8

Medical Aerosols

Coordinating Lead Authors
Paul J. Atkins (United States), Ashley Woodcock (United Kingdom)

Lead Authors
Olga Blinova (Russia), Javaid Khan (Pakistan), Roland Stechert (Germany), Paul Wright (United Kingdom), You Yizhong (China)

Review Editors
David Fakes (United Kingdom), Megumi Seki (Japan)

Contents

EXECUTIVE SUMMARY

Asthma and COPD (Chronic Obstructive Pulmonary Disease) are major illnesses worldwide affecting over 300 million people. Inhaled therapy is, and is likely to remain, the gold standard for treatment. There are two main methods of delivering respiratory drugs for most patients: these are the metered dose inhaler (MDI) and the dry powder inhaler (DPI). The choice of the most suitable inhaler is a complex medical decision taken in consultation between the doctor and patient.

When the MDI was introduced in the mid-1950s, CFCs were used as propellants and these have been replaced in recent years with HFCs, although the complete phase-out of CFCs in MDIs is not expected to be before 2010. CFCs and HFCs are used in MDIs because of their chemical and physical properties and no other propellants have been developed to date that might constitute alternatives. Multidose DPIs, which do not require a propellant, have also become more widely available in the past decade as a not-in-kind replacement and this has mitigated the growth of the use of MDIs.

MDIs remain the dominant form of treatment for asthma and COPD worldwide in terms of units prescribed. In developed countries, the proportion of MDI to DPI varies substantially from country to country: from 9:1 MDI:DPI in the USA to 7:3 in UK and 2:8 in Sweden. The variation is accounted for by a number of factors, including availability (e.g. multidose DPIs only recently became available in the USA; by contrast, there is a local manufacturer and a long tradition of DPI use in Sweden), patient and physician choice, and relative cost. CFC MDIs are being phased out, and being replaced by HFC MDIs and DPIs. The use of DPIs in developing countries is negligible. Both MDIs and DPIs play an important role in the treatment of asthma/COPD and no single delivery system is universally acceptable for all patients. It is critical to maintain the range of therapeutic options.

The CFC transition under the Montreal Protocol is still in progress, with rates varying between countries. CFC inhalers are being replaced by both HFC MDIs and DPIs. The main impact on GWP is made by the transition from CFC to HFC MDIs. Recently, a number of new drugs have been launched in DPIs. DPIs are generally more expensive than MDIs (especially for salbutamol) and not all drugs are available in DPIs. As approximately 50% of CFC MDIs have historically contained salbutamol, it is likely that this rescue medication will continue to be given in MDIs and will necessitate the continued use of HFCs. As the development and regulatory time scales for new inhaled delivery systems are lengthy (10 years or longer) no major technical breakthroughs are expected to become available for patients for 10 to 15 years (Table 8a).

Predicting HFC usage in MDIs for developing countries is quite difficult and depends on a number of factors, some of which are under the control of national governments:

- the timing of CFC phase-out by local MDI manufacturers (including HFC intellectual property and manufacturing issues);
- nationally-produced DPIs will emerge, but it is likely these will still cost more per dose than HFC MDIs;
- disease trends and the continued uptake of multidose DPIs;
- general availability of affordable medicines.

Switching patients from reliable and effective medications has significant implications for patient health and safety. The provision of a range of safe alternatives is critical before enforcing change on environmental grounds. Any environmental policy measures for the future that could impact patient use of HFC MDIs would require careful consideration and consultation with physicians, patients, national health authorities and other health-care experts.

The overall use of HFCs for MDIs for asthma/COPD (rounded off to the nearest 100 tonnes) is predicted to be up to 15,000 metric tonnes (13,500 tonnes HFC-134a, 1500 tonnes HFC-227ea) by 2015. On the basis of these forecasts, the maximum environmental benefit of the hypothetical extreme case of switching all HFC MDIs to DPIs would be in the order of 23 million tonnes of CO_2 per year.

The estimated incremental cost of switching HFC MDIs to DPIs would be mainly related to inexpensive salbutamol HFC MDIs, and is of the order of an incremental and annually recurrent US$ 1.7–3.4 billion. This is equivalent to 150–300 US$/$tCO_2$-eq.

Small amounts of HFC are also used in non-inhalational topical aerosols, but most applications have non-HFC alternatives (mechanical pumps, hydrocarbon propellants, etc.).

Table 8a. Summary of estimates of global use of CFCs and HFCs in MDIs (IPAC, 2004; derived from UNEP-TEAP (2003), page 120).

Time scale	Annual CFC use in MDIs		Annual HFC use in MDIs	
	metric tonnes	$MtCO_2$-eq yr^{-1}	metric tonnes	$MtCO_2$-eq yr^{-1}
1987–2000	15,000	128	<500	<1
2001–2004	<8,000	<69	3,000–4,000	<5–6
2005–2015	<2,000	<17	13,000–15,000	23–26

8.1 Introduction

Medical aerosols include metered dose inhalers (MDIs) for asthma and COPD, and non-MDI medical aerosols.

8.1.1 Metered dose inhalers

Asthma and chronic obstructive pulmonary disease (COPD)
Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic diseases of the air passages (airways or bronchi) of the lung and are thought to affect over 300 million people worldwide. These illnesses account for high health-care expenditure, cause significant absence from work and school, and premature death. Modern treatment for these conditions involves the inhalation of aerosol medication with a specific particle size (1–5 micron), which is deposited into the airways of the lung (bronchi). This allows maximal local effect in the airways where it is needed and minimizes the side-effects of the drug elsewhere in the body.

Asthma
Asthma is a chronic condition with two main components: airway inflammation and narrowing. Most patients have symptoms every day, with more severe attacks intermittently, during which coughing and wheezing develop and the airways narrow, making it very difficult to breathe. Attacks of asthma may occur spontaneously or be triggered by many environmental factors or viral infections. Attacks of asthma may require urgent additional medication, they sometimes require hospitalization and they are occasionally fatal.

Asthma most often starts in childhood, and persists into adult life, causing frequent attacks, chronic ill health and incapacity. A recent international study of asthma in childhood has shown a prevalence of asthma that varies from approximately 1 percent in some countries such as Indonesia to over 30 percent in the United Kingdom, New Zealand, and Australia (ISAAC-SC, 1998). It is more common in affluent countries, but has been increasing rapidly in developing countries over the last two decades. This increasing prevalence is likely to be due to multiple factors including 'westernization', changes in house design, greater exposure to house dust mite, maternal smoking, diet, air pollution and/or tobacco smoking.

Chronic obstructive pulmonary disease (COPD)
COPD is a condition involving the narrowing and inflammation of the airways in conjunction with damage to the lung tissue (emphysema). COPD is caused primarily by cigarette smoking, with inhalation of occupational dusts or environmental air pollution as potential co-factors. COPD is persistent and progressive if the patient continues to smoke, and further deterioration can still occur even after smoking cessation. COPD ultimately leads to permanent disability and death. Acute exacerbations of COPD frequently require hospitalization.

The prevalence of COPD in many developed countries is around 4–17 percent in the adult population aged over 40 years (summarized in Celli *et al*., 1999). Data are less certain in developing countries but figures as high as 26 percent have been quoted. Rates in men are generally higher than women and reflect smoking prevalence. Smoking is beginning to decline in some developed countries, but trends in developing countries indicate that both smoking and the prevalence of COPD are of increasing concern.

In the 1996 Global Burden of Disease Study sponsored by the World Health Organization, COPD was ranked 12 in terms of disability, but is projected to rank 5 in 2020, behind ischaemic heart disease, major depression, traffic accidents and cerebrovascular disease. In 1998, COPD was the fourth most common cause of death in the United States after heart disease, cancer and stroke. In most developed countries, the male death rate from COPD has been declining. By contrast, the female mortality rate is increasing and it is expected that mortality rates amongst females will overtake those men by about 2005.

Treatment
Modern treatment of asthma and COPD consists of inhaled therapy (Dolovich, 2000). This affords highly effective treatment with few side-effects.

There are two main categories of inhaled treatment for asthma and COPD: bronchodilators (also called acute relievers), and anti-inflammatory medication (also called controllers or preventers).

Bronchodilators (reliever medication)
Virtually all patients with asthma and COPD require short-acting bronchodilators. Bronchodilators reduce muscle tightening, which contributes to the narrowing in the airways. They are the key treatment for acute attacks and are lifesaving in severe attacks. In intervals between attacks, they may be needed frequently through the day, particularly in children for whom exercise-induced asthma is common.

Inhaled bronchodilators fall into three classes:

- *Beta-agonists* – These are the main reliever treatment for asthma and COPD. *Short acting beta-agonists* include salbutamol (known as albuterol in the United States), terbutaline, and fenoterol. They act within a few minutes, and have an effect lasting approximately 4 hours.
- *Long-acting beta-agonists* - salmeterol and formoterol have an effect that may last for up to 12 hours.
- *Anti-cholinergics* including ipratropium bromide and tiotropium bromide. These are commonly used as first-line bronchodilator therapy in COPD.

Anti-inflammatory medication (controllers or preventers)
Inflammation of the airways is a fundamental part of asthma, and suppression of this inflammation is recommended in all but those with mild infrequent symptoms. Anti-inflammatory treatment stabilizes lung function and prevents acute exacerbation of asthma if used regularly, hence the term 'preventer'.

Preventers are commonly used in COPD, but are less effective in this condition. Inhaled preventers are usually one of two classes of drug:

- *inhaled steroids* (e.g. beclomethasone, budesonide, flunisolide, fluticasone or triamcinolone): these are the mainstay of preventer medication for asthma and COPD;
- *cromoglycate-like drugs* (e.g. sodium cromoglycate or nedocromil sodium): these are less effective than inhaled glucocorticosteroids.

Oral treatments

Oral treatments have a limited, but sometimes important, role in asthma/COPD. Theophyllines are an old inexpensive therapy, which is both relatively ineffective and has major side-effects. Newer oral leukotriene antagonists are safe but have generally been found to be less effective clinically and, in any event, they are not a substitute for inhaled steroids in asthma, and are ineffective in COPD.

8.1.2 Non-MDI medical aerosols

Before the Montreal Protocol phase-out of CFCs in non-Article 5(1) countries in 1996, CFCs were commonly used in aerosols outside the asthma/COPD indication, namely for:

- topical (skin) therapy for local anaesthesia and cooling for sports injuries;
- sub-lingual sprays for angina pectoris;
- nasal sprays for allergic rhinitis and sinusitis;
- vaginal foams for contraception;
- rectal foams for colitis.

All these uses have been replaced mainly by mechanical pump sprays, hydrocarbon, di-methyl ether and compressed gas, and a few by HFC pressurized aerosols. There are also some early technical developments of novel treatments formulated in DPIs or aqueous sprays by biotechnology companies (e.g. buccal insulin). At this point it can be concluded that it is unlikely that significant volumes of HFCs will be used in applications other than MDIs for asthma/COPD.

8.2 Technical performance characteristics

Inhalation aerosols have been the subject of significant investment in research and development for most of the past twenty years. The science and technology have taken leaps forward in response to both therapeutic (Hickey and Dunbar, 1997) and environmental needs (Molina and Rowland, 1974).

The requirement to phase out ozone-depleting chlorofluorocarbon propellants (in MDIs) has increased the interest in alternative systems, most notably dry powder inhalers (DPIs). Significant progress has been made in all aspects of their principles of operation, including formulation, metering and dispersion in the past decade.

Pressurized metered dose inhalers

A metered dose inhaler (MDI) is a complex system designed to provide a fine mist of medicament for inhalation directly to the airways as treatment for respiratory diseases such as asthma and COPD. The propellant-driven metered dose inhaler (MDI) has been the dominant inhaler for almost half a century. The combination of the drug dispersed in a high vapour pressure propellant, metered accurately in tens to hundreds of micrograms and administered directly to the lungs was a powerful new tool for the treatment of pulmonary diseases (Hickey and Evans, 1996). The historical confluence of this new technology with potent new therapeutic agents revolutionized the treatment of asthma and COPD.

The main components of MDIs are:

- the active ingredient;
- excipient(s);
- the propellant (a liquefied gas);
- a metering valve;
- a canister;
- an actuator/mouthpiece.

Traditionally, MDIs have contained CFCs, primarily CFC-12 and CFC-11, and sometimes CFC- 114. However, because of the detrimental effect of CFCs on the Earth's ozone layer (Molina and Rowland, 1974), there was an extensive search in the 1990s for propellants that could be used as alternatives and had much less of an effect on the ozone layer and potentially on the environment in general. The hydrofluorocarbons 134a and 227ea are both now being used in the pharmaceutical industry as propellants for MDIs (Pischtiak *et al*., 2001). These materials are pharmacologically inert and have similar properties to the CFC propellants they replaced (see Table 8.1). However, they

Table 8.1. Hydrofluorocarbon (HFC) propellants used in MDIs.

Substance	CFC-11	CFC-12	HFC-134a	HFC-227ea
Density (kg litre^{-1})	1.49	1.33	1.21	1.41
Vapour Pressure (at 20°C)				
in kPa	12.4	466	472	386
in psig	1.8	67.6	68.4	56.0
Boiling Point (°C)	23.7	-29.8	-26.5	-17.3

are so different from CFCs that they require a significant investment in formulation strategies for the range of drugs traditionally delivered by MDIs.

There are two types of MDI formulations: suspension formulations, in which micro-particulate drug (typically micronized material) is dispersed in a combination of propellants; and solution formulations, in which the drug freely dissolves in either the propellant or a combination of propellant and an acceptable co-solvent, typically ethanol (June *et al*., 1994; Smith, 1995). Both types of formulation have inherent advantages and disadvantages. Traditionally, suspension formulations have been the more common dosage form, but with the advent of the hydrofluoroalkane propellants (HFC-134a; HFC-227ea), which have poor solvency characteristics, the use of co-solvents has become more common and solution formulations being used more (Leach *et al*., 1998; Brown, 2002). Other potential propellants (e.g. hydrocarbons, pressurized gases) do not possess the safety profile of CFCs, or are impossible to reformulate.

Globally, there are a number of companies involved in developing HFC MDIs. They include: 3M Pharmaceuticals (USA); Aventis (France/Germany); Boehringer Ingelheim (Germany); Chiesi (Italy); Cipla (India); GlaxoSmithKline (UK); and Ivax Healthcare (USA/UK) (see Table 8.2). The development of HFC MDIs has provided many challenges for the pharmaceutical industry, requiring new formulations, novel surfactants and cosolvents, new valves and canisters, and new manufacturing plants. HFC MDIs are manufactured according to 'good manufacturing practices' regulated and inspected by government authorities, and efforts are made to ensure that fugitive HFC emissions and waste are strictly controlled (Medicines Control Agency, 1997).

An HFC MDI, for the widely prescribed short-acting beta-agonist salbutamol, was introduced in the United Kingdom for the first time in 1994. Today, there are over 60 countries where at least one HFC MDI containing salbutamol has been approved and marketed. In addition to the introduction of beta-agonist HFC MDIs, there are a growing number of controller medications (e.g. inhaled corticosteroids) available as HFC MDIs. It is estimated that there were approximately 100 million HFC MDIs produced globally in 2002 (UNEP-TEAP, 2002), representing approximately 25% of worldwide MDI production.

Nebulizers

Nebulizers for the delivery of solutions of drugs were in existence prior to the development of the MDI. These systems found their application in acute ambulatory care and domiciliary situations since the droplet size of the aerosol was slightly smaller than that of the MDI, could penetrate more deeply into the lungs of the patients and did not require a degree of coordination to deliver the drug effectively (Dalby *et al*., 1996). Nebulizers continue to play a valuable role in severely compromised patients and for applications other than asthma, notably cystic fibrosis (Garcia-Contreras and Hickey, 2002).

Nebulizers can be used to generate aerosols for inhalation from liquid solutions or suspensions. Patient coordination of aerosol delivery with inhalation is not as critical as for MDIs or DPIs for achieving a therapeutic effect. In addition, aqueous solutions are often easily formulated for use in nebulizers (Niven, 1996). However, most nebulizers are bulky, inconvenient and too expensive for routine use.

Nebulizer systems typically fall into the categories of air jet or ultrasonic depending on the physical principle used for aerosol droplet generation. Jet nebulizers draw solution through a capillary tube using the Bernoulli effect and disperse droplets in air at high velocity. Ultrasonic nebulizers use high-energy ultrasonic vibration to create droplets suitable for inhalation. Until very recently, nebulizer use was limited to the hospital or home due to the energy requirements and poor portability of conventional systems. In general, the performance of nebulizers tends to vary significantly depending on the type and formulation.

A number of new 'portable' nebulizer technologies are being developed, although these may take some years to become commercially available (DeYoung *et al*., 1998).

Dry powder delivery systems

DPIs contain dry powder formulations of inhalable drug, but do not use propellants. DPIs were used on a limited scale in the 1960s and 1970s, when the Spinhaler and Rotahaler were used

Table 8.2. Currently available formulations (by company) for the most widely prescribed inhaled drugs, salbutamol, beclomethasone, budesonide and cromoglycate.

Drug Compound	Formulation	Producer
Salbutamol	Ethanol/Surfactant/HFC-134a	3M Pharmaceuticals Ivax Healthcare
	HFC-134a alone	GlaxoSmithKline Cipla
Beclomethasone	Ethanol/HFC-134a	3M Pharmaceuticals Ivax Healthcare
	Ethanol/HFC-134a/Glycerol	Chiesi
Budesonide	Ethanol/HFC-134a/Glycerol	Chiesi
	HFC-134a alone	Cipla
Cromoglycate	HFC-227 only	Sanofi-Aventis

for the delivery of disodium cromoglycate and albuterol/salbutamol respectively (Dunbar *et al*., 1998). These were relatively inconvenient single-dose capsule-based devices that delivered the drug directly into the inspiratory airflow of the patient in a manner considered passive since additional energy was not used to support dispersion. DPIs have continued to evolve. Two new devices for once- or twice-daily medications remain as unit dose devices, whereas several others are multidose blister or reservoir devices (Maggi *et al*., 1999).

The powder formulation is a critical component of a DPI. Several key attributes are necessary for successful respiratory drug delivery. First, the active drug must be produced in the appropriate particle size range of 1–5 microns (Schuster *et al*., 1998), whether these fine particles are delivered as pure drug or as a formulation with acceptable excipients. Second, the drug particles must be chemically and physically stable following their manufacture, storage, and subsequent processing when preparing the final drug product.

Powders of respirable size tend to have poor flow characteristics due to adhesive interparticle forces. To facilitate powder filling and dispersion, the drug particles can be formulated with additional excipients, usually lactose. Regardless of the composition, regulatory requirements mean that the final powder formulation must provide a stable and reproducible aerosol. This is mainly assessed by the total emitted dose and fine particle fraction (Hickey, 1992; US FDA, 1998). DPIs may be less suitable for some patients with low inspiratory flow rates, such as the elderly and young children.

Most DPI formulations are sensitive to moisture during processing and moisture ingress into packaging during storage. The presence of moisture in the ultimate product has been shown to reduce the de-aggregation of the powder, thereby decreasing the fine particle fraction of the aerosol (Boekestein *et al*., 2002; Staniforth, 2002). One approach proposes the use of magnesium stearate as a lubricant and anti-caking agent to maintain an inhalation powder's fine particle fraction under extreme temperature and humidity conditions (Staniforth, 2002).

Sensitivity of asthmatics to excipients must be considered when developing new products. For example, a metaproterenol MDI product reformulated with a new surfactant was withdrawn shortly after launch due to escalating reports of coughing, gagging, and asthma exacerbation (Poochikian and Bertha, 2000). A powder's sensitivity to moisture can also be overcome by designing and manufacturing packages (multi- or single-dose) with a proper moisture barrier. Exploiting advances in packaging technology can improve inhalation powder stability while avoiding the risk of new excipients.

8.3 Health and safety considerations

Inhaled therapy is the mainstay of treatment for asthma and COPD. MDIs are currently the most widely used inhalation device and millions of patients around the world rely on these products to manage their chronic, lifetime illnesses effectively (Wright, 2002). In order to accomplish the phase-out of CFCs under the Montreal Protocol, the MDI industry undertook an exhaustive search for an appropriate alternative aerosol propellant. An inhalation propellant must be safe for human use and meet several additional strict criteria relating to safety and efficacy: (i) liquefied gas, (ii) low toxicity, (iii) non-flammable, (iv) chemically stable, (v) acceptable to patients (in terms of taste and smell), (vi) appropriate solvency characteristics, and (vii) appropriate density (Tansey, 1997; Smith, 1995). It was extremely difficult to identify compounds fulfilling all of these criteria and in the end only two hydrofluorocarbons – HFC-134a and HFC-227ea – emerged as viable alternatives to CFCs. Two international consortia (IPACT-I and IPACT-II) were then established to conduct thorough toxicological testing and ensure that these propellants were safe for inhalation by humans (Tansey, 1997; Emmen, 2000).

Once suitable non-CFC propellants had been identified, the MDI industry undertook to reformulate the CFC MDIs so that they could use HFCs. The components and formulations had to be substantially modified to use the new HFC propellants. As drug products, MDIs are subject to extensive regulation by national health authorities to ensure product safety, product efficacy and manufacturing quality. The process for developing CFC-free MDIs was therefore essentially the same as the development of a wholly new drug product, involving full clinical trials for each reformulated MDI. Research and development for a new product is a lengthy, challenging, and resource-intensive process; typically, it takes about ten years to reach the prescribing doctor.

After identifying alternate medical propellants and developing safe, effective CFC-free MDIs, the final step in the phase-out of CFC MDIs is to switch millions of patients to reformulated MDIs and other CFC-free products. Switching patients from reliable and effective medications for an environmental, rather than therapeutic, reason is a large and unprecedented exercise with significant implications for patient health and safety (Wright, 2002; Yellen, 2003; Price, 2004). Patients depend on MDIs for the treatment of serious illnesses that frequently impact activities of daily life, and that have potentially life-threatening consequences. For these reasons, asthma and COPD patients may be particularly sensitive to a change in a trusted treatment regimen. Changes in medicine may also impact patient compliance with necessary therapy. Comprehensive educational programmes for patients and physicians are therefore important to ensure a smooth transition from CFCs to HFCs.

HFC MDIs play a central role in the timely and effective phase-out of CFC MDIs. These products came into existence under unique circumstances and solely because of an international environmental treaty. Any additional environmental policy measures taken in the future with a potential effect on patient use of HFC MDIs will necessarily raise significant health and safety issues. They will require careful consideration and consultation with physicians, patients, national health authorities, health-care experts and the pharmaceutical industry. In particular, it is important to bear in mind the realities of medical decision-making and the central role of physicians and pa-

tients when considering any measures that could impact MDIs. Therapeutic decisions, including the choice of delivery system, are made by the prescribing physician and are based primarily on the individual circumstances of each patient. The optimal therapeutic approach varies depending on a variety of factors, including a patient's symptoms, physiology and compliance patterns. Each of the existing inhalation delivery systems has an important role in the treatment of respiratory illnesses and no single delivery system is universally acceptable for all patients. DPIs do provide an alternative for patients with asthma/COPD, but are not available for some drugs. They do not use propellants, but are complex and usually disposable devices, which are generally more expensive than HFC MDIs. It is therefore critical to preserve a range of therapeutic options (ICF, 2003; UBA, 2004; US-EPA, 2004).

8.4 Cost issues

Cost of development

The development costs (technical, pharmaceutical and clinical) up to 1999 for the CFC–HFC transition were estimated to exceed US$1 billion (Everard, 2001) and significant additional investment is continuing as reformulation and clinical testing has expanded. Similar costs would be expected for the development of new DPI products.

Device/treatment costs

The cost of the HFC propellant is a negligible proportion (~ 5–10%) of the total cost of an MDI. There is general consensus in the literature that MDIs are less expensive than DPIs for asthma and COPD (Consumer Association, 2001; Dalby and Suman, 2003; Yellan, 2003). However, quantitative data are more limited. The UK is a good model for MDI/DPI usage since it is a market with high MDI use and a history of DPI usage. Salbutamol is also an important cost model since it is the most widely prescribed drug and it is off patent so there are a number of generic products competing on price (British National Formulary, 2003).

The UK Drug and Therapeutics Bulletin (Consumer Association, 2000) has compared salbutamol on the basis of cost per single dose; the result was US$0.030/0.035 for MDIs and US$0.078/0.143 for DPIs. For another widely prescribed generic drug, beclomethasone dipropionate, treatment costs for a year were approximately double for DPIs compared to MDIs. In a wider study, which included a comparison of costs across seven European countries, the average percentage increase was 160% for DPIs (Enviros March, 2000). No salbutamol DPI products are available at present in the USA. However, generic salbutamol CFC MDIs are less expensive than both branded CFC and HFC MDIs. Should a salbutamol DPI come to the market, it is anticipated that it would be substantially more expensive than the generic salbutamol CFC MDIs that are currently available.

In the treatment of asthma and COPD, it is less expensive, and at least as effective, to use an MDI with a spacer rather than a nebulizer (Barry and O'Callaghan 2003, Stark, 1999, Carnago and Kennedy, 2000). In developing countries, the cost of therapy is a prime consideration (Gupta, 1998), and DPIs are therefore used less (Fink, 2000).

Society costs

Asthma and COPD involve huge costs for society, both at a personal level for individual patients and also for society as a whole in the form of direct costs (hospitalization, for example), and indirect costs (absence from school or work). For example, in the USA in 1997, there were nearly 2 million emergency hospital visits (Carnago and Kennedy, 2000) for asthma and, according to the National Heart, Lung and Blood Institute, asthma cost an estimated US$11 billion in 1998. It should also be borne in mind that 26,000 people died of COPD in England and Wales in 1999.

Patient choice is important for compliance (Cochrane, 1999; Milgrom, 1996) and patients must therefore be satisfied with their MDI or DPI. Any restriction of patient choice may result in reduced compliance with medication, with an increase in the already substantial cost for society. Switching patients from reliable and effective medications has significant implications for patient health and safety. The provision of a range of safe alternatives is critical before enforcing change on environmental grounds. Any environmental policy measures for the future that could impact patient use of HFC MDIs would require careful consideration and consultation with physicians, patients, national health authorities and other health-care experts.

The future

The price of HFCs in the future is expected to vary with normal commercial factors and not to rise out of line with economies. This is supported by the present example of CFCs, where the price is only beginning to rise at the end of the transition period. In addition, pharmaceutical-grade HFC is already 2 to 3 times more expensive than normal technical-grade HFC due to purification costs, and is therefore less dependent on the supply cost of technical-grade HFC.

More sophisticated nebulizers (Smart, 2002) or effort-assisted DPIs will probably be even more expensive than the DPIs in use at present and there will therefore be an increased cost penalty compared to MDIs (Dalby, 2003). However, if they provide more effective delivery of the drug, treatment costs may be reduced. By contrast, some less complex DPIs currently under development (e.g. FlowCaps ™, Hovione; DirectHaler™ Pulmonary, DirectHaler) may prove less expensive, and over a longer time frame they become more comparable in cost to MDIs.

Reimbursment

It should be noted that, although some patients pay directly or indirectly via insurance for their medicines, many are reimbursed in some way by governments.

8.5 Regional considerations

MDIs are the dominant form of treatment for asthma and COPD worldwide. In *developed countries*, the proportion of MDI to DPI varies substantially from country to country: from 9:1 MDI:DPI in the USA to 7:3 in UK and 2:8 in Sweden This is linked to a number of factors, including availability (e.g. multidose DPIs only recently became available in the USA), patient and physician choice, and relative cost. CFC MDIs are being phased out and replaced by HFC MDIs, and increasingly by DPIs. The transition has proceeded slowly as alternatives become available and countries accept the overall increased cost, balancing the environmental benefits against the availability of affordable medications to patients. A transition to another new form of treatment could be both costly and time-consuming, without clinical benefits for patients. Whilst the proportion of HFC MDIs to DPIs is likely to decrease slowly because of availability, cost and patient choice, both forms of inhaled therapy will continue to be available.

In *developing countries*, inhaled therapy is mainly with salbutamol/albuterol, almost exclusively with pressurized MDIs from either multinationals or local manufacturers. CFCs are due to be phased out completely by 2010, and this is a major challenge for developing countries. The rates of both asthma and COPD are rising in these countries, and statistical data probably underestimate disease prevalence. Guidelines recommending the replacement of old and ineffective oral treatments with inhaled therapy are gaining increasing acceptance. Improved economic circumstances are likely to result in a substantial increase in the use of inhaled therapy. One company in India is locally producing and marketing a range of HFC MDIs. Affordable single dose DPIs are technically feasible and could be locally manufactured in developing countries. There would be significant pharmaceutical difficulties in hot and humid climates (Maggi *et. al*., 1999), and DPIs would still be more expensive than MDIs on a cost per dose basis. If these became available and achieved a significant market share, they would reduce the future volumes of HFC needed for MDIs. Multidose DPIs from multinational companies are either unavailable or too expensive for many patients. MDIs are likely to remain the most affordable and acceptable form of inhaled therapy in the long term in developing countries. For all the above reasons, predictions of HFC needs for inhaled therapy in developing countries are uncertain.

8.6 Future developments and projections

It is always challenging to project market dynamics in areas like pharmaceutical use, where commercial and regulatory pressures have such a major impact. It is anticipated that global market growth in inhaled medicine in the coming decade will be approximately 7% (Enviros March, 2000) whereas growth in MDIs is lower at between 1.5 and 3%. Also, provided that the MDI transition in developing and industrialized countries proceeds according to schedule, it may be assumed that all MDIs produced globally will contain HFCs instead of CFCs by 2010.

Estimates have been made by IPAC (shown in Table 8.3) that provide a range for HFC consumption in both 2010 and 2015, based on various scenarios of market growth and dynamics within the market. Actual growth rates will vary depending on the rate of introduction of new therapies for asthma/COPD.

The above projections are based on certain assumptions. These include:

- Market growth will be 7% per annum and MDI growth within this will range from between 1.5 and 3%. The total number of MDI units will be 680 million in 2015.
- Salbutamol MDIs will still represent approximately 50% of the overall MDI market.
- Two HFCs will continue to be used in MDIs for asthma/COPD. These will be HFC-134a and HFC-227ea, in an approximate ratio of 90:10.

The above information makes it clear that the maximum projected usage of HFCs for MDIs in 2015 will be approximately 15,000 metric tones. This information allows us to calculate, on the basis of hypothetical scenarios, the potential mitigation cost for reducing the projected HFC use in MDIS.

There are essentially two approaches to projecting these costs. In the first case one can take the full amount of projected HFC use, assume a certain percentage will be attributable to salbutamol HFC MDIs and calculate the likely incremental annual costs to switch them to DPIs on the basis of published price differences in certain countries. In this example, we have used an average increase of US$5.0 per inhaler.

If we assume that approximately half of the HFC usage will be for salbutamol HFC MDIs (i.e. around 7,500 metric tonnes) and this equates to 340 million salbutamol inhalers, the economic burden to patients or healthcare payers will be around US$1.7 billion per annum for a reduction of 11.45 million tonnes of CO_2. This is equivalent to a mitigation cost of 148.5 US$/t$CO_2$-eq.

Alternatively, using the same set of assumptions, one can evaluate the change for a single canister of salbutamol and project the cost using a similar approach. In this case, for each salbutamol MDI, the amount of propellant in an individual canister is approximately 13.2 grammes of HFC-134a. As 134a has a GWP of 1300, the CO_2 equivalent of an individual HFC-134a MDI is 0.01716 tonnes (13.2 x 1300 / 1,000,000). With an incremental cost for each salbutamol inhaler converted from HFC MDI to DPI of US$ 5, this is equivalent to a mitigation cost of US$ 5/0.01716 tonnes or approximately 292 US$/t$CO_2$-eq.

In both cases, these estimates do not include any costs associated with the development of new multidose salbutamol dry powder inhalers, but these would be minimal with respect to the projected additional cost burden to health-care systems.

The calculations provide a range of potential cost impact on health-care systems for further HFC MDI mitigation. These estimates are of the same order as one available for Europe, based

Table 8.3. IPAC HFC volume projections (IPAC, 2004).

2010 PROJECTIONS (1999 IPAC ORIGINAL ESTIMATES)	2015 PROJECTIONS (1999 IPAC ORIGINAL ESTIMATES)
7,500 to 9,000 metric tonnes of HFCs *10.8 to 12.9 million metric tonnes of CO_2 equivalent* • This projection was developed by IPAC in 1999 and is primarily based upon a survey of IPAC member companies (including 3M) for 1998 data. The data were most reliable for IPAC companies' major markets (e.g. Europe and North America). The projections include an estimate for non-IPAC companies and the developing world. The range reflects assumed MDI market growth rates of 1.5% to 3.0%.	**9,000 to 10,500** metric tonnes of HFCs *12.9 to 15.0 million metric tonnes of CO_2 equivalent* • This range extrapolates from IPAC's 1999 estimated projections and, beginning with the 'high end' figure of 9,000, assumes a range of flat growth to 3% growth from a baseline of 9,000 tonnes of HFCs.
2010 PROJECTIONS (TEAP/IPAC 2001 DATA)	**2015 PROJECTIONS (TEAP/IPAC 2001 DATA)**
11,275 to 12,865 metric tonnes of HFCs *18.26 to 20.84 million metric tonnes of CO_2 equivalent* • In response to the request from the authors of the MDI chapter of the IPCC Special Report, IPAC recently reviewed its emissions projections and analyzed more recent data and information available since 1999. The range above is primarily based upon TEAP figures for the volume of CFCs used in the production of MDIs for 2001 and IPAC data on HFCs collected for 2001. • This range is somewhat higher than IPAC's original estimate given above. This is probably due to the fact that IPAC's 1999 estimate was based on hard data only from IPAC member companies. The 2001 TEAP figures are presumably more accurate for volumes used in the developing world and non-IPAC MDI companies. • IPAC's 2010 projections are also consistent with the 2010 emissions projection estimated by Enviros March (2000) in its December 2000 report, submitted to the European Climate Change Programme: 10,230 metric tonnes.	**12,865 to 14,915** metric tonnes of HFCs *20.84 to 24.16 million metric tonnes of CO_2 equivalent* • This range extrapolates from the 2010 estimated projection (TEAP/IPAC 2001) and, beginning with the 'high end' figure of 12,865, assumes a range of flat growth to 3% growth from a baseline of 12,865 tonnes of HFCs.

on data from the 1990s, of US$461 per tonne CO_2 (Enviros March, 2000). This figure has been quoted in environmental reports from a number of governments.

Conclusions

- Most reduction of GWP from MDIs will be achieved through the completion of the transition from CFC to HFC MDIs.
- No major breakthroughs for inhaled drug delivery are anticipated in the next 10–15 years given the current status of technologies and the development time scales involved.
- The health and safety of the patient is of paramount importance in treatment decisions and policymaking that might impact those decisions.
- If one assumes a hypothetical switch for the most widely used inhaled medicine (salbutamol) from HFC MDIs to DPI, the projected recurring annual costs would be on the order of US$ 1.7 billion with an effective mitigation cost of between 150–300 US$/t$CO_2$-eq.
- The environmental benefits of converting HFC MDIs to DPIs are small.

References

AAP (American Academy of Pediatrics), 1997: Policy statement: "Inactive" ingredients in pharmaceutical products. *Pediatrics,* **99**, 268–278.

Barry, P.W. and C. O'Callaghan, 2003: The influence of inhaler selection on efficacy of asthma therapies. *Advanced Drug Delivery Reviews,* **55**, 879–923.

BNF (British National Formulary), 2003 (September), British Medical Association and Royal Pharmaceutical Society of Great Britain, London, UK, pp. 134–147.

Boekestein, V.J., A.J. Hickey and T.M. Crowder, 2002: Uniform and reproducible delivery of albuterol from a variety of lactose powder blends using the Oriel active dispersion platform. In *Drug Delivery to the Lungs XIII*, T.A. Society, London, UK, pp. 107–110.

Brown, B.A.-S., 2002: 5 Myths about MDIs. *Drug Delivery Technology*, **2**, 52–59.

Carnago, C.A. and P.A. Kennedy, 2000: Assessing costs of aerosol therapy. *Respiratory Care*, **45**(6), 756–763.

Celli, B., J. Benditt and R.K. Albert, 1999: Chronic obstructive pulmonary disease. In *Comprehensive Respiratory Medicine*, R.K. Albert, S.G. Spiro and J.R. Jett (eds.), Mosby International Ltd., London, UK, pp. 371-395.

Cochrane, G.M., R. Home and P. Chanez, 1999: Compliance in asthma. *Respiratory Medicine*, **9**, 763–769.

Consumer Association UK, 2000: Inhaler devices for asthma. *Drug and Therapeutics Bulletin*, **38**(2), 9–14.

Consumer Association UK, 2001: Managing stable COPD. *Drug and Therapeutics Bulletin*, **39**(11), 81–85.

Dalby, R.N., A.J. Hickey and S.L. Tiano, 1996: Medical devices for the delivery of therapeutic aerosols to the lungs. In *Inhalation Aerosols*, A.J. Hickey (ed.), Marcel Dekker Inc., New York, NY, USA, pp. 441–473.

Dalby, R., 2003: Pulmonary devices – what's used. *European Pharmaceutical Review*, **8**(2), 70–73.

Dalby, R. and J. Sumas, 2003: Inhalation therapy: technological milestones in asthma treatment, *Advanced Drug Delivery Reviews*, **55**, 779–791.

DeYoung, L.R., F. Chambers, S. Narayan and C. Wu, 1998: The aerodose multidose inhaler device design and delivery characteristics. In *Respiratory Drug Delivery VI*, R.N. Dalby, P.R. Byron, and S.J. Farr (eds.), Interpharm Press Inc., Buffalo Grove, IL, USA, pp. 91–95.

Dolovich, M.A. and N.R. MacIntyre, 2000: Consensus statement: aerosols and delivery devices. *Respiratory Care*, **45**(6), 1–22.

Dunbar, C.A., A.J. Hickey and P. Holzner, 1998: Dispersion and characterization of pharmaceutical dry powder aerosols. *KONA,* **16**, 7–45.

Emmen,**H.H**, 2000: Human safety and pharmacokinetics of the CFC alternative propellants HFC 134a and HFC 227. *Regulatory Toxicology and Pharmacology*, **32**, 22–35.

Enviros March, 2000: Study on the Use of HFCs for Metered Dose Inhalers in the European Union. Report by Enviros March for the International Pharmaceutical Aerosol Consortium (IPAC), submitted to European Climate Change Programme, Washington, DC, USA, 45 pp.

Everard, M.L., 2001: Inhaler development: Where shall we be in 10 years'time? *Asthma Journal*, **6**(2), 84–88.

Fink, J.B., 2000: Metered-dose inhalers, dry powder inhalers and transitions. *Respiratory Care*, **45**(6), 623–635.

Garcia-Contreras, L. and A.J. Hickey, 2002: Pharmaceutical and biotechnological aerosols for cystic fibrosis therapy. *Adv. Drug Deliver. Rev.*, **54**, 1491–1504.

Gupta, S.K., K.S. Mazumdar, S. Gupta, A.S. Mazumdar and S. Gupta, 1998: Patient education programme in bronchial asthma in India: Why, how, what and where to communicate. *Indian Journal of Chest Dis. Allied Science,* **40**(2), 117–124.

Hickey, A.J., 1992: Methods of aerosol particle size characterization. In *Pharmaceutical Inhalation Aerosol Technology*, A.J. Hickey (ed.), Marcel Dekker, New York, USA, pp. 219–250.

Hickey, A.J. and R.M. Evans, 1996: Aerosol generation from propellent-driven Metered Dose Inhalers. In *Inhalation Aerosols: Physical and Biological Basis for Therapy*, A.J. Hickey (ed.), Marcel Dekker Inc., New York, USA, pp. 417–439.

Hickey, A.J. and C.A. Dunbar, 1997: A new millennium for inhaler technology. *Pharm. Tech.*, **21**, 116–125.

ICF, 2003: The Use of Alternatives to Synthetic Greenhouse Gases in Industries Regulated by the Montreal Protocol. Report prepared by ICF Consulting for the Australian Greenhouse Office, Canberra, Australia, 46 pp.

IPAC, 2004. International Pharmaceutical Aerosol Consortium. HFC usage projections in MDIs, (www.ipacmdi.com) and in Ensuring Patient Care, IPAC, Washington. Supplement Appendix B, 2004.

ISAAC-SC (International Study of Asthma and Allergies in Childhood Steering Committee), 1998: Worldwide variation in prevalence of symptoms of asthma, allergic rhino-conjunctivitis, and atopic eczema. *Lancet*, **351**, 1225–1232.

June, D.S., R.K. Schultz and N.C. Miller, 1994: A conceptual model for the development of pressurized metered-dose hydrofluro-alkane based inhalation aerosols. *Pharm. Tech.*, **17**, 40–52.

Keller, M. and R. Muller-Walz, 2000: Dry Powder for Inhalation. PCT Patent WO 00/28979, 25 May 2000.

Leach, C.L., P.J. Davidson and R.J. Boudreau, 1998: Improved airway targeting with the CFC-free HFC-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur. Respir. J.,* **12**, 1346–1353.

Maggi, L., R. Bruni and U. Conte, 1999: Influence of moisture on the performance of a new dry powder inhaler. *Int. J. Pharm.*, **177**, 83–91.

Medicines Control Agency, 1997: Rules and Guidance for Pharmaceutical Manufacturers and Distributors 1997, The Stationery Office, London, UK.

Milgrom, H., B. Bender, L. Ackerson, P. Bowry, B. Smith and C. Rand, 1996: Non-compliance and treatment failure in children with asthma. *Journal of Allergy and Clinical Immunology*, **98**(6), 1051–1057.

Molina, M.J. and F. S. Rowland, 1974: Stratospheric sink for chlorofluoromethanes: chlorine atom catalyzed destruction of ozone. *Nature*, **249**, pp. 1810.

Niven, R.W., 1996: Atomization and nebulizers. In *Inhalation Aerosols: Physical and Biological Basis for Therapy*, A.J. Hickey (ed.), Marcel Dekker Inc., New York, USA, pp. 273–312.

Pischtiak, A.H., M. Pittroff and T. Schwartze, 2001: Characteristics, supply and use of the hydrofluorocarbons HFC 227ea and HFC 134a. *Aerosol Europe*, **9**(10), 44–47.

Poochikian, G. and C.M. Bertha, 2000: Inhalation drug product excipient controls: Significance and pitfalls. In *Respiratory Drug Delivery VII*, R.N. Dalby, P.R. Byron, S.J. Farr and J. Peart (eds.), Serentec Press, Inc., Raleigh, NC, USA, pp. 109–115.

Price, D., E. Valovirta and J. Fischer, 2004: The importance of preserving choice in inhalation therapy: the CFC transition and beyond. *Journal of Drug Assessment*, **7**, 45–61

Schuster, J., S. Farr, D. Cipolla, T. Wilbanks, J. Rosell, P. Lloyd and I. Gonda, 1998: Design and performance validation of a highly efficient and reproducible compact aerosol delivery system: AERx(TM). In *Respiratory Drug Delivery VI*, R.N. Dalby, P.R. Byron, and S.J. Farr (eds.), Interpharm Press Inc., Raleigh, NC, USA, pp. 83–90.

Smart, J., E. Berg, O. Nerbrink, R. Zuban, D. Blakey and M. New, 2002: Touchspray technology: Comparison of the droplet size measured with cascade impaction and laser diffraction. In *Respiratory Drug Delivery VIII (Volume 2)*, R.N. Dalby, P.R. Byron, J. Peart and S.J. Farr (eds.), Davis Horwood International Publishers Ltd., Surrey, UK, pp. 525–527.

Smith, I.J., 1995: The challenges of reformulation. *J. Aerosol Med.*, **8** (Suppl 1), S19–27.

Staniforth, J.N., 2002: Powders comprising anti-adherant materials for use in Dry Powder Inhalers. US Patent 6,475,523.

Tansey, I., 1997: The technical transition to CFC-free inhalers. *Br. J. Clin. Pract.*, **89** (suppl.), 22–27.

UBA, 2004: Fluorinated Greenhouse Gases in Products and Processes – Technical Climate Protection Measures. [K. Schwaab and W. Plehn (eds.)] Umweltbundesamt (German Federal Environmental Agency), Berlin, Germany, 240 pp.

UNEP-TEAP, 2003: 2002 Report of the Technology and Economic Assessment Panel (Pursuant to Article 6 of the Montreal Protocol). UNEP Ozone Secretariat, Nairobi, Kenya, 117 pp.

US EPA, 2004: Analysis of Costs to Abate International Ozone-Depleting Substance Substitute Emissions. US Environmental Protection Agency report 430-R-04-006, D.S. Godwin (ed.), Washington, D.C. 20460, USA, 309 pp.

US FDA, 1998: Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Chemistry, Manufacturing and Controls Documentation, US Food and Drug Administration, Washington, DC, USA, 66 pp.

Voss, A. and W.H. Finlay, 2002: Deagglomeration of dry powder pharmaceutical aerosols. *Int. J. Pharm.*, **248**, 39–50.

Yellen, D. 2003: The role of HFC MDIs in the CFC transition: A case study in the European Union. Proceedings of the 14th Annual Earth Technologies Forum, April 22-24, 2003, Washington, D.C., USA.