IPAC

INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM

INFORMATION ON MEDICAL USES OF HFCS

SUBMISSION BY
THE INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM
TO THE UNITED NATIONS FRAMEWORK CONVENTION ON CLIMATE CHANGE

1 MARCH 2002

IN RESPONSE TO
DECISION FCCC / SBSTA / 2001 / L.16 (6 NOVEMBER 2001)
Relationship Between Efforts to Protect the Stratospheric Ozone Layer and Efforts to Safeguard the Global Climate System: Issues Relating to Hydrofluorocarbons and Perfluorocarbons

INFORMATION ON MEDICAL USES OF HFCS

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I. INTRODUCTION

In *Decision FCCC/SBSTA/2001/L.16*, the Subsidiary Body for Scientific and Technological Advice invited non-governmental organisations to provide updated information on "available and potential means of limiting emissions of hydrofluorocarbons and perfluorocarbons, including their use as replacements for ozone depleting substances." The International Pharmaceutical Aerosol Consortium[1] (IPAC) appreciates the opportunity to inform SBSTA on issues related to medical uses of hydrofluorocarbons (HFCs).

As discussed below, HFCs are the replacement propellant for chlorofluorocarbons (CFCs) in metered dose inhalers (MDIs), a drug delivery system used by millions of patients world-wide. Under the Montreal Protocol on Substances that Deplete the Ozone Layer, the use of CFCs in MDIs is still considered "essential," but efforts are underway to transition patients to HFC MDIs. Important linkages therefore exist between efforts to limit emissions of HFCs under the Kyoto Protocol and the Montreal Protocol's objective of phasing out CFC MDIs. This submission, which serves to update IPAC's 15 July 1999 submission to the UNFCCC, (i) provides a brief background on medical applications of HFCs and the interrelationship between the Montreal and Kyoto Protocols, (ii) examines health policy issues related to potential measures impacting medical uses of HFCs, (iii) reviews the conclusions of recent research, and (iv) discusses possible policy approaches for HFC MDIs.

II. METERED DOSE INHALERS: A BACKGROUND ON CFCS AND HFCS IN MEDICAL APPLICATIONS AND THE INTERRELATIONSHIP BETWEEN THE MONTREAL AND KYOTO PROTOCOLS

The preferred means of treating patients with serious respiratory illnesses is to deliver medication directly into the lungs via inhalation therapy.[2] Three types of inhalation delivery systems are currently available for patient use – metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulisers.[3] At present, MDIs are the most widely

[1] IPAC is an association of pharmaceutical companies that manufacture medications for the treatment of respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD). The following companies are IPAC members: Armstrong Pharmaceuticals, AstraZeneca, Aventis Pharmaceuticals, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, and IVAX.

[2] National Heart, Lung, and Blood Institute, National Institutes of Health, International Consensus Report on Diagnosis and Management of Asthma, US Dept. of Health & Human Svcs. Pub. No. 92-3091, 28 (June 1992); *The Implications to the Montreal Protocol of the Inclusion of HFCs and PFCs in the Kyoto Protocol*, Report of the HFC and PFC Task Force of the Technology and Economic Assessment Panel, UNEP (October 1999) at 41 (hereinafter TEAP HFC Task Force Report). Attachment 1.

[3] For a detailed background on these inhalation delivery systems and the diseases they treat, please see *Ensuring Patient Care, the Role of the HFC MDI*, 2nd Edition, International Pharmaceutical Aerosol Consortium (1999). Attachment 2.

prescribed inhalation therapy, accounting for approximately 70% of the market. MDIs are available in nearly all drug formulations, are well established medically, and are frequently less expensive than other inhalation products.[4] DPIs and nebulisers each account for approximately 15% of the market. This range of treatment options is discussed in more detail in Section III.

The Phase-out of CFCs under the Montreal Protocol

MDIs are aerosol devices that rely on a propellant vapour to deliver the active drug ingredient to a patient's lungs. CFCs have served as the propellant in MDIs since they were first developed in the 1950's. In response to the Montreal Protocol, pharmaceutical companies invested substantial resources over more than a decade to identify appropriate alternatives to CFC-based delivery systems.[5] After substantial research, only two propellants – HFC 134a and HFC 227ea – emerged as suitable replacements for medical use in MDIs.[6]

Concurrent with the CFC MDI reformulation effort, companies also undertook to improve existing non-propellant inhalation respiratory products, initiate development of new non-propellant inhalation technologies, and develop new chemical entities effective orally. In addition, pharmaceutical companies reformulated other drug delivery systems formerly using CFCs, such as angina treatments, topical sprays, and nasal aerosols, to non-fluorocarbon technologies.

The global effort to reformulate MDIs and transition patients to CFC-free alternatives is progressing, but it is not yet complete. Significant numbers of MDIs on the market still rely on CFCs. In light of the importance of the CFC MDI to patient health, production of CFCs for MDIs is still allowed until the transition to non-CFC products is complete.

For a variety of reasons, the transition has been more challenging than initially anticipated, and its successful conclusion now depends on the execution of comprehensive governmental policy initiatives in both the developed and developing world. Though national circumstances vary, it is anticipated that the patient transition away from CFC MDIs will be nearly completed in the EU by 2005 and all other developed countries by 2008. In the developing world, it is difficult to predict the future pace of the CFC transition as it will depend on several factors, including

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[4] CLIMATE CHANGE 2001: MITIGATION, Appendix III at A3.5.1 (*Medical Applications)*, Intergovernmental Panel on Climate Change (2001) (hereinafter, IPCC, Appendix III). Attachment 3. *See also* Managing stable chronic obstructive pulmonary disease. *Drug and Therapeutics Bulletin*: 81-85 (November 2001).

[5] TEAP HFC Task Force Report at 42.

[6] *Id.*; Meeting Report of the Joint IPCC / TEAP Expert Meeting on Options for the Limitation of Emissions of HFCs and PFCs, Petten, The Netherlands (May 1999) at 20 (hereinafter IPCC / TEAP Report). Attachment 4.

development of national MDI transition policies and adequate funding of national health care systems. It is important to understand these elements of the CFC transition in the developed and developing worlds when considering potential measures to reduce future HFC MDI emissions.

Climate Change and the CFC MDI Transition

The continued use of CFCs is significant from a climate change perspective. In addition to depleting the ozone layer, CFCs are a potent greenhouse gas contributing to global warming. HFC 134a and HFC 227ea have significantly lower global warming potentials than the CFCs they are replacing, and, according to recent reports, the switch to HFC MDIs will result in a greater than 50% reduction in global warming impact. *See Figure 1.*

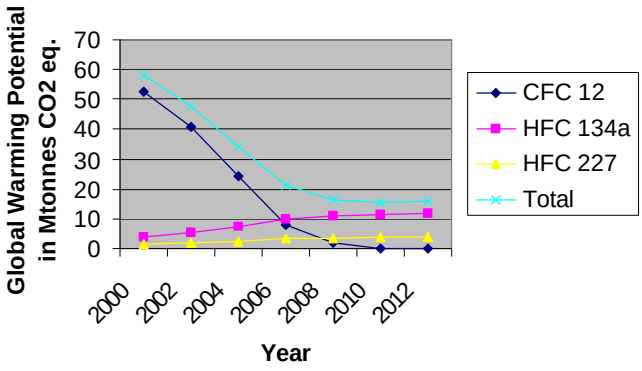

Figure 1: Global warming world-wide impact of emissions from MDIs for 2000 to 2012.

While non-MDI delivery systems, such as the DPI and nebuliser, play important roles in respiratory therapy, the MDI is the most widely prescribed inhalation delivery system. The success of the CFC MDI transition depends entirely on patient use and acceptance of non-CFC products. Because asthma and COPD are life threatening diseases, patients who have come to rely on CFC MDIs may be reluctant to switch to other drug therapies. Recognising the risk of patient reluctance to switch therapies and the risk of reduced patient compliance with new devices and treatment regimens, pharmaceutical companies have designed HFC MDIs to look, feel, and operate almost identically to CFC MDIs. Any measure that would cause patients to question the safety, efficacy, or future availability of HFC MDIs, or that would cause patients to question the environmental value of the CFC MDI transition, would be detrimental both to efforts to protect the stratospheric ozone layer and efforts to respond to climate change. The

importance of the relationship between the two international environmental treaties was recognised in *Decision FCCC/CP/1999/6/Add.1* wherein Parties were requested to take into account "health, medical, environmental and safety considerations" when considering potential ways and means to limit HFC emissions.

III. WAYS AND MEANS OF LIMITING HFC EMISSIONS FROM MDIS: A DISCUSSION

When considering possible reduction measures for the MDI sector, it is important to keep in mind the MDI's limited contribution to overall GHG emissions. The preliminary projections indicate that by 2010 total world-wide HFC emissions from MDIs will range from approximately 7,500 to 10,200 tonnes per year.[7] These figures make certain assumptions regarding market growth for MDIs, the progression of the CFC transition by 2010, and other factors. While it is difficult to make precise estimates and projections will need to be revised as additional data becomes available, these projections provide a useful perspective on the scale of MDI emissions as compared to other greenhouse gas emissions. Comparing these MDI projections with recent projections for total world-wide emission of all six Kyoto gases shows that MDIs will only account for 0.02-0.05% of world-wide emissions in 2010.[8]

Two categories of emissions are associated with HFC MDIs: (i) HFCs emitted during patient use and (ii) fugitive emissions during the manufacturing process.

Addressing HFC Emissions from Patient Use of MDIs

MDIs are inherently emissive devices. Each time a patient uses an inhaler, unavoidable emissions, albeit extremely small, occur. Addressing these emissions, therefore, would require decreasing patient use of an effective, reliable treatment option. Consideration of substituting a not-in-kind alternative for HFC MDIs would reasonably be an initial step under a conventional environmental policy analysis. As discussed below, however, medical uses of HFCs necessitate a broader view and understanding of the patient health care context.

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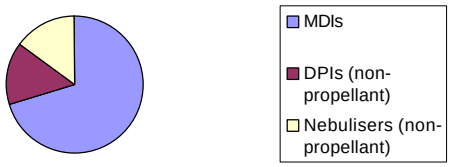
[7] *See* IPCC, Appendix III at A3.5.1; Enviros March 2000 at 10-11.

[8] The comparative worldwide figure for 2010 emissions of the six Kyoto gases (11,500-13,800 million metric tonnes of carbon equivalent) was derived from: Intergovernmental Panel on Climate Change, Special Report on Emissions Scenarios at Appendix 7 (Data tables), 2000.

Review of Current and Future Inhalation Treatment Options

As an initial matter, the current landscape of treatment options for respiratory illnesses should be understood. Figure 2 summarises the world-wide market for the three currently available inhalation therapies.

Figure 2: World Market for Inhalation Products*



*** Representative for the world's 15 largest patient populations**

Neither DPIs or nebulisers require aerosol propellants and both are used successfully by many patients, although neither currently has the universal application of the MDI. While each constitutes about 15% of the world-wide market for inhalation products, use of these products varies greatly on a national level. Oral tablets are also sometimes used to treat respiratory illnesses, although to a much lesser extent than inhalation therapies[9].

DPIs are used most extensively in some European countries, such as the Netherlands and Sweden, where they account for 40 and 80% of the market, respectively. They represent approximately 15% of the overall market share in Europe. It is important to note that the market for DPIs in Europe is increasing at a higher rate than for MDIs. Use of DPIs is expected to increase naturally over the next several years even without any regulatory measures, and current estimates predict that these devices could account for roughly half of the European market by 2012.[10] In contrast, patient use of DPIs in other developed countries, such as Canada and the US, is significantly lower, closer to 2-3%. For a variety of reasons, particularly cost issues, DPIs are not prevalent in developing countries. The current generation of nebulisers are used largely for

[9] Inhalation therapies are generally favoured over oral tablets because they are faster acting and have reduced incidence of systemic side effects. TEAP HFC Task Force Report at 43. However, many pharmaceutical companies have improved oral therapies under development, and in the future these may represent a greater segment of the market for asthma and COPD.

[10] *Study on the Use of HFCs for Metered Dose Inhalers in the European Union*, Enviros March (December 2000) at 10-11 (hereinafter, Enviros March 2000). A fuller discussion of this report appears at pp. 7-8.

hospitalised patients as they are costly, require an independent power source, and are bulky and less convenient than MDIs and DPIs.

In addition to currently available non-propellant products, future technologies will likely play an important role in inhalation therapy. All IPAC companies are actively engaged in research and development of new drugs and delivery systems. Examples of technologies under development include: (i) systems that would create an aerosol mist without the use of a propellant; (ii) a drug-containing solution that could be forced through a nozzle with two small channels, generating an aerosol by impaction; (iii) the use of piezoelectric materials, which change their shape in response to an alternating electrical current, and which may be transmitted to a liquid, causing droplets to be thrown off the surface of the liquid; and (iv) use of an ultrasonic horn to generate an aerosol cloud by capillary wave action. In addition, research is also underway to develop improved oral medications and to address the underlying causes of disease through genetic testing and gene therapy.

In order to bring these new treatments and devices to the market, pharmaceutical companies will formulate new drug molecules, undertake toxicology and stability testing on the elements of the product, conduct rigorous clinical patient trials, and undergo stringent regulatory reviews in numerous national markets. Timelines for completion of this process for each product will vary depending on the complexity of the product development, the length of regulatory review cycles, and reimbursement procedures. The TEAP HFC Task Force (October 1999) concluded that "there is likely to be an evolution of inhaled therapies away from propellant MDIs over the next 10-20 years to a broad range of alternatives giving patients many options."[11]

Patient Health Issues

Consideration of ways and means to limit HFC emissions from patient use of MDIs – an environmental policy objective – necessarily implicates important health policy issues. The realities of the medical decision-making process, the central role of the patient / physician relationship, existing health care policies and reimbursement schemes are important factors to consider, particularly when analysing measures that would promote switching patients to different therapy options.

Therapeutic decisions, including the choice of delivery system, are made by the prescribing physician and are based primarily on the individual circumstances of each patient. The optimal therapeutic option varies depending on a variety of factors, including a patient's symptoms, physiology and compliance patterns. Asthma and

[11] TEAP HFC Task Force Report at 43.

COPD are complex diseases with idiosyncratic underlying physiological processes that produce a range of symptoms in individual patients. In addition, each inhalation therapy is unique and has different advantages and limitations. A recent Dutch study emphasises that physicians should consider inhaler device characteristics, such as dose delivery, particle size distribution, dependence on inspiratory flow rate, and drug deposition, when prescribing medications to asthma and COPD patients.[12] The same study concluded that the current generation of DPIs is not appropriate for patients with insufficient inspiratory flow or in cases where conscious inhalation is not possible. In such circumstances, an MDI or nebuliser should be used.[13] It is also important to remember that while over twenty active drug substances are delivered via inhalation, each is not available in all three delivery systems.

Treatment decisions are also driven by existing health care reimbursement schemes, as well as by local prescribing practices and medical cultures. Cost of treatment is frequently an important factor in the decision-making process.[14] Health care funding is a complicated process that varies greatly between national governments. Cost issues should be carefully considered in the development of policies impacting national health care reimbursement systems, particularly those that would require increased governmental funding for drug reimbursement.

Addressing HFC Emissions from Manufacturing Losses

Unlike emissions from patient use, MDI companies have direct control over MDI manufacturing and production processes, and their associated emissions. IPAC companies are committed to implementing sound manufacturing practices and have undertaken a range of improvements over the years to minimise the leakage of propellants during manufacture. Examples of waste minimisation practices employed include: use of a vapour return hose; redesign of the delivery truck and canister processes; installation of systems to detect and prevent pump failure; and minimisation of mixing vessel waste material.[15]

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[12] Dekhuijzen, R. 2001. Inhalation Therapy in Asthma and COPD: Who, Where and How*? European Pharmaceutical Review*: 74-78.

[13] *Id.* at 77.

[14] *See* 2000 *Drug and Therapeutic Bulletin*: Inhaler Devices for Asthma: 9-14. (This article contains a chart analysing the costs of MDIs and DPIs and states that on grounds of cost and convenience, most of the study's consultants still recommend that in adults with the required coordinating skills, a pressurised MDI should usually be tried first for the delivery of bronchodilator therapy.) *See also* Brocklebank, D. 2001. Systemic review of clinical effectiveness of pressurised meter dose inhalers versus other hand held inhaler devices for delivery corticosteroids in asthma. *BMJ:* 896-900, 900 (concluding that "the cheapest inhaler device that patients can use adequately should be used as first line treatment.")

[15] Enviros March 2000 at 18.

In addition, a recent study identified the recovery of gas from "reject" MDIs as a cost-effective measure to reduce emissions.[16] "Reject" MDIs are full, unused aerosol cans that are rejected during the manufacturing process for failure to meet the stringent quality control requirements in place for MDIs. It is possible to recover the propellant from these cans so that it can be recycled or destroyed. If fully implemented, this measure could potentially result in a savings of 0.3 metric tonnes of CO_2 equivalent per year.

IV. RESEARCH AND CONSIDERATION OF HFC MDIS IN THE EUROPEAN UNION

Since IPAC's 1999 UNFCCC submission, an independent environmental consultant and a European Commission Working Group have reviewed potential emission reduction measures for the MDI sector within the European Union. This section provides an update on these efforts.

European Climate Change Programme

In June 2000, the European Commission launched the European Climate Change Programme (ECCP) to identify "the most environmentally and cost-effective measures" to enable the EU to meet its emission reduction target agreed under the Kyoto Protocol.[17] The ECCP was a consultative process engaging relevant stakeholders from national governments, industry and the environmental community, as well as relevant technical experts. Pursuant to the ECCP, a Working Group on Fluorinated Gases was created to develop the basis for an EU framework policy to limit emissions of HFCs, PFCs, and SF_6. The HFC MDI sector was reviewed during this process. The final report of the Working Group identifies several potential emission reduction opportunities, but notes that "high costs, the reality of lengthy research and development timelines, and the need to phase out CFC MDIs "make the MDI sector a difficult one to address."[18] The report recognises the relevant patient health care context, stating "under all circumstances consultation with all stakeholders, including health ministries, physicians and patients is needed to avoid possible risks to human health." The final report of the ECCP also emphasises that policies to limit fluorinated gases should not undermine the phase-out of ozone depleting substances. [19]

[16] Enviros March 2000 at 19-20. *See also* Final Report of European Climate Change Programme Working Group Industry Work Item Fluorinated Gases (June 2001) at 33.

[17] Final Report of the European Climate Change Programme (June 2001), Executive Summary. *Attachment 5.*

[18] Final Report of the European Climate Change Programme Working Group Industry Work Item Fluorinated Gases (June 2001) at 34. *Attachment 6.*

[19] Final Report of the European Climate Change Programme (June 2001) at 28.

Recent Study on HFC MDIs

In 2000, IPAC commissioned a health, economic, and environmental study on the MDI in Europe to review policy options for reducing HFC emissions associated with MDIs. Enviros March, a UK-based environmental consultant with significant experience on climate change policy issues, conducted the study. This study included an evaluation of the relevant environmental and health policy issues for the MDI sector, as well as a cost-effectiveness analysis.

Based on background research and interviews with propellant suppliers, health care professionals, patient representatives, and MDI manufacturers in seven European countries - France, Germany, Italy, Poland, the Netherlands, Sweden and the UK - the study found that: (i) completion of the CFC transition under the Montreal Protocol is critical, both to protect the ozone layer and to reduce emissions of GHGs; (ii) HFC emissions from MDIs represent an extremely small percentage of total GHG emissions; and (iii) the current opportunities to reduce MDI emissions are considerably more expensive than many of the opportunities available in other areas. As discussed in Section IV, the study did conclude that recovery of HFCs from reject MDIs during the manufacturing process provides a cost-effective reduction opportunity. The conclusions of the Enviros March study were presented to the ECCP Working Group on Fluorinated Gases. A copy of the full report is provided as *Attachment 7*.

V. POLICY CONCLUSIONS AND SUGGESTED APPROACHES

HFC MDIs represent an effective, reliable treatment option for millions of patients. These products are vitally important to the successful completion of the CFC transition under the Montreal Protocol. The phase-out of CFC MDIs will also benefit the climate and, therefore, it is critical to allow the CFC transition to progress substantially before considering more prescriptive measures, particularly those that would discourage the use of HFC MDIs. Such measures could undermine patient confidence in HFC MDIs, thereby prolonging the CFC transition.

In addition to the link between the Montreal and Kyoto Protocols, the relationship between environmental and health policies is critical when addressing the HFC MDI sector. Measures aimed at influencing therapeutic choice for patients should be reviewed carefully to ensure that they are both environmentally and cost effective, as well as rational from a health care perspective. Given the myriad of complex medical and public health issues involved, proposals to adopt measures to reduce patient use of MDIs should not be taken without in-depth consultation with health care providers, relevant health care authorities, drug registration agencies, and affected patient

populations. Regulations should not foreclose research and treatment options or impose significant burdens on health care systems.

The transition to CFC-free MDIs under the Montreal Protocol has demonstrated that switching patients to different medications for purely environmental reasons, rather than any therapeutic benefit, presents significant challenges. In addition to the lengthy timelines associated with research and development of CFC-free alternatives and the requisite regulatory review, the process of educating patients and physicians on the switch has proven to be a complex and slow-moving process. A similar transition from HFC MDIs is not recommended or warranted under the Kyoto Protocol. Initiating such a transition would be extremely expensive. As shown in the Enviros March report, when the costs and hurdles are balanced against the relatively minor emission reductions that could be realised from such action, it is clear that the CFC transition model does not represent an expedient, pragmatic policy option.

Nevertheless, it is important to keep in mind that several factors, such as increased market share of DPIs and introduction of new technologies, will likely contribute to decreased usage of HFC MDIs over the next decade (and beyond) even without regulatory measures. In addition, MDI companies can contribute positively to the Kyoto Protocol's objectives by instituting practical procedures to monitor and report HFC emissions, and where cost-effective and technically feasible, implementing measures to reduce losses during the manufacturing process, such as recovery of HFCs from reject MDIs.

APPENDIX

ATTACHMENTS
TO
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1 March 20002

Attachment 1	Report of the HFC and PFC Task Force of the Technology and Economic Assessment Panel, UNEP (October 1999).
Attachment 2	*Ensuring Patient Care, the Role of the HFC MDI*, 2nd Edition, International Pharmaceutical Aerosol Consortium (1999).
Attachment 3	Climate Change 2001: Mitigation, Appendix III, at A3.5.1 (*Medical Applications*), Intergovernmental Panel on Climate Change (2001) (*Excerpts).*
Attachment 4	Meeting Report of the Joint IPCC / TEAP Expert Meeting on Options for the Limitation of Emissions of HFCs and PFCs, Petten, The Netherlands (May 1999) (*Excerpt Section 1.1*).
Attachment 5	Final Report of the European Climate Change Programme (June 2001), Executive Summary.
Attachment 6	Final Report of the European Climate Change Programme Working Group Industry Work Item Fluorinated Gases (June 2001).
Attachment 7	Study on the Use of HFCs for Metered Dose Inhalers in the European Union, Enviros March (December 2000).