

ENVIROS MARCH

**STUDY ON THE USE OF HFCs FOR METERED DOSE
INHALERS IN THE EUROPEAN UNION**

Final Report

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CONTENTS

MANAGEMENT SUMMARY	1
1. INTRODUCTION	5
2. EMISSIONS FROM MDIs.....	7
2.1 The Role of MDIs	7
2.2 The Impacts on the Environment of MDIs	8
2.3 Historical Emissions of Propellants from MDIs.....	9
2.4 Business As Usual Emission Projections.....	10
2.5 MDI Emissions in Perspective.....	12
3. POTENTIAL OPPORTUNITIES FOR REDUCTIONS IN EMISSIONS	14
3.1 DPIs.....	14
3.2 Other MDI Replacements	17
3.3 Reducing GWP Emissions from MDI Usage	18
3.4 Reducing Emissions from “Waste” MDIs	19
3.5 Alternative MDI propellants.	20
4. EMISSION REDUCTIONS IN PRACTICE.....	22
5. SUMMARY AND CONCLUSIONS	25
APPENDIX A ANALYSIS OF EMISSION REDUCTION ISSUES	27
A1 Comparison of MDIs, DPIs and Nebulisers	27
A2 Implications of an accelerated switch from MDIs to DPIs.....	33
A3 Recovery and Destruction.....	36
APPENDIX B REGIONAL VARIATIONS	38
APPENDIX C TECHNOLOGY STATEMENTS	42

MANAGEMENT SUMMARY

- a) This report gives the results of an independent study into the EU emissions of greenhouse gases from metered dose inhalers (MDIs) and reviews options for reducing these emissions.
- b) The study was carried out by Enviro March on behalf of IPAC (International Pharmaceutical Aerosol Consortium). The study was based on detailed background research and interviews with MDI manufacturers, propellant suppliers, health care professionals and patient representatives in 7 European countries. The research and interviews for the study took place in the period June to September 2000.
- c) MDIs are aerosols that rely on the evaporation of a propellant gas to deliver drugs into the patients lungs. MDIs are used to deliver the drugs required by patients suffering from asthma and COPD (chronic obstructive pulmonary diseases such as chronic bronchitis and emphysema). MDIs are aerosol devices that use a propellant vapour to propel the drug into a patient's lung. They have been in use since the late 1950s.
- d) Although there are a number of alternative ways of delivering asthma and COPD drugs, MDIs are the dominant delivery system, representing about 90% of relevant drugs worldwide and 85% in the EU. The main reasons for this dominance are that MDIs represent a low cost delivery option and the large majority of the patient population can conveniently and easily use MDIs.
- e) The main currently available alternatives to MDIs are dry powder inhalers (DPIs) and nebulisers. The main differences between the three delivery systems relate to cost and usability. The major pharmaceutical companies are researching other alternatives such as oral treatments.
- f) It is interesting to note that the main pharmaceutical companies offer many of their drugs with a variety of different delivery systems and therefore have no vested interest in promoting MDIs. For example, an individual company can supply salbutamol (which represents over 50% of the drugs used for asthma and COPD) as an MDI, a DPI, an oral treatment and a nebuliser.
- g) Until the mid-1990s all MDIs used CFCs as the aerosol propellant. Because of the high ozone depleting potential of CFCs these propellants are being phased out under the Montreal Protocol. Because of the importance of MDIs and the difficulty of bringing suitable and safe alternatives to the market, MDIs are the only category of CFC usage that has been granted "essential use" status under the Montreal Protocol. This allows licenced production of CFCs for MDIs until the Parties to the Protocol consider that suitable alternatives are available.
- h) Pharmaceutical companies have undertaken extensive work to identify alternatives and to reformulate their drugs with new propellants. This has been a lengthy and expensive process for numerous reasons. For example the toxicology tests must be exhaustive because the propellant is directly inhaled by the patient. It can take between 8 to 12 years to bring an MDI using a new propellant to the market.
- i) The only new MDI propellants that have thus far been identified as suitable and fully tested are two members of the HFC family (hydrofluorocarbons) – HFC 134a and HFC 227ea.

- j) The first MDIs using an HFC propellant came on to the market in 1995. It is expected that by 2005 all drugs delivered by MDIs will be available with HFC propellants in the EU.
- k) The uptake of HFC MDIs has been relatively slow. The research for this study shows that both patients and doctors are very conservative in relation to drug selection. If patients have found a satisfactory drug and delivery system they are generally reluctant to change. Although an HFC MDI delivers the same treatment as the CFC MDI it replaces, it may taste and feel slightly different, causing a lack of patient confidence. This innate conservatism has an even greater effect if one considers a switch from an MDI to a DPI.
- l) The slow switch from CFC to HFC MDIs is obviously of concern in relation to ozone depletion, but it is important to note that it is also of significance in relation to global warming. HFC MDIs have a considerably lower global warming impact than CFC MDIs for two reasons:
 - The global warming potential (GWP) of the primary HFC propellant is 6 times lower than the CFC propellant (HFC 134a has a GWP of 1300 compared to CFC 12 with a GWP of 8100).
 - The density of the HFC propellant is about 30% lower than for the CFC propellant, so on a mass basis the quantities emitted are reduced by 30%.

Taking these two effects together it is clear there is a significant global warming benefit to phase out CFC MDIs as soon as possible. On a like-for-like basis the reduction in global warming impact is 85%. However, it is important to recognise the slightly perverse impact of the structure of the Kyoto Protocol – emissions of CFCs are ignored in baseline calculations. Hence the highly significant emission reduction described above tends to be overlooked.

- m) A clear conclusion from the discussion above is that it is essential for both ozone depletion and global warming to maximise the rate of phase out of CFC MDIs, while preserving patient healthcare. Any policies that prevent this happening will be counter-productive.
- n) Estimates have been made of Business-as-Usual Scenario greenhouse gas emissions from MDIs up to 2012. These estimates take into account the likelihood of significant growth of the market for asthma and COPD drugs. They also take into account the current trend within pharmaceutical companies to introduce most new forms of treatment in the form of DPIs or other devices. The estimates show the 2010 world wide emissions of greenhouse gases from MDIs will be approximately 16 Mtonnes CO₂ equivalent. This represents a fall of 73% from the MDI emissions expected in 2000 of 60 Mtonnes CO₂ equivalent
- o) MDIs represent a very small proportion of total greenhouse gas emissions. In 1995 there were no HFC emissions, but the CFC emissions represented about 1% of the total EU emissions of greenhouse gases. It is expected that there will be no CFC emissions from MDIs after 2005 in the EU. In 2010 HFC emissions from MDIs will represent about 0.13% of the total EU emissions of greenhouse gases.
- p) A detailed investigation was made of ways of reducing greenhouse gas emissions from the MDI market. A number of options were researched including replacement of MDIs with alternative delivery systems such as DPIs, use of alternative propellants such as hydrocarbons and minimisation of the quantities of HFCs emitted from HFC MDIs. Each option was investigated with regard to cost, practicality and patient impact.

- q) DPIs are a promising alternative that has already achieved significant market penetration in Sweden (81%) and the Netherlands (40-50%). Whilst DPIs cannot satisfy all patients currently using MDIs there is some evidence that a market penetration of up to about 80% is feasible in some countries. In other countries, the natural saturation level appears to be around 50%.
- r) The medical effectiveness of DPIs compared to MDIs is good, for those patients able to use them, providing patients receive adequate training. The biggest drawback is cost. Salbutamol DPIs cost about 160% more than Salbutamol MDIs. For example a 200 dose MDI might cost €5 whereas the equivalent 200 dose DPI might cost €13. There are other drawbacks including the difficulty of transition (as already stated above, the market is reluctant to move from CFC to HFC MDIs, which is a much easier transition).
- s) In addition to direct costs, a transition from one treatment to another will also incur indirect costs as physicians time will be required to train patients in the use of differing treatments and these costs must also be considered.
- t) Other new alternatives such as oral treatments, metered liquid inhalers and hydrocarbon propelled MDIs would need significant further technical advances before they could reach the market. At this time it is not clear whether such treatments could gain a significant market share within the Kyoto Protocol time frame.
- u) A number of ways of reducing emissions from HFC propelled MDIs were investigated. It was found that significant improvements to manufacturing techniques have already led to reduced losses during manufacture. Recovery of propellant from reject MDIs (rejected for quality control reasons) and used MDIs (there is a little propellant left in MDIs at end of life) can provide small reductions in HFC emissions. A bigger opportunity relates to reducing the size of the metering valves used in new MDI designs. If all manufacturers minimised the size of metering valves in new MDIs there is the potential for a significant reduction in HFC emissions. However, this would require additional research on a product by product basis to determine if the amount of propellant could be reduced without reducing drug delivery to the lungs. In cases with demonstrated feasibility, the necessary reformulation and retesting would be a very costly and time consuming process.
- v) The costs of the above opportunities for emission reduction were compared to other opportunities currently being investigated to ensure the EU meets its Kyoto Protocol target. We have calculated costs in terms of €per tonne of CO₂ saved. The table below compares the costs for various MDI measures with other options for both HFCs and other greenhouse gases including CO₂. From the table below it is clear that the major opportunities to reduce emissions from MDIs (in particular, use of DPIs) are considerably more costly than many of the opportunities available in other markets.

Technical Option	Cost Effectiveness €/tonne CO ₂ equiv.
Low cost energy efficiency measures	Negative cost (i.e. savings are made)
HFC 23 from HCFC 22 manufacture	1
Recovery from reject MDIs	1
Low cost XPS foam measures	5 - 10
Many energy efficiency measures	1 - 20
Refrigeration system containment	5 - 20
Low cost general aerosol measures	16
Low cost HFC solvents measures	33
Destruction of HFC from used MDIs	50
Switch to DPIs	>500
Reduction in MDI valve size	not known, probably high
Hydrocarbon propellants in MDIs	not known, probably very high

- w) Whilst widespread adoption of DPIs could reduce emissions of greenhouse gases in MDIs by up to 80% the costs to achieve this are very high.
- x) There is some cost effective potential related to recovery of HFCs from reject units (saving potential: 0.3 Mtonnes CO₂ equivalent per year, which is about 5% of predicted emissions from MDIs in 2010). There is a smaller less cost effective opportunity related to destruction of HFCs from used units (estimated saving potential 0.15 Mtonnes CO₂ equivalent per year, which is about 3% of predicted emissions from MDIs in 2010).
- y) The impact of the costs described above would be borne mainly by Member State health schemes and by patients. Hence environmental policy makers need to negotiate with health ministries rather than the pharmaceutical industry.
- z) The pharmaceutical industry should, nevertheless, be encouraged to take part in a programme that ensures HFC emissions are minimised. Such a programme could be based on a negotiated agreement that addresses:
- Continued promotion by the manufacturers of DPI usage, with annual reporting on market penetration achieved
 - Consideration of minimised valve sizes for future MDI developments
 - Targets for manufacturing leakage rates
 - Targets for recovery and destruction of reject units
 - Development of a voluntary collection and destruction scheme for “used” units

1. INTRODUCTION

This report provides a review of the current and likely future use of fluorinated gases in metered dose inhalers (MDIs). The information presented in this report has been compiled through a programme of desk research on the available medical literature and market sector databases together with detailed discussions with General Practitioners (GPs), MDI and alternative treatment product manufacturers, propellant manufacturers and sector specialists throughout Europe. In all, in excess of 50 interviews were conducted. These interviews were conducted in July and August 2000.

MDIs are an invaluable tool in modern medicine, however, their use, with fluorocarbons as the propellant, contributes to the emissions of gases thought to be harmful to the environment. MDIs currently use two types of propellants, chlorofluorocarbons (CFCs) and hydrofluorocarbons (HFCs¹). The use of HFCs in MDIs was developed during the 1990s to help reduce the reliance on CFC propellant. Unlike CFCs, HFCs are not ozone depleters and they are also less powerful greenhouse gases (Table 1.1). By 2005, the use of CFCs in MDIs is likely to have been phased out in favour of HFCs within Europe. This report will focus primarily on the use of HFCs. MDIs are one of a range of technologies which currently use HFCs. Other technologies that use these gases include refrigeration and air-conditioning equipment, foam blowing, general aerosol use and fire-fighting apparatus.

Table 1.1 ODP and Global Warming Potential of propellants

Propellant	Global Warming Potential	Ozone Depletion Potential
CFC 11	4000	1.0
CFC 12	8100	1.0
HFC 134a	1300	0.0
HFC 227ea	2900	0.0

Under the terms of the Kyoto protocol, Governments are committed to limit emissions of a “basket” of six greenhouse gases including HFCs. The European Union, for instance, is committed to reduce its emissions of greenhouse gases by 8% by 2010. HFCs from all sectors are only a very small proportion of the total world-wide greenhouse gas emissions, they currently account for only 1% of all greenhouse gas emissions. The majority of greenhouse gas emissions (nearly 90%) are from CO₂ as a result of fossil fuel use. Despite the relatively small current contribution of HFCs towards greenhouse gas emissions, the use of this gas is coming under increasing scrutiny by Governments around the world as they seek to reduce emissions. Environmental action groups are particularly concerned about the emissions of HFCs, since HFCs are seen as one of three gases (HFCs, PFCs and SF₆) which are man-made, highly potent greenhouse gases and with the potential for much market growth over the coming years.

This report is intended to provide an independent source of information to policy makers on the complex environmental and health related issues concerning the MDI, including information on the scale of emissions of greenhouse gases from the MDI

¹ HFCs are commonly referred to as hydrofluoroalkanes (HFAs) within the medical profession

sector in the EU, historically, currently and projected to 2010. The MDI sector raises unique and important issues of health and safety, as MDIs are critical to the treatment of serious public health conditions – asthma and Chronic Obstructive Pulmonary Diseases (COPD).

It is intended that this report will provide input into the discussions currently taking place at Government level, both within the European Union (EU) and elsewhere, into the options available for reducing greenhouse gas emissions and the likely outcome of actions taken to reduce these emissions. This report will thus be presented to the European Commission Climate Change Policy Group to help facilitate understanding of this sector as policy options for emission reductions are formulated.

The use of MDIs is an extremely complex issue. Many different drugs and drug combinations are used and many of these drugs are patent protected. To simplify the analysis, we have focussed primarily (but not exclusively) on the drug Salbutamol. Salbutamol is the most widely used drug in MDIs, representing more than half of total sales around the world. In assessing the cost effectiveness of alternatives to MDI treatments, the price to the markets of these products must be determined. Salbutamol is a good choice for study as its patent has expired and generic alternatives exist in the market place, thus a range of product prices are available.

The report begins by considering the need for MDIs and their valuable role in reducing deaths and alleviating suffering in victims of asthma and COPD. Progress made to date in restricting emissions of harmful gases and in particular, progress towards the successful phase out of the use of CFCs in MDIs is reviewed. The replacement of CFCs with HFCs is contributing to both the complete elimination of the use of ozone depleting substances (ODS) and a large reduction in the emission of greenhouse gases from MDIs.

In section 2, best estimates for the likely emissions of HFCs during the Kyoto timeframe (to 2012) are made. The main alternatives to MDIs which might facilitate further reductions in emissions are then considered. At present, the most widely available alternative to the MDI is the dry powder inhaler (DPI). The suitability of substituting MDI use with DPIs is reviewed in section 3 along with further opportunities for reducing emissions of fluorinated gases. In each case the likelihood of implementation of the measure is considered along with any cost and patient healthcare implications. In section 4, the emissions reduction opportunities identified are compared to other greenhouse gas emission reduction opportunities that exist in the EU in terms of cost effectiveness and other parameters. Possible policy options for implementing reduction measures are then discussed.

In reading this report it is important to consider the vital role which MDIs play in the alleviation of suffering and death. For this reason MDIs are the only “special case” exemptions from the total ban of the use of CFCs under the Montreal Protocol. The industry has invested well over €1 billion to date in reformulating MDIs to use HFC propellants and will invest another €1 billion before the transition is complete. These HFC propelled MDIs are the only available technology for directly replacing CFC MDIs at present and any action taken to restrict their use will result directly in a delay in the reduction of the use of CFCs. Thus, paradoxically, both increasing global warming gas emissions and resulting in the prolonged emission of ozone depleters.

2. EMISSIONS FROM MDIs

2.1 The Role of MDIs

Asthma and COPD are serious public health issues. Asthma and chronic obstructive pulmonary diseases, such as emphysema and chronic bronchitis, interfere with normal respiratory function. The airways become inflamed and hyper-reactive which causes coughing, wheezing and breathing difficulties. Both asthma and COPD not only diminish the quality of life for patients and their families but also causes significant mortality. COPD diseases produce inflammation, swelling and mucous plug production in the airways. It is the fifth leading cause of death world-wide. COPD, which develops over many years, is progressive and generally irreversible.

The total incidence of asthma is estimated to be around 5-8% world-wide and the incidence of chronic obstructive pulmonary diseases is estimated to be up to 15%. According to the World Health Organisation (WHO), together these diseases resulted in around 3 million deaths world-wide in 1999. Diagnosis of asthma around the globe is increasing at around 5% per year. The demand for effective treatments is expected to continue to grow.

MDIs are the most frequently used medium for delivering drugs to people with asthma and COPD, their effectiveness is well proven and they have been in general use since the 1950s. The MDI is convenient, well liked by patients and less expensive than other delivery systems. It has been estimated that total production of these units currently runs to around 500 million world-wide.

Asthma is a chronic and debilitating respiratory disease which can have sudden and unpredictable effects which, in extreme cases, can be life threatening. It is the most frequently reported chronic condition among children in the UK². COPD is responsible for around 28,000 deaths in Europe each year and asthma claims around 4,000 lives in Europe each year³. The prevalence of the disease across regions is not constant and asthma is responsible for the deaths of about 1700 people each year in the UK, thus approaching half of all deaths caused by asthma in Europe⁴.

There is international consensus that treatment by inhalation is the preferred form of therapy for asthma and COPD sufferers because it reduces the risk of significant side effects experienced with other medications⁵. The inhaled route allows treatment to be delivered quickly and efficiently to the airways. Therapy for respiratory diseases necessitates regular treatment, often with more than one drug. Overall use of inhaled medication is increasing because of increased disease prevalence. The World Health Organisation (WHO); the US National Heart, Lung and Blood Institute (NHLBI) and

² McDonald K J, Martin G P, Transition to CFC-free metered inhalers-into the new Millennium. *International Journal of Pharmaceutics* 201, 89-107 (2000)

³ World Health Organisation Report 1997

⁴ *ibid*

⁵ National Heart, Lung and Blood Institute, National Institutes of Health, International Consensus Report on Diagnosis and Treatment of Asthma, US Dept of Health and Human Svcs. Pub. No. 92-3091, 28 (June 1992, revised in 1998).

the Global Initiative on Asthma (GINA) all describe the inhaled route as the preferred method of administering medicine⁶.

There are currently 3 types of inhalation delivery devices available, MDIs; nebulisers and dry powder devices (DPIs). These devices are described in more detail in Appendix A. The MDI is overwhelmingly the most widely used device as it has characteristics which render it useable by all patients in almost all situations. Nebulisers and DPIs cannot be used by all groups of patients. Overall the MDI accounts for over 70% of all inhalation therapy and is likely to remain the mainstay of inhaled therapy for many years.

2.2 The Impacts on the Environment of MDIs

By their nature, MDIs are an “emissive” technology, that is to say that almost all of the gas contained within an MDI will be emitted to the atmosphere during use by the patient. This is not the situation in some other applications of HFC gases such as refrigeration equipment, where it is theoretically possible to use HFCs without them ever being emitted to the atmosphere, by recovering the gas at the end of life of the equipment.

MDIs have been in use for the treatment of patients since the 1950s and historically, the propellants used were CFCs. Over the last two decades it has become clear that this gas is both a very powerful greenhouse gas and damaging to the ozone layer. The Montreal Protocol has phased out the production of CFCs in the developed world. The only exception allowed is under the “essential use” category. MDIs are the only application now deemed to be an essential use of CFCs. The pharmaceutical aerosol industry is making great efforts to eliminate the use of CFCs from MDIs, but gaining regulatory approval for new drug formulations is an expensive and time-consuming process. In response to the mandate of the Montreal Protocol the industry has spent well over €1 billion on the transition from CFCs to the more environmentally benign HFC propellants. Significant additional investment will be required to complete this transition. In developing new treatments, the healthcare of the patient is obviously of paramount importance. New drug delivery systems as well as new drugs must be thoroughly tested for health benefits and toxicological effects before gaining approval. Each new combination of a drug and the MDI delivery system require complete toxicology and clinical studies which require from 8 to 12 years. There are in excess of 20 molecules that could potentially be reformulated and thus the transition to HFCs, work on which began in the early 1990s, is still incomplete.

It is vital that environmental regulators seeking to reduce emissions of HFCs do not take actions that effectively delay the elimination of CFCs from MDI use. All measures considered must be consistent with the goals of the Montreal Protocol.

Although the first salbutamol HFC MDI was introduced in the UK in 1995, and others have since been introduced throughout Europe, the transition from CFC MDIs has been slow, but not atypical for the introduction of a new medication, and is not yet complete. Complete transition is not now anticipated until 2005 in the European Union (and later in the USA). Some of the reasons for this are as follows:

⁶ Report of the TEAP HFC & PFC task force, October 1999, page 25

- Governments did not give expedited review to reformulated MDIs as there was no therapeutic benefit over the CFC MDI. Consequently the HFC MDIs have not been considered a priority by the Health Ministries.
- There was no incentive for physicians to change their prescribing habits. Asthma and COPD patients are well known to have a strong affinity for their own particular form of treatment and are resistant to change. Physicians and patients are conservative about changing medications when the current medication is working effectively.
- Despite pressure from the UNEP Technical Options Committee it took time for governments to formulate a strategy for the transition. It is a complicated subject which has to primarily ensure that patient care is not compromised during what has been described as the biggest change to medicines for many years.
- Some countries even now continue to give approvals to CFC containing MDIs.
- There has been a lack of specific health professional guidance on the management of the transition process. An earlier co-ordinated approach through the groups of health professionals would have been beneficial.

It is vital that any actions taken to restrict the emissions of HFCs from MDIs, do not delay the phasing out of CFC usage. The lessons learned from this phase out should also be heeded.

2.3 Historical Emissions of Propellants from MDIs

Until 1995, all MDIs used CFCs as the propellant and the emissions of HFCs from this sector were essentially zero (some small emissions will have occurred from product development testing). The transition from CFCs to HFCs is still far from complete and CFCs still represent two thirds of the propellant used in MDIs world-wide at present.

Table 2.1 shows that the use of CFCs in the manufacture of MDIs in the EU fell by over 15% between 1997 and 1998. The importance of ensuring that this trend continues cannot be overstated. It should be noted that use of CFC propellant in the USA in the same period did not fall.

Table 2.1 CFC Use 1996-98⁷

	Tonnes of Propellant		
	1996	1997	1998
EU	4822	5592	4660
USA	2368	2255	2426

⁷ 1999 UNEP TEAP Report, page 166

2.4 Business As Usual Emission Projections

During this study, data has been gathered on current and likely future usage of propellant gas. From this data, emissions projections have been estimated based on a classical top down plus bottom up approach. Propellant gas manufacturers have provided accurate total gas sales figures to this sector (top down approach). This has been correlated with sales estimates taken from manufacturers data (bottom up).

Since all the gas delivered to this sub sector is manufactured separately and to a higher quality standard than for general industrial usage it is relatively simple to identify the quantity of gas delivered. However care must be taken since some gas will be stockpiled and some will be destroyed. Estimates for these proportions have therefore been made. The baseline CFC usage data is also reported to UNEP each year and thus a reasonably high degree of confidence can be placed in the data for current sales of propellant to MDI companies. Future trends are more difficult to predict accurately. To model projected growth in the emissions of HFCs several factors are considered:

- The reduction in gas usage achieved through switching from CFC to HFC, as CFC is phased out due to the lower density of HFCs (estimated at a 30% reduction).
- Improvements in the manufacturing process providing reduced losses during manufacturing. Losses vary by manufacturer. Current losses average around 6% of which only 1-2% is emitted to atmosphere, the rest is recovered or destroyed.
- Overall market growth in the use of asthma and other treatment products, which is estimated to be around 7% per annum over the study lifetime.
- Increased market penetration of alternative treatments (primarily DPIs, but also considering oral treatments and metered liquid inhalers). This growth is estimated to account for all but 2% per annum of the total market growth predicted. (i.e. nearly all new patients “suitable” for DPIs will, over time, be prescribed DPIs not MDIs, irrespective of cost issues).

Thus, at a total market growth rate of 7%, the total market for asthma and related products is predicted to grow by 125% between 2000 and 2012. The market for MDIs will grow by a more modest 27%, the rest of this new market being supplied by DPIs or other new devices. This implies that the proportion of the market served by MDIs (as opposed to DPIs) will fall from around 90% globally at present⁸, to approximately 50% in 2012. This is an important point. Manufacturers are already making strong efforts to market DPIs for the medications they are available in and there is clear evidence in most of the countries surveyed that the market share of DPIs is growing at this pace (see Appendix B).

Table 2.2 shows the predicted world-wide emissions of gas in tonnes of propellant. It should be noted that this table shows world-wide and not European emissions.

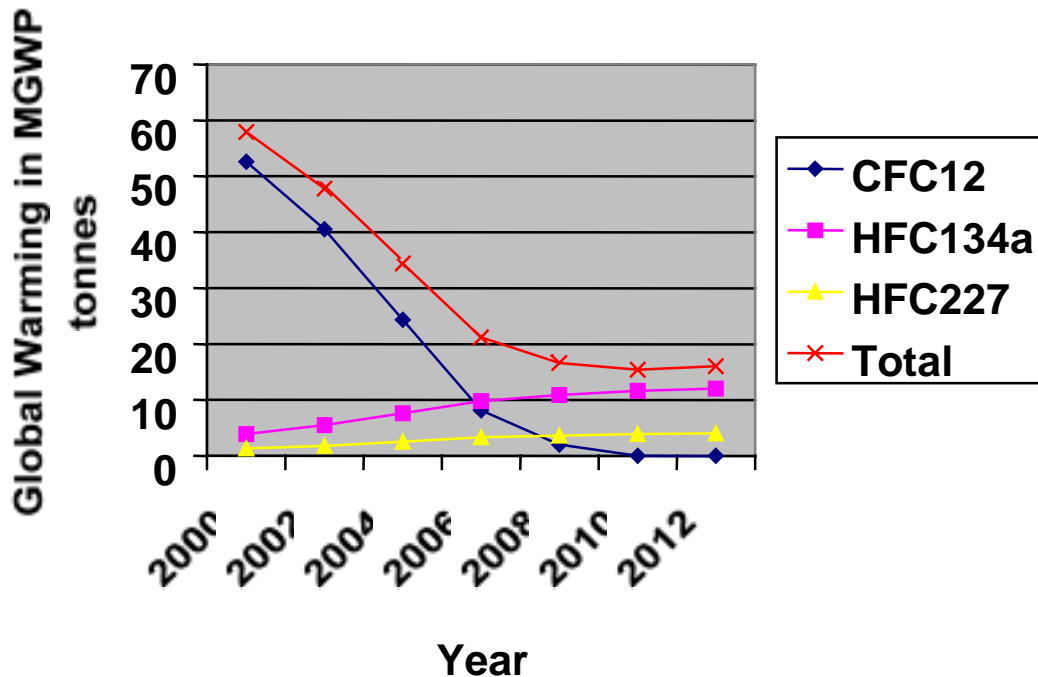
⁸ From audited industry data, market share of nebulisers is assumed static. 90% is the MDI market share of the MDI and DPI market – nebulisers are not included.

Table 2.2 Predicted World-Wide use in metric tonnes of fluorinated gas used in MDIs from 2000 to 2012⁹

	2000	2002	2004	2006	2008	2010	2012
All CFCs	6500	5000	3000	1000	250	0	0
HFC 134a	3000	4200	5800	7500	8400	8900	9250
HFC 227ea	500	630	870	1130	1250	1330	1390
Total	9000	9830	9670	9630	9900	10230	10640

Determining European emissions is complicated since the precise export rate over each year would also need to be determined. It should also be noted that this table shows emissions in tonnes of propellant gas. If we translate these emissions into their relative global warming impacts for the different gases (figure 2.1) we can see that there is a very large improvement from nearly 60 Mtonnes CO₂ equivalent at present, to only 16 Mtonnes CO₂ equivalent in 2012. This improvement is due entirely to the shift in use from CFC 12 to HFC 134a.

Figure 2.1 Global Warming world-wide impact of emissions from MDIs for 2000 to 2012.



⁹ Predicting future emissions depends on estimating growth rates and thus can never be entirely accurate. A recent IPAC report estimates emissions in 2010 to be 9,000 tonnes of gas, compared to the 10,200 tonnes predicted here.

2.5 MDI Emissions in Perspective

The total EU greenhouse gas emissions of CFCs from MDIs in 1990 are estimated to have been around 35 Mtonnes CO₂ equivalent¹⁰. However, because of the distinction between the Montreal and Kyoto Protocols, most greenhouse emission figures are quoted without the CFC global warming impact. Thus in Kyoto terms, the 1990 greenhouse gas emission from MDIs would be zero since no HFCs were used at that time.

The total EU emissions of the 6 Kyoto Protocol greenhouse gases in 1990 was 4,200 Mtonnes CO₂ equivalent¹¹. Thus the contribution to global warming of the CFC emissions from the MDI sector in 1990 was less than 1% of the “Kyoto” emissions. In section 2.4 we estimated the “Business As Usual” scenario for emissions of greenhouse gases (both CFCs and HFCs) from MDIs in the EU in 2010.

In a previous Enviro March study on emissions from MDIs we estimated that emissions in the EU from MDIs would fall to around 5 Mtonnes CO₂ equivalent¹² by 2010. Our current projections for world wide emissions in 2010 are 16 Mtonnes CO₂ equivalent. Thus, assuming that the EU continues to represent around 35-40% of the world wide market¹³, EU emissions would be 5.5-6.0 Mtonnes CO₂ equivalent. European emissions of HFCs in 2010 therefore appear likely to be in the range 5-6 Mtonnes CO₂ equivalent.

This reduction in emissions is achieved despite continued market growth. This fall is directly attributable to the replacement of CFCs with the less powerful HFC greenhouse gases. Total emissions of all greenhouse gases in the EU in 2010 will be around 3,850 Mtonnes CO₂ equivalent even if the EU hits its Kyoto target¹⁴ (the “Business As Usual” figure is much higher). This implies that the contribution of the MDI sector to total EU global warming emissions in 2010 will be around 0.13%. It should also be noted that the contribution of the MDI sector to total global warming is falling over the Kyoto time frame. Table 2.3 shows the very small contribution that the whole of the HFC sector is predicted to make in 2010.

¹⁰ Reliable estimates for emissions in 1990 are difficult to obtain. This figure is based on discussions with CFC manufacturers

¹¹ www.unfccc.de

¹² Opportunities to minimise HFCs from the EU – March Consulting Group 1999.

¹³ According to audited industry data, the EU represented 38% of the world market for MDIs in 1999. The EU is also a net exporter so there would be some additional emissions from manufacture.

¹⁴ The EU is committed to achieving an 8% reduction on 1990 emissions by 2010.

Table 2.3 Global warming impact by gas in the EU¹⁵

	1995	2010
	%	%
Carbon Dioxide	78.5	77.5
Methane	13	12.8
Nitrous Oxide	6.9	6.8
HFCs (MDIs)	<0.01	0.13
HFCs (other uses)	1.0	1.45
PFCs	0.3	0.6
SF ₆	0.3	0.6

¹⁵ 1995 estimates from “Opportunities to minimise emissions of HFCs from the European Union” – March 1998.
2010 estimates from “Joining European Efforts to limit emissions of HFCs PFCs and SF₆” – Ecofys 2000 –
note methane, CO₂ and N₂O emissions are pro rata to 95 emissions to simplify the calculation.

3. POTENTIAL OPPORTUNITIES FOR REDUCTIONS IN EMISSIONS

In this section, all the potential emission reduction options identified during the course of the study for reducing emissions of HFCs from MDIs are examined. Appendix A provides a detailed review of the information sources used for each of these options where confidentiality issues allow. Issues addressed include price information, additional training requirements, patient healthcare and potential for increased hospitalisation.

In total ten possible measures to reduce emissions have been assessed. These options fall into four main categories:

- Replacing MDIs with a different treatment form – This includes DPIs, nebulisers, oral treatments and future technologies.
- Reducing greenhouse warming emissions from MDI usage – This includes minimising losses during manufacture, minimising the propellant required per dose and using lower GWP gases (HFC134a instead of HFC227ea).
- Reducing emissions from “waste” MDIs – This includes recycling or destroying gas from both reject MDIs and “used” MDIs.
- Using alternative lower GWP MDI propellants – This includes the use of hydrocarbons as propellants.

All of these options are considered in turn. The use of DPIs as an alternative to MDIs is considered first and in detail. DPIs are the main currently available alternative and these products already have a high market share in Sweden and the Netherlands.

3.1 DPIs

The major alternative treatment currently available to the General Practitioner is the DPI. The DPI does not use a propellant to supply the drug, but instead relies on the patient to supply the inspiratory effort. This simple difference has two key implications for the use of MDIs and DPIs.

- DPIs do not require a propellant gas and thus have no direct global warming impact (some energy use and hence CO₂ emissions will be associated with manufacture).
- DPIs require the patient to provide the inspiratory effort and there are therefore a number of patient groups for whom DPIs are not suitable. These include:
 - Patients with an acute asthma attack cannot use a DPI and must have access to an MDI
 - Patients with advanced COPD who have very restricted inspiratory effort and may well be unable to use a DPI
 - Young patients cannot use DPIs and all asthma guidelines mandate the use of MDI, with a spacer device, for young children.
 - The elderly.

In addition, some patients rely on medication for which DPIs are not or cannot be developed and thus DPIs cannot fully replace MDIs in the market place. The relative merits of treatment via MDI or DPI is a complex issue. A more detailed analysis is provided in Appendix A. Many research papers have been written in favour of both MDI and DPI treatment. However, during the course of this study we identified no conclusive evidence that in the long term patients are better treated by either MDI or DPI. Both treatments appear equally beneficial, however the transition from one treatment to the other can be traumatic for the patient.

The relative strengths and weaknesses identified in Appendix A, coupled with the fact that the MDI has been available since the 1950s, whilst the DPI in its current form has only been available for around 10 years have led to wide regional variations in the current uptake of DPI treatment.

A number of European countries have been selected to provide a good representation of the economic and social variations present across Europe. The regional variations in market penetration and price of MDIs and DPIs are documented in Appendix A and summarised in Table 3.1. World-wide, the usage of DPIs represents only 9% of doses received by patients, however, in Sweden, the DPI currently accounts for 81%¹⁶ of doses.

Individual country market characteristics are discussed in Appendix B. These reveal that in most European countries, market share of DPIs is approximately 5-15%. However, in two of the smaller and more affluent European countries, Sweden and the Netherlands, the market share is much higher. The market share of DPIs is highest in Sweden. From our discussions with Swedish GPs and treatment manufacturers, it appears that this figure of 81% may represent approximately the maximum technically achievable market penetration for DPIs. This is due to the unsuitability of DPIs for treating some groups of patients. The reason that the DPI has already achieved such a high market share in Sweden appears to be due to an extensive and highly effective marketing campaign by the local Swedish manufacturer of DPIs coupled with some Government intervention. The Swedish Government took particularly early action to restrict the use of CFCs in MDIs and no license for new CFC propelled MDIs have been granted in the last decade. This, coupled with 8-9 years of extensive marketing has led to the market share saturating at 81%. Similar marketing campaigns in other countries have not achieved such high levels of DPI market penetration.

In addition to market share, cost data on the difference in price to the pharmacist has been gathered for a range of European countries. Table 3.1 shows the cost difference by dose. The cost differential per dose (Salbutamol) € is the cost of a dose from a DPI minus the cost of a dose delivered from an MDI. In calculating the cost difference between an MDI and a DPI it is important to compare the same level of medication. During the course of this study we have compared “doses” which provide the same level of medication to the lungs. Some treatment methods may require 3 “puffs” to provide one dose, whilst others may only need one. The table also gives the percentage cost difference between an MDI and a DPI to provide perspective on the scale of difference that the health service would need to fund if DPIs are to be used instead of MDIs.

¹⁶ Identified from audited industry data.

In our investigations into the cost implications, we have concentrated on the molecule salbutamol. Over 20 other molecules have been available in CFC form, and most of these will ultimately be switched to HFC form. Analysis of the cost implications for these molecules is complicated since certain drugs are patent protected and generic alternatives are not yet available for any of these drugs. Salbutamol represents over half of the European market and is available in generic form, creating a competitive market. Salbutamol thus provides a useful starting point for a cost analysis. Table 3.1 shows that a salbutamol DPI costs on average around 160% more than an MDI and that the cost difference per dose is around €0.04. Thus a 200 dose MDI would cost around €5 compared to €13 for a similar 200 dose DPI.

Table 3.1 Regional variations in DPI usage

Region	Cost differential per dose (Salbutamol) €	% increased costs for DPIs	% Market share of DPIs (by dose) 1999
World-Wide	Not known	Not Known	9
Europe	0.04	~160	15
Sweden	0.037	200	81
Netherlands	0.045	100	40-50
France	0.033	160	16
Germany	0.0275	35	15
UK	0.055	200	8
Italy	0.012	35	6
Poland	0.015	35	1

In addition to gathering data on cost and market penetration, we interviewed a range of GPs from a selection of these countries. Our conclusion from these interviews plus a thorough review of the literature available is that there are no identified healthcare issues in the use of either MDIs or DPIs for the majority of patients (i.e. around 81%). There would however, be enormous implications for both health and financial costs if a switch was to be made (see Appendix A). In a gradual transition, (perhaps over 8-12 years, the time taken to achieve 81% market share in Sweden), DPIs could eventually service around 80% of the market, but the cost of this switch is prohibitive in comparison to other control measures. We have thus assumed in our analysis that 80% is the maximum technically achievable market share for DPIs at present.

Table 3.2 summarises the emission reduction potential available for switching from salbutamol MDI to DPI. A thorough analysis of the methodology for calculating this cost is provided in Appendix A. The major barriers to the use of DPIs identified by our study and prioritised with the most difficult first, assuming a gradual transition (see Appendix A) are:

- Price
- Market Awareness
- Patient re-training
- Health care impacts

In addition, patient and physician resistance to change is also a major barrier to change, but it is beyond the scope of this study to thoroughly investigate this area.

Each of these problems contributes to the cost of the transition. Appendix A also considers the costs required if an “accelerated” transition were to be attempted. It can be seen that due to increased marketing, retraining and hospitalisation costs, this is a much less attractive option, even before patient healthcare issues are taken into consideration. Significant patient healthcare issues would be associated with any “accelerated” transition.

Table 3.2 Cost effectiveness of switching to DPI Salbutamol treatment.

Transition	Potential Emission Saving (Mtonnes) per annum	Estimated Cost M€ per annum	Timescale for change (years)	Cost effectiveness €/tonne
Gradual	1.8	900	8-12 years	500
“Accelerated”	1.8	>1300	5-8 years	> 710

3.2 Other MDI Replacements

Two other alternatives currently exist for treatment of asthma and COPD, namely oral treatments and nebulisers. Metered liquid inhalers, novel non-inhaled treatments and new DPIs/nebulisers may one day prove to be viable substitutes for MDIs. However, none of these treatments is widely used at present:

Replacement of MDIs with oral treatments – Oral treatments are available but currently have several drawbacks rendering them a poor option for most patients. They are slow acting and thus of less use for recovery treatment and they are non-targeted, thus exposing the whole body to the medication. Large doses must therefore be used. Whilst it is possible that new oral treatments may overcome some of these difficulties, currently available medicines are not suitable as a replacement for MDIs.

Replacement of MDIs with nebulisers – Nebulisers are bulky and require a power supply. They are also more expensive and slower at administering the drug dose than MDIs and DPIs. Use of nebulisers is generally restricted to hospitals and home care. Currently nebulisers account for around 15%¹⁷ of the total market. However, because of the limitations noted, market share is not expected to grow. In the rest of our analysis, for simplicity we consider the market share of MDIs and DPIs only.

Replacement of MDIs with Future Technology – New developments in “metered liquid inhalers” may ultimately lead to increased use of this technology (see Appendix C). The rate of change to this or other technologies will be determined by product development cycles, manufacturing capacity, regulatory approvals and affordability.

¹⁷ “Ensuring Patient Care – The Role of the MDI”, IPAC, June 1999

3.3 Reducing GWP Emissions from MDI Usage

Since we have seen that the replacement of MDIs with DPIs is expensive and that no other treatments currently exist which can replace MDIs it is desirable to ensure that all opportunities to minimise emissions from MDIs are taken. Whilst the use of MDIs is necessarily emissive, there are still some opportunities to reduce the total amount of propellant released into the atmosphere.

Minimisation of losses during MDI manufacture - Manufacturers have made a whole range of improvements to their manufacturing process over recent years to ensure that the absolute minimum of leakage of gas occurs during the manufacturing process. Measures identified by IPAC as having been taken include:

- Modifications to both flexible and permanent hosing to minimise leakage
- Redesign of the delivery truck and canister process
- Detection and prevention of leaks and pump failure
- Minimisation of mixing vessel waste
- Improved elastomer seals and gas adapters
- Destruction and/or reclamation of gas from rejects.

During the study we contacted all major MDI manufacturers to estimate both current and historic leakage and reject rates. The measures noted above have contributed towards reducing the observed leakage rate to between 1-2% from over 4% in 1990. In addition, the amount of gas not directly ending up in the finished product has been reduced from 10% to 5%. Gas recovered in the factory may be destroyed in situ or collected and sent for destruction or recovery. This provides evidence that control of the manufacturing process is improving. It is possible that current leakage rates of 1-2% can be reduced to below the 1% level in the next 10 years. This would achieve an EU emission saving of around 50 tonnes of propellant or 0.06 Mtonnes CO₂ equivalent p.a.

Minimisation of propellant charge per dose – The quantity of propellant used to administer treatments varies both by manufacturer and by drug. Some molecules require high quantities of propellant to ensure correct delivery, whilst for other molecules there may be opportunities to reduce the propellant required to administer a dose. It is important to keep in mind, however, that the critical parameter for drug delivery is the amount of drug that reaches the airways of the lung. Even for salbutamol there are wide variations in propellant charge per dose between manufacturers. In reformulating MDIs for the switch from CFCs to HFCs, pharmaceutical companies have primarily sought to minimise changes in drug delivered to the lungs and the clinical management of respiratory diseases. In addition reducing the propellant charge could materially affect the “feel” of the MDI to a patient and it is thus not a change to be entered into lightly. However, minimising the quantity of propellant used to administer a drug is clearly an opportunity to minimise emissions of HFCs and is thus worthy of further detailed research. This is a possible area where the industry could make a voluntary agreement to work towards minimising the propellant used in all future formulations. This would also provide

some cost benefit to the manufacturer, as less gas would be used. However development times are likely to be of the order of 8-10 years and require a significant amount of capital. Factors relevant to the delivery of a drug deep into the lungs would have to be taken into account. Development would require clinical studies with high numbers of patients.

The use of HFC 227ea.

Whilst the transition from CFC to HFC is not complete, it has become clear that some of the molecules undergoing reformulation are likely to use HFC 227ea as a propellant. HFC 227ea is a more powerful greenhouse gas than HFC 134a. It has a global warming potential of 2900 compared to 1300 for HFC 134a. The choice of which propellant is used for each molecule or combination is determined by the physical characteristics required. HFC 227ea is used only where it provides significant performance enhancements on HFC 134a. From our research we expect around 15% of future MDIs to use HFC 227ea. A switch to the use of HFC134a could in many cases actually increase the greenhouse warming impact since more gas could be required per dose. It does not seem likely that there will be any opportunity for emission reduction through the avoidance of the use of HFC227ea.

3.4 Reducing Emissions from “Waste” MDIs

Essentially, there are two forms of “waste” MDIs produced. The first we have chosen to term “reject” MDIs. These are MDIs rejected by manufacturing quality control as not passing the strict requirements required for this market. These reject MDIs will often contain a full charge of propellant. Rejects are generally either destroyed or sent for recycling, where the propellant is recovered to be used in non pharmaceutical applications such as mobile air conditioning. The aluminium is also generally recovered. The second form of “waste” MDIs we refer to as “used”. Used MDIs covers the fate of all MDIs once they reach the market place. Thus they include fully used MDIs with only a small residue of propellant left inside, expired product with a full charge of HFC, plus a range of part-used MDIs which have not been completely used up for a number of possible reasons. Recovery and destruction of these units has already been attempted in some countries such as the “SNIP” scheme in France. It is difficult to estimate exactly how much propellant is left in an “average” used MDI, but our research indicates that this figure may be around 10%. Possible routes for disposing of propellant from these waste MDIs are discussed below.

- **Recovery of gas from Reject MDIs** – At present CFC containing “reject” MDIs are often sent to a recycling centre in Oklahoma, USA. Around half of all reject units manufactured world-wide, including many from the EU, are returned via this route. Here the CFC gas is removed and recycled into the refrigeration or automobile industry. The recovered gas must be filtered and fractionated to ensure that dose levels of drugs are reduced to tolerable levels, thus adding some extra cost. No CFC gas is allowed to return into the pharmaceutical industry, it is generally used in the car air conditioning market. This practice could be extended to include both reject HFC units and potentially could also include “used” units. However, it should be noted that there may be technical difficulties to overcome, especially with solution products and a significant amount of “sorting” would be required, especially during the transition period from CFC to HFC, but also afterwards when both HFC 134a and HFC 227ea will be in use. In addition a good

marketing campaign to encourage patients to return old MDIs will be required and some additional transport costs will be incurred.

Type	Potential Emission Saving (Mtonnes)	Estimated Cost M€	Timescale for change (years)	Cost effectiveness €/tonne
Rejects	0.3	0.33	1-3 years	1.1

- Destruction of used units** – In addition to recycling it is also possible to recover and destroy propellant from MDIs. Again, this practice is already happening to some extent with CFC MDIs. No sorting is required but less cash is generated since no gas is recovered (but aluminium can be recovered). Additionally, since HFCs are excellent flame retardants (used in fire-fighting) the energy required to destroy these chemicals is also not inconsiderable and both the cost and the global warming impact of the fuel used is also considered in our calculations.

Potential Emission Saving (Mtonnes)	Estimated Cost M€	Timescale for change (years)	Cost effectiveness €/tonne
0.154	7.8	2-5 years	50

3.5 Alternative MDI propellants.

Hydrocarbons have the potential to be used as propellants in MDIs as they are liquefied gases at room temperature. In a suspension MDI the drug must remain resuspended for a sufficient length of time after the unit is shaken for the patient to receive a reproducible dose. This requires a minimal difference in density between the drug and propellant, as is the case with CFCs and HFCs. However in the case of hydrocarbons the density difference is such that it will be very difficult to make an acceptable suspension MDI. Salbutamol is insoluble in hydrocarbons. There is also a need for substantial toxicology to be carried out, as hydrocarbons have never been given by inhalation. Flammability, toxicology and the “oily” taste of isobutane will all be potential issues to be covered. To meet global standards the required tests will take a minimum of 3 years. Additionally, in future years, VOC emission regulations may also be of concern.

Despite these caveats one German manufacturer is working on an MDI of salbutamol using isobutane as the propellant. The product has been in development for 8 years and is nearing the stage where reproductive toxicology tests will begin in the 3rd quarter of 2000. In parallel they plan to conduct clinical trials and hope to submit a change to their German marketing authorisation in mid 2001 which could allow a launch in Germany in Autumn 2001. Assuming these tests are successfully completed the product would only be available in Germany and would require further testing

before it could be introduced into other European markets. This product cannot be regarded as a proven technology until it has European medical registration. It is unlikely that this product will take a major share of the European market within at least the next 5 years.

4. EMISSION REDUCTIONS IN PRACTICE

Our analysis of the MDI market has revealed a number of key features. The first of these features is that the market is currently changing rapidly. Whilst HFC MDIs are playing a vital role in facilitating the phased withdrawal of CFC MDIs from the market place, DPIs are also playing a smaller but significant role. From our analysis of the market we have estimated that emissions of greenhouse gases from this sector will be between 5-6 Mtonnes CO₂ equivalent in 2010. Our baseline scenario for 2010 assumes that:

- HFC MDIs continue to be developed to allow the complete phase out of CFC MDIs
- Asthma prevalence and diagnosis is increasing. However, even with a market growth rate as high as 7%, global warming emissions from this sector will be less than a quarter of those emitted in 1990
- The production process for MDIs has improved and losses have been halved in the last decade
- Manufacturers are heavily marketing DPIs and market share by 2010 is predicted to be 40-50% in the EU without any regulatory intervention.

The MDI market is dominated by a small number of multi-national pharmaceutical manufacturers. In other markets where this is the case, such as car or semiconductor manufacture, we have seen a general willingness to react responsibly to limit emissions and this is likely to be the case in the pharmaceutical sector. We can see above that the situation by 2010 is likely to have acted to restrict emissions without any further action. However, this report has identified a number of additional steps that could be taken to further reduce emissions. These include:

- A commitment to investigate options and minimise valve size where possible on future MDI developments
- Improved collection and destruction of old units
- A commitment to continue to proactively market DPIs
- New technology advances such as
 - Metered liquid inhalers
 - Oral treatments
 - Hydrocarbon MDIs (if health and safety issues can be addressed)
 - micronebulisers

Whilst the last of these measures requires technical advances to be made, the first three measures can be achieved, but only through industry or Government action and at a significant cost. If we compare the costs of these measures to other options for limiting

emissions of HFCs (Table 4.1) we can see that these options are certainly not the most economic¹⁸.

Table 4.1 Cost effectiveness of various emission reduction options

Technical Option	Cost Effectiveness €/tonne CO ₂ equiv.
Low cost energy efficiency measures	Free
HFC 23 from HCFC 22 manufacture	1
Recovery from reject MDIs	1
Low cost XPS foam measures	5-10
Refrigeration system containment	5-20
Low cost general aerosol measures	16
Low cost HFC solvents measures	33
Destruction of old MDI units	50
Switch to DPIs	>500
Reduction in MDI valve size	not known, probably high
Hydrocarbon propellants in MDIs	not known, probably very high

Thus we can see that some of the measures, which could be envisaged for achieving MDI emission reduction, do not appear to be economically attractive.

In addition, policy makers will be keen to consider the trade implications of any potential actions. Our analysis suggests that the EU represents approximately 38% of the world-wide market for MDIs. This equates to around 190 million units per year. In addition, the EU exports an extra 40% (76 million units), mostly to developing countries. Export of MDIs is worth at least €200 m per annum to the EU balance of trade. Any legislation which restricted the manufacture or export of MDIs would have clear negative impacts on both the EU balance of trade and also potentially on patient healthcare in developing countries, most of whom could not afford the premium price required for DPI treatment.

Policy makers will be keen to ensure that the improvements projected in the baseline scenario, plus other cost-effective opportunities are acted on. Policy makers essentially have three options to achieve this:

- **A Voluntary/Negotiated Agreement** – The starting point for any agreement, whether negotiated or voluntary is to determine who must negotiate that

¹⁸ “Opportunities to minimise emissions of HFCs from the European Union” – March 1998.

agreement. In the case of seeking to reduce emissions from MDIs this will depend upon which measures are to be discussed in the agreement. Any negotiations which implied an increase in health spending would clearly need to include Government health departments. An agreement which sought to specify minimum levels of DPI usage would also need to include GPs since it is the GP (plus the patient) who ultimately control the market penetration of these units.

It would thus be a complex issue to negotiate an agreement. However all parties may gain from the development of a **voluntary** agreement. There are only a few MDI manufacturers and these are very well known and thus it would be relatively easy to conduct negotiations. Identifying representatives of GPs may be somewhat more difficult. The manufacturers would seek to ensure that no punitive taxation was enacted for environmental reasons, GPs would not want legislation harmful to patients and Governments would seek assurances that stated improvement targets were achieved. Commitments which might be included in a voluntary agreement could include:

- Continual promotion of DPI usage with annual reporting on market penetration achieved
 - Conduct research to minimise valve sizes and where possible develop smaller valves for future MDI developments
 - Targets for manufacturing leakage rates
 - Targets for recovery and destruction of reject units
 - Development of a voluntary collection and destruction scheme for “used” units
-
- **Taxation/Subsidy** - The level of taxation (or value in a carbon trading scheme) currently envisaged by most observers is around 10-20€ tonne CO₂ equivalent¹⁹. At this level, a 200 dose Salbutamol MDI containing around 15 grammes of propellant would face a cost increase of no more than 0.4€ The current cost difference between an MDI and a DPI is around 20 times this much. It is therefore unlikely that a taxation system would incentivise the market to move towards DPIs. Especially as we have found that price is not the main driver for most GPs and patients in delivery system selection.
 - **Legislation** – In principle, legislation could be developed which would mandate the future level of, for instance, DPIs. However, this legislation would be extremely difficult to develop, since Governments would clearly wish to avoid any possibility of a patient not having access to a particular drug treatment. The political implications of any mistakes made in this legislation appear to rule this option out as anything other than a measure of last resort.

¹⁹ OECD estimates

5. SUMMARY AND CONCLUSIONS

This study has sought to provide an independent, in-depth review of the greenhouse gas emissions from MDI usage in the European Union. The historical, current and likely future emissions of greenhouse gases from this sector have been estimated and possible methods for reducing emissions have been identified.

During the course of this study information has been compiled through a programme of desk research plus detailed discussions with General Practitioners and patient care groups throughout Europe. In addition, contact has been made with the eight major MDI manufacturers and most have responded with information. Alternative treatment product manufacturers, propellant manufacturers and sector specialists throughout Europe have been contacted. In all, in excess of 50 interviews were conducted. These interviews were conducted in July and August 2000. Our conclusions from this extensive desk and field research programme are:

- MDIs are an invaluable tool in the treatment of asthma and Chronic Obstructive Pulmonary Diseases (COPD)
- Asthma and COPD kill around 32,000 people in Europe each year
- The incidence of these diseases varies widely between countries and diagnosis is increasing
- MDIs use CFCs and HFCs as propellants. CFCs are ozone depleters and powerful greenhouse gases. HFCs are not ozone depleters and are less powerful greenhouse gases
- The pharmaceutical industry has already invested well over €1 billion in switching MDIs from CFCs to HFCs, as mandated by the Montreal Protocol
- The on-going transition from CFC to HFC propellant will reduce the global warming impact of MDI emissions by nearly 75% from 2000 to 2010
- Business As Usual emissions from MDIs in the EU in 2010 are predicted to be around 5-6 Mtonnes CO₂ equivalent, or approximately 0.125% of total emissions
- MDIs are totally emissive in use by patients but losses through emissions from the manufacture of MDIs have been more than halved in the last decade
- Almost all propellant contained in reject MDIs is destroyed or reclaimed for use in other industries
- There may be some scope for recovering and destroying propellant contained in used MDIs. The cost effectiveness of this measure has been estimated to be around €50 per Mtonnes CO₂ equivalent
- No alternative treatment currently exists which can completely replace MDIs
- DPIs are the only significant alternative treatment available to the market at present

- MDIs and DPIs provide approximately equivalent patient healthcare for patients suitable for these treatments
- Most manufacturers of MDIs also manufacture DPIs and thus appear to have little vested interest in promoting one product to the exclusion of the other
- Transferring patients from one treatment to the other can be traumatic to the patient and costly to the health service
- DPIs cannot completely replace MDIs as they are unsuitable for certain patient types. Experience in Sweden suggests that a maximum market penetration for DPIs of around 80% could be achieved in some markets
- Where generics are available MDIs are consistently cheaper than DPIs per dose. This price difference is estimated to be approximately €0.04 per dose.
- At this price difference, the cost effectiveness of replacing MDIs with DPIs is over €500 per tonne CO₂ equivalent avoided. This is not a cost-effective option.
- Both patients and physicians tend to stick with what they know. The main reason for a lack of desire to switch treatment in either direction is good patient satisfaction (both with MDIs and DPIs)
- Market share of DPIs is growing at between 5-25% per annum (dependent on Country). Long term, and without regulatory interference market share of DPIs is seen as likely to rise to between 40-50%.
- A range of possible initiatives to ensure that emissions from this sector continue to be minimised have been identified. The initiatives identified are:
 - Continued promotion by the manufacturers of DPI usage with annual reporting on market penetration achieved
 - Development of minimised valve sizes for future MDI developments
 - Targets for manufacturing leakage rates
 - Targets for recovery and destruction of reject units
 - Development of a voluntary collection and destruction scheme for “used” units
 - MDI replacements such as oral treatments, nebulisers, hydrocarbon propelled MDIs and metered liquid inhalers have been investigated. None of these treatments are yet ready to gain major market share.

APPENDIX A ANALYSIS OF EMISSION REDUCTION ISSUES

A1 Comparison of MDIs, DPIs and Nebulisers

The pressurised metered dose inhaler was first introduced in 1956 as a significant improvement over the squeeze bulb nebulisers in use at that time. The MDI is a pressurised multiple dose system which can easily be carried in the pocket and is very convenient for use. The essential components are the metal canister; the formulation consisting of at least the drug and propellant; a metering valve which ensures consistent doses and a plastic actuator. The propellant, which is a liquefied gas, provides the energy to release the drug from the canister. On exiting the valve the propellant rapidly evaporates providing a fine mist of drug particles suspended in the gas which is then inhaled by the patient.

A development of the MDI is the breath actuated MDI which has a mechanical system where the patient does not have to co-ordinate inhalation with pressing down on the canister. In the breath actuated devices the dose is automatically released into the airstream when the patient inhales.

The second class of devices used to administer drugs to the lung are non-pressurised and rely on the inspiratory effort of the patient to provide the energy to disperse and deliver the drug particles. These Dry Powder Inhaler (DPI) devices are, like the MDI, small pocket sized and portable. In DPIs the active ingredient is presented as a dry powder either as pure drug or mixed with a diluent. When the patient inhales through the DPI the force of the inspiration lifts particles out of the chamber of the device into the airstream and into the patient's lungs. In contrast to the MDI, where the components and method of use of all the products are essentially the same, there are several different types of DPIs, which have individual methods of use. There are 3 main classes of DPIs, single dose; multiple unit dose which are refillable and multiple dose reservoir devices which are not refillable.

Single dose DPIs, which were introduced in the late 1960s, have a drug dose contained in a gelatin capsule. In use the capsule is inserted into an actuator which pierces or splits open the capsule so that the contents can be inhaled.

Multiple unit dose DPIs contain pre-measured doses sealed in individual blisters which are presented in packs or strips. Some provide 8 doses as a pack and others up to 60 doses. In use the packs are used in an actuator which pierces or peels open the blister to release the drug. When the blister pack is empty another pack is easily inserted into the device.

Reservoir devices contain up to 200 doses of drug powder in a chamber or reservoir. The product has a metering chamber, which is filled as the patient turns or opens the device. On inhalation the dose is delivered into the airstream. These DPIs are not refillable.

A third alternative is the nebuliser. Nebulisers use either ultrasonics or other technologies as the energy source to propel an aqueous solution of drug into the lungs. They are generally large bulky devices which rely on a supply of electricity as the power source and consequently are used only in the home or hospital. There are a few less bulky more portable nebulisers under development but their use is unlikely to be widespread in the near future.

Table A1 Summary of the main characteristics of the 3 types of inhalation system.²⁰

	NEBULISERS	MDIs	DPIs
Energy source for drug delivery	Provided by external source	Provided by the device	Provided by patients inspiratory effort
Consistency of dose delivered	Depends on nebuliser used and duration of therapy	Independent of patient inhalation	Dependent on inspiratory effort of patient
Device operation	Varies from product to product	Similar provided same type of actuator is used	Varies from product to product
Co-ordination	Do not need to co-ordinate inspiration with actuation	Must co-ordinate inspiration with actuation except when using a breath actuated device or a spacer	Do not need to co-ordinate inspiration with actuation
Protection from humidity	Aqueous product	Good	Dependent on design
Paediatric use	Accepted practice	Accepted practice (only with a spacer)	Not suitable for children under 5 years
Availability	Widely available	Widely available	Less widely available

Salbutamol is available from many different manufacturers. As an example in the UK several different inhalation devices are available from the 5 sources shown below

Table A2. Devices in which salbutamol is available in the UK

	GLAXO WELLCOME	3M	Norton	MEDEVA	Generic Suppliers
CFC MDI			Salamol inhaler	Asmasal Spacehaler	Several Generics
CFC MDI BREATH ACTUATED	Ventolin Easi-breathe	Aerolin			
HFC MDI	Ventolin Evohaler	Airomir, Salbulin	Salamol CFC free inhaler		
HFC MDI BREATH ACTUATED		Airomir Autohaler			
SINGLE DOSE DPI	Rotacaps				
MULTI DOSE DPI- REFILLABLE	Diskhaler, Accuhaler				
RESERVOIR DPI				Asmasal Clickhaler	

²⁰ "Ensuring Patient Care – The Role of the MDI", IPAC, June 1999

PATIENT USE OF DEVICES

The standard MDI is often referred to as a “press and breathe” device. However, there are several steps, which have to be carried out in order for the device to be used correctly. Similarly, although the DPIs are different from MDIs and different from each other there are also a number of steps, which must be carried out for correct use. Table A3 is the standard checklist from the Dutch Asthma Foundation.

Table A3 The standard checklist from the Dutch Asthma Foundation

DRY POWDER INHALER	METERED DOSE INHALER
1. Prepare inhaler before use	1. Shake the inhaler
2. Keep inhaler horizontal	2. Remove protective cap
3. Exhale to residual volume	3. Hold inhaler upright
4. Place mouthpiece between lips and teeth	4. Exhale to residual volume
5. Inhale forcefully and deeply	5. Place mouthpiece between lips and teeth
6. Take inhaler out of mouth	6. Inhale slowly and simultaneously press down on the canister
7. Hold breath for 5 seconds	7. Continue slow and deep inhalation
8. Exhale	8. Take inhaler out of mouth and hold breath for 5-10 seconds

There have been many published papers since 1976 on the way in which patients use their inhalers. The techniques and method of assessment varies but the percentage of patients carrying out all the necessary operations varies from 2 to 85%. One of the key factors in patient's ability to use their devices is training and it has been shown that training and education have a beneficial effect on the use of inhalers. There have been several recent publications evaluating the use of MDIs and DPIs. In a group of 66 children between 1 and 14 years old, 60 of who had been trained, 67% carried out all the essential steps for an MDI but only 30% used a DPI correctly²¹. In a group of 316 patients, 88.9% made at least one error in the inhalation technique, whether an MDI or a DPI²². This study showed that fewer non-skill errors were made with MDIs than any

²¹ Kamps A W A et al. Poor inhalation technique, even after inhalation instructions, in children with asthma. *Paediatric Pulmonology* **29** 39-42 (2000)

²² Van Beerendonk I et al. Assessment of the inhalation technique in outpatients with asthma or chronic obstructive pulmonary disease using a metered dose inhaler or dry powder device. *Journal of Asthma* **35** (3) 273-279 (1998)

of the 3 DPIs used—this is in contrast to 2 other studies where 3 DPIs were easier to use than an MDI²³.

In all the studies referred to the patients were using only one device. Where patients are using more than one inhaler they made more errors than patients having only one device did. Of patients using a combination of DPIs 68% performed all the essential items versus 54% with an MDI/DPI combination. Patients using only 1 type of DPI made the fewest errors²⁴. While all MDIs operate in the same manner, there are a variety of DPIs that require various methods. For patients who require a number of drugs, switching from MDIs to DPIs may therefore result in an initial increase of non-compliance.

The conclusion of our literature search on the relative merits of MDIs and DPIs is that in both devices a significant number of people make errors and that a clear preference cannot be identified.

PATIENT GROUPS.

There are a considerable number of patient groups for whom DPIs are not suitable:

- Patients with an acute asthma attack cannot use a DPI and must have access to an MDI
- Patients with advanced COPD have very restricted inspiratory effort and may well be unable to use a DPI
- Young patients cannot use DPIs and all asthma guidelines mandate the use of MDI, with a spacer device, for young children.
- The elderly
- Patients who rely on medication for which DPIs are not or cannot be developed.

During the course of this study we identified no data nor information on any aspects of increased costs of non-compliance with medication. We have no evidence that patients are less likely to be compliant with a DPI than an MDI—with a single DPI. As the study has dealt mainly with salbutamol, patients will not have a variety of DPIs to use and most of the evidence is that a single DPI is as easy or easier to use correctly than an MDI. This will not be the case when multiple drugs are considered.

²³ Van der Palen J et al. Evaluation of the effectiveness of four different inhalers in patients with chronic obstructive pulmonary disease. *Thorax* **50**, 1183-1187 (1995). **See also** Hilton S. An audit of inhaler technique among asthma patients of 34 general practitioners. *British Journal of General Practice* **40**, 505-506 (1990)

²⁴ Van der Palen J et al. Multiple inhalers confuse asthma patients. *European Respiratory Journal* **14(5)** 1034-1037 1999

A1.1 Barriers to Market Penetration for DPIs

During the course of the study, four major potential barriers to market penetration of DPIs were identified:

- Price
- Market Awareness
- Patient re-training
- Health care impacts

In addition, the natural resistance of the patient and physician to move to new treatments was also identified as a major issue, but unfortunately investigation of this is beyond the scope of the current study. These first four issues are considered in turn:

Cost and Price Issues

Cost comparisons are difficult to make on patent protected treatments. The molecule salbutamol, which represents over half the asthma treatment market, is now available in generic form and a situation much more analogous to a free market exists. However, even for salbutamol, obtaining accurate final price data is difficult. In some countries, price lists are published for general reference, but discounting of these published prices does occur. In other countries prices are negotiated directly between Governments and pharmaceutical companies, sometimes with prices being calculated based on historical data.

Treatments also differ, packs may come in a wide range of dosages and thus care must be taken when comparing prices. In our analysis we have attempted to cost the most widely used MDI and DPI by dose. In addition, there is the question of who will pay this additional cost. In most countries prescriptions are charged at a flat fee, with exemptions for sections of the community less able to pay. However, this is not the case in all countries. Thus the final “bill” for transition from MDIs to DPIs will be picked up by both the Government and the patient. Our assessment of the costs incurred in switching from MDIs to DPIs in each country is shown in table A4. For more information on the situation in individual countries reference should be made to Appendix B.

Table A4 – Salbutamol usage and cost differences across Europe.

Country	Cost difference (€)	Total National Dosage (millions)	Total Cost for 100% DPI (m€)	Prescription, Patient pays:
France	0.033	1,787	59	35%
Germany	0.025	906	24	fixed ~ 10 DM
Italy	0.012	1,042	12.5	fixed 6,000 lira
Poland	0.015	179	0.25	dependent on treatment
Netherlands	0.045	230	10	Fully re-imbursed
Sweden	0.037	75	2.8	up to 700Kr p.a
UK	0.055	5,322	293	fixed £6
Average*	0.04	9,541	401	

* Weighted by market size across the seven European markets assessed.

Thus for a cost difference of 0.04€ per dose, a DPI treatment of 200 doses costs, on average, around 8 € more than an MDI. An “average” patient using say 5 of these units a year will “incur” an extra cost of 40 €. In most cases this cost will be borne by the Government, but in France 35% of the cost will be borne by the patient.

A single 200 dose MDI contains on average 15 grammes of propellant including “overage” (extra drug and gas to ensure that all units contain a minimum of 200 doses). The greenhouse warming potential of this gas (HFC 134a for Salbutamol) is 1300 times that of CO₂. If a DPI unit is used instead, then this emission is avoided, but at an additional average European cost of around 8 €. Thus a saving of around 19.5 kg CO₂ equivalent is made per 200 dose unit. This equates to an average European cost benefit for replacing Salbutamol MDIs with DPIs of around 410 € per tonne CO₂ equivalent avoided. This is a very high cost compared to many other sectors, see section 5, where costs of emission avoidance are typically less than 10 € per tonne.

The market price of switching to DPIs is estimated to be over €400 per tonne.

Market Awareness

Both GPs and patients are relatively conservative in considering moving to new drug delivery systems. In most of Europe this is reflected by a very low uptake in the newer DPI treatment. However, in Sweden (and to some extent the Netherlands) the reverse situation is true. In Sweden the DPI has been the subject of sustained marketing by a national manufacturer to GPs and patients since the early 1990s. This has led to a situation where almost all patients who can use DPIs do use them. This is despite there being a significant cost difference in favour of MDIs.

Drug marketing campaigns to achieve significant market penetration are expensive and must be sustained, year on year to be effective. Astra Zeneca for instance is reported to be investing over €200 million globally on marketing its new gastrointestinal drug Nexium. It is difficult to accurately estimate the size of marketing campaign that would be required to convince GPs and patients to move towards greater use of DPIs but it is likely to require many 10's of € millions. If we assume that a campaign budget of 45 € million per annum could eventually raise market penetration in Europe from current levels (16%) to Swedish levels (81%), there are 9.3 billion doses of Salbutamol so this corresponds to a switch of around 6 billion doses or 30 million 200 dose units (450 tonnes of gas).

The extra cost required to market this switch thus equates to 0.1 € per gramme of gas. That is to say an extra €7 per tonne CO₂ equivalent avoided. This cost alone is significantly higher than many other options for emissions abatement in other sectors.

The marketing costs of switching to DPIs is estimated to be €77 per tonne.

Patient Retraining

The costs of retraining patients are extremely difficult to calculate. In most countries GPs are required to provide an annual check up to their asthma patients. Many GPs believe that patients can be encouraged to consider using a DPI at this meeting, thus requiring minimal extra GP time. To switch from MDI to DPI will take (we estimate) two 15 minute sessions of a nurses time. If the switch from MDIs is managed slowly over a number of years and new patients are trained immediately with DPIs not MDIs, then the extra burden to the healthcare service will be low. However, the cost of

retraining will be much higher if a rapid transition is required (see next section). The cost of retraining is a one off cost which provides a lifetime of savings of gas. Assuming a nurse’s time costs 50€ per hour and she can retrain two patients in this time – each of whom will live for another 35 years. This will save 420 MDI units or 6300 grammes of gas. This equates to a cost of only around 6 € per tonne CO₂ equivalent avoided. For patients who would need to use a number of different DPIs, training costs could be higher.

The retraining costs of switching to DPIs is estimated to be €6 per tonne.

Healthcare Impacts

Patient satisfaction with DPIs is good with only a small number (estimate 10%)²⁵ requiring a second consultation, since the patient is sometimes concerned that the dose is not being administered (this is caused since no gas is emitted from a DPI and hence the patient does not “feel” the drug). Hospitalisations are generally felt to be no higher for DPI users than for MDI users. Overall we have found no evidence to support extra costs in this area. However, the healthcare impacts of a rapid or mandated transition may well be substantial (see next section).

The healthcare costs of switching to DPIs is estimated to be €0 per tonne.

Total Costs to Switch from MDIs to DPIs

To summarise, the costs we have identified in a gradual switch from MDIs to DPIs can be summarised as follows:

	Cost (€tonne CO₂ equivalent avoided)
Price	410
Market Awareness	77
Patient re-training	6
Health care impacts	0
Total Cost	493 €tonne CO₂ equivalent avoided

A2 Implications of an accelerated switch from MDIs to DPIs

In our analysis so far we have considered the potential for a slow and measured approach towards moving to higher usage of DPIs. However it is possible that environmental regulation could be enacted that that would force large numbers of asthma and COPD patients to switch their inhalation therapy for purely environmental reasons.

It is clear from the literature and from practical experience in countries such as Sweden that DPIs are safe, reliable and an important inhalation therapy for asthma and COPD patients. Unfortunately, available studies do not address the issues which would occur if a rapid mandated switch were to be enforced. This

²⁵ Estimate from UK GPs in Asthma Group (GPIAG).

would force patients, perhaps against their will, to switch from MDIs to DPIs for environmental reasons not, therapeutic reasons. It is not surprising that such data does not exist given the unprecedented nature of such a measure. Such uncertainty, particularly in light of concerns related to patient health, safety, and fairness, calls for a cautionary approach and further research. Specific issues which cause concern in a mandated switch include:

Financial costs

- A rapid transition from MDIs to DPIs would require large investment in new DPI manufacturing capacity, plus additional losses as old MDI manufacturing capacity becomes redundant. Manufacturers have invested well over €1 billion on developing HFC MDIs and a rapid transition to DPIs would provide a much shorter timeframe for manufacturers to recover these costs. The EU represents around 38% of the total MDI market²⁶, thus on a simple analysis, the pharmaceuticals market will need to recover an additional €380m from its DPI and MDI sales. If the industry recovers this cost against the 110 million units sold per annum in Europe over a two year “rapid transition” this equates to an additional cost of €1.72 per MDI. This adds an additional cost of €85 per tonne to the original estimated manufacturing costs of €10.

The manufacturing costs of switching to DPIs is estimated to be around €500 per tonne.

- The marketing costs required to achieve a rapid transition would clearly be much higher. A conservative estimate might place the value of such a campaign to be twice that of a more measured transition. This would still leave a cost estimate of around €150 per tonne.

The marketing costs of a rapid switch to DPIs is estimated to be €150 per tonne.

- A rapid transition would require an enormous amount of GP and nurse time to retrain millions of patients. Whilst the cost of this could be maintained at relatively low levels if phased in over many years and provided only to “willing” patients, the costs of retraining over a short timescale would be much higher. It is impossible to estimate the exact cost of such a programme, but it is likely to be an order of magnitude greater at a minimum.

The retraining costs of a rapid switch to DPIs is estimated to be at least €60 per tonne.

- A rapid transition implies encouraging patients who have misgivings about switching treatment to use DPIs. This raises a whole range of problems:
- Asthma and COPD patients are sensitive to changes in the taste, smell, appearance and “feel” of their medication. It is highly likely that some

²⁶ From audited industry data

patients will be uncomfortable with DPIs for subjective reasons, and issues of compliance could arise. In the worst-case scenario, a patient who avoids using medication properly could suffer serious health problems.

- Patient preference is an important consideration when prescribing medication for respiratory diseases²⁷. Serious ethical and fairness issues arise if patients are forced to switch to medications they are uncomfortable with.
- The transition to CFC-free MDIs has been more difficult and time-consuming than initially anticipated. In some instances, patients have resisted switching to CFC-free MDIs, despite the new medication having equal therapeutic benefit.

In summary, a rapid transition from MDIs to DPIs would increase the costs substantially as well as raising many healthcare issues. These cannot be quantified at this stage.

The total costs of a more rapid transition are thus estimated to be at least €10 per tonne, plus additional unquantified health costs.

In addition several other factors should also be considered:

- Asthma patients are particularly sensitive to medication. Some drugs provide a patient with substantial relief from their symptoms, whilst others would not. You need the right drug for the right patient.
- Not all asthma and COPD medications are available in DPI form.
- MDIs are critical for significant patient populations (e.g., the elderly, young children, those with severe asthma or COPD) for whom DPIs are not medically suitable. Actions against the HFC MDI could negatively impact patient's access to this form of inhalation therapy.
- Creating the regulatory structure necessary for a mandated transition would be an extremely complex process. For example, which patients could use MDIs and which would have to use DPIs?
- The transition to HFC MDIs is still in its infancy. Attempting to undertake a second transition from MDIs to DPIs before this transition is complete would create "duelling transitions" and could jeopardise the transition from CFC MDIs.
- The European Union is the primary exporter of MDIs to developing nations. A transition to DPIs would effect both developing nations' access to important medication and valuable trade to Europe.

²⁷ See, e.g., Consensus Statement: Aerosols and Delivery Devices, *Journal of American Association of Respiratory Care*, June 2000, Volume 45, No. 6 ("Patient preference should also be considered when selecting an aerosol delivery device.").

- A mandated MDI/DPI ratio as opposed to a ban on MDIs (which is not technically achievable) may present legal and competition issues and may conflict with national health care policies and goals.

It is thus our conclusion, that an acceleration of the transition to DPIs would cause both very large economic and social costs.

A3 Recovery and Destruction

At present around 10-15 million CFC containing “reject” MDIs from around the world, including Europe, are sent to a recycling centre in Oklahoma each year. Here the CFC gas is removed and recycled into the refrigeration industry. This situation has arisen due to the high price achievable for CFCs in the American car air conditioning market. The recovered gas must be filtered and fractionated to ensure that dose levels of drugs are reduced to tolerable levels, thus adding some extra cost. No gas is allowed to return into the pharmaceutical industry due to safety concerns. In fact the gas is generally used in the American car air conditioning market. This practice could be extended to include both reject HFC units and also potentially “used” units. However, it should be noted that for used units a significant amount of “sorting” will be required, especially during the transition period from CFC to HFC, but also afterwards when both HFC 134a and HFC 227ea will be in use. In addition a good marketing campaign to encourage patients to return old MDIs will be required.

The table below shows our estimates of the quantities of material recoverable and their relative worth, from each “batch” of 1 million reject units. We have assumed that there is approximately 5g of Aluminium in each MDI canister and that these reject canisters are full and therefore contain on average, 15g of HFC or 20g of CFC. For used units we assume that the canisters contain on average only 10% of a full charge, i.e.1.5g of HFC.

Table A5 Material recovery value estimates.

	Cost/kg €	Tonnes (Per million units)	Income €000's
Aluminium	1.5	5	7.5
CFC	500 ²⁸	20	10000
HFC	20	15	300
HFC (used)	20	1.5	30

Income stream per 1,000 CFC reject units – 10,007.5

Income stream per 1,000 HFC reject units – 307.5

Income stream per 1,000 HFC used units – 37.5

²⁸ This can rise much higher in times of shortage.

At present the recycler pays for transport and recovery costs (even from the EU) due to the high value of CFC gas. We can see from the above, that the lower value of HFC gas makes this a much less attractive option and for reject HFC units there is a shortfall of €9,700 per million units. However, the cost of incineration of HFCs is around €3,000 per tonne of propellant, that is to say €45,000 per million units. Thus for reject units it is cheaper to pay the recoverer to take the units away than to have them destroyed. This is not the case for used units, where destruction costs €4,500 per million units against recovery “costs” of nearly €10,000. (This assumes that costs include a normal operating profit for the recycler and thus are equivalent to the value of material recovered). In this case, the best economic option is to recover gas from reject units, but to destroy gas from used units. When potential health issues surrounding the reclaiming of “used” units are considered this is even clearer.

At present, there is little recovery and destruction of used units in the EU. But for illustration we have made estimates of a possible scenario. If we assume that a 25% recovery rate of used units could be achieved and that an average 10% of gas remains in the can, then this gives a potential for recovering around 100 tonnes of propellant gas in the EU in 2010. This gas will be both HFC 134a and HFC 227. Assuming 15% is 227 gives a combined GWP of this gas of 1540. Thus the total GWP of the recovered gas would be 0.154 Mtonnes CO₂ equivalent. Costs to achieve this emission reduction will consist of three portions:

- Destruction costs (€3,000 per tonne)
- Collection and transportation costs. Collection schemes where patients return their old units when picking up new units will minimise transportation costs. If we assume the average trip from collection point to incinerator is 250 miles then transportation costs should be no higher than €500/tonne – but most of this weight will be container and the cost of transportation of the gas will be nearer €5,000 per tonne.
- Marketing costs to advertise the scheme. This is difficult to estimate but might consist of a “one-off” push of €20 million, plus ongoing costs of around €5 million per annum. Over a ten year period this equates to an annual cost of approximately €7 million.

Thus the total costs would be €3,000 per tonne of the order of €7.8 million to save 0.154 Mtonnes CO₂ equivalent. Representing a cost of around €50 per tonne.

APPENDIX B REGIONAL VARIATIONS

During the course of the interview programme we visited web sites and spoke directly to manufacturers, physicians and patient groups in each of the countries listed below. The opinions expressed were surprisingly consistent in several key areas:

- For salbutamol, MDIs are consistently cheaper than DPIs per dose
- The main reason for a lack of desire to switch treatment in either direction is good patient satisfaction (both with MDIs and DPIs)
- It is previous experience rather than price that is the main motivator in prescription choice for both GP and patient.
- Market share of DPIs is growing at between 5-25% per annum (dependent on country).
- Apart from Sweden, market share is expected to saturate at around 50% DPI in the long term
- The market size varies widely between countries and is not linked to population (Table B1)

Table B1 Variation in markets by country analysed.

Country	Total Market Size (MDI and DPI) billion doses p.a	Population million	Dose per head p.a	DPI Market share 1999
France	3.9	58	68	16
Germany	3.6	82	45	15
Italy	2.2	57	39	6
Poland	1.3	38.5	35	1
Netherlands	0.8	15.5	55	40-50
Sweden	0.5	9	56	81
UK	9.8	59	168	8
EU	28.4	372	76	15

The individual circumstances of each country analysed are considered below:

France

In France asthma affects 2.5 million people, of which around a third are children. Asthma diagnosis is on the increase and France is the second largest market in Europe for MDIs after the UK.

Information on prices of MDIs and DPIs is not widely publicly available in France. Conversations with manufacturers have produced estimates for the cost differential at around 0.033 €/per dose.

In France, only 65% of the prescription charge is recoverable by the patient and thus France is unique in the countries listed in table B1 in that the patient directly bears part of any increase in the costs of treatment. This does not appear to be limiting uptake of

DPIs. Market share of DPIs in France was 16% in 1999, but this is rising rapidly and is expected to be at least 25% by the end of this year.

Germany

Information on prices is publicly available on the internet (www.gelbe-liste.de) and in book format via the “red list” and “yellow list”. Prices for salbutamol are published on the yellow list. Prescription costs to patients are fixed at around 10 DM for all patients not exempt. Both MDIs and DPIs typically cost more than 10 DM and thus the health service bears the additional costs. As elsewhere, prices do vary between MDIs, but “average costs” per dose for Salbutamol are of the order of 15 pfennigs for MDIs and 20 pfennigs for DPIs. The price differential per dose is therefore around 5 pfennigs or 0.025 €

Market share of DPIs is currently 15% and this is expected to rise to 20-25% over the next two years and eventually is expected to rise to 40%.

Italy

The Italian Government has become increasingly concerned in recent years at the lack of awareness of physicians to the relative costs of the drugs they are prescribing. They are developing a listing of all drug costs to provide physicians with the information to minimise costs more simply. However this is yet to be published. Drug prices are available at the following websites: www.sanita.it/Farmaci/ricerca.htm (the website of the Drugs Department of the Italian Ministry of Health although it should be noted that quite often prices are not updated on this site) and www.federfarma.it/set4/set4.html (the website of the Italian Federation of Pharmacists) which only covers “reimbursed” drugs.

In Italy, there are 3 classes of drugs “C” class which are not re-imbursed to patients, “B” class which are 50% re-imbursed and “A” class (including salbutamol) which are 100% reimbursed but subject to a prescription charge of around 6,000 lira. Since both MDIs and DPIs typically cost more than 6,000 lira the health service bears the additional costs. In Italy drug prices are negotiated between manufacturers and the Government and are calculated according to a complex formula based on the costs of these drugs in a number of other countries. According to this formula, the price of Salbutamol is set to rise slowly for the next few years.

Current cost difference per dose of MDI and DPI is currently around 0.012€ The market share of DPIs is currently low at around 6% but this is expected to rise over the next few years.

Netherlands

The Netherlands represents a unique market place for DPIs. The market share of DPIs is currently between 40-50% (estimates vary according to source) and has levelled out. When DPIs were first released onto the Dutch market in the early 1990s they were given a financial boost. This took the form of a subsidy from Government which meant that the cost of a DPI was completely re-imbursed whilst the cost of an MDI was only partially re-imbursed. In fact, this subsidy only existed for a few months, but this action, coupled with intensive marketing of the benefits of DPIs to both GPs and patients has resulted in a much higher market share than the European average.

Price information of treatment is available on an official price list called “taxe”. This is distributed to GPs monthly by the pharmacist association. This price list shows the cost difference per dose of MDI and DPI to be 0.045 €

Poland

The attractiveness of DPIs to both GPs and patients and also any cost difference in the units in Poland is difficult to assess, as they are currently poorly known. Some evidence exists to suggest that the average price difference may be around 0.015€/per dose, but there is no published data. Market share was probably less than 1% in 1999, but this is growing and a market share of around 5% may be more likely by the end of this year.

Sweden

Sweden is a very individual market for DPIs. Since the product was launched in the early 90s a national manufacturer has invested heavily in marketing the product to both Government and physicians. This marketing campaign has been extremely successful, to the extent that, despite costing more, DPIs now enjoy 81% of the total market and promoters of MDIs find it difficult to gain market share even at much lower sales costs. The prescription system in Sweden is illustrated in Table B2.

Table B2 The prescription system in Sweden

Annual Drug Cost (SKr)	Proportion paid	Total paid
0-400	100%	400
400-800	50%	600
800-1200	25%	700
Over 1200	Free	700

Most users of MDIs and DPIs will spend over 700 Swedish Kr per year on treatment and the health service bears this cost. The latest published prices (to the pharmacist) published by the Government show a price difference of 0.037€/per dose.

United Kingdom

Asthma affects 3.4 million people in the UK, including 1.5 million school children. The National Asthma Campaign estimate the total cost of asthma treatment to the UK economy is now in excess of £1000 million a year. The UK is by far the largest single market in Europe for MDIs.

In the UK, price information on all prescribed drugs is published monthly in MIMS (Monthly Index of Medical Specialities) and circulated to GPs. These GPs hold responsibility for monthly spending and are thus incentivised to minimise treatment costs. However, drugs are often discounted from the published price and a true picture of costs is probably more difficult to identify. According to MIMS June 2000, the price difference per dose was 0.055€

Market share of DPIs in the UK is comparatively low at 8%. This could be partially due to the greater responsibility of the UK GP for their own budgets. However,

interviews with GPs suggest that this is not the case and that the main reason for lack of DPI market penetration as in other countries is good patient satisfaction with the current treatment (i.e MDI).

The UK is the largest single market for asthma and COPD treatment in Europe. It represents around 35% of the total market by dosage, but only around 16% by population. The reasons for this are as yet not clear. However, this market will be the single most important market to consider in developing any emission reduction programme.

APPENDIX C TECHNOLOGY STATEMENTS

Each of the major manufacturers of MDIs and DPIs were asked to provide a technology statement as part of this study. The technology statements are intended to give a balanced view of likely future technical developments in this sector. Here are the responses received:

Astra Zeneca

Prospects for Future Technologies

1. Pharmaceutical companies already supply the DPI and nebuliser as alternatives to MDIs for those patients whose doctors consider them medically appropriate. Hence “future” technologies in one sense are already fully available.
2. The propellant MDI aerosols powered by CFC/HFC are restricted to respiratory conditions, since there is no alternative propellant identified at present. Topical (skin) propellant aerosols have been changed to hydrocarbons and nasal propellant aerosols have been converted to aqueous pumps. Please note that aqueous pumps cannot produce the droplets less than 5 µm necessary to reach the lung.
3. Oral (ie tablets/capsules) products will be of increasing importance. Some oral products have been in existence for a considerable time, eg salbutamol, steroids and theophylline but are not widely prescribed due to side effects. A new class of orally active compounds the anti-leukotrienes (Merck’s Singular and AstraZeneca’s Accolate), has recently been launched but has yet to establish a major place in asthma therapy. Companies are continuing to develop oral therapies, eg phosphodiesterase IV inhibitors (SKB Ariflo). VLA-4 antagonists (Texas Biotechnology/Schering-Plough) and in general increasing emphasis is being placed on the oral route. Naturally oral therapy would replace all types of device, not just MDIs.
4. Other Device Technologies

Device research and development is actively continuing across major pharmaceutical companies and specialist inhalation device companies. One area of investigation is how to produce the required fine particle aerosol cloud without using a propellant gas (CFC or HFA). Water is a natural choice and such droplets could be formed by forcing it through a nozzle with very small channels, by piezoelectric crystals or by ultrasonics. A major problem with water is to retain sterility in a multidose device without the use of preservatives.

Dry powder research is also continuing with particle engineering to produce systems that are more easily fluidised to give the aerosol cloud. In addition independent power sources are being investigated for DPIs such as compressed gas, mechanical energy or a fan.

5. Systemic Biotechnology Delivery

Systemic delivery of biotechnology molecules via the lung for non-respiratory diseases is in its infancy but is a potential growth area. However, it is not envisaged that MDIs will be significantly employed here for two reasons. Firstly, the patients do not have respiratory diseases and hence have a normal strong lung function and can use DPIs adequately. Secondly, many biotechnology molecules may be denatured by

CFC/HFA propellant or degraded by the shear forces in the MDI nozzle. As an example, one of the most advanced projects in this area is inhaled insulin and of the three companies most active, one is DPI and two are nebuliser.

Boehringer-Ingelheim

The challenge does not end with the HFA MDI. An ideal inhaler may be considered to be one which uses no propellant at all, is economical, reliable, portable, simple to use and pleasant to inhale.

Boehringer-Ingelheim are already committed to a very comprehensive range of HFA MDI developments (reformulating 6 products), Boehringer Ingelheim is also well on the way to delivering an affordable and reliable propellant-free soft mist inhaler that comes close to the ideal non-propellant inhaler.

Chiesi

In the respiratory area, substantial effort is devoted to develop a line of products capable of responding to the patient's needs with complete and innovative therapeutic solutions for treating asthma and COPD.

- **Nebuliser products:** a series of preservative-free formulations - based on salbutamol, ipratropium bromide, beclomethasone dipropionate (BDP) and budesonide have been developed in unit-dose vials;
- **Inhalation powders:** the development of a complete range of antiasthmatic drugs in Chiesi's proprietary Pulvinal® multidose dry powder inhaler is ongoing;
- **Pressurised metered dose inhalers:** also mindful of the environmental concerns, Chiesi has developed the proprietary Modulite® technology, based on the ozone-friendly HFA propellants. Application of this technology to a BDP formulation has lead to the first marketing authorisation of the CFC-free version of Beclojet® in France. Several other formulations are undergoing development. The Modulite® technology has been developed in collaboration with the Centre for Drug Formulation Studies of the University of Bath (UK);
- **Nasal products:** aqueous formulations of steroids for nasal administration are being developed for use in rhinitis.
- **EPI-2010:** as further confirmation of the importance given to asthma therapy, the Chiesi Group has signed an agreement with EpiGenesis Pharmaceuticals (Cranbury, NJ - USA) for the development of EPI-2010, an antisense oligonucleotide with the capability to inhibit the over-expression of adenosine A1 receptors in the lungs and targeted to the prevention and chronic treatment of bronchial asthma. It is a promising drug endowed with a highly innovative mechanism of action that could bring about concrete improvement in controlling the asthmatic disease.

Glaxo Wellcome

GlaxoWellcome is committed to the replacement of essential CFC-based MDIs with equivalent non-CFC alternatives. The transition, which is still in progress, has been a long and complex process involving the resolution of significant technical issues. Concurrently, development programmes within GlaxoWellcome have led to the introduction of dry powder inhalers and formulations for nebulisation. Within GlaxoWellcome, research and development of new technologies and delivery systems for the pulmonary delivery of drugs remains a high priority. However, in achieving device performance that gives targeted and efficient deposition of drug in the lungs, which meets contemporary regulatory standards, the programmes are technically demanding and are expected to be long-term.