MONTREAL PROTOCOL

ON SUBSTANCES THAT DEPLETE

THE OZONE LAYER

UNEP

2006 REPORT OF THE MEDICAL TECHNICAL OPTIONS COMMITTEE

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On Substances that Deplete the Ozone Layer

Report of the
UNEP Medical Technical Options Committee

2006 Assessment

ASSESSMENT REPORT

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2006 REPORT OF THE MEDICAL TECHNICAL OPTIONS COMMITTEE

2006 ASSESSMENT

TABLE OF CONTENTS **PAGE**

EXECUTIVE SUMMARY

Metered Dose Inhalers

Global CFC use for MDIs

In 2005, 2,754 tonnes of CFCs were used for the manufacture of metered dose inhalers (MDIs) for asthma and chronic obstructive pulmonary disease (COPD) in non-Article 5(1) countries under essential use exemptions. This represents a 70 per cent reduction in use compared to peak usage in 1997.

It appears that MDIs are manufactured in at least 16 Article 5(1) countries. The amount of CFCs used in these countries in 2005 for the manufacture of MDIs is estimated at 1,875 ODP tonnes (this equates to production of approximately 75 million MDIs). About 65 per cent of this consumption (1,283 ODP tonnes) is by nationally owned manufacturing companies.

Technically satisfactory alternatives are available

Technically satisfactory alternatives to CFC MDIs are now available for short-acting beta-agonists and other therapeutic categories for the treatment of asthma and COPD. Whilst much effort has been focused on developing in-kind replacements for CFC MDIs (i.e. HFC MDIs) there are other methods of delivering drugs to the lung. Alternative methods to CFC MDIs for pulmonary drug delivery include: HFC MDIs; dry powder inhalers (DPIs), single or multi-dose; nebulisers; and soft-mist inhalers.

By the end 2005, around 40 per cent of the short acting beta-agonist salbutamol MDIs marketed around the world contained HFC as a propellant. Both propellants HFC-134a and -227ea are being widely used to formulate drugs in MDIs. There is widespread availability of salbutamol HFC MDIs, with almost 60 countries where there are at least two products approved. This is also true for a number of inhaled corticosteroids, including budesonide, beclomethasone and fluticasone propionate.

The introduction and acceptance of multi-dose powder inhalers has continued, along with single-dose DPIs (particularly in some Article 5(1) countries). Global use of DPIs has increased to over 30 per cent of total inhaler units (MDI+DPI). The use of DPIs in Europe is now comparable to HFC MDI usage.

By the end of 2005 all countries of the European Union had declared CFC MDIs for salbutamol non-essential. Salbutamol CFC MDIs may continue to be sold in the United States until the end of 2008, following which their sale will be illegal. Both the European Union and the United States are actively considering the phase-out of the remaining non-salbutamol CFC MDIs, which is likely in 2008/9.

As anticipated, there have been no major problems with transition, including no major product issues. The lack of problems may be attributed in part to the use of widespread education campaigns (primarily conducted by the pharmaceutical industry) to both healthcare professionals and patients.

It is likely that a number of CFC MDI products (usually older drug moieties or generic products) may never be reformulated due to technical challenges, economic considerations or changes in medical practice so suitable medical alternatives will need to be sought. For most of these, there are either suitable CFC-free alternatives in the same therapeutic category or other satisfactory alternative therapies. Increased regulatory involvement is likely to be needed as the transition reaches the phase where there will be a few CFC MDI products remaining.

Experience of transition

The rate of transition from CFC MDIs to CFC-free products has varied from country to country. Even when new products have been introduced, the rate of their uptake has varied. This has occurred for a number of reasons including price considerations and the varied regulatory frameworks that cover product withdrawals in various countries.

It is very clear that the development of CFC-free products, their registration and launch into the market is only partially effective in achieving transition. Experience has indicated that transition can best be achieved by pharmaceutical companies ceasing CFC MDI manufacture and by regulatory policies that phase out corresponding CFC products on a drug-by-drug or category-by-category basis once alternatives are widely available.

However some pharmaceutical companies have not ceased supplying the CFC MDIs. There are also some companies, such as some generic pharmaceutical manufacturers, that have not developed CFC-free MDIs and they will continue to produce CFC MDIs for as long as they are allowed. It has proved necessary for national governments to implement regulatory policies to ensure that the transition is completed in a timely and safe manner, once sufficient, CFC-free alternatives are available.

There are continued concerns over the cost and/or availability of healthcare in all countries, particularly in Article 5(1) countries. The price of CFC alternatives could be a major barrier to transition if they are more expensive than comparable CFC products, unless governments and other payors agree to cover the higher cost of CFC-free alternatives.

Despite widespread educational initiatives, transition does not appear to be a high priority among most healthcare providers, many of whom have taken a passive approach to transition. Pharmaceutical companies' educational and marketing endeavours have been the main driving force in the uptake of alternatives.

Significant progress in Article 5(1) countries; considerable challenges remain

The CFC MDI transition in Article 5(1) countries has proved to be complicated, as it is influenced by medical, technical, economic and regulatory factors. Nonetheless, significant progress has already been made towards transition in Article 5(1) countries for certain key moieties. In many Article 5(1) countries, more than one CFC-free product is available. In over fifty Article 5(1) countries, at least two CFC-free salbutamol products have been approved.

Given the widespread availability of technically and economically feasible alternatives, the Medical Technical Options Committee (MTOC) believes that global phase-out of CFCs in MDIs is achievable by 2010. However considerable challenges will need to be addressed to achieve transition particularly in Article 5(1) countries. These challenges can be overcome through the transfer of technology, product launches of CFC-free alternatives and implementation of comprehensive transition strategies.

There is an urgent need for all Article 5(1) countries that have not already done so to develop effective national transition strategies in accordance with Decision XII/2. MTOC strongly recommends that these activities be made a priority to ensure a smooth transition to CFC-free alternatives by about 2010. Countries will need to set an end-date for transition that accounts for the Montreal Protocol phase-out schedule.

Multi-national pharmaceutical producers provide the majority of MDIs in most Article 5(1) countries. In a few countries, local manufacture accounts for some MDIs, while the majority comes from multinational producers. In other countries (e.g. People's Republic of China, Cuba and India), local manufacture supplies the majority of MDIs to the market.

In countries that rely mainly on imports, the transition to CFC-free products will be driven mainly by marketing strategies of the multinational pharmaceutical companies. The national health and trade authorities will also drive transition. Transition strategies will be relatively simple, and be mainly concerned with regulatory approval of CFC-free alternatives and patient and physician education programmes. In most of these countries the affordability of alternative CFC-free products may be a factor in transition.

Countries that manufacture MDIs will each need to develop a detailed national transition strategy to phase out CFC MDIs. In some of these Article 5(1) countries there are a relatively large number of local companies producing CFC MDIs who have not yet gained access to the skills or knowledge to introduce suitable CFC-free alternatives. It is critical to ensure that appropriate technical expertise is identified, that funds for technology transfer and equipment acquisition are available, and that the management of the implementation is monitored.

The cost of access to CFC-free MDI technology will depend on whether patents exist that cover the product being contemplated and whether these patents are enforceable in the Article 5(1) country. However, based on a preliminary evaluation by MTOC it does not appear that formulation patents will constitute a major barrier to the introduction of CFC-free MDIs in Article 5(1) countries.

A limited number of Article 5(1) countries may face specific problems. Firstly, they may not achieve the allowable levels of CFC consumption in 2007, and thus be in a potential non-compliance situation with their obligations under the Montreal Protocol. The MTOC is aware of at least two cases where such a potential non-compliance situation could arise once the major part of their CFC phase-out is completed. A recent report to the Executive Committee addressed the compliance issue (UNEP/OzL.Pro/ExCom/49/39).

Secondly, some countries may face difficulties in phasing out the consumption of CFCs for MDIs without incurring economic losses to local MDI manufacturers if they do not receive Multilateral Fund financing. Thirdly, without adequate planning for transition by national governments, patients may be deprived of inhaled therapy that is essential for health.

After 2009, the economics of CFC production may make pharmaceutical-grade CFC production for MDIs impractical. If Article 5(1) countries face difficulties in achieving transition in their CFC MDI manufacturing plants by 2010, stockpiling may need to be considered to ensure a supply of pharmaceutical-grade CFCs for MDI manufacturing to meet patient needs beyond 2009. In these circumstances, it may be appropriate to arrange for a final campaign to produce pharmaceutical-grade CFCs before 2010, or to acquire pharmaceutical-grade CFCs through a transfer of existing stockpile in non-Article 5(1) countries.

Future CFC requirements for MDIs

Future CFC requirements are difficult to predict given the uncertainties of transition, particularly in Article 5(1) countries. However, the volume of CFCs required under the essential use process in non-Article 5(1) countries is reducing and will likely be less than 500 tonnes in 2008, which may be the last year a request will be made. CFC use in Article 5(1) countries for MDI manufacture is currently estimated at about 1,800 ODP tonnes per annum.

If quantities of pharmaceutical-grade CFCs are needed to allow the transition to occur globally and there is a need for a final campaign production in the later part of the decade or for the transfer of existing stockpile, then this will need careful consideration and management. Issues that will need to be considered include: timeframe for transition; estimation of CFC quantities; existing stockpile of suitable quality; logistics, commercial, and legal requirements for stockpile transfer; storage; and destruction.

The management of stockpiles at this final stage of the phase-out will be extremely important to avoid unnecessary production of CFCs. An efficient process is required to allow for transfers of CFC volumes between parties and / or companies in order to maximize the use of existing CFCs and minimize the need for future CFC license and production volumes.

Pharmaceutical aerosol products other than MDIs

Technically and economically feasible alternatives are available for all medical aerosol products. The amount of CFCs used globally as propellants for pharmaceutical aerosol products (medical aerosols) other than MDIs has reduced substantially.

The manufacture of most CFC-containing medical aerosols in non-Article 5(1) countries ceased around 1996, or possibly shortly thereafter if stockpiled CFCs were utilised. It is only in some Article 5(1) countries that CFCs are still used in medical aerosols. China alone uses up to about 500 tonnes per year for Chinese traditional medicines, topical sprays and nasal sprays.

The worldwide phase-out of CFC-containing medical aerosols will occur as CFC production for developing countries is phased out under the Montreal Protocol schedule and as part of individual Article 5(1) country plans.

Sterilants

The use of ethylene oxide (EO)/CFC blends (12/88) for sterilization has been successfully phased out in non-Article 5(1) countries and in many Article 5(1) countries. Although it is difficult to estimate, it is believed that the global total use of CFCs in 2001 for this application was less than 500 metric tonnes, and has continued to decrease. In 2006, global CFC use for this application is likely to be minimal. Remaining worldwide use can be easily substituted, as there are a number of viable alternatives.

EO/HCFC mixtures (10 per cent by weight EO in a mix of HCFC-124 and HCFC-22) are virtual drop-in replacements for the 12/88 mixture and were introduced as transitional products for sterilization in those countries that employed 12/88 extensively. HCFC mixtures are now used mostly in the United States and in countries that allow venting of HCFCs to the atmosphere. The European Union has legislation restricting the use of HCFCs in emissive applications such as sterilization.

In 2005 the estimated use of HCFC replacement mixtures was thought to be less than 1,000 metric tonnes, which amounts to some 30 ODP tonnes worldwide. EO/HCFC use has been significantly reduced by using less mix per sterilizer load and by hospital conversion to other technologies.

EO/HCFC blends have a small ozone depletion potential (ODP) (0.03) and should not be promoted in countries that have not been major users of the 12/88 EO/CFC blend. EO/HFC blends are expected to replace the EO/HCFC mixtures, where they are used.

Alternative technologies to which hospitals have converted include: use of more heat-sterilizable devices, more single-use devices, pure ethylene oxide sterilizers and other methods that will sterilize or disinfect some of the low temperature devices used in hospitals. These other low temperature processes include hydrogen peroxide gas plasma, steam-formaldehyde, ozone and liquid phase peracetic acid.

Sterilization is an important process in the provision of good quality health services. It is also a process that requires strict application of the principles of quality management, reliability and long-term materials compatibility. Therefore, any alternative to the use of ozone-depleting substances needs to be well proven and tested to avoid putting the health of patients unnecessarily at risk.

1 Background to the 2006 Assessment

1.1 The Technology and Economic Assessment Panel

Four Assessment Panels were defined in the original 1987 Montreal Protocol, that is, Assessment Panels for Science, Environmental Effects, Technology and Economics. The Panels were established in 1988-89.

The Technical and Economics Assessment Panels were merged after the 1990 Meeting of Parties in London to the Technology and Economic Assessment Panel (TEAP). Currently the TEAP has six standing Technical Options Committees (TOCs) (apart from other temporary subsidiary bodies).

1. **Chemicals** Technical Options Committee
2. **Flexible and Rigid Foams** Technical Options Committee
3. **Halons** Technical Options Committee
4. **Medical** Techical Options Committee (MTOC)
5. **Methyl Bromide** Technical Options Committee
6. **Refrigeration, Air Conditioning and Heat Pumps** Technical Options Committee

1.2 The Medical Technical Options Committee and the 2006 Assessment

This report is part of the sixth assessment under Article 6 of the Montreal Protocol. The first assessment report was prepared in 1989, and subsequently updated in 1991, 1994, 1998 and 2002. This report is in response to Decision XV/53 of the Parties to the Montreal Protocol, which requested an assessment to be undertaken for completion by 31 December 2006 for consideration by the Open-ended Working Group and by the Nineteenth Meeting of the Parties in 2007.

Article 6 specifically directs Parties to assess whether the control measures, as provided for in Article 2 of the Protocol, are sufficient to meet the goals for reducing ozone depletion based on a review of the current state of knowledge on technical, scientific, environmental, and economic issues related to stratospheric ozone protection. The assessment reports assist with this review.

Since the 2002 assessment, the TEAP and its TOCs have been reorganised. In 2005, TEAP implemented the Chemicals Technical Options Committee to integrate topics including process agents and feedstocks, destruction, laboratory and analytical uses, non-medical aerosol products, solvents, and carbon tetrachloride. The Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee (ATOC) was reorganised as the Medical Technical Options Committee to address topics relating to metered dose inhalers, pharmaceutical aerosol products other than metered dose inhalers, and sterilants, which are covered in this assessment report.

MTOC is made up of experts from industry, government, scientific, research and academic institutions. In 2006, there were 24 members from 14 countries – Australia, Brazil, China, France, Germany, Ghana, India, Japan, Pakistan, Sweden, Switzerland, United Kingdom, the United States and Venezuela. MTOC membership information is presented at the end of this report.

This 2006 assessment report re-examines the current use of, phase-out and alternatives to ozone-depleting substances in medical aerosols, including metered dose inhalers, and sterilants. MTOC met in March 2006 and undertook extensive written communication in the preparation of this report during 2006. The report has undergone a peer review among experts from organisations and companies globally.

2 Metered Dose Inhalers

2.1 Introduction to lung diseases, epidemiology, treatment options and medical trends

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic diseases of the air passages (airways or bronchi) of the lung. Asthma alone is estimated to affect over 300 million people worldwide. These illnesses account for high health care expenditure, cause significant loss of time from work and school, and COPD in particular is responsible for premature death.

Treatment of these conditions most commonly involves inhalation of aerosol medication, which is deposited into the airways of the lung (bronchi). This allows maximal local effect in the airways where it is needed and minimum side effects of drug elsewhere in the body.

2.1.1 Asthma

Asthma is a chronic condition that affects around 300 million people worldwide with estimates that its prevalence is increasing rapidly in developing countries (in some countries by 50-100 per cent per decade). It has two main components, airway inflammation and bronchoconstriction (a spasm of the airway muscles). In many cases it causes few symptoms for weeks or months. Attacks occur intermittently, during which cough and wheeze develop and the airways narrow, making it very difficult to breathe.

Attacks of asthma may occur spontaneously or be triggered by many factors such as viral infections (colds), inhaled allergens (e.g. pollens), exercise, occupational dusts and fumes, medication (including aspirin) and others. Severe attacks of asthma usually require urgent additional medication and medical attention. They sometimes require hospitalisation. Such exacerbations can be fatal: asthma accounts for 1 in every 250 deaths worldwide. The rate of morbidity and mortality of attacks of asthma may be favourably modified if effective preventive medications are available and used, and if exacerbating, trigger factors such as air pollution are controlled.

Asthma causes considerable morbidity, and mortality, and affects all races. An international study of asthma in childhood has shown a prevalence of asthma that varies from approximately 1 per cent in some countries such as Indonesia to over 30 per cent in the United Kingdom, New Zealand, and Australia. In Western Europe 30 million individuals have asthma and the prevalence rate has doubled over the last decade.

While there are large differences in prevalence between affluent and less affluent countries, asthma has been increasing worldwide over the last two decades. This increasing prevalence is likely to be due to multiple factors including “westernisation”, reduced infections in infancy, changes in house design, greater exposure to house dust mite, maternal smoking, and diet. There may also be a synergistic action of air pollution and/or tobacco smoking.

Asthma most often starts in childhood. There is 50 per cent chance of improvement or remission from asthma in early adult years if the condition has been mild. It may however continue into or even start in adult life. In such cases it often causes persistent symptoms and may cause frequent attacks, chronic ill health, incapacity and high utilisation of the health care system. Globally, the

costs associated with asthma exceed those of tuberculosis and HIV/AIDS combined. The number of disability-adjusted life years (DALYs) lost due to asthma worldwide has been estimated to be currently about 15 million per year. This number is similar to that for diabetes, cirrhosis of the liver and schizophrenia.

2.1.2 Chronic obstructive pulmonary disease

COPD is a condition of narrowing and inflammation of the airways (bronchitis) in conjunction with damage to the lung tissue (emphysema). These two components may vary considerably in prominence from patient to patient, with some patients having predominantly chronic bronchitis and others having predominantly emphysema. COPD is caused primarily by cigarette smoking but may result, in part, from inhalation of certain occupational dusts or environmental air pollution. Once present, COPD is persistent and usually progresses at an increasing rate if the patient continues to smoke. Even after smoking is ceased, continued deterioration of lung capacity occurs (though at a rate similar to that seen in normal aging). This contrasts with asthma, in which regular treatment can generally maintain normal lung function and minimise the frequency of acute attacks. Deterioration of lung function in COPD ultimately leads to a poor quality of life and permanent disability.

Exacerbations of COPD, or intermittent, sudden worsening in breathing, may occur and are often associated with acute infections. Due to the already impaired lung function, exacerbations of COPD frequently require hospitalisation and impose a considerable financial burden to the individual and to society. In many countries 50-75 per cent of the costs of COPD are attributable to COPD exacerbations.

COPD prevalence and mortality data that are currently available greatly underestimate the burden of disease because it is usually not recognised and diagnosed until it is clinically apparent and moderately advanced. The estimated prevalence of COPD in many developed countries is around 4-17 per cent in the adult population aged over 40 years. Data are less certain in developing countries but figures as high as 26 per cent have been quoted. Until recently population-based studies showed a markedly greater prevalence and mortality of COPD among men compared to women. Recent studies in the United States show a different pattern emerging, with the prevalence of COPD higher in women and mortality in this group doubling over the past 20 years. In developing countries some studies have also shown a higher prevalence of COPD in women compared to men.

Smoking is beginning to decline in some developed countries, but trends in developing countries indicate that both smoking and the prevalence of COPD are of increasing concern.

The 1996 Global Burden of Disease Study compared the leading causes of disability in 1990 and those projected for 2020. In 1990 COPD was ranked 12th and in 2020 is projected to rank 5th among the conditions that are likely to be the highest burden to society on a worldwide scale (behind ischaemic heart disease, major depression, traffic accidents and cerebrovascular disease).

COPD is currently the fourth most common cause of death worldwide, behind heart disease, cancer and stroke. In 2001 over 2.5 million people around the world died from COPD. This number is expected to double by 2020 when COPD is projected to rise to the 3rd leading cause of death.

2.1.3 Treatment

Primary prevention of asthma is not yet feasible. The primary means to prevent the development of COPD is to avoid smoking. Once the conditions have been established, treatment depends on avoiding trigger factors and the use of regular medications to control the condition.

Avoidance of asthma trigger factors is only possible for some factors. Most trigger factors, such as viral infection, pollution, changes in weather, are impossible to avoid. In patients with COPD, smoking cessation is crucial to minimising the progress of the condition. Medication to help patients cease smoking is available but is not associated with aerosols and will not be discussed further here.

The preferred method of drug therapy for asthma and COPD is by medications that are delivered to the airways by means of a hand-held inhaler device. This has the advantage that the medication is delivered directly to the site of the problem, minimising the dose of drug needed and thereby minimising systemic side effects. It also permits a more rapid onset of action than administration by tablets or other oral dosage forms. Drug therapy for asthma is usually highly effective. Drug therapy for COPD is somewhat less effective but has an important role in minimising symptoms and frequency of exacerbations.

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

2.1.3.1 Bronchodilators (reliever medication)

Bronchodilators reduce muscle tightening that contributes to the narrowing in the airways. Virtually all patients with asthma and COPD require short acting bronchodilators. They are the key treatment for acute attacks and may be lifesaving in severe attacks. In intervals between attacks, bronchodilators may be needed through the day; particularly in children for whom exercise induced asthma is common. Bronchial muscle tightening is a greater feature of asthma than COPD, hence the greater effect of the drugs in asthma than COPD.

Bronchodilators fall into four main classes:

- *Short acting beta-agonists* – These are the mainstay of rescue therapy for asthma and COPD. Short acting beta-agonists include albuterol/salbutamol (e.g. Ventolin™), levalbuterol/levosalbutamol (Xopenex™), terbutaline (Bricanyl™), and fenoterol (Berotec™). They act within a few minutes, and have an effect lasting approximately 4 hours.

- *Long acting beta-agonists* (salmeterol (Serevent™), formoterol (Oxis™ or Foradil™)) have an effect that may last for up to 12 hours. Due to their prolonged duration of action they are often included in the "preventer" or "controller" category, but they are not anti-inflammatory in action. They are also combined in a single inhaler with inhaled steroids (Symbicort™ from Astrazeneca; Seretide™ or Advair™ from GlaxoSmithKline). Bambuterol (Bambec™ from AstraZeneca) is a long acting beta-agonist produced only as an oral formulation.

- *Anti-cholinergics* (e.g. short-acting ipratropium bromide (Atrovent\), long-acting Tiotropium (Spiriva)) – These are commonly used in COPD, where cholinergic tone plays an important role in bronchodilation.

- *Methylxanthines* (e.g. theophylline/ aminophylline) – These are widely available and inexpensive oral medications but not particularly effective. They have a high rate of side effects. Inadvertent excess dosage can cause serious, potentially fatal side effects.

2.1.3.2 Anti-inflammatory medication (controllers or preventers)

Inflammation of the airways is a fundamental part of asthma, and suppression of this inflammation is recommended in all but those with mild and infrequent symptoms. Anti-inflammatory treatment stabilises lung function and prevents acute exacerbations of asthma if used regularly, hence the term "preventer" that is sometimes applied. Some preventers are used in COPD, particularly the glucocorticosteroids, but are not as effective in this condition. Preventers are usually one of four classes of drug:

- *Inhaled glucocorticosteroids (or inhaled steroids)* (e.g. beclomethasone, budesonide, flunisolide, fluticasone, mometasone or triamcinolone) – These are the mainstay of preventer medication for asthma and COPD.

- *Inhaled cromoglycate-like drugs* (e.g. sodium cromoglycate or nedocromil sodium) – Though individual patients may find this class of drugs quite effective for their asthma and though cromoglycate drugs have proven to be quite safe, these agents are not as broadly effective as the inhaled glucocorticosteroids, and are rapidly falling from favour. Sodium cromoglycate has recently been withdrawn from the market in the United Kingdom.

- *Oral Leukotriene modifying drugs* (montelukast, zafirlukast, zileuton) – These are oral drugs that are less effective overall than inhaled steroids but particularly useful to some groups of patients. In the United States, one oral drug, montelukast (Singulair, Merck), a leukotriene receptor antagonist has gained approximately 50 per cent of the market share (by prescriptions) for preventer drugs and has led to some reduction in the use of inhaled preventers.

- *Oral glucocorticosteroids* (dexamethasone, prednisolone, prednisone) – These are only used to treat acute severe episodes of asthma and COPD and are considered lifesaving. Used long term they have major side effects and are restricted to patients with extremely severe disease.

2.1.4 Aerosol Delivery

Aerosol medication is most conveniently administered with hand held inhaler devices. The most commonly used and convenient devices are the metered dose inhaler (MDI) and the dry powder inhaler (DPI). A number of devices have been developed for delivery of aerosol medication to the lungs since no single device is likely to be effective for all users. These are described in more detail in the next section.

Inhaler devices are only effective if used correctly. Many patients are not able to correctly coordinate actuation (that is, spraying) and inhalation of an MDI. Patients will often be able to use one device correctly but not another (e.g. a DPI but not an MDI). Incorrect use of inhalers is most common in young children, older adults, those with certain manual disabilities and those who have not been instructed correctly. Due to these considerations, a variety of devices is needed so that patients can find a device which is effective for them.

Hand-held devices may be less effective during an acute attack of asthma, where inhalation may be impaired, and when respiratory distress may lead to panic. In addition, higher than usual doses of inhaled medication may be needed to treat attacks of asthma. Patients require training in management of acute asthma, over and above routine use of an inhaler device. In some cases either nebulised or injected medication is needed. Other methods of delivery are also available and these include oral medications and injectable products.

2.1.5 Oral medication

The optimum method of administration is determined by the drug's mechanism of action, pharmacokinetics, metabolism and therapeutic index (effect/side effect ratio). Oral medications, including tablets, capsules and oral liquids, have been the standard form of therapy for most diseases for many years. However, chronic administration of drugs by the inhaled route has been favoured for asthma and COPD because of the superior therapeutic index for some medications (e.g. beta-agonists and corticosteroids).

Oral medication is taken by mouth, swallowed and absorbed in the gastrointestinal tract. The active moiety circulates throughout the body and contacts many tissues (including the respiratory tract). Oral administration has the advantage of delivering therapeutic concentrations of medication to areas of lung or small airways not reachable by inhaled drugs. Many patients also prefer the oral route to inhalation. However, with oral administration, higher circulating concentrations are required for efficacy (versus inhaled therapy) and this may lead to unwanted systemic effects. These may be due to either side effects of the drug itself, or due to interactions with other drugs.

A newer class of oral medication, leukotriene receptor antagonists (LTRA), has been approved for the treatment of asthma. This class is particularly useful to some asthmatic patients, as discussed in the previous section.

It is considered unlikely that any novel oral medication now under development would significantly change these guidelines for the treatment of asthma or COPD if approved in the next five years.

2.1.6 Injectable therapy

Some drugs used for the treatment of asthma and COPD are also available for administration parenterally and are used in a hospital setting. However, regular injections (i.e. daily) are neither justifiable, nor feasible for general use in ambulatory asthma or COPD patients. Even during a life threatening asthma attack in a hospital, a successful outcome is usually achieved, and with greater comfort for the patient, by delivery of appropriate medication by the oral or inhaled route.

Nonetheless, an injectable antibody to immunoglobulin-E (the antibody type largely responsible for allergic reactions) is marketed by Novartis in several markets, including the United States,

Australia and Brazil. In addition, a number of biological response modifiers are under development and may prove to have utility in the treatment of asthma. These are often delivered by injection, but may require only weekly or monthly administration.

At this point, it does not appear that the oral and parenteral therapies can be expected to generally replace inhaled therapies as the preferred manner of treatment, as the current systemic medications have limited efficacy and therefore limited roles in therapy. However, since some oral therapies are quite inexpensive (e.g. theophylline), some of these therapies are more commonplace in Article 5(1) countries.

2.2 Aerosol Delivery

2.2.1 CFC MDIs

An MDI is a complex system designed to provide treatment for respiratory diseases such as asthma and COPD. It produces a fine mist of medication, generally with an aerodynamic particle size less than 5 microns, for inhalation directly to the airways. These products have now been in widespread medical use for over 50 years.

Historically, MDIs have used chlorofluorocarbons (CFCs) as a propellant. CFC-containing MDIs contain CFC-12 and CFC-11, and sometimes CFC-114. It is essential that the propellant is a liquefied gas, as the constant vapour pressure above the liquid generates a consistent spray throughout the life of the MDI. Hydrofluorocarbon (HFC) propellants are now replacing these gases.

Technically satisfactory alternatives to CFC MDIs are now available for short-acting beta-agonists and other therapeutic categories for the treatment of asthma and COPD. These have been developed over a number of years by a number of pharmaceutical companies.

Whilst much effort has been focused on developing in-kind replacements for CFC MDIs (i.e. HFC MDIs) there are other methods of delivering drugs to the lung. Alternative methods to CFC MDIs for pulmonary drug delivery include:

- HFC MDIs;
- DPIs, single or multi-dose;
- Nebulisers; and
- Soft-mist inhalers.

2.2.2 HFC MDIs

The process of reformulating MDIs with HFCs began over 15 years ago when HFC-134a and HFC-227ea were proposed as alternatives to CFCs. These HFCs then underwent extensive toxicological testing and were deemed to be safe for human use. Since that time, individual pharmaceutical companies have been working to reformulate their MDI product(s) to replace CFCs with the appropriate HFC. This has been difficult since the most common surfactants used in CFC-based inhalation aerosols (e.g. lecithin, Span 85) are not soluble in HFCs and new formulation strategies have had to be developed. The valve elastomers used on CFC valves are also not always compatible with HFCs. Furthermore the absence of an acceptable HFC that is

liquid at room temperature has meant the development of new manufacturing processes. Therefore companies have had to be innovative in their reformulations and each product has been treated as a completely new development, sometimes including excipients previously not used in inhaled products.

Both propellants HFC-134a and -227ea are now being widely used to formulate drugs in MDIs. There are several products whose reformulation is essentially complete and their registration has taken place globally (e.g. products containing salbutamol and a range of inhaled corticosteroids). It is likely that a number of products (usually older drug moieties or generic products) may never be reformulated due to technical challenges, economic considerations or changes in medical practice so suitable medical alternatives will need to be sought. For most of these, there are either suitable CFC-free alternatives in the same therapeutic category or other satisfactory alternative therapies. In addition, there have also been recent introductions of new moieties, such as Altana's ciclesonide, that were developed directly as an HFC MDI.

All the HFC MDIs contain the same physical components as the CFC MDI products (e.g. drug, propellant, canister, metering valve and actuator) but the very different physical properties of the HFC propellants has meant that significant changes have had to be made to the technology in these components. Although the active ingredient remains the same in most cases, there are now a growing number of HFC-propelled MDIs that have the drug in solution whereas almost all CFC MDIs were presented as suspensions. Some formulations contain a co-solvent such as ethanol to help dissolve the surfactant or drug. There are also products on the market that do not contain a surfactant, simply being a suspension of micronised drug in propellant.

Although the elastomeric components of the metering valve have had to be changed to accommodate the HFCs (and in some cases the actuator has also been modified), this may not be noticeable to the patient. While the HFC MDI used by the patient may superficially look the same as the CFC MDI, the HFC products often have a different taste and mouth feel.

2.2.3 Dry Powder Inhalers

The DPIs are devices that deliver powdered medication (and sometimes excipients) of specific particle size. The first DPI became available in 1968 and like all DPIs until the late 1980s, consisted of single pre-measured doses stored in gelatine capsules (single-dose products). New single-dose products are still being introduced today, along with new multi-dose formulations.

DPIs have been formulated successfully for most anti-asthma drugs and are now widely available, although only a few drugs are available in any specific device. These inhalers represent currently available alternatives for a large proportion of patients. Some patients prefer DPIs because of their ease of use; and in some countries DPIs are the delivery system of choice for the treatment of asthma and COPD. However, at present they are not an alternative to the pressurised MDIs for all patients or for all drugs.

Some dry powder formulations contain the active drug alone while others have a carrier powder such as lactose. The drug particles must be of sufficiently small aerodynamic diameter to reach and be deposited in the airways. Micronised dry powder can be inhaled and deposited effectively in patients with adequate breathing capacity. However, younger children and some patients with severe asthma or severe COPD (particularly the elderly) may not always be able to generate an adequate inspiratory flow to ensure optimal medication delivery from all DPIs.

Powdered drug particles tend to aggregate, thus delivery devices usually contain a mechanism to ensure adequate de-aggregation of the drug powder or separation of drug powder and carrier (where the product contains carrier) so that the drug particles are sufficiently small to be inhaled deeply into the lungs. It is essential that patients handle and use their DPIs properly, for example in hot humid climates where excessive powder aggregation otherwise might impair its efficacy.

Single-dose powder inhalers are devices in which a powder-containing capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled. The capsule must be discarded after use and a new capsule inserted for the next dose.

Several introductions of single-dose DPIs have occurred over the last few years (e.g. Aerolizer™ for formoterol from Novartis/Schering-Plough). Where launched, their use has not been significant to the overall uptake of DPIs.

However, in many developing countries, single-dose DPIs may have a role because they require simple manufacturing technology, and can provide the opportunity to purchase a small number of doses at an affordable cost. In India, for example, it is estimated that up to 50 per cent of inhaled medication sold is in the form of single-dose DPIs. Though there are concerns regarding aggregation of particles in the hot and humid climate, they have been generally found to be effective.

Multi-dose powder inhalers can deliver many doses without the need to refill the device after each inhalation. They typically either have drug in a blister or contain drug that is metered from a drug reservoir. Current products vary from four to up to two hundred doses. There is an increasing use of the multi-dose DPI and this is likely to accelerate with the more widespread availability of commonly prescribed products as new multiple dose devices.

Historically, DPI usage was estimated to be less than 20 per cent of all inhaled medication globally (in unit terms). In the past, the DPI was widely accepted in Europe but only a limited number of products were available in the United States, and even less in Japan.

Global use of DPIs has increased to over 30 per cent of inhaler units. The use of DPIs in Europe in absolute unit numbers has now grown to over 50 million units per annum and is now comparable to HFC MDI usage. In Scandinavia, DPIs now account for about 90 per cent of inhaled therapy. This increase in use is mainly due to expansion of established products and the launch of new products, such as corticosteroid/long-acting beta-agonist combinations in established DPIs. In addition, there is increased availability of generic drug substances in novel multi-dose DPIs.

The United States was traditionally an MDI market, with few DPIs used up until the year 2000. However, a number of DPI products have been introduced in the past several years (GlaxoSmithKline the combination of salmeterol and fluticasone, in the Diskus™, Novartis' formoterol Aerolizer™, Boehringer Ingelheim's tiotropium HandihalerTM; Schering Plough's mometasone furoate TwisthalerTM). The use of newly available DPIs in the United States has increased markedly reaching nearly 27 per cent of the total inhaler market share by 2005, supporting the global acceptability of modern DPIs.

In Japan, since 1998, a number of multi-dose and single-dose DPI products have entered the market and there are now a range of DPI products available. GlaxoSmithKline's fluticasone Diskhaler™ was initially introduced and multi-dose DPIs of budesonide fluticasone,

beclomethasone, salmeterol, and procaterol are now available. Two single-dose DPIs of cromoglycate and tiotropium are also available. DPI usage in Japan was estimated to be at approximately 55 per cent of inhaled medications in 2005.

Likewise multi-dose DPI products are available in other countries, which also report steady market penetration.

Substantial development efforts are being pursued in the DPI segment by a number of pharmaceutical and technology based device companies. This includes the development of new devices as well as new products in established DPI systems. Also, some generic multi-dose DPI products have entered the European market during the last few years. A number of novel devices, mainly multiple-dose, are reported to be in late phase of clinical evaluation or subject to regulatory approval; few have yet reached the market. The introduction of new and improved DPI products is likely to further stimulate the expansion of this treatment alternative over the next decade.

In general, DPIs and branded MDIs of the same drug are, on a cost per dose basis, priced similarly. However, in some countries there is a significant price difference between DPIs and generic MDIs of the same drug. This is due, in part, to the true differential in production costs between DPI and MDI devices, and may also be related to national pricing policies and local market considerations. The gradual introduction of generic DPI products may however change the present price difference.

2.2.4 Nebulisers

Nebulisers are devices that are filled with drug dissolved or suspended in aqueous solution, which is converted to inhalable droplets using compressed air or ultrasonic waves. The situation is different than that with portable inhalers, in that the pharmaceutical companies supply drug formulations, but not the delivery device. Thus, in principle, any formulation could be used with any nebuliser. However, differences in nebuliser performance have led to recommendations for the use of a particular formulation only with selected nebulisers, usually those with clinical data to support their use. Thus, nebulisers have generally not been considered as alternatives to MDIs and have been restricted mainly to the treatment of infants and severely ill patients where patient cooperation is minimal; or to situations when larger doses of drug and/or prolonged administration times are desired.

Air jet nebulisers use a source of compressed air to provide the energy to break up the liquid into small droplets. Established systems are not readily portable, are powered by compressed gas or electricity, and largely restricted to home or hospital use. Some portable systems have been recently introduced in their first markets. However they are still dependent on external power supply and therefore restricted in their use.

Ultrasonic nebulisers utilise a vibrating crystal at the bottom of a nebulising chamber. The crystal vibration causes droplets to form on the surface of the liquid. These can be entrained in a stream of air created either by a fan or by the patient inhaling. Ultrasonic nebulisers are efficient but require either a battery or external power source. They tend to be expensive and cannot be used for all drug formulations particularly suspensions.

2.2.5 Soft mist inhalers

Small portable devices that produce aerosols of respirable diameter from aqueous formulations have been under development for a number of years (so-called Soft Mist Inhalers). These new-generation devices produce an aerosol through mechanisms different from those described for nebulisers. The mechanisms include collision of two jets of liquid to produce an aerosol, forcing liquid through tiny micron-sized holes, vibrating mesh or plate, or other novel mechanisms (e.g. electro-hydrodynamic effects). The combination of improved efficiency and smaller aerosol particle size from these devices ensure that the aerosol they generate can be deposited deeply into the lungs and therefore serve as local delivery for treating lung disease or for absorption for systemic delivery.

One of these devices, Boehringer Ingelheim's RespimatTM utilises the collision of two liquid jets to generate an aerosol and has been launched in the European Union for delivery of a combination-bronchodilator product for use in COPD patients. A vibrating mesh device approved in the United States is used for delivering drugs other than for asthma and COPD (Pari eFlow). While some of the other devices in development may serve as alternatives in the future, their contribution to the asthma and COPD management is likely to be limited as the majority are being developed for either systemic drug delivery or for local delivery of drugs other than asthma and COPD drugs (e.g. antibiotics). These devices are also likely to be much more expensive than standard MDIs and DPIs.

2.3 Availability of CFC-free alternatives

Progress in the transition to CFC-free alternatives has been evaluated by reviewing data provided by the International Pharmaceutical Aerosol Consortium (IPAC) on products from its constituent members, together with those from 3M and Ivax (Teva) and other publicly available documents. It is clear that progress has continued in the development and registration of HFC MDIs and DPIs and now a number of companies are well underway in phasing out their CFC MDIs. Listed below in Table 1.1 are the HFC MDI products that have been developed and registered as of the end of 2005.

Table 1.1 Progress in CFC-free MDI introduction by moiety and company: table data refer to numbers of countries

Moiety	Company	Launched by Apr 04	Launched by Dec 05
Beclomethasone	3M	22	22
	Chiesi	11	22
	GlaxoSmithKline	6	19
	Ivax	27	27
Budesonide	AstraZeneca	0	0
	Chiesi	1	15
Fenoterol	Boehringer Ingelheim	20	20
Fenoterol and Ipratropium	Boehringer Ingelheim	19	19
Fluticasone	GlaxoSmithKline	44	111
Formoterol	Chiesi	0	11
Ipratropium	Boehringer Ingelheim	13	28
Levosalbutamol	Sepracor	0	1
Nedocromil	Sanofi-Aventis	9	9
Salbutamol	3M	30	30
	GlaxoSmithKline	86	96
	Ivax	34	39
Salmeterol	GlaxoSmithKline	0	1
Sodium cromoglycate	Sanofi-Aventis	*14	*14

*Includes one launch of sodium cromoglycate in combination with reproterol.

Further analysis of the data, which is presented in Table 1.2, shows that in many countries more than one product is widely available.

Table 1.2 Device approvals and subsequent launches in all countries: table data refer to numbers of countries (as of October 2006)

Moiety	Device	Approved	Launched
Beclomethasone	DPI	45	39
	HFC MDI	77	61
Budesonide	DPI	83	76
	HFC MDI	*17	15
Fenoterol	DPI	0	0
	HFC MDI	62	25
Fenoterol and Ipratropium	DPI	0	0
	HFC MDI	41	27
Fluticasone	DPI	94	77
	HFC MDI	145	111
Formoterol	DPI	61	52
	HFC MDI	12	11
Ipratropium	DPI	0	0
	HFC MDI	74	40
Levosalbutamol	DPI	0	0
	HFC MDI	1	1
Nedocromil	DPI	0	0
	HFC MDI	9	9
Salbutamol	DPI	74	66
	HFC MDI	176	112
Salmeterol	DPI	84	65
	HFC MDI	3	1
Sodium cromoglycate	DPI	2	2
	HFC MDI	**14	**14
Terbutaline	DPI	74	51
	HFC MDI	0	0

*Includes 1 approval from AstraZeneca in February 2006
**Includes one launch of sodium cromoglycate in combination with reproterol.

It is also important to consider the data in Table 1.3 that presents the number of countries where at least one product has been approved. It is recognised that this is likely to be an underestimation of the true situation, as it takes no account of CFC-free products that have been introduced by producers other than IPAC member companies, 3M and Ivax (Teva).

There is widespread availability of salbutamol (short-acting beta-agonist and the primary treatment for asthma in many countries) HFC MDIs in many countries, with almost 60 countries

where there are at least two products approved. This is also true for a number of inhaled corticosteroids, including budesonide, beclomethasone and fluticasone propionate. The introduction and acceptance of multi-dose powder inhalers has continued, along with single-dose DPIs (particularly in some Article 5(1) countries).

However, it is clear from accumulating experience that the development and registration of alternate products cannot alone lead to a full uptake in the market without additional regulatory action.

Table 1.3 The number of countries where at least one alternative to CFC MDIs is available (as of October 2006)

Moiety	Approved	Launched
Beclomethasone	85	79
Budesonide	85	79
Fenoterol	62	25
Fenoterol and Ipratropium	41	27
Fluticasone	148	128
Formoterol	61	52
Ipratropium	74	40
Nedocromil	9	9
Salbutamol	176	136
Salmeterol	84	65
Sodium cromoglycate	*14	*14
Terbutaline	74	51

*Includes one launch of sodium cromoglycate in combination with reproterol.

2.4 Transition to alternatives to CFC MDIs

It is now over 12 years since the first introduction of an HFC MDI for the short acting beta-agonist salbutamol in the United Kingdom in 1994. In 2002, MTOC estimated that at least 25 per cent of salbutamol MDIs marketed around the world contained HFC as a propellant. By the end 2005, this had risen to around 40 per cent. By the end of 2005 all countries of the European Union had declared CFC MDIs for salbutamol non-essential. Salbutamol CFC MDIs may continue to be sold in the United States until the end of 2008, following which their sale will be illegal.

Both the European Union and the United States are actively considering the phase-out of the remaining non-salbutamol CFC MDIs, which is likely in 2008/9. One of the last products to be converted will be the combination bronchodilator inhaler of salbutamol and ipratropium bromide (Combivent, Boehringer Ingelheim). The separate products are available as HFC MDIs, but the combination in a single inhaler has been valuable for convenience, compliance and cost for patients with COPD. Both a propellant-free device and an HFC MDI are in development but they have proved very difficult to reformulate, and the continued availability of the CFC product until an adequate alternative is available may necessitate an adequate and safe supply of pharmaceutical-grade CFCs for a further 6 years of use. If it ultimately proves technically impossible, safe but separate alternatives to the combination product are widely available.

As anticipated, there have been no major problems with transition, including no major product issues. The lack of problems may be attributed in part to the use of widespread education campaigns (primarily conducted by the pharmaceutical industry) to both healthcare professionals and patients on why the MDI needs to change and what the changes entail.

Moreover it is very clear that the development of HFC MDIs and their registration and launch into the market is only partially effective in achieving transition. There is also a need for an additional step; for MDI companies to cease supplying the CFC MDIs. Some pharmaceutical companies have not done this. There are also some companies, such as some generic pharmaceutical manufacturers, that have not developed CFC-free MDIs and they will continue to produce CFC MDIs for as long as they are allowed. It has proved necessary for national governments to identify, adopt, and implement regulatory policies to ensure that the transition is completed in a timely and safe manner, once sufficient, CFC-free alternatives are available.

In the past decade, as well as the introduction of HFC MDIs, there has also been a rapid increase in the introduction and acceptance of multi-dose DPIs. This has been partly fuelled by the availability of state-of-the-art therapy options (a combination of long-acting beta-agonists and inhaled corticosteroids) in at least two widely accepted powder inhalers.

It is encouraging that pharmaceutical companies are introducing all new drugs directly in CFC-free devices. Following the successful introduction of products such as mometasone furoate in a multi-dose dry powder inhaler and tiotropium bromide as a single-dose dry powder inhaler, there have been recent launches of ciclesonide and levalbuterol, both as HFC MDIs. These products, introduced without a direct antecedent CFC-based counterpart, offer important new treatment options.

2.4.1 Transition strategies

The transition strategies of six Parties are listed on the UNEP web site. Pursuant to Decision XV/5(4), plans of action regarding the phase-out of the domestic use of CFC-containing MDIs from the European Community, the Russian Federation and the United States are listed on the UNEP web site.

The rate of transition from CFC MDIs to CFC-free products has varied from country to country. Even when new products have been introduced, the rate of their uptake has varied. This has occurred for a number of reasons including price considerations and the varied regulatory frameworks that cover product withdrawals in various countries.

The introduction of an HFC MDI alone does not lead to a successful transition. Experience has indicated that transition can best be achieved by pharmaceutical companies ceasing CFC MDI manufacture and by regulatory policies that phase out corresponding CFC products on a drug-by-drug or category-by-category basis once alternatives are widely available.

In predominantly importing countries such as Australia, Japan and Canada, transition has been successfully accomplished.

For example, in Japan companies that manufactured or imported CFC MDIs organized a committee to address ozone layer protection in 1989. Later, in December 1998, the Japanese Government submitted a transition strategy, which resulted from cooperation with the committee. The strategy included a timeline of "by 2005" for the phase-out and allowed for brand-by-brand substitution.

The committee and each pharmaceutical company made considerable effort to develop CFC-free alternatives and introduce them to the market. The first introduction of an HFC MDI was in 1997, and there are now a total of 21 brands of CFC-free alternatives (HFC MDIs and DPIs) on the market in Japan. These alternatives cover the full range of the CFC MDIs they replaced. All companies completed both production and import of CFC MDIs in 2004.

Although the successful development of alternative products is important, the transition to CFC-free alternatives was made possible by the cooperation of the government authorities and industry, which resulted in an appropriate transition strategy.

Increased regulatory involvement is now likely to be needed as the transition reaches the phase where there will be a few CFC MDI products remaining. These products will either be technically very challenging to reformulate or low volume products that cannot justify resources to support reformulation. As such, physicians and pharmaceutical companies will need to indicate their intentions as to how they plan to serve the needs of the remaining patients who take these medicines. In the United States there has begun a process to evaluate older medications that are unlikely to be reformulated or may now no longer be needed by physicians. The list of drugs under review includes flunisolide, metaproterenol, ipratropium and salbutamol combination, pirbuterol, epinephrine, triamcinolone, cromoglycate and nedocromil.

In some countries there is a large proportion of generic CFC MDIs that are priced significantly lower than the brand name CFC MDIs and HFC alternatives. Since payors (purchasers, health authorities, insurance companies or patients) will continue to favour lower priced medicines, countries will have to address the means to have payor acceptance of the CFC-free alternatives.

Despite widespread educational initiatives, transition does not appear to be a high priority among most healthcare providers, many of whom have taken a passive approach to transition. Pharmaceutical companies' educational and marketing endeavours have been the main driving force in the uptake of alternatives.

2.4.2 Potential barriers to CFC MDI phase-out

Experience to date suggests that transition plans will only be successfully implemented if there are frank discussions among the major stakeholders, that is, MDI manufacturers, health and environmental agencies. In addition, the involvement of national medical professional organisations will be needed. International organisations or programmes, such as the Global

Initiative for Asthma (GINA), the Global Initiative on Obstructive Lung Disease (GOLD), the International Union Against Tuberculosis and Lung Disease (IUATLD) and the World Health Organization (WHO), may also have roles to play.

There are continued concerns over the cost and/or availability of healthcare in all countries, particularly in Article 5(1) countries. Notably, inhaled therapies are usually more expensive than commonly available oral medications that are less effective and maybe more hazardous. Price (which means the acquisition cost for the patient or for the government which partly or wholly assumes responsibility for the cost of medicine) is an important factor in the use of inhaled therapy. The price of CFC alternatives could be a major barrier to transition if they are more expensive than comparable CFC products, unless governments and other payors agree to cover the higher cost of CFC-free alternatives.

Concerns have been raised regarding intellectual property and its potential impediment to transition, particularly in Article 5(1) countries. MTOC recently undertook a preliminary evaluation of the existing intellectual property in Article 5 (1) countries and it does not appear that formulation patents will provide an insurmountable barrier to the introduction of HFC MDIs into Article 5(1) countries. While the situation varies between active moieties, and between countries, there are no overarching patents that would prevent a general introduction of HFC MDIs. However, it should be emphasised that this observation is based on a survey of formulation patents that have been prosecuted by major multinational pharmaceutical companies in those Article 5(1) countries comprising the top ten users of MDIs by volume. Process patents, such as those in India, have not been considered here. There may also be patents from domestic researchers and producers in individual countries, such as China, which have also not been addressed.

There are some local exceptions to this situation that are worthy of note, which are described in the *Report of the TEAP, Progress Report, May 2006* (section 2.4.4, page 47).

2.5 Transition in Article 5(1) countries

The situation in a number of regions and Article 5(1) countries has been described recently in the *Report of the TEAP, Progress Report, May 2006*[1], and in the report prepared by the Fund Secretariat for the Executive Committee of the Multilateral Fund for the Montreal Protocol (UNEP/OzL.Pro/ExCom/49/39). MTOC does not have complete information for all Article 5(1) countries and instead has described the general situation for Articles 5(1) countries for this report.

The CFC MDI transition has proved to be complicated, as it is influenced by medical, technical, economic and regulatory factors. In Article 5 (1) countries, this transition is occurring as a part of the overall phase-out of CFCs. Competition for supply of CFC between all uses may compromise

[1] As an update of information regarding Pakistan, most inhalers are imported either by multinational companies (90 per cent) or by local companies (10 per cent). For 2005, Pakistan was reported to use about 86 tonnes of CFCs for local MDI manufacture, with about 20 tonnes used by nationally owned companies. Currently over 90 per cent of inhalers available in the market are CFC-containing MDIs. Last year, two companies introduced CFC-free inhaled corticosteroids, which cost approximately 10 per cent more than their CFC counterparts. The first DPI (a corticosteroid) was also introduced. New CFC-based MDIs imported from China are also still being launched.

supply of CFCs for MDIs. As the phase-out schedule for CFCs in Article 5(1) countries approaches 85 per cent reduction from baseline in 2007 and 100 per cent in 2010, Parties have raised concerns about difficulties facing some Article 5(1) countries that consume CFCs for the manufacture of MDIs.

The Montreal Protocol mandates that all CFC production must be phased out by the end of 2009. Given the widespread availability of technically and economically feasible alternatives, MTOC believes that global phase-out of CFCs in MDIs is achievable by 2010. However, to ensure this occurs, there is an urgent need for all Article 5(1) countries that have not already done so to develop effective national transition strategies in accordance with Decision XII/2. MTOC strongly recommends that these activities be made a priority to ensure a smooth transition to CFC-free alternatives congruent with the Montreal Protocol phase-out schedule. The development of transition strategies could be facilitated by a series of regional workshops.

There are diverse conditions prevailing across these countries that make it difficult to recommend a uniform strategy for transition to CFC-free alternatives. In particular, there is a need to differentiate between the following.

Countries that rely mainly on imports

In countries that rely mainly on imports, the transition to CFC-free products will be driven mainly by marketing strategies of the multinational pharmaceutical companies and their desire to introduce products globally once developed. Also, as the availability of pharmaceutical-grade CFCs reduces, multinational companies will continue to rapidly introduce CFC-free alternatives in Article 5(1) countries.

The national health and trade authorities will also drive transition. Transition strategies will be relatively simple, and be mainly concerned with regulatory approval of CFC-free alternatives and patient and physician education programmes. In most of these countries the affordability of alternative CFC-free products may be a factor in transition.

Countries will need to set an end-date for transition that accounts for the Montreal Protocol phase-out schedule.

Countries that manufacture MDIs

Countries that manufacture MDIs, such as Argentina, Bangladesh, Brazil, China, Colombia, Cuba, Egypt, India, Indonesia, Iran, Jordan, Mexico, Pakistan, South Africa, Turkey and Uruguay, will each need to develop a detailed national transition strategy to phase out CFC MDIs. Details of such strategies would include the following:

- Set a date for cessation of sales of CFC MDIs that takes into account the Montreal Protocol phase-out schedule;

- Involve stakeholders (national departments of health, environment, NGOs, MDI manufacturers, physician and patient groups) in developing the strategy. This group would also lead on the education of physicians, other healthcare workers, and patients. In countries where only a small percentage of patients use MDIs, increasing the use of inhaled medication could be achieved by single-dose DPIs or other low cost alternatives;

- Ensure adequate supplies of inhaled therapy through phase-out. This will need adequate supplies of bulk pharmaceutical-grade CFCs, which may be affected by the CFC production phase-out schedule from 2007 until the end of 2009 under the Montreal Protocol. If Article 5(1) countries do not take effective action now, they will face difficulties in achieving transition by 2010. In these circumstances, a final campaign production or a transfer of existing stockpile may need to be considered to ensure CFC supply for MDI manufacturing beyond 2009;

- Ensure adequate supplies of CFC-free alternatives. A range of HFC MDIs and DPIs are now approved for use in many Article 5(1) countries. Companies will need to ramp up production of alternatives during transition. Patents do not appear to provide a significant impediment to transition in Article 5(1) countries. National and international procurement programmes (such as www.globaladf.org) implemented to procure inexpensive inhalers for developing countries should only use CFC-free inhalers. Local manufacturing companies should avail themselves of technology transfer, which may require funding.

In some of these Article 5(1) countries there are a relatively large number of local companies producing CFC MDIs who have not yet gained access to the skills or knowledge to introduce suitable CFC-free alternatives. It is critical to ensure that appropriate technical expertise is identified, that funds for technology transfer and equipment acquisition are available, and that the management of the implementation is monitored.

The cost of access to CFC-free MDI technology will depend on whether patents exist that cover the product being contemplated and whether these patents are enforceable in the Article 5(1) country. However, based on a preliminary evaluation by MTOC it does not appear that formulation patents will constitute a major barrier to the introduction of CFC-free MDIs in Article 5(1) countries.

In planning for the final phase-out in Article 5(1) countries, it will be essential for Montreal Protocol decision-makers to have an understanding of the situation of all of the countries that are manufacturing CFC MDIs domestically.

2.5.1 Progress in transition in Article 5(1) countries

It should be noted that significant progress has already been made towards transition in Article 5(1) countries for certain key moieties. Evaluation of data provided by IPAC on products from its constituent members, together with those from 3M and Ivax (Teva), shows that there is now a range of alternatives available in Article 5(1) countries.

In many Article 5(1) countries, more than one CFC-free product is available. It therefore important to consider the data in Table 1.4 that presents the number of Article 5(1) countries where at least one product has been approved. It is recognised that this is an underestimation of the true situation, as it takes no account of CFC-free products that have been introduced by domestic producers. It is important that Article 5(1) countries collect their own basic data on inhaler use. This will aid the development of effective transition plans within each country.

Based on these data, transition should be occurring in these countries. However, it is clear from accumulating experience in non Article 5(1) countries that the development and registration of alternate products cannot alone lead to a full uptake in the market without additional regulatory action and a clear national transition strategy. Nevertheless, in over fifty Article 5(1) countries, at least two CFC-free salbutamol products have been approved. This further supports the

conclusion that transition in Article 5(1) countries should be achievable by the Montreal Protocol phase-out at the end of 2009.

Table 1.4 The number of Article 5(1) countries where at least one alternative to CFC MDIs is available (as of December 2005)

Moiety	Approved	Launched
Beclomethasone	42	37
Budesonide	43	39
Fenoterol	4	4
Fenoterol and Ipratropium	6	3
Fluticasone	93	75
Formoterol	27	21
Ipratropium	3	3
Nedocromil	0	0
Salbutamol	115	91
Salmeterol	43	37
Sodium cromoglycate	0	0
Terbutaline	36	23

2.6 CFC production for MDIs and the Montreal Protocol phase-out

Given the widespread availability of technically and economically feasible alternatives, MTOC believes that global phase-out of CFC production for MDIs should be possible by 2010. However, the Montreal Protocol phase-out date is less than four years away and considerable challenges will need to be addressed to achieve transition particularly in Article 5(1) countries. These challenges can be overcome through the transfer of technology, product launches of CFC-free alternatives and implementation of comprehensive transition strategies.

The figure below shows the use of CFCs for the production of MDIs for asthma and chronic obstructive pulmonary disease (COPD) in non-Article 5(1) countries. In 2005, 2,754 tonnes of CFCs were used by non-Article 5(1) countries in MDI manufacture under essential use exemptions, as reported through accounting frameworks. This represents a 70 per cent reduction in use compared to peak usage in 1997. The figure also shows a recent relative increase in total stock held compared with amount of CFCs used in MDI manufacture, so that more than one year's supply of CFCs was available in stock at the end of year 2005 (in aggregate, but with large variations across countries and companies).

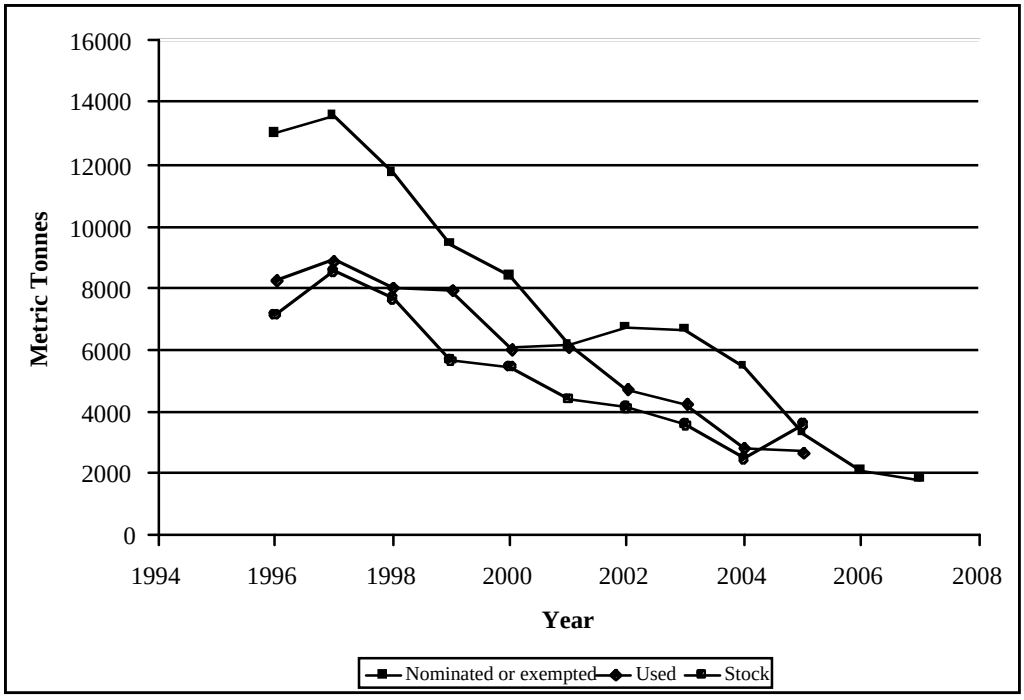

Figure 1.1 Quantities of CFCs for MDI manufacture in non-Article 5(1) countries

*Note that in 2005, 'stock' includes 605 tonnes of pre-1996 stock in the United States. 400 tonnes of this stock has been sold to a United States' manufacturer of CFC MDIs for domestic use. The remainder is yet to be allocated by the United States, yet to be sold by Honeywell, and available only under agreement with certain United States companies.

Multi-national pharmaceutical producers provide the majority of MDIs in most Article 5(1) countries. In a few countries, local manufacture accounts for some MDIs, while the majority comes from multinational producers. In other countries (e.g. People's Republic of China, Cuba and India), local manufacture supplies the majority of MDIs to the market. The estimates of CFC use within Article 5(1) countries have been drawn from a variety of sources and are outlined below in Table 1.5.

Table 1.5 Estimated CFC consumption in ODP tonnes for MDI Manufacturing in Article 5(1) countries in 2005 (UNEP/OzL.Pro/ExCom/49/39)

Country	CFC Consumption for MDI Manufacturing Total	CFC Consumption for Nationally owned MDI Manufacturing
Argentina	187.69	130.85
Bangladesh	61.81	51.40
Brazil	153.25	1.53
China	431.50	369.00
Colombia	31.00	1.80
Cuba	109.00	109.00
Egypt	154.00	154.00
India	375.00	300.00
Indonesia	30.10	30.10
Iran	98.00	98.00
Jordan	5.00	5.00
Mexico	47.00	0.94
Pakistan	85.77	19.57
Philippines	30.00	1.80
Turkey	65.00	-
Uruguay	10.00	10.00
Total	1,874.12	1,282.99

On the basis of the information shown in Table 1.5, it appears that MDIs are manufactured in at least 16 Article 5(1) countries. The amount of CFCs used in these countries in 2005 for the manufacture of MDIs is estimated at 1,875 ODP tonnes (this equates to production of approximately 75 million MDIs). About 65 per cent of this consumption (1,283 ODP tonnes) is by nationally owned manufacturing companies. These are the companies that will need assistance in effecting the transition to CFC-free alternatives.

Currently two countries (Cuba with a CFC consumption of 109 ODP tonnes and Uruguay with a CFC consumption of 10 ODP tonnes) have approved investment projects for the complete phase-out of eligible CFC consumption used in the production of MDIs, and a further four countries (Argentina, China, Egypt and Indonesia) have approved national and/or sectoral plans for the complete phase-out of CFCs excluding additional amounts of CFCs used for the manufacturing of MDIs. Funding for the phase-out of CFCs used in all of these countries has been taken into account in the 2006-2008 replenishment of the Multilateral Fund.

A further four countries (Bangladesh, Colombia, Iran and Jordan) have approved national and/or sectoral plans for the complete phase-out of CFCs and have recently reported CFC consumption used for the manufacturing of MDIs. These countries were precluded from applying for or receiving any further funding from the Multilateral Fund in respect of CFCs. Furthermore,

funding for phase-out of CFCs used in these countries for the manufacturing of MDIs has not been include in the 2006-2008 replenishment of the Multilateral Fund.

India is the only Article 5(1) country currently producing both CFC- and HFC-based MDIs. The Government of India has stated that it "has allocated its total remaining CFC consumption eligible for funding to the refrigeration sector and had reached an understanding with the Multilateral Fund that it would not submit any request for funding for investment projects for aerosols used in metered dose inhalers".

A limited number of Article 5(1) countries may face specific problems. Firstly, they may not achieve the allowable levels of CFC consumption in 2007, and thus be in a potential non-compliance situation with their obligations under the Montreal Protocol. A recent report to the Executive Committee addressed the compliance related issue and this presumably will be monitored on an on-going basis (UNEP/OzL.Pro/ExCom/49/39). Secondly, some countries may face difficulties in phasing out the consumption of CFCs used for the manufacturing of MDIs without incurring economic losses to local manufacturers if they do not receive Multilateral Fund financing. Thirdly, without adequate planning for transition by national governments and their health and environmental agencies, patients with asthma and COPD may be deprived of inhaled therapy that is essential for health.

2.6.1 CFC manufacturing during transition and phase-out

In 2006, two producers of pharmaceutical-grade CFCs remain in non-Article 5(1) countries; one is situated in Spain and the other in the United States. Both have sufficient capacities to meet future CFC requirements for the manufacture of MDIs both for Article 5(1) and non-Article 5(1) countries, while CFC production remains economic. At the present time, pharmaceutical grade CFCs that are being used to manufacture MDIs are produced jointly with CFCs for Basic Domestic Needs production in non-Article 5(1) countries for Article 5(1) countries. Under the Montreal Protocol CFC phase-out schedule, the quantities produced for Basic Domestic Needs must reduce from 1st January 2007. Furthermore, quantities of CFCs produced for Basic Domestic Needs must cease on 1st January 2010. After this date, only stockpiled CFCs, if they exist, would be available for the manufacture of MDIs in Article 5(1) if the transition to CFC-free alternatives has not been completed by that time.

As overall CFC consumption is being stepped down under the Montreal Protocol, a reduction to 15 per cent of baseline consumption will have to be met in 2007. If some Article 5(1) countries still have CFC requirements for MDI manufacture that are greater than the allowed amount for that year, those countries might be in a potential non-compliance situation. Although CFC consumption for MDIs has normally been a very small fraction of total CFC use in a country, the MTOC is aware of at least two cases where such a potential non-compliance situation could arise once the major part of their CFC phase-out is completed.

No producer of CFCs in an Article 5(1) country has been approved by a regulatory authority in a non-Article 5(1) country as a supplier of pharmaceutical-grade for use in CFC MDI manufacture in non-Article 5(1) countries. It is not known whether local Article 5(1) country MDI manufacturers are using CFCs other than that produced by the two non-Article 5(1) producers of pharmaceutical CFCs.

To produce pharmaceutical-grade CFCs some CFCs that do not meet pharmaceutical specifications need to be manufactured. Currently, the non-Article 5(1) producers of

pharmaceutical CFCs market those CFCs that do not meet pharmaceutical specifications for basic domestic consumption of Article 5(1) countries. This will not be possible after 2009 when these non-pharmaceutical-grade CFCs would need to be destroyed. Although the expectations for purity may vary between Article 5(1) countries, the percentage of production not fit for pharmaceutical use in any CFC production run may be as high as 50 per cent and no lower than 25 per cent. Given these considerations, one company in a non-Article 5(1) country has indicated that the economics of production of CFCs are only likely to remain favourable through to 2009, when use for domestic consumption can utilise that part of production that is non-pharmaceutical grade.

Therefore, opting for an essential use process after 2009 may be counter-productive. The economics of CFC production may make this impractical because the costs of destruction of CFCs that do not meet the required pharmaceutical specifications may be prohibitive. If Article 5(1) countries face difficulties in achieving transition in their CFC MDI manufacturing plants by 2010, stockpiling may need to be considered to ensure a supply of pharmaceutical-grade CFC for MDI manufacturing to meet patient needs beyond 2009. In these circumstances, it may be appropriate to arrange for a final campaign to produce pharmaceutical-grade CFCs before 2010, or to acquire pharmaceutical-grade CFCs through a transfer of existing stockpile in non-Article 5(1) countries.

For campaign production, appropriate volumes would need to be determined and the liability for the destruction of any unused volumes decided. A definitive end-date for pharmaceutical-grade CFC production would provide certainty for CFC manufacturers.

2.6.2 Future CFC requirements for MDIs

Future CFC requirements are difficult to predict given the uncertainties of transition, particularly in Article 5(1) countries. However, the volume of CFCs required under the essential use process in non-Article 5(1) countries is reducing and will likely be less than 500 tonnes in 2008, which may be the last year a request will be made. CFC use in Article 5(1) countries for MDI manufacture is currently estimated at about 1,800 ODP tonnes per annum.

If quantities of pharmaceutical-grade CFCs are needed to allow the transition to occur globally and there is a need for a final campaign production in the later part of the decade or for the transfer of existing stockpile, then this will need careful consideration and management. Issues that will need to be considered include:

- Estimating the projected time for complete transition, in particular in Article 5(1) countries;
- Estimating quantities of CFCs for MDI manufacture that will provide an adequate supply of MDIs to protect patient needs, while avoiding over-production and subsequent destruction costs;
- The availability of suitable pharmaceutical-grade CFCs in existing stockpile;
- The logistics, commercial and government requirements for the transfer of existing stockpile;
- Storage arrangements that can avoid spoilage of stockpile and catastrophic loss;
- Destruction arrangements.

The management of stockpiles at this final stage of the phase-out will be extremely important to avoid unnecessary production of CFCs. An efficient process is required to allow for transfers of CFC volumes between parties and/or companies in order to maximize the use of existing CFCs and minimize the need for future CFC license and production volumes.

Parties may wish to remind CFC MDI producers that any CFCs obtained under essential use exemptions must be used for the essential uses (including through a transfer), transferred to an Article 5(1) country for basic domestic need, or destroyed. MTOC is concerned that some users may try to circumvent this rule by claiming that their remaining stockpiles are pre-1996. To ensure transparency, any pre-1996 stocks should be accounted for in the Reporting Accounting Framework for Essential Uses. In addition, according to the TEAP interpretation of Decision IV/25 (*Report of the TEAP, Progress Report, May 2005*, section 1.1.4.1, pg 35), companies that hold pre-1996 stocks should first use them before using newly produced CFCs.

3 Pharmaceutical aerosol products other than MDIs

Many types of pharmaceutical aerosol products (medical aerosols) other than MDIs use CFCs as propellants. The amount of CFCs used globally for medical aerosols has reduced substantially. The manufacture of most CFC-containing medical aerosols in non-Article 5(1) countries ceased around 1996, or possibly shortly thereafter if stockpiled CFCs were utilised. It is only in some Article 5(1) countries that CFCs are still used in medical aerosols. China alone uses up to about 500 tonnes per year for Chinese traditional medicines, topical sprays and nasal sprays.

The types of medical aerosols in which CFCs are still used include: nasal preparations; local anaesthetics; burn and wound sprays; antibiotics; antiseptics; vaginal and contraceptive products; and ancillary products. Some of these products are sold over the counter while others require medical prescription. These products do not require the narrow particle size range considered necessary for the MDIs. Technically and economically feasible alternatives are used in many countries for all of these products. Medical aerosols can be reformulated through the use of non-CFC propellants, or by using other dispensing means such as barrier spray systems, mechanical pump sprays, powders, liquids or creams.

Most sprays that are applied over the skin can use alternative propellants such as hydrocarbon aerosol propellants, dimethyl ether, nitrogen, and compressed air. HFC-134a or HFC-152a are more likely to be used as propellants for sprays used in the oral cavity like local anaesthetics. Not all medical aerosol products that used CFCs in non-Article 5(1) countries may have been reformulated, with some manufacturers opting to discontinue products if their volume did not justify the expense of validating and registering a new formulation.

Usually regulatory bodies consider a product with a different propellant as a new formulation. Any new formulation requires time for toxicological and efficacy tests, thus approval by regulatory agencies for therapeutic use can take up to several years.

The worldwide phase-out of CFC-containing medical aerosols will occur as CFC production for developing countries is phased out under the Montreal Protocol schedule and as part of individual Article 5(1) country plans. For example, CFC production in China will halt in 2007, and while the manufacture of medical aerosols may continue with stockpiled CFCs, their manufacture should cease by 2010. China is currently developing a sectoral phase-out plan for medical aerosols in discussion with the Multilateral Fund.

4 Sterilants

4.1 Introduction

Sterilization of health care products is an important process in the provision of good quality health services. It is also a process that requires strict application of the principles of quality management, reliability and long-term materials compatibility. Sterilization of medical devices can be performed in industrial settings with large outputs of similar items (such as manufacturers of syringes) and in hospitals with much smaller outputs, but great diversity of items. Process requirements for these two settings are similar but the challenges presented to assuring sterility differ greatly.

There is a range of sterilization methods; including heat (moist heat or dry heat), ionising radiation, alkylating processes (ethylene oxide (EO), formaldehyde) and oxidative processes (chlorine dioxide, hydrogen peroxide, gas plasma, ozone, peracetic acid).

Sterilization with EO is used to treat heat and moisture sensitive medical devices, which are packaged in materials that maintain sterility once the product is removed from the sterilization chamber. EO has the ability to penetrate packaging materials, destroy micro-organisms and diffuse away from the package; adequate aeration is essential after processing to achieve acceptable levels of residues. EO is toxic, mutagenic, carcinogenic, flammable and explosive. Great efforts have been made to replace EO, particularly in hospitals where the potential for personnel exposure is of great concern. The fact that EO is still used as a sterilant is evidence that in numerous applications the benefits of its use outweigh these disadvantages.

EO can be used as a sterilant either alone or diluted with other gases to make non-flammable mixtures. On an industrial scale, non-flammable mixtures can be created *in situ* within the sterilizer chamber using nitrogen. Non-flammable EO mixtures are also supplied for industrial or hospital use with diluents such as CFC-12, hydrofluorocarbons (HCFCs), HFCs or carbon dioxide (CO_2). A mixture of 12 per cent by weight EO and 88 per cent CFC-12 (12/88) had previously been widely used for this purpose.

Some hospitals continue to rely on non-flammable EO/HCFC blends and have added new sterilizers for this purpose. These new sterilizers are used more efficiently than the previous EO/CFC units. One way efficiency has increased is by hospital consolidation. When several hospital sites become part of a single institution, they shut down their under utilised sterilizers and concentrate EO/HCFC sterilization in one hospital; by loading the remaining sterilizers more fully, the institution uses less sterilant. Also, techniques have been validated to use up to 25 per cent less sterilant per load. In the United States, a control system for these techniques has received regulatory approval and has been validated in different model sterilizers at three hospitals. Other United States hospitals are now in the process of installing the new control system on their existing sterilizers.

4.2 CFC and HCFC use for sterilization worldwide

The use of EO/CFC blends for sterilization has been successfully phased out in non-Article 5(1) countries and in many Article 5(1) countries. Although it is difficult to estimate, it is believed that the global total use of CFCs in 2001 for this application was less than 500 metric tonnes and has continued to decrease. In 2006, global CFC use for this application is likely to be minimal.

EO/HCFC mixtures (10 per cent by weight EO in a mix of HCFC-124 and HCFC-22) are virtual drop-in replacements for the 12/88 mixture using CFC, and were introduced as transitional products for sterilization in those countries that employed 12/88 extensively. HCFC mixtures are now used mostly in the United States and in countries that allow venting of HCFCs to the atmosphere. The European Union has legislation restricting the use of HCFCs in emissive applications such as sterilization. Estimated use of HCFC replacement mixtures in 2005 was thought to be less than 1,000 metric tonnes, which amounts to some 30 ODP tonnes worldwide. EO/HCFC use has been significantly reduced by using less mix per sterilizer load and by hospital conversion to other technologies.

4.3 Available options for replacing ozone-depleting substances

Methods for sterilization of medical/surgical equipment and devices developed differently in each country, due to the respective regulations on fire protection, occupational safety, validation of results, liability considerations, availability of sterilization equipment and materials, and medical practices.

Quality health care is dependent upon sterility of medical devices. Validation of processes for the intended application is important to avoid materials compatibility problems or deficiencies in the attainment of sterility. Not every sterilant or sterilization process is compatible with all products. The nature and size of items to be sterilized will vary according to the user. Some items are more robust than others with regard to temperature and radiation. Thus, a number of different processes can be used, and each will offer specific advantages.

Alternative technologies to which hospitals have converted include: use of more heat-sterilizable devices, more single-use devices, pure ethylene oxide sterilizers and other methods that will sterilize or disinfect some of the low temperature devices used in hospitals. These other low temperature processes include hydrogen peroxide gas plasma, steam-formaldehyde, ozone and liquid phase peracetic acid.

A summary of alternatives to reduce or phase out the use of ozone-depleting substances (ODS) follows. More detailed descriptions were included in the *UNEP, Assessment Report of the Aerosols Technical Options Committee, 1994.*

4.3.1 Heat

Dry heat - This process is non-toxic, economical, and relatively safe. Devices treated must be able to withstand a temperature greater than 160ºC.

Steam - This process is non-toxic, economical, and relatively safe. Devices treated must be able to withstand a temperature greater than 115ºC and very high moisture levels.

4.3.2 Ionising radiation

Radiation sterilization is usually used in large, industrial facilities; for this reason it is not generally applicable for hospitals. Not all materials are compatible with radiation.

Gamma radiation and *electron beam* are well established. Facilities using gamma radiation need to dispose of spent isotopes.

X-ray applications and facilities are becoming commercially available.

4.3.3 Alkylating agents

Formaldehyde – Used mainly in Europe and parts of South America for materials that are able to withstand temperatures of 80-85ºC, although uses at 60-65ºC have also been reported. Formaldehyde is toxic and a suspected carcinogen.

100 % EO – EO can be used as a flammable gas if proper safety requirements are met. Equipment ranges from large industrial sterilizers to small sterilizers used in hospitals. On an industrial scale, nitrogen may also be added to the sterilizer chamber *in situ* to render the process non-flammable.

Blends of EO and CO_2 – Carbon dioxide is used to produce flammable and non-flammable mixtures with EO. Those containing more than 8.5 per cent by weight EO are flammable. Usually, EO/CO_2 mixes are not used to replace the non-flammable mixes. Container pressures are about ten times higher than for 12/88 EO/CFC mixtures; chamber pressures are about three times higher. Use of EO/CO_2 blends has other disadvantages, such as composition changes during the use of a single tank or cylinder, increased polymerization, and compatibility and corrosion problems caused by the acidity of CO_2.

Blends of HCFCs and EO – These HCFC-124 containing blends are virtual drop-in replacements for 12/88 CFC blends and have been validated for different applications and compatibility with the products and their packaging established. They have been used since 1993 and allow continued use of expensive sterilizers with minor control adjustments. In the European Union, the use of HCFCs in closed sterilization equipment produced before 1998 is permitted, but by 2010 no new HCFC blends can be sold; reclamation and reuse of HCFCs is permitted until the end of 2014.

Blends of HFCs and EO - HFC mixtures (10.4 per cent by weight EO in a mix of HFC-125 and HFC-227) have been tested and validated by hospitals in the United States and by medical device manufacturers, using existing sterilization equipment and changing only process controls. Several agencies need to give regulatory approval before new HFC blends can be broadly used worldwide. It is expected that the EO/HFC blends will replace the EO/HCFC mixtures, where they are used. In the European Union, there are restrictions on certain uses of HFCs, for example as refrigerants; these do not currently explicitly exclude the use of HFCs in sterilizing equipment. EO/HFC blends have also been validated to replace EO/methyl bromide blends to fumigate archives and antiquities[2].

[2] *Blends of methyl bromide and EO* – Methyl bromide or mixtures of methyl bromide and EO are used for disinfestation of historical artefacts, archives and antiquities. Methyl bromide is also an ODS and its use is controlled under the Montreal Protocol. Blends of HFCs and EO have been validated to replace methyl bromide and EO fumigation blends. There is also a range of other alternatives that can be suitable for these fumigation uses depending on the infestation, including: nitrogen (insects); carbon dioxide (insects); sulfuryldifluoride (insects); heat (fungi); irradiation (fungi). There may be rare occasions where no alternative to methyl bromide is appropriate.

4.3.4 Oxidising agents

Chlorine Dioxide – A system for sterilizing medical devices using chlorine dioxide has been developed. Chlorine dioxide is generated in situ from sodium chlorite and chlorine gas in a nitrogen carrier. Gaseous chlorine dioxide is drawn into an evacuated chamber to achieve a concentration in the range 10-50 mgl^{-1}, at 25-30ºC and a relative humidity of 70-90 per cent.

Hydrogen Peroxide Gas Plasma – Many sterilizers have been sold worldwide, mostly to hospitals, and the system continues to be used extensively.

Liquid Peracetic Acid – Available equipment uses cassettes where items to be sterilized such as endoscopes are placed. The cassette is designed to provide a chamber for exposure to the peracetic acid solution, flushing out, rinsing with a neutralising agent, rinsing with sterile, filtered water, and final drying. Sterilized items are not packaged and need to be used immediately after removal from the cassette.

Ozone – A process operating a less than 30˚C is available for use in hospitals. The process must be carefully controlled since it has the potential to effect most materials. Selected medical devices packaged in non-cellulosic material are processed.

Peracetic Acid Gas Plasma - A process was commercialised but was associated with patient injuries when ophthalmic surgical instruments sterilized with this system were used. The process had not received US FDA approval for this application and a global recall was mandated.

4.4 Conclusions

Sterilization is an important process in the provision of good quality health services. It is also a process that requires strict application of the principles of quality management, reliability and long-term materials compatibility. Therefore, any alternative to the use of ozone-depleting substances needs to be well proven and tested to avoid putting the health of patients unnecessarily at risk.

CFC-12 use in the sterilization sector has been phased out in non-Article 5(1) countries and in many Article 5(1) countries. Remaining worldwide use can be easily substituted, as there are a number of viable alternatives. EO/HCFC blends have a small ozone depletion potential (ODP) (0.03) and should not be promoted in countries that have not been major users of the 12/88 EO/CFC blend. EO/HFC blends are expected to replace the EO/HCFC mixtures, where they are used.

5 MTOC Membership Information

Medical Technical Options Committee (MTOC)

Co-chairs	Affiliation	Country
Jose Pons Pons	Spray Quimica	Venezuela
Helen Tope	Energy International Australia	Australia
Ashley Woodcock	University Hospital of South Manchester	UK

Members	Affiliation	Country
Emmanual Addo-Yobo	Kwame Nkrumah University of Science and Technology	Ghana
Paul Atkins	Oriel Therapeutics	USA
Sidney Braman	Rhode Island Hospital	USA
Yingyun Cai	Zhongshan Hospital	China
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Christer Carling	Private Consultant	Sweden
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Kristine Whorlow	National Asthma Council Australia	Australia
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5.1 MTOC Member Biographies

The following contains the background information for all MTOC members as at December 2006.

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Emmanuel Addo-Yobo, member of the Medical Technical Options Committee since 2005, is a full time Specialist Paediatrician and Senior Lecturer in the Department of Child Health, Kwame Nkrumah University Sciences and Technology, and the Komfo Anokye Teaching Hospital, Kumasi, Ghana, with a special interest in paediatric pulmonology. Emmanuel is the physician in charge of paediatric asthma in the hospital and has been involved in several research activities on childhood asthma epidemiology in Ghana as Principal or Co-Investigator, some of which have been sponsored partly or fully by pharmaceutical companies. He has attended an American Academy of Allergy Asthma and Immunology (AAAAI) meeting sponsored by a pharmaceutical company in 1999. He does not receive any form of remuneration from any drug companies. His travels for MTOC meetings are funded by the UNEP's Ozone Secretariat. His spouse is a business secretary working with a local financial institution.

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Paul Atkins, member of the Medical Technical Options Committee since 1993, is the Chief Executive Officer of Oriel Therapeutics Inc, a privately held pulmonary drug delivery company. He has an extensive background in both MDI and DPI product development and commercialisation and is an internationally recognised expert in this area. Previously Paul was employed by GlaxoSmithKline a leading provider of inhaled medicines, and his spouse is currently a GlaxoSmithKline employee and owns stock in the company. Funding to support Paul's attendance at the MTOC meetings has been provided either by his employer or paid for out of his personal funds.

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Sidney Braman, member of the Medical Technical Options Committee since 2005, is a Professor of Medicine at Brown Medical School and Director of the Division of Pulmonary and Critical

Care Medicine at Brown University and the Rhode Island Hospital. He has received research grant support and been a consultant to several pharmaceutical companies relating to research on new drug development. He has not received any consultancy fees for work related to or associated with the Montreal Protocol and he and his wife do not own shares in any relevant drug companies. The American Thoracic Society provides support for travel to the MTOC meetings.

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Prof. Yingyun Cai is the professor in the Institute of Respiratory Deseases, Zhongshan Hospital, Fudan University. He also is the Vice Chairman of Shanghai Drug Treatment Association. He has been a member of MTOC since 2004. Prof. Cai and his spouse have no conflicts of interest relevant to medical aerosols or the CFC phase-out. UNEP's Ozone Secretariat pays travel costs, subsistence allowances and other expenses related to participation in MTOC.

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Nick Campbell has been a member of this Technical Options Committee since 1991. Nick has spent 19 years working primarily on the ozone layer issue and climate change. He works for ARKEMA SA, based in Paris, as the Environment Manager for the Fluorinated Products Division. ARKEMA SA is a producer of CFCs, HCFCs and HFCs. ARKEMA SA supports his participation on MTOC. Nick has stock options in ARKEMA SA. Nick is Chairman of the European Fluorocarbon Technical Committee (EFCTC) that represents the producers of fluorocarbons in the European Union and the European Chemical Industry Council (CEFIC) Working Party on Climate Change. Nick is also the Chairman of the International Chamber of Commerce (ICC) Working Party on Climate Change and the Chairman of the UNICE Climate Change Working group, representing European Union Employers' federations. Nick was a Coordinating Lead Author for the IPCC/TEAP joint Report on HFCs and PFCs (April, 2005). Nick was awarded a 1997 United States EPA Stratospheric Ozone Protection Award for his role in the phase-out of ODS.

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Hisbello Campos, member of the Medical Technical Options Committee since 1997, is a medical physician (pulmonologist) who works for Brazil´s Ministry of Health at Centro de Referencia Prof. Helio Fraga. His professional activities include teaching and researching in the areas of

Public Health involving lung diseases. He is part of the National Tuberculosis Control Program supervisor team and member of the National Asthma Campaign. He also attends patients at his private office. Occasionally, he has received support for travels to Medical Meetings from pharmaceutical companies. He has never received any consultancy fee for work associated with the Montreal Protocol and does not own shares in any relevant drug companies. His wife has no activity related to the work of MTOC. His participation on MTOC has been solely funded/sponsored by UNEP's Ozone Secretariat.

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Christer Carling, member of the Medical Technical Options Committee since 1993, is an independent consultant in the pharmaceutical area. He has a 35-year long background in the pharmaceutical industry, mainly in project management, project evaluation and business development in the respiratory area. During 2006 Christer has not been involved in any consultation for companies active in the medical aerosols area. Christer's spouse is a Qualified Person for inhaled asthma products in a multinational pharmaceutical company. Christer and his family are minor shareholders in AstraZeneca. The International Pharmaceutical Aerosols Consortium (IPAC) covered costs for Christer's accommodation in connection with the 2006 MTOC meeting.

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Robert Meyer, member of the Medical Technical Options Committee since 1998, is a pulmonary physician who works at the US FDA evaluating new drugs for a variety of disease states, including asthma and COPD. Dr. Meyer and his spouse have no conflicts of interest relevant to medical aerosols or the CFC phaseout. The US FDA funds Dr. Meyer's participation in the MTOC.

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Robert Morrissey, member of the Medical Technical Options Committee since 1995, has been with Johnson & Johnson for over 32 years. He is currently Vice President, Operations Preparedness & Technology. In this capacity he is responsible for the worldwide Business Continuity and Sterilization Science functions. This includes business continuity planning, crisis management, worldwide process development and technology support programs in sterilization science and engineering, packaging, microbiology, and aseptic pharmaceutical operations. He is a Member of the International Standards Organization (ISO) Technical Advisory Group on Sterilization of Healthcare Products (ongoing) and also a Member of the Association for the Advancement of Medical Instrumentation (AAMI) Sterilization Standards Committee (25 years) and Executive Committee (current). Johnson & Johnson makes in-kind contributions of wage and miscellaneous expenses.

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Jose Pons Pons, Co-chair of the Technology and Economic Assessment Panel since 2003 and Co-chair Medical Technical Options Committee since 1991. He co-chaired the 2002 Task Force on Collection, Recovery and Storage, the 1999 Replenishment Task Forces, and served on the Steering Committee to the "IPCC/TEAP Special Report Safeguarding the Ozone Layer and the Global Climate System: Issues Related to Hydrofluorocarbons and Perfluorocarbons". He is President and co-owner of Spray Quimica. His spouse is also co-owner of Spray Quimica. Spray Quimica is an aerosol products filler who produces its own brand products and does contract filling for third parties. Jose is chair of the Venezuelan Aerosol Association. Spray Quimica, purchases HCFCs and HFCs for some of its products. Costs of travel expenses related to participation in the TEAP, its CTOC and MTOC, and relevant Montreal Protocol meetings, are paid by UNEP's Ozone Secretariat. Spray Quimica makes in-kind contributions of wage, and miscellaneous and communication expenses.

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John Pritchard, member of the Medical Technical Options Committee since February 2006, is currently Strategic Technology Director for Pharmaceutical and Analytical R&D in AstraZeneca, having previously held a variety of roles within 3M, GlaxoSmithKline and AEA Technology (formerly UK Atomic Energy Authority). He has published extensively in the field of aerosol science and is a past President of The Aerosol Society, a past member of the UK Government Committee on the Medical Effects of Airborne Pollutants and has served as editor on a number of journals. Participation in MTOC is supported by AstraZeneca, which develop and supply medicinal products, including inhalable drugs in a range of dosage forms, some of which are pMDIs. John is also a minor shareholder in a range of companies, including GlaxoSmithKline.

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Dr Raj B Singh is a clinical respiratory physician engaged in private practice in Chennai, South India. Nearly 90 per cent of his work concerns clinical respiratory medicine, with outpatients at the Chest Centre and in-patient facilities at the Apollo Hospital, Chennai where he is a senior consultant. He is the founder of the Chest Foundation of India and its Managing Trustee. He has been a member of the Executive Committee of the Global Initiative for Asthma (GINA) since 2003 and a member of MTOC since 2005. The Ozone Secretariat funds his travel expenses for participation on MTOC.

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Roland Stechert, member of the Medical Technical Options Committee since 2000, is a Medical Director for Boehringer Ingelheim in Switzerland. As an expert of respiratory research he was involved in the development of CFC-free MDIs with Boehringer Ingelheim. Roland headed the German regional International Pharmaceutical Aerosol Consortium (IPAC) Group until 2002. Since he took over his recent role in 2003 in Switzerland he is no longer a member of IPAC. Participation costs are all borne by the affiliate in Switzerland.

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Helen Tope, Co-chair Medical Technical Options Committee since 1995, is an independent consultant to government and non-governmental organisations on greenhouse gases and ozone-depleting substances and alternative technologies. Until mid-2006 (during the preparation of this report), Helen worked as a Senior Policy Officer Global Issues (climate and ozone layer protection), EPA Victoria, Australia. EPA Victoria has an interest in protecting the ozone layer for the benefit of public health. Helen has no stock in companies with significant involvement in matters of the Montreal Protocol. Helen's spouse is an independent consultant working in areas of environmental engineering and energy efficiency for mining, oil and gas, and other interests. EPA Victoria made in-kind contributions of wage and miscellaneous expenses. The Ozone Secretariat provides a grant for travel, communication, and other expenses of the Medical Technical Options Committee out of funds granted to the Secretariat unconditionally by the International Pharmaceutical Aerosol Consortium (IPAC). IPAC is a non-profit corporation.

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Adam Wanner, member of the Medical Technical Options Committee since 1995 has had a long-standing interest in aerosol therapy for obstructive lung disease, both as a researcher and clinician. On occasion, the American Lung Association has sponsored his travel to MTOC meetings. He has received academic grants (unrelated to the CFC phase-out) from several pharmaceutical companies. He and his spouse have no financial interests relevant to his work on MTOC.

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Kristine Whorlow, a new member of the Medical Technical Options Committee in 2006, is the CEO of the National Asthma Council Australia, the national body for asthma. The National Asthma Council Australia and the Australian Department of the Environment co-chaired the asthma stakeholder group in the late 1990s to phase out CFC-containing inhalers. Ms Whorlow is advising on the establishment of national asthma councils in Sri Lanka, Bangladesh, Korea, Taiwan, Malaysia and Thailand. The pharmaceutical companies in asthma, the Australian Government and other corporations support the work of the National Asthma Council Australia.

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Dr. Ashley Woodcock, Co-chair Medical Technical Options Committee since 1996, is a Consultant Respiratory Physician at the NorthWest Lung Centre, Wythenshawe Hospital, Manchester, UK. Prof. Woodcock is a full-time practising physician and Professor of Respiratory Medicine at the University of Manchester. The NorthWest Lung Centre carries out drug trials (including those on CFC-free MDIs and DPIs) for pharmaceutical companies, for some of which Prof. Woodcock is the principal investigator. Prof. Woodcock has received support for his travel to educational meetings and consults for pharmaceutical companies on the development of study designs to evaluate new drugs. He is a consultant to a company developing a dry powder inhaler for treatment of Cystic Fibrosis, which will not be a replacement for current CFC or HFC MDIs used in the treatment of Asthma or COPD. He does not receive any consultancy fees for work associated with the Montreal Protocol and does not own shares in any relevant drug companies. Wythenshawe Hospital makes in-kind contributions of wages and communication. The UK Department of Environment, Food and Rural Affairs sponsors travel expenses in relation to Prof. Woodcock's Montreal Protocol activities.

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You Yizhong, member of Medical Technical Options Committee since 1997, is a chief pharmacist and associate chief physician. Dr.You has been devoted to promoting the wide use of inhalation therapy in China for 35 years and to phasing out CFCs from aerosols for 15 years. Dr.You developed some anti-asthmatic drugs including MDI, tablet, syrup and suppository. Dr.You receives his salary from Changzhou No.1 Hospital and has no interest or economic relationship with pharmaceutical companies, and does not receive any fees for work associated with MTOC. UNDP/UNEP's Ozone Secretariat bears his travel expenses to attend MTOC meeting and other UN meeting.