

# 2010 Report of the Medical Technical Options Committee (MTOC) 2010 Assessment

MONTREAL PROTOCOL ON SUBSTANCES  
THAT DEplete THE OZONE LAYER

*Celebrating 25 years of success in 2012*



**MONTREAL PROTOCOL  
ON SUBSTANCES THAT DEplete  
THE OZONE LAYER**



**UNEP**

**2010 REPORT OF THE  
MEDICAL TECHNICAL OPTIONS COMMITTEE**

**2010 ASSESSMENT REPORT**



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**Montreal Protocol  
On Substances that Deplete the Ozone Layer**

Report of the  
UNEP Medical Technical Options Committee

2010 Assessment

**ASSESSMENT REPORT**

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# 2010 REPORT OF THE MEDICAL TECHNICAL OPTIONS COMMITTEE

## 2010 ASSESSMENT REPORT

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## EXECUTIVE SUMMARY

### Metered Dose Inhalers

#### *Global CFC use for MDIs*

The global use of chlorofluorocarbons (CFCs) to manufacture metered dose inhalers (MDIs) has decreased to about 2,300 tonnes in 2009 and is projected to decrease further to about 2,000 tonnes in 2010. In 2009, Article 5(1) countries used about 1,700 tonnes and the Russian Federation and the United States used about 580 tonnes of CFCs for the manufacture of MDIs. The total use of CFCs by Article 5(1) countries reduced by about 200 tonnes between 2008 and 2009, with some countries increasing (e.g. China) and others decreasing (e.g. India) consumption. There has been significant global progress in the transition of CFC MDIs to CFC-free inhalers, with substantial capacity to manufacture CFC-free inhalers.

CFC stockpiles are available in Venezuela and the United States (total of about 951 tonnes of CFC-11 and -12, with 367 tonnes of CFC-114 that may not be consumed). These may be enough to cover estimated CFC requirements for MDIs for 2010, 2011 and 2012. It could be possible to complete the phase-out of CFC MDIs with careful management of existing global CFC stockpiles without manufacture of new pharmaceutical-grade CFCs, except for China that can manufacture for its own needs and those of the Russian Federation. A cautious approach to CFC production is advisable since transition is moving quickly and CFC production that is surplus to actual needs ought to be avoided, as the excess would subsequently require costly destruction.

#### *Technically satisfactory alternatives are available*

It is now over 16 years since the first introduction of a hydrofluorocarbon (HFC) MDI for the short-acting beta-agonist salbutamol in the United Kingdom in 1994. Technically satisfactory alternatives to CFC MDIs (HFC MDIs and dry powder inhalers (DPIs)) to treat asthma and chronic obstructive pulmonary disease (COPD) are now available in almost all countries worldwide. There are sufficient CFC-free alternatives available to cover all key classes of drugs used in the treatment of asthma and COPD.

By 2010 every developed country had phased out the use of CFCs in MDIs, except the Russian Federation, which is yet to complete manufacturing conversion, and the United States, which is well advanced in its phase-out. Substantial global progress has continued in the development and launch of HFC MDIs and DPIs and now most companies based in non-Article 5(1) countries have completed their phase-out of CFC MDIs.

Most developing countries are well advanced in their transition plans to phase out the use of CFCs. Despite initial challenges such as access to technology transfer and economic barriers, progress has been significant with a number of countries nearing completion of their transition to CFC-free inhalers faster than expected. CFC consumption by Article 5(1) countries is estimated to have peaked in 2008 and 2009, and now appears to be decreasing. Current predictions are that most Article 5(1) countries will have largely completed transition by about the end of 2012. A notable exception is China, which in recent years has shown increasing consumption of 15-30 per cent year on year, with current plans to complete the phase-out of CFC MDIs in 2016.

A barrier for developing countries has been that replacement hydrofluorocarbon (HFC) MDIs manufactured by multinational companies in developed countries can be more expensive than CFC MDIs manufactured in developing countries, meaning that poor patients cannot afford them. However, there has been substantial progress in the development and marketing of

affordable CFC-free MDIs, especially those manufactured in Article 5(1) countries. HFC MDIs are now becoming more competitively priced compared to CFC MDIs. As a consequence, there is now an adequate range of technically satisfactory and affordable CFC-free alternatives for CFC MDIs for beta-agonists (in particular, salbutamol) and inhaled corticosteroids (in particular, beclomethasone) available in many developing countries. Taking these issues into consideration, salbutamol and beclomethasone CFC MDIs can now be considered non-essential in most importing countries.

### ***Global HFC use for MDIs***

It is estimated that about 4,000 tonnes of HFCs are used to manufacture MDIs, accounting for a very small proportion of total HFC usage (estimated at 1-2 per cent). Based on current consumption and projected growth rates of MDI use, annual consumption of HFCs for MDIs is estimated to be between 7,000-10,500 tonnes by 2015.

By moving from CFC MDIs to HFC MDIs and DPIs, not only have emissions of ozone depleting substances been eliminated, but there have also been benefits for climate change. According to rough estimates of carbon footprints of inhaler products, HFC MDIs have about 10 times less climate impact than CFC MDIs. DPIs have an even lower comparative climate impact, about 100 times less than CFC MDIs and 10 times less than HFC MDIs.

### ***Patient health considerations***

It is important to note that MDIs, DPIs and novel delivery systems play an important role in the treatment of asthma and COPD, and no single delivery system is considered universally acceptable for all patients. Healthcare professionals continue to consider that a range of therapeutic options is important. Any consideration of policy measures to control HFCs should carefully assess patient health implications with the goals of ensuring patient health and maintaining a range of therapeutic options. Each country has its own unique and complex makeup in terms of availability of medicines, overarching health care systems, and patient preferences.

### **Pharmaceutical aerosol products other than MDIs**

Technically and economically feasible alternatives are available for all medical aerosol products. Other than MDIs, the manufacture of most CFC-containing medical aerosols in non-Article 5(1) countries ceased around 1996, and in Article 5(1) countries would have ceased around the end of 2009.

However, there are some countries that are yet to complete the conversion of CFC-based medical aerosols to alternatives. In 2009, Argentina (1.2 tonnes), China, Dominican Republic (24 tonnes), and Serbia (18.1 tonnes) were still consuming CFCs to manufacture medical aerosols. With the 2010 phase-out date for CFCs in developing countries, any current CFC consumption for medical aerosols could only be sourced from existing stockpile.

In China, some of the traditional Chinese aerosol manufacturers have encountered technical difficulties in their conversion to alternatives, with new formulations not meeting relevant quality standards. Government authorities are coordinating with the enterprises to resolve these technical issues. It is expected that, other than MDIs, full conversion of the medical aerosol sector in China will be completed in 2012.

## **Sterilants**

The use of ethylene oxide (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 be certain, global total use of CFCs in 2010 for this application is believed to be close to zero.

EO/hydrochlorofluorocarbon (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. Estimated global use of HCFCs in sterilization in 2010 is between about 500-700 metric tonnes, which amounts to less than 25 ODP tonnes worldwide. EO/HCFC use in non-Article 5(1) countries is estimated to be declining with regulatory restrictions being introduced. EO/HCFC use in Article 5(1) countries is estimated to be between about 200-400 tonnes.

With the Montreal Protocol phase-out schedule for HCFCs for Article 5(1) countries, an orderly phase-out of HCFCs in sterilization uses is readily achievable in Article 5(1) countries. The useful lifetime of an EO/HCFC steriliser is about 20 years when well maintained. Therefore by 2030 current sterilisers should be ready for replacement with available alternative technologies that do not use ozone-depleting substances. Hospital procurement should take the HCFC phase-out, and the coming redundancy of EO/HCFC sterilization equipment, into consideration in making future investment decisions.

There is a range of commercially available sterilization methods that can replace the use of ozone-depleting substances in this sector, including: heat (moist heat or dry heat), radiations, alkylating processes (such as EO, formaldehyde) and oxidative processes (including hydrogen peroxide vapour, hydrogen peroxide gas plasma, liquid peracetic acid, and ozone). Further sterilization methods are under investigation for commercialization.

The provision of good quality health services requires effective sterilization of health care products to prevent transmission of infection. Sterilization requires strict application of the principles of quality management to ensure validation of the selected process and implementation of effective routine control; reliable equipment; and knowledge of materials compatibility. Validation of sterilization processes is important to ensure the attainment of sterility and to avoid materials compatibility problems. No sterilant or sterilization process is compatible with all potential products.



# **1 Background to the 2010 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** Technical 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 2010 Assessment**

This report is part of the seventh assessment under Article 6 of the Montreal Protocol. The first assessment report was prepared in 1989, and subsequently updated in 1991, 1994, 1998, 2002 and 2006. This report is in response to Decision XIX/20 of the Parties to the Montreal Protocol, which requested an assessment to be undertaken for completion by 31 December 2010 for consideration by the Open-Ended Working Group and by the Twenty-third Meeting of the Parties in 2011.

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.

MTOC is made up of experts from industry, government, scientific, research and academic institutions. In 2010, there were 28 members from 17 countries – Argentina, Australia, Bangladesh, Brazil, China, France, Germany, Ghana, India, Iran, Italy, Japan, Pakistan, Sweden, United Kingdom, the United States and Venezuela. MTOC members' disclosures of interests are presented at the end of this report.

This 2010 Assessment Report re-examines the current use of alternatives to ozone-depleting substances in medical aerosols, including metered dose inhalers, and sterilants. MTOC undertook written communication in the preparation of this report during 2010. The report has undergone a peer review among experts from global organisations and companies.



## **2 Metered Dose Inhalers**

### **2.1 Asthma and COPD: prevalence, treatment options and medical trends**

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic diseases of the air passages of the lungs. Asthma increased rapidly in the second half of the 20th century and now affects over 300 million people worldwide. The World Health Organization (WHO) estimates that there will be an additional 100 million sufferers by 2025, with 428,000 deaths per annum by 2030.<sup>1</sup> COPD affects at least this number, and its prevalence continues to rise with increasing tobacco consumption in developing countries. Both of these illnesses account for high healthcare expenditure, and COPD in particular is responsible for premature death. COPD is currently the fourth commonest cause of death worldwide, but by 2030 it will have advanced to third.

Treatment for these conditions has increasingly involved inhalation of aerosol medications into the lungs. These inhaled drugs are targeted by modulating particle size to the major airways, where they have maximal benefit with least side effects.

#### **2.1.1 Asthma**

Asthma is a chronic inflammatory condition of the airways. Its prevalence increased and then stabilised in developed countries in the late 20th century, but its prevalence continues to increase in developing countries. There is still a wide difference in prevalence between some countries, such as Indonesia where prevalence is about 1 per cent, to the UK where it is over 30 per cent.

Asthma can vary in severity from the very mild with intermittent symptoms, through to severe and/or chronic requiring specialist support, frequent hospital admissions, and in some cases even resulting in death.

Asthma has two primary features, airway inflammation and bronchoconstriction, in which there is a spasm of the airways. Inhaled treatments were originally targeted at relieving the symptoms associated with bronchoconstriction, but are now much more focused on preventing and controlling inflammation using inhaled anti-inflammatory drugs.

#### **2.1.2 Chronic obstructive pulmonary disease**

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). The relative severity of these two features may vary from patient to patient, but they both contribute to progressive obstruction of the airways. By far the commonest cause of COPD is cigarette smoking, but in some patients occupational dusts, or environmental pollution, or a small genetic component in patients with alpha 1-antitrypsin deficiency, may cause COPD.

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<sup>1</sup> WHO Fact Sheet No. 307, 2008; WHO Fact Sheet No. 315, 2009; WHO projections of mortality and burden of disease, 2004-2030; Global surveillance, prevention and control of chronic respiratory diseases (WHO publication), 2007; WHO World Health Statistics, 2008.



Patients become progressively and irreversibly disabled if they continue to smoke, and smoking cessation is a major individual as well as general public health issue.

The prevalence of COPD is hard to estimate, since it is not usually recognised until it is moderately advanced. However it affects 5-15 per cent of the population in developed countries, with mortality doubling in females in the last 20 years in the United States. Rates of COPD are increasing rapidly in developing countries as cigarettes become affordable, and where tobacco advertising and sales are less regulated.

COPD provides a substantial burden to healthcare systems worldwide with infective exacerbations frequently requiring expert support and hospital admission, accounting for between 50 and 75 per cent of overall costs of COPD.

### **2.1.3      *Treatment***

There has been no major global change in treatment since the 2006 Assessment Report of the Medical Technical Options Committee<sup>2</sup> (MTOC), with inhaled medications remaining the mainstay of treatment. Nonetheless, some countries have extended their range of treatment options to include oral long-acting beta-agonists, oral leukotrienes and injectable anti-immunoglobulin E. Some countries have taken regulatory action with implications for treatment options, for example US FDA<sup>3</sup> recently required labelling changes that significantly restrict the use of long-acting bronchodilator, formoterol and salmeterol.

Prevention of asthma remains impossible until it is clearer what has driven the increased prevalence. This seems to be a cohort effect, with increased levels of asthma in children now leading to increased levels in adults. The pathology of asthma usually arises in early life, and even if a form of prevention were to be developed today, it seems likely that this would not impact significantly on the prevalence of asthma for many decades.

The prevention of COPD requires public health leadership so that rates of tobacco smoking decline. Controls on advertising and bans on smoking in public places have been associated with significant declines in tobacco consumption in developed countries, assisted in some countries by nicotine replacement therapies. However, increasing affordability of tobacco and lack of advertising controls are driving an epidemic of COPD in developing countries.

Inhaled therapy remains the mainstay of treatment for asthma and COPD. Inhalers offer effective symptomatic benefit and control of disease, by delivering drugs directly to the airways, whilst minimising systemic side effects. The precise particle size is critical in targeting the drug to the relevant part of the airway. If the particles are too large, then the drug is deposited in the mouth and throat and is ineffective. If the particles are too small, either they get to the periphery of the lung and are systemically absorbed, or they are simply exhaled and wasted.

For both asthma and COPD, there are two main categories of inhaled treatment, bronchodilators and anti-inflammatory medications. These are detailed in the 2006 MTOC

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<sup>2</sup> 2006 Report of the UNEP Medical Technical Options Committee, 2006 Assessment Report, [http://ozone.unep.org/Assessment\\_Panels/TEAP/Reports/MTOC/index.shtml](http://ozone.unep.org/Assessment_Panels/TEAP/Reports/MTOC/index.shtml).

<sup>3</sup> United States' Federal Drug Administration

Assessment Report<sup>4</sup>, and there have been no significant new classes of inhaled drugs over the last four years. There has been a trend for increased use of combination long-acting bronchodilators and inhaled steroids in developed countries.

Oral drugs are also prescribed for asthma. In developing countries, inexpensive methylxanthines (theophylline) are widely available, but can have serious side effects (excess dosage can be fatal). In developed countries and especially the United States, an oral leukotriene modifying drug (montelukast), which is prescribed as a non-steroidal anti-inflammatory medication in paediatric asthma, occupies a significant proportion of the market for preventive drugs although it is less effective than inhaled steroids.

There are new developments in injectable drugs. The first injectable preventive therapy against IgE<sup>5</sup> is now marketed worldwide. However, it has very low uptake outside developed countries, and only then in patients with very severe asthma because of its cost (~\$10,000/year per patient, compared with ~\$200/year for an inhaled steroid inhaler) and relatively low efficacy. Nevertheless, over the next decade, a new range of expensive injected anti-inflammatory drugs is likely to be developed, targeting patients with severe asthma.

None of these developments will impact the need for inhaled therapies for virtually every patient with asthma and COPD worldwide.

## **2.2 Aerosol Delivery**

There are two primary types of inhalers for the delivery of respiratory drugs: these are the (pressurised) metered dose inhaler (MDI) and the dry powder inhaler (DPI) in single or multi-dose. Other methods of delivering drugs to the lung include soft mist inhalers and nebulisers. The choice of the most suitable treatment method is a complex decision taken between doctor and patient.

### **2.2.1 CFC MDIs**

An MDI is a complex system designed to produce a fine mist of medication for inhalation directly to the airways. These products were first developed over 50 years ago and are particularly suited to administration of therapy when respiratory function is compromised.

MDIs that use chlorofluorocarbons (CFCs) as a propellant were historically the inhaled delivery device of choice. They were affordable, reliable and extremely effective. CFCs are being phased out under the Montreal Protocol, with the phase-out in MDI manufacture almost completed in developed countries and likely to be completed in developing countries no later than 2015.

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<sup>4</sup> 2006 Report of the UNEP Medical Technical Options Committee, 2006 Assessment Report, pp. 11-12, [http://ozone.unep.org/Assessment\\_Panels/TEAP/Reports/MTOC/index.shtml](http://ozone.unep.org/Assessment_Panels/TEAP/Reports/MTOC/index.shtml).

<sup>5</sup> IgE, Immunoglobulin E, is associated with allergy.

### **2.2.2 HFC MDIs**

The process of reformulating MDIs with hydrofluorocarbons (HFCs) began about 20 years ago when HFC-134a and HFC-227ea were proposed as alternatives to CFCs. These HFCs underwent extensive toxicological testing and were deemed to be safe for human use. Since 1994, pharmaceutical companies have gradually replaced the CFC propellants in MDIs with HFCs. This has been difficult because the components and formulations had to be substantially modified to use HFC propellant. Furthermore the absence of an acceptable HFC that is liquid at room temperature has meant the development of new manufacturing processes. The new MDI products have also been subjected to extensive regulatory assessments of safety, efficacy and quality, much the same as for the development of a wholly new drug product. Development costs for the transition in MDIs from CFCs to HFCs have been estimated well in excess of US\$2 billion, with investment still continuing.

There are now sufficient HFC MDI alternatives available to cover all key classes of drugs used in the treatment of asthma and COPD. 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. On the other hand, many new products have been developed directly using HFC propellants.

It is estimated that approximately 250 million HFC-based MDIs are currently manufactured annually worldwide, using approximately 4,000 tonnes of HFCs and accounting for a very small proportion of global HFC usage (estimated at 1-2 per cent).

A barrier for developing countries has been that replacement HFC MDIs manufactured by multinational companies in developed countries are generally more expensive than the corresponding CFC MDIs manufactured in developing countries, meaning that poor patients cannot afford them. Nonetheless, the cost of bulk CFC propellant today is greater than that of HFC due to falling demand. The Multilateral Fund for the Implementation of the Montreal Protocol (MLF) has funded projects in developing countries mainly focussed on technology transfer and institutional strengthening to convert CFC MDI manufacture to HFC MDIs. MLF funding approved by the Executive Committee of the Montreal Protocol for MDI projects is USD 52.2 million. These may still, in some cases, take a few more years to complete.

### **2.2.3 Dry Powder Inhalers**

Dry powder inhalers (DPIs) are devices that deliver powdered medication without the need for a propellant. 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.

DPIs can provide a not-in-kind alternative to MDIs 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. Nevertheless, they are not an alternative to the pressurised MDIs for all patients or for all drugs.

Micronized 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, therefore 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 their efficacy.

DPIs fall into two categories: single-dose and multi-dose. Single-dose DPIs, which have been in use for more than 60 years, utilise a single capsule inserted into the device. 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. They are inexpensive but may be more susceptible to humidity than some more recent multi-dose DPIs. Despite this, they are generally found to be effective. In 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. Single-dose DPIs have the advantage in developing countries that they permit low-income patients to avoid the expense of buying one month's therapy at a time.

Multi-dose DPIs, which have been in use for more than 20 years, typically contain enough doses for at least one month's treatment. Multi-dose DPIs manufactured by multinationals in developed countries generally have a similar price to the equivalent dose of drug in an MDI made by multinationals in developed countries, except for salbutamol, which is more expensive in multi-dose DPIs. It is important to note that pricing varies among products and countries, and depends on the local health care system, reimbursement schemes and other factors. Multi-dose DPIs made by multinationals in developed countries generally remain more expensive than MDIs manufactured in developing countries. This is partly due to the true differential in production costs between DPI and MDI devices (DPIs typically require customised equipment) but may also be related to national pricing policies and local market considerations. The introduction of branded generic multi-dose DPI products will likely change the present price structure.

There are two types of multi-dose DPI, one with individual doses pre-metered during manufacture, and the second that loads a measured amount for inhalation from a reservoir in the device. Older reservoir multi-dose DPIs can suffer from water ingress in high humidity environments that leads to clumping of the powder formulation. Some HFC MDIs are also affected by high humidity. Both can be partially addressed by supplying the device in a foil pouch opened on first use. Newer multi-dose DPIs function equally well in areas of high humidity, such as experienced in many developing countries.

DPIs can be easier for the patient to use because the drug delivery is effected by the patient's inhalation, and they do not require as much patient co-ordination as MDIs. Studies<sup>6</sup> have shown that for many patients single- and multi-dose DPIs are easier to use correctly than

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<sup>6</sup> Atkins, P.J., Dry powder inhalers: an overview, *Respir. Care*. 2005; 50; 1304-12; Timsina MP, Martin SP et al., Drug delivery to the respiratory tract using dry powder inhalers, *Int. J. of Pharmaceutics*. 1994, Vol. 101, pp 1-13; Singh M and Kumar L., Randomized Comparison of a Dry Powder Inhaler and Metered Dose Inhaler with Spacer in Management of Children with Asthma, *Indian Paediatrics*. 2001; 38: 24-28; Zeng X Macritchie H B Marriott C Martin G P., Humidity-induced changes of the aerodynamic properties of dry powder aerosol formulations containing different carriers, *International Journal of Pharmaceutics*. 2007; 333: 45-55.

MDIs. In some studies as many as 50 per cent of patients cannot use an MDI efficiently, although issues of coordination may be overcome through use of a spacer or breath-actuated inhaler. However, the efficiency with which powder is disaggregated into respirable particles is often dependent on the patient achieving an adequate inspiratory flow. Therefore, the MDI used with a spacer may be the only device suited for treating the very young or the elderly and for treating acute asthma attacks when inspiratory flow is compromised; it has been estimated that up to 30 per cent of elderly COPD patients could not achieve satisfactory inspiratory flows through common DPIs<sup>7</sup>.

The International Pharmaceutical Aerosol Consortium (IPAC)<sup>8</sup> analysed market data of global inhaler usage from 2002-2007 and 2008-2009, which has been interpreted by MTOC<sup>9</sup>. Worldwide usage of CFC MDIs is declining, and is less than either DPI or HFC MDI usage, based on dose equivalence. Meanwhile there has been an increased overall use of inhalers mainly due to the increased use of DPIs. The data show a slight decrease in the total consumption of all MDIs during this period, but a smaller decrease than the increased consumption of DPIs. DPIs account for around one-third of all inhaled medication, based on dose equivalence, and CFC MDIs for around 19 per cent. In some parts of Europe, multi-dose DPIs account for more than 90 per cent of inhaled therapy, and in India, single-dose DPIs account for more than 50 per cent of inhaled therapy. One multinational company, GlaxoSmithKline (GSK), is now developing new respiratory drugs exclusively as DPIs. GSK continues to market globally its established HFC MDIs.

Substantial development efforts are being pursued in the DPI segment by a number of pharmaceutical and technology based device companies. A number of pharmaceutical companies are now developing their new chemical entities by first intent as dry powder products. This includes the development of new devices as well as new products in established DPI systems. Similar challenges and costs would be expected for the development of new DPI products as there have been for HFC MDIs developments. Some generic multi-dose DPIs 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; however very 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 decades, especially since they have low global warming impact.

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<sup>7</sup> W. Janssens, P. VandenBrande, E. Hardeman, E. De Langhe, T. Philips, T. Troosters and M. Decramer, Inspiratory flow rates at different levels of resistance in elderly COPD patients, *Eur. Respir. J.* 2008; 31: 78–83.

<sup>8</sup> The International Pharmaceutical Aerosol Consortium is a group of companies (Abbott, Astrazeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Glaxosmithkline, Teva. and Sepracor.) that manufacture medicines for the treatment of respiratory illnesses, such as asthma and COPD.

<sup>9</sup> *Report of the UNEP Technology and Economic Assessment Panel*, May 2009, *Progress Report*, pp. 38-39, and *Report of the UNEP Technology and Economic Assessment Panel*, May 2010, Volume 2, *Progress Report*.

#### **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, ultrasonic waves or vibrating mesh. The situation is different than that with portable inhalers, in that the pharmaceutical companies supply drug formulations, but not the delivery device. Therefore, 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. Therefore 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. For patients with asthma and COPD, drug delivery via an MDI plus a spacer is at least as efficacious as nebulised therapy and costs far less. However, in many countries nebuliser use is still seen as optimal treatment in the acute situation in hospital and for chronic severe patients at home. Over time, nebuliser use for asthma treatment could be replaced by the use of an MDI plus spacer.

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 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.

The most recent development has been to vibrate a mesh containing micron-sized holes at ultrasonic frequencies. This vibration serves to pump liquid through the holes thereby creating a respirable spray. This process is very efficient and has resulted in portable devices that can be battery powered. The use of electronics also allows introduction of more sophisticated features, such as only triggering spray generation during a portion of the inspiratory manoeuvre, thereby minimising waste and environmental discharge. Nonetheless, these devices remain substantially more expensive than a portable device of the MDI or DPI type.

#### **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. 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). They can be distinguished from nebulisers in that they endeavour to deliver a complete dose within one or two breaths. 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 Respimat™, utilises the collision of two liquid jets to generate an aerosol and has been launched internationally for delivery of a long-acting

bronchodilator and two short-acting combination-bronchodilator for use in COPD and asthma patients.

While some of the other devices in development may serve as alternatives in the future, their contribution to 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 currently more expensive than standard MDIs and DPIs. The development and regulatory timescales for new inhaled delivery systems are lengthy and new technical breakthroughs are not common.

#### **2.2.6      *New propellants***

An inhalation propellant must be safe for human use and meet several other criteria relating to safety and efficacy: (i) liquefied gas, (ii) low toxicity, (iii) non-flammable, (iv) chemically stable, (v) acceptable to patients (in terms of taste and smell), (vi) appropriate solvency characteristics, and (vii) appropriate density. It is extremely difficult to identify chemicals fulfilling all of these criteria.

At the time of the introduction of the Montreal Protocol, extensive research had already identified two hydrofluorocarbons as alternative propellants – HFC-134a and HFC-227ea. Two international consortia (IPACT-I and IPACT-II) conducted toxicological testing to ensure that these propellants were safe for inhalation by humans. Once identified, the MDI industry reformulated the CFC MDIs so that they could use HFCs. The components and formulations were substantially modified to use the new HFC propellants.

MDIs are subject to extensive regulation by national health authorities to ensure product safety, product efficacy and manufacturing quality. The process for developing CFC-free MDIs was therefore essentially identical to the development of a wholly new drug product, involving full clinical trials for each reformulated MDI. Research and development for a new product is a lengthy, challenging, costly and resource-intensive process. Typically, it can take about ten years to reach the prescribing doctor. After identifying alternate medical propellants and developing safe, effective CFC-free MDIs, the final step is to switch millions of patients to reformulated MDIs and other CFC-free products.<sup>10</sup>

An MLF-funded project has been approved for the conversion of Argentina's inhaler manufacturers, including a project to eliminate the use of CFC by pharmaceutical company Pablo Cassara for the production of salbutamol CFC MDI by 2014 using isobutane as a propellant. Pablo Cassara supplies 60-70 per cent of the salbutamol CFC MDI market.

While an MDI formulated with isobutane propellant could be potentially beneficial in reducing greenhouse gas emissions due to HFC-propelled MDIs, there has been no successful isobutane reformulation worldwide despite several research projects over the past decade. MTOC has identified toxicological concerns for isobutane in combination with a beta-agonist<sup>11</sup>. A safety study for an entirely novel MDI propellant in asthma/COPD would require at least 12 months clinical trial experience in thousands of patients. This may be

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<sup>10</sup> *Special Report on Safeguarding the Ozone and the Global Climate System*, IPCC/TEAP, 2005, page 355.

<sup>11</sup> Final report of the Safety Assessment of isobutane, isopentane, n-butane, and propane. *Int. J. Toxicology*, 1; 4: 127-142, 1982.

prohibitively expensive for this volume of production. MTOC does not believe that this project can provide a safe CFC MDI alternative in a timely and cost-effective fashion. In addition, a secure supply of pharmaceutical-grade CFCs is increasingly unlikely in 2012 and beyond, which may not provide protection for patient health in Argentina if conversion does not occur well before 2014.

Chemical companies are promoting a new type of commercially available unsaturated HFC, also called a hydrofluoroolefin (HFO), with attractive chemical, physical and environmental properties for a range of applications. HFC-1234yf has a GWP of 4 and zero ODP, and can be used as a replacement for HFC-134a (GWP of 1430) in automobile air conditioning systems. HFC-1234yf is described as mildly flammable and has a lower flammability limit of 6.5% by volume in air, compared with isobutane that has a lower flammability limit of 1.6% by volume in air. Unsaturated HFCs offer a number of advantages over saturated HFCs, such as HFC-134a, being better solvents, less hygroscopic, and more compatible with a broader range of surfactants. Chemical companies claim that tests also show favourable toxicity.

However, this does not mean that unsaturated HFCs represent a viable alternative to saturated HFCs as propellants in MDIs. These new chemicals are not as advanced for pharmaceutical usage as were HFCs -134a and -227ea when the Montreal Protocol was introduced. For a new propellant development programme, there is major risk, significant investment, and no guarantee of success. Substantial time and resources would be required to (i) test the safety of unsaturated HFCs for direct and chronic human inhalation, and (ii) research, develop, reformulate and conduct safety and efficacy testing of whole new products with unsaturated HFCs, followed by regulatory review. For existing products, it would likely be particularly difficult for a pharmaceutical company to justify an investment in unsaturated HFCs given the limited benefit to patients (i.e., the active ingredient will remain the same and the performance characteristics are likely to be comparable to saturated HFCs), and in light of the large investments they have already made over the past two decades in developing and marketing saturated HFC MDIs.

#### **2.2.7      *Other environmental considerations***

With obligations under the Kyoto and Montreal Protocols to address climate impacts of alternative technologies, this section considers the climate impacts of alternatives to CFC MDIs.

Based on current consumption and projected growth rates<sup>12</sup> of MDI use, total annual consumption of HFCs for MDIs is estimated to be between 7,000-10,500 tonnes by 2015. This represents about 13 million tonnes of CO<sub>2</sub> equivalents per year.

IPAC has provided some rough internal estimates of carbon footprints of the manufacture and use of various respiratory devices and treatment methods based on a 200-dose equivalence (Table 2.1).

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<sup>12</sup> Most of the growth in MDI use is expected to occur in developing countries. Annual growth rates in MDI use are estimated to be between about 3-10 per cent.



**Table 2.1** *Rough estimates by IPAC of carbon footprints of respiratory devices and treatment methods*

<b>Respiratory devices and treatment methods</b>	<b>Carbon footprint Per 200 doses (Kilograms CO<sub>2</sub>eq.)</b>	<b>Carbon footprint Per 2 puffs (Grams CO<sub>2</sub>eq.)</b>
<b>CFC MDI</b>	150-200	1,500-2,000
<b>HFC-134a MDI</b>	20-30	200-300
<b>HFC-227 MDI</b>	60-80	600-800
<b>Dry Powder Inhaler</b>	1.5-6.0	<20
<b>Tablets</b>	1.5-5.0	<20

These rough estimates indicate that by moving from CFC MDIs to HFC MDIs and DPIs, not only have emissions of ozone depleting substances been eliminated, but there have also been benefits for climate change. According to these IPAC estimates, HFC MDIs have about 10 times less climate impact than CFC MDIs. DPIs have an even lower comparative climate impact, about 100 times less than CFC MDIs and 10 times less than HFC MDIs.

The estimated carbon dioxide equivalent of a 2-puff dose of an HFC MDI (200g CO<sub>2</sub>eq.) is comparable to the climate impact of everyday items, such as a 330ml can of Cola (170g CO<sub>2</sub>eq.)<sup>13</sup>, 250ml of orange juice (360g CO<sub>2</sub>eq.)<sup>14</sup>, and a kilometre driven in a Seat Ibiza Ecomotive (99g CO<sub>2</sub>eq.)<sup>15</sup>. This can also be compared with the carbon impact of a one-way economy class flight from London to Frankfurt (180kg CO<sub>2</sub>eq./passenger)<sup>16</sup>, a popular burger (4kg CO<sub>2</sub>eq.)<sup>17</sup>, or a loaf of commercially made bread (1.3kg CO<sub>2</sub>eq.)<sup>18</sup>. Estimates of carbon dioxide equivalents associated with a dose of an asthma inhaler and everyday items are presented in Figure 2.1.

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<sup>13</sup> <http://www.cokecorporateresponsibility.co.uk/big-themes/energy-and-climate-change/product-carbon-footprint.aspx>

<sup>14</sup> [http://www.tesco.com/greenerliving/greener\\_tesco/what\\_tesco\\_is\\_doing/carbon\\_labelling.page](http://www.tesco.com/greenerliving/greener_tesco/what_tesco_is_doing/carbon_labelling.page)

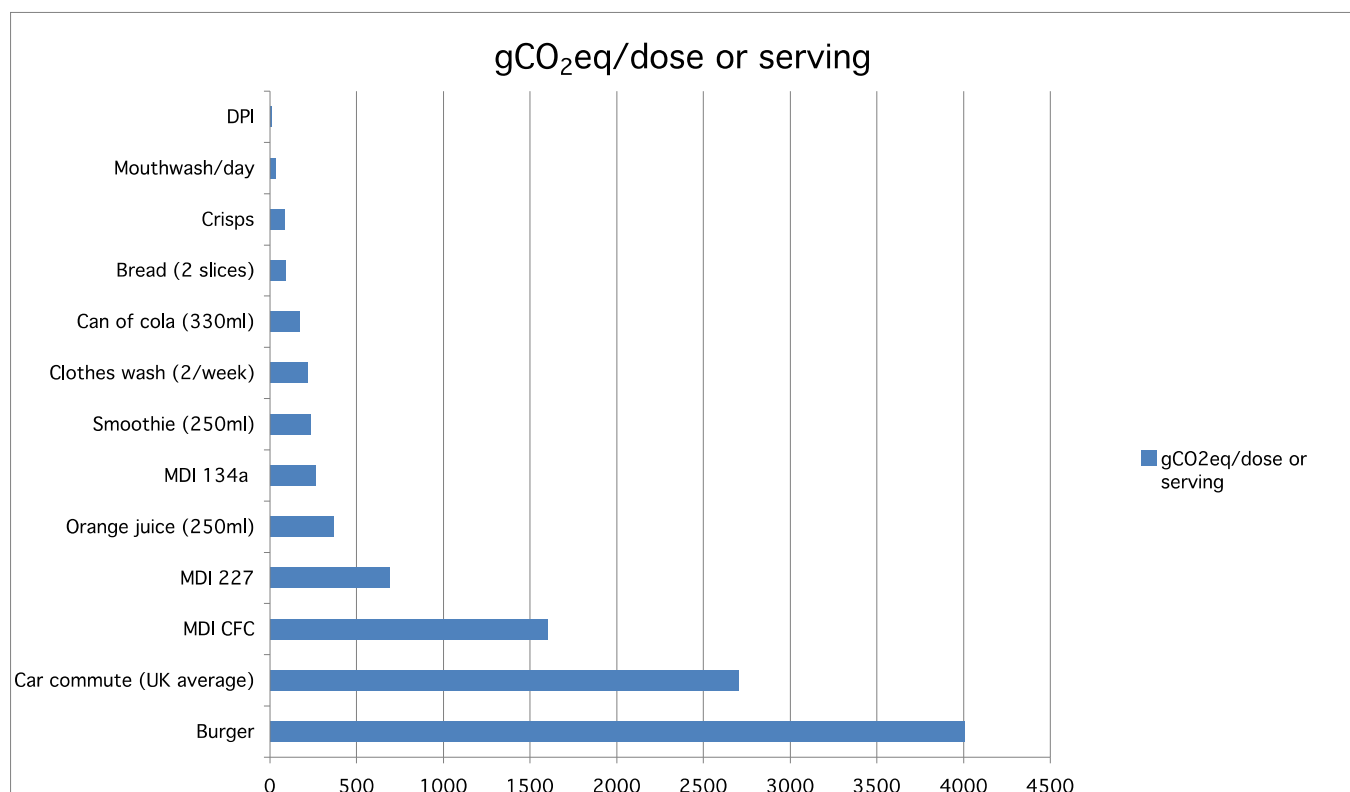
<sup>15</sup> <http://www.seat.co.uk/generator/su/com/SEATRange/site/start/main.html>

<sup>16</sup> <http://www.gco2.ie/flightemissions.aspx#>.

<sup>17</sup> <http://fatknowledge.blogspot.com/2007/01/carbon-footprint-of-cheeseburger.html>

<sup>18</sup> <http://www.kingsmillbread.com/carbon-footprint>

**Figure 2.1 Estimated relative carbon dioxide emissions of everyday items compared with asthma inhalers<sup>19</sup>**



<sup>19</sup> Sources of carbon footprint estimations:

- (1) Asthma inhalers from internal estimates by IPAC;
- (2) Mouthwash (GlaxoSmithKline, unpublished data);
- (3) Crisps ([http://www.walkerscarbonfootprint.co.uk/walkers\\_carbon\\_footprint.html](http://www.walkerscarbonfootprint.co.uk/walkers_carbon_footprint.html));
- (4) Bread (<http://www.kingsmillbread.com/carbon-footprint>);
- (5) Cola (<http://www.cokecorporateresponsibility.co.uk/big-themes/energy-and-climate-change/product-carbon-footprint.aspx>);
- (6) Clothes wash  
([http://www.tesco.com/greenerliving/greener\\_tesco/what\\_tesco\\_is\\_doing/carbon\\_labelling.page](http://www.tesco.com/greenerliving/greener_tesco/what_tesco_is_doing/carbon_labelling.page));
- (7) Smoothie (calculated from  
[http://www.innocentdrinks.co.uk/us/ethics/sustainable\\_production/carbon/how\\_much](http://www.innocentdrinks.co.uk/us/ethics/sustainable_production/carbon/how_much));
- (8) Orange juice  
([http://www.tesco.com/greenerliving/greener\\_tesco/what\\_tesco\\_is\\_doing/carbon\\_labelling.page](http://www.tesco.com/greenerliving/greener_tesco/what_tesco_is_doing/carbon_labelling.page));
- (9) Car commute, UK average (calculated from the following sources,  
<http://www.defra.gov.uk/environment/business/reporting/pdf/101006-guidelines-ghg-conversion-factors.pdf>, page 19;  
<http://www.bbc.co.uk/bloom/actions/trainandbus.shtml>;  
<http://www.livingstreets.org.uk/news/uk/useful-facts>).

## **2.2.8 Patient Health Considerations**

It is important to note that MDIs, DPIs and novel delivery systems play an important role in the treatment of asthma and COPD, and no single delivery system is considered universally acceptable for all patients. Similarly, not all active ingredients are available equally as either an MDI or DPI, for example, there is currently no salbutamol DPI available in the United States. Nevertheless, DPIs may play an increasing role over the next decade. Healthcare professionals continue to consider that a range of therapeutic options is important. Any consideration of policy measures to control HFCs should carefully assess patient health implications with the goals of ensuring patient health and maintaining a range of therapeutic options. Each country has its own unique and complex makeup in terms of availability of medicines, overarching health care systems, and patient preferences.

## **2.3 Availability of CFC-free alternatives**

### **2.3.1 Global situation**

Substantial global progress has continued in the development and launch of HFC MDIs and DPIs and now most companies based in non-Article 5(1) countries have completed their phase-out of CFC MDIs. There are two exceptions. First, in the United States, the phase-out of flunisolide will occur at the end of 2011, and the phase-out of pirbuterol and the combination of albuterol (salbutamol) and ipratropium bromide will occur at the end of 2013. The other exception is the Russian Federation where, as detailed in the 2010 Progress Report of the Technology and Economic Assessment Panel<sup>20</sup>, phase-out of salbutamol CFC MDIs is projected for the end of 2012.

Detailed 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 other publicly available documents. Listed below in Table 2.2 are the HFC MDI products that have been developed and launched as of May 2010.

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<sup>20</sup> *Report of the UNEP Technology and Economic Assessment Panel*, May 2010, Volume 2, Progress Report, [http://ozone.unep.org/Assessment\\_Panels/TEAP/Reports/TEAP\\_Reports/index.shtml](http://ozone.unep.org/Assessment_Panels/TEAP/Reports/TEAP_Reports/index.shtml).

**Table 2.2 Progress in CFC-free MDI introduction by moiety and company: table data refer to numbers of products available in all markets**

<b>Moiety</b>	<b>Company</b>	<b>Launched by Dec 05</b>	<b>Launched by May 10</b>
Beclomethasone dipropionate	Chiesi	22	52
	GlaxoSmithKline	19	29
	Teva	27	76
Budesonide	AstraZeneca	0	20
	Chiesi	15	31
Fenoterol	Boehringer Ingelheim	20	45
Fenoterol and Ipratropium	Boehringer Ingelheim	19	42
Fluticasone	GlaxoSmithKline	111	144
Formoterol	Chiesi	11	35
Ipratropium	Boehringer Ingelheim	28	70
Nedocromil Sodium	Sanofi-Aventis	9	9
Salbutamol	GlaxoSmithKline	96	184
	Teva	39	81
Salmeterol	GlaxoSmithKline	1	83
Sodium cromoglycate	Sanofi-Aventis	*14	*14

\* Includes two products containing sodium cromoglycate in combination with reproterol.

Table 2.3 summarises the total numbers of CFC-free products available at the time of the 2006 MTOC Assessment Report compared to May 2010. Overall, there has been a 48 per cent increase in the number of products available with global rollout of CFC-free MDIs containing drugs in three of the major treatment categories (short- and long-acting bronchodilators, and corticosteroids), but not for the cromoglycates. This is complemented both by newer drugs that were developed directly as HFC products, such as ciclesonide, and by the wide availability of dry powder inhalers.

### **2.3.2 Situation in Article 5(1) countries**

The situation in Article 5(1) countries is also very encouraging. Manufacturers in both developed and developing countries supply CFC-free inhalers. Table 2.3 provides data on Article 5(1) countries where an inhaler manufacturer that is a member of IPAC has launched at least one CFC-free product. Comparative data are not available for manufacturers based in developing countries.

**Table 2.3 Number of products launched globally and within Article 5(1) countries**

<b>Moiety</b>	<b>Device</b>	<b>Globally launched by Dec 2005</b>	<b>Globally launched by May 2010</b>	<b>Article 5(1) countries with at least one product launched</b>	<b>Article 5(1) countries with more than one product launched</b>
Beclomethasone dipropionate	DPI	42	22	58	28
	HFC MDI	93	175		
Budesonide	DPI	76	119	66	19
	HFC MDI	15	52		
Fenoterol	DPI	0	0	20	0
	HFC MDI	20	45		
Fenoterol and Ipratropium	DPI	0	0	16	0
	HFC MDI	20	42		
Fluticasone propionate	DPI	87	73	100	*29
	HFC MDI	115	144		
Formoterol	DPI	52	63	48	8
	HFC MDI	17	34		
Ipratropium bromide	DPI	0	5	33	1
	HFC MDI	28	70		
Nedocromil sodium	DPI	0	0	0	0
	HFC MDI	9	9		
Salbutamol	DPI	77	71	131	43
	HFC MDI	166	288		
Salmeterol xinaofate	DPI	83	59	65	*8
	HFC MDI	1	83		
Sodium cromoglycate	DPI	2	2	0	0
	HFC MDI	**14	**14		
Terbutaline	DPI	50	57	29	0
	HFC MDI	0	0		

\* Two products supplied by the same manufacturer

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

Based on data of inhalers supplied by IPAC member companies, there is widespread availability of salbutamol HFC MDIs in many countries, with over 40 Article 5(1) 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. Table 2.4 shows the data according to therapeutic classes of inhalers for Article 5(1) countries.

**Table 2.4**     *The number of Article 5(1) countries where alternatives to CFC MDIs are available (as of May 2010)*

<b>Therapeutic class</b>	<b>At least one product launched</b>	<b>More than one product launched</b>
Short-acting bronchodilator	132	58
Long-acting bronchodilator	80	28
Corticosteroid	118	67
Anticholinergic	52	*8
Bronchodilator and steroid combination	120	56

\* Two products supplied by the same manufacturer

Since 2006 there has also been a substantial increase in HFC MDIs made in Article 5(1) countries. Many domestic producers now have the capability to supply HFC MDIs both for domestic use and for export, and this is hastening the transition for those Article 5(1) countries that rely on imports. For example, Cipla, an Indian multinational pharmaceutical company, now markets 51 different CFC-free inhalers (including DPIs), some of which are combination products not yet available in non-Article 5(1) countries. This has led to India announcing the completion of its phase-out of CFCs in MDIs in late 2010, and withdrawing its essential use nomination for 2011. Three local manufacturers in Bangladesh will soon have HFC MDIs on the market with a combined manufacturing capacity of up to five times domestic use. In contrast, MDI manufacturers in a few remaining countries, such as Russia and China, have yet to convert plant from CFC MDIs. Based on likely manufacturing conversions in developing countries, it is anticipated that transition will essentially have been completed by about the end of 2012, except in China.

Even without taking account of products manufactured in Article 5(1) countries, it is clear that there are now widespread options to treat respiratory diseases with CFC-free products. IPAC has also analysed progress in the transition to CFC-free alternatives based on available prescribing data. Although not wholly accurate for information from some developing countries, IMS<sup>21</sup> data show an encouraging global trend towards CFC-free therapy. In 2009, CFC MDIs formed only 30 per cent of all MDI sales, compared to over 60 per cent in 2005. This is against a background of an 8 per cent increase in global MDI usage over the same period. Generally MDIs require 2 puffs per dose, whereas DPIs only require 1 puff per dose. Currently, CFC MDIs represent only 19 per cent of the total number of doses taken.

While MTOC believes that there could be difficulties in some markets with IMS data collection, the manufacturing transition has not yet been reflected in marketing data. Over the last 4 years, CFC MDI sales in South East Asia and Africa have steadily increased as access to health care improves, and asthma and COPD increase in the population. There will be an inevitable lag between cessation of CFC bulk supply, CFC manufacturing transition and

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<sup>21</sup> IMS Health is a company that gathers and analyses pharmaceutical market data. IMS Health granted IPAC permission to submit this data to MTOC/TEAP.

subsequent reduction in CFC MDI use in Article 5(1) country markets. At present the reduction in CFC usage has been driven mainly by a reduction in developed country markets.

In the TEAP Progress Report 2010<sup>22</sup>, MTOC noted the worldwide availability of affordable CFC-free alternative inhalers. CFC MDI phase-out is now feasible in the very near future.

## **2.4 Transition in Article 5(1) countries, the Russian Federation and the United States**

It is now over 16 years since the first introduction of an HFC MDI for the short-acting beta-agonist salbutamol in the United Kingdom in 1994. By 2010 every developed country had phased out the use of CFCs in MDIs, except the Russian Federation, which is yet to complete manufacturing conversion, and the United States, which is well advanced in its phase-out. Most developing countries are well advanced in their transition plans to phase out the use of CFCs.

### **2.4.1 Progress in Article 5(1) countries that manufacture CFC MDIs**

CFC MDIs may have been manufactured in at least 20 Article 5(1) countries (Algeria, Argentina, Bangladesh, Brazil, China, Colombia, Croatia, Cuba, Egypt, India, Indonesia, Iran, Jordan, Mexico, Pakistan, South Africa, Syria, Tunisia, Uruguay, and Venezuela).

Many MDI manufacturers are locally owned companies that are not affiliated with multi-national pharmaceutical companies. These companies have either financed their own conversion to manufacture CFC-free inhalers or have received finance for their conversion through the Multilateral Fund for the Implementation of the Montreal Protocol (MLF). Some multi-national companies operating in Article 5(1) countries completed the transition to CFC-free inhalers prior to the 2010 CFC phase-out (e.g. Brazil).

Some countries (e.g. Cuba, Croatia, Iran and Tunisia) have successfully completed their manufacturing transition to CFC-free inhalers. A number of countries (Argentina, Bangladesh, China, Cuba, India, Iran, Pakistan, Uruguay) received financial assistance from the MLF for projects to convert MDI manufacturing enterprises to produce CFC-free alternatives. A number of countries (e.g. Algeria, Brazil, Jordan, South Africa, Syria, Venezuela) were not eligible for funding by the MLF under decisions of the Executive Committee.

The MLF has funded projects in developing countries mainly focussed on technology transfer and institutional strengthening to convert CFC MDI manufacture to CFC-free alternatives. MLF funding approved by the Executive Committee of the Montreal Protocol for MDI projects is USD 52.2 million.

The implementing agencies of the MLF (UNDP, UNIDO and the World Bank) are responsible for implementing MLF-funded MDI investment projects and work with the companies and the respective governments to achieve the agreed timelines. This has proven to be a challenging task, with most MLF-funded conversion projects incomplete before the 2010 CFC phase-out. This has necessitated making use of the essential use provisions of the

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<sup>22</sup> *Report of the UNEP Technology and Economic Assessment Panel*, May 2010, Progress Report, Volume 2.

Montreal Protocol with Article 5(1) countries that manufacture CFC MDIs nominating them as essential uses after the CFC phase-out.

Despite initial challenges, such as access to technology transfer and economic barriers, progress has been significant with a number of countries nearing completion of their transition to CFC-free inhalers faster than expected a little more than a year ago. CFC consumption by Article 5(1) countries is estimated to have peaked at about 1,700 tonnes in 2008 and 2009, and appears to be decreasing in 2010. In 2010, most countries have decreased their consumption of CFCs to manufacture MDIs. Current predictions are that most Article 5(1) countries will have largely completed transition by about the end of 2012. A notable exception is China, which in recent years has shown increasing consumption of 15-30 per cent year on year.

For Article 5(1) countries that manufacture CFC MDIs and submit essential use nominations, there are a number of requirements for developing and submitting transition strategies and plans for CFC MDI phase-out schedules and regulatory measures. Decisions IX/19(5bis) and XV/5(4bis) set out requirements for the development of national transition strategies and preliminary plans of action for the phase-out of salbutamol CFC MDIs respectively.

Decision IX/19(5bis) states:

*“To require Parties operating under paragraph 1 of Article 5 submitting essential-use nominations for chlorofluorocarbons for metered-dose inhalers for the treatment of asthma and chronic obstructive pulmonary disease to present to the Ozone Secretariat an initial national or regional transition strategy by 31 January 2010 for circulation to all Parties. Where possible, Parties operating under paragraph 1 of Article 5 are encouraged to develop and submit to the Secretariat an initial transition strategy by 31 January 2009. In preparing a transition strategy, Parties operating under paragraph 1 of Article 5 should take into consideration the availability and price of treatments for asthma and chronic obstructive pulmonary disease in countries currently importing chlorofluorocarbon-containing metered-dose inhalers;”*

Decision XV/5(4bis) states:

*“That no quantity of chlorofluorocarbons for essential uses shall be authorized after the commencement of the Twenty-First Meeting of the Parties if the nominating Party operating under paragraph 1 of Article 5 has not submitted to the Ozone Secretariat, in time for consideration by the Parties at the twenty-ninth meeting of the Open-ended Working Group, a preliminary plan of action regarding the phase-out of the domestic use of chlorofluorocarbon containing metered-dose inhalers where the sole active ingredient is salbutamol;”*

Decision XVII/5(3bis) requests nominating Article 5(1) countries to submit a date to the Ozone Secretariat prior to the Twenty-Second Meeting of the Parties, by which time a regulation or regulations to determine the non-essentiality of the vast majority of chlorofluorocarbons for metered-dose inhalers where the active ingredient is not solely salbutamol will have been proposed. Decision XV/5(6) requests Parties to submit to the Ozone Secretariat specific dates by which time they will cease making nominations for essential use nominations for CFCs for MDI where the active ingredient is not solely salbutamol.



The TEAP Progress Report 2010 summarises current knowledge of transition strategies and measures of Article 5(1) countries according to these Decisions.<sup>23</sup>

The following sections describe current knowledge on progress in transition in a number of Article 5(1) countries with domestic MDI manufacture.

#### *2.4.1.1 Algeria*

The Government of Algeria has one CFC MDI manufacturing enterprise, the Algerian Pharmaceutical Laboratory (LPA), which is 100 per cent nationally owned. One production line for salbutamol CFC MDIs was installed in 2005 under licence from Chiesi Italy, with full production commencing in 2006 for domestic consumption only. Production capacity is 5 million units annually. In 2007, about 11 tonnes of CFCs were used to manufacture MDIs. No essential use nominations have been submitted by Algeria. Algeria was not eligible for funding under the MLF. LPA intends to commence HFC MDI production in 2012. It is currently in discussion with technology providers to attain machinery and know-how.

#### *2.4.1.2 Argentina*

CFC MDIs are manufactured in Argentina by a range of companies, for both domestic and export consumption: Laboratorio Pablo Cassará (100 per cent local ownership), which supplies 60-70 per cent of the market; 3M, a multinational company that fills MDIs for a group of 15 laboratories, five of which are nationally owned; and Denver Farma, a local company (100 per cent local ownership) that used to fill its MDIs through 3M but established its own CFC MDI production line in 2007. Two multinational companies stopped production of CFC MDIs in Argentina before the end of 2009.

An MLF-funded project has been approved for the conversion of the domestic inhaler manufacturers. The objectives of the project are: to eliminate the use of CFC at Pablo Cassara for the production of salbutamol CFC MDI by 2014 by using isobutane as a propellant; to eliminate the use of CFCs at Denver Farma for the production of salbutamol and budesonide; and to provide technical support for alternative formulations for four locally owned companies filling their own MDIs through third parties.

Laboratorios Pablo Cassara has carried out tests with more than 60 formulations using isobutane as propellant and has identified some candidate formulas. Preliminary stability studies on these formulas are planned during October 2010, and pilot batches manufactured before the end of 2010. While an MDI formulated with isobutane propellant could be potentially beneficial in avoiding greenhouse gas emissions due to HFC-propelled MDIs, there has been no successful isobutane reformulation worldwide. MTOC has identified toxicological concerns for isobutane in combination with a beta-agonist, such as salbutamol (Final report of the Safety Assessment of isobutane, isopentane, n-butane, and propane. *Int. J. Toxicology*, 1; 4: 127-142, 1982.). A safety study for an entirely novel MDI propellant in asthma/COPD may require at least 12 months clinical trial experience in thousands of patients, followed by post marketing surveillance on many thousands of patients. This may be prohibitively expensive for this volume of production. Therefore MTOC has concerns

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<sup>23</sup> *Report of the UNEP Technology and Economic Assessment Panel*, May 2010, Progress Report, Volume 2.

about the viability of this project, and its ability to provide a safe CFC MDI alternative in a timely fashion.

#### *2.4.1.3 Bangladesh*

Bangladesh developed a national transition strategy for phasing out the use of CFCs in MDI manufacture in Bangladesh in 2007. CFC-free MDIs were introduced in 2006 and their launch and adoption has continued to expand. Currently, three companies manufacture HFC MDIs while two companies manufacture DPI inhalers. Total combined capacity of HFC MDI manufacture of salbutamol and beclomethasone among Bangladesh MDI manufacturers by the end of 2010 will be 25 million HFC MDI units per year. Bangladesh MDI consumption is estimated at 5 million per year. In general, the pricing of CFC-free alternatives is comparable to their CFC counterparts.

In a 2010 update to its transition strategy, Bangladesh states that it will phase out CFC use completely by 2012, four years earlier than was originally proposed. This development has been aided by the MLF funding of manufacturing conversion projects, which appear to have progressed well and account for the availability of multiple HFC products from multiple manufacturers (for salbutamol and beclomethasone) that can meet domestic needs. In addition, two single inhalers (ipratropium and budesonide) and two combination inhalers (salmeterol/fluticasone and salbutamol/ipratropium) have been developed and marketed by one local manufacturer (Beximco), which is indicative of Bangladesh's continued efforts and commitment towards achieving phase-out. At the 22<sup>nd</sup> Meeting of the Parties in November 2010, Bangladesh announced that it would not be seeking an essential use exemption for CFCs to manufacture salbutamol, beclomethasone or levosalbutamol MDIs after 2011. In a recent status report, UNDP indicates that the expected date when the companies will manufacture only HFC MDIs is December 2012.<sup>24</sup> Bangladesh is to be commended for being proactive and diligent in its efforts to transition from CFC MDIs to CFC-free inhalers.

#### *2.4.1.4 China*

There is an approved MLF project for CFC phase-out in China's MDI sector, which is due for completion in 2015. In July 2010 at the 61<sup>st</sup> Meeting of the Executive Committee of the MLF, UNIDO reported that the Sector plan for phase-out of CFC consumption in the MDI sector in China has been delayed. A range of reasons for delays is offered, such as lengthy clinical trials, expensive equipment for industrial production, and research and development activities still at a pre-clinical stage. HFC MDIs are not expected to be approved until the end of 2013, and would not enter the market until 2015. UNIDO reports that contracts will be awarded when policies and regulations for essential use of CFCs are in place. UNIDO expects the project to be completed in December 2015, two years later than originally planned.<sup>25</sup>

An initial transition strategy for China has been formulated and was submitted to the Ozone Secretariat in early 2010. Subsequently in December 2010, according to Decision XX/3 of the 20<sup>th</sup> Meeting of the Parties, China submitted the schedule by which it will determine the non-essentiality of the vast majority of chlorofluorocarbons for metered-dose inhalers in China. The first product planned for phase-out is salbutamol, which will officially begin on

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<sup>24</sup> MDI Status Report provided by UNDP to MLF Secretariat, October 2010.

<sup>25</sup> UNEP/OzL.Pro/ExCom/61/17, <http://www.multilateralfund.org/files/61/6117.pdf>.

December 31, 2013 and will be determined to be non-essential in 2016. The strategy anticipates that CFC MDIs will co-exist on the market with HFC MDIs for a period of one year. Consumption of CFCs for salbutamol MDIs represents about 73 per cent of the total CFC quantity requested. The second largest quantity requested (accounting for another 12 per cent) is for beclomethasone, which will no longer be essential when two CFC-free alternatives are available from two different producers. Phase-out of beclomethasone will be completed in 2016 when it will be determined to be non-essential. The remaining active ingredients will also be phased out and determined to be non-essential in 2016. In order to regulate CFC production and use in the MDI sector, and to accelerate the phase-out of CFCs, China has issued regulations regarding CFC stockpiles and management, and plans to provide strategic support for CFC phase-out in the MDI sector, such as by organizing seminars on alternative technologies and enhancing public awareness.

Research and development of HFC MDIs by local companies started in China in 2002. Salbutamol HFC MDI files were submitted in 2004 but production has not yet started. The nomination states that drug regulatory approvals can take many years. According to China's document that reports when CFC MDI products will be determined as non-essential, two manufacturers in China have made an application for registration of salbutamol HFC MDIs and may complete substitution in 2014. Fast track regulatory processes may assist in expediting approvals. At least one imported salbutamol HFC MDI manufactured by a multinational is already on sale in China, which could provide clinical experience that might allow an expedited process for those drug products. One MDI manufacturer in China has completed beclomethasone HFC MDIs formulation, which is likely to be marketed in 2014; other manufacturers will not complete formulation of beclomethasone MDI in the short term.

There are imported HFC MDIs (e.g. salbutamol) and DPIs (e.g. formoterol and budesonide) available. The current retail prices of locally produced CFC MDIs are considerably cheaper than the prices of imported CFC-free inhalers (MDIs or DPIs). Therefore pricing is an important reason for the lack of market penetration of imported CFC-free inhalers in China. Government may wish to consider pricing policies for local and imported inhalers that do not discourage CFC-free inhalers.

Between 2004 and 2009, CFC consumption for MDI manufacture had an annual growth rate of up to 24 per cent. Increases in consumption are explained by China to result from an increasing number of patients being treated with CFC MDI therapy, reflecting the reform and enlargement of medical insurance, basic medicine and the special support for chronic diseases such as asthma and COPD.

For traditional Chinese medicines, the Chinese Government has indicated it will organize re-evaluation and substitution studies to consider their essentiality and status. If re-evaluation considers these as non-essential or ready for complete substitution, they will not be included in future essential use applications. Currently, China has scheduled traditional Chinese medicines to be determined as non-essential in 2016.

#### *2.4.1.5 Colombia*

MDI market is supplied by imported CFC and HFC MDIs and locally produced CFC MDIs in lower proportions. Laboratorios Chalver is the sole locally owned company that manufactures CFC MDIs. MDI production commenced at the end of 2002. The company has developed CFC MDIs with seven different MDI products. Colombia has an approved MLF-funded project to convert production of three of its MDI products to HFC technology by 2012. In July 2010 at the 61<sup>st</sup> Executive Committee of the MLF, UNDP reported no disbursements under the project for 2009 due to the lengthy administrative processes to have the project document signed and to agree on implementation arrangements with the company

and the Government. The development of formulations has commenced and proposed stability protocols are being reviewed.<sup>26</sup> Salbutamol HFC MDI has completed product development including registration. Beclomethasone is undergoing stability testing prior to registration. Ipratropium bromide is still in the process of reformulation. Project completion is anticipated in mid-2011. Colombia has been using stockpiled CFCs to maintain MDI production while the conversion project is undertaken. An essential use exemption has not been requested, and the company has indicated that it will not require newly manufactured CFCs.<sup>27</sup>

#### *2.4.1.6 Cuba*

Cuba was the first country to undertake an MLF project to convert its CFC MDI production to HFC MDIs. UNDP has reported that the project was completed in May 2010 with a successful industrial batch of fluticasone HFC MDI. Stability tests and registration for this product are on-going. Production of salbutamol HFC MDI had already previously commenced.

#### *2.4.1.7 Egypt*

MDI production in Egypt began in 1984. There are two locally owned manufacturers of MDIs in Egypt, the Arab Drug Company and the Egyptian International Pharmaceutical Industries Co. An MLF project to convert Egypt's CFC MDI production to HFC MDIs was approved in 2006. In July 2010 at the 61<sup>st</sup> Meeting of the Executive Committee of the MLF, UNIDO reported that progress in Egypt has been slow in the construction of new premises for HFC MDI production at both companies. Consequently CFCs are likely to be used to manufacture MDIs in 2011 and are expected to be supplied from stocks acquired under the approved 2010 essential use exemption.<sup>28</sup> An essential use nomination was not received for CFC MDI production in 2011. UNIDO expects the project to be completed in June 2011, although all drug products may not be converted, manufactured with HFCs and available on the market until mid-2012.<sup>29</sup>

#### *2.4.1.8 India*

India produces CFC MDIs, HFC MDIs and DPIs for domestic and export markets. India's National Transition Strategy, submitted to the 56th Executive Committee of the MLF, indicated 2012 as the completion date for transition of all CFC products. In its nomination for 2011, India revised the completion date to be 2013. One company (Cipla), which produces 51 different CFC-free inhalers and has a significant portion of the market, reported its commitment to phase out domestic supply of CFC MDIs by the end of 2009. There are at least two other manufacturers of HFC MDIs in India. In addition, there is a wide range of available single- and multi-dose DPIs. In October 2010, India announced its successful completion of transition from CFC MDIs to CFC-free MDIs, indicating that it would not

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<sup>26</sup> UNEP/OzL.Pro/ExCom/61/15, <http://www.multilateralfund.org/files/61/6115.pdf>

<sup>27</sup> MDI Status Update Report provided by UNDP to MLF Secretariat, October 2010.

<sup>28</sup> UNEP/OzL.Pro/ExCom/61/17, <http://www.multilateralfund.org/files/61/6117.pdf>

<sup>29</sup> MDI Status Report provided by UNIDO to MLF Secretariat, October 2010.

require any CFCs for 2011 or beyond. India is to be congratulated for this outstanding achievement in accelerating its anticipated phase-out.

#### *2.4.1.9 Indonesia*

The 56<sup>th</sup> Meeting of the Executive Committee of the MLF approved a technical assistance program for Indonesia for the phase-out of 30 ODP tonnes of CFCs used in the pharmaceutical aerosol sector, including MDIs. Indonesia committed to phase-out CFC consumption in MDI manufacturing by the end of 2009.

#### *2.4.1.10 Iran*

Sina Darou Laboratories Co. is the only locally owned manufacturer of MDIs in the Islamic Republic of Iran. MDI production was initiated in 1993, and the first CFC MDI produced was salbutamol. Other active ingredients followed including beclomethasone, salmeterol and cromoglycate. Current total production levels are 5.2 million MDIs per annum<sup>30</sup>. Iran also imports a smaller proportion of imported MDIs and DPIs. In 2007, the 52<sup>nd</sup> Meeting of the Executive Committee of the MLF approved a CFC phase-out project for MDI manufacture and a project to assist with Iran's national transition strategy. On 15<sup>th</sup> September 2010, Dr Haji-zadeh announced that Sina Darou had successfully produced the first batches of HFC MDIs for salbutamol, beclomethasone, and salmeterol. These batches are undergoing stability testing for legal requirements. Cromoglycate will not be reformulated as an HFC MDI. On this basis, the Islamic Republic of Iran notified the Ozone Secretariat of the withdrawal of its essential use nomination for 2011 and the completion of its CFC phase-out in the MDI sector. Iran is to be commended for this outstanding achievement, despite significant challenges, accomplished through a collaborative partnership between industry, government, and non-governmental and implementing agencies.

#### *2.4.1.11 Mexico*

Laboratorios Salus have produced MDIs in Mexico since 1999, for the active ingredients salbutamol, beclomethasone, and cromoglycate. Current production for CFC MDIs is 4.4 million MDIs per annum. It produces about 70 per cent of MDIs for Mexican Government health services and the remaining 30 per cent for the local market. A large proportion of CFC-free MDIs are also imported by Mexico. The 53<sup>rd</sup> Meeting of the Executive Committee of the MLF approved a project for the phase-out of CFCs in MDI production. Mexico has not nominated for essential use production of CFCs for MDI production and is understood to be producing from available stockpile. In July 2010 at the 61<sup>st</sup> Meeting of the Executive Committee of the MLF, UNIDO reported that equipment had been delivered and was being installed in Mexico.<sup>31</sup> UNIDO expects the project to be completed by the end of 2011 with the final newly formulated HFC MDI in the market by the first quarter of 2012.<sup>32</sup>

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<sup>30</sup> MDI Status Report provided by UNIDO to MLF Secretariat, October 2010.

<sup>31</sup> UNEP/OzL.Pro/ExCom/61/17, <http://www.multilateralfund.org/files/61/6117.pdf>

<sup>32</sup> MDI Status Report provided by UNIDO to MLF Secretariat, October 2010.

#### *2.4.1.12 Pakistan*

In Pakistan there are three local CFC MDI manufacturers: GSK Pakistan, Macter, and Zafa. Until recently the majority of CFC MDIs was manufactured in Pakistan by GSK Pakistan (as salbutamol CFC MDI) until the company committed to stop all manufacture of CFC MDIs at the end of 2009. The halt in manufacturing at GSK Pakistan has resulted in a substantial drop in Pakistan's CFC consumption in the MDI sector. GSK Pakistan launched an imported salbutamol HFC inhaler (Aerolin™) in 2007. A range of other CFC-free products is also available in Pakistan.

A national transition strategy for the phase-out of CFCs in MDIs for Pakistan was submitted in July 2008. It outlines plans for the conversion of MDI production, the projected costs and planned timelines. An approved MLF investment project is for conversion of the eligible portion of the manufacturing of GSK Pakistan and Zafa. Conversion of the manufacturer with the largest CFC MDI capacity, Macter, was not eligible for funding. The investment components are complimented by measures for education and awareness as well as legislative and regulatory measures. The 2008 national phase-out strategy anticipates complete transition by the end of 2012. A recent update report from UNDP indicates the expected date when the companies will manufacture only HFC MDIs as December 2013.<sup>33</sup>

If the GSK Pakistan conversion is delayed, there could be insufficient capacity from the other two companies to supply the entire Pakistan market with affordable salbutamol CFC MDIs, and the only substitute for the locally manufactured CFC MDIs will be imported HFC MDIs. The prices of these imported products are currently considerably higher than locally produced CFC MDIs, and this may significantly limit patient access to this therapy. The Government of Pakistan may need to carefully manage the price of imported salbutamol HFC MDIs to ensure affordability and accessibility of these products.

#### *2.4.1.13 South Africa*

South Africa previously manufactured CFC MDIs. The last local facility that was manufacturing these products in Pretoria was closed down at the end of 2005, under requirements of the Medicines Control Council in the Ministry of Health. South Africa now imports finished inhaler products to cover the anticipated market need for the medicine on a yearly basis.

#### *2.4.1.14 Syria*

Syria has one MDI manufacturing company, K.C. Pharma, which is 100 per cent nationally owned. The first CFC MDI production was in 1999. The company produces seven products, with MDI production at around 2 million MDIs per year. These products are being produced under license from Chiesi, Italy. Other than two imported DPI inhalers, other imports of inhalers are prohibited. Syria was not eligible for funding under the MLF. K.C. Pharma anticipates phase-out of CFC consumption in its MDI manufacture by the end of 2012.

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<sup>33</sup> MDI Status Update Report provided by UNDP to MLF Secretariat, October 2010.

#### *2.4.1.15 Uruguay*

Uruguay has an approved MLF investment project to assist with conversion of its CFC MDI manufacture. Equipment to manufacture MDIs with HFCs was installed successfully in 2007 and was used to produce stability batches for five new formulations. The company developed the formulations using its own laboratory capacity and receiving assistance from a UNDP expert. This project has now been successfully completed.

#### *2.4.1.16 Venezuela*

Venezuela imports MDIs and DPIs. Venezuela had one company manufacturing MDIs, Laboratoris L.O. Oftalmi, CA., which is 100 per cent nationally owned. The company commenced MDI production in 1991, and supplied to the National Health Service and to the country's free market. The company did not export MDIs. Until recently, the company had been working towards converting its CFC MDI manufacture to HFC MDIs, and had been using stockpiled CFCs during transition. Venezuela was not eligible for funding under the MLF. However MTOC understands that the company now no longer manufactures CFC MDIs and has shifted to MDI importation instead.

### **2.4.2 Progress in Article 5(1) countries that rely on imports**

Technically satisfactory alternatives to CFC MDIs (HFC MDIs and DPIs) to treat asthma and COPD are available in almost all countries worldwide. Since 1994, the propellant in MDIs has been gradually replaced with HFCs, and there are now sufficient HFC MDI alternatives available to cover all key classes of drugs used in the treatment of asthma and COPD. A barrier for developing countries has been that replacement HFC MDIs manufactured by multinational companies in developed countries can be more expensive than CFC MDIs manufactured in developing countries, meaning that poor patients cannot afford them.

However, there has been substantial progress in the development and marketing of affordable CFC-free MDIs, especially those manufactured in Article 5(1) countries. With economies of scale, and a range of different brands from local manufacturers, HFC MDIs are now becoming more competitively priced compared to CFC MDIs. As a consequence, there is now an adequate range of technically satisfactory and affordable CFC-free alternatives for CFC MDIs for beta-agonists (in particular, salbutamol) and inhaled corticosteroids (in particular, beclomethasone) available in many developing countries. Taking these issues into consideration, salbutamol and beclomethasone CFC MDIs can now be considered non-essential in most importing countries.

For Article 5(1) countries that rely on imports, according to Executive Committee Decision 45/54, Low Volume Countries (LVCs) submitting Terminal Phase-Out Management Plans (TPMPs) can obtain up to US\$30,000 to develop and implement a transition strategy for CFC MDIs to CFC-free alternatives. Some national transition strategies have been approved under national ODS/CFC phase-out plans, others have been approved as part of MLF-funded MDI investment projects; and yet others as stand alone projects. For example, Singapore and Thailand are importing countries whose transition strategies state that they have phased out CFC MDIs. However, MTOC has not reviewed importing country transition strategies, as they are not submitted for its consideration.

### **2.4.3      *Affordable asthma medicine for low-income patients via the Asthma Drug Facility***

Some countries may also wish to consider application to the Asthma Drug Facility<sup>34</sup> (ADF) of the International Union Against Tuberculosis and Lung Disease for the supply of low cost HFC MDIs ([www.GlobalADF.org](http://www.GlobalADF.org)). The ADF provides access to affordable good quality essential asthma medicines, and promotes the use of CFC-free inhalers and the monitoring of asthma management for quality health care.

The ADF organises qualification of HFC inhaler manufacturers and products, establishes contracts with selected manufacturers, and then proposes selected products to countries, organisations and programmes. This allows countries to procure generic HFC inhalers at affordable prices. The ADF also provides training materials and an information system to monitor asthma management for patients with access to medicines offered by ADF. The main products offered are HFC inhalers of salbutamol and beclomethasone (each at 100µg/puff, 200 doses) or alternative corticosteroids, budesonide (200µg/puff, 200 doses) and fluticasone (125µg/puff, 120 doses). Clients of the ADF are required, *inter alia*, to submit routine monitoring reports to the ADF including initial and annual follow-up data on patients treated with corticosteroids, relating to lung function, prescribed dose, and number of emergency visits and hospitalisations.

Potential clients are generally countries implementing the Practice Approach to Lung Health strategy that are also receiving funds from the Global Fund to Fight AIDS, Tuberculosis and Malaria<sup>35</sup>, and other client connections through asthma, tuberculosis, and non-communicable diseases<sup>36</sup> networks. The yearly cost for treating severe asthma when purchasing through the ADF can be reduced by up to about 50 per cent compared with national procurement.

Countries that have already received their orders are Kenya, with pilot projects in Benin, El Salvador and Sudan. Countries with current orders are Burundi and Vietnam. The minimum average time commitment for ADF application processes is 170 days, although examples range from 113 days to 296 days from application date to delivery. These indicative timelines would need to be taken into account by interested Parties and expedited where necessary.

### **2.4.4      *Progress in the Russian Federation***

The Russian Federation has used about 240 tonnes of CFCs per annum to manufacture salbutamol MDIs from 2007–2009. This has reduced from a peak of about 400 tonnes in 2006. However, progress in the Russia has stalled in recent years, with both the Russian Federation and MTOC reporting to the Parties increasing concerns about the lack of progress and the potential future risk to Russian patient health.

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<sup>34</sup> [www.GlobalADF.org](http://www.GlobalADF.org)

<sup>35</sup> [www.theglobalfund.org](http://www.theglobalfund.org)

<sup>36</sup> The World Health Organization has developed an Action Plan for the years 2008-2013 for NCDs – cardiovascular disease, diabetes, cancer, and chronic respiratory disease. These conditions share common risk factors (including tobacco use, physical inactivity and unhealthy diets) and also share common solutions, which provide a mutual platform for collaboration and joint advocacy.



Subsequently, in response to Decision XXI/4(8) for TEAP and its MTOC to “organize and undertake a mission of experts to examine the technical, economic and administrative issues affecting the transition from CFC metered-dose inhalers to CFC-free alternatives in the Russian Federation”, a team of TEAP/MTOC experts visited the Russian Federation in February 2010. TEAP/MTOC reported its detailed findings in the 2010 TEAP Progress Report<sup>37</sup>. A summary of these findings is included here, with an update of information received since the report’s publication in May 2010.

There is a range of domestically produced and imported MDI products that currently meet patient demand. There are two domestic manufacturers of salbutamol CFC MDIs in the Russian Federation. A third Russian company, which did not previously manufacture CFC MDIs, has now also entered the market with beclomethasone HFC MDIs. Multinational companies also import a variety of inhalation products, as HFC MDIs and DPIs. Russian-made salbutamol CFC MDIs have the cheapest unit price and dominate the market. Some imported products are competitively priced based on price per dose, and one imported product (Cipla) is competitively priced based on price per unit but currently has limited market share.

Russian patients are price-sensitive to pharmaceutical expenses. Increases in the unit price of their inhalers may exceed the threshold price that they can afford to pay. Market transition to imported CFC-free inhalers is technically feasible but patient perceptions of price and/or sensitivity to unit price could be a barrier.

The Global Environment Facility (GEF) funded CFC phase-out programme for countries with economies in transition omitted the MDI sector from the Russian Federation’s ODS Consumption Phase-out Project in the 1990s. Subsequent efforts have been unsuccessful in securing adequate investment to assist the two MDI manufacturers to convert to HFC MDI manufacture. Nevertheless, through their own investment, the two companies have completed the formulation of the new salbutamol HFC MDIs, with initial dossiers submitted to health authorities. Additional funds (US\$4-6million) are needed for technology conversion and equipment investment. The Ministry of Natural Resources and Environment officially requested UNIDO to formulate an MDI project to provide the financial and technical assistance necessary to achieve transition of CFC to HFC MDI manufacturing. UNIDO has prepared a project for consideration by the GEF. The GEF has now authorised UNIDO to begin preparations of the project on the understanding that the final grant amount will be confirmed at the November session of the GEF Council, expected to be to a value of US\$2.5 million with co-funding contributions from the enterprises of US\$5.5 million.

The overall time for conversion of the 2 companies is estimated to be about 24 months once finance becomes available. The Russian Federation has stated that if the GEF funds become available phase-out could be achieved by the end of 2012, and UNIDO has recently reported plans to complete the phase-out of CFCs in MDIs by December 2012<sup>38</sup>. To meet this schedule, the regulatory authorities and the companies have agreed that many activities associated with transition should be carried out in parallel. Accelerated approval processes by the responsible health regulatory authority could greatly facilitate timely transition. An Inter-Ministerial co-ordination group chaired by the Ministry of Health and Social Development

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<sup>37</sup> *Report of the UNEP Technology and Economic Assessment Panel*, May 2010, Volume 2, Progress Report, [http://ozone.unep.org/Assessment\\_Panels/TEAP/Reports/TEAP\\_Reports/index.shtml](http://ozone.unep.org/Assessment_Panels/TEAP/Reports/TEAP_Reports/index.shtml).

<sup>38</sup> MDI Status Report provided by UNIDO to MLF Secretariat, October 2010.

has been convened to facilitate transition activities to CFC-free MDIs in Russia. The group also includes representatives of the Ministry of Natural Resources and Environment, Ministry of Industry, MDI manufacturers, CFC/HFC importers, and medical experts. Recent progress includes preparations by the Russian MDI manufacturers to renovate their production facilities to accommodate the new production lines, with works aimed to begin in May-June 2011. A bilateral Russia/United States Government workshop on Exchange of Experience in Implementation of Transition to CFC-free MDI Production was held in Moscow in late September 2010.

If CFCs become unavailable before the Russian Federation companies complete the transition to HFC MDIs, or transition is delayed, HFC MDI imports will need to be increased to make up any shortfall in available medicine and protect patient health in the Russian Federation.

#### **2.4.5      *Progress in the United States***

The United States has phased out the use of CFCs in MDIs for all but a few active ingredients and drug products. At the end of 2008, the United States designated as non-essential CFCs in salbutamol MDIs. Consumption has reduced from a peak of 2,645 tonnes in 1999 to 339 tonnes in 2009. Stockpiles of CFCs produced pre- and post-1996 have been reduced in recent years from almost 3,000 tonnes at the end of 2005 to 525 tonnes at the end of 2009.

On April 14, 2010, the US FDA published in the Federal Register its final rule to remove the essential-use designations for CFC MDIs where the active ingredients are flunisolide, triamcinolone, metaproterenol, pirbuterol, salbutamol and ipratropium in combination, cromolyn, and nedocromil. For triamcinolone and cromolyn, the effective date of removal of essential use designation is December 31, 2010; for metaproterenol and nedocromil, the effective date is 60 days after publication in the Federal Register on April 14, 2010; for flunisolide, the effective date is June 30, 2011; for pirbuterol and for salbutamol and ipratropium in combination, the effective date is December 31, 2013.

The publication also notes that after the effective date of this rule there will remain only three designated essential uses of ODSs in the United States: anaesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application; metered dose atropine sulfate aerosol human drugs administered by oral inhalation; and sterile aerosol talc administered intrapleurally by thoracoscopy for human use.

The United States has never submitted an essential use nomination for CFC quantities associated with these uses. There are suitable, commonly used CFC-free alternatives for all of these applications, including common methods of anaesthesia without the use of ODS, anti-cholinergic drugs as a superior medical alternative to atropine, and an aqueous suspension of sterile talc used for pleurodesis. These are not essential uses approved under the Montreal Protocol. Either the applications are no longer produced with CFCs but retain regulatory status in the United States as designated essential uses, or the applications are manufactured with CFCs produced prior to 1996. According to the FDA database, metered dose atropine sulfate aerosol has been withdrawn, and sterile talc is now administered in 50-100ml of saline.

### **2.5            CFC consumption and production for MDIs**

#### **2.5.1        *CFC Consumption for MDI Manufacture***

The global use of CFCs to manufacture MDIs in 2009 is estimated to be about 2,300 tonnes. Article 5(1) countries used about 1,700 tonnes and the Russian Federation and the United States used about 580 tonnes of CFCs for the manufacture of MDIs in 2009. The total use of

CFCs by Article 5(1) countries reduced by about 200 tonnes between 2008 and 2009, with some countries increasing (e.g. China) and others decreasing (e.g. India) consumption. There has been significant global progress in the transition of CFC MDIs to CFC-free inhalers, with substantial capacity to manufacture CFC-free inhalers expected by 2011-2012.

### **2.5.2 CFC Stockpiles**

Decision XXI/4 encouraged Parties with stockpiles of pharmaceutical-grade CFCs potentially available for export to notify the Ozone Secretariat by 31<sup>st</sup> December 2009. As a result of this request, Parties reported that there are about 1,017 tonnes of pharmaceutical-grade CFCs (about 225 tonnes CFC-11, 425 tonnes CFC-12, 367 tonnes CFC-114) available in stockpiles in the United States and 301.4 tonnes of pharmaceutical-grade CFC-12 available in Venezuela. The stockpile of CFC-114 may not be fully consumed since it is less commonly used in MDI formulations. Stockpiles are available for export under commercial agreement with holders of those stocks. Regulatory processes for exporting CFCs from the United States' stockpiles for essential uses are not complicated. The cost of CFCs available from stockpiles has increased the price of pharmaceutical-grade CFCs from about \$4-5/kg to \$12-16/kg, which may help to encourage transition. Any remaining stockpiles in the European Union are not available for export due to regulations prohibiting the production and export of CFCs from 1st January 2010.

More information on CFC stockpiles in Article 5(1) countries should be available in January 2011 when accounting frameworks for those Article 5(1) countries with essential use exemptions will be received for the first time.

### **2.5.3 Production of pharmaceutical-grade CFCs for MDIs**

Production of pharmaceutical-grade CFCs is now limited to a few sources.

Honeywell, in the United States, has a swing plant producing HCFC-22 that can also produce CFCs. However, regulatory processes to allow export of newly produced CFCs would likely take more than a year to complete.

China and India both have production facilities capable of manufacturing pharmaceutical-grade CFCs but they are subject to MLF production phase-out agreements. Under its existing CFC production phase-out agreement, China is allowed to manufacture pharmaceutical-grade CFCs for authorised essential uses for itself and for export to the Russian Federation only. Decision XXI/4 requested the Executive Committee to consider reviewing both of the CFC production phase-out agreements with China and India with a view to allowing production of pharmaceutical-grade CFCs to meet authorised levels of CFC production for essential uses. The 60<sup>th</sup> Executive Committee Meeting, April 12-15, 2010, decided to modify the production sector agreements for China and India to allow the production for export of pharmaceutical-grade CFCs for 2010, with an annual review. This was agreed to be only for the purpose of meeting essential use requirements of other countries provided that the exporting countries had specified reporting and verification systems in place.

Any new source of supply of CFCs (including from stockpile) would require that CFC MDI producers validate the suitability of the newly sourced propellant in each specific MDI product. Validation takes time to complete, and in some cases would require the approval of health authorities. Total time to register a new source can take up to 6 months.

#### 2.5.4 *Estimated CFC usage for MDIs until phase-out*

Table 2.5 shows estimated future global usage of CFCs for MDIs. MTOC estimates that less than about 2,000 tonnes of pharmaceutical-grade CFCs will have been used to supply global MDI uses in 2010, with about 650 tonnes CFCs needed to supply MDI manufacture in countries excluding China, India, the Russian Federation and the United States (see Table 2.5)<sup>39</sup>. In future years under existing agreements, China could continue to manufacture for itself and the Russian Federation, and the United States could manufacture for itself or use stockpiles. India will no longer manufacture CFCs to supply its own MDI use: it has achieved CFC phase-out in MDIs. Estimates of CFC consumption for 2010 and 2011 are based mainly on quantities exempted by Parties, although not all of these quantities may be needed given the rate of transition in some countries.

Based on essential use quantities of CFCs for 2011 approved at the 22<sup>nd</sup> Meeting of the Parties, about 200 tonnes of pharmaceutical-grade CFCs might be required in 2011 to supply CFCs for essential MDI uses in countries excluding China and, the Russian Federation. For 2012 onwards, estimated CFC consumption for essential MDI uses might be about 55 tonnes in countries excluding China and, the Russian Federation.

CFC stockpiles are available in Venezuela and the United States (total of about 951 tonnes of CFC-11 and -12, with 367 tonnes of CFC-114 that may not be consumed). These may be enough to cover estimated CFC requirements for MDIs for 2010, 2011 and 2012 (about 910 tonnes) for countries excluding China, India, the Russian Federation and the United States (or about 1,000 tonnes if United States' MDI manufacturers source their CFC requirements from stockpile). This depends on, *inter alia*, Parties' future decisions regarding essential use exemptions, whether stockpile is acquired under commercial arrangements, and also whether the CFC mix and specifications of the stockpile meets the needs of MDI manufacturers. However, it could be possible to complete the phase-out of CFC MDIs with careful management of existing global CFC stockpiles without manufacture of new pharmaceutical-grade CFCs, except for China that can manufacture for its own needs and those of the Russian Federation. A cautious approach to CFC production is advisable since transition is moving quickly and CFC production that is surplus to actual needs ought to be avoided, as the excess would subsequently require costly destruction.

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<sup>39</sup> Decisions taken at the 60th Executive Committee meeting allow CFC production for export in 2010 for the purposes of meeting essential use requirements under modified production sector agreements with China and India. Conclusions for 2011 and onwards do not assume continued production for export by China (other than to the Russian Federation) or by India since this would be the subject of annual review by the Executive Committee.

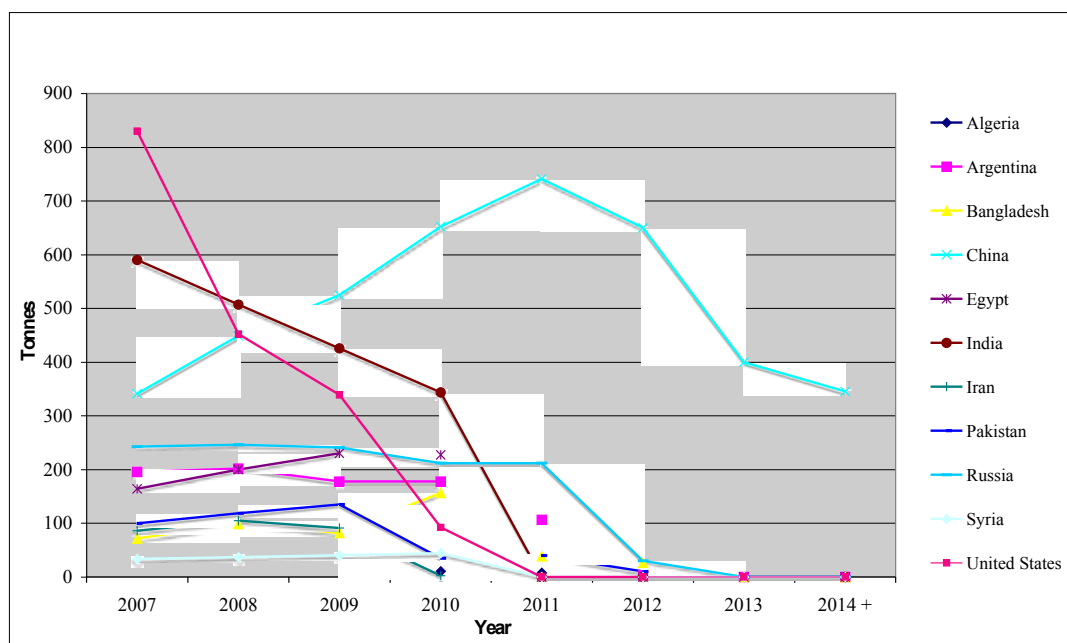
**Table 2.5** *Estimated CFC usage for MDI manufacture by nominating Parties<sup>40</sup>, 2010-2014+*

<b>Country</b>	<b>2010</b>	<b>2011</b>	<b>2012</b>	<b>2013</b>	<b>2014 +</b>	<b>Total</b>
Algeria	11	8	0	0	0	19.0
Argentina	178	107	3	0	0	288.2
Bangladesh	156.7	57	27	0	0	240.7
China	652.0	741.2	650	400	345	2,788.2
Colombia	-	-	-	-	-	0.0
Cuba	-	-	-	-	-	0.0
Egypt	227.4	0	0	0	0	227.4
India	344	0	0	0	0	343.6
Indonesia	-	-	-	-	-	0.0
Iran	2.2	0	0	0	0	2.2
Mexico	-	-	-	-	-	0.0
Pakistan	35	39.6	10	0	0	84.5
Russian Federation	212	212	30	0	0	454.0
Syria	44.7	0	0	0	0	44.7
United States	92.0	-	-	-	-	92.0
Uruguay	-	-	-	-	-	0.0
Venezuela	-	-	-	-	-	0.0
<b>Total</b>	<b>1,954.6</b>	<b>1,165.0</b>	<b>720.0</b>	<b>400.0</b>	<b>345.0</b>	<b>4,584.5</b>

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<sup>40</sup> For 2010 and 2011, usage data is based mainly on exempted quantities or estimates provided by countries in 2011 essential use nominations. For 2012 onwards, estimated usage does not take into account whether use meets the essential use criteria and does not pre-judge decisions taken by Parties.

**Figure 2.2** *Estimated CFC usage<sup>41</sup> for MDI manufacture by nominating Parties, 2010-2014+*



### 2.5.5 HFC Consumption for MDI manufacture

It is estimated that approximately 250 million HFC-based MDIs are currently manufactured annually worldwide, using approximately 4,000 tonnes of HFCs and accounting for a very small proportion of total HFC usage (estimated at 1-2 per cent). Based on current consumption and projected growth rates<sup>42</sup> of MDI use, annual consumption of HFCs for MDIs is estimated to be between 7,000-10,500 tonnes by 2015.

<sup>41</sup> For 2010 and 2011, usage data is based mainly on exempted quantities or estimates provided by countries in 2011 essential use nominations. For 2012 onwards, estimated usage does not take into account whether use meets the essential use criteria and does not pre-judge decisions taken by Parties.

<sup>42</sup> Most of the growth in MDI use is expected to occur in developing countries. Annual growth rates in MDI use are estimated to be between about 3-10 per cent.

### 3            **Pharmaceutical aerosol products other than MDIs**

Many types of pharmaceutical aerosol products (medical aerosols) other than metered dose inhalers (MDIs) have traditionally used chlorofluorocarbons (CFCs) as propellants. The manufacture of *most* CFC-containing medical aerosols in non-Article 5(1) countries ceased around 1996, and in Article 5(1) countries would have ceased around the end of 2009.

Medical aerosols have been 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. Not all medical aerosol products that used CFCs 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. Most sprays that are applied over the skin can use alternative propellants such as hydrocarbon aerosol propellants, dimethyl ether, nitrogen, and compressed air. Hydrofluorocarbons (HFCs) -134a or -152a are more likely to be used as propellants for sprays used in the oral cavity like local anaesthetics. HFC consumption in this sector is likely to be small.

However, there are some countries that are yet to complete the conversion of CFC-based medical aerosols to alternatives. In 2009, Argentina (1.2 tonnes), China, Dominican Republic (24 tonnes), and Serbia (18.1 tonnes) were still consuming CFCs to manufacture medical aerosols<sup>43</sup>. With the 2010 phase-out date for CFCs in developing countries, any current CFC consumption for medical aerosols can only be sourced from existing stockpile.

In China, some of the traditional Chinese aerosol manufacturers have encountered technical difficulties in their conversion to alternatives, with new formulations not meeting relevant quality standards. Relevant government authorities are coordinating with the enterprises to resolve these technical issues. It is expected that, other than MDIs, full conversion of the medical aerosol sector in China will be completed in 2012.

On April 14, 2010, the US FDA published in the Federal Register its final rule regarding the essential use designation for CFC MDIs for certain active ingredients. This final rule also noted that after the effective date of this rule there would remain only three designated essential uses of ODSs in the United States: anaesthetic drugs for topical use on accessible mucous membranes of humans where a cannula is used for application; metered dose atropine sulfate aerosol human drugs administered by oral inhalation; and sterile aerosol talc administered intrapleurally by thoracoscopy for human use. As noted in section 2.4.5, it is not clear whether these products remain in use today.

There are suitable, commonly used CFC-free alternatives for all of these applications, including common methods of anaesthesia without the use of ODS, anti-cholinergic drugs as a superior medical alternative to atropine, and an aqueous suspension of sterile talc used for

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<sup>43</sup> These countries have MLF-funded projects to convert the manufacture of CFC-based medical aerosol to alternatives. Some projects are in progress but not yet completed.

pleurodesis. These are not essential uses approved under the Montreal Protocol. Either the applications are no longer produced with CFCs but retain regulatory status in the United States as designated essential uses, or the applications are manufactured with CFCs produced prior to 1996.





## **4 Sterilants**

### **4.1 Background**

The provision of good quality health services requires effective sterilization of health care products to prevent transmission of infection. Sterilization requires strict application of the principles of quality management to ensure validation of the selected process and implementation of effective routine control; reliable equipment; and knowledge of materials compatibility. Sterilization of medical devices can be performed in industrial settings with large outputs of similar items (such as manufacturers of sterile, single-use 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 commercially available sterilization methods including: heat (moist heat or dry heat), radiations, alkylating processes (such as ethylene oxide (EO), formaldehyde) and oxidative processes (including hydrogen peroxide vapour, hydrogen peroxide gas plasma, liquid peracetic acid, and ozone). Further sterilization methods are under investigation for commercialization.

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 many types of 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, particularly in industrial-scale applications, 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. A mixture of 12 per cent by weight EO and 88 per cent chlorofluorocarbon-12 (CFC-12) (12/88) had previously been widely used for this purpose. On an industrial scale, non-flammable mixtures can be created *in situ* within the sterilizer chamber using nitrogen. Non-flammable EO mixtures can be supplied for industrial or hospital use with carbon dioxide (CO<sub>2</sub>) as a diluent. Hydrochlorofluorocarbons (HCFCs) were introduced as drop-in replacement for EO/CFC-12 mixtures but have been, or are being, phased out in Europe and the United States; HCFC/EO may continue to be used in Article 5(1) countries. Hydrofluorocarbons (HFCs) were investigated as further replacement diluents but not widely adopted for technical reasons and the greenhouse gas potential of HFCs.

Some hospitals continue to rely on EO sterilization and new sterilizers are used more efficiently than the previous EO/CFC units. One way efficiency has increased in developed economies is by centralising the provision of sterilization facilities, enabling more efficient use of a smaller number of sterilizers and thereby reducing sterilant consumption. Furthermore, improvements in validation practices have enabled processes to use lower EO concentrations, reducing sterilant concentrations and levels of residues in products. Use of abatement equipment in conjunction with an EO sterilizer also reduces emissions.

### **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 be certain, global total use of CFCs in 2010 for this application is believed to be close to zero.

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. Estimated global use of HCFCs in sterilization in 2010 is between about 500-700 metric tonnes, which amounts to less than 25 ODP tonnes worldwide. EO/HCFC use in Article 5(1) countries is estimated to be between about 200-400 tonnes.

Under a United States' final rule on HCFC production, import and export allowances, HCFC-22 was restricted on 1 January 2010 and the HCFC-124 blend is being phased out on 31 December 2014<sup>44</sup>. Regulations under the Clean Air Act require that HCFC-22 cannot be produced or imported for uses other than servicing existing appliances as of 1 January 2010. However, there is an exception for the continued use of HCFC-22 as a sterilant but only if the HCFC was produced prior to 1 January 2010. This exception applies until 31 December 2014. It is expected that only a small amount of HCFC-22 would be used for sterilant applications under this exception. Most hospitals (greater than 90 per cent) in the United States have demonstrated technical feasibility by converting away from EO/HCFC use. Adequate space and finance are the remaining limitations for converting sterilization equipment in hospitals. Medical device manufacturers that use EO/HCFC are also converting to alternatives.

European Union regulations banned the use of HCFCs as carrier gas for sterilization in closed systems from 1 January 1998.

With the Montreal Protocol phase-out schedule for HCFCs for Article 5(1) countries, an orderly phase-out of HCFCs in sterilization uses is readily achievable in Article 5(1) countries. The useful lifetime of an EO/HCFC steriliser is about 20 years when well maintained. Therefore by 2030 current sterilisers should be ready for replacement with available alternative technologies that do not use ozone-depleting substances. Hospital procurement should take the HCFC phase-out, and the coming redundancy of EO/HCFC sterilization equipment, into consideration in making future investment decisions.

EO/HCFC use has been significantly reduced by using less mix per sterilizer load, use of 100 per cent ethylene oxide and by hospital conversion to other technologies; use will be reduced further by the phase-out in the United States.

### **4.3 Available options for replacing ozone-depleting substances**

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

An effective infection control strategy requires the availability of sterile medical devices. Validation of sterilization processes is important to ensure the attainment of sterility and to avoid materials compatibility problems. No sterilant or sterilization process is compatible with all potential 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, moisture and

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<sup>44</sup> US EPA, *Protection of Stratospheric Ozone: Adjustments to the Allowance System for Controlling HCFC Production, Import, and Export; Final Rule*, Federal Register, Volume 74, No. 239, December 15, 2009 (74 FR 66445-66446).

radiation. Therefore a number of different processes are available for use and each will offer specific advantages.

Technologies to which hospitals have converted to avoid the ozone-depleting processes using EO/CFC blends include: use of more heat-sterilizable devices; more single-use devices; pure ethylene oxide sterilizers; and other methods that will sterilize or disinfect most of the low temperature devices used in hospitals. These other low temperature processes that have been commercialised include hydrogen peroxide gas plasma, hydrogen peroxide vapour, ozone, liquid phase peracetic acid and steam-formaldehyde. Further low temperature methods have been reported but have yet to be widely deployed.

A summary of alternatives to reduce or phase out the use of ozone-depleting substances (ODS) follows. A number of processes and systems have been described or are under development but the examples described herein are not an exhaustive list of such developments. This summary updates information included in the 2006 *Assessment Report of the Medical Technical Options Committee*<sup>45</sup>. A more detailed description of options was included in the 1994 *Assessment Report of the Aerosols Technical Options Committee*.

#### **4.3.1 Heat**

*Dry heat* – This process is non-toxic, economical and relatively safe. Devices must be able to withstand a temperature greater than 160°C in order to withstand the process.

*Steam* – This process is non-toxic and relatively safe. Sterilizing equipment ranges from small, self-contained units to large installations requiring supporting utilities. Devices must be able to withstand a temperature greater than 115°C, very high moisture levels and changes in pressure levels in order to withstand the process.

#### **4.3.2 Radiations**

*Ionising radiation* – Ionizing radiations (gamma rays, accelerated electrons, X-rays) are widely used for sterilization, usually in large, industrial facilities; in many Article 5(1) countries, governments operate these facilities. Operation of ionising radiation facilities is not generally appropriate for hospitals or centralised sterilization facilities supplying 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. Systems using low energy electron beams have been introduced for in-line treatment of certain materials being introduced into the aseptic processing of pharmaceuticals, thereby reducing the need for treatment with gaseous sterilants. *X-ray* applications and facilities are also commercially available.

*Ultraviolet (UV) radiation and intense pulsed light* – UV radiation has been widely employed for sanitization of water systems and air. The lack of penetration limits the application to surface treatment and provision to prevent shadowing is required. Specialised industrial applications for sterilization of particular medical devices have been developed and small-scale units for non-industrial applications have been commercialised. Intense pulsed light, including a significant element in the UV range of the spectrum, has also been investigated for specific sterilization applications.

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<sup>45</sup> 2006 *Report of the UNEP Medical Technical Options Committee, 2006 Assessment Report*, [http://ozone.unep.org/Assessment\\_Panels/TEAP/Reports/MTOC/index.shtml](http://ozone.unep.org/Assessment_Panels/TEAP/Reports/MTOC/index.shtml).

### 4.3.3 Alkylating agents

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

*100 % EO* – Despite being a flammable gas, EO can be used when 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<sub>2</sub>* – Carbon dioxide (CO<sub>2</sub>) 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<sub>2</sub> mixes are not used to replace other 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<sub>2</sub> 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<sub>2</sub>.

*Blends of HCFCs and EO* – 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. In the USA, HCFC-22 was banned in January 2010 and HCFC-124 blend is being phased out by 2015.

*Blends of HFCs and EO* – HFC mixtures (10.4 per cent by weight EO in a mix of HFC-125 and HFC-227) used in existing sterilization equipment with modified process controls were tested in the United States. Technical problems were identified that would require re-engineering, perhaps new equipment, in addition to re-validating. The technical problems include: higher vapour pressure mixes, requiring higher pressure feed lines and ancillary equipment; tendency of the mix to separate; and, for users that recover fluorocarbons, more complicated, less efficient operation unless the entire recovery system re-engineered and re-built. New HFC blends have not been broadly used worldwide although suppliers in Asia continue to explore the potential application. 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 investigated to replace EO/methyl bromide blends to fumigate archives and antiquities<sup>46</sup>.

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<sup>46</sup> *Blends of methyl bromide and EO* – Methyl bromide or mixtures of methyl bromide and EO are used for deinfestation 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 and patented but not widely deployed. Chlorine dioxide is generated *in situ*, for example from sodium chlorite and chlorine gas in a nitrogen carrier. Gaseous chlorine dioxide is drawn into an evacuated chamber to achieve the required concentration at the appropriate temperature and relative humidity.

*Combination processes* – Combinations of oxidising agents such as hydrogen peroxide and ozone or nitric oxide and nitrogen dioxide in combination have been investigated but not commercially established.

*Hydrogen Peroxide Gas Plasma* – These vacuum-based processes generally use hydrogen peroxide gas for sterilization and plasma for residual gas/liquid removal from the load. Plasma may also be used for heating purposes, depending on the sterilizer design. A wide variety of sterilizer processes are in commercial use with many sold worldwide, mostly to hospitals, and the system continues to be used extensively.

*Hydrogen Peroxide Vapour* – This process uses hydrogen peroxide gas (non-condensed) for sterilization alone in a vacuum-based process at <50°C. A variety of equipment configurations have been sold worldwide for hospital and, to a limited extent, industrial facilities.

*Liquid Peracetic Acid* – Available equipment uses cassettes in which 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, to date, packaged for storage and need to be used immediately after removal from the cassette in order to ensure sterility at point of use.

*Low Temperature Plasmas* – a variety of methods of surface treatment with plasmas generated from different gases/combinations of gases have been investigated for their antimicrobial effectiveness. Examples of systems under investigation use plasma directly for sterilization are nitrogen and nitrogen/oxygen gas plasma. Systems using low temperature plasma are under development for in-line treatment of certain materials being introduced into the aseptic processing of pharmaceuticals. None have yet reached commercial application.

*Ozone* – A process operating at less than 30°C is available for use in hospitals. Ozone is generated within the sterilizer from an oxygen source. The humidified process must be carefully controlled to ensure efficacy and can have the potential to affect surface materials.

*Peracetic Acid Gas Plasma* – A process was commercialised but was unfortunately associated with patient injuries when ophthalmic surgical instruments sterilized with this system were used. The process had not received US FDA approval for this specific application and a global recall was mandated. No further processes or equipment have been deployed.

*Supercritical Carbon Dioxide* – Carbon dioxide in a supercritical state<sup>47</sup> has been reported as having activity against vegetative micro-organisms. However it has little activity against

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<sup>47</sup> Carbon dioxide in a supercritical state is where the liquid and vapour phases become indistinguishable and is formed at temperatures around 32°C and pressures above 74 atmospheres.

bacterial spores without further chemical additives in the process, thus limiting its application as a sterilizing agent. No processes or equipment have reached commercial application.

#### **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 small ozone depletion potentials (ODP) (0.03) and should not be promoted in countries that have not been major users of the 12/88 EO/CFC blend.

## 5 MTOC Membership Information

### Medical Technical Options Committee (MTOC)

<b>Co-chairs</b>	<b>Affiliation</b>	<b>Country</b>
Jose Pons Pons	Spray Quimica	Venezuela
Helen Tope	Energy International Australia	Australia
Ashley Woodcock	University Hospital of South Manchester	UK
<b>Members</b>	<b>Affiliation</b>	<b>Country</b>
Emmanuel Addo-Yobo	Kwame Nkrumah University of Science and Technology	Ghana
Paul Atkins	Oriel Therapeutics Inc.	USA
Sidney Braman	Rhode Island Hospital	USA
Nick Campbell	Arkema SA	France
Hisbello Campos	Centro de Referencia Prof. Helio Fraga, Ministry of Health	Brazil
Jorge Caneva	Favaloro Foundation	Argentina
Christer Carling	Private Consultant	Sweden
Guiliang Chen	Shanghai Institute for Food and Drug Control	China
Antoine Haddad	Chiesi Farmaceutici	Italy
Charles Hancock	Charles O. Hancock Associates	USA
Eamonn Hoxey	Johnson & Johnson	UK
Javaid Khan	The Aga Khan University	Pakistan
Suzanne Leung	3M	USA
Nasser Mazhari	Sina Darou Laboratories Company	Iran
Gerald McDonnell	STERIS	UK
Hideo Mori	Otsuka Pharmaceutical Company	Japan
Tunde Otulana	Aerovance Inc.	USA
John Pritchard	Philips Home Healthcare Solutions	UK
Rabbur Reza	Beximco Pharmaceuticals	Bangladesh
Raj Singh	The Chest Centre	India
Roland Stechert	Boehringer Ingelheim	Germany
Ping Wang	Chinese Pharmacopoeia Commission	China
Adam Wanner	University of Miami	USA
Kristine Whorlow	National Asthma Council Australia	Australia
You Yizhong	Journal of Aerosol Communication	China



## 5.1 Disclosures of Interest

The following describes the disclosures of interest for MTOC members as at December 2010.

### **Emmanuel Addo-Yobo Ghana (A5)**

Emmanuel Addo-Yobo, member of the Medical Technical Options Committee since 2005, is a full time Senior 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. Dr Addo-Yobo 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. Dr Addo-Yobo has attended an American Academy of Allergy Asthma and Immunology (AAAAI) meeting sponsored by a pharmaceutical company in 1999. Dr Addo-Yobo does not receive any form of remuneration from any drug companies. Dr Addo-Yobo has given educational lectures to medical personnel on childhood asthma in Ghana, which were sponsored by drug companies in a purely academic capacity. The UNEP's Ozone Secretariat funds his travels for MTOC meetings. Dr Addo-Yobo's spouse is a business secretary working with a local financial institution and has no interests in matters before the Protocol.

### **Paul J. Atkins USA (Non-A5)**

Dr Paul Atkins, member of the Medical Technical Options Committee since 1993, is the full time Vice President, Operations of Oriel Therapeutics Inc., a wholly owned subsidiary of Sandoz/Novartis, a publicly traded pharmaceutical company, is based in Research Triangle Park, USA. Oriel Therapeutics Inc. has an interest in the topics of the Montreal Protocol because it is developing dry powder inhalers. Dr Atkins has a proprietary interest in developing alternatives to ODS-based MDIs. Dr Atkins has an extensive background in both MDI and DPI product development and commercialisation and is an internationally recognised expert in this area. Previously Dr Atkins was employed by GlaxoSmithKline, a leading provider of inhaled medicines including CFC-based MDIs, and his spouse is currently a GlaxoSmithKline employee and owns stock in that company. Dr Atkins has worked occasionally as a consultant for both MLF and UNDP on matters related to the Montreal Protocol. Travel to MTOC meetings has been paid by either his employer or out of his personal funds.

### **Sidney Stuart Braman USA (Non-A5)**

Dr Sidney Braman, member of the Medical Technical Options Committee since 2005, is a Professor of Medicine at Brown Medical School in the Division of Pulmonary and Critical Care Medicine at Brown University and the Rhode Island Hospital. These organizations have no direct interest or business relating to the topics of the Montreal Protocol. Dr Braman has no proprietary interest to alternatives or substitutes to ODS, does not own stock in companies producing ODS or alternatives or substitutes to ODS, does not have an interest in the outcome of essential use nominations and does consulting for organizations seeking to phase out ODS but does not consult on these products. He has received research grant support and been a consultant to several pharmaceutical companies relating to research on new drug development. Dr Braman has not received any consultancy fees for work related to or associated with the Montreal Protocol. Dr Braman's spouse has no interest in matters before the Protocol. Dr Braman does not work as a consultant on matters relates to the Montreal Protocol. Travel to the MTOC meetings is provided by the American Thoracic Society.

### **Nick Campbell France (Non-A5)**

Dr. Nick Campbell has been a member of this Technical Options Committee since 1991. Dr Campbell has spent 20 years working primarily on the ozone layer issue and climate change. Dr Campbell 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 and travel on MTOC. Dr Campbell has stock options in ARKEMA SA. He 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. Dr Campbell is also the Chairman of the International Chamber of Commerce (ICC) Working Party on Climate Change and the Chairman of the BusinessEurope Climate Change Working group, representing European Union Employers' federations. Dr Campbell has been a member of the World Bank's Ozone Operations Resource Group. Nick was a Coordinating Lead Author for the IPCC/TEAP

joint Report on HFCs and PFCs (April, 2005). Dr Campbell was awarded a 1997 United States EPA Stratospheric Ozone Protection Award for his role in the phase-out of ODS.

**Hisbello Campos Brazil (A5)**

Dr. Hisbello S. 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. Dr Campos is a full time physician at the Centro de Referencia Prof. Helio Fraga and gives medical consultations at his private office. The Centro de Referencia Prof. Helio Fraga has an interest in the topics of the Montreal Protocol because it is the government department responsible for proposing guidelines for respiratory diseases control. Dr Campos has no proprietary interest in alternatives or substitutes to ODS, does not own stock in companies producing ODS or alternatives or substitutes to ODS, does not have an interest in the outcome of essential use nominations, and does not consult for organizations seeking to phase out ODS. Dr. Campos gives educational lectures for physicians or goes to international medical meetings (American Thoracic Society, European Respiratory Society or World Asthma Meeting, for example), sponsored by pharmaceutical companies, some of which have continued to produce CFC MDIs, and some of which have sought to accelerate phase out of CFC MDIs. Dr Campos's spouse has no interest in matters before the Protocol. Dr Campos works occasionally as a consultant to the Brazilian Government on matters related to the Montreal Protocol. Dr. Hisbello Campos' spouse has no interest in matters before the Protocol. UNEP's Ozone Secretariat pays travel to MTOC meetings.

**Jorge Osvaldo Cáneva Argentina (A5)**

Dr. Jorge Osvaldo Cáneva, member of the Medical Technical Options Committee since 2007, is the Chief of the Pulmonary Section at of the University Hospital of the Favaloro Foundation (Buenos Aires, Argentina) since it was established in 1992, and Professor of the University School of Medicine at the same institution. Currently Dr. Cáneva states as Ex-President of the Argentine Association of Respiratory Medicine (Asociación Argentina de Medicina Respiratoria), main association in pulmonary medicine in Argentina. He was Governor of the American College of Chest Physician in Argentina between 2006-2009. He is the coordinator of the Bi-National Programme for pulmonary and cardiopulmonary transplantation between Argentina and Uruguay. He has been involved in severe respiratory diseases, pulmonary vascular diseases and lung transplantation programmes. During 2003 and 2004 Dr Cáneva has been involved in consultation for AstraZeneca Argentina about dry powder inhalers. Between 1993 and 2008, Dr Cáneva has served as independent consultant on long-term oxygen therapy for Air Liquide Argentina. Furthermore, he serves as independent consultant about inhaled (nebulized) therapy for the treatment of pulmonary vascular diseases. Dr Cáneva does not own stock in companies producing ODS or alternatives or substitutes to ODS; he does not consult for organizations seeking to phase out ODS. Dr Cáneva's spouse has no relationship with any pharmaceutical company. He does not receive any honorarium or grant from the government, national or international non-profit organization. UNEP's Ozone Secretariat pays travel to MTOC meetings.

**Christer Carling Sweden (Non-A5)**

Christer Carling, member of the Medical Technical Options Committee since 1993, is retired from a position as Director Global Licensing at the pharmaceutical company AstraZeneca, which is developing and supplies inhalable drugs such as DPIs and MDIs for the treatment of asthma and COPD. Mr Carling is at present an independent consultant in the pharmaceutical area. His on-going consultancy activities do not involve services to any organization with an interest in the topics of the Montreal Protocol. Mr Carling is a minor shareholder in AstraZeneca but has no proprietary interest in substitutes to ODS, does not own stock in companies producing ODS or substitutes to ODS, does not have an interest in the outcome of essential use nominations, and does not consult for organizations seeking to phase out ODS. During 2009 and 2010 Mr Carling participated in regional UNEP seminars in South Asia, presenting on aspects of the Essential Use Nomination (EUN) process and assisting individual Article 5(1) countries in the South Asia region in their EUN preparations. As a consequence, during the 2009 and 2010 MTOC meetings Mr Carling abstained from participation in decisions regarding the EUNs from Bangladesh, China, India, Iran and Pakistan. Mr Carling also participated in the TEAP/MTOC mission on CFC MDI transition in the Russian Federation in February 2010. His spouse is currently an AstraZeneca employee but has no direct interest in matters before the Protocol. The Ozone Secretariat provided reimbursement for Mr Carling's travel associated with the TEAP/MTOC mission to the Russian Federation from funds granted to the Secretariat for this purpose by the Governments of Finland and Sweden and by pharmaceutical companies, JSC

Moschimpharmpreparaty and JSC Altayvitamin, in the Russian Federation. Mr Carling's travel to MTOC meetings is paid entirely out of his own pocket.

**Gui-liang Chen China (A5)**

Dr Gui-liang Chen, member of the Medical Technical Options Committee since 2008, is a chief pharmacist, and a full time deputy director at the Shanghai Institute for Food and Drug Control (SIFDC). The SIFDC has an interest in the topics of the Montreal Protocol because it is an official institute for drug quality control in China. Gui-liang Chen has been engaged in assessing the safety, efficacy and quality of inhalation products since 2002. Gui-liang Chen has no proprietary interest in alternatives or substitutes to ODSs, does not own stock in companies producing ODS or alternatives or substitutes to ODSs, and does not consult for organizations seeking to phase-out ODSs. Gui-liang Chen's spouse works at a local hospital in Shanghai, and has no interest in matters before the Protocol. Dr Chen works occasionally as a consultant to the China Government on matters related to the Montreal Protocol. Travel to MTOC meetings is paid by UNEP's Ozone Secretariat.

**Antoine Haddad Italy (Non-A5)**

Antoine Haddad, member of the Medical Technical Options Committee since 2007, is, from 1st January 2010, Consultant to the Area Manager Middle East at Chiesi Farmaceutici S.p.A. located in Parma, Italy. Mr Haddad has significant experience with more than 20 years of activity in the specific field, in licensing, technology and know-how transfer, for local production in many Middle East countries. Chiesi Farmaceutici S.p.A. has an interest in the topics of the Montreal Protocol as a producer and licensor of MDIs, including Egypt, Iran and Syria and has proprietary interest in alternatives or substitutes to ODS, and an interest in the outcome of the Egypt, Iran and Syria essential use nominations made in 2009. As a consequence, during the 2009 MTOC meeting Mr. Haddad abstained from participation in decision-making regarding the essential use nominations from Egypt, Iran and Syria. Mr Haddad does not own stock in companies producing ODS or alternatives or substitutes to ODS, and does not consult for organizations seeking to phase out ODS. Mr Haddad's family members and parents have no direct or indirect interest in matters relative to the Protocol. He does not work as a consultant on matters related to the Montreal Protocol. Travel to MTOC meetings is paid by Chiesi Farmaceutici S.p.A., which do not receive contributions for this travel.

**Charles Hancock USA (Non-A5)**

Charles O. Hancock, member of the Medical Technical Options Committee since 1991, is a private medical device sterilization consultant with Charles O. Hancock Associates, Inc. Mr Hancock has an interest in the topics of the Montreal Protocol because he is actively engaged in the safe and effective delivery of sterilization processes for medical devices in healthcare applications. Mr Hancock has proprietary interest in alternatives or substitutes to ODS, owns stock in a company producing alternatives or substitutes to ODS, does not have an interest in the outcome of essential use nominations, and does provide consulting for organizations seeking to phase out ODS. Mr Hancock's spouse has no interest in matters before the Protocol. Mr Hancock works frequently as a consultant to governments, companies, and healthcare institutions on matters related to the Montreal Protocol. Travel to MTOC meetings is paid by Mr Hancock.

**Eamonn Hoxey UK (Non-A5)**

Dr. Eamonn Hoxey, member of the Medical Technical Options Committee since 1996, is Vice President for Regulatory Compliance for Johnson & Johnson Medical Devices and Diagnostics companies. Dr Hoxey is a full time employee based in the UK. Johnson & Johnson has an interest in the topics of the Montreal Protocol as a manufacturer of healthcare products, including sterile products, and utilize in-house and external sterilization facilities that do not employ ODS. Dr Hoxey is chairman of the International standards committee on sterilization of healthcare products. Dr Hoxey has no stock in companies involved in ODS, with the possible exception of stock held in portfolio accounts where he has no control over purchase or sale. Dr Hoxey's partner has no interest in matters before the Protocol. Johnson & Johnson makes in-kind contributions of wage and miscellaneous expenses.

**Javaid Khan Pakistan (A5)**

Prof. Javaid Khan, member of the Medical Technical Options Committee since 1999, is a Professor and Head Section of Pulmonology and Critical Care Medicine at the Aga Khan University, Karachi Pakistan. Dr Khan has attended Chest Conferences, such as ATS, sponsored by pharmaceutical companies. Dr Khan takes an active role in educating doctors and the public on asthma and COPD.

Pharmaceutical companies have sponsored some of these meetings. Dr Khan has received honorarium from Pfizer Company for his lectures to doctors on smoking cessation in 2007 in Pakistan. He is also a member of the Global Initiative for Asthma (GINA) assembly and GOLD (Global Alliance of Obstructive Lung Disease National leader from Pakistan. In 2009 Prof. Javaid Khan responded to a request made by the Ministry of Environment Pakistan to provide information about the availability and cost of inhalers for Pakistan's essential use nomination. He has no interest in the outcome of Pakistan's essential use nomination other than a physician's interest in ensuring MDIs remain available to patients at affordable prices. UNEP funds Dr Khan's travel expenses to attend the meetings of MTOC.

**Suzanne Leung USA (Non-A5)**

Suzanne Leung, Ph.D., Regulatory Affairs Manager for 3M Sterilization Assurance Products, is a new member of the Medical Technical Options Committee as of 2010. 3M has an interest in the topics of the Montreal Protocol, as it is involved in development, manufacturing and supply of both sterilization products and metered dose inhalers to global markets. Dr. Leung is a member of American standards committees for sterilization of healthcare products and various industry groups for sterilization. She has laboratory experience with the use of ODS and ODS-alternatives in sterilants, topical aerosols and metered dose inhalers. Dr. Leung and her spouse hold stock in companies involved in the manufacture of products containing ODS and ODS alternatives. 3M makes in-kind contributions of wage and miscellaneous expenses for Dr. Leung's participation on MTOC.

**Nasser Mazhari Motlagh Iran (A5)**

Dr. Nasser Mazhari Motlagh, member of the Medical Technical Option Committee since 2007, is a pharmacist at the Sina Darou Laboratories Company plc. Nasser Mazhari is a full time Quality Assurance Manager and Executive Deputy at the Sina Darou pharmaceutical and hygienic manufacturing plant, Tehran. Nasser Mazhari holds a doctorate in pharmacy and has more than 40 years experience in pharmaceutical industry (manufacturing), including more than 13 years in MDIs. The Sina Darou Laboratories Co. plc. has an interest in the topics of the Montreal Protocol because it is manufacturing CFC MDIs and it is in the process of phasing out CFCs. Nasser Mazhari has no proprietary interest in alternatives or substitutes to ODSs, does not own stock in companies producing ODS or alternatives or substitutes to ODS. At the time the Iran essential use nomination for 2011 was made, Nasser Mazhari's employer had an interest in the nomination's outcome. As a consequence, Nasser Mazhari abstained from participation in decision-making regarding Iran's essential use nomination. Nasser Mazhari does consulting and working for Sina Darou to phase-out CFCs. Nasser Mazhari is a minor stockholder of Sina Darou Labs Co. plc. Nasser Mazhari's spouse has no interest in matters before the Protocol. Travel expenses of Nasser Mazhari to MTOC meetings are paid by UNEP's Ozone Secretariat.

**Gerald McDonnell United Kingdom (Non-A5)**

Dr. Gerald McDonnell, member of the Medical Technical Options Committee since 2010, is Vice President for Research and Technical Affairs for STERIS Corporation, as supplier of infection and contamination prevention/control and surgical support products and services. Dr McDonnell is a full time employee based in the UK. STERIS has an interest in the topics of the Montreal Protocol as a manufacturer and service provider of cleaning, disinfection and sterilization technologies. Dr. McDonnell is an active participant and country representative for British, European and International standards committees on sterilization of healthcare products. Dr McDonnell is a minor stockholder of STERIS, which provides sterilization products and services discussed in this report. Dr McDonnell's partner or family has no interest in matters before the Protocol. STERIS makes in-kind contributions of wage and miscellaneous expenses for Dr. McDonnell to participate on MTOC.

**Hideo Mori Japan (Non-A5)**

Hideo Mori, member of the Medical Technical Options Committee since 1999, retired from the Regulatory Department at Otsuka Pharmaceutical, based in Tokushima Japan, and now works as an adviser at the same company. Otsuka Pharmaceutical accomplished the phase-out of CFC MDIs and manufactures CFC-free MDIs and DPIs. Mr Mori is the former chair and an adviser of the CFC Committee of the Federation of Pharmaceutical Manufacturers' Association of Japan, which was organized to accomplish the phase-out of CFCs in MDIs and smooth transition to the alternatives. Mr. Mori does not own stocks in companies producing ODS, or alternatives or substitutes to ODS, does not have an interest in the outcome of essential use nominations. During 2008, 2009 and 2010 Mr Mori

participated in regional UNEP workshops in South Asia, presenting on aspects of the Essential Use Nomination (EUN) process and assisting individual Article 5(1) countries in the South Asia region in their EUN preparations. As a consequence, during the 2010 MTOC meeting Mr Mori abstained from participation in decisions regarding the EUNs from Bangladesh, China, India, Iran and Pakistan. The CFC Committee provides a grant for Mr Mori's travel to attend MTOC and MOP/OEWG meetings.

#### **Tunde Otulana USA (Non-A5)**

Dr Tunde Otulana, member of the Medical Technical Options Committee since 1995, is Senior Vice President and Chief Medical Officer at Aerovance Inc. Dr Otulana is a full time executive at Aerovance in Berkeley, California. Aerovance has an interest in the topics of the Montreal Protocol because it operates in the general field of respiratory diseases. Dr Otulana has no proprietary interest in alternatives or substitutes to ODS, does not own stock in companies producing ODS or alternatives or substitutes to ODS, does not have an interest in the outcome of essential use nomination, and does no consulting for organizations seeking to phase out ODS. Dr Otulana's wife has no interest in matters before the Protocol. Dr Otulana's travel to MTOC meetings is paid by Aerovance.

#### **Jose Pons Pons (co-chair) Venezuela (A5)**

Jose Pons, co-chair of the Technology and Economic Assessment Panel since 2004 and of the Medical Technical Options Committee since 1991, is President of Spray Química C.A. Spray Química had an interest in the topics of the Montreal Protocol because it used ODS in some of its aerosol products for industrial maintenance. Mr. Pons is president of the Venezuelan Chamber of Aerosols, CAVEA and has worked in ozone layer protection since 1989. He has participated in several TEAP Task Forces and 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". Mr Pons has no proprietary interest in alternatives or substitutes to ODS, does not own stock in companies producing ODS or alternatives or substitutes to ODS, does not have an interest in the outcome of essential use nominations, and does not consult for organisations seeking to phase out ODS. Mr Pons's spouse has no interest in matters before the Protocol; she is also a manager/engineer at Spray Química. Mr Pons has worked occasionally as a project reviewer for the MLF and implementing agencies on matters related to the Montreal Protocol. Travel related to participation in the TEAP and MTOC, and relevant Protocol meetings, are paid by UNEP's Ozone Secretariat. Spray Química makes in-kind contributions of wage, and miscellaneous and communication expenses.

#### **John Pritchard UK (Non-A5)**

Dr. John Pritchard, member of the Medical Technical Options Committee since 2006, will be Chief Technology Officer in the Respiratory Drug Delivery Group of Philips Home Healthcare Solutions from January 2011, having previously held a variety of roles within AstraZeneca, 3M, GlaxoSmithKline and AEA Technology (formerly UK Atomic Energy Authority). Dr. Pritchard 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, has represented AstraZeneca on the Board of the International Pharmaceutical Aerosols Consortium (a group of companies that manufacture medicines for the treatment of respiratory illnesses) and has served as editor on a number of journals. Philips has an interest in the topics of Montreal Protocol, as it is engaged in the diagnosis, development, manufacturing and supply of products to treat respiratory illness across international markets. Dr. Pritchard is also a minor shareholder in a range of companies, including AstraZeneca and GlaxoSmithKline that manufactured CFC MDIs and now offer HFC MDIs and DPIs as alternatives. Travel expenses for participation in MTOC is provided by Philips.

#### **Rabbur Reza Bangladesh (A5)**

Rabbur Reza, member of the Medical Technical Option Committee since 2009, is the full time Chief Operating Officer at Beximco Pharmaceuticals Ltd, Bangladesh. Beximco Pharmaceuticals is the largest MDI manufacturer in Bangladesh and has an interest in the topics of Montreal Protocol, as it is engaged in development, manufacturing and marketing of MDIs in local and international markets. He has no proprietary interest in alternatives or substitutes to ODS, does not own stock in companies producing ODS or alternatives or substitutes to ODS; however, his employer has an interest in the outcome of the Bangladesh essential use nomination made in 2010. As a consequence, during the 2010 MTOC meeting Mr. Reza abstained from participation in decision-making regarding Bangladesh's essential use nominations. Rabbur Reza has considerable experience in MDI product and business development and does consulting and working for Beximco Pharmaceuticals to phase out CFC-based

MDIs. Rabbur Reza's spouse is a medical practitioner and has no interest in matters before the Protocol. UNEP's Ozone Secretariat funds his travel expenses for participation on MTOC.

**Raj Bright Singh India (A5)**

Dr Raj B Singh, member of the Medical Technical Options Committee since 2005, 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 out-patients 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. Dr Singh was a member of the Executive Committee of the Global Initiative for Asthma (GINA) from 2003 to 2007. He uses a portfolio management service that may buy shares of pharmaceutical companies from time to time. Attendance of the European Respiratory Society 2009 was funded by CIPLA. He received Rs 13500 (US\$ 280) from GSK and Rs 6000 (US\$130) from Astra Zeneca in 2009 for lectures. UNEP's Ozone Secretariat funds his travel expenses for participation on MTOC.

**Roland Stechert Germany (Non-A5)**

Dr. Roland Stechert, member of the Medical Technical Options Committee since 2000, is the Head of Clinical Trial Services and Regional Medical Advisor Cardio-Vascular in the Medical Department of Boehringer Ingelheim, Germany. Boehringer Ingelheim has an interest in the topics of Montreal Protocol, as it is engaged in development, manufacturing and marketing of MDIs and DPIs in international markets. As an expert of respiratory research, Dr. Stechert was involved in the development of CFC-free MDIs with Boehringer Ingelheim. Dr Stechert headed the German regional International Pharmaceutical Aerosol Consortium (IPAC) Group until 2002. Since he took over his role from 2003-2010 as a medical director in Switzerland, and more lately his role in Germany, Dr Stechert has not been a member of IPAC. Participation costs are all borne by the affiliate in Germany.

**Helen Tope (co-chair) Australia (Non-A5)**

Helen Tope, co-chair Medical Technical Options Committee since 1995, is Principal Consultant of Energy International Australia and also Director of Planet Futures with whom she is an independent consultant providing strategic, policy and technical advice and facilitation services to government, industry and other non-governmental organisations on climate change, ozone-depleting substances, and other environmental issues. Dr Tope's business has an interest in the topics of the Montreal Protocol because her potential clients are also interested in these topics. Dr Tope has no proprietary interest in alternatives or substitutes to ODS, does not own stock in companies producing ODS or alternatives or substitutes to ODS, does not have an interest in the outcome of essential use nominations, and consults for organisations that support the Montreal Protocol in phasing out ODS. Dr Tope's spouse, Mr. Michael Atkinson, is also her business partner, whose business has an interest in the topics of the Montreal Protocol. During 2010, TEAP Co-Chair Dr. Stephen O. Andersen, Mr. Atkinson and Dr. Tope were unpaid advisors to a UNEP project on investment metrics for identifying technology that minimizes climate and other impacts when replacing ozone-depleting and high-GWP substances. In 2010 Dr Tope's funding for travel to MTOC, TEAP and other meetings are provided from several sources. The Ozone Secretariat provides reimbursement for Dr Tope's travel associated with the TEAP/MTOC mission to the Russian Federation on CFC MDI transition from funds granted to the Secretariat for this purpose by the Governments of Finland and Sweden and by pharmaceutical companies, JSC Moschimpharmpreparaty and JSC Altayvitamin, in the Russian Federation. The Ozone Secretariat provides a grant for Dr Tope's travel to the MTOC and TEAP meetings from funds granted to the Secretariat unconditionally by the International Pharmaceutical Aerosol Consortium (IPAC), which is a non-profit corporation. The Australian Government Department of the Environment, Water, Heritage and the Arts provides funding for the cost of travel and accommodation for Dr Tope's attendance of the OEWG-30. She makes considerable in-kind contributions of her time without compensation.

**Ping Wang China (A5)**

Dr Wang Ping, MD, a member of the Medical Technical Options Committee since 2008, is the deputy secretary general of Chinese Pharmacopoeia Commission. Dr Wang Ping is a full time Chief pharmacist at the Chinese Pharmacopoeia Commission, Beijing, P.R. China. The Chinese Pharmacopoeia Commission has an interest in the topic of the Montreal Protocol because it making the standards for all the drugs sold in China, including for CFC MDIs for asthma and COPD. Dr Wang Ping has no proprietary interest in alternatives or substitutes to ODS, does not own stock in companies

producing ODS or substitutes to ODS, does not have a financial interest in the outcome of essential use nominations, and does not consult for organizations seeking to phase out ODS. Dr Wang Ping's spouse also has no financial or other interest in matters before to the Montreal Protocol. UNEP's Ozone Secretariat funds his travel expenses for participation on MTOC.

**Adam Wanner USA (Non-A5)**

Dr. 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 and American Thoracic Society have sponsored his travel to MTOC meetings. Dr Wanner has received academic grants (unrelated to the CFC phase-out) from several pharmaceutical companies. Dr Wanner and his spouse have no financial interests relevant to his work on MTOC.

**Kristine Whorlow Australia (Non-A5)**

Kristine Whorlow, member of the Medical Technical Options Committee since 2006, is the CEO of the National Asthma Council Australia. The National Asthma Council Australia has an interest in the Montreal Protocol because it led the phase-out of CFC-containing inhalers for respiratory disease in partnership with the Australian Department of the Environment in Australia. Ms Whorlow has no proprietary interest in alternatives or substitutes to ODS, does not own stock in companies producing ODS or alternatives or substitutes to ODS, does not have an interest in the outcome of essential use nominations. The National Asthma Council Australia receives funding from some pharmaceutical companies for projects in Australia and Asia Pacific not associated with the phase-out of ODS. At the invitation of UNEP ROAP, in 2009, Ms Whorlow participated in the national workshops in Iran, Pakistan and India, and the Bangladesh "Inauguration of National CFC Phase-out Program and Launching of CFC-free MDIs" and the Presentation by the Montreal Joint Compliance Mission to the Minister of Environment. In 2009, UNEP ROAP contracted the National Asthma Council Australia to produce a package of resources on raising awareness of the transition to CFC-free MDIs to assist countries preparing for phase-out. The National Asthma Council Australia funds Ms Whorlow's travel to MTOC meetings. Ms Whorlow's partner has no interest in matters before the Protocol.

**Ashley Woodcock (co-chair) UK (Non-A5)**

Prof. Ashley Woodcock, co-chair of the Medical Technical Options Committee and Member of the Technology and Economic Assessment Panel, is a Professor of Respiratory Medicine at the University of Manchester, and Respiratory Physician at the University Hospital of South Manchester, United Kingdom. The Hospital and University have no direct interest in the topics of the Montreal Protocol. Prof. Woodcock has no proprietary interest in alternatives or substitutes to ODS, does not own stock in companies producing ODS or alternatives or substitutes to ODS, does not have an interest in the outcome of essential use nominations. Prof. Woodcock carries out unrelated consulting and educational lectures for pharmaceutical companies, all of which have phased out CFC MDIs. He regularly advises companies on study design for new drugs, some of which have been ODS replacements. Prof. Woodcock's spouse has no interest in matters before the Protocol. Prof. Woodcock does not work as a consultant to the UN, UNEP, MLF or Implementing Agencies. In the past, he has responded to requests for technical information on CFC MDI phase-out from the European Community and the United Kingdom Government. Travel and subsistence for meetings of TEAP, MTOC, OEWG, MOP meetings is paid from Hospital and University funds, and Prof. Woodcock's employers allows leave of absence.

**You Yizhong China (A5)**

Dr. You Yizhong, member of the 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 organized 14 aerosol conferences, seminars on the phase-out of CFCs from aerosols in China, including 4 special conferences on the phase-out of CFCs from pharmaceutical aerosols and MDIs. Dr You receives his salary from The First People's Hospital of Changzhou and has no interest or economic relationship with pharmaceutical companies, and does not receive any fees for work associated with MTOC. UNEP's Ozone Secretariat funds his travel expenses to attend MTOC meetings.

## Ozone Secretariat

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