EUROPEAN COMMUNITY

STRATEGY FOR THE

PHASEOUT OF CFCs

IN

METERED DOSE INHALERS

A Communication from the European Commission to the Council and the European Parliament

CONTENTS

CHAPTER 1 INTRODUCTION

1.1 Decision IX/19 of the Parties to the Montreal Protocol requires Parties requesting essential use nominations for chlorofluorocarbons CFCs for metered-dose inhalers (MDIs) to present to the Ozone Secretariat an initial national or regional transition strategy if possible by 31 January 1998, and in any case by 31 January 1999. The European Community is a Party to the Montreal Protocol, and this document is its transition strategy prepared in accordance with decision IX/19 of the Parties. The European Community believes that a transition strategy is necessary to set out how the transition out of CFCs in MDIs is to be managed such that the CFCs can be phased out as quickly as possible without putting in jeopardy supplies of necessary medicines to patients in need.

1.2 The European Community, on behalf of the Member States, submits a joint request every year to the Parties for the continued use of CFCs to manufacture MDIs. Under Regulation (EC) 3093/94 on Substances that Deplete the Ozone Layer, the European Commission, with the assistance of a Management Committee of Member States, determines every year:

- the essential uses which shall be permitted in the Community
- the users who may take advantage of these essential uses
- the quantities of CFCs which may be used for essential uses

Given that the supply of CFCs for MDIs is managed on a Community-wide basis, the transition away from the use of CFCs should also be managed on a Community-wide basis. As far as possible, the approval and introduction of CFC-free products and the withdrawal of CFCs from the manufacture of MDIs should be coordinated across the Community. This will prevent any part of the Community remaining dependent on obsolete CFC-containing medicines long after the rest of the Community has moved over to the new CFC-free products.

1.3 This transition strategy draft has been prepared by the European Commission with the assistance of an ad hoc working group comprising representatives of the Community's pharmaceutical and ozone management committees, Member State Health Authorities, the European Federation of Pharmaceutical Industries' Associations (EFPIA), the International Pharmaceutical Aerosols Consortium (IPAC), the Standing Committee of European Doctors, the European Federation of Asthma and Allergy Associations (EFA), the European Chemical Industry Council (CEFIC) and other experts in the field. Detailed comments have also been received and incorporated from many organisations including representatives of Nurses, Pharmacists, Asthma Patients, Doctors, and the manufacturers of asthma medicines The European Commission is most grateful for the invaluable help and co-operation of these individuals and organisations in preparing this strategy.

CHAPTER 2 EXECUTIVE SUMMARY

2.1 This document is the European Community's transition strategy for the phaseout of CFCs in metered-dose inhalers (MDIs). It is to be submitted to the Parties to the Montreal Protocol in accordance with Decision IX/19. The purpose of the strategy is to describe how the phaseout of CFC-containing MDIs and their replacement by CFC-free MDIs is to be managed in the Community.

2.2 The phaseout of CFCs in MDIs is necessary because, under the Montreal Protocol on substances that deplete the ozone layer, the production and consumption of CFCs is now banned in the European Community and throughout the developed world. Developing countries have a grace period under which the production and consumption of CFCs may continue to meet their basic domestic needs. Developing countries will phase out these substances in 2010.

2.3 CFCs are still currently available in Europe for the manufacture of MDIs through the essential uses exemption. This permits the continued production and use of CFCs for agreed essential uses where technical and economically feasible alternatives are not available. The treatment of asthma and chronic obstructive pulmonary disease (COPD) by metered-dose inhalers containing CFCs has been acknowledged as an essential use by the Parties to the Montreal Protocol. Some 10,000 tonnes per year of CFCs are used worldwide to manufacture around 500 million MDIs.

2.4 Alternatives to CFC-containing MDIs are now becoming available throughout the European Community. Suitable alternatives include dry powder inhalers (DPIs) and MDIs with HFC instead of CFC propellant. Under the rules of the essential uses exemption, CFCs will no longer be authorised for products where acceptable alternatives are available. In some parts of the European Community, a majority of patients are already treated with DPIs rather than MDIs. Throughout the entire Community, CFC-free MDIs are now being introduced such that, by the year 2003, there should be no further need for CFC-containing MDIs in the Community.

2.5 Before CFC-free MDIs can be prescribed to patients, they need to receive marketing authorisation from the competent authorities. Such authorisation is only granted when the competent authority is satisfied that the proposed alternative product is safe and effective. Obtaining marketing authorisation for CFC-free MDIs across the entire European Community is currently a lengthy process, because each Member State conducts its own review and authorisation procedures. This strategy proposed a means whereby Member States, the Commission and the manufacturers can co-operate to streamline the approvals procedure. An efficient, streamlined procedure for approving CFC-free products across the Community is an important and necessary part of the strategy to phaseout CFCs in MDIs. Competent authorities should no longer give marketing authorisation for new CFC-containing inhalers.

2.6 While the early phaseout of CFCs is important, so too is the health of the millions of patients, including children and the elderly, who currently depend on their CFC inhaler. CFCs should only be withdrawn once these patients have access to a satisfactory alternative. This strategy confirms the commitment of the European Commission to safeguard supplies of necessary medicines and the health and safety of patients during the transition. This is to be done by ensuring that CFCs will only be withdrawn from particular CFC products or categories of product when a sufficient number of acceptable alternatives is available. The number of alternatives required before CFCs can be phased out varies from product to product and from category to category, depending on the extent and pattern of use.

2.7 The strategy recognises that there are differences between Member States regarding the CFC products prescribed, the balance between DPIs and MDIs, and the number of products which will require alternatives. Nevertheless, there are important similarities for some of the most widely-prescribed products, and it is likely that the transition out of CFC-MDIs will occur quickly across the entire Community once alternatives are available for the main types of inhaler. Where particular problems persist, small quantities of CFCs for specific MDI products may be authorised as part of the annual Commission decision in essential uses in the Community.

2.8 The European Community is a major exporter of CFC-containing MDIs to both developed and developing countries. These exports will need to continue even after the transition has been accomplished in the Community in order to ensure that patients, especially in developing countries, are not deprived of essential medicines. MDI manufacturers based in the European Community are expected to help promote the transition away from CFC-containing MDIs in their export markets. They should ensure that, wherever possible, patients relying on MDIs produced in Europe are given access to CFC-free inhalers and thereby benefit from the experience of transition in Europe.

2.9 Patients are at the centre of the transition and need to be fully aware of the issues involved. Most if not all patients will successfully switch from a CFC inhaler to a CFC-free inhaler given sufficient information, advice and help. Information needs to be coordinated to ensure that doctors, other health professionals and patients' associations provide accurate, coherent and useful information to patients before, during and after transition. Wherever possible, new patients should be started on CFC-free inhalers, and manufacturers should no longer develop and market new inhalers containing CFCs.

2.10 The Community's annual essential use nomination for CFCs to UNEP will be based on the best available forecasts of the future availability of alternatives - the so-called 'targets and timetables' approach. Through its decision on essential uses each year, the Commission will ensure that CFCs remain available for those products where they are still required, but are not authorised for products where acceptable alternatives are available. In this way, and with the co-operation and involvement of Member States, MDI manufacturers, patients and health professionals, the phaseout

of CFCs in MDIs in the European Community can take place quickly and smoothly while safeguarding the health and safety of patients.

CHAPTER 3 CFCs and MDIs

3.1 CFC-containing MDIs have proved to be a low-cost, effective and reliable means to treat respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). These medicines are important as the incidence of asthma in developed countries is around 5 - 8% of the population and increasing at an average rate of around 5% per year. On average throughout the European Community, some 80% of inhaled medicines are delivered by MDIs, with the rest delivered by dry powder inhalers (DPIs) and nebulisers. There are currently some 500 million MDIs used annually worldwide, resulting in the use and emission of around 10,000 tonnes CFCs per year. In general, CFC 12 is used as a propellant in the MDIs, and CFC 11 or CFC 114 is used to dissolve or suspend the drug being delivered to the patient.

3.2 CFCs released to the atmosphere eventually find their way up to the stratosphere where they destroy the ozone layer which protects the earth's surface from harmful ultra-violet radiation. During the last few years, the ozone layer has been severely depleted, both over the Antarctic region where the "ozone hole" now appears annually, but also over the northern hemisphere. Ozone depletion up to 40% has been recorded in each of the last three years over Northern Europe.

3.3 In order to prevent the destruction of the earth's ozone layer, the international community has agreed a Convention (the Vienna Convention, 1985) and a Protocol (the Montreal Protocol, 1987). The Montreal Protocol requires the progressive phaseout of the production and consumption of substances which destroy the ozone layer. It is therefore vital for those industries which use CFCs to find alternatives as quickly as possible.

3.4 Under the Montreal Protocol, the production and consumption of CFCs was phased out in developed countries from 1 January 1996. This phaseout occurred one year earlier in the European Community. However, under the Montreal Protocol, temporary exceptions to the phaseout can be made under the "essential uses" procedure. This procedure provides that a particular use of CFCs may be declared "essential" where:

a) it is necessary for the health, safety or is crucial for the functioning of society (encompassing cultural and intellectual aspects); and

b) there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health

Further, the production and consumption of CFCs for essential uses may be permitted only if:

a) all economically feasible steps have been taken to minimise the essential use and any associated emissions of the controlled substance; and

b) the controlled substance is not available in sufficient quantity and quality from existing stocks of banked or recycled controlled substances, also bearing in mind the developing countries' need for controlled substances.

(Decision IV/25 of the Parties to the Montreal Protocol)

3.5 The use of CFCs for the manufacture of MDIs has qualified for essential use status since the initial phaseout of CFCs. This is because the provision of asthma medication is clearly necessary to the health of society, and, at least until recently, no technically and economically feasible alternatives or substitutes to CFCs have been available. The following quantities of CFCs have been approved by the Parties for the manufacture of MDIs in the European Community:

Year of use	Tonnes of CFCs approved by the Parties
1996	7546
1997	6635
1998	5610
1999	5000

3.6 Since the phaseout of CFCs was first agreed, the international pharmaceutical industry has been researching into alternative substances to use in MDIs. The result is that some technically and economically feasible alternatives to CFCs now exist and are becoming increasingly available for the successful treatment of some types of asthma and COPD. The increased availability of clinically effective, technically and economically feasible alternatives will mean that, progressively, CFCs will no longer meet the essential use criteria under the Montreal Protocol and will therefore no longer be authorised for the manufacture of those types of MDI for which alternatives exist.

3.7 All the signatories to the Montreal Protocol, including all the Member States of the European Community, are committed to phasing out the production and consumption of ozone-depleting substances as quickly as possible. Part of this commitment includes minimising exemptions from the Protocol under the essential uses procedures. Therefore, the European Commission and Member States will be seeking early opportunities to reduce the quantities of CFCs approved for use in the manufacture of MDIs in the European Community. Equally, however, all those involved recognise an equally important obligation to ensure that asthma and COPD patients continue to receive the medicines they require. Therefore, the following principles have been agreed to guide the phase out of CFCs in MDIs:

Principle 1: That all those involved will promote the transition to non-CFC alternatives

Principle 2: That the health and safety of patients during the transition will be safeguarded

Principle 3: That the nomination, approvals and licensing systems will be operated with efficiency**,** consistency and transparency.

3.8 This draft strategy sets out a policy for the management of the transition out of CFC-containing inhalers based on these three principles. In particular, the strategy;

- reviews current and future demand for asthma and COPD therapy in the European Community
- summarises current progress in the development of alternatives to CFC inhalers, including forecasts of the rate of introduction of alternatives
- sets out a policy to facilitate the efficient and fast review and approval of non-CFC alternatives throughout the European Community as a whole
- sets out an approach to pharmacovigilance and safety monitoring of the new products to ensure that patient safety is maintained
- sets out a procedure by which CFCs can be progressively phased out as alternative medicines and treatments become available
- makes recommendations to raise the awareness of doctors and patients and to promote the rapid and successful acceptance of CFC-free medicines
- considers how to treat MDIs manufactured in the European Community for export, particularly to developing countries
- reviews the continued production and supply of CFCs in the EC during the transition

3.9 The European Community is the world's largest manufacturer of MDI inhalers, 25% of which are exported. This means that we have a particular responsibility to develop and promote environmentally safe inhalers while, at the same time, meeting the needs of patients throughout the world who depend on our products. This strategy puts forward a means through which both these responsibilities can be met, and the transition away from CFCs be successfully managed across all the Member States of the European Community.

CHAPTER 4 ***PATIENT NEEDS***

4.1 The prevalence of asthma and chronic obstructive pulmonary disease (COPD) is increasing world-wide. There are at least 25 million people with asthma in Europe. The prevalence of asthma has risen over the last 20 years, especially amongst children where it now approaches 15% in Western Europe. Asthma has enormous health and economic costs and is probably responsible for 16000 deaths per year in Europe. The incidence of COPD is related to tobacco smoking, and affects 20-30 million adults in Europe. Whilst levels are relatively static in men, they are rising in females following the increase in smoking in European women. It is estimated that COPD accounts for over 5% of all deaths in Europe.

4.2 It is likely that the prevalence and diagnosis of asthma and COPD will continue growing in the EC over the next decade. In addition, there is considerable potential for increased prescription of inhaled therapy for both conditions in a number of Member States as international treatment guidelines are implemented more widely than at present. For these reasons, IPAC has forecast that annual usage of MDIs in the European Community may increase by 5% per year between now and 2010. This growth rate assumes that there will be increased usage of DPIs and other new types of non-MDI inhaler, as well as a potential increase in the use of newer oral therapies for some patients.

4.3 There is international (WHO/GINA) consensus that the primary treatment of these diseases should be by the inhaled route. This permits treatment to be delivered quickly and efficiently to the airways, with minimal risk of adverse reactions. Therapy necessitates regular treatment, often with more than one medicine. Inhaled therapy is delivered mainly by Metered-dose inhalers (MDIs) or Dry Powder Inhalers (DPIs) and less commonly by nebulisers.

Categories of drugs used for asthma/COPD

4.4 It is possible to recognise the following categories of drugs currently used for the treatment of asthma/COPD:

Category A: Short acting beta agonist bronchodilators, such as salbutamol, terbutaline, fenoterol

Category B: Inhaled Steroids, such as beclomethasone, budesonide, fluticasone,

Category C: Non Steroidal anti-inflammatories, such as cromoglycate, nedocromil

Category D: Anticholinergic bronchodilators, such as ipratropium, oxytropium

Category E: Long acting beta agonists bronchodilators; salmeterol, formoterol

Category F: Combination products containing two or more different active substances

4.5 It is important to realise that categories A and B combined account for approximately 80% of CFC MDIs currently used in Europe. For these categories A and B, there are several different active substances and alternative brands available for

the most widely prescribed products**,** but in other categories there may be no more than one or two brands or products which require substitution by a non-CFC product

MDIs

4.6 The predominant form of inhaled therapy in most of Europe is the MDI which accounts for approximately 80% of prescribed inhalers. The remaining 20% are mainly DPIs, together with a much smaller proportion of nebulised drugs. However in some countries, especially Scandinavia and the Netherlands**,** there is far greater use of DPIs (up to 85%). MDIs are an inexpensive, reliable and effective therapy for respiratory diseases. Currently, some 500 million MDIs are used annually world-wide, mainly in developed countries. Of these approximately 200 million are made in Europe requiring during 1997 the use of some 6635 tonnes of CFCs

4.7 CFC-containing MDIs have a forty year record of safety and efficacy. They are designed to deliver drugs in an appropriate particle size to target the lung airways. Reproducing the particle size in reliable, safe and effective MDIs without CFCs has proved to be a tough technical challenge.

Alternatives to MDIs

4.8 Dry Powder Inhalers (DPIs): Although the European market for inhaled therapy is traditionally dominated by MDIs, almost all active substances are also available in DPI formulations. The impending ban on CFCs in the 1980's led to considerable innovation in DPI technology and, in particular, to the transition from single-dose DPIs to multidose systems. These new-generation multidose DPIs can, like MDIs, deliver up to 200 doses. Multidose DPIs are now quite widely available (as Turbuhaler, Easyhaler and Accuhaler, for example), and can in many respects be considered equivalent to MDIs**.**

4.9 As a result of developments such as these, DPI use has increased, but since the overall use of inhaled therapy has increased further, the greater use of DPIs has not reduced the sales of MDIs. Penetration of DPIs into a market depends on their acceptance by health professionals and patients and also on their cost. In some countries, especially Scandinavian countries where action has been taken by governments to support the transition from MDIs to DPIs, the DPIs dominate the market. In other countries, DPIs can often be considerably more expensive than cheaper generic MDIs. A complete change from MDIs to DPIs in such countries would increase the costs of inhaled medicines. New DPIs are likely to be introduced over the next few years which may be cheaper and will increase patient choice. DPIs may become an increasingly appropriate and accepted alternative for MDIs, especially for new patients, although they are not suitable for all patients (for example some very young children may experience difficulties). Nevertheless, the wide range of available DPIs provides a safety back-up during transition to CFC-free MDIs and provides additional options for patients.

4.10 As far as DPIs are concerned, products are already available in each category such as the following:

Category A: Salbutamol (Diskhaler™, Diskus™, Rotahaler™, Easyhaler™); terbutaline (Turbuhaler™)

Category B: Beclomethasone (Rotahaler, Diskhaler, Easyhaler);budesonide (Turbuhaler); fluticasone (Diskhaler)

Category C: Cromoglycate (Spinhaler)

Category D: Ipratropium(Aerohaler)

Category E: Salmeterol(Diskhaler, Diskus, formoterol(Turbuhaler, Aerolizer)

This suggests that, subject to greater acceptance by doctors and patients, and given sufficient manufacturing capacity**,** there may be scope for an increase in the numbers of patients treated by DPIs rather than by MDIs. This of itself would contribute to reducing the current use of CFCs in the treatment of asthma and COPD.

4.11 Nebulisers: These devices produce aerosols by agitation of solutions, and account for 1-2% of the market. They are generally reserved for patients with special needs, such as very young babies or patients with severe disease, who need much higher doses of active substance. They are currently an expensive form of inhaled therapy, but new devices may make this a more viable option in the future.

4.12 New Oral Therapy A novel tablet (leukotriene modifier) for the treatment of asthma is currently under regulatory review in Europe. This type of oral therapy may be of value to some asthma patients, but is highly unlikely to become a significant substitute for the current inhaled preventative therapy. The mainstay of therapy for asthma/COPD is likely to remain that administered by the inhaled route.

MDIs Reformulated Without CFCs

4.13 As a result of a major research and development effort, pharmaceutical companies have made good progress in developing CFC-free MDIs. In March 1995, Europe's first approval for a CFC-free MDI was granted to 3M in the UK for its product 'Airomir', a salbutamol product reformulated with HFC-134a propellant. By September 1997, this product had been approved for use in over 40 countries and in nearly all the Member States of the European Community Glaxo Wellcome has recently launched CFC-free versions of 'Ventolin' (salbutamol) and the first reformulated inhaled steroid 'Flixotide' (fluticasone) in some Member States. Other companies have also submitted applications to market CFC-free inhalers, and further approvals are anticipated during 1998 and beyond. It is therefore expected that, during the course of 1998**,** two salbutamol CFC-free MDIs will be become available in a number of countries, including a number of EC Member States.

4.14 IPAC (International Pharmaceutical Aerosols Consortium) predicted in January 1997 that, in Europe, between 36 and 42 HFC MDI 'entities' (individual dosage formulations of individual brands) would be reformulated and launched by the year 2000. It is anticipated that at least two salbutamol CFC-free MDIs could be available throughout the EC by the end of 1998. Since salbutamol MDIs are estimated to comprise half the total use of MDIs, the potential exists for a significant reduction in consumption of CFCs in 1999. This is dependent on regulatory and pricing approval, good acceptance and uptake by patients and physicians, and the consequent timely phaseout of CFC inhalers. In addition, two or more CFC-free inhaled steroids should be available in some Member States by 1998. Reformulation efforts for most of the remaining inhaled medications are well advanced, using the propellants HFC-134a and HFC-227. Alternative technologies such as portable hand-held nebulisers are also being evaluated.

Experience to date

4.15 Almost two years after the introduction of the first CFC-free salbutamol MDI into the European Community, it had only reached 1.5% market share. Factors influencing the slow uptake of this CFC-free product might include lack of incremental benefit to patients, apathy of physicians to environmental benefits, continued easy availability of CFC-products and higher cost than unbranded CFC salbutamol products. Experience in Germany with a second CFC-free salbutamol product is more encouraging. Three months after the launch it has achieved considerable success, but to maintain the growth in uptake, the manufacturer intends voluntarily to withdraw the CFC version. However, it is unlikely that voluntary action by manufacturers and education programmes alone will produce a significant switch away from CFC products in the absence of a clearly defined and properly implemented transition policy. This needs to be accompanied by a clear message to physicians and other health professionals that the transition is not optional. Where a CFC-free alternative is available and suitable, it should be prescribed in favour of the CFC product unless this would compromise patient treatment.

Considerations in devising a transition strategy

4.16 A number of factors have been considered when developing a European transition strategy. In particular, before the use of CFCs can be phased out in the manufacture of MDIs:

- A sufficient number of clinically effective, technically and economically feasible alternatives (including DPIs) needs to be available to ensure an uninterrupted supply of medication.

- A sufficient period of post marketing surveillance of the reformulated products has to be carried out

- There needs to be sufficient choice of alternatives available to meet the needs of different patient sub-groups

Chapter 5 DEVELOPING ALTERNATIVES TO CFC-CONTAINING MDIs

Current treatment by inhalation: MDIs, DPIs and nebulisers

5.1 The three main types of inhaled treatment for respiratory disease include MDIs, DPIs and nebulisers. Each type presents certain advantages and disadvantages. Efforts are being made to overcome disadvantages, for example by improving powder delivery in DPIs to facilitate their use by small children and the elderly. However, nebulisers and DPIs are not interchangeable with MDIs for all patients. It is vital to develop CFC-free MDIs with the same advantages for patients as the current CFC-containing MDIs but without the disadvantage of depleting the ozone layer.

Developing non-CFC MDIs

5.2 The pharmaceutical industry has put significant resources into researching and developing CFC-free MDIs. More than 70 separate programmes, involving 1,400 scientists and 90 laboratories in 10 countries around the world, have been involved in reformulating MDIs with alternative propellants. Investment to date in this task by the pharmaceutical industry worldwide exceeds 1 billion ECUs.

5.3 The first step in this research was to identify propellants which could be substitutes for CFCs. The principal criteria for successful MDI propellants are the following:

- a liquefied gas of very low toxicity, non-flammable and chemically stable
- acceptable to patients in terms of taste and smell
- possessing appropriate solvent characteristics and a suitable density.

Other considerations include sufficient commercial availability of the proposed propellant, whether it can be made sufficiently pure for pharmaceutical use, and its continued future availability in quantities sufficient to meet patient needs. It has been extremely difficult to identify a single compound which meets all of these criteria.

5.4 After extensive research,[1] HFC 134a and HFC 227 have been identified as the only real alternatives to CFCs for MDI use. They are non-flammable, safe for human inhalation and have the required vapour pressure and density for MDI usage. HFCs have zero ozone-depleting potential, but both HFC 134a and HFC 227 are greenhouse gases and part of the basket of gases whose emissions must be reduced under the Kyoto Climate Change Protocol. However, both these HFCs have a lower global warming potential (GWP) than the CFCs which they replace. For example, HFC 134a, the most frequently chosen replacement propellant, has a GWP of 1300,

[1] Studies have been carried out to determine whether any compounds other than HFCs could be substituted for CFCs in MDI usage. Some 15,000 compounds have been reviewed in light of the various criteria set out above but none of them, with the exception of HFCs, appears to be a promising CFC substitute.

compared with CFC 12 which has a GWP of 8500. Note that, as a point of reference, the GWP of CO_2 is 1. Therefore, a change from CFCs to HFCs as propellants in MDIs will contribute to reducing both ozone depletion and greenhouse gas emissions in the future. Nevertheless, there remains scope to continue research into products which have even less environmental impact.

5.5 Once identified as possible CFC substitutes on the basis of their chemical characteristics, HFCs were subjected to extensive research and testing. In January 1989, the pharmaceutical industry set up its own consortium (ultimately known as IPAC), and began toxicology testing of propellants for pharmaceutical usage. These testing programmes, designed to meet world-wide regulatory requirements, including those of the US, the EC and Japan, were substantially completed by the end of 1995, and concluded that both HFC-134a and HFC-227 were safe for use in MDIs. The Committee on Proprietary Medicinal Products (CPMP) of the European Community assessed both propellants as suitable alternatives for CFCs (in July 1994 for HFC-134a and in September 1995 for HFC-227), subject to completion of additional safety studies on the medicinal products concerned.

5.6 Having identified HFCs as the best alternative to CFCs and shown that they have no adverse toxicological effects, the second step was for the pharmaceutical industry to reformulate their MDIs using these propellants. In the EC, the European Commission has published guidelines on the replacement of CFCs in medicinal products[2]. These identify the questions of product efficacy, safety and quality which must be taken into account by companies when they prepare submissions for marketing authorisation of products containing alternative propellants. A guideline on **post-**marketing surveillance has also been prepared (CPMP/180/95).

5.7 The reformulation effort has involved several steps in order to fulfill the regulatory guidelines and create replacement products which are comparable in all respects to the existing ones. First, there is intensive research and testing to identify and develop new formulations of the active anti-asthmatic drugs with the new HFC propellants. Such formulations have to meet rigorous quality criteria, for example, with respect to accurate dose reproducibility throughout the life of an MDI, and maintenance of a consistent particle size distribution in the spray. Next, the components of the primary packaging (metal cans, valves, elastomers and actuators) have to be redeveloped to be compatible with the new propellant and formulation. Toxicological studies are carried out on the final formulation (which possibly contains new inactive ingredients) before, or in parallel with, stability testing of the new MDI. The latter is undertaken to ensure that quality is maintained over the entire shelf-life of the new product. Finally, clinical studies are carried out on the new product, over a treatment period of up to one year, to demonstrate that it is as safe and effective as the CFC product.

---

[2] Note for Guidance Replacement of Chlorofluorocarbons (CFCs) in metered-dose inhalation products (III/5378/93 - final). CPMP Cover note - Matters relating to the

Difficulties encountered in reformulating MDIs

5.8 The reformulation of CFC MDIs has proved to be much more technically difficult than originally envisaged. In addition to the complexity of identifying and testing alternative propellants, the pharmaceutical industry has encountered a number of other challenges in its reformulation efforts. For example, the usual surfactants used in CFC MDIs are generally not compatible with HFCs. New surfactants, lubricating agents and co-solvents had to be identified. Some valve elastomers are affected by HFCs and do not function with sufficient reliability so new elastomers had to be developed. In some cases actuators had to be redesigned together with the manufacturing process to accommodate the more volatile HFC propellants, sometimes involving building new manufacturing facilities and finding new manufacturers of components.

5.9 It is only after reformulation and clinical testing have been successfully completed that the regulatory review phase can begin, encompassing pharmaceutical safety and efficiency assessments of the data submitted by companies against the guidelines described earlier. A new marketing authorisation would be required from the appropriate regulatory authorities, where the MDI is fundamentally altered by the change in propellant and modifications to the formulation and manufacturing process. Where the change is not fundamental; a national variation procedure may be used. Efforts are ongoing to enable CFC-free MDIs to be approved as rapidly as possible by all the Member States of the EC (see Chapter 6). Regulatory authorities must also review pricing and reimbursement of CFC-free MDIs, as price differentials can significantly influence acceptance by patients and prescribers.

Prioritizing reformulation efforts

5.10 Although the decision to reformulate a specific MDI product is taken by each individual pharmaceutical company in respect of each of its CFC MDIs, the priorities are common throughout the industry. In general, each company has focused its reformulation efforts on the MDI products which are the most commonly prescribed and which use the most CFCs. Products which are used less frequently are the second priority, even though these MDIs may be important for certain patient sub-groups.

5.11 In addition to the above considerations, the pharmaceutical industry is limited by the technical feasibility of reformulating MDIs. Particular molecules and/or dosage strengths may be more difficult than others to reformulate. Failure to satisfy product quality criteria fully could necessitate multiple attempts at reformulation and testing. Important products which are given a high priority could therefore still take time to come through the development pipeline.

Strategy/risk analysis for products which are not reformulated

5.12 Some products may not be reformulated for economic reasons while others may ultimately prove impossible to reformulate for technical reasons. It is important

to note that Decision VIII/10 of the Parties to the Montreal Protocol requires that companies applying for continued essential use of CFCs for MDIs should "demonstrate ongoing research and development of alternatives with all due diligence and/or collaborate with other companies in such efforts." Therefore, CFCs will not continue to be available to MDI companies which are not actively engaged in developing and marketing CFC-free alternatives**.** After the bulk of the transition to non-CFC MDIs is accomplished, the Commission and Member States will need to assess whether any remaining CFC-containing inhalers are still essential, for example because there is no other way to meet the medical requirements of particular patients. Where they are not essential, physicians and patients will have to switch to an alternative treatment within a reasonable time-frame. Where they are essential, a mechanism for continuing but temporary supply will need to be found. Note that there can be no long-term dependency on CFCs as both the propellant and the products will progressively disappear from the market**.**

Naming, packaging and identifying the alternatives

5.13 Decision VIII/10 (3) of the Parties to the Montreal Protocol states that the CFC and non-CFC products must be differentiated in terms of packaging and marketing. To ensure a smooth transition from CFC-containing MDIs to CFC-free MDIs and for maximum transparency, it has been agreed that CFC-free products will be differentiated from CFC-containing ones. This should be done by changing the brand name or by adding a logo or "flash" to the existing packaging to indicate clearly that the product is CFC-free. CFC-free products should also include a leaflet to explain about the new propellant and the reasons for change**.** This differentiation is vital to post-marketing safety monitoring so that any reported adverse effects can correctly be attributed to the type of product concerned.

5.14 Directive 92/27/EEC sets out the normal procedure whereby the proposed labeling for medicinal products is submitted to the appropriate regulatory authorities with the application for marketing authorisation. Pharmaceutical companies will decide whether they wish to retain the existing brand name and adapt its existing labeling, including the addition of the term "CFC-free" o*r* to introduce a completely new brand name for the non-CFC MDI. These provisions should ensure that CFC-free MDIs are appropriately and adequately differentiated from CFC-containing MDIs. It would also be useful for the name and characteristics of the propellant used to be written on the container**.**

Forecasts of future availability of alternatives

5.15 It is difficult to forecast with any certainty the dates by which CFC-free versions of particular products will be available on the Community market. At the beginning of 1996, IPAC forecast that there would be between 36 and 42 HFC MDIs launched on the European market by the year 2000. However, that forecast has since been revised downwards in light of technical problems some companies have encountered with reformulations and unanticipated delays in the granting of market authorisations. To try to obtain some more recent information, the Commission

recently asked MDI manufacturers in the Community to forecast when they planned to submit applications for marketing authorisation for CFC-free versions of their current CFC inhalers. The results indicate that, by the year 2000 we can expect companies to have submitted applications for marketing authorisation for CFC-free versions of over 30 different MDI products. This does not include different strengths or dosage versions of the same active substance.

A Summary of planned dates reported by companies for filing of marketing authorisation in the European Community for selected active substances is shown below. Not all the details can be given for reasons of commercial confidentiality.

Active Substance	**First mentioned filing date**	**Last mentioned filing date**	**When product is likely to lose essential use status***
Salbutamol	1994	2001	1998-1999
Terbutaline	2000	2004	2001-2002
Fenoterol	1998	2002	1999-2000
Beclomethasone	1996	2002	1999-2000
Budesonide	2000	2002	2001-2002
Cromoglicic Acid	1998	1999	1999-2000
Ipratropium Bromide	1999	2000	2000-2001

* period during which CFCs for a particular product are likely to lose their essential use status in some or all of the Member States under the provisions of this strategy if the granting of marketing authorisations for the CFC-free alternatives is not unduly delayed.

5.16 The survey indicates that some companies are expecting to file applications after a CFC product is likely to have lost its essential use status. For example, Salbutamol is likely to be available throughout the Community in CFC-free versions by the year 2000. CFCs for the manufacture of salbutamol would not then meet the essential uses criteria in 2000 and none would be approved. This may pose problems for the few companies which expect to submit their application for marketing authorisation of the CFC-free alternative in 2001.

5.17 It should be emphasised that even with questionnaire surveys like this, it is not possible to predict with any certainty how quickly the alternatives will become available and therefore how quickly the demand for CFCs will fall. Much depends on how quickly and efficiently Member States grant marketing authorisation for the alternatives. When taking decisions on quantities of CFCs to approve, it will remain a priority to ensure that patients continue to have access to the medicines they need..

CHAPTER 6 APPROVAL OF NEW PRODUCTS and POST-AUTHORISATION SURVEILLANCE

6.1 At their November 1996 meeting in Costa Rica, the Parties to the Montreal Protocol agreed *"to request national authorities to expedite review of marketing/licensing/pricing applications of CFC-free treatments of asthma and COPD, provided that such expedited review does not compromise patient health and safety"* (Decision VIII/11). A clear statement of how this decision is to be implemented in the EC is an important part of this phaseout strategy. In particular, the strategy identifies marketing authorisation procedures which will ensure the earliest possible introduction of CFC-free MDIs. The availability of CFC-free products to patients in the EC should not be delayed by slow, repetitive procedures for obtaining marketing and pricing authorisation independently in each Member State of the Community.

Co-operation between Member States

6.2 Recognising the large number of CFC-free products which may be submitted to Regulatory Authorities over a relatively short time period, it is in the general interest of Member States to co-operate and share the workload of review. Procedures for reviewing replacements for existing CFC products and approving new CFC-free products should include at least the following elements:

- that companies should submit applications across the whole of the Community simultaneously
- that competent authorities should co-operate in sharing out the work and its results
- that CFC-free products should be authorised for use without delays and, as far as possible, simultaneously across the Member States**.**

In addition, Member States should ensure that their procedures for agreeing pricing and reimbursement do not cause unnecessary delays to the availability of CFC-free medical inhalers on the European market. Decision VIII/11 of the Parties to the Montreal Protocol requests national authorities "*to review the terms for public MDI procurement and reimbursement so that purchasing policies do not discriminate against non-CFC alternatives*". Manufacturers of alternatives can assist this process by pricing their CFC-free products at similar levels to the CFC products they are intended to replace.

6.3 Although it is important to ensure that CFC-free products are brought to market quickly, this should not compromise patient safety. The prime objective of the review and approval procedures is to ensure that products submitted for approval meet all the necessary standards of quality, safety and efficacy.

6.4 There is a number of possible routes to obtain marketing authorisation in the European Community for CFC-free MDIs. Further details are shown on Figure 1.

- **A referral under Article 12 of Council Directive 75/319/EEC:** this is the preferred route in order to gain access to the entire Community market. The Commission considers the rapid and safe replacement of CFCs in MDIs to be a matter of Community interest. Therefore, if other procedures fail to operate successfully, the Commission reserves the right to use the Article 12 referral mechanism as a means to expedite the evaluation of marketing authorisations for reformulated CFC-free MDIs.

- **a Centralised Procedure, as set out in Council Regulation (EEC) No. 2309/93:** this includes submission of the application to the EMEA (European Medicines Evaluation Agency), scientific evaluation and opinion by the CPMP (Committee of Proprietary Medicinal Products), and a Commission Decision granting a marketing authorisation valid for the entire Community market. CFC-free MDIs containing new active substances are eligible for evaluation under this centralised procedure only if they comply with part A or part B of the annex to the Regulation.

- a **Mutual Recognition Procedure**: this involves submissions to all Member States which need to place the CFC-free MDI on their market. One Member State prepares a scientific evaluation and grants marketing authorisation for its own territory. The other Member States recognise the decision and grant their own national marketing authorisation.

- **an ad-hoc co-operation mechanism agreed between the Commission and Member States:** this will enable a series of national marketing authorisations to be granted quickly by promoting the mutual sharing of information and work among Member States.

6.5 From 1 January 1998, the mutual recognition procedure applies for new applications for the same medicinal product in more than one Member State. For "stand-alone" applications (i.e. those made in accordance with Articles 4.8 or 4.8 (a) ii of Council Directive 65/65/EEC as amended), the mutual recognition procedure is mandatory. Even when a company does not request mutual recognition, Member States will recognise decisions of other Member States for the same medicinal product where the same application is submitted in all concerned Member States.

6.6 Where the ad hoc co-operation mechanism is used, two situations can apply;

a) where the company wishes to use a different brand name or to introduce a second product which is CFC-free. Under these circumstances, an abridged application (cf Article 4.8 (a) (i) of Directive 65/65/EEC) should be submitted.

b) where the company wishes to retain the same brand name with the addition of a flash "CFC-free". Under these circumstances, a submission in the form of a national variation, should be submitted.

Note that if reformulation results in changes to the content per actuation or dosing schedule or includes a quantitative change in the active substance or a change in bioavailability, then the application could not be classified as a variation but should be submitted as an abridged application. (cf Annex II of Commission Regulation on Variations to the terms of a marketing authorisation, (EC) No. 541/95)

6.7 Whether or not the submission is made as an abridged application (a) or national variation (b), the agreed procedures are very similar.

The applicant:

a) - provides a list of the Member States in which the same abridged application or variation has been submitted or will be submitted in parallel and, in the latter case, the dates at which the applications are planned to be submitted. Note that companies should simultaneously submit the information to all the Member States where authorisation is going to be required.

b) includes a commitment that he has submitted or will submit exactly the same data package to each Member State

c) provides copies of the current and proposed new labelling to allow review of the information to be provided on the replacement and to ensure that patients will receive sufficient detailed information

d) provides a draft Summaries of Product Characteristics (SPC) of the CFC-free product consistent with SPC of the CFC-containing product it is intended to replace, including all relevant details of the replacement so that health professionals will receive complete information.

The Member States:

a) One Member State prepares an assessment report on the abridged application or the variation

b) as soon as the assessment is completed, the Member State circulates the assessment report to other Member States listed in the applicant's dossier.

c) based on their own assessment or assessment report(s) circulated by other Member States, will grant the authorisation or variation and issue the marketing authorisation within a period of 180 days**.** To expedite this process, all usual forms of contact between Member States will have to be used, including phone calls, ancillary information requests on the assessment report, answers to requests etc

d) inform other Member States of the date at which the variation to the terms of the marketing authorisation has been granted.

e) prepare a schedule for substituting the CFC-containing product by the CFC-free product. This substitution process should not exceed twelve months, which allows adequate time for post-marketing surveillance of the CFC-free product.

f) keep the Commission and the EMEA informed by sending details on the approvals granted, active substance by active substance, and on the progress of substituting CFC-containing products by CFC-free products in their territories.

The European Commission

For both abridged applications and national variations, to facilitate the centralisation of data for the Community as a whole, the Commission requests the EMEA to keep an up to date list of the submissions received and approved for each active substance in each Member State; and the rate of progress of substituting CFC-containing products by CFC-free products in each Member State.

Post Authorisation surveillance and safety studies

6.8 The legal framework for pharmacovigilance of medicinal products for human use in the Community is given in Council Directive 75/319/EEC. Detailed guidelines on pharmacovigilance are included in Volume 9 of the Rules governing medicinal products for human use in the European Community.

Safety Issues relating to new products

6.9 When products are marketed, their use may include patient groups which differ in various respects from those represented in clinical trials performed prior to issuing or varying of a MA. How products are prescribed and how patients use them will also differ from the clinical trial situation. Clinical trials designed to demonstrate efficacy of the new products for authorisation are frequently not large enough to detect rare side effects. For these reasons intensive post-authorisation surveillance is critical in confirming the safety of new CFC-free products.

6.10 Safety issues possibly relevant to the introduction of CFC-free products include paradoxical bronchospasm and rare adverse effects from the new excipients. New formulations may result in altered lung deposition and hence bioavailability. For this reason the occurrence of significant systemic adverse reactions to the reformulated products may differ considerably from the equivalent CFC- containing product. In addition, changing from CFC-containing to CFC-free products could result in short-term deterioration in disease control for some patients. Long-term use of CFC-free inhaler devices will occur following marketing, and their performance will need to be established.

6.11 Intensive post-authorisation surveillance will be needed, with regulatory authorities and MA holders working in close partnership. Doctors and pharmacists can also play a useful role in evaluating the success and safety of CFC-free inhalers as their use increases.

Phase Out Time Of CFC- Containing Products

6.12 CFC-containing products should be phased out quickly, so the time that a CFC-free product and it's equivalent CFC-containing product will be available concurrently is limited. Sufficient time needs to be available for data collection. It has been agreed that, normally, the CFC product could remain available in the market for up to twelve months following launchof the replacement product. During that time, MA holders and pharmacies will run down stocks of the CFC product as take up of the replacement product increases. Any safety issues with the CFC-free products will need to be rapidly identified, evaluated and acted on so that they are resolved before the equivalent CFC-containing product is finally withdrawn. MA holders should prepare plans so that, if important safety concerns arise relating to their CFC-free product, they will be able to supply patients with an equivalent CFC- containing product.

Spontaneous Adverse Drug Reaction Reporting

6.13 The requirements for MA holders to report spontaneous adverse drug reactions are set out in Directive 75/319/EEC. No change in these requirements is necessary for CFC-free products.

Post-Authorisation Studies

6.14 A guideline for post-marketing surveillance of new CFC-free inhalers has been prepared[3]. MA holders are encouraged to perform large safety studies of CFC-free products. These studies will usually include comparisons of CFC-free and CFC-containing inhalers following a randomised clinical trial, or observational cohort design. The use of single-dose studies should also be considered. The trials should be set up in such a way that it is clear that the patients who complete them are representative of the whole patient population, including children and the elderly. The study design may encompass an assessment of the changeover from the original CFC-containing product to the CFC-free product.

6.15 Adverse event and haematological and biochemical monitoring should be undertaken in all safety studies, together with specific assessments, pertinent to the drug substance, to look for local and systemic effects which might not necessarily be recorded as, or manifest themselves as, adverse events (e.g. adrenal suppression with inhaled corticosteroids).

[3] EEC/100/95

6.16 MA holders will submit proposals to the regulatory authority to monitor the introduction of the CFC-free products in order to identify rare and unexpected adverse effects. A method such as the use of record linkage schemes should be considered, as this could provide a means for monitoring the CFC-free products against historical data relating to the products using CFC propellants. Careful observation of patients and a specific assessment of cough, wheezing and bronchospasm on first administration of the product, paying particular attention to the time to onset of any effect, would be useful. Specific questioning and assessment of paradoxical bronchospasm would be appropriate in single-dose studies and after the first dose of each limb in crossover studies.

Liaison with regulatory authorities

6.17 Companies proposing to perform a post-authorisation safety study are advised to discuss the draft protocol with the relevant regulatory authorities when the application for a MA or variation is made. Particular consideration should be given to specific safety issues which may require investigation. National legislative requirements or guidelines should be taken into account in those Member States where these exist.

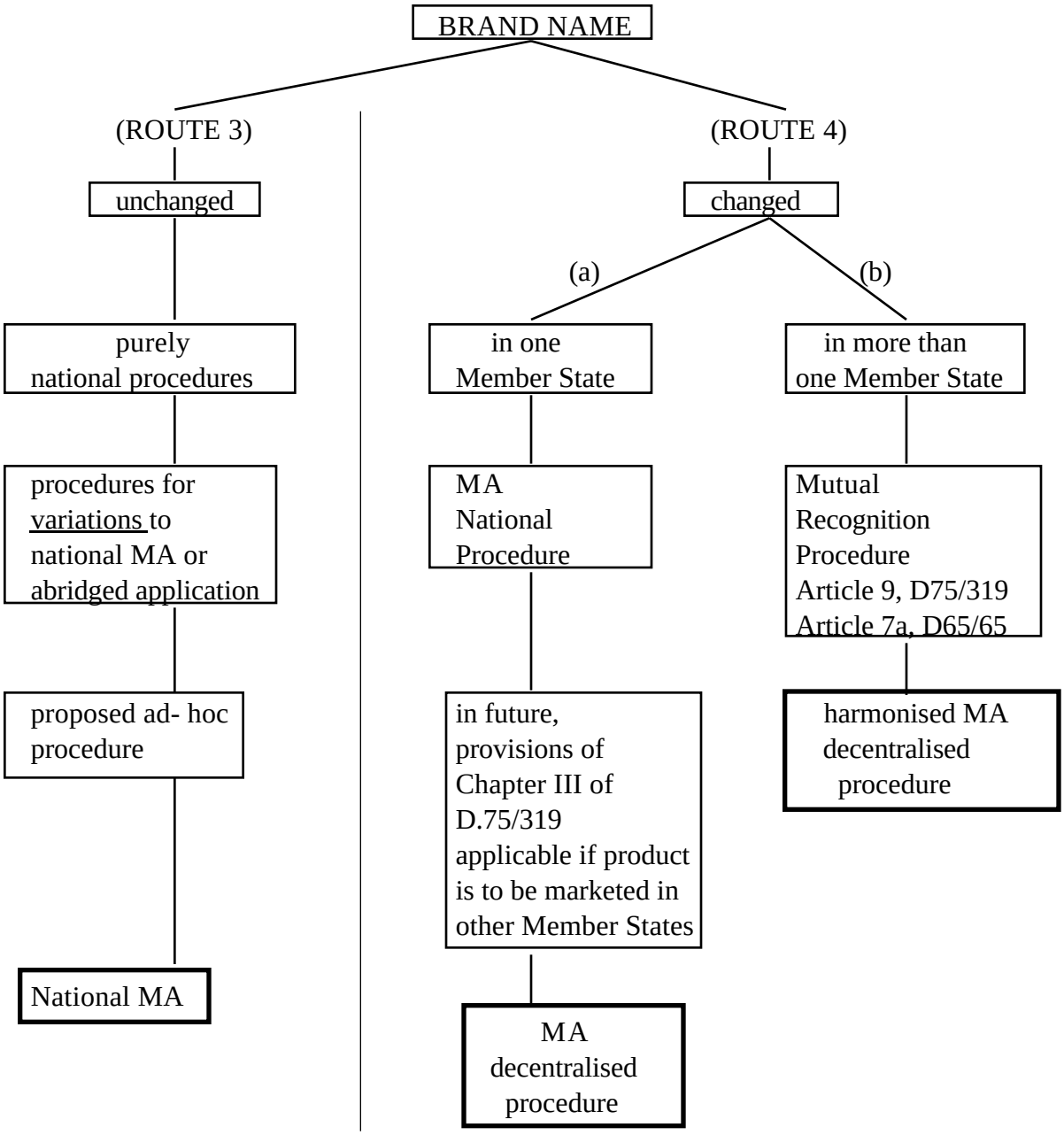
6.18 A final report on the study should be sent to the relevant regulatory authorities within 1 month of follow-up being completed. Ideally this should be a full report but a preliminary report within 1 month, followed by a full report within 3 months of completion of the study would normally be acceptable. The findings of the study should be submitted for publication.

Figure 1: POSSIBLE ROUTES TO APPROVAL

Route 1: Referral under Article 12 of Council Directive 75/319 (EEC)

Route 2: Referral under the centralised procedure of Council Regulation No. (EEC) 2039/93

Either Route 3 or Route 4 depending on whether or not the brand name changes



In practice, the approval procedures in route 4a and 4b rely on the initial dossiers (pseudo-abridged application) with two conditions: a) all the initial dossiers have to be identical and updated b) initial dossier to be completed, where necessary, with

additional information including (Council Directive No 75/318(EEC)) parts II and/or III and/or IV (in particular biodisponibility.)

CHAPTER 7 PHASING OUT CFCs

Possible approaches to the CFC phaseout

7.1 The essential use exemption for CFCs in MDIs cannot continue indefinitely. As alternative propellants become available, together with alternative methods of treating asthma and COPD, CFCs will progressively be withdrawn. Based on the expected rate of development and timely approval of alternatives, it is likely that many metered dose inhalers used in the European Community will be CFC-free by 2000.

7.2 During this transition period it is vital that patients continue to have access to the medicines they require. At the same time, it is necessary to ensure that the production and use of CFC-containing MDIs declines at a rate consistent with the introduction of alternatives. Balancing these two imperatives requires a clear strategy. This strategy sets out the circumstances and procedures under which any new CFC-free inhaler will be determined to be a technically and economically feasible alternative or substitute for one or more existing CFC-containing products. The strategy also specifies the mechanism and timetable for the withdrawal of CFCs from the manufacturing process once satisfactory alternatives are available and advice on how to deal at that stage with stocks of CFCs and CFC-containing inhalers.

7.3 Some useful information on CFC phaseout strategies has been provided by the Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee of the Montreal Protocol in their April 1997 report. The committee notes that the following points should be considered when developing a CFC phaseout strategy:

- there should be sufficient technically and economically feasible alternatives available to assure an uninterrupted supply of medication
- one or more separate formulations of the same therapeutic substances need to be available
- there should be sufficient post marketing surveillance of the reformulated products
- there should be sufficient choice of alternatives to meet the needs of different patient sub-groups
- sufficient time and resources should be available for educating health professionals and patients
- companies manufacturing CFC products must be committed to reformulation
- the strategy should be consistent with the relevant legal and economic framework covering such things as approval, registration and pricing of medicines

7.4 In addition to these general points, the Technical Options Committee report sets out four possible approaches to designing a strategy for the phaseout of CFCs in metered dose inhalers. These include:

1) **Phasing out CFCs brand by brand**: With this approach, when a company produces a new or reformulated product which replaces its CFC product, it would be required to introduce the new product and phase out the old over a given timescale. The timescale would be consistent with the company's production and distribution capacity and reasonable post-marketing surveillance.

2) **Phasing out CFCs active substance by active substance**: With this approach, once a CFC-free MDI containing a particular active substance (eg salbutamol) had been launched and satisfactory post-marketing surveillance data obtained, CFCs would be withdrawn for all MDIs containing that particular active substance and, after a given period, licenses for the further sale of the CFC product would be withdrawn

3) **Phasing out CFCs category be category**: With this approach, existing CFC products are grouped into categories according to the type of disease being treated or the way the active substance operates. The categories are as follows:

   Category A: short-acting beta agonist bronchodilators (eg salbutamol)

   Category B: inhaled steroids (eg beclomethasone)

   Category C: non steroidal anti-inflammatories (eg cromoglycate)

   Category D: anticholinergic bronchodilators (eg ipratopium)

   Category E:long acting beta agonist bronchodilators (eg salmeterol)

   Category F:combinations

   For each of the categories (A) to (F), when sufficient CFC-free alternatives become available in that category, all the remaining CFC-containing products in that category can be phased out. What is defined as a "sufficient" number of CFC-free products will vary from category to category according to the importance and extent of use of the products concerned.

4) **Phasing out CFCs according to targets and timetables**: With this approach, the strategy would set targets for CFC reduction to zero over a given time period, in line with the expected availability of CFC-free alternative products or treatments. The timetable could be reviewed regularly and amended in the light of actual progress in the development and launch of alternatives. Under another variant of this approach, the strategy might simply plan to reduce the availability of CFCs by a given percentage each year (eg 20% cut each year to zero over 5 years), leaving manufacturers, doctors and patients to find ways to work successfully within these limits.

7.5 Among these different options, different strategies might be appropriate to different circumstances. When it comes to selecting the most appropriate strategy for the EC, it is useful to consider the criteria which it must meet to be successful. These include:

· phasing out CFCs as soon as reasonably possible

· ensuring that patients continue to have access to necessary medicines

- being clear, equitable, consistent and transparent
- being understood and supported by doctors and patients
- setting a clear direction to allow future planning with confidence
- being able to reflect the different circumstances of each Member State

7.6 If patients are to continue to have access to the medicines they require, including where necessary a choice of suitable therapies, it will be important to ensure that CFCs are not withdrawn prematurely before adequate alternatives are available. In this context, 'availability' will mean sufficient manufacturing and distribution capacity, together with evidence of the effectiveness of the alternative and the absence of any serious side-effects. A simple targets and timetable approach could not meet these criteria. A general cut in CFCs, for example 50% in 1999, would be somewhat arbitrary, and could not protect the patients using CFC products for which no alternative had yet been developed. It is therefore safer to adopt a strategy where the phaseout of CFCs is triggered by the real availability of alternatives, rather than being based on predictions of when these alternatives might be available.

7.7 It is also difficult to defend a strategy under which CFCs have to remain available until every single product now using them has been individually reformulated. This would prolong the phaseout indefinitely, as certain products currently using CFCs may never be reformulated and others may take many years before successful reformulations are launched. Under the Protocol's essential uses exemption, CFCs must be withdrawn once there is available *"a technically and economically feasible alternative or substitute which is acceptable from the standpoint of environment and health."* This does not imply that the alternative must be identical either in brand or active substance to the CFC product it replaces. For example, some patients currently using one brand of beta agonist might find they could switch to an alternative manufactured by another company. Others currently using an inhaled steroid such as beclomethasone might find they could easily change to another active substance with similar properties, whether or not manufactured by the same company. Some patients currently using a CFC MDI could change to an existing or new multi-dose dry powder inhaler.

<u>Phase out of existing CFC MDIs in the EC</u>

7.8 A strategy based simply on a brand by brand or active substance by active substance substitution would, without any particular justification, freeze the current production and use patterns of branded medicines. It would also restrict some of the flexibility between different brands and between different types of products which will be a necessary part of a successful transition away from CFC inhalers Not all the current CFC products will be reformulated and some switching between brands and between products will be necessary. Therefore this strategy is based on phasing out CFCs as far as possible category by category while taking account of known limitations to substitution within categories of active substance, the need to ensure that all patients continue to have access to the medicines they require and the different circumstances operating in different Member States and.

7.9 As has already been noted, products for the treatment of asthma and COPD are classified into the following 6 categories:

A Short acting beta agonist bronchodilators e.g. salbutamol terbutaline, fenoterol
B Inhaled Steroids e.g. beclomethasone, budesonide, fluticasone,
C Non Steroidal anti-inflammatories e.g. cromoglycate, nedocromil
D Anticholinergic bronchodilators e.g. ipratropium bromide, oxytropium bromide
E Long acting beta agonists bronchodilators e.g. salmeterol, formoterol
F Combination drugs

Categories A and B together account for approximately [80%] of CFC MDIs used in the EC. There are many different brands currently available in these two categories while in the other categories there are only one or two brands on the market. The active substances in each category are pharmacologically closely related, are indicated for the treatment of the same conditions and, with adequate consideration of dosages and action, most patients would be able to use another product within the category as an alternative. In addition to MDIs, there is also a complete range of DPIs for each of the Categories A to E. While they may not currently be the alternative of choice for many doctors and patients, dry powder inhalers could provide an effective and environmentally benign alternative for a significant number of patients, if appropriate actions are taken at national level to encourage their use. For these reasons and under this strategy, CFCs can be phased out for the manufacture of MDIs within the EC without waiting for each individual MDI currently using CFCs to be reformulated.

7.10 Pharmaceutical companies who have developed CFC free MDI alternatives will need actively to manage the transition through doctor and patient education programmes. A company which has introduced an alternative and has adequate production and distribution capacity for the new product and successful post-marketing surveillance should withdraw the CFC product over a maximum of 12 months following the introduction of the new product onto the market.

Technically and Economically Feasible Alternatives

7.11 Under the Montreal Protocol, essential use exemptions are granted only where there are "no available technically and economically feasible alternatives or substitutes acceptable from the standpoint of environment and health." This section of the strategy explains how it can be determined when technically and economically feasible alternatives are available, and the essential use exemption withdrawn.

7.12 Among existing CFC products, there is a number of active substances identified as necessary for patient health which will have to be available as CFC-free products before CFCs can finally be withdrawn. Other CFC products are not considered necessary for patient health and some may never be reformulated. Salbutamol accounts for over 90% of the European MDI short-acting beta agonist market and some 50% of the total MDI market. Beclomethasone accounts for over 90% of the European MDI

steroid market and some 25% of the total MDI market, while in some Member States, budesonide is the most important inhaled steroid**.** For active substances like these, it is necessary to ensure that sufficient alternatives are available to meet the requirements of patients before CFCs are withdrawn.

7.13 Conversely, the products 'Epinephrine' and 'Phenyl Ephrine' are no longer considered essential. Therefore, the Commission will not approve any CFCs for their manufacture after 1 January 1999.

Criteria for determining when sufficient alternatives are available

7.14 The criteria fall into two groups: those for determining when the use of CFCs would no longer be considered essential for individual products**,** and those for determining when the use of CFCs would no longer be considered essential for a whole category. These two systems will operate in parallel.

Individual products

7.15 CFCs for inhalers containing salbutamol will no longer be considered essential when two alternative CFC-free MDIs containing salbutamol are available in an adequate range of doses from two different producers.

7.16 CFCs for inhalers containing beclomethasone will no longer be essential when two alternative CFC-free MDIs containing beclomethasone are available in an adequate range of doses from two different producers**.**

7.17 CFCs for inhalers containing any other active substance will no longer be considered essential when one alternative CFC-free MDI containing the same active substance is available.

Categories of products

Category A - Short acting beta agonist bronchodilators

7.18 CFCs for inhalers in this category will no longer be considered essential once two CFC-free products containing salbutamol and one other CFC-free product containing an active substance defined as necessary under this strategy are available in an adequate range of doses.

Category B - Inhaled Steroids

7.19 CFCs for inhalers in this category will no longer be considered essential once two CFC-free products containing beclomethasone and two other CFC-free products containing different active substances defined as necessary under this strategy are available in an adequate range of doses.

Categories C, D and E

7.20 CFCs for inhalers in each of these categories will no longer be considered essential once one CFC-free product containing an active substance(s) defined as necessary under this strategy for the category concerned is available in an adequate range of doses.

Category F - Combination products

7.21 CFCs for inhalers in this category will no longer be considered essential once there are CFC-free MDI alternatives for each of its component active substances or when the essential use status has been withdrawn from the relevant category or product. A CFC free combination MDI would not be considered an alternative for either of its components when deciding whether there are sufficient technically and feasible alternatives available.

TABLE A

CATEGORY A SHORT-ACTING BETA AGONIST BRONCHIODILATORS		
PRODUCTS	# ALTERNATIVES	#PRODUCERS
Salbutamol*	2 non-CFC Salbutamol products	2 different producers
Terbutaline* Clenbuterol Fenoterol* Bitolterol Orciprenaline Procaterol Reproterol Carbuterol Hexoprenaline Pirbuterol	CFCs for all category A products will no longer be considered essential once there are available 2 alternative Salbutamol products produced by 2 different producers PLUS 1 other product defined as necessary under this strategy Therefore, these products will be replaced by a minimum of 3 CFC-free inhalers (two salbutamol + one other)	

CATEGORY B INHALED STEROIDS		
PRODUCTS	# ALTERNATIVES	#PRODUCERS
Beclomethasone*	2 non-CFC Beclomethasone products	2 different producers
Dexamethasone Flunisolide Fluticasone* Budesonide* Triamcinolone	CFCs for all category B products will no longer be considered essential once there are available 2 alternative Beclomethasone products produced by 2 different producers PLUS 2 other products containing different active substances defined as necessary under this strategy. Therefore these products will be replaced by a minimum of 4 CFC-free products (2 Beclomethasone + 2 others).	

CATEGORY C NON-STEROIDAL ANTI INFLAMMATORIES	
Cromoglicic Acid* Nedocromil* Note both these products are considered necessary in some Member States	CFCs for both category C products will no longer be considered essential once there is one alternative CFC-free product available to replace either of the two current CFC products. Therefore, the 2 CFC products will be replaced by a minimum of one CFC-free product, except where both products are considered necessary.

CATEGORY D ANTICHOLINERGIC BRONCHIODILATORS	
Ipratropium Bromide Oxitropium Bromide	CFCs for both category D products will no longer be considered essential once there is one alternative CFC-free product available to replace either of the two current CFC products.

CATEGORY E LONG-ACTING BETA AGONIST BRONCHIODILATORS	
Salmeterol* Formoterol* Note: Both these products are considered necessary in some Member States	CFCs for both category E products will no longer be considered essential once there is one alternative CFC-free product available to replace either of the current CFC products. Therefore, the ***2*** category E CFC products will be replaced by a minimum of one CFC-free product, except where both products are considered necessary.

CATEGORY F COMBINATION PRODUCTS	
	Combination products will be treated on a case-by-case basis. CFCs for combination products will no longer be considered essential once CFC-free products are available for each of the separate components in the combination.

* this denotes products deemed necessary under this strategy in one or more Member States

7.22 The European Commission will apply the criteria set out in paragraphs 7.15 to 7.21 and in Table A to determine whether CFCs remain essential for a given MDI product. However, to reflect the different circumstances of Member States, CFCs may have to be approved for a particular product in a particular Member State even after the criteria for transition have been met. This would be the case, for example, where the competent authority of that Member State confirms to the Commission that the product remains necessary despite the availability of alternatives. Note, however, that any derogation along these lines would have to be temporary and would not delay the transition elsewhere in the Community. It is important to note that the continued use of CFCs is only possible with the agreement of the Parties to the Montreal Protocol.

7.23 The following conditions will also need to be met before it is considered that there are sufficient technical and feasible alternatives available for CFCs to be withdrawn:

- Adequate production and distribution capacity of the CFC-free MDIs to meet the needs of all patients covered by the product or category concerned:
- An adequate range of doses and strengths to cover distinct patient subgroups such as the elderly or young children
- Efficacy of the alternative products and treatments generally comparable to the CFC product they are replacing. Some patients may have a personal preference for CFC MDIs, but this is likely to be overcome by education and would not be the basis of a continued exemption under the Montreal Protocol.
- Sufficient post marketing surveillance of the reformulated products and no safety problems identified

The Commission will seek advice from the competent authorities of the Member States and other experts to determine when all these conditions have been met and the CFCs withdrawn from a particular product or category.

<u>How CFCs will be phased out once alternatives are available</u>**<u>.</u>**

7.24 Manufacturers of metered dose inhalers for asthma and COPD currently obtain their CFCs after agreement to their essential use requests in two stages. In stage 1, the European Commission applies to the Parties to the Montreal Protocol for authorisation of a total quantity of CFCs to be used to manufacture MDIs in the European Community in a future year. The Parties to the Montreal Protocol review the application and approve a certain quantity, usually two years in advance. At their 8th Meeting in Costa Rica in 1996, the Parties agreed on a total of 5610 tonnes to be used by manufacturers in the Community during 1998. At their 9th meeting in Montreal in 1997, the Parties agreed a total of 5000 tonnes for use by manufacturers in the Community during 1999**.** These CFCs are intended for the manufacture of MDIs both for the European market and also for export.

7.25 In stage 2, each manufacturer applies to the European Commission for authorisation to acquire and use a quantity of CFCs to produce MDIs. Their requests

to the Commission are received in the autumn of each year in respect of the following year. The Commission reviews the requests and, after seeking the opinion of a Management Committee composed of representatives of all Member States, takes a decision on the precise quantities allocated to each producer for the following year. This decision is notified directly to the companies concerned, and is published in the Official Journal. The total quantity authorised by the Commission in stage 2 for use by the manufacturers cannot exceed the total quantity approved by the Parties to the Protocol under stage 1 for the year in question.

7.26 This two stage process means that the Community has a rather flexible means to ensure that CFCs can be phased down carefully in line with the availability of CFC-free alternatives for each of the categories in Table A. Using forecasts from the MDI manufacturers about the likely submission, approval and registration of alternatives, it is possible to predict some years into the future the likely demand for CFCs. These forecasts can be used as a basis for the Community's nomination to the Parties to the Montreal Protocol two years in advance of need. This is the 'targets and timetables' approach to transition advocated by the MDI manufacturers

7.27 Within these overall totals, the Commission, working in cooperation with the Management Committee of Member States and the companies concerned, can use the annual decision on CFC quantities to "fine tune" the actual quantities approved for each company. For example, should alternatives be approved earlier than forecast or producers have large stockpiles of CFCs, the quantities approved by the Commission would be reduced accordingly. Conversely, should alternatives not be available as quickly as predicted, there would be some flexibility to distribute the available CFCs among producers and among particular products in order to ensure that vital medicines remained available. Should the Community's transition be delayed for some reason, the Commission could even submit a revised bid to the Parties one year ahead requesting additional CFCs. However, such a request would only be submitted under exceptional circumstances.

7.28 As regards the likely timetable for phasing out CFCs in line with the availability of alternatives, much depends on how "availability" is defined. A new alternative could not be considered "available" on the day of launch. Some considerable time is necessary for doctors and patients to become aware of the new product, to try it out and to gather information on its performance and acceptability. This information would form part of the post-marketing surveillance information which would be a vital part of the transition. Only when adequate post-marketing surveillance data is available to show that the new alternative is effective, acceptable, and without serious side-effects would it be justified to remove the CFC product from the market.

7.29 Gathering adequate post-marketing surveillance data would take 12 months. Therefore, once an alternative is launched, the Community could reflect that launch in a reduced quantity of CFCs requested from the Parties to the Protocol. The next year, when the Commission comes to take its decision on CFC quantities, the post-marketing surveillance data would be available and if the alternative has proved successful, no more CFCs need be authorised for the manufacture of that product.

Within a maximum of 12 months from the launch of an alternative, the CFC version it replaces would no longer be manufactured for use in the EC.

Stockpiles of CFCs and CFC containing MDIs

7.30 Using the essential use decision to phaseout CFCs for particular products or categories would not of itself ensure that all the CFC products concerned were taken off the market in due time. Companies might continue manufacture using CFCs intended for MDIs in other categories, and manufacturers outside the EC might try to import CFC MDIs to fill the gap in the market. These problems will be addressed by careful monitoring of production and stockpiles, import controls and making CFCs available only for those products still met the essential uses criteria.

7.31 Once sufficient technically and economically feasible alternatives exist to enable the essential use exemption to be withdrawn for a particular CFC product or category of products, no more CFCs will be available for the manufacture of those CFC products. Companies may still be able to sell stockpiled MDIs which have already been manufactured, as there is no obligation to withdraw marketing authorisation. However, companies should quickly reduce their sales of CFC products as this would be an important means to ensure the successful take up of their CFC-free alternative. It is possible to envisage a period of 12 months during which the CFC product and its CFC-free alternative are both available, particularly to assist post-marketing surveillance. After that time, however, the continued presence of CFC products on the market will be unnecessary, and might confuse doctors and patients involved in the transition. Companies should prepare plans to withdraw their CFC products within the suggested timeframe and in accordance with their doctor and patient education programmes.

New MDIs

7.32 This strategy will not succeed if new MDIs containing CFCs are being introduced onto the European market during the transition. To do so would confuse patients and health professionals and needlessly prolong our reliance on CFCs. Therefore, as part of this strategy from 1 January 1998,

- competent authorities should not give marketing authorisation to any new CFC-containing inhalers
- the European Commission will not approve the allocation of CFCs for the manufacture of any new MDI product
- Companies should cease developing and promoting CFC-containing MDIs.

CHAPTER 8 AWARENESS RAISING

8.1 The transition away from CFC MDIs has already started in Europe and should largely be completed by the year 2003. The level of awareness of dry powder inhalers (DPIs) and CFC-free MDIs among health professionals and patients is still limited, however, and this has to change. As more alternatives become available, it is essential that an active strategy to inform and involve patients is developed. This will require a concerted effort, led and coordinated by National Governments with the support and input of health professionals, health services, patient associations and the manufacturers of asthma medicines. Adequate funds need to be identified for raising awareness among health professionals and patients if successful transition is to occur.

Changeover and education

8.2 Changeover to CFC free products is unlikely to occur smoothly without a national or regional strategy being in place. Although the strategies may differ in detail between Member States, some common features can be recognised. There should be co-operation between the professionals involved on a local or regional basis to discuss how the transition is to be implemented. Contacts with patient representatives should be established at an early stage to ensure that patients receive adequate information, both orally and in writing. This is essential to build the confidence of patients in the new products. Further, the changeover of patients in one region or area should be done at roughly the same time to reduce the problems of providing primary and secondary care and the difficulties which would arise from a long period during which both the old and the new products would be available.

8.3 Choice of medication is invariably made by the physician and not by the patient. Patients consider this within the competence of the physician and a reason for consultation. The patient expects an explanation for the choice of a specific medicine, especially where a change from a familiar product is involved. Surveys have shown that when a change from CFC inhalers to alternatives is recommended by the physician and adequate information is given, most patients are happy to change and do so successfully.

8.4 Education is a continuous process, a partnership between professionals and patients involving an exchange of information and adequate opportunity for patients to express their fears and concerns. Although physicians are the patients' first source of information on medication, patients do consult other professionals in asthma treatment, including pharmacists and patient associations, when they have questions about the treatment of their disease. It is therefore of the utmost importance that all these parties have the same information and give consistent advice to patients. With adequate preparation and reinforcement of the key messages, most patients are expected to enjoy a trouble-free transfer from their CFC inhaler to a CFC-free device.

Asthma Patient Associations

8.5 Most European countries have asthma patient associations, although in the majority of cases they are rather small. The large associations in the Netherlands, United Kingdom, Italy and the Scandinavian Countries have already established their reputation as an important source of information for patients. The smaller associations can also provide vital information for patients. Some associations have already produced written information for patients on the transition. The European Federation of Asthma and Allergy Associations (EFA) supports the provision of information by distributing fact sheets and other written information to members and associated organisations.

Raising Awareness

8.6 To raise awareness, the following actions should be taken :

(i) at government level:

Health Departments should ensure that information is provided to health professionals, including unbiased information leaflets for patients. Appropriate sources of finance should be identified to support the awareness raising campaign. National Health Systems and/or Health Insurance Schemes should prepare a plan to manage the period during which new products become available while cheaper CFC products remain on the market.

(ii) at professional and patient association level:

8.7 Doctors, nurses and pharmacists need to be aware that the transition is not optional, and that, over the next few years, all patients currently using CFC products will have to change to CFC-free devices. They should be prepared to help patients understand the reasons for the change and assist them during the transition. Patients will require reassurance that:

- The new inhaler is as safe and as effective as the previous CFC inhaler
- The new inhaler devices operate in very similar ways to the CFC inhalers
- CFCs are damaging to the global environment and not damaging to the health of the individual when inhaled from an MDI.
- Although they will experience differences in appearance, dosage, taste and sensation when using the new products, these differences do not imply any reduction in effectiveness of the medicines

8.8 In cooperation with Patient Associations, an awareness campaign for patients should be started. To prepare patients for the change to alternatives, various methods are needed. Spoken advice, together with written and audio-visual reinforcement is likely to be necessary, involving some or all of the following:

- Patient associations: - Patient Associations have opportunities for direct contact with patients through telephone helplines, support groups, regional branches and regular meetings. These associations can help to produce written material in a form which patients understand. Similarly, articles in medical journals inform professionals of the need and timetable for transition .
- Treatment guidelines - National Asthma Guidelines should include reference to the phaseout of CFCs in MDIs and the new reformulated products. The US National Heart Lung and Blood Institute (NHLBI) and WHO have introduced a Global Initiative on Asthma (GINA). This will increase international awareness of this subject at symposia throughout Europe, and on the Internet.
- Medical Symposia - Physicians, researchers and pharmaceutical development experts will present, discuss and evaluate the advances and latest development of alternative treatment. During the next few years, many more symposia are planned. In December 1998, the World Asthma Meeting in Barcelona will have CFC transition as a plenary session. The different associations of General Practitioners and Lung Physicians can provide a forum for discussion and evaluation of the latest developments in alternative treatments, and the promotion of a wider understanding of the timetable and management of the transition.
- Promotional Material - Advertising and promotional material placed in medical journals and circulated to physicians by pharmaceutical companies. It will be critical that patients understand that the need for the change is based on environmental considerations and not for reasons of product safety or cost.
- Support Groups - which provide information, seminars and programmes aimed at both the general community and targeted through schools, sporting groups etc. For example, the UK National Asthma Campaign has produced a fact sheet to help prepare patients for changeover of their inhalers.
- Media Coverage - both national and local media can play an important role in raising awareness among patients and, in particular, encouraging them to discuss their transition with health professionals. As with all media contacts, care is required to ensure that the right messages are communicated in a positive way.

(iii) at industry level:

8.9 Manufacturers of MDIs can help in educating the medical profession by advertising and placing educational material in medical journals, by supporting medical symposia and by making available reprints of pertinent articles and reports. They can also produce information sheets for patients and invent strategies to help inform both professionals and the public of developments and alternatives. A good example is the brochure for professionals entitled “Moving Towards CFC-free Metered Dose Inhalers”, produced by the International Pharmaceutical Aerosol Consortium(IPAC).

8.10 This educational activity should involve increasing awareness of DPIs as well as the reformulated MDI products. As more alternatives become available it is essential that a more active patient strategy is developed to prevent confusion.

How and When to proceed

8.11 The awareness raising campaign should start as soon as possible, as many new products are expected to become available during 1998. Strategies to manage the transition of most patients to non-CFC alternatives will need to be ready by the end of 1998. General information on the phaseout of CFCs and their replacement by alternative forms of treatment have to be available when the campaign starts or soon afterwards. Specific information and relevant facts on reformulated MDIs should be provided by the pharmaceutical industry in advance of the launch of new products, and during the period of transition from CFC MDIs to the new alternatives. Sources of financial support for these activities have to be identified as some partners in the awareness raising campaign might not have sufficient means to cover the costs of their contributions.

8.12 References

EFA: The Patient, Your Partner. Symp. EFA in ERS Congress, Nice, 4 Oct.1994. Abstracts.
EFA: Information and Decision: Patients' Rights. Symp.EFA in EAACI Congress, Budapest, 4 June 1996. Abstracts.
M.R. Partridge: The transition in practice: health professionals and patients. BJCP suppl. 89,1997:32-36.
M.R. Partridge: CFC-free inhalers: are we ready?, Asthma Journal, June 1997, vol.2: no 2: 48.
M.R. Partridge: Managing the change: issues for healthcare professionals, physicians and patients. Eur. Resp. Rev. 1997:7:41. 40-41.
National Asthma Campaign (UK): NAC CFC Free Inhalers Survey 1997, press release, 7 May 1997.
J. Molema, E.M.A.L. Rameckers, T Rolle: Empowerment of Patients: a Threat or a Help?. Monaldi Arch. Chest Dis., 1995; 50:5, 337-339.
E.M.A.L. Rameckers, What do Patients Want?. ECACI 1995 Proceedings, Monduzzi Editore 1995.

CHAPTER 9 EXPORTS OF MDIs FROM THE EC

9.1 Half of the world's production of MDIs takes place in the EC, and 25% of the Community's MDI production is exported. Approximately 10 million units go to developing countries each year. In addition, MDI manufacturing facilities located in developing countries and operated by multinational companies often import supplies of pharmaceutical quality CFCs from the EC. It is important that the transition to CFC-free MDIs in the EC does not in disrupt the supply of important asthma and COPD medicines to developing countries. .Decision VIII/10 of the Parties to the Montreal Protocol requests companies to report on steps being taken to provide a continuity of supply of asthma and COPD treatments (including CFC MDIs) to developing countries. Decision IX/19 says that *in preparing a transition strategy, Parties should take into consideration the availability and price of treatments for asthma and COPD in countries currently importing CFC MDIs"*.

Special situation of developing countries under the Protocol:

9.2 The Montreal Protocol distinguishes between developed and developing countries in the phaseout of ozone-depleting substances. Whereas CFCs have been phased-out since January 1 1996 in developed countries (January 1 1995 in the EC), except for essential uses, developing countries have a "grace period" under which CFCs may continue to be produced and consumed until 2010 to meet "basic domestic needs".

9.3 Developing countries currently obtain their MDIs from one or more of three possible sources:

- Imports from developed countries, particularly the EC;
- Production within developing countries by multinational companies;
- Production within developing countries of low-cost generic products by independent local companies

9.4 Demand for MDIs in developing countries is likely to increase with increased incidence of asthma and COPD, better access to health care, improved diagnosis and effective treatment becoming affordable for more people. Access to medicines in developing countries is constrained by costs, particularly for chronic conditions like asthma and COPD. Maintaining access to affordable treatment for asthma and COPD is a priority for developing countries, and will inevitably involve the MDI producers in the EC.

Strategies and targets for moving export markets to alternatives:

9.5 While the EC is managing its own transition to CFC-free MDIs, we should also consider what to do about MDI exports to developing countries. Steps should be taken to ensure that the benefits of the development and educational efforts carried out in the EC to enable the transition to CFC-free MDIs are transferred to developing

countries. As part of the nomination process to obtain essential use CFCs for exports of MDIs, companies will be asked to report on what measures they are taking to facilitate the transition among their customers in developing countries.

9.6 For example, each MDI manufacturer should strive to obtain regulatory approval for their CFC-free MDIs in developing countries, and make them available there as soon as possible. It makes little sense to start new patients other countries on CFC inhalers when the CFC-free version is already available. Companies should also make efforts to increase awareness and acceptance of alternative inhalation treatment methods, like DPIs and nebulizers. In accordance with Protocol Decision VIII/10, companies should consider upgrading their MDI manufacturing facilities in developing countries to enable them to produce CFC-free MDIs.

Forecast of CFC requirements to manufacture MDIs for export until 2010:

9.7 Currently, companies request quantities of CFCs for MDI manufacture for both their home and export markets together. Decision VIII/9 sets outs an accounting framework for essential use requests which will separately identify the volumes of CFCs used in MDIs sold in the Community and those used in MDIs for export. Even with this change, it will remain difficult to make long-term forecasts of CFC requirements, particularly for developing countries, where economic growth rates will drive future demand for asthma treatments. This will be further complicated by difficulties in predicting the timing of the transition away from CFC MDIs in these countries. Despite these difficulties, predictions of future CFC requirements in MDIs for export will have to be made to ensure that sufficient pharmaceutical grade CFC is available to meet demand.

9.8 Production of CFC-containing MDIs for export will have to continue in the European Community for some time after our own transition has been accomplished. Companies applying for essential use CFCs to manufacture MDIs for export need will need to demonstrate that they are taking active steps, in co-operation with the competent authorities of the countries to which they export, to promote the transition to CFC-free inhalers as quickly as possible, while maintaining the supplies of necessary medicines to patients.

Obtaining CFCs to manufacture MDIs for export after phase-out in the Community

9.9 In order to meet the commitment entered into in Decision VIII/10 of ensuring adequate and continuing supplies of MDIs to developing countries, MDI producers will need access to reliable sources of pharmaceutical grade CFCs in sufficient quantities to meet the requirements for CFC MDIs until these are phased out in developing countries. Three possibilities exist:

- continued CFC production in the EC as normal
- periodic "campaign" production in the EC
- import of CFCs from producers in Developing countries.

These possibilities are discussed further in Chapter 10, ‘CFC Production Issues’

CHAPTER 10 CFC PRODUCTION ISSUES

Introduction

10.1 CFCs for use in the production of MDIs are manufactured in the EC by 4 producers. These are:

AlliedSignal (The Netherlands)
Ausimont (Italy)
Elf-Atochem (Spain)
Rhone Poulenc (UK)

These producers also produce CFCs for the manufacture of MDIs in a number of developed and developing countries.

10.2 These manufacturing facilities produce CFCs to a defined purity specification as laid down by the individual MDI manufacturer. CFCs of specified purity are necessary to meet the requirements of product registration in the countries where the CFC MDIs are sold. If an MDI manufacturer had to change to a different CFC producer (even amongst those within the EC) with a different product purity profile, this could mean that the MDI manufacturer would have to re-submit its MDIs for registration. As a result, MDI manufacturers tend to purchase their CFC supplies from one or two CFC producers only.

Future Supply of CFCs for MDI Manufacture within the EC

10.3 CFC producers within the EC produce mainly CFC 11 and CFC 12 for use in MDI manufacture within the EC and worldwide. They also produce CFCs to meet the basic domestic needs of countries operating under paragraph 1 of article 5 of the Montreal Protocol. In 1996, EC CFC producers produced 3,062 tonnes of CFC 11 and 4,757 tonnes of CFC 12 for MDI manufacture worldwide and 9,430 tonnes of CFC 11 and 14,280 tonnes of CFC 12 to meet the basic domestic needs of Developing countries.

10.4 There has been extensive industrial rationalisation of CFC production within the EC during the last few years, and the number of producers has reduced by half. CFC production has been concentrated upon small manufacturing facilities which are more economically viable. These facilities are only cost-effective while their production remains above a minimum level. This minimum level is determined by a number of parameters and will be different for each producer. The remaining plants stay above the minimum level of production through a combination of production for MDIs and for the basic domestic needs of developing countries. The reduction in the quantity of CFCs required by MDI manufacture during the transition period will cause CFC producers in the EC to review the operation of their facilities and may lead to further closures. However, although further rationalisation of production capacities cannot be excluded, over the next five years it is likely that demand for CFCs for the

basic domestic needs of developing countries will enable the continued operation of at least some CFC production facilities within the EC.

10.5 It has been indicated in the April 1997 TEAP Report that once demand for CFCs reduces to below the minimum cost-effective level for the producers, CFC production could be maintained by running 'production campaigns' and storing the CFCs until needed. For the reason set out above, it is unlikely that this will be necessary for the EC during the transition period. However, the option of a final production campaign should be maintained for the period towards the end of the EC phase-out of CFC MDIs. Such a 'final campaign' would help maintain the economic viability of CFC producers. The implications for developing countries are discussed below.

10.6 It is important to remember that integrated pollution control licensing of CFC plants requires forward planning and does not allow for 'ad hoc' production or extensions of production periods. A managed transition strategy will help to forecast future CFC requirements, including the possible need for a 'final production campaign'.

Production of CFCs for MDI Manufacture for Export to Developing countries

10.7 Decision VIII/10 (9) of the Parties to the Montreal Protocol requests MDI manufacturing companies to take steps to provide a continuity of supply of asthma and chronic obstructive pulmonary disease (COPD) treatments (including CFC MDIs) to importing countries. In order that these supplies can be maintained, MDI producers need access to reliable sources of pharmaceutical-grade CFCs in sufficient quantities to meet the needs of importing countries where the transition to non-CFC products will proceed more slowly.

10.8 Whilst this is unlikely to present a problem during the EC transition period for the reasons already discussed, there is a concern that once CFC MDIs have been phased out in the EC, pharmaceutical-grade CFCs could become in short supply for the continued manufacture of MDIs within the EC for export.

10.9 Given that there is no immediate prospect of CFC shortages for MDIs, it is premature to make firm decisions on CFC production for the future manufacture of MDIs for export to developing countries. A number of possibilities exist, and it is not yet clear which would represent the best way forward. One option would be ‘production campaigns’ whereby CFC manufacturing facilities would be operated from time to time to produce a sufficient stockpile of CFCs to supply MDI manufacture for export. Considering this approach, the April 1997 Technical and Economic Assessment Panel (TEAP) Report indicated that a period of 2 years might be required to establish an adequate stockpile of CFCs through 'campaign production’, should this be required.

10.10 While this idea is prima facie appealing in terms of possible production cost savings, its main disadvantage is the difficulty of accurately assessing future demand for CFCs. Further, there are no assurances that CFCs which are stockpiled for

perhaps 5 years will not degrade, nor that the MDIs ultimately produced with these stockpiled CFCs will not deteriorate faster than MDIs produced with freshly-produced CFCs. Current experience is that CFCs are stable over 2 years storage. Another potential risk from the point of view of patient health is that CFC producers will produce large batches of CFCs and will then close down their production facility. This could mean that CFC would no longer be available to manufacture MDIs for export to countries where they remain essential to patient health.

10.11 A second possible source of CFCs for MDI producers would be from production facilities located in developing countries. This is not currently thought to be a realistic option. Production facilities in developing countries would need to be registered and the CFCs obtained approved by the competent Regulatory Authorities, including those in the country of MDI manufacture. The CFC production would have to comply with stringent Good Manufacturing Practice (GMP) and demonstrate reliable and consistent production to a defined purity specification. This could present a challenge for CFC producers in developing countries.

10.12 Given the continued production of CFCs within the EC to supply the basic domestic needs of Developing Parties, it is most unlikely that, over the period of the EC transition, there will be a shortage of pharmaceutical grade CFCs for the manufacture of MDIs in the EC, whether for use in the Community or for export.

CHAPTER 11

THE ESSENTIAL USE PROCESS: OVERVIEW AND TIMETABLE

11.1 This Chapter describes the process by which an essential use exemption for the Metered Dose Inhaler (MDI) is obtained in the European Community and outlines the timetable for the completion of that process.

THE ESSENTIAL USE PROCESS: OVERVIEW

11.2 The Parties to the Montreal Protocol established the framework for the essential use process at their Fourth Meeting in 1992 in Copenhagen. The essential use process in the Community is implemented through the provisions of Regulation (EC) 3093/94.

11.3 The essential use process in the European Community involves three distinct elements:

1. the **nomination** of essential uses for future years, including a request for specific quantities of CFCs for essential uses in a given year;

2. the **assessment** of those nominations and a decision by the Parties to the Montreal Protocol;

3. the **review and licensing** of essential use quantities by the European Commission assisted by the Management Committee of Member States.

The steps that must be taken under each of these elements are as follows:

11.4 Nomination

- IPAC prepares and submits nomination requests in each Member State where MDIs are manufactured;

- Member States review the IPAC submissions, add any approved quantities requested by non-IPAC companies and forward nomination requests to the European Commission;

- The European Commission reviews the nominations received from Member States, combines them and forwards a nomination on behalf of the European Community to the United Nations Environment Programme (UNEP).

  Time Required: Approximately 6 Months

11.5 Assessment

- The Technical Options Committee (ATOC) and the Technology and Economic Assessment Panel (TEAP) of the Parties to the Montreal Protocol review nominations and determine if they meet the criteria for an essential use established by Decision IV/25 and whether the quantities requested are justified. TEAP reports its findings and recommendations to the Open-Ended Working Group (OEWG) to the Montreal Protocol;

- The OEWG reviews TEAP's recommendations and forwards a draft decision on essential uses for consideration by the Meeting of the Parties;

- The Meeting of the Parties decides whether to the nominations meet the essential use criteria and, if so, what quantities of controlled substances are to be authorised.

Time Required: Approximately 6 - 9 months

11.6 Licensing

- The Commission issues a Notice to Users calling on MDI manufacturers to submit applications for essential use authorisation indicating the quantities of CFCs they require for the following year;

- MDI manufacturers submit applications for essential use authorisation to the Commission;

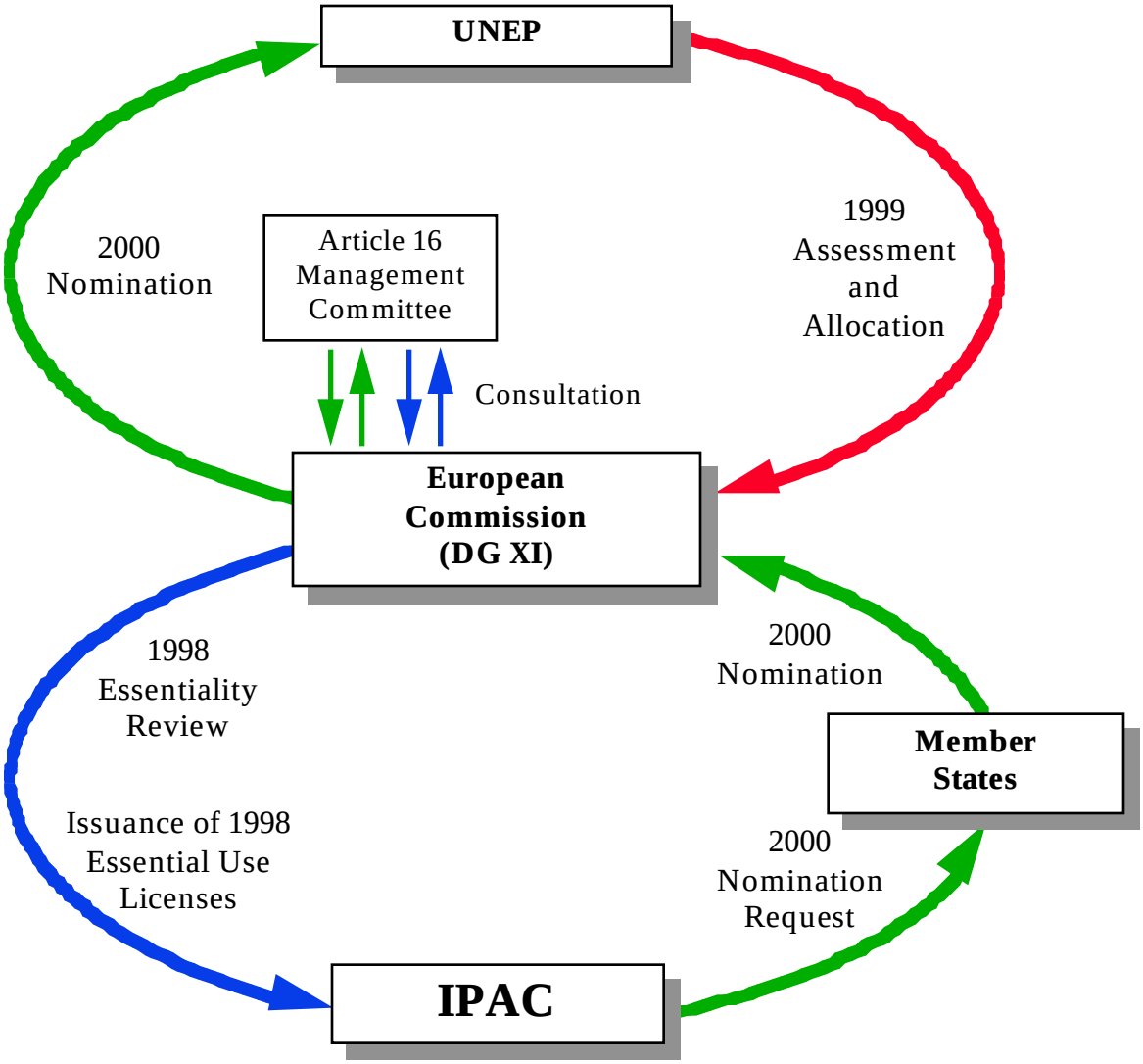
- The Commission, in consultation with the Article 16 Management Committee, reviews applications submitted by MDI manufacturers, allocates quantities of CFCs for essential uses, and issues essential use licenses.

Time Required: Approximately 3-6 months

11.7 In any given year, each element of the essential use process is being undertaken concurrently. For example, the essential use process in the European Community in 1997 involved the approval and licensing by the Commission for 1998, assessment by TEAP and the Parties of the nomination for 1999, and preparation by IPAC and other companies of the nomination for 2000.

The diagram below shows the Essential Use Process in the European Community in 1997

The Essential Use Process in the European Community: 1997



PLANNING FOR THE ESSENTIAL USE PROCESS: TIMETABLE

The diagram below describes the timetable for the essential use process in 1997: