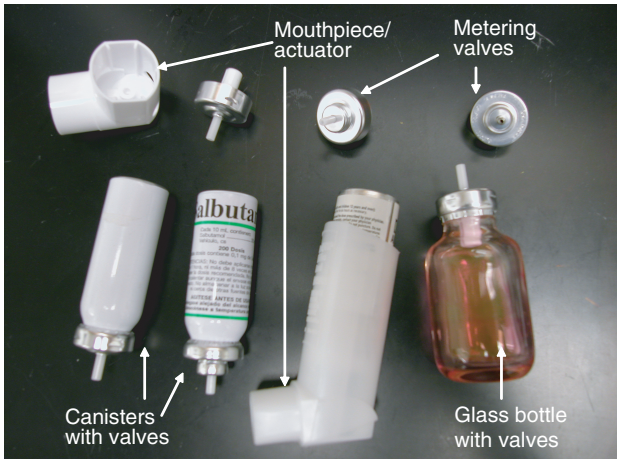

Figure 1. Basic components of pressurised metered-dose inhalers.

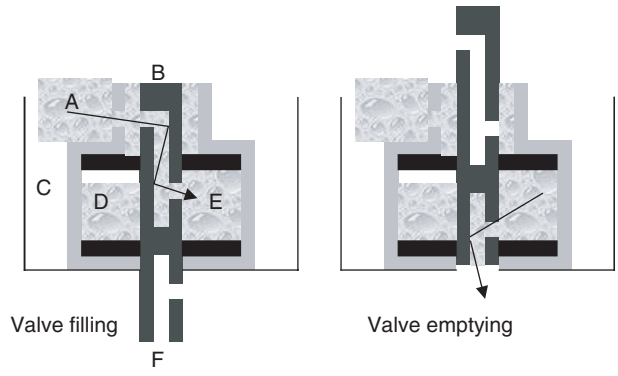

Figure 2. Schematic diagram of an example of the mechanism by which valves are used to dispense a metered volume of liquid. (**A**) Refill volume from the reservoir within the canister. (**B**) Valve stem that has two channels. (**C**) Canister interior. (**D**) Air bubble present in the metering chamber. (**E**) The filled metering chamber. (**F**) Exit of the valve to the atomisation orifice.

be driven by the discovery of new compounds, the regulatory approval of systemically acting compounds, and, significantly, the device technology that is promoted with the leading marketed products. Although consumer preference and superior device performance play significant roles in marketing decisions, it is clear from several well-known examples that these are not essential for product success (or failure). Thus, ultimately, the case is made that the future of pMDIs is dependent on a combination of scientific and market forces, the result of which will become more apparent as we emerge from the current pulmonary drug delivery 'bottleneck'.

2. Metered-dose inhaler fundamentals

MDIs generate aerosols suitable for inhalation by releasing a metered volume of pressurised liquid propellant-containing drug and excipients through an orifice that is usually part of a mouthpiece adapter (**Figure 1**). The system is described as a pressurised MDI to avoid confusion with other metered inhalers (DPIs, soft mist inhalers [SMIs] etc.). There may also be other components associated with the pMDI such as dose counters and spacers. The following discussion of the principles of aerosol generation from pMDIs considers each component separately. Subsequent discussion will evaluate the performance features of pMDIs as these components operate as a single system.

3. Device design

3.1 Valves

The design of the metered valve, originally for cosmetic purposes, facilitated the initial conception of sprays as a potential method of delivering medication to the lung. In 1955 Riker Laboratories began development of the first pMDI following the patenting of a metered valve by Emson Research and pressure-resistant vials by Wheaton Glass Company. Simple exposure studies and clinical trials were performed in June 1955, an NDA filed January 1956, and the Medihaler® (Riker Pharmaceuticals [now 3M Pharmaceuticals]) was then approved in March of 1956. Valve design has been modified over the years, but the basic principle remains the same. This principle is illustrated in **Figure 2**. The liquid propellant fills the metering chamber when a channel is opened that links the propellant contained in the canister to the metering chamber. This volume of liquid is then released to the atomisation orifice when the valve stem is depressed, and the second channel is opened to the valve exit while the channel to the canister is closed.

There are many variations on this basic metering principle: groove filling valves, clearance filling, filling via capillary ports, plug type metering, and chamberless valves. All valves are used in the inverted position (relative to valves that are used for household consumer aerosol products); consequently, no dip-tube is used.

Compatibility of propellants, excipients and solvents with the components of the valve influences performance of MDIs. HFA propellant formulation compatibility with pMDI valve elastomers has been reported [6]. Mixtures of HFA 134a and ethanol were used with several different types of valve elastomer material (Nitrile 01117, White Buna and Type 674 [B]). Formulations without ethanol adversely affected the function of the valves, but at higher concentration of ethanol the improved valve performance was offset by increased leakage from the valve. Better performing valves with cleaner extractive profiles have been sought by the industry since the phase-out of chlorofluorocarbons (CFCs) began [7]. Different materials have been identified for use with HFA propellants [7,8].

3.2 Canisters

The canister holding the propellant, drug and any excipients (i.e., surfactants) must have several characteristics for

optimum function: i) the canister must be able to withstand the high pressures of the propellant in liquid form at conditions that may be experienced under normal use by patients; ii) the canister materials must be inert and not interact adversely with the propellant formulation; and iii) the material must be able to withstand impact. Most marketed pMDIs have canisters constructed out of aluminum. However, glass bottles and various polymer materials are also under investigation for use in marketed products (e.g., Schott Purgard® [Schott AG]). Materials used with CFCs sometimes cause suboptimal operation of the device because of elastomer swelling, extraction, poor lubrication, and adsorption of the formulation to container walls [6]. The patent literature contains most information regarding canister materials and modifications. For example, fluorinated coatings, polymers of fluorinated monomers selected from the group consisting of CH_2FCF_3 and C_3F_6 are described [201]. Such a coating is claimed to prevent adhesion of drug particles to the internal surfaces of the canister and/or valve [201].

3.3 Actuators

Actuators combine an atomising orifice with a mouthpiece adaptor and a stem coupling for the valve and pressurised canister. Thus, the actuator is a multifunctional and surprisingly overlooked component in the publicly available scientific literature. Several studies have reported the orifice size influences on droplet sizes. Reducing the spray orifice diameter has been shown to reduce the particle size and alter the fine particle fraction (FPF) of pMDIs [9-13]. Polli *et al.* reported the first systematic study of orifice size effects on particle size [9]. The orifice diameter was decreased from 0.076 to 0.061 cm without a decrease in mass median aerodynamic diameter (MMAD). However, an orifice size of 0.046 cm resulted in a MMAD decrease from 11 to 3.2 μm. MMAD is a frequently used particle size parameter for inhalation aerosols because it relates the particle size distribution as a function of mass (important for therapeutic effect) and the behaviour of the particles in an airflow (relevance to aerosol deposition). Warren and Farr showed that as a consequence of the smaller orifice, a wider spray cone was produced and greater actuator deposition was observed [13]. Using data from obsolete propellant systems may not be relevant for HFA formulations [14]. Using a HFA solution formulation, the MMAD was not affected by a reduction in orifice diameter (0.42 – 0.25 mm), but the fine particle mass (FPM) was significantly increased [10]. In another study, a solution HFA formulation had marked increases in FPM and small decreases in MMAD with a reduction in the orifice diameter [13]. Recently, Stein and Myrdal conducted studies using pMDIs with various metered valve volumes and actuator orifice diameters using HFA 134a ethanol formulations [15]. Valve size did not have a statistically significant influence on the droplet aerodynamic size distribution for the tests in which the pMDI was actuated into a large-volume chamber; yet, valve size did affect the initial droplet size in the experiments using the USP inlet [16]. Droplet diameters increased with increasing valve size. Initial droplet diameter also increased with increasing actuator orifice diameter, but this increase was small for formulations with low ethanol levels, and was larger for formulations with higher ethanol levels. Due to the nonlinear interaction of multiple factors (formulation composition, valve volume, valve geometry and mechanism, orifice size, and other actuator geometries) actuator design features cannot be considered singly. Statistical design of experiments or complexity analysis has yet to be performed to facilitate prediction of droplet size output from a wide range of actuator designs.

A poorly studied and understood component of the actuator is the expansion chamber. Only Clark [17], Dunbar *et al.* [18,19] and Finlay [20] have discussed the influence of the expansion chamber on atomisation. The expansion chamber is the area within the actuator that connects the metering valve to the atomisation orifice. Clark's analysis yielded an empirical correlation that enabled prediction of the mass median diameter from pressures and vapour mass fractions within the expansion chamber for a particular system selected for investigation [17]. Dunbar considered the flow within the geometry of the expansion chamber and exit orifice, and compared it with the similar case of flow in a constriction [19]. Finlay discusses these examples together with further theoretical calculations [20]. As yet, no studies have been published that examine the influence of expansion chamber geometry on the characteristics of the emitted aerosol. This may be partly due to the complexity associated with numerical or theoretical models for flows within the actuator. These flows are characterised by high Reynolds number, turbulent, cavitating multiphase flow [20].

The lack of significant new developments and novel nozzle technology may also be a response to the lack of fundamental understanding of the mechanisms by which atomisation occurs in these propellant-driven systems.

Recent regulatory changes have signalled the potential for increased sophistication for actuators. Specifically, dose-counting devices will probably be included on newly developed actuators so patients can accurately determine the number of doses remaining in their inhaler [301]. In addition, during development, increased characterisation of the aerosol plume has been suggested. Plume analysis methods, previously very qualitative, now use sophisticated image analysis techniques and may lead to improved actuator design [21].

3.4 Spacers and holding chambers

The difficulty of inhalation-actuation coordination (particularly for children and elderly users) has been shown to be a significant component of noncompliant use of pMDIs [22]. Spacers have been developed for use with pMDIs in an attempt to obviate coordination difficulties, improve dosing reproducibility, and reduce unwanted oral deposition of aerosol droplets [23]. Spacers function by reducing aerosol velocity, allowing time for evaporation and sedimentation, thus reducing deposition of large particles in the mouth and throat [23].

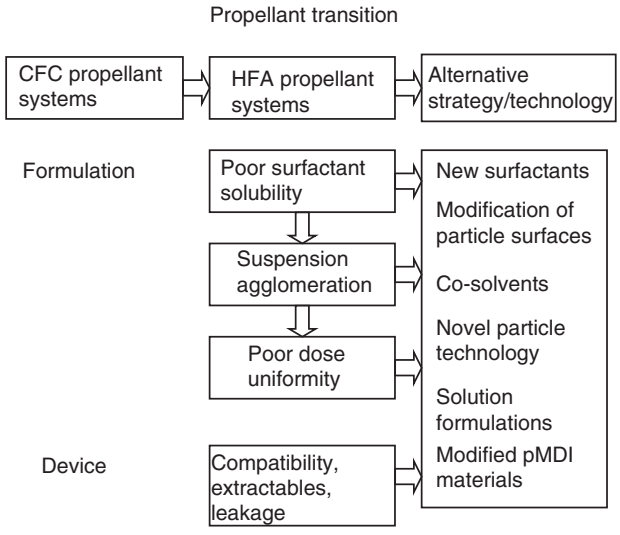

Figure 3. The reformation of CFC pMDIs to HFA propellant systems. Modified from [40].
CFC: Chlorofluorocarbons; HFA: Hydrofluoroalkane; pMDI: Propellant-driven metered-dose inhalers.

Some studies have shown that spacers increase the FPM *in vitro* and *in vivo* [24,25]. Therefore, spacers offer several clinically relevant advantages: i) there is a reduction in local mouth and throat complications such as oral candidiasis and dysphonia (e.g., corticosteroid therapy side effects); ii) poor inhaler technique related to coordination difficulties can be obviated using a spacer [26]; and iii) increased deep lung deposition of drug due to finer particle size may be desirable for certain drugs/disease states [27]. Unfortunately, very few investigations have considered pMDI systems containing HFA propellants which are replacing CFC systems. Indeed, there is some equivocal evidence to suggest that spacers may or may not have significant effects on FPM emitted from HFA-pMDIs depending on the formulation characteristics [25]. For solution formulations containing a high propellant concentration, little or no effect on the FPM was observed with or without spacer devices. However, when lower propellant concentrations were used, spacers were observed to have significant influences on FPM (e.g., 3.9 µg with no spacer versus 5.9 µg with the Aerochamber® spacer [3M Pharmaceuticals]). The study by Ahrens *et al.* [28] showed different *in vitro* performance with several holding chambers with different CFC-based pMDI formulations. A study by Mitchell *et al.* also demonstrated non-equivalence of *in vitro* performance between CFC- and HFA-formulated salbutamol for a given holding chamber type [29].

Spacer devices combined with pMDIs are the most common form of antiasthma medication in children, and, therefore, need more extensive characterisation with respect to performance [30]. One factor that has received considerable attention in recent years is electrostatic deposition in spacer devices [30-35]. Ionic detergents reduce electrostatic charge on plastic spacers, thereby improving *in vitro* drug delivery [35]. *In vitro*, detergents have been shown to reduce the electrostatic charge on the spacer surface, resulting in a mean increase of 37.4% in small particle (< 6.8 µm) salbutamol output compared with water-rinsed spacers [35]. *In vivo*, the mean lung deposition of radiolabelled salbutamol in healthy subjects was 45.6% through a detergent-coated spacer compared with 11.5% through a static spacer ($p < 0.001$) [35]. In another study using HFA propellant-based pMDIs the electrostatic charge in plastic spacers reduced lung dose in children by more than twofold [36].

Breath-actuated pMDIs have also been developed to address the issue of poor actuation-breath coordination in some patients; for example, the Autohaler™ (3M Pharmaceuticals) and the Easibreathe (Norton Heathcare Ltd). These devices typically use a flow rate trigger (in response to patient inhaling through the device) to activate the aerosol generation through the atomisation nozzle [37].

3.5 Dose counters and content indicators

Recently the FDA issued guidance documents on dose counters for pMDIs: 'Guidance for Industry: Integration of Dose-Counting Mechanisms into pMDI Drug Products' [301]. This marks a concerted effort to integrate dose-counting or content-indicating mechanisms into pMDI drug products. These include mechanisms that use numeric counting and dose-indicating mechanisms that have colour-coding or other means. Currently there is no practical way for patients to track the remaining numbers of doses or amount of medication. This is important due to the 'overage' of formulation that is added to pMDI canisters during manufacture. Commonly, a pMDI may contain sufficient drug for 20 – 30 additional doses. However, the amount of drug per spray in those additional 20 – 30 actuations may in many cases be inconsistent and unpredictable. Thus, FDA guidance seeks to overcome these problems, and regulation of pMDI dosing information appears likely. The addition of an accurate dose counter to an individual pMDI unit would allow the patient to track reliably the numbers of actuations used from that individual inhaler (i.e., to identify when the label claim number of actuations has been reached). This would prevent the patient from discarding an inhaler unnecessarily or using the product beyond the recommendations provided in the labelling for that product. In addition, ensuring that the counter never undercounts (i.e., indicates medication is present when none, in fact, exists) is equally important. The draft guidance document stipulates that these mechanisms be accurate; that is, do not undercount at all, but also minimise overcounting so that medication is not wasted. Appropriate engineering and design are necessary to optimise both precision and accuracy, which is critical for these components.

4. Formulation design

Clearly, the performance of pMDIs is a result of the combination of device and formulation design. Formulation

development should, therefore, proceed in parallel with device selection/design. In practice, formulation characteristics often drive device selection decisions [14]. The reasons for formulation lead development are discussed below, and the main reformulation issues associated with HFA propellant systems are summarised in **Figure 3**.

Several recent reviews have considered propellant and pMDI formulation issues [14,38]. The review by Vervaet and Byron considers the differences between the physicochemical properties of CFC and HFA propellant systems. This is an important issue for formulation scientists as the differences between propellants have challenged formulators in several major respects. First, conventional surfactants used in pMDIs were soluble in CFC propellants, but effectively insoluble in HFA 134a and HFA 227ea. As a result, cosolvents have been used more widely in HFA propellant formulations. Although the HFA propellants have similar boiling points and vapour pressures to dichlorodifluoromethane (CFC 12), the transition to HFAs was also accompanied by an increase in molecular polarity and an unpredictable change in solubility characteristics [14,38,39].

4.1 Propellant properties

HFAs are polar relative to CFC propellants. This results from the multiple fluorine atoms attached to the carbon backbone. In the case of HFA 134a, the strongly electron-withdrawing fluorine atoms result in the molecule having two electropositive protons [38]. HFA 227ea has one asymmetrical electropositive proton. As a consequence of these molecular interactions, HFAs are relatively polar but have very low intermolecular attractive forces when compared with CFCs systems. The strong electronegative repulsive interactions between HFA molecules (both HFA 134a and HFA 227ea) result in high vapour pressures and low boiling points [38].

The solubility characteristics of HFA propellants are not widely reported in the scientific literature, but presumably in-house databases exist in the industry. Those reports that have specifically addressed HFA solubility issues have shown that traditional solubility parameters have poor predictive power [38,39,41,42]. The lack of a direct relationship between the experimental data and solubility parameters and calculated log partition coefficient (clogP) indicates that a different approach is required to predict solubility.

Knowledge of the solubility of drug and excipients in propellant formulations is critical for optimal inhaler performance. The active drug substance in pMDIs is either suspended or dissolved in the propellant or propellant mixture. The case where drug is neither fully dissolved or suspended (partial solubility) is undesirable as it leads to crystal growth via a process known as Ostwald ripening [43]. As a consequence, irregularities in particle size and emitted doses may result, especially after storage. Thus, the determination of drug solubility in a range of propellant formulations is usually screened at early stages of development. The selections of lead formulation types are usually drawn from these studies. If a solution formulation is chosen the drug must have sufficient solubility in the formulation to allow therapeutic doses to be delivered. Thus, a wide range of data are required before specific formulations are selected for further development. In addition, studies of the effect of different drug forms, compatibility studies and stability screens, are usually performed in parallel. In suspension systems, drugs should have no solubility in the propellant formulation and, consequently, have good chemical stability [44]. This advantage is often counterbalanced with the need for stabilising excipients such as surfactants. Surfactants help to prevent agglomeration of micron-sized particles in suspension formulations. The choice of surfactants, as already discussed, is limited due to their poor solubility. Furthermore, the need to avoid crystal growth and/or adhesion of micronised suspended drugs to internal container surfaces are problems that may be catalysed by some combinations of surfactant type/concentration, vehicles and physical forms of drug substance [38]. These issues, coupled with the increase in polarity of HFA propellants compared with CFCs, may have contributed to the overall decrease in the number suspension systems developed with HFA propellants. Currently, there is a limited range of propellant systems available, and the selection of a solution or a suspension system may be by necessity rather than by choice [14].

4.2 Drug effects

Although drug compounds are usually present in low concentrations in pMDIs for local delivery to the lung, the physicochemical properties and concentration of the drug may exert significant influence on the aerosol produced. The effect of drug concentration on the aerosol particle size emitted from suspension pMDIs has been investigated. In a CFC system, the MMAD increased significantly when high drug concentrations were included in the formulation (2.86 mg/g) compared with when lower drug concentration formulations (0.175, 1.43 mg/g) were used (18 versus 3.2 µm, respectively) [9]. Similar observations have been reported by other authors [1,13,45]. Increases in particle size are possibly related to decreased propellant fraction and decreased efficiencies of atomisation at the nozzle and expansion chamber. Drug concentration is also related to suspension stability and dose uniformity [6]. An apparent limit to drug concentration has been suggested to be ~ 2% w/w or 20 mg/ml due to valve clogging issues [1].

Physicochemical properties of the drug may also influence pMDI function [46]. Specifically, drug properties such as particle size, lipophilicity, molecular weight, and crystal form may significantly influence dissolution rate, drug absorption, and chemical and physical stability [46,47]. Potentially, the performance of antiasthma medications may be improved by modifying these characteristics.

Recently, there has been an increase in the number of combination drug products for the treatment and prevention of asthma. Combining two drugs within the same inhaler may have several therapeutic advantages, including increased

patient compliance. Literature on combination pMDIs is sparse, but formulation challenges due to hetero-aggregate formation in suspension systems have been reported [48,49].

4.3 Excipients

Historically, few excipients have been included in pMDI products that have been successfully marketed. Cosolvents (ethanol) and surfactants (oleic acid, sorbitan trioleate and soya-derived lecithin) are currently the only excipients found in approved products in the US. Several alternative excipients have been suggested, but their use remains limited by an insufficient toxicological profile with respect to lung delivery. However, there are recent examples of new products with novel excipients achieving regulatory approval (e.g., Vfend® IV, intravenous voriconazole; Pfizer, Inc.). Thus, in the future it is expected that additional excipients will be found in approved products. These cases will occur when significant therapeutic advantages are realised due to the use of novel excipients.

Examples of novel pMDI excipients include: novel surfactants (e.g., 3M oligolactic acids, acyl amide acids, monofunctionalised M-PEGS [50,51,202], taste-masking excipients [52], microemulsion excipients [53,54], microspheres and hollow porous microspheres [55,56], cyclodextrins [203], nanoparticles [57], and alternative propellant systems [dimethylether and propane] [58]).

4.4 Patent issues

The innovative environment that has surrounded pMDI systems in recent years has been accompanied by a wealth of patent applications. Clark recently reviewed patent activity for pulmonary drug delivery devices since 1965 [40]. Beginning around the mid-1980s the number of pMDI patents filed steadily climbed to a peak in the mid-1990s. The major issue resulting in these patents was the transition from CFCs to HFAs and the requirement for newer materials, components, stabilisation techniques and manufacturing processes. Clark identified examples of key pMDI patents as those relating to the use of the HFA propellants [59,60]. These have led to a complicated situation, particularly in the US, in which licensing deals have predominated over legal challenges of patent coverage. In Europe the patent landscape has also changed dramatically in recent years [61]. Similarly, many patents have arisen from formulation alterations, HFA formulations relating to specific drugs or drug classes, processes of manufacture, and modifications to the container/closure system. Many of these patents have been opposed on the grounds of obviousness, yet the complete picture of which patents are valid has yet to be clarified [61].

5. Performance comparisons

Alternative devices such as DPIs, SMIs and various hand-held nebuliser systems are regularly compared with pMDIs. Unfortunately, many of these performance comparison studies have been performed using CFC-based inhalers. However, the state-of-the-art pMDIs have certainly moved forward since HFA systems were introduced, and the 'gold standard' should be adjusted accordingly. Performance comparisons can be made using a variety of quantitative measures including *in vitro* measurements (particle size distributions, FPF, FPM), geometric standard deviation, and plume characteristics) and *in vivo* measurements (pharmacokinetics/pharmacodynamics, scintigraphic studies and imaging) [14]. In this section, the performance of pMDIs will be critically examined with respect to CFC-pMDIs versus HFA-pMDIs, and HFA-pMDIs versus other types of portable inhalers.

5.1 CFC- versus HFA-pMDIs

Table 1 reviews some of the clinical studies that have been performed over the last decade and compares the performance of CFC- and HFA-pMDIs. A quick review of the overall findings of these studies reveals two distinct scenarios: i) the safety and efficacy profile of HFAs is equivalent to the CFC-based pMDIs; or ii) HFA-based pMDIs are clinically equivalent at much lower doses compared with their CFC counterparts, and, in general, performance of the HFA-pMDI is superior to CFC systems. These contradictory findings can be reconciled by realising the different approaches adopted by the industry to the CFC to HFA transition. The most common and easiest route in terms of regulatory approval is to show bioequivalence between the existing product and the HFA replacement. Alternatively, formulations with differing aerosol characteristics require more safety and efficacy testing. Scenario ii) applies specifically to solution formulations, such as HFA-beclomethasone dipropionate (Qvar®; 3M Pharmaceuticals), in which the particle size distribution of the emitted aerosol is significantly finer than its CFC predecessor. In these cases, a deliberate decision was taken to reformulate at finer size to achieve greater therapeutic benefit [62].

When the purpose of reformulation has been to improve deposition patterns, the outcome has typically been a reduction in particle size, decreased oropharyngeal deposition, and increased peripheral lung deposition. The original work with solution formulations was performed with QVAR and has been reviewed by Leach [62]. Improved delivery characteristics for steroids were sought to reduce unwanted oropharynx deposition and increase large and small airway lung deposition. This was investigated by creating a solution of HFA 134a formulation that generated aerosol with a median particle size of 1.1 μm. Scintigraphy studies in asthmatics showed that 56% of the drug was deposited in the lungs with concomitant decreased oropharynx deposition compared with typical CFC-beclomethasone dipropionate lung deposition of 5 – 30% [62].

A more recent example is the development of flunisolide HFA-pMDIs [63]. In this review of flunisolide HFA development, the aerosol was found to have a MMAD of 1.2 μm, which is smaller than the 3.8 μm MMAD of the CFC formu-

Table 1. Clinical studies comparing CFC pMDI with HFA pMDI performance for a variety of drugs from 1995 to 2004.

Reference	Drugs	Performance comparison
[66]	Salbutamol, salmeterol, FP	Similar effects observed for all inhaler comparisons (CFC vs HFA) on morning PEFR and inhaler use
[67]	Salbutamol	HFA 134a salbutamol sulfate and CFC 11/12 salbutamol produced clinically and statistically similar airway responses and side effects
[68]	BDP	HFA-BDP achieves a level of asthma control that is clinically and statistically equivalent to CFC-BDP in terms of efficacy and safety, at total daily doses ranging from 200 to 600 µg in asthma patients previously stabilised on inhaled CFC-BDP
[69]	Albuterol (salbutamol)	Proventil HFA provides protection against exercise-induced bronchoconstriction comparable to Ventolin and Proventil and protection superior to placebo. Proventil HFA has a safety profile similar to Ventolin when used to prevent exercise-induced bronchoconstriction
[70]	Fenoterol and ipratropium bromide	A dose of 100 µg fenoterol/40 µg ipratropium bromide inhaled from a MDI containing HFA 134a propellant is safe and provides effective bronchodilatation of equivalent degree, onset and duration of action to the same dose from the conventional CFC formulation
[71]	Salbutamol	Data indicated that salbutamol formulated in HFA 134a and that in CFC propellant are bioequivalent
[72]	Cromolyn sodium	Either formulation of cromolyn sodium MDI (CFC or HFA) showed a statistically significant ($p < 0.05$) improvement of 12 – 18% compared with placebo in symptom summary score, daytime asthma symptoms, and albuterol use. Patient and physician opinions favored HFA-cromolyn sodium over placebo ($p = 0.01$). No statistically significant differences existed among groups in the incidence of treatment-related adverse events
[73]	BDP	HFA-BDP extrafine aerosol was found to provide equivalent control of moderately severe asthma to CFC-BDP at approximately half the daily dose with a favourable safety profile, suggesting an improved therapeutic ratio
[74]	Disodium cromoglycate	Systemic exposure (the plasma concentrations of DSCG at 1 h) was slightly higher with the HFA-MDI compared with the CFC-MDI. It was concluded that the safety, tolerability and *in vivo* performance of the CFC-free MDI was at least as well tolerable as the already marketed CFC formulation
[75]	BDP	55 – 60% of the HFA-BDP ex-actuator dose was deposited in the lungs, with 29 – 30% deposited in the oropharynx. CFC-BDP deposition was 4 – 7% in the lungs and 90 – 94% in the oropharynx. The pattern of deposition within the lung showed that HFA-BDP was spread diffusely throughout the lung airways, whereas CFC-BDP was confined to the central airways with little, if any, peripheral airway deposition. A second study with asthmatics ($n = 16$) confirmed that 56% of the HFA-BDP dose was deposited in the airways, with 33% in the oropharynx. HFA-BDP deposition was much greater in the airways than CFC-BDP, with a concomitant reduction in oropharyngeal deposition
[76]	Albuterol sulfate	HFA 134a albuterol sulfate provides bronchodilation comparable to CFC albuterol and has a similar safety profile
[77]	BDP	CFC-BDP had lower bioavailability compared with HFA-BDP perhaps due to large fraction of CFC-BDP was swallowed and absorbed from the gastrointestinal tract, relative to the HFA-BDP MDI
[78]	BDP	Equivalent efficacy at a lower dose and equivalent safety at the same dose imply that HFA-BDP may have a more favourable risk:benefit ratio than CFC-BDP when used at the recommended lower doses
[79]	BDP	HFA 134a BDP propellant system proved as safe and was as well-tolerated as the current CFC-11/12 BDP system. The two propellant systems without active drug were also equally well tolerated
[80]	Albuterol	Patients with asthma switched from CFC albuterol to HFA albuterol receive comparable bronchodilation with a similar safety profile as those continuing to receive CFC albuterol. No significant differences in bronchodilator efficacy between the patients continuing to receive CFC albuterol and those switched to HFA albuterol were found in the 12 weeks after the switch
[81]	BDP	Increasing doses of inhaled BDP using HFA pMDIs lead to improved lung function and asthma control. Moreover, the reformulation of BDP in HFA enables effective asthma control at much lower doses than CFC-BDP

Table 1. Clinical studies comparing CFC pMDI with HFA pMDI performance for a variety of drugs from 1995 to 2004.

Reference	Drugs	Performance comparison
[82]	Albuterol	HFA albuterol is as effective as albuterol products formulated in CFCs and more effective than placebo in protecting asthmatic children from EIB
[83]	BDP	HFA-BDP efficacy was found to be equivalent to that of CFC-BDP in that no statistically significant difference was observed between the two groups. Asthma control was maintained over 8 weeks, with few asthma exacerbations, in patients switching from previous CFC-BDP therapy to HFA-BDP at half the dose
[84]	Cromolyn sodium	The HFA formulation of cromolyn sodium MDI was well tolerated and effective treatment for asthma patients ≥ 12 years old. The safety and efficacy profile of the HFA formulation was comparable to that of the CFC formulation
[85]	BDP	No significant difference was demonstrated between the two treatment groups with respect to improvement in symptoms, spirometry, or methacholine responsiveness assessed by FEV(1), except for a greater reduction in breathlessness in the HFA-BDP group ($p < 0.05$)
[86]	BDP	HFA-BDP provided equivalent control of moderate or moderately severe asthma as CFC-BDP in the population studied but at half the total daily dose
[87]	BDP	Significant differences in pharmacokinetics following HFA- and CFC-BDP were observed. Following a 400 µg BDP dose, the HFA formulation gave mean C_{max} and AUC values of beclomethasone esters two- to threefold those seen with the CFC formulation
[88]	TAA	The TAA-HFA 225 mg exhibited similar safety and efficacy profiles to the two equivalent doses of TAA-CFC studied. The higher strength 225 µg/puff formulation provides effective control of asthma with fewer inhalations
[89]	BDP	HFA-BDP (400 µg/d) was as effective as CFC-BDP (800 µg/d) in sustaining improvements in asthma quality of life following withdrawal of 7 to 12 days of prednisone treatment in moderate asthma
[90]	BDP	Both formulations were well-tolerated with no difference in the pattern of adverse events, effect on serum cortisol or Candida colonisation. The HFA-formulated BDP-pMDI was equivalent to, and directly substitutable for, the CFC-formulated product at the same dose
[91]	Salbutamol	Proventil-HFA salbutamol was bioequivalent to Ventolin-CFC salbutamol
[92]	Albuterol	HFA albuterol had a safety profile similar to that of CFC albuterol during chronic, scheduled use, and both were well-tolerated. HFA albuterol and CFC albuterol provided comparable bronchodilator efficacy, but bronchodilator efficacy decreased for both products with 1 year of use
[93]	FP	Based on an overall analysis of the two treatment groups at week 6, equivalence was demonstrated. There was a comparable improvement in secondary efficacy variables, including clinic lung function measurements, in the two treatment groups. The incidence and type of most adverse events were similar in the two treatment groups. There was no difference in the adjusted geometric mean morning serum cortisol levels after treatment with the HFA 134a and CFC-pMDI
[94]	TAA	Improvements in morning PEF and FEV1 were similar between the two treatments. Albuterol (salbutamol) use was significantly reduced with triamcinolone-HFA (-0.67 puffs/day) vs beclomethasone-CFC (-0.11 puffs/day). There were no clinically significant differences between the two treatment groups with respect to safety
[95]	Salbutamol	The median daily use of inhaled study medication remained constant at four actuations per day throughout the study in both treatment groups and statistical analysis indicated that the two formulations were equivalent
[96]	Albuterol	Canister use for HFA patients was consistently lower (2.7 ± 3.2 vs 5.4 ± 6.7) than for CFC-MDIs for the entire cohort over the 20-month assessment period. This difference was consistently observed for albuterol canister use in patients with and without concomitant ICS use (3.3 ± 3.8 HFA vs 7.2 ± 7.5 CFC for ICS users and 2.1 ± 2.1 HFA vs 4.1 ± 5.7 CFC for non-ICS users). Time to next prescription also was longer for HFA patients than for CFC patients (61.6 ± 50.9 days HFA vs 47.3 ± 40.8 days CFC). These data suggest that CFC patients use an average of 1.3 more canisters per year compared with HFA patients independent of asthma severity as measured by ICS use. This improvement in dosing characteristics has the potential to translate into enhanced economic outcomes

Table 1. Clinical studies comparing CFC pMDI with HFA pMDI performance for a variety of drugs from 1995 to 2004.

Reference	Drugs	Performance comparison
[97]	BDP	The two formulations were statistically equivalent with respect to efficacy. For mean morning PEF the estimated treatment difference (BDP-CFC/BDP-HFA ratio) was 102.6% (95% CI 99.1, 106.2). Similar equivalence was shown for the other efficacy parameters. Both products were well-tolerated, with no difference in the adverse event profiles, effects on 24 h urinary cortisol or *Candida* colonisation
[98]	Fenoterol hydrobromide	No difference between the two groups was observed in PEF or in the use of rescue medication. The long-term safety and efficacy profile of fenoterol HFA-MDI was comparable to that of the fenoterol CFC-MDI
[99]	Fenoterol/ipratropium bromide	Fenoterol/ipratropium bromide combination via HFA pMDI was as safe as delivery by the currently available CFC-metered-dose inhaler, in an extended population of patients with CAO under normal prescribing conditions
[100]	FP	Similar or lower FP systemic exposure was observed with the HFA 134a pMDIs compared with the corresponding CFC inhalers. The differences in systemic exposure observed for the HFA 134a and CFC pMDIs were too small to produce a differential effect on urinary cortisol excretion. Because FP has negligible oral bioavailability, the systemic exposure, which arises only from pulmonary absorption, is a measure of lung deposition
[101]	FP	The bioavailability values of fluticasone after inhalation via a CFC-MDI and an HFA-MDI were similar. The two formulations delivered comparable amounts of fluticasone, and systemic exposures to fluticasone from the two devices, measured by urinary cortisol excretion, were not significantly different
[102]	BDP	Treating the population of the HFA-BDP group (n = 72) at 400 µg/day and the CFC-BDP group (n = 78) at 1000 µg/day did not show significant differences in terms of symptoms, lung function, airway hyperresponsiveness and serum markers of inflammation at the end of the run-in period and the end of the study phase
[103]	TAA	The incidence of adverse events was similar in the two treatment groups. No clinically relevant suppression of the HPA axis was observed. Pulmonary function tests were not adversely affected by use of either study medication
[104]	FP	The two groups were shown to be clinically equivalent in terms of all efficacy variables and there were no differences in tolerability
[105]	Albuterol	Ventolin HFA was clinically comparable to Ventolin formulated with the conventional CFC-containing propellant when administered to children with asthma
[106]	FP	There were no clinically relevant differences in adverse events or serum cortisol levels between the two groups
[107]	BDP	In patients with moderate-to-severe symptomatic asthma, HFA-BDP extra-fine aerosol 800 µg (-1) was at least as effective and equally well tolerated as 1000 µg day(-1) HFA-FP
[108]	Flunisolide	Flunisolide HFA, at a third the daily dose (median daily dose of 340 µg) of flunisolide CFC, was well tolerated and effective when administered to adult and adolescent patients with mild-to-moderate asthma
[109]	BDP	Asthma control was maintained in patients switched from a stable dose of CFC-BDP (400 – 1600 µg daily) to HFA-BDP at approximately half the CFC-BDP dose (200 – 800 µg daily), and was maintained over the next 12 months. HFA-BDP demonstrated a similar safety profile to CFC-BDP; there were no differences between the agents with regard to systemic effects
[110]	Albuterol	Patients who were switched from Ventolin CFC to Ventolin HFA maintained pulmonary function and other measures of asthma control at levels comparable with run-in baseline
[111]	Flunisolide	Day 1 mean dose-adjusted AUC was significantly greater in the flunisolide CFC 1000 µg b.i.d. group than in either flunisolide HFA group, indicating greater systemic availability of flunisolide CFC. Oral clearance and volume of distribution were significantly higher for flunisolide CFC than for flunisolide HFA. This may be due to greater oropharyngeal deposition by the flunisolide CFC formulation. Another indicator of greater flunisolide CFC oropharyngeal deposition was observed in C_{max} and AUC(0-tlast) values for 6-β-OH flunisolide, the first-pass metabolite of flunisolide. The values of these pharmacokinetic parameters were significantly higher in the flunisolide CFC group than in the 340 µg b.i.d. flunisolide HFA group on days 1 and 14
[112]	Ipratropium bromide	Ipratropium bromide HFA, provided bronchodilation comparable to the marketed ipratropium bromide CFC over 12 weeks of regular use

Table 1. Clinical studies comparing CFC pMDI with HFA pMDI performance for a variety of drugs from 1995 to 2004.

Reference	Drugs	Performance comparison
[113]	BDP	HFA-BDP 800 µg/d provided control of moderate- to-severe asthma with efficacy and safety at least similar to BUD TH 1600 µg/d
[114]	BDP	The BDP-HFA 134a formulation proved to be statistically equivalent to the standard BDP CFC product over 12 weeks in adult patients with mild-to-moderate asthma
[115]	BDP	All studies demonstrated equivalence of efficacy for morning PEFR for BDP Modulite versus BDP-CFC when compared on a microgram for microgram basis. The secondary outcome variables also consistently support similar efficacy of the two products. The safety and tolerability profile for BDP Modulite was similar to BDP-CFC; the incidence of adverse events was comparable between treatments and plasma and urinary cortisol were generally unchanged in patients receiving 1000 µg day-1 for 6 – 12 weeks
[116]	FP	All treatments significantly improved PD20 values and morning peak expiratory flow versus placebo, whereas 1000 µg/d was significantly better than 500 µg/d for the CFC formulation of FP (CFC-FP) but not the HFA formulation of FP (HFA-FP). Only 1000 µg/d of CFC-FP caused significant suppression of overnight urinary cortisol/creatinine compared with placebo. There were no differences between formulations at either dose
[117]	Albuterol	Albuterol in HFA 134a pMDI was not different in efficacy in the treatment of EIB in asthmatic patients. Single doses of albuterol HFA and CFC from an MDI are comparable in terms of efficacy and safety on a microgram per microgram basis
[118]	BDP	Clinically important improvements in the Asthma Quality of Life Questionnaire (AQLQ) score were observed at month 12 for HFA-BDP vs CFC-BDP, whereas conventional clinical indices of pulmonary function and asthma control were similar in the two groups
[119]	Albuterol	The study demonstrated comparability in terms of efficacy and safety between albuterol/HFA 134a and albuterol/CFC
[120]	BDP and FP	Lung deposition was greater with HFA-BDP compared with CFC-FP and CFC-BDP. Deposition values appeared to be related to the particle size distribution of each inhaler, with the smaller particles of HFA-BDP providing the greatest lung deposition and least oropharyngeal deposition
[121]	Flunisolide	Pharmacokinetic parameters were determined after single doses of 1000 µg CFC flunisolide delivered without a spacer, 340 µg HFA flunisolide delivered through a spacer, and 516 µg HFA flunisolide delivered without a spacer. Peak plasma concentrations were similar for the three treatments. Area under the was similar for the CFC and HFA flunisolide, plus spacer groups; however, AUC for the HFA flunisolide without spacer group was comparatively lower than for the CFC group. 6-β-OH flunisolide measurements, the first-pass metabolite of flunisolide and an indicator of oropharyngeal deposition, were significantly higher in the CFC flunisolide group than in either HFA flunisolide group
[122]	BDP	HFA-BDP was a cost-effective intervention when compared with CFC-BDP in a group of patients with stable asthma. In the majority of scenarios HFA-BDP provided more effective asthma control at a similar cost to CFC-BDP
[123]	BDP	Patients were randomised to continue on CFC- BDP+Spacer or switch to HFA-BDP Autohaler at half the daily dose. The change from baseline in morning peak expiratory flow was significantly greater in patients receiving 100 – 200 µg of HFA-BDP compared with those receiving 200 – 400 µg of CFC-BDP+S. There were no significant differences between treatments in mean change from baseline in FEV(1), percentage of days or nights without asthma symptoms, and daily β-agonist use over the 6-month treatment period. The proportion of patients who had one or more asthma exacerbations, the incidence of adverse events, and the percentage change from baseline in 24-h urinary free cortisol levels were similar in the two treatment groups
[124]	Albuterol	There were no statistically significant differences between pharmacodynamic parameters for HFA versus CFC propellants. The area under the plasma albuterol concentration versus AUC was 72% greater for the HFA formulation, indicating a greater lung bioavailability ($p = 0.015$). This difference in bioavailability did not result in a statistically significant difference in FEV1 values between the two propellants
[125]	Ipratropium bromide	Ipratropium bromide HFA had similar efficacy and tolerability to Ipratropium bromide CFC over 1-year study period
[126]	Budesonide	A budesonide HFA 134a formulation given with a spacer device provided an equivalent asthma control with that of a corresponding CFC product, when administered in stable patients treated with inhaled corticosteroids in a broad range of daily doses

Table 1. Clinical studies comparing CFC pMDI with HFA pMDI performance for a variety of drugs from 1995 to 2004.

Reference	Drugs	Performance comparison
[127]	FP	FP propelled by HFA 134a has equivalent efficacy and comparable safety to FP propelled by CFC propellants at a µg equivalent dose in pediatric asthmatic patients
[128]	BDP	There was no significant difference between CFC and HFA in the concentration of BDP metabolites in bronchi. These concentrations were lower in peripheral tissue and in serum taken immediately after inhalation for the CFC-pMDI. Furthermore, the CFC group showed a higher concentration of BDP in the mouthwash indicating a predominantly peripheral deposition and a faster uptake and metabolism of HFA-BDP

AUC: Area under the curve; BDP: Beclomethasone dipropionate; CAO: Chronic airways obstruction; CFC: Chlorofluorocarbon; Cmax: Maximum concentration; EIB: Exercise-induced bronchospasm; FEV1: Forced expiratory volume in 1 sec; FP: Fluticasone propionate; HFA: Hydrofluoroalkane; HPA: Hypophyseal-pituitary-adrenal; ICS: Inhaled corticosteriods; MDI: Metered-dose inhaler; PEF: Peak expiratory flow; PEFR: Peak expiratory flow rates; pMDI: Propellant-driven metered-dose inhaler; TAA: Triamcinolone acetonide.

lation. Compared with flunisolide CFC, more of the flunisolide HFA nominal dose reached the lungs and less was deposited in the oropharynx. Scintigraphic studies have shown that flunisolide HFA had greater deposition in the small airways. In short- and long-term clinical studies, flunisolide HFA significantly increased pulmonary function relative to placebo, but was not statistically superior to the CFC formulation when given at lower doses. Flunisolide HFA exhibited small improvements in secondary efficacy measures, such as as-needed albuterol use and asthma symptoms, relative to flunisolide CFC [63]. The literature also suggests that the HFA formulation had a lower risk of systemic corticosteroid effects (e.g., hypothalamic–pituitary–adrenal axis suppression, growth inhibition in children) [63].

Salbutamol (albuterol) has also been compared in HFA- and CFC-based systems. Airomir™ (3M Healthcare) was formulated with an ethanol cosolvent, and had significantly different aerosol characteristics and efficacy from that of the CFC existing product [64]. An alternative HFA salbutamol formulation, Ventolin® HFA (a microcrystalline suspension of salbutamol sulfate in propellant HFA 134a and no other excipients) (GlaxoSmithKline) is also marketed. This suspension formulation demonstrated similar efficacy to the CFC product [64].

Beclomethasone was reformulated from a CFC-based suspension to an HFA-based solution. Clinical trials using 3M's beclomethasone product, QVAR, showed that efficacy increased on the order of 2- to 2.6-fold (depending on the design of the trial and outcomes measured) [64].

5.2 Spacer issues

A related issue of HFA pMDI performance is compatibility with spacers and holding chambers. There appears to be some evidence to suggest that HFA-based pMDIs perform with greater uniformity when used with a range of different spacer devices and holding chamber designs [25,27,65]. This spacer-independent behaviour is not observed with CFC-based formulations in some recent studies [28]. Although more rigorous investigation is required, the selection of spacer device may have less importance for HFA-pMDIs than CFC systems [25].

5.3 HFA-pMDIs versus DPIs, aqueous systems, SMIs and hand-held nebulisers

Although several studies comparing MDIs with DPIs have used HFA propellant formulations, surprisingly, many, even very recent studies, have used pMDIs containing CFC propellants as the comparator [134-140]. Similar comparisons with CFC-based systems have also been made with SMIs [141-145]. One of the reasons for these comparison studies to use CFC-pMDIs is the lack of HFA formulation available. The situation is somewhat different in Europe where HFA formulations have been widely available for several years. In addition, CFC-based systems may be used to show equivalence. However, CFC systems no longer represent current technology or the state-of-the-art for pMDIs, and, therefore, should not be used routinely in product performance comparison studies. For many relevant drug molecules, HFA-pMDI formulations are currently marketed or are near to commercialisation. CFC systems are old technology and the detuned bioequivalent HFA systems may perform similarly [146]. However, improved performance in any class of inhaler will not be achieved on the scale that is possible if CFC products are used as the 'gold standard'.

The efficacy of pMDIs versus nebulisers [164] and other hand-held devices [147,148] has not yet been established. It is important to note that not all studies and comparisons differentiate between pMDIs that contain different propellant systems. In addition, no review considers pMDI design beyond basic formulation or propellant type. Thus, the importance of pMDI components on performance cannot be elucidated from these sources.

A Cochrane review has recently compared pMDIs versus all other hand-held inhaler devices for the delivery of β_2-agonist bronchodilators for non-acute asthma [147]. From the 90 studies that were included in the review, the authors conclude that HFA-pMDIs were as effective as DPIs and CFC-pMDIs. However, such an outcome might be anticipated from the steep dose–response curves for this class of formulations (i.e., all products get a saturated response). This hypothesis has not been addressed in the literature. The authors also highlight the need for improved study design (statistical power, more randomised controlled studies, washout periods, and adequate

Table 2. Examples of HFA pMDI versus DPI clinical comparison studies for various devices and drug substances.

Reference	Drugs/devices	Performance comparison
[113]	HFA-BDP Autohaler versus budesonide Turbuhaler DPI	HFA-BDP 800 mg/day provided control of moderate-to-severe asthma with efficacy and safety at least similar to budesonide DPI 1600 mg/day
[129]	Combined formulations of salmeterol/FP; HFA-pMDI versus Diskus DPI	At a dosage of 50/500 mg twice daily, the SALM/FP 25/250 mg HFA MDI (two actuations twice daily) is clinically equivalent to the SALM/FP 50/500 mg Diskus (one actuation twice daily)
[130]	Triamcinolone acetonide (Azmacort HFA 225 µg inhalation aerosol) pMDI and budesonide (Pulmicort Turbuhaler 200 µg) DPI	Chronic dosing did result in a statistically significant 20% reduction. in basal 24-h serum cortisol AUC for both compounds. There were no clinically significant adverse effects noted during the study. Overall, the study drugs were well tolerated, with adverse events characterised as mild-to-moderate in severity
[131]	Albuterol delivered via HFA 134a pMDI and the Turbuhaler DPI in asthmatic children	FEV1 increased similarly after cumulative doses of salbutamol on each of the study days, irrespective of device. Mean treatment difference in AUC was 0.01 l/min (95%CI -0.05 to 0.08 l). Heart did not differ at any dose. It is concluded that salbutamol delivery from a HFA-pMDI and Turbuhaler is equivalenton a microgram basis in asthmatic children for efficacy and safety
[132]	MF administered by both DPI and pMDI	Following intravenous administration, MF was detected in all subjects 8 h postdose. In contrast, following DPI administration, blood plasma MF levels were below the limit of quantification (LOQ, 50 pg/ml). Only two plasma samples following HFA-pMDI administration had plasma levels of MF above the LOQ
[133]	Salbutamol via HFA pMDI Airomir used with metal spacer (NebuChamber) versus Turbuhaler DPI	Significant differences ($p < 0.001$) were found between the NebuChamber and the Turbuhaler for salbutamol C_{max} and C_{av}. This amounted to a 1.89-fold difference between these devices for C_{max}, and a 1.78-fold difference for C_{av}. *In vivo*, salbutamol from a HFA pMDI given via a metal spacer (NebuChamber) produces significantly greater delivery than from a DPI (Turbuhaler)

AUC: Area under the curve; BDP:Beclomethasone dipropionate; DPI: Dry powder inhaler; HFA: Hydrofluoroalkane; MF: Mometasone furoate; pMDI: Propellant-driven metered-dose inhaler.

outcome reporting) in these comparative studies. At this point there appear to be many gaps in the clinical understanding of the different performance of each type of device. A similar review has also been presented for the comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airway disease [148]. The review of three trials in children and 21 trials in adults demonstrated no evidence to suggest clinical benefits of any other inhaler device over a pMDI in corticosteroid delivery. The finding that HFA-pMDIs may reduce treatment failure and oral steroid requirement (systemically administered via gastrointestinal tract) in β-agonist delivery needs further confirmatory research in adequately randomised clinical trials [148]. The patients' ability to use pMDIs was also reviewed. Differences among studies and the heterogeneity of the results made it difficult to draw conclusions about inhaler technique differences between device types. The review of technique after teaching the correct technique suggests that there is no difference in patients' ability to use DPIs or pMDIs. In terms of economic analysis, the total number of prescriptions for inhaler therapy for asthma in 1998 in the UK was > 31 million, with a net ingredient cost of > £392 million. The economic assessment in this report used decision analysis to estimate the relative cost-effectiveness of inhaler devices for the delivery of bronchodilator and corticosteroid inhaled therapy. Overall, there were no differences in patient outcomes among the devices. On the assumption that the devices were clinically equivalent, pMDIs were the most cost-effective devices for asthma treatment.

In one recent study comparing CFC inhalers, HFA-pMDIs and DPIs, 100 patients with obstructive airway disease on regular CFC aerosol inhaler medication were interviewed regarding inhaler preference and use [149]. Most patients (96) agreed to change from their CFC to the HFA inhaler, and of those, only 12 did so with some reservation. Properties (taste, user-friendliness, design) of the HFA inhaler were rated favourably, whereas the DPIs also represented an acceptable alternative to aerosol inhalers. A total of 57 patients preferred a DPI to the HFA inhaler, but not all powder devices were equally acceptable. The investigators found that replacing the CFC inhaler with patients' preferred alternative devices resulted in a more than threefold increase in costs. Studies comparing HFA-pMDIs with some DPI devices are summarised in **Table 2**.

5.4 Environmental concerns: what are the issues and what are the risks?

For nearly 60 years CFCs refrigerants were widely used for refrigeration, foam blowing and aerosol sprays. Their harmful effect on the Earth's protective ozone layer was first postulated by Molina and Rowland in 1974 [150]. Subsequently, the ozone hole over the Antarctic was discovered and heightened world attention that led to the Montreal Protocol of 1987. The

Table 3. Global warming and ozone depletion data.

	Industrial/ human output (emissions) Mln tonnes (1995)	Predicted contribution to manmade global warming	Atmospheric life/years	ODP	GWP 100 yr (CO_2)	GWP 50 yr (CO_2)
Carbon dioxide	26,030	71%	500	0	1	1
Methane	375	21%	14.5 (± 2.5)	0	21	6.5
Nitrous oxide	9	7.5%	120	0	310	170
HFA 134a	0.020*	<< 0.05%	14	0	1300	420
HCFC 22	0.224*	<< 0.5%	13.3	0.055	1700	520
CFC 12	0.189*	< 0.5%	102	1	8500	4200

Source: Climate Change 1995: contribution of working group 1 to the second assessment report of the IPCC, 1996.
*Source: AFEAS report on production, sales and atmospheric release of Fluorocarbons through 1995.
Used with permission from the Inergovernmental Panel on climate change [302].
GWP: Global warming potential; ODP: Ozone depleting potential.

Montreal Protocol committed the signatory nations to cease production of CFCs by 1996. Although specific essential exemptions were granted, the pharmaceutical industry was forced to find alternative propellants for pMDIs. Several HFAs shared similar desirable characteristics (nonflammable, chemically stable, similar vapour pressures, and non-ozone depleting), and they were investigated as possible substitutes for CFCs. After extensive testing, the propellant tetrafluoroethane (HFA 134a) was demonstrated to have toxicology and safety profiles at least as safe as CFC propellants, and since then has been incorporated into pMDIs approved by regulatory agencies [14]. HFA 227ea has undergone a similar path and is now incorporated in marketed products.

5.5 Non-ozone depleting but greenhouse gas contributing

Over the same period, it was discovered that CFCs also contributed significantly to the world's global warming problem. The global warming potential (GWP) of CFC-12 is 8500-times that of carbon dioxide over 100 years. The global warming implications of CFC substitutes are now perceived as a major issue. Several recent reviews of pulmonary drug delivery cite concerns over the regulation of HFAs as a negative factor on the future development of pMDIs [4,40,151].

Since the elimination of CFCs was initiated there has been a rapid growth in the abundance of HFAs in the environment. **Table 3** illustrates the relative GWP of various common greenhouse gases. HFAs have a relatively high GWP compared with carbon dioxide, the single most important greenhouse gas, but less than the CFCs they are replacing. However, despite this relatively high GWP, HFAs currently account for 0.06% of manmade global warming, and it has been calculated that HFA-pMDIs will account for < 0.02% of the total greenhouse gas emissions by 2010 [3].

Despite these projections indicating the relatively low impact of HFAs on global warming, industry analysts view regulatory controls over greenhouse gases as a burden on the continual marketing of HFA-pMDIs [151]. In this respect, the perceived environmental issues related to HFA propellants for use in pMDIs may not equate to the actual risks. Several reviews, notably those detailing DPI technology, have rapidly concluded that the future of HFA pMDIs will be limited by the greenhouse nature of the propellants used. Indeed, at some point, HFA 227ea and HFA 134a propellants may be controlled under the Kyoto Climate Change Protocol but if the Montreal Protocol experience and the recent non-ratification by the US of the Kyoto Protocol are predictive, then HFAs in pMDIs will exist for many years to come.

5.6 Paediatric patients

Several excellent reviews on the growing importance and unique problems of aerosol therapy in neonates and paediatric patients have been published recently [152,153]. The importance of aerosol therapy in the management of respiratory disorders of paediatric patients has continued to increase over the past 15 years [152]. It has been suggested that this rise in aerosol therapy in paediatrics is due to an increase in the occurrence of reactive airway disorders, greater utilisation of aerosol therapy among paediatric patients with reactive airway disease [154], and expanded applications of aerosol therapy for other disorders such as cystic fibrosis [155,156], intervention for infectious processes [157], and neonatal chronic lung disease (or bronchopulmonary dysplasia) [158]. However, unique delivery challenges exist in infants and young children. The therapeutic efficacy of aerosolised medication for treating pulmonary disorders depends on adequate and efficient delivery of drug to the targeted sites within the lung. In general, this depends on aerosol particle size, the amount of respirable aerosol delivered, and the patients' breathing characteristics during aerosol generation, and the nature and use of the delivery system [159]. However, in children and infants, it has been suggested that the most important factors influencing lung deposition are breathing parameters [160]. Children have low tidal volumes and greater

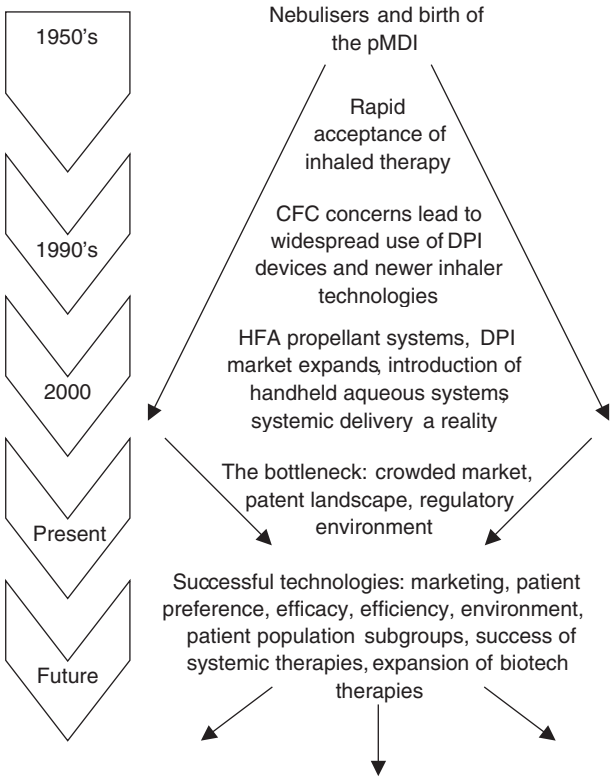

Figure 4. The growth of pulmonary drug delivery and its culmination at the bottleneck, through which only some successful technologies will emerge depending on a wide range of dynamic pressures.

CFC: Chlorofluorocarbon; DPI: Dry powder inhaler; HFA: Hydrofluoroalkane; pMDI: Propellant-driven metered-dose inhaler.

variability in breathing patterns [152,153,160]. Thus, choice of device will be important for maximising dose delvery under these low flow and variable conditions [160].

Current DPI devices are not recommended for children < 4 – 6 years of age, due to the high pressure drop required to be generated across the device for adequate aerosolisation to occur [160]. Active devices under development may facilitate improved dry powder delivery to young patients. Using a standard DPI device, unreliable lung deposition was observed in young children due to the flow-dependent properties of the device [161]. Flow-dependent deposition will be significant as the reduced peak inspiratory flow that can be generated by younger children results in a lower dose to the lungs [161]. The effect of age on lung deposition of radiolabelled budesonide, delivered as a dry powder via Turbuhaler® (AstraZeneca) to asthmatic children, was assessed using a γ-scintigraphy methods [162]. Total lung deposition of 99mTc-labelled budesonide was positively and significantly correlated with age, height and peak inspiratory flow.

Nebulisers are commonly used in clinical practice for the administration of aerosols to infants and small children. A comparison study of aerosol delivery to wheezy infants from a nebuliser and from a pMDI via two small volume spacers (250 – 350 ml) was performed [163]. It was observed that aerosol delivery from a pMDI through small-volume spacers was effective and that a higher percentage of the total amount of drug (salbutamol) was delivered than that observed from a nebuliser. These observations have also been made by other investigators [160]. Newer technologies, such as breath-coordinated nebulisers, may improve efficiency and decrease variability [164]. In a recent study, a pMDI and spacer was compared with a hand-held nebuliser system with an 'adaptive aerosol' technology [164]. Although the pMDI with spacer was more variable, parents generally preferred the shape, size and weight of the pMDI. In addition, the costs of these more technologically complex devices must be considered.

MDIs are associated with difficulty in coordination of breathing and atomisation of the drug formulation. This problem is thought to be exacerbated in young children. Thus, spacer devices or valved holding chambers (VHCs) are widely used when administering drugs via pMDIs to this age group. VHCs enable tidal breathing and do not necessitate breath coordination [160]. The key distinguishing feature between VHCs and spacers is the presence of an inhalation valve to contain the aerosol until inhaled. Some VHCs also have an exhalation valve to enable multiple breaths to be taken without the patient having to remove the device to exhale. The Canadian Standards Association International provides a good summary of the differences between these devices (CAN/CSA/Z264.1-02:2002).

The development of spacer as accessories to pMDIs has significantly improved effective inhalation treatment in young children [165]. The addition of a face-mask improves spacer performance in infants and children who are too young to breathe through a mouth piece, and has greatly advanced our ability to adequately treat even neonates and infants [166,167]. In a recent study comparing face-masks with different patient interfaces, an improved seal improved total drug delivery *in vivo* to paediatric patients [165]. However, improvements in face-mask sealing properties did not influence the interpatient variability in delivery.

Despite these clinical observations, pMDIs are highly inefficient delivery devices for patients in this age group. With the introduction of HFA propellants, and the associated improvement in performance (discussed previously), the opportunity exists for further development for delivery to paediatric patients. Aerosol delivery systems for older infants and very young children have essentially been adaptations of devices initially developed for adult use [153]. This opportunity has not yet been realised by the industry, but with increasing pressures from environmental regulation, loss of adult market to alternative devices, and expansion of the market of paediatric aerosol therapy, the pMDI may be well suited to providing this patient group/market with much needed improvement in pulmonary drug delivery performance. However, in a recent review of pulmonary drug delivery to paediatric patients, the author concludes that behavioural aspects have a greater impact on therapeutic outcomes than technical aspects, and understanding these is vital for the development and selection of devices [153].

6. Expert opinion: at the bottleneck

Between the years 1991 and 2000, > 1300 patents in the pulmonary delivery technology area were filed [40]. Now, after two decades of very active research, pulmonary drug delivery is at a bottleneck (**Figure 4**). The phrase 'bottleneck' has been widely used in recent times, particularly with reference to global environmental and ecological issues [168], and is defined as a narrow entrance or stretches in a road, comparable to the of the neck of a bottle. The future of the pulmonary drug delivery will involve those technologies that successfully navigate through the pressures of market consolidation and regulatory influences. In terms of the future of pMDIs and associated technology advances, the following pressures are likely to influence the extent to which these devices continue to dominate the pulmonary drug delivery market.

6.1 HFAs and greenhouse gases

The major issue confronting continued marketing and development of pMDIs is the prospect of government regulation of the HFA propellants due to their role as greenhouse gases when emitted into the atmosphere. However, given that the Intergovernmental Panel on Climate Change estimates the contribution of HFA 134a to be < 0.05% of the total greenhouse gas emissions, regulation in the pharmaceutical industry appears unlikely. However, the most influential factor will be industry's perception of the risks of continued research and development of HFA-based systems. Overestimation of the risks may result in premature abandonment of a technology that has yet to be optimised and is likely to provide superior performance at lower cost for several years to come. Clearly, it makes good business sense to manage the risk and continue development of alternative delivery systems.

6.2 Growth of DPIs

The recognition of asthma as a chronic inflammatory disorder has had a major impact on the market for asthma therapeutics: a shift from rescue bronchodilator therapies to prophylactic strategies has resulted in intensified use of inhaled corticosteroids, long-acting 2-adrenoceptor agonists and antileukotrienes [169]. The market for asthma therapies exceeded US $7 billion in 2002, with prophylactic therapies accounting for nearly 80% of those sales [169]. The growth of the DPI market has been rapid and represents the biggest challenge to pMDIs as the delivery system of choice for inhaled therapy. Highlighting the expansion of the DPI market, Advair®/Seretide® (GlaxoSmithKline) sales continue to increase (US sales increased 18% in the second quarter of the 2004 financial year [303]). Advair is a combination DPI containing the corticosteroid fluticasone and the long-acting 2-adrenoceptor agonist salmeterol, and has reached blockbuster status by offering convenience and safety, which have led to improved patient compliance and market success.

The acceptance of DPIs by clinicians and patients will continue to broaden, particularly if the devices are combined with active pharmaceutical ingredients that offer significant advantages over current therapeutic agents, as in the case of the Advair product. Similarly to pMDI devices, the scope for improving DPI performance is considerable. In addition, active DPIs present an opportunity for universal technology platforms to be developed using active dispersion mechanisms [170]. If these technologies come into fruition it can be expected that development times for bring new drugs to market (in terms of pharmaceutical and drug delivery issues) will be minimised. Thus, DPIs, with further development and significant improvements in existing performance, can be expected to grow as alternative devices for the delivery of compounds to the respiratory tract.

6.3 Patent landscape

The recent surge in patent applications for a variety of pMDI-related technologies has led to a complicated legal situation that has not yet been resolved. The impact on development of new products and devices is an increase in licensing deals rather than legal challenges of patent coverage. In-house intellectual property for pMDIs continues to be developed in addition to increased assessment of external technologies for potential development and business extension. It seems that given the right mix of technologies and negotiation, the apparent limitations of the current patent landscape will unfold either by rights acquisition or by collaborations.

6.4 Bioequivalence and ambivalence

The persistence of pMDI devices that demonstrate bioequivalence to CFC predecessors is likely to stall technological improvements possible for propellant-driven systems. The 'detuning' of HFA-based systems to match existing technological performance (50 years old) is a short-term solution to the regulations imposed after the signing of the Montreal Protocol. However, these products should only be viewed as short-term solutions, and parallel development of pMDIs with newer atomisation technologies, formulation components, and device enhancements must continue. Ambivalence in progressing pMDI technology will be rapidly revealed by the impending improvements in alternative inhaler technologies. In addition, investment in understanding the mechanisms of spray formation and atomisation of propellant-based systems is required. CFC systems were largely developed using empiricism and this led to unnecessary long development times and suboptimal products. The future of pMDI improvements lies in understanding their principles of operation on a physical basis. Advanced mathematical models and computational fluid dynamics are tools by which these processes may be more thoroughly understood.

Among these threats there are significant opportunities for growth of pMDIs:

6.4.1 Biotechnological therapeutics: new avenues

Clearly, the development of drug delivery systems for large molecule therapies, such as proteins and peptides, appears

well aligned with the capabilities of respiratory delivery systems. The entire inhaled drug market will benefit from the successful marketing of an inhaled systemic macromolecule (i.e., insulin). Inhaled insulin technologies are under all phases of development, and one product (Exubera®; Pfizer and Aventis) has been submitted to European Regulatory Agencies for approval. Further studies are required to establish the viability of using pMDI technologies to administer macromolecules and biotechnology related therapies (e.g., dose ranges, stability, compatibility issues etc.).

6.4.2 Technology advances and performance improvements

Alongside new drug compound development, technological advances in device design and formulation platforms will promote enhanced pMDI performance and efficiency. As discussed already, the continued success of pMDI systems will depend on improvements driven by an understanding of the fundamental principles of propellant-based atomisation.

6.4.3 Patient groups

Some of the discussion above has addressed the growing market and unmet needs associated with paediatric inhaled therapy. pMDI devices are well positioned to meet these needs for successful delivery to the young. Costs, patient preference, and nature of the aerosol plume make pMDIs the most suited device for efficient and portable aerosol administration for children. However, as several clinicians have commented [153], significant changes to the existing technology are required to make pMDIs for the young more than mere adaptations of adult devices. Furthermore, the behavioural aspects of inhaled therapy (i.e., patient coordination with inhaler actuation, breath-holding, crying in infants/small children, fear of devices etc.) need to be addressed to ensure patient acceptance and compliance.

7. Summary: what is in the future for pMDIs?

Several years ago an editorial appeared that addressed the myth of technological improvements associated with the CFC transition entitled '…the Emperor's New Clothes…' [146]. Several relevant issues pertaining to poor inhaler design and patient misuse were highlighted. However, the issue raised that addressed the most significant challenge for the future development of pMDI systems is the perpetuation of delivery systems that are unable to reproducibly deliver drug to the lungs of patients. For pMDIs to continue to share the inhaled therapy market with rapidly developing DPIs and other SMIs, significant improvements must be made. As outlined in this review, these improvements should be well within the reach of future propellant-driven inhaler technologies, including formulation design developments and device design developments, via an understanding of atomisation and aerosol formation.

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