

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

UNEP

**2014 REPORT OF THE
MEDICAL TECHNICAL OPTIONS COMMITTEE**

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

Report of the
UNEP Medical Technical Options Committee

2014 Assessment

ASSESSMENT REPORT

The text of this report is composed in Times New Roman.

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Reproduction: UNON Nairobi

Date: February 2015

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UNITED NATIONS ENVIRONMENT PROGRAMME
Ozone Secretariat, P.O. Box 30552, Nairobi, Kenya

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Ozone Secretariat's website:

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ISBN: 978-9966-076-07-6

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Acknowledgements

The Technology and Economic Assessment Panel, its Technical Options Committees and Task Forces, co-Chairs and members, acknowledge with thanks the outstanding contributions from all of the individuals and organisations that provided support to the Panel, its Committees and Task Forces, co-Chairs and members. The Medical Technical Options Committee also acknowledges with appreciation the generous contributions of experts and peer reviewers to this report. The opinions expressed are those of the Panel, its Committees and Task Forces, and do not necessarily reflect the views of any sponsoring or supporting organisation.

2014 REPORT OF THE MEDICAL TECHNICAL OPTIONS COMMITTEE

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EXECUTIVE SUMMARY

Metered Dose Inhalers

Global CFC use for MDIs

There has been significant global progress in the transition from chlorofluorocarbon (CFC) metered dose inhalers (MDIs) to CFC-free inhalers, with substantial and growing capacity to manufacture CFC-free inhalers. The global use of CFCs to manufacture MDIs in 2013 was about 300 tonnes, a reduction of almost 90 per cent from the last assessment. Since global CFC use to manufacture MDIs peaked in 1997 at about 10,000 tonnes, there has also been a dramatic decrease in annual CFC consumption in MDIs of 97 per cent.

Of those Parties that reported, Article 5 Parties (China only) used about 165 tonnes, and non-Article 5 Parties (Russian Federation and the European Union) about 150 tonnes, of CFCs for the manufacture of MDIs in 2013. Annual CFC consumption by Article 5 Parties peaked at about 2,000 tonnes in 2007-2009, dropping to less than 200 tonnes in 2013. Only one Article 5 Party, China, nominated CFCs for MDI manufacture in 2015, which is likely to be its last Essential Use Nomination. No non-Article 5 Party nominated CFCs for MDI manufacture in 2015. These developments signal the imminent global phase-out of CFC MDIs, which in the last two decades has consumed almost 70,000 tonnes of CFCs under Essential Use Exemptions.

Stockpiles of pharmaceutical-grade CFCs are difficult to quantify accurately. Of the Parties that disclosed accounting frameworks, pharmaceutical-grade CFC stockpiles were reported to be about 545 tonnes at the end of 2013, with China possessing the majority of stockpiles (477 tonnes). Some Parties have gradually depleted their stocks, while other Parties are still manufacturing CFC MDIs and/or using CFC stockpiles as strategic reserves (China and possibly Russia). Some CFC stockpiles are surplus and may need to be destroyed. In practice, it has proved difficult to transfer stockpiles of pharmaceutical-grade CFCs between Parties and/or between companies due to complex commercial, technical, regulatory and logistical reasons. There are only a few examples of stockpile transfers that have occurred successfully.

Technically satisfactory alternatives are available

Technically satisfactory alternatives to CFC MDIs to treat asthma and chronic obstructive pulmonary disease (COPD) are available in all countries worldwide. There are sufficient CFC-free alternatives available for all key classes of drugs used in the treatment of asthma and COPD. The new treatments have different characteristics, which need explaining to patients, and training to use properly. Some patients have switched to hydrofluorocarbon (HFC) MDIs (different taste, softer spray, less cooling in the throat), and some switched to dry powder inhalers (DPIs), which require breath actuation (cheap single-dose capsules, or more expensive multi-dose devices).

With the exception of China, the phase-out of CFC MDI manufacturing has been completed worldwide. Russia is in the final stages of manufacturing conversion to HFC MDIs, with completion likely in 2015, and no reported use of CFCs to manufacture MDIs during 2014. Multinational pharmaceutical companies in non-Article 5 Parties have completed the development of alternatives to CFC MDIs for all major classes of drug. Some manufacturers continued to produce CFC MDIs until stocks were exhausted or regulatory requirements prohibited sale. Consequently, there was a small proportion of CFC MDIs still being manufactured and/or sold in non-Article 5 Parties until the end of 2013.

Manufacturing conversions in Article 5 Parties are almost completed, with China likely to cease CFC MDI manufacturing in 2015-2016. Despite initial challenges, such as access to technology transfer and economic barriers, progress has been significant with a number of Article 5 Parties completing

their transition to CFC-free inhalers faster than expected. A range of alternatives are becoming available as CFC MDI manufacturing ceases, HFC MDI manufacturing increases, single- and multi-dose DPI availability increases, and imported CFC-free alternatives become more available. Some pharmaceutical companies in Article 5 Parties continued to manufacture and export CFC MDIs after manufacturing conversions to CFC-free alternatives commenced or were already well underway. These export practices probably slowed the introduction of CFC-free alternatives in importing Article 5 Parties.

Global HFC use for MDIs

Approximately 630 million HFC based MDIs are currently manufactured annually worldwide, using approximately 9,400 tonnes of HFCs in 2014 (95 per cent HFC-134a, 5 per cent HFC- 227ea). This corresponds to direct emissions with a climate impact of approximately 0.013 Gtonnes CO₂-equivalent. HFC emissions from MDIs are estimated as about 0.03 per cent of annual global greenhouse gas emissions. Global HFC demand for MDI manufacture is estimated to increase annually by 2 per cent for the period to 2025.

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 estimates of carbon footprints of inhalers, the climate impact of HFC MDIs is more than one-tenth the climate impact of CFC MDIs, and DPIs have about one-hundredth of the impact of CFC MDIs and less than one-tenth the impact of HFC MDIs.

DPIs are technically and economically feasible alternatives that could minimise the use of HFC MDIs. Nebulisers and emerging technologies may also be technically feasible alternatives for avoiding the use of some HFC MDIs. The exception is for salbutamol; currently salbutamol HFC MDIs account for the large majority of HFC use in inhalers, and are significantly less expensive per dose than multi-dose DPIs, making them an essential and affordable therapy. At present, it is not yet technically or economically feasible to avoid HFC MDIs completely because there are economic impediments in switching from HFC MDIs to multi-dose DPIs for salbutamol, and because a minority of patients (10-20 per cent or less) cannot use available alternatives to HFC MDIs. Nevertheless, DPIs may play an increasing role over the next decade.

Patient health considerations

Asthma and COPD are increasing in prevalence worldwide; the acceptance and use of inhalers are also increasing, especially in Article 5 Parties. The conversion to CFC-free inhalers has not had any adverse impact on patients. On the contrary, the extensive educational campaigns have had a positive impact on the health of patients by increasing the awareness of the benefits of inhaled therapy.

MDIs, DPIs and novel delivery systems all 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. Healthcare professionals continue to consider that a range of therapeutic options is important. Each country has its own unique and complex makeup in terms of availability of medicines, overarching health care systems, and patient preferences. Clinicians and patients have their own preferences based on their own experiences in practice. What is common to all devices is the need to provide adequate training for correct usage to minimise errors, and for clinicians to prescribe the device that the patient can most easily use and afford. 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.

Other medical aerosols

The term aerosol product describes a product *pressurized* with a propellant that expels its content from a canister through a nozzle. Propellants can be compressed gases (nitrogen, nitrous oxide, carbon dioxide), or can be liquefied gases that are a liquid inside the pressurized container; these liquefied gas propellants include CFCs. Medical aerosols are used to deliver topical medication mostly onto the skin, but also to the mouth, and other body cavities. When the Montreal Protocol identified essential uses for CFCs, it differentiated oral inhalation (MDIs) from other medical aerosols, for which CFCs were considered non-essential.

Medical aerosols, that are not MDIs, cover a wide range of uses from simple numbing of pain, nasal inhalation, to the dosage of corticosteroids for the treatment of colitis. The availability and number of different medical aerosol products varies within countries and regions, and is closely related to the development of the local aerosol industries.

Technically and economically feasible alternatives to ozone-depleting propellants (CFCs and hydrochlorofluorocarbons (HCFCs)) are available for all other medical aerosols. Other medical aerosol products were reformulated to use CFC-free propellants. CFC propellants were replaced mostly by hydrocarbons (butane, propane, isobutane, dimethyl ether (DME)), but also by HCFCs and HFCs, in specific applications. Medical aerosol products for use on or near nose or mouth, and also on babies, tend to use HFCs or nitrogen. For treatments where there is a significant risk of inhalation into the respiratory tract, HFCs are preferred, as their safety is well proven through use in MDIs. Propane or isobutane (and their blends) tend to cause an "oily" or slightly stinging taste. All other pressurised medical aerosol products tend to use propane/butane mixtures or DME and compressed gases to a lesser extent. Aqueous sprays and drops are well-established not-in-kind alternatives to nasal aerosol products. Aqueous formulations in general and other not-in-kind alternatives, such as creams, are also used in many applications.

Many external factors affect the selection of a given propellant, including regulatory approval of products, industry codes of conduct, Volatile Organic Compounds controls, and supplier controls of HFC-134a.

HCFC use is about 100 ODP tonnes or less worldwide (HCFC-22 and HCFC-141b), with the majority used in China. In 2010, the total amount of HFCs used for all aerosol products was equivalent to 5 per cent of global HFC consumption, and was estimated as 0.054 Gtonnes CO₂-equivalent. Seventy-six per cent of this GWP-weighted amount was used for medical aerosols (0.041 Gtonnes CO₂-equivalent). Less than an estimated 10 per cent of all other medical aerosols use HFC propellants, with estimated HFC consumption of less than 1,000 tonnes per year. The majority of these would be for nasal inhalation, throat topical medication, and nitroglycerin sublingual application. This consumption is not likely to grow in the near future.

Sterilants

Sterilization is an important process in the provision of good quality healthcare 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. It is legal requirement in pharmaceutical and medical devices industries that any change in manufacturing processes, including sterilization, must be validated using appropriate guidelines before implementation.

There is a range of viable sterilization methods that can replace the use of ozone-depleting substances in this sector, including: 100 per cent ethylene oxide, aldehydes, heat (moist heat or dry heat), radiation, and oxidative processes (including hydrogen peroxide gas, liquid peracetic acid, and ozone gas). Further sterilization methods, based on these and other chemicals, are now available or are under investigation for commercialization. Many of these alternative technologies provided significant advances, such as better safety profiles and turn-around times, and reduced cost per cycle.

CFC-12 used in blends with ethylene oxide (EO) in the sterilization sector has been successfully phased out in non-Article 5 Parties, and in many Article 5 Parties. Although it is difficult to be certain, global use of CFCs for this application is believed to be zero.

EO/HCFE mixtures (10 per cent by weight EO in a mix of HCFC-124 and HCFC-22) are virtual drop-in replacements for the EO/CFC blends and were introduced as transitional products for sterilization in those countries that employed EO/CFC blends extensively. Estimated global use of HCFCs in sterilization is less than 500-700 metric tonnes, which amounts to less than 25 ODP tonnes worldwide. EO/HCFE use in Article 5 Parties is estimated to be less than 200-400 tonnes. EO/HCFE use has been significantly reduced by using less gas per sterilizer load, 100 per cent ethylene oxide, and by hospital conversion to other technologies. The complete phase-out of HCFCs in sterilization uses to meet the Montreal Protocol schedule is readily achievable. Hospital procurement should take the HCFC phase-out, and the coming redundancy of EO/HCFE sterilization equipment, into consideration in making future investment decisions.

1 Background to the 2014 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 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 2014 Assessment

This report is part of the eighth assessment under Article 6 of the Montreal Protocol. The first assessment report was prepared in 1989, and subsequently updated in 1991, 1994, 1998, 2002, 2006 and 2010. This report is in response to Decision XXIII/13 of the Parties to the Montreal Protocol, which requested an assessment to be undertaken for completion by 31 December 2014 for consideration by the Open-Ended Working Group and by the Twenty-Seventh Meeting of the Parties in 2015.

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 of technical, scientific, environmental, and economic issues related to stratospheric ozone protection. The assessment reports assist with this review.

Previously, the Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee (ATOC) assessed, *inter alia*, medical aerosols and sterilants. ATOC was reconstituted in 2005 to form the Medical Technical Options Committee to assess medical applications of ozone-depleting substances (ODS) including medical aerosols and sterilants.

MTOC is made up of experts from industry, government, scientific, research and academic institutions. In 2014, there were 25 members contributing to this assessment from 15 countries – Argentina, Australia, Bangladesh, Brazil, China, Germany, Ghana, India, Italy, Japan, Pakistan, Sweden, United Kingdom, the United States and Venezuela.

This 2014 Assessment Report re-examines the current use of alternatives to ODS in three sectors; metered dose inhalers, other medical aerosols, and sterilants. MTOC undertook written communication in the preparation of this report during 2014 and early 2015. The report has undergone a limited peer review among experts from some relevant global organisations.

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 2030.¹ COPD affects at least an equivalent number of patients, 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, and by 2030 it will have advanced to third.

Inhalation therapy is the mainstay of treatment for asthma and COPD. Inhaled drugs are targeted to the lungs, where they have maximal benefit with least side effects. This is achieved by modulating particle size through inhaler design, and by adjusting excipients and propellants.

Other diseases treated by the inhaled route include cystic fibrosis, bronchiectasis, pulmonary arterial hypertension and respiratory tract infections. These diseases require treatment with relatively high doses of drugs, which are often delivered by nebuliser rather than a portable inhaler. Systemic delivery of drugs via the respiratory tract is also becoming an area of increasing interest, with inhaler products approved for the treatment of diabetes and schizophrenia. This report will mainly focus on inhalation therapy for the treatment of asthma and COPD.

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. In some regions of Africa, especially in urban areas, the prevalence has been doubling every decade and now approaches that of developed countries. There remains a wide difference in prevalence between some countries, such as Indonesia where prevalence is about 1 per cent, to the United Kingdom and New Zealand where it is approaching 20 per cent. Some of these trends may relate to the proportion of patients that are accurately diagnosed.

Asthma can vary in severity from mild asthma with intermittent symptoms through to severe and/or chronic asthma requiring specialist support, frequent hospital admissions with extensive medication, and despite this, in some cases, death. WHO estimates that 80 per cent of asthma deaths occur in low- and middle-income countries.

Asthma has two primary features, airway inflammation and bronchoconstriction, in which there is a muscular 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.

¹ 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. diseases (WHO publication), 2007; WHO World Health Statistics, 2008.

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. The commonest cause of COPD is cigarette smoking though there is some evidence that exposure to biomass fuel smoke may also play an important role in less developed countries^{2,3}. In some patients, occupational dusts, or environmental pollution (including household air pollution), or a small genetic component in patients with alpha 1-antitrypsin deficiency, may cause COPD. 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. The increase in cigarette consumption in China is a major reason why COPD will advance to the third highest cause of mortality by 2030.

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 of asthma and COPD*

Prevention of asthma remains impossible for the majority, 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.

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 increasing prevalence of COPD in developing countries.

Inhaled therapy remains the mainstay of treatment for established 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 lungs. 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, they are simply exhaled and wasted.

For both asthma and COPD, there are two main categories of inhaled treatment, bronchodilators and anti-inflammatory medications. Inhaled salbutamol (a short acting reliever) remains by far the most used treatment, mainly as inexpensive hydrofluorocarbon (HFC) metered dose inhalers (MDIs), but

² S. S. Salvi, P. J. Barnes, Chronic obstructive pulmonary disease in non-smokers, *The Lancet*. Volume 374, Issue 9691, Pages 733 - 743, 29 August 2009.

³ WHO, Household air pollution and health, Fact sheet N°292, Updated March 2014. <http://www.who.int/mediacentre/factsheets/fs292/en>. Accessed February 2015.

with a small amount of multi-dose dry powder inhalers (DPIs) used in developed countries, and single capsule DPIs used e.g. in South Asia. There has been a recent trend for increased use of a combination of long-acting bronchodilators and inhaled steroids in a single inhaler. A number of new once-daily, mainly DPI-delivered, treatments have been introduced recently by multinational pharmaceutical companies.

Oral drugs are also prescribed for asthma. In developing countries, inexpensive methylxanthines (theophylline) are widely available, but these 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 generally less effective than inhaled steroids.

There are new developments in injectable drugs. The first injectable preventive therapy against Immunoglobulin E (IgE) 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 (~\$20,000/year per patient, compared with <\$500/year for an inhaled steroid inhaler, and <\$1000/year for a combination inhaler). Novel injectable biologic drugs will likely be launched in the next 2 years, but will also be expensive and restricted to very few 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 inhalation devices for the delivery of respiratory drugs: (pressurised) metered dose inhaler and the dry powder inhaler 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. It is not uncommon for patients to be prescribed a mix of medications in a range of devices.

The sections below briefly describe each main type of inhaler and their use. One feature generally common to the use of inhalers (MDIs and DPIs) is incorrect technique; a large proportion of patients who are prescribed inhaled medications do not use their inhalers correctly⁴. Studies have observed critical errors in the use of both MDIs and DPIs. Some studies show comparable frequency in critical errors in the use of both MDIs and DPIs; other studies show either more or fewer critical errors for either MDIs or DPIs, depending on the study. Clinicians and patients have their own preferences based on their own experiences in practice. What is common to all devices is the need to provide adequate training for correct usage to minimise errors, and for clinicians to prescribe the device that the patient can most easily use and afford.

2.2.1 MDIs

An MDI is a complex device 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 as they were affordable, reliable and extremely effective. Under the Montreal

⁴ National Asthma Council Australia. *Inhaler technique in adults with asthma or COPD*. Melbourne: National Asthma Council Australia, 2008. <http://www.nationalasthma.org.au/publication/inhaler-technique-in-adults-with-asthma-or-copd>. Accessed February 2015.

Protocol, CFCs have almost been phased out from the manufacture of MDIs, with CFC MDI phase-out completed in developed countries and anticipated for completion in developing countries by the end of 2015.

The process of reformulating MDIs with HFCs began over 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 (HFC-134a and to a lesser extent HFC-227ea). This has been difficult because the components and formulations had to be substantially modified to use the 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 underwent extensive regulatory assessments of safety, efficacy and quality, much the same as for the development of any new drug product. Development costs for the transition of MDIs from CFCs to HFCs have been estimated well in excess of US\$2 billion, and has taken over 20 years to complete. The cost to research and develop a new medicine was recently estimated to be US\$2.6 billion⁵.

Following reformulation, the MDI remains popular because it is the cheapest device for salbutamol worldwide. The relative low cost to the patient of MDIs for the major bronchodilator salbutamol has remained relatively constant over 50 years, even with the new HFC re-formulation⁶. Accurate co-ordination of drug release and inhalation is required for correct use. Studies have shown that many patients do not use MDIs correctly. In clinical practice, as many as 50 per cent of patients fails to use MDIs correctly, mainly due to poor synchronisation of actuation with inhalation and lack of training. A spacer device or breath-actuated inhaler (more costly in many markets) can be used to overcome coordination issues. With information and training, misuse of MDIs can be minimised. MDIs with spacers provide a cost-effective option for patients with low inspiratory flow, such as patients with severe lung disease and very young children, and for severe asthma attacks (where nebulisers provide the only other alternative).⁷

Some studies suggest a potential therapeutic benefit associated with extra-fine HFC MDIs, with some therapies, particularly corticosteroids, shown to be more effective when delivered as ultrafine HFC MDI aerosols than DPI aerosols⁸. However, some MTOC experts do not believe that the ultrafine HFC MDIs have gained a clinically significant advantage.

2.2.2 Dry powder inhalers

Dry powder inhalers (DPIs) are devices that deliver powdered medication (active ingredient alone or mixed with excipient) without the need for a propellant. There are many different devices that deliver powder medication. Most are available exclusively from a single pharmaceutical company that has

⁵ J.A. DiMasi, H.G. Grabowski, R.W. Hansen, Tufts Center for the Study of Drug Development, Costs Study, November 18, 2014, http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study. Accessed February 2015. The figure includes out of pocket costs of \$1,395 million and time costs of \$1,163 million (i.e., expected returns that investors forego while a drug is in development).

⁶ This may not be the case in some countries, in particular the United States.

⁷ T. Burnham, Inhaler use technique and related interventions, an annotated bibliography. *National Electronic Library for Medicines*, Medicines Management Overview, August 2012. https://use-inhalers.com/sites/default/files/publicationpdf/Reference_Studies_Tom_Burnham.pdf. Accessed February 2015.

⁸ M. van den Berge, N. H. T. ten Hacken, E. van der Wie1, D. S. Postma, Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma, *Allergy* 2013; 68: 16–26; J. Cohen, D.S. Postma, W.R. Douma, J.M. Vonk, A.H. De Boer, N.H.T. ten Hacken, Particle size matters: diagnostics and treatment of small airways involvement in asthma, *Eur. Respir. J.* 2011; 37: 532–540.

patented the device. Most commonly used respiratory drugs have been formulated successfully for DPIs and are now widely available.

Micronized dry powder can be inhaled and deposited effectively in patients with adequate breathing capacity. Some studies have indicated that DPIs can be easier for some patients to use than MDIs because drug delivery is effected by the patient's inhalation, and they do not require patient co-ordination. Some patients prefer DPIs because of their ease of use. In some countries DPIs are widely prescribed for the treatment of asthma and COPD. 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. Studies have also shown that many patients do not use DPIs correctly. The variety of different DPI designs can lead to confusion in the correct usage of each DPI. With information and training, misuse of DPIs can be minimised.⁹

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 capsule, containing one dose, 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 more recently developed 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 they can provide the opportunity for patients to purchase a small number of doses at an affordable cost. However, this purchasing behaviour, of a small number of doses, has the potential to undermine compliance for products that are required on a daily basis (e.g. corticosteroids or combination therapies).

Correct training in the usage of single-dose DPIs is important. In 2008, an FDA public health advisory was issued to highlight the correct use of Spiriva® HandiHaler® (tiotropium bromide inhalation powder) and Foradil® Aerolizer® (formoterol fumarate inhalation powder) capsules following reports of misuse of these products, where patients had swallowed the capsules instead of using them in the device¹⁰. With information and training, misuse of single-dose DPIs can be minimised.

Multi-dose DPIs, which have been in use for more than 20 years, typically contain enough doses for at least one month's treatment. There are two types of multi-dose DPI, one with individual doses pre-metered during manufacture, and the second that loads a measured amount of medicine 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 aggregation of the powder formulation. These issues can be partially addressed by supplying the device in a foil pouch opened upon first use. Newer multi-dose

⁹ T. Burnham, Inhaler use technique and related interventions, an annotated bibliography. *National Electronic Library for Medicines*, Medicines Management Overview, August 2012. https://use-inhalers.com/sites/default/files/publicationpdf/Reference_Studies_Tom_Burnham.pdf. Accessed February 2015.

¹⁰ *Public Health Advisory: Important Information on the Correct Use of Spiriva and Foradil Capsules*, US Food and Drug Administration, 29th February 2008. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051132.htm>. Archived content accessed, February 2015.

DPIs have improved moisture protection and are approved in countries with humid climates, such as experienced in many developing countries.

Substantial product development efforts are being pursued in the DPI segment by a number of pharmaceutical companies. Almost all new chemical entities (drugs) for the last decade have been commercialised in DPI formulations. Several of these companies are now developing their new chemical entities exclusively as dry powder products, indicating that it is not cost-effective to develop both DPI and MDI formulations of new treatments.

The challenges and costs associated with the development of new DPI products are similar to those that were incurred for HFC MDIs developments. Multi-dose DPIs containing off-patent molecules have entered the European market and a number of new devices, mainly multiple-dose, are reported to be in the late phase of clinical evaluation or subject to regulatory approval in the United States.

2.2.3 *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 to that of 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, with widely different outputs, and dose to the patient. 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 are now recommended mainly for the treatment of infants and severely ill patients, where patient assistance is not needed; or to situations when larger doses of drug and/or prolonged administration times are desired. A nebuliser takes 5-10 minutes to deliver its dose, and is relatively inconvenient to use. Currently, there are only formulations of short-acting bronchodilators, corticosteroids, antibiotics and DNA-ase widely available for nebulised use.

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 in portable battery-powered devices. The vibration serves to pump liquid through the mesh creating a respirable spray. 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.

2.2.4 *Aqueous mist inhalers*

Small portable devices that produce aerosols of respirable diameter from aqueous formulations have been under development for a number of years and one (Respimat™)¹¹ is now commercially available in a number of countries.

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, or forcing liquid through tiny micron-sized holes, or vibrating mesh/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.

Boehringer Ingelheim's Respimat™, which utilises the collision of two liquid jets to generate an aerosol, has been launched internationally for delivery of tiotropium for COPD, and in some markets, asthma patients, and as a combination short-acting bronchodilator and ipratropium bromide for use in COPD patients.¹²

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. They also rely upon the drug to be sufficiently potent that it can be concentrated within 25-50 µl in order to deliver it within a single breath. These devices are currently more expensive than standard MDIs and DPIs. The development and regulatory timescales for new aqueous inhaled delivery systems are lengthy and new technical breakthroughs are not common.

2.2.5 *Novel devices*

There is also a class of devices under development that vaporizes an excipient-free drug to form a condensation aerosol that, when inhaled, allows for systemic drug delivery. The Staccato® device (Alexza) is approved for systemic administration of loxapine in the treatment of schizophrenia (marketed as Adasuve™ by Teva). This technology will only work with drugs that have relatively low boiling points and are thermally stable.

2.2.6 *New propellants for MDIs*

An inhalation propellant must be safe for human use and meet several other criteria relating to safety and efficacy. Traditionally the list would include: (i) liquefied gas, (ii) low toxicity, (iii) non-flammable, (iv) chemically inactive and stable, (v) acceptable to patients (in terms of taste and smell), (vi) appropriate solvency characteristics, and (vii) appropriate density. Not all of these requirements may be essential for an alternative propellant, but careful study and justification would be required to support any significant change. It is, however, extremely difficult to identify chemicals fulfilling all of these criteria, and which are also environmentally acceptable.

¹¹ <https://www.respimat.com/home1.html>. Accessed January 2015.

¹² <http://www.spiriva.respimat.com/spiriva-respimat/spiriva-respimat-in-COPD.html>; <http://www.combivent.com/>. Accessed January 2015.

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. The direct cost of this testing was tens of millions of dollars. 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 product quality. The process for developing CFC-free MDIs was therefore essentially identical to the development of a wholly new drug product, involving full safety testing, stability testing and clinical trials for each reformulated MDI. Research and development for a new product is a lengthy, challenging, costly and resource-intensive process. A safety study for an entirely novel MDI propellant in asthma/COPD requires at least 12 months clinical trial experience in hundreds¹³ of patients, as well as lifetime studies in laboratory animals. 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.¹⁴

Under an MLF-funded project, one company in Argentina, Pablo Cassara, is undertaking research and development to use isobutane as the propellant, planning to launch a salbutamol MDI in 2016. The registration process for the isobutane-based salbutamol MDI has been initiated and completion of the project is expected for end of 2014. An MDI formulated with isobutane propellant could be beneficial in providing a low-GWP alternative to HFC-propelled MDIs. To date, there has been no successful isobutane reformulation worldwide despite several research projects. In the 1990s and early 2000s, a German company had also been developing isobutane-propelled salbutamol MDIs, although that work appears to have ceased. Previous studies have reported toxicological concerns for isobutane used in combination with a beta-agonist¹⁵.

Chemical companies are promoting a new range of unsaturated HFC, also called a hydrofluoroolefin (HFO), with attractive chemical, physical and environmental properties for a range of applications. However, it is not clear whether there will be any role for unsaturated HFCs as safe propellants for MDIs, especially as there are low-level toxicological concerns associated with all of the HFOs currently in development¹⁶. 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 test the safety of unsaturated HFCs for direct and chronic human inhalation, and to 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

¹³ The number of patients varies on the clinical trial and/or the country where the trial is conducted. Patient numbers can range from the low hundreds to more than a thousand.

¹⁴ *IPCC/TEAP Special Report: Safeguarding the Ozone Layer and the Global Climate System: Issues Related to Hydrofluorocarbons and Perfluorocarbons*, 2005, B. Metz, L. Kuijpers, S. Solomon, S. O. Andersen, O. Davidson, J. Pons, D. de Jager, T. Kestin, M. Manning, and L. Meyer (Eds), page 355.

¹⁵ Final report of the Safety Assessment of isobutane, isopentane, n-butane, and propane. *Int. J. Toxicology*, 1; 4: 127-142, 1982.

¹⁶ Consideration of Hydrofluoroolefins (HFOs) as potential candidate medical propellants, A.A. Lindley and T. J. Noakes, Mexichem Fluor, April 2010. http://www.mexichemfluor.com/europe/medical_products.php. Accessed February 2015.

remain the same and the performance characteristics are likely to be comparable to saturated HFCs), and in light of the large investments already made over the past two decades in developing and marketing saturated HFC MDIs and the alternative available through dry powder formats.

2.2.7 *Technical and economic assessment of alternatives*

CFC-propelled MDIs were historically the inhaled delivery device of choice. They have been replaced as follows:

- HFC MDIs: the CFC propellant in MDIs has been gradually replaced with HFCs (HFC-134a and to a lesser extent HFC-227ea), and there are now HFC MDI alternatives available to cover all key classes of drugs used in the treatment of asthma and COPD.
- Dry powder inhalers (DPIs): do not require a propellant, are a not-in-kind alternative to MDIs. DPIs fall into two categories: single-dose DPIs, which have been in use for more than 60 years, and multi-dose DPIs, which have been in use for more than 20 years. There are two main types of multi-dose DPI, reservoir and multi-unit dose devices. New drugs continue to be developed in the DPI format, sometimes exclusively.
- Nebulisers: are used to inhale drug solutions and account for about 10 per cent or less of the market on a dose basis.
- Propellant-free aqueous mist inhalers have been recently launched.
- Emerging alternatives are in the earlier stages of development, commercialisation or marketing, such as isobutane propelled MDIs.

An analysis was recently conducted on the technical and economic feasibility of the two main alternatives to CFC-propelled MDIs, HFC MDIs and DPIs¹⁷. Some of the key findings are summarised below.

By the end of 2014, a range of HFC MDIs and DPIs were commercially available for all key classes of drugs used in the treatment of asthma and COPD. In China, manufacturing transition to HFC MDIs is anticipated by the end of 2015 and widespread commercial availability probable by 2016-2017. In some regions, there can be more of one alternative (HFC MDI or DPI) used in preference to another. For example, the proportion of MDIs prescribed compared with DPIs varies considerably across Europe, with 70 per cent of MDIs prescribed in the UK and only 10 per cent in Sweden¹⁸. This is more to do with market factors and physician/patient practices and preferences than it is to do with commercial availability.

There are now HFC MDI and DPI alternatives available for all key classes of drugs used in the treatment of asthma and COPD. HFC MDIs and DPIs have been subjected to extensive regulatory assessments for safety, efficacy and quality. Clinical trials have shown HFC MDIs to have a safety and efficacy profile comparable to that of CFC MDIs, with more consistent dosing¹⁹. Clinical

¹⁷ Report of the UNEP Technology and Economic Assessment Panel, Decision XXV/5 Task Force Report, Additional Information on Alternatives to ODS (Final Report), October 2014.

¹⁸ T. Hillman, F. Mortimer, N. S. Hopkinson, Inhaled drugs and global warming: time to shift to dry powder inhalers: Propellants in metered dose inhalers are powerful greenhouse gases, *British Medical Journal*. 2013; 346: f3359.

¹⁹ Asthma patients to benefit from advancement in inhalers, *Business Recorder*, November 3, 2013, Pakistan.

evidence also indicates that MDIs and DPIs are equally effective for the treatment of asthma and COPD for patients who use both devices correctly. New drugs are mainly being developed as DPIs. Salbutamol HFC MDIs account for the large majority of HFC use in inhalers, and are significantly less expensive per dose than multi-dose DPIs.

Short-acting bronchodilators (e.g. salbutamol) are generally cheaper when in MDIs than in multi-dose DPIs, although the price differential is coming down in some markets, as the number of salbutamol DPI devices increases. Hillman *et al.* argue that DPIs will need to be cheaper if they are to be used more widely, particularly in emerging economies and health systems where patients pay for their own drugs.¹⁸

Single-dose DPIs are affordable and available for the short-acting bronchodilator salbutamol, as well as other inhaled therapies such as beclomethasone. Patients (in Article 5 Parties) buy the re-usable inhaler device once and generally re-use that device for about 12 to 24 months. Patients buy the medicines (capsules) for the inhaler as needed. Single-dose DPIs have the advantage that they permit low-income patients to afford single doses of their medication, where they may otherwise be unable to afford the expense of buying one month's therapy at a time (as necessary with MDIs and multi-dose DPIs). However, this purchasing behaviour also has the potential to undermine compliance for products that are required on a daily basis (e.g. corticosteroids or combination therapies). In India and Bangladesh, doctors prefer single-dose DPIs for the majority of their economically challenged patients. In India, for example, single-dose DPIs account for more than 50 per cent of inhaled therapy, and DPIs generally for about half of the market value²⁰. The use of single-dose DPIs for daily use medications may not necessarily be as cost effective over the long term as MDIs or multi-dose DPIs.

Similar economic drivers are apparent in other markets, dominating the choice of inhaled treatment; for example, in Russia, the domestically produced salbutamol CFC MDI with 90 doses has been preferred to imported HFC MDIs with 200 doses because the imported inhaler is more expensive, even though the price per dose is almost halved.

Some studies have indicated that DPIs can be easier for some patients to use than MDIs because drug delivery is effected by the patient's inhalation, and they do not require patient co-ordination.²¹ On the other hand, DPIs have a minimum threshold inspiratory effort that is needed for proper use and drug efficacy. Therefore DPIs are generally not used in very young children, or patients with very severe disease and poor inspiratory flow. Either MDIs used with spacers, or nebulisers, or aqueous sprays are suited for treating the very young or the elderly and for treating acute attacks. In one study, it was shown that between 12.5 and 30 per cent of elderly COPD patients could not achieve the authors' pre-specified flow rate through some older high resistance DPIs, although no data were provided on any change in therapeutic efficacy²².

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. In both cases the issue can be partially addressed by supplying the device in a foil pouch opened on first

²⁰ D Waite, *Comparison of OIP Experiences in Different Markets*. IPAC-RS Respiratory Conference, March 18-20, 2014.

²¹ For a general bibliography see: T. Burnham, Inhaler use technique and related interventions, an annotated bibliography. *National Electronic Library for Medicines*, Medicines Management Overview, August 2012. https://use-inhalers.com/sites/default/files/publicationpdf/Reference_Studies_Tom_Burnham.pdf. Accessed February 2015.

²² 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.

use. Newer multi-dose DPIs have improved moisture protection and are approved in countries with humid climates, such as experienced in many Article 5 Parties. Single-dose capsule DPIs can be more susceptible to humidity than some of the more recent multi-dose DPIs. However, an effective drug dose is likely to be delivered even with the effects of humidity, and pharmaceutical companies are working to improve blister pack technology and to ameliorate humidity problems.

DPIs are technically and economically feasible alternatives that could minimise the use of HFC MDIs. Nebulisers and emerging technologies may also be technically feasible alternatives for avoiding the use of some HFC MDIs. The exception is for salbutamol; salbutamol HFC MDIs are currently an essential and affordable therapy. It is not yet technically or economically feasible to avoid HFC MDIs completely in this sector because, currently:

- There are economic impediments in switching from HFC MDIs to multi-dose DPIs for salbutamol;
- 10-20 per cent, or probably less, of patients cannot use available alternatives to HFC MDIs.

Finding an affordable alternative to salbutamol HFC MDIs is a major challenge. One company has a regulatory application in progress for isobutane-propelled salbutamol MDI.

Some argue that there may be more opportunities associated with the replacement of HFC MDIs containing preventer medicines such as corticosteroids, where there is little difference in cost between DPIs and HFC MDIs. Others disagree, contending that some therapies, particularly corticosteroids, have been shown to be more effective when delivered as ultrafine HFC MDI aerosols than DPI aerosols²³. However, some other experts do not believe that the ultrafine HFC MDIs have gained a clinically significant advantage. Despite these differences, MTOC experts agree that a range of therapeutic options is important because some devices, and/or drug products, are more effective for some patients.

2.2.8 *Environmental assessment of alternatives*

Previously, the IPCC/TEAP Special Report (2005) concluded that “...most reduction of GWP from MDIs would be achieved through the completion of the transition from CFC to HFC MDIs” and “...the environmental benefits of converting HFC MDIs to DPIs are small”. This report also opined that hypothetically replacing HFCs in MDIs with DPIs was one of the least cost-effective greenhouse gas replacement options.²⁴

HFCs are now becoming subject to regulation in some applications. Regulators and some pharmaceutical companies continue to consider the relative climate impacts of alternatives to CFC MDIs to gain understanding for decision-making purposes, and in some cases, have been taking steps to minimise those impacts. For example, one multinational is seeking to reduce the dose of HFC per puff by 50 per cent. Throughout these considerations, it is accepted that the priority is the health and safety of the patient.

This section addresses the latest available information about the climate and other environmental impacts of alternatives to CFC MDIs.

²³ M. van den Berge, N. H. T. ten Hacken, E. van der Wiel, D. S. Postma, Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma, *Allergy* 2013; 68: 16–26.

²⁴ *IPCC/TEAP Special Report: Safeguarding the Ozone Layer and the Global Climate System: Issues Related to Hydrofluorocarbons and Perfluorocarbons*, 2005, B. Metz, L. Kuijpers, S. Solomon, S. O. Andersen, O. Davidson, J. Pons, D. de Jager, T. Kestin, M. Manning, and L. Meyer (Eds), page 358.

For the 2010 assessment²⁵, IPAC provided estimates of carbon footprints for the manufacture and use of various respiratory devices and treatment methods based on a 200-dose equivalence (Table 2-1).

Table 2-1 Estimates by IPAC of carbon footprints of respiratory devices and treatment methods

| Respiratory devices and treatment methods | Carbon footprint Per 200 actuations (Grams CO₂eq.) | Carbon footprint Per dose (Grams CO₂eq.)²⁶ |
|--|--|---|
| CFC MDI | 150,000-200,000 | 1,500-2,000 |
| HFC-134a MDI | 20,000-30,000 | 200-300 |
| HFC-227 MDI | 60,000-80,000 | 600-800 |
| Dry Powder Inhaler | 1,500-6,000 | <20 |
| Tablets | 1,500-5,000 | <20 |

These 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, the climate impact of HFC MDIs is more than one-tenth the climate impact of CFC MDIs. DPIs have an even lower comparative climate impact, about one-hundredth of the impact of CFC MDIs and less than one-tenth the impact of HFC MDIs.

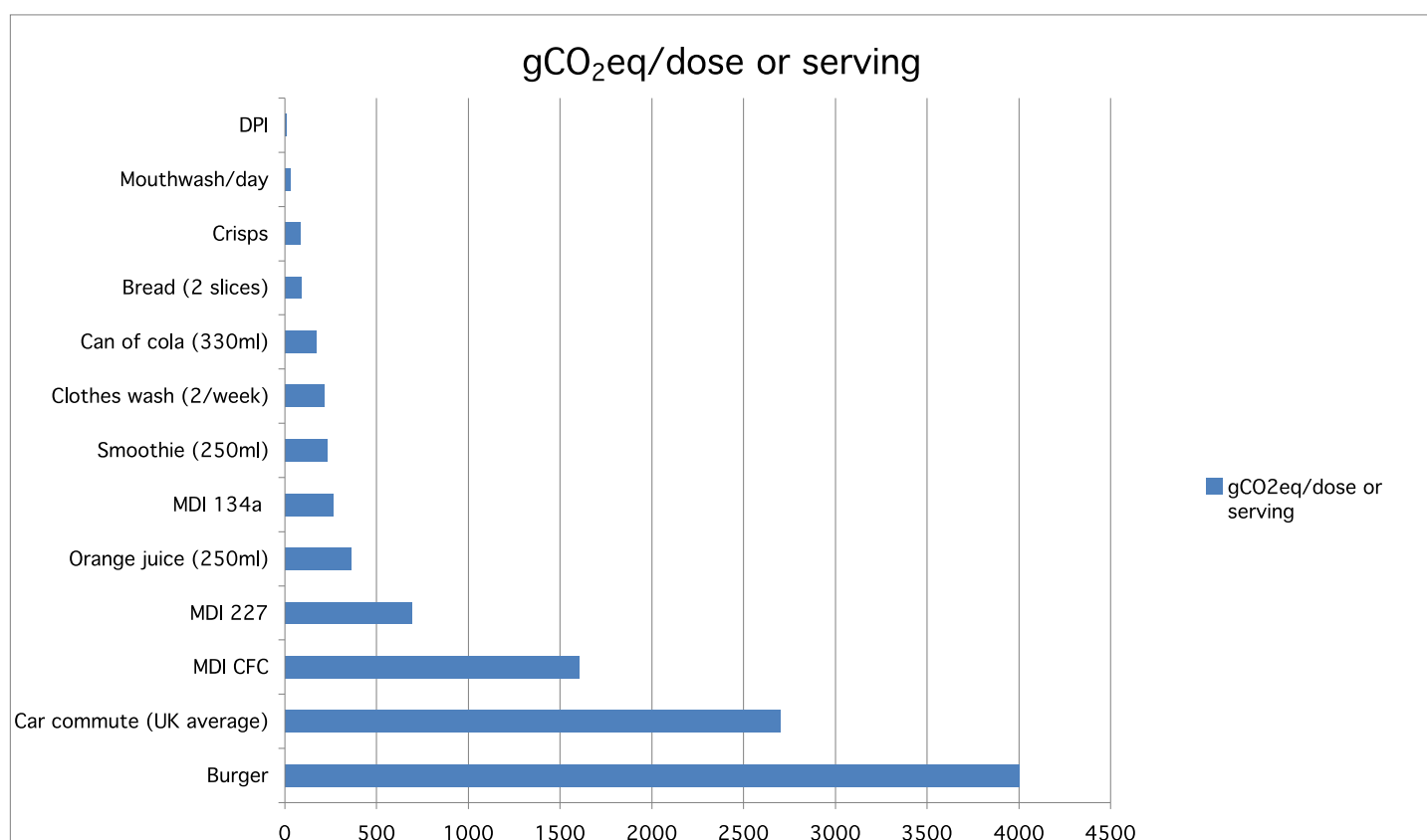
The estimated carbon dioxide equivalent of a 2-puff dose of an HFC MDI (200g CO₂eq.) is comparable to the climate impact of everyday items, such as a 330ml can of Cola (170g CO₂eq.), 250ml of orange juice (360g CO₂eq.), and a kilometre driven in a Seat Ibiza Ecomotive (99g CO₂eq.). This can also be compared with the carbon impact of a one-way economy class flight from London to Frankfurt (180,000g CO₂eq. per passenger), a popular burger (4,000g CO₂eq.), or a loaf of commercially made bread (1,300g CO₂eq.). Estimates of carbon dioxide equivalents associated with a dose of an asthma inhaler and everyday items are presented in Figure 2-1.²⁷

²⁵ 2010 Report of the UNEP Medical Technical Options Committee, 2010 Assessment Report.

²⁶ One dose for an MDI is two actuations; for a DPI is one actuation; and for a tablet is one tablet.

²⁷ The climate impact of everyday items was originally reported in the 2010 Report of the UNEP Medical Technical Options Committee, 2010 Assessment Report, from sources mentioned therein.

Figure 2-1 *Estimated relative carbon dioxide emissions of everyday items compared with asthma inhalers*



A recent study has noted that HFC MDIs can account for a substantial proportion of the total annual carbon footprint of a country's health sector (e.g. 8 per cent of the total carbon footprint of the United Kingdom's NHS, which corresponds to 0.24 per cent of the United Kingdom's total carbon footprint)²⁸.

Pharmaceutical companies are also considering their carbon footprints as part of corporate responsibility programs, and the contributions, *inter alia*, from the HFC MDIs and DPIs that they manufacture. For example, one company, GSK, has assessed its overall value chain carbon footprint (including Scope 1, 2, and 3 emissions²⁹). In 2012, emissions associated with the use and disposal of MDIs accounted for about 35 per cent of its value chain carbon footprint, in addition to smaller contributions from MDI production-related emissions of HFC-134a. This company's long-term goal is for its value chain to be carbon neutral by 2050, and is looking at every process associated with its products – from sourcing raw materials to manufacturing use and product disposal – to find

²⁸ T. Hillman, F. Mortimer, N. S. Hopkinson, Inhaled drugs and global warming: time to shift to dry powder inhalers: Propellants in metered dose inhalers are powerful greenhouse gases, *British Medical Journal*. 2013; 346: f3359.

²⁹ The GHG Protocol Corporate Standard classifies a company's greenhouse emissions into three 'scopes'. Scope 1 emissions are direct emissions from owned or controlled sources. Scope 2 emissions are indirect emissions from the generation of purchased energy. Scope 3 emissions are all indirect emissions (not included in scope 2) that occur in the value chain of the reporting company, including both upstream and downstream emissions.

opportunities to reduce its carbon footprint³⁰. GSK assessed the relative carbon footprint of its HFC MDI and DPI products to find that 1 month's treatment with its HFC MDI (Seretide® MDI 250/25) has about the same carbon footprint as more than a year's treatment with its DPI (Seretide® Accuhaler® 500/50) of the equivalent drug³¹, with carbon footprints certified by Carbon Trust Certification Ltd³².

Waste and CO₂ emissions can be reduced by collecting unused and waste inhalers for recycling. One global pharmaceutical company (GSK) has implemented pilot programs to collect unused and waste inhalers for recycling propellant, plastics and aluminium in several countries, including in the United Kingdom, the United States, and Chile.

Regulatory authorities appear to be proceeding cautiously with controls for HFCs with regard to MDIs. Recent amendments to the European Union's F-Gas Regulations exclude MDIs from mandated HFC reductions from 1st January 2018 onwards.

2.2.9 Patient health considerations

It is important to note that MDIs, DPIs and novel delivery systems all 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.

Early in the CFC MDI transition to CFC-free alternatives, Price *et al.*³³ observed that measures potentially affecting patient use of HFC MDIs should be carefully considered, especially if measures were imposed while the transition of patients from CFC MDIs was still in progress. They also noted the importance of maintaining a choice of inhaler devices in providing effective treatment.

2.3 Availability of CFC-free alternatives

Asthma and COPD are increasing in prevalence worldwide; the acceptance and use of inhalers are also increasing. These two factors combined mean that the overall numbers of inhalers used worldwide are also increasing, especially in Article 5 Parties.

Technically satisfactory alternatives to CFC MDIs to treat asthma and chronic obstructive pulmonary disease (COPD) are available in all countries worldwide. There are sufficient CFC-free alternatives available for all key classes of drugs used in the treatment of asthma and COPD.

³⁰ GSK Corporate Responsibility Report 2012, <http://www.gsk.com/media/325167/cr-report-2012.pdf>. Accessed November 2014.

³¹ GSK, personal communications, 2014.

³² Carbon Trust Certificate of Achievement to GlaxoSmithKline PLC, Awarded: 26/03/2014 Valid Until: 25/03/2016, Carbon Trust Certification Ltd., United Kingdom.

³³ D. Price, E. Valovirta, and J. Fischer, The Importance of preserving choice in inhalation therapy: the CFC transition and beyond, *Journal of Drug Assessment* 2004; 7: 45-61.

2.3.1 *Global trends in the availability of CFC-free alternatives*

Since the 2010 assessment, multinational pharmaceutical companies in non-Article 5 Parties have completed the development of alternatives to CFC MDIs for all major classes of drug. In some cases, it was not possible to reformulate drugs in an HFC MDI, and so drugs were introduced in an alternative inhaler device. Where CFC stockpiles remained, some companies sought to make surplus available to supply approved essential uses in other countries, without success. Other manufacturers continued to produce CFC MDIs until stocks were exhausted or regulatory requirements prohibited sale. As a consequence, there was a small proportion of CFC MDIs still being manufactured and/or sold in non-Article 5 Parties until the end of 2013. Russia is in the final stages of manufacturing conversion to HFC MDIs, with the necessary filling equipment due for delivery in late 2014, and with completion likely in 2015. There was no reported use of CFCs to manufacture MDIs in Russia during 2014.

Manufacturing conversions in Article 5 Parties are almost completed, with China the remaining Article 5 Party where CFC MDI manufacturing continues, and is likely to cease in 2015-2016. A range of alternatives are becoming available as CFC MDI manufacturing ceases, HFC MDI manufacturing increases, single- and multi-dose DPI availability increases, and imported CFC-free alternatives become more available. Some pharmaceutical companies in Article 5 Parties continued to manufacture and export CFC MDIs after manufacturing conversions to CFC-free alternatives commenced or were already well underway. For example, India's final Essential Use Exemption was in 2010, with a reported pharmaceutical-grade CFC stockpile of about 200 tonnes remaining at the end of 2010. In 2014, Mexico reported it was still receiving imported CFC MDIs manufactured in India and was aiming to remove registrations to stop these obsolete products. Similarly, until the end of 2013, Pakistan was also receiving imported CFC MDIs manufactured in China, which made up to 70 per cent of unit sales. These export practices probably slowed the introduction of CFC-free alternatives in importing Article 5 Parties.

When assessing the overall market situation and recent trends, different parameters can be considered, namely volume of doses, volume of devices or monetary value. Each of these reflects slightly different aspects of the market dynamics and has relative merits and drawbacks. All measures suffer from the greater difficulty of obtaining data in markets where electronic prescription records are not available, thus typically providing less accuracy in data from Article 5 Parties than in non-Article 5 Parties. However, broad trends and conclusions can be drawn, which are presented below.

The International Pharmaceutical Aerosol Consortium (IPAC)³⁴ provided IMS Health³⁵ market data of global inhaler usage from 2007-2012. While data on trends is available until 2012, substantial changes have been taking place from 2013 onwards, with CFC MDI phase-out almost completed worldwide. 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 due to the increased use of both MDIs and DPIs. The data show an increase in the total consumption of all MDIs during the period 2007-2012 (2.1 per cent per annum), and an increase in the consumption of DPIs (3.0 per cent per annum). In 2012, CFC MDIs accounted for about 16 per cent of all inhaled medication globally, based on dose equivalence, HFC MDIs for about 43 per cent, DPIs about 32 per cent, and nebulised solutions about 8 per cent. Based on IMS Health market data, approximately 300 million

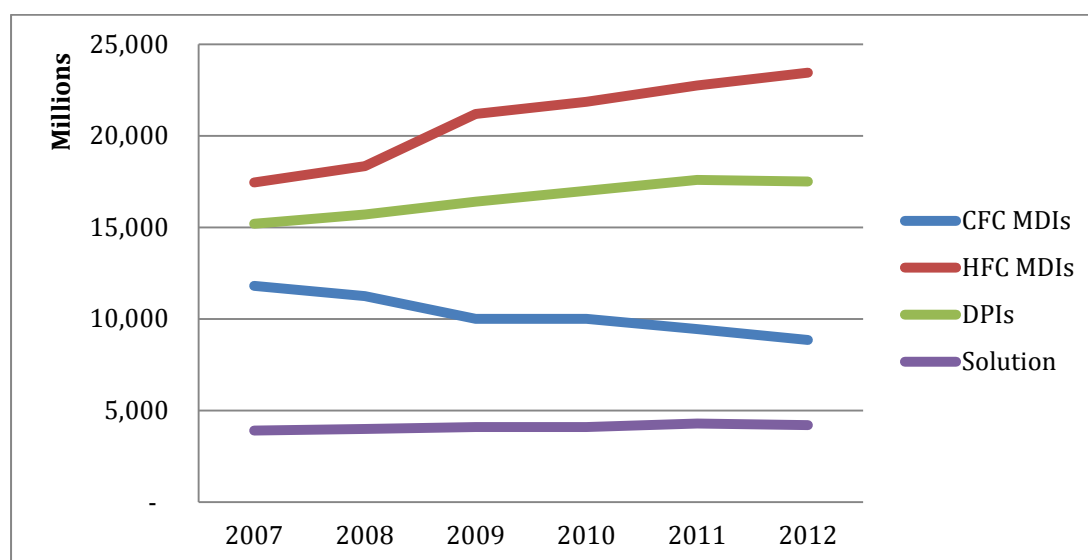
³⁴ The International Pharmaceutical Aerosol Consortium is a group of companies (Astrazeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Glaxosmithkline, Teva) that manufacture medicines for the treatment of respiratory illnesses, such as asthma and COPD.

³⁵ IMS Health is a respected company that has been gathering and analyzing pharmaceutical market data for decades. IMS Health; IMS MIDAS granted IPAC permission to submit this data to MTOC/TEAP.

DPIs are manufactured annually worldwide. Based on HFC manufacturing industry estimates³⁶, approximately 630 million HFC based MDIs (with an average 15g/MDI) are currently manufactured annually worldwide.

Figure 2-2 shows global sales performance on a dose basis (derived from standard units³⁷) for different treatment types (CFC MDIs, HFC MDIs, DPIs and nebulised solutions) for the period 2007-2012.

Figure 2-2 Global sales performance of inhaled medication on a dose basis, 2007-2012



In China, India, Latin America and Russia, total doses of inhaled medication are increasing more rapidly than in Europe and North America where they are increasing slowly or not at all. In North and Latin America and in Russia, DPI use is lower as a proportion of total doses of inhaled medication than the global average. Whereas, as previously reported³⁸, 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.

Figure 2-3 summarizes the proportions of doses delivered by CFC MDIs, HFC MDIs and DPIs³⁹ in different global regions in 2012. CFC MDIs delivered an average of 6 per cent of doses in Europe and

³⁶ T.J. Noakes, Mexichem Fluor, United Kingdom, personal communications, 2014. HFC consumption data derived from this HFC industry source differs from that derived from IMS Health market data. For the purposes of this report, the “top-down” industry data has been used to derive HFC MDI production and HFC consumption.

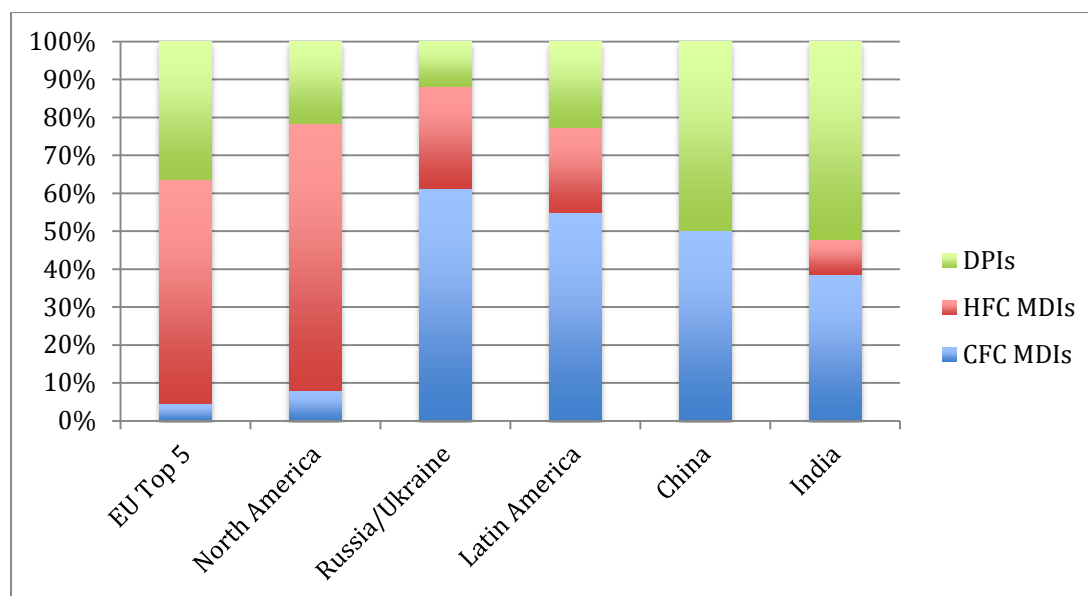
³⁷ A standard unit is defined by IMS as the number of dose units, such as the number of inhalations/puffs, tablets, the number of 5ml doses, or the number of vials, sold for a particular product. For standard unit comparisons of DPIs versus MDIs it is important to note that for DPIs: 1 puff (1 SU) = 1 dose, whereas in general for MDIs: 2 puffs (2 SUs) = 1 dose. Translating standard units into the absolute number of actual MDIs or DPIs can be complex because different devices provide a range of doses. A rough estimate is made for MDIs by dividing the SUs by 200 and for DPIs by 60.

³⁸ Report of the UNEP Technology and Economic Assessment Panel, May 2009, Progress Report, pp. 38-39, and Progress Report, May 2010.

³⁹ Excludes solution inhalants that account for about 10 per cent or less of the market on a dose basis.

North America combined in 2012, compared with an average of about 50 per cent of doses in Russia/Ukraine, Latin America, China and India combined.

Figure 2-3 Proportions of doses delivered by MDIs and DPIs in different regions, 2012⁴⁰



In Article 5 Parties and Russia/Ukraine, transition away from CFC MDIs was less than 50 per cent completed in 2012. Russia is now in the final stages of manufacturing conversion to HFC MDIs, with completion likely in 2015. With the phase-out of CFC MDIs now completed in Europe and the United States, and well advanced in Article 5 Parties, the global use of CFC MDIs is likely to have decreased significantly by the end of 2014. Nevertheless, these data indicate the differences in global markets that can exist at a point in time.

Many factors influence patient and physician choices including: pricing, reimbursement, drug availability in a particular device, prescribers' views on the suitability of a device for a particular patient, and patient preferences. These factors can lead to significant differences in device usage around the world. For example, around three quarters of all inhaled therapy prescriptions are for MDIs in the United States⁴¹, Canada, New Zealand, and around 70 per cent in the United Kingdom and Australia⁴². On the other hand, DPIs account for around 90 per cent of prescriptions in Sweden, around 50 per cent in Japan and possibly also in China⁴¹; and single-dose DPIs account for more than 50 per cent in India. Consumption of DPIs in some Article 5 Parties can be much less than in others for a variety of reasons. Currently MDIs are prescribed more often than DPIs on a global basis. Rescue medications (short-acting bronchodilators) are prescribed commonly as MDIs, especially in non-Article 5 Parties. For example, in the United States about 70 per cent of prescriptions were for rescue medications including salbutamol (or albuterol)⁴³.

⁴⁰ There are notable caveats for IMS Health data for China and India, which is extrapolated from China Hospital panel and India Retail panel data. The European Union top 5 are Germany, Spain, France, Italy, and the United Kingdom.

⁴¹ D Waite, *Comparison of OIP Experiences in Different Markets*. IPAC-RS Respiratory Conference, March 18-20, 2014.

⁴² IMS Health data for Australia for 2013, provided with the assistance of AstraZeneca Australia.

⁴³ http://media.mmm-online.com/documents/82/resp_14_20476.pdf. Accessed December 2014.

MDIs for rescue medications are among the cheapest respiratory products on the market. In an analysis of IMS data of total sales value of different devices⁴⁴, the proportion of total sales value for MDIs shrinks in comparison to the values for both DPI and nebulised products, reflecting the lower average sales price for MDI rescue medications. This lower average sales price reflects the fact that, firstly, salbutamol and ipratropium are off-patent molecules and, secondly, rescue medication MDIs benefit from economies of scale that reduce component costs. DPIs are often bespoke to one company, often in multiple dose strengths, and sometimes restricted to one or two drugs, often making them more expensive. The exception is single-dose DPIs that are emerging as an affordable choice for the poorest asthma patients in some Article 5 Parties. It should be noted that national authorities frequently set sales prices and so local policies can also impact issues of affordability, and hence transition.

2.3.2 Progress in Article 5 Parties

Despite difficulties in collecting accurate sales data for Article 5 Parties, it is clear that overall consumption in Article 5 Parties is increasing, due largely to increased access to medicines. In some countries, notably China, there is also an increasing incidence of disease, especially COPD associated with increased levels of cigarette smoking. In China, India, Latin America and Russia/Ukraine, total doses of inhaled medication are increasing more rapidly than in Europe and North America. Whereas, as noted above, global growth for inhaled medication was less than 3 per cent per annum between 2007 and 2012, in Latin America growth was 4 per cent per annum⁴⁵, India 8 per cent, and China 18 per cent, representing a more than doubling of inhaled doses taken in China during this period. These growth rates also reflect emerging markets in these countries and the relatively lower starting points in sales. Despite the much larger population, total doses delivered in China were about 5 per cent of those in Europe's top 5 countries in 2012. The growth in inhaled medicines in developing countries has come at the same time as manufacturing conversions by local manufacturers, required in response to the Montreal Protocol phase-out of CFCs used in MDIs.

2.4 Transition to CFC-free alternatives

The following information is compiled from a number of sources including MTOC members, IPAC, and a recent report to the Executive Committee of the Multilateral Fund⁴⁶.

Experiences in the transition from CFC MDIs to CFC-free alternatives varied from country to country and were dependant on many factors. Some factors were generally common to all countries: national transition strategies and/or regulations set the framework for change while commercial considerations often drove the pace of change.

2.4.1 Experiences in non-Article 5 Parties

With the possible exception of Russia⁴⁷, all non-Article 5 Parties phased out the production of CFC MDIs by the end of 2013. Many experiences gained in non-Article 5 Parties proved invaluable for

⁴⁴ D Waite, *Comparison of OIP Experiences in Different Markets*. IPAC-RS Respiratory Conference, March 18-20, 2014.

⁴⁵ IMS Health. There are notable caveats for IMS Health data for China and India, which is extrapolated from China Hospital panel and India Retail panel data. The European Union top 5 are Germany, Spain, France, Italy, and the United Kingdom.

⁴⁶ Report on evaluation of projects for the conversion of CFC based metered dose inhalers to CFC-free technologies, UNEP/OzL.Pro/ExCom/72/9, April 2014.

Article 5 Parties in managing the safe phase-out of CFC MDIs. There were a number of key success factors, including:

- Early preparation and planning
- Engagement of stakeholders including Government Departments of Health, Environment and Industry; pharmaceutical Industry; professional bodies e.g. national respiratory Societies; patients and patient organisations; all health care professionals, e.g. general practitioners, nurses, pharmacists
- A clear agreed phase-out programme, based on adequate supplies of CFC-free inhalers in all therapeutic categories
- Key simple messages e.g. that the new MDIs are just as effective but have a different taste;
- National programmes of education to patients, and information to the public through the media
- Opportunistic updating of treatment guidelines

Salbutamol HFC MDIs have been introduced in most countries with little if any price increase, and have remained cheaper than salbutamol DPIs. In the US, a price increase occurred for some patients through the change from cheap “over-the-counter” epinephrine MDIs, to physician-prescribed salbutamol HFC MDIs.

For other treatment classes, there has been a trend in non-Article 5 Parties towards DPIs, with many new medications (ICS, LABA, anti-cholinergics, combinations) over the last few years being launched in DPI formulations. Over the previous decade, where new products have been launched in both formulations, the DPI and equivalent MDI were priced the same. DPI formulations are now comparable in price to MDIs for all drugs except for salbutamol.

Russia has had delays in conversion of its local salbutamol CFC MDI manufacturing plants to HFC MDIs. Conversion now seems likely to be completed in 2015. Russia announced that its Essential Use Exemption for 2014 was its last. While some CFCs were acquired, there was no reported use of CFCs to manufacture MDIs in Russia during 2014. A full range of affordable imported CFC-free inhalers is available to Russian patients.

⁴⁷ Russia has not announced that it has phased out production of CFC MDIs but did not use CFCs to manufacture MDIs in 2014.

Australia – In the late 1990s, in order to prepare Australia for the phase-out of CFC containing MDIs, the National Asthma Council Australia (NAC)⁴⁸ formed the CFC-Free MDI Working Group with the Australian Department of Environment as Co-chair. The stakeholders involved were the Australian Government drug regulatory and financing authorities, the pharmaceutical companies in asthma and their industry body, the Thoracic Society of Australia and New Zealand and the UNEP Aerosol Technical Options Committee (now Medical Technical Options Committee). This Working Group developed plans for each stage of phase-out with stakeholder collaboration and input into the process. In January 1999, the three salbutamol MDIs were replaced with CFC-free MDIs with two preventer/controller MDIs quickly following. A national information and media campaign informed relevant health professionals in advance of transition, and then reminded them as each new CFC-free MDI was introduced. An essential message was that there would be no change to DPIs, as they do not contain a propellant. The 2002 asthma treatment guidelines produced by the NAC covered the issue thoroughly and were distributed to all GPs, pharmacists and other relevant health professionals. Transition of most MDIs occurred in the next few years, with the very last one in 2007. Few incidents of patient or health professional confusion were reported during transition.

European Union – The first CFC free MDI was introduced in Europe in 1994. In some parts of Europe, and especially Scandinavia, DPI's already accounted for almost 90% of inhaler use, whereas in the UK and Mediterranean countries, MDI's predominated. Many of the large pharmaceutical companies producing inhalers were based in Europe, and started to develop CFC free inhalers. Patient groups and government health departments developed patient friendly information to support transition. The European Union developed a category-based phase-out strategy, limiting the production of CFC for use in MDIs. In 2005, the Member States determined that CFCs '*are no longer essential for the manufacture of CFC MDIs that contain active ingredients belonging to the therapeutic categories of short-acting beta agonist bronchodilators, inhaled steroids and anticholinergic bronchodilators*'. As a result the European Union did not request any CFCs for the manufacture of salbutamol MDIs as part of its Essential Use Nomination in 2006, or in any year thereafter. The European Union's last Essential Use Exemption was for 2009. CFCs continued to be used in small quantities for MDI manufacture until 2013. During 2013, Italy ceased using CFCs to manufacture a combination inhaler sold into that market. CFCs used by an Italian company in the manufacturing process for valves supplied to CFC MDI manufacturers also ceased during that year. At the end of 2013, the European Union had completely depleted its CFC stockpile.

⁴⁸ The National Asthma Council is the national body for asthma in Australia. In order to achieve its aims the NAC works with organisational and individual stakeholders, mainly health professionals and Government.

Japan – In 1989, fourteen Japanese pharmaceutical companies, which manufacture and/or import MDIs for the treatment of asthma and COPD, organized a special committee called the “CFC Committee” as an affiliated group under the Federation of Pharmaceutical Manufacturers’ Associations of Japan (FPMAJ). The committee and each member company undertook extensive efforts to develop CFC-free alternatives and introduce them to the market. In 1996, there were 22 brands of CFC MDIs in the market. Since the first introduction of an HFC MDI in 1997, a total of 21 brands of CFC-free alternatives (HFC MDIs and DPIs) have now been launched to replace the full range of CFC MDIs. In December 1998, the Japanese government submitted a transition strategy that was developed in cooperation with the CFC Committee. The strategy was unique in that it included a clear timeline of ‘by 2005’ for the complete phase-out, and it allowed for brand-by-brand substitution by each company. All companies finished both production and import of CFC MDIs in 2004, and completed the delivery of the last CFC MDI in 2005 when Japan accomplished the complete phase-out of CFC MDIs. The key success factors for the transition were the technologies to manufacture CFC-free alternatives, the cooperation of the companies, the close cooperative relationship between the authorities and industry, and an appropriate transition strategy with a clear timeline. The phase-out of CFC MDIs also contributed to a significant reduction of greenhouse gas emissions.

Russian Federation – The Russian Federation experienced many delays in the phase-out of CFCs in MDI manufacturing. Two local pharmaceutical companies have been manufacturing CFC MDIs. The first National Action Plan was developed in 2004 to phase-out CFCs for MDI production in 2005-2007. The Action Plan was revised several times due to economic and technical reasons before being put on hold in 2007. In 2009- 2010, the Russian Federation, together with the two local pharmaceutical companies, worked with UNIDO to initiate a GEF co-funded project to phase-out CFCs in MDIs. Although the project received in principle approval in March 2011, approval for the full project to commence was not made until December that year. The project funding was based on the premise that GEF would provide \$2.5M of funding and the manufacturers would provide \$5.5M. During early 2012, UNIDO negotiated the terms of reference with both manufacturers for a tendering exercise (for conversions) that took place between July and September 2012. Having reviewed the tender submissions, the MDI manufacturers requested modifications to the terms of reference to reduce the manufacturing capacity and thus the cost of the equipment, so that the overall cost of the project (and their contribution) could be reduced. As a consequence, a new bidding process for a revised tender was required. The two Russian companies were reportedly also engaged in clinical trials during 2012. The completion of equipment installation was initially expected to be mid-2014 and, following further delays, the filling equipment to produce HFC MDIs was later planned for delivery in November 2014. A further 12-24 months would likely be required to validate and launch HFC MDIs at full capacity. For some years, there has been a range of affordable CFC-free inhalers available in the Russian Federation. In 2013, MTOC considered the affordability of salbutamol inhalers for Russian patients, when about 80 per cent of salbutamol inhalers bought by Russian patients were locally made CFC MDIs. The prices for imported 200-dose HFC MDIs were mostly higher than the locally produced 90-dose CFC MDIs because the pack sizes are more than double. A low-income patient might find it easier to afford a salbutamol inhaler at a lower unit price within a limited monthly budget. However, on a dose-for-dose basis, four of the six imported HFC MDIs were cheaper than the more expensive of the two locally produced CFC MDIs. The Russian Federation recently reported that in 2014 the total quantity of CFCs acquired was less than the quantity authorised under its Essential Use Exemption. CFCs were not used to manufacture MDIs in that year. A stockpile of about 175 tonnes CFCs remained at the end of 2014.

United States – In the United States, preparation for CFC phase-out started soon after the Montreal Protocol was signed. A close collaboration between the US Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) resulted in the development of a phase-out strategy with focus on both substitution of active drug moieties and therapeutic class of drugs used for the treatment of asthma and COPD. Aerosol treatments of other diseases such as nasal sprays for rhinitis were also addressed. The final phase-out strategy was published in 2007. The United States chose to enact legislation that set dates beyond which the sale of CFC MDIs was banned. A sustained and broad-based educational campaign was instituted targeting health care providers, patients and advocacy groups. This helped to promote an understanding of the phase-out plans and to provide assurance and support. Emphasis was placed on striking a balance between protecting the environment and ensuring patients' continued access to aerosol drugs critical for the management of their airway diseases. Groups, including the American Lung Association, American Thoracic Society, American Academy of Allergy Asthma and Immunology, Mothers of Asthmatics, organized campaigns to educate their membership on the phase-out. From a regulatory perspective, the combination product consisting of short-acting beta-adrenergic/short-acting anticholinergic (Combivent® CFC MDI) and the over-the-counter medication epinephrine MDI required special attention due to the unique factors surrounding the development of alternatives and the therapeutic use of these products. Ultimately, alternatives including HFC MDIs, DPIs and solution-based inhalers were substituted for the CFC MDIs, with the last CFC MDI essential use removed in December 2013; five years after albuterol (salbutamol) products were removed from use in December 2008.

2.4.2 Experiences in Article 5 Parties that manufacture MDIs

CFC MDIs have been manufactured in at least 20 Article 5 Parties (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 multinational pharmaceutical companies. These companies either financed their own manufacturing conversion to CFC-free inhalers or received finance for their conversion through the Multilateral Fund for the Implementation of the Montreal Protocol (MLF). Some multinational companies operating in Article 5 Parties completed the transition to CFC-free inhalers prior to the 2010 CFC phase-out (e.g. Brazil).

A number of Parties (Argentina, Bangladesh, China, Colombia, Cuba, Egypt, India, Iran, Mexico, Pakistan, Uruguay) received financial assistance from the MLF for projects to convert MDI manufacturing enterprises to produce CFC-free alternatives. A number of Parties (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 investment projects in Article 5 Parties 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 US\$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 necessitated Article 5 Parties making use of the essential use provisions of the Montreal Protocol and nominating essential use production of CFCs for MDI manufacture after the CFC phase-out in 2010.

Despite initial challenges, such as access to technology transfer and economic barriers, progress has been significant with a number of countries completing their transition to CFC-free inhalers faster than expected. In 2009, the first year of the essential use process for Article 5 Parties, MTOC reviewed nominations from eight Article 5 Parties. It is very encouraging to note that, four years later,

only one Article 5 Party nominated CFCs for MDIs for 2015. There have been significant reductions from about 2,400 tonnes of authorised essential use CFCs for Article 5 Parties in 2010 to about 220 tonnes of CFCs nominated by China for 2015, which is stated to be its last nomination.

With the exception of China, the phase-out of CFC MDI manufacturing has been completed worldwide. Russia is in the final stages of manufacturing conversion to HFC MDIs, with completion likely in 2015. There was no reported use of CFCs to manufacture MDIs in Russia during 2014. China will likely be the last to complete local manufacturing conversions and should phase out CFC MDI manufacturing in 2016. Despite being the last, there has been substantial progress demonstrated. In 2010 there were 19 domestic manufacturers requesting CFCs under Essential Use Nominations covering 18 different active ingredients; by 2014 this has reduced to 12 enterprises for 8 active ingredients. In 2013, local manufacturers sold more than 14 million HFC MDIs, including for export. Pakistan had been using its CFC stocks while local CFC MDI manufacturing was being converted. CFC MDI manufacturing has now ceased, with one company producing HFC MDIs locally, and another company's HFC MDI in the testing phase.

Regulatory framework

Article 5 Parties requested Essential Use Exemptions (EUE) to authorise CFC production for manufacturing MDIs after the 2010 phase-out. Parties authorised EUEs for India for 2010, for Argentina and Bangladesh for 2010 and 2011, and for Pakistan for 2010, 2011, and 2012. Parties have authorised yearly EUEs for China from 2010 onwards and, by the Meeting of the Parties, in November 2014 China was the only remaining Party with an authorised exemption for CFCs for MDI manufacture for 2015. China's authorised EUEs for CFC MDI manufacture have declined substantially, from 972 tonnes in 2010 to 183 tonnes in 2015.

Eleven Parties received funding from the MLF for manufacturing conversion from CFC MDIs. All investment projects included educational and awareness packages. Almost all projects were to convert *salbutamol* CFC MDIs to HFC-134a-propelled MDIs. One company in Argentina has a project to convert to salbutamol inhalers with isobutane as the propellant, and two companies in India have used HFC-227.

The structures and rules for managing the manufacturing transition varied in complexity from country to country. Generally, Ministries of Environment, Industry and Health were involved. Argentina created a coordinating body ("PRESAO"); the Ministry of Industry led the technical reformulation project. Cuba involved multiple agencies; transition occurred at the same time as an integration of the pharmaceutical industry into a single state-owned enterprise, which delayed the project. China established "the National Leading Group (NLG) for Ozone Layer Protection" with the task of providing strategic guidance and inter-sector coordination in ozone-depleting substance (ODS) phase-out activities, including MDIs. The NLG involved many government departments, but especially Environment, and the China Food and Drug Administration (CFDA). In China the MDI sector plan was slowed by the detailed agreements required between the multiple internal agencies and the external agency (UNIDO). Bangladesh, India and Pakistan introduced transitional project payments against milestones, which may have hastened completion of the projects.

The requirements for regulatory approvals for new inhalers varied from country to country. In China, the CFDA implemented strict procedures for the pharmaceutical approvals of the new HFC MDIs (with different excipients). Since China has many smaller MDI manufacturers, the technical challenges, together with the strict safety assessments, have meant that the market has consolidated to fewer, larger manufacturers. China has a detailed transition strategy and timetable, based on the availability of drugs in specific therapeutic categories, and has mostly adhered to that timetable. Meanwhile, other countries accepted technical data from elsewhere on the safety of HFC MDI use for approvals' processes, and did not require any new regulations. Transition has provided the opportunity to improve medicine formulations and packaging, and to promote more widely safe inhaler use for asthma and COPD in developing countries.

Technical issues

Each company in each country had different issues to surmount. Some companies found conversion from CFC MDIs to CFC-free alternatives too difficult or expensive, and have withdrawn from MDI manufacture. Some companies only reformulated salbutamol MDIs with HFC propellant, while others had a wide range of products to reformulate. Specific issues associated with the new HFC inhalers included additional excipients, particle size, can coating, water ingress, valves, stability, shelf life, and new strict regulatory approvals in some countries. Some companies reformulated themselves, while others licensed in the new technology. Production lines were either retrofitted CFC lines or new HFC high-pressure lines. Funding for investment projects did not cover all costs; all companies with MLF investment projects have had to top-up investments with their own financial and in-kind contributions. Nevertheless, some of those companies investing will see returns through the opening up of new export markets, including the recent approval in the European Union of new MDI products from India.

Clinical issues and affordability

The use of inhalers to treat asthma and COPD is rising steadily in developing countries worldwide. The impact of the transition has depended on the maturity of the market for inhaled therapy, and affordability. Parties with MDI manufacturing have a relatively high use of inhalers. Every Party with reformulation projects had educational programmes to mitigate the change in inhalers for patients. The new treatments have different characteristics, which need explaining to patients, and training to use properly. Some patients switched to HFC MDIs (different taste, softer spray, less cooling in the throat), and some switched to DPIs, which require breath actuation (cheap single-dose capsules, or more expensive multi-dose devices). The new inhalers were generally well accepted, with a comment that some HFC MDIs could occasionally require that the actuator be washed to clear blockage. The change of inhaler has often provided the opportunity for revisions of treatment, and improvements in care.

Inhaled therapy is relatively expensive for developing countries. In Bangladesh, MDIs were not available until 1997, and there is still a tradition for oral and injected therapies; only 10 per cent of asthma /COPD patients take inhaled therapy. In India, single-dose capsules provide the only way that poorer patients can access inhaled drugs, and account for more than 50 per cent of the inhaler market. In most countries, richer patients in urban areas, with better-developed health services, take more inhaled therapy than poorer patients in rural areas.

Affordability also depends on the supply from locally manufactured inhalers versus multinational imported products. In China and Pakistan, inhalers are available from both sources, with locally produced and affordable inhalers rising steadily in volume and variety. In Bangladesh, which has three local MDI manufacturers completing transition, laws prohibit the import of products from foreign companies when similar products are produced locally. China caps the price of inhalers, where the locally produced generic salbutamol inhalers are less expensive (25-30 per cent lower, about US\$3) than the imported branded product (about US\$4). Imported branded products for other active ingredients (combinations and patented molecules) are significantly more expensive than generic molecules in single agent devices. This limits the use of imported inhalers mainly to more affluent urban areas in China, and continues to make cheap oral asthma treatment a major slice of the market.

The price to patients of the new HFC MDIs has gone up by 10-30 per cent compared with CFC MDIs over the period of transition in e.g. Argentina, Bangladesh, India and Pakistan. This increase is mainly due to inflation, with the impact of local price regulations and increasing local competition limiting any major price rises.

The conversion to CFC-free inhalers has not had any adverse impact on patients. On the contrary, the extensive educational campaigns to healthcare workers, the public and patients have had a positive impact on the health of patients by increasing the awareness of the benefits of inhaled therapy. In Argentina, India and Pakistan, campaigns were mainly led by local industry, through their sales forces. In Bangladesh, the President and Ministers were involved with the Bangladesh Lung Foundation and local manufacturers, in a broad-based campaign. In China, patient surveys before and after a government-led campaign showed an improvement in the acceptance of inhaled therapy. In Cuba, a vigorous government campaign led to an approximate 90 per cent knowledge about the hazards of CFCs in MDIs, and the correct use of new inhalers among patients.

Bangladesh – Despite being among the least developed countries in the world, Bangladesh made tremendous efforts to meet CFC reduction targets under the Montreal Protocol, well ahead of schedule. Bangladesh signed the Protocol in 1990, agreeing to completely phase out CFCs by the year 2010. For a country like Bangladesh, constantly faced with socio-economic challenges, this was an uphill task. A major obstacle was the initial lack of awareness and understanding from policy makers and bureaucrats regarding CFC usage in the pharmaceutical industry. CFC MDI production was not included in the country's National Phase-out Plan and was only first identified in 2004 during the preparation of the Country Program Update. The Government raised the issue with the pharmaceutical sector in 2005, 15 years after signing the agreement, through the Ozone Cell of the Department of Environment (DoE).

In 2006, at the 18th MOP, Bangladesh indicated that it may fall into non-compliance and requested technical and financial assistance to phase out CFCs in MDIs. In 2007 the Executive Committee of the Multilateral Fund approved an investment project to phase out 76.3 ODP tonnes CFCs at three locally-owned manufacturing enterprises, thus helping Bangladesh eliminate CFCs while preserving local jobs and employment. More importantly, CFC-free inhalers are available to the 16 million asthma and COPD sufferers in the country at very low cost, thereby significantly reducing the burden on the nation's health budget.

With financial and technical assistance from UNDP and the Multilateral Fund, three local manufacturers converted to CFC-free MDI formulations. Beximco Pharmaceuticals Ltd. completed transition first, followed by Acme Laboratories, which stopped CFC-based production by the end of 2011, and Square Pharmaceuticals, by the end of 2012. Multinational company GSK also converted its CFC-based formulations and adopted alternatives, which are contract manufactured by Beximco. The success story of Bangladesh in this transition is an enormous achievement: Bangladesh achieved zero CFC status from January 2013 and not a single patient had to suffer due to the introduction of CFC-free MDIs.

One pharmaceutical company, Beximco Pharmaceuticals Ltd., which is the largest MDI producer in Bangladesh, played a pioneering and proactive role that led to a classic public-private partnership, facilitated by UNEP, to achieve the goal to phase out CFC-based inhalers. This company undertook the major initiative to make the transition away from CFC inhalers in 2004, requiring extensive R&D skills and technical expertise. Two years later, in 2006, Beximco became one of the first generic pharmaceutical companies in the world to successfully convert its facility for CFC formulations to HFC inhalers. As a follow-up to UNEP's Langkawi Declaration on public-private partnership, Beximco and the Bangladesh Lung Foundation (BLF) designed an effective awareness raising strategy for CFC-free MDIs among physicians. Seminars were held for doctors across Bangladesh to disseminate key clinical information related to CFC-free MDIs. This was done with technical support from UNEP and DoE, and this Bangladeshi partnership is now regarded as a successful model of public-private partnership involving government, the pharmaceutical industry, and doctors, that could be replicated in other countries. A series of awareness materials for physicians were developed and published to promote the use of CFC-free MDIs and DPIs. CFC-free MDIs have a different taste and feel to the previous CFC inhalers, which had the potential to cause confusion among patients. More than 40 meetings were conducted to educate doctors about the new formulation.

Iran – In 2005, the necessity of conversion of the CFC MDI production line in Iran to non-CFC products was recognised and discussed between the Ozone Unit, industry and the Ministry of Health (MoH) to prepare the country for the phase-out process. Iran was in the unique position of having only one MDI manufacturer and only a small quantity of imported inhaler products.

In early 2006, project documents were prepared and submitted to UNIDO. In 2007, the National Transitional Strategy Plan for the project ahead was prepared and submitted. The project document was finalized and submitted to ExCom in the same year. Iran's conversion project was approved at the 52nd ExCom meeting in July 2007. Terms of Reference for machinery and for technology transfer/formulations were prepared by UNIDO in 2007-2008 for the processing of international bids. Machinery was ordered by UNIDO in December 2007. The implementing agency faced difficulties in selecting the provider of technology and formulations during the bid process. This was challenged by the project stakeholders; and was finalized at the end of 2008. The machinery was received in May 2009, and installed and tested for operation along with the training of local technicians in December 2009.

The first awareness workshop was held at the manufacturer's site in Tehran in March 2009, followed later by further workshops and other awareness activities.

Careful planning and measures were undertaken by industry and the MoH to ensure the preparation of enough stockpiles of products at the manufacturer's site to cater for local market needs during the period when no production took place because of construction works, installation of machinery, and the different approvals by authorities.

Due to the delay in the selection of the technology provider, there was a consequent delay in the provider supplying technical documents to Iran. Eventually, local registration documents were submitted to the MoH when the technical dossiers were received from the technology provider. Permission for manufacturing stability batches of the HFC MDIs (salbutamol, beclomethasone and salmeterol) was obtained and the manufacturing of the first 3 batches of CFC-free products (as stability batches and acceptance of the technology) was executed with some delay in mid-2010. In early 2011, upon completion of accelerated stability tests and MoH review of the submitted documents, the official license for manufacturing and marketing of commercial batches of HFC MDIs was granted.

Awareness activities were planned and executed successfully throughout the country with collaboration between the Ozone Unit, MoH, and SinaDarou (the MDI manufacturer), and later also the Universities of Medical Sciences of Iran. The audiences were university medical professors, specialist and GP physicians and pharmacists.

2.4.3 Experiences in Article 5 Parties relying on imports

The large majority of Article 5 Parties do not have domestic manufacturing, and therefore rely on imported inhalers. A barrier for developing countries had previously been that replacement HFC MDIs manufactured by multinational companies in developed countries were priced more expensively than CFC MDIs manufactured in developing countries, meaning that poorer patients could not afford the former. Imported inhalers now come from manufacturers in both non-Article 5 and Article 5 Parties, with the latter more affordably priced. Technically and economically satisfactory alternatives to CFC MDIs to treat asthma and COPD are now available in all countries worldwide.

For salbutamol, it was reported, with some reports as recently as early 2014 (Mexico), that manufacturers in India and China were exporting competitively priced CFC MDIs into South America and Pakistan, while stocks in the pipeline were depleted. In some importing countries, this slowed the adoption of salbutamol HFC MDIs. Many countries were forced to prohibit these imported products.

Nevertheless, the transition has now all but been completed worldwide. Affordable generic salbutamol HFC MDIs from several manufacturers are now available worldwide, along with more expensive branded MDIs. Affordable salbutamol single-dose capsule DPIs, in small packs, are increasingly popular in Asia.

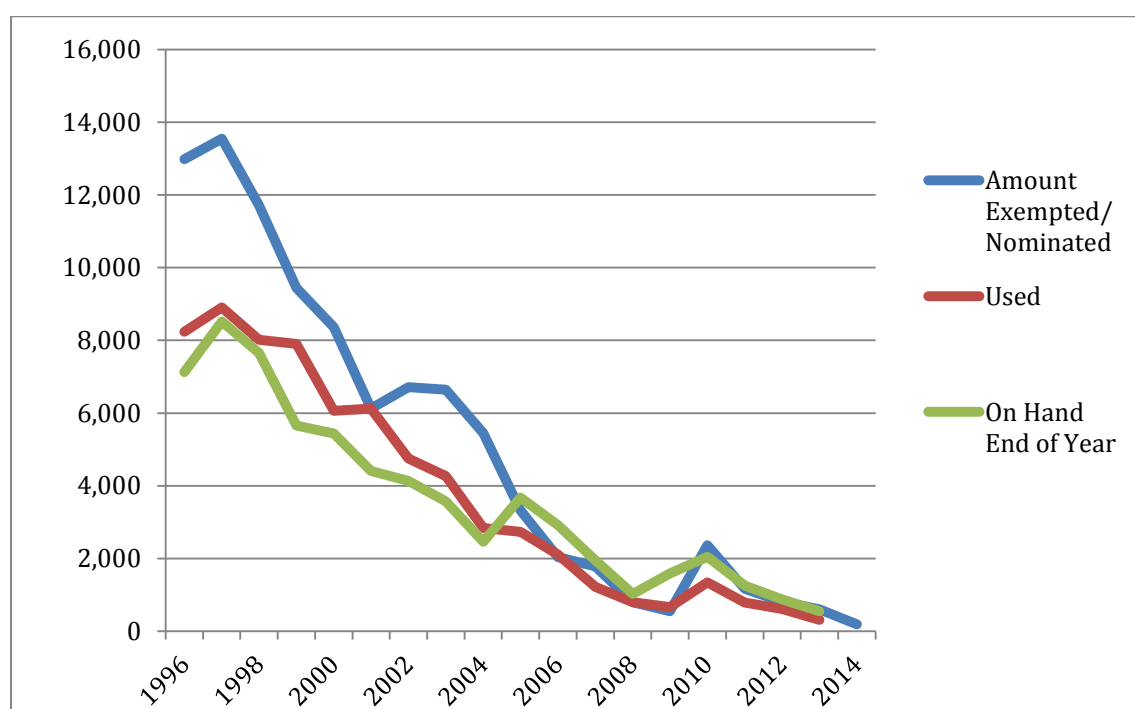
Up until 2010, the transition was driven mainly by conversion of MDI manufacturing in developed country markets. In 2010⁴⁹, MTOC noted the worldwide availability of affordable CFC-free alternative inhalers, especially from multinational companies. Since 2010, market forces have shown the pace of transition in Article 5 Parties to be determined by the availability of cheaper inhalers from manufacturers in Article 5 Parties. With recent market authorisation approvals in the European Union, non-Article 5 Parties will likely see increasing numbers of inhalers imported from Article 5 Parties appearing in pharmacies, signifying a paradigm shift in traditional market dynamics.

2.5 CFC consumption and production for MDIs

2.5.1 CFC Consumption for MDI manufacture

Based on information provided in reporting accounting frameworks under Essential Use Exemptions, the amounts of CFCs exempted, used and on hand at the end of each year from 1996 onwards are presented in Figure 2-4.

Figure 2-4 Amounts of CFCs exempted, used, on hand at the end of each year (tonnes), 1996-2014



The global use of CFCs to manufacture MDIs in 2013 was about 300 tonnes, a reduction of almost 90 per cent from the last assessment (in 2009, 2,300 tonnes). Since global CFC use to manufacture MDIs peaked in 1997 at about 10,000 tonnes, there has also been a dramatic decrease in annual CFC consumption in MDIs of 97 per cent. Article 5 Parties (China only) reportedly used about 165 tonnes

⁴⁹ Report of the UNEP Technology and Economic Assessment Panel, May 2010, Progress Report, Volume 2.

and non-Article 5 Parties (Russian Federation and the European Union) used about 150 tonnes of CFCs for the manufacture of MDIs in 2013. On average, the total use of CFCs by Article 5 Parties reduced by about 40 per cent each year between 2009 and 2013, with all countries decreasing consumption year on year, with the exception of China in 2010 to 2011 when there was a small increase. Russia's consumption of CFCs for MDIs was about 250 tonnes in 2009, remained at about 210 tonnes from 2010-2012, and reduced to 140 tonnes in 2013 due to a production lag resulting from the late delivery of CFCs in that year.

There has been significant global progress in the transition from CFC MDIs to CFC-free inhalers, with substantial and growing capacity to manufacture CFC-free inhalers. CFC consumption by Article 5 Parties peaked at about 2,000 tonnes per annum in about 2007-2009, dropping to less than 1,000 tonnes by 2010, and less than 200 tonnes in 2013. Only one Article 5 Party nominated CFCs for MDI manufacture in 2015, China for 220 tonnes, which is likely to be its last nomination. Also, no nomination was received from Russia, meaning that no non-Article 5 Party nominated CFCs for MDI manufacture in 2015. These developments signal the imminent global phase-out of CFC MDIs, which in the last two decades has consumed almost 70,000 tonnes of CFCs under Essential Use Exemptions.

2.5.2 *Production of pharmaceutical-grade CFCs for MDIs*

Production of pharmaceutical-grade CFCs is now limited to China. China (and its CFC producer) is subject to a CFC production phase-out agreement made by the Executive Committee of the Multilateral Fund. Under its existing agreement, China is allowed to manufacture pharmaceutical-grade CFCs for authorised essential uses for itself and for export to other Parties, with the requirement for annual review. This was agreed to be only for the purpose of meeting essential use requirements of other Parties provided that the exporting Parties had specified reporting and verification systems in place. In recent years, China has been authorised under its CFC production phase-out agreement to produce and export CFCs to the Russian Federation to meet its essential use needs for MDI manufacture.

Any new source of supply of pharmaceutical-grade CFCs (including from surplus 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 requires the approval of health authorities. Total time to register a new source can take up to 6 months.

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 might subsequently require costly destruction.

2.5.3 *CFC stockpiles*

Stockpiles of pharmaceutical-grade CFCs exist around the world, however it has been difficult to quantify stockpiles accurately in the absence of information, such as through accounting frameworks, being provided by some Parties. Of the Parties that disclosed accounting frameworks for the year 2013 under authorised Essential Use Exemptions (China, the European Union, Russia), pharmaceutical-grade CFC stocks were reported to be about 545 tonnes at the end of 2013. China possessed the majority of stockpiles (477 tonnes) reported in accounting frameworks for 2013. Other Parties with Essential Use Exemptions ceased reporting on stockpiles at certain points. Accounting frameworks have never been received from Egypt and Syria. Table 2-2 below lists all Parties for which data are available, what is known about their stockpiles, and the year for which the stockpile was reported.

Table 2-2 CFCs stockpiles reported by Parties

| Parties | Stockpile (tonnes) | Year |
|--|--------------------|------|
| Argentina | 5 | 2012 |
| China | 477 | 2013 |
| India | ~200 | 2011 |
| Mexico | 18 | 2014 |
| Pakistan | 12 | 2012 |
| Russian Federation ⁵⁰ | 69 | 2013 |
| United States (CFC MDI manufacturers' stockpiles) | 169 | 2010 |
| United States (Boehringer Ingelheim/Honeywell stockpile) | 280 | 2013 |

Some Parties reported that many CFC MDI manufacturers were gradually depleting their own stocks (United States), and other country's CFC MDI manufacturers were believed to be doing the same (India). Some Parties are still manufacturing CFC MDIs and/or using CFC stockpiles as strategic reserves (China and possibly Russia⁵⁰). Some CFCs are surplus and may need to be destroyed (Mexico, United States – Boehringer Ingelheim/Honeywell). Having information on stockpiles allows Parties to track the management and deployment of stockpile until depleted. Judicious management of these stockpiles may also avoid the need for new CFC manufacture. However, in practice, it has proved difficult to transfer stockpiles of pharmaceutical-grade CFCs between Parties and/or between companies due to complex commercial, technical, regulatory and logistical reasons. There are only a few examples of stockpile transfers that have occurred successfully. There are other examples where commercial negotiations failed.

2.5.4 HFC consumption for MDI manufacture

Based on HFC manufacturing industry estimates⁵¹, approximately 630 million HFC based MDIs (with an average 15g/MDI) are currently manufactured annually worldwide, using approximately 9,400 tonnes of HFCs in 2014. HFC-134a makes up the major proportion of MDI manufacture (~8900 tonnes in 2014), with HFC-227ea accounting for about 5 per cent (~480 tonnes in 2014). This corresponds to direct emissions with a climate impact of approximately 0.013 Gtonnes CO₂-equivalent, which is about 3 per cent of global GWP-weighted emissions of HFCs used as ODS replacements in 2014⁵². HFC emissions from MDIs are estimated as about 0.03 per cent of annual global greenhouse gas emissions⁵³. HFC emissions from MDIs were estimated previously as 0.02-0.05 per cent of annual global greenhouse gas emissions by 2010 in an earlier study by Price *et al*⁵⁴.

⁵⁰ Recent information from the Russian Federation indicates CFC MDIs were not manufactured in 2014, although CFCs were acquired and added to stockpile (175.2 tonnes at the end of 2014).

⁵¹ T.J. Noakes, Mexichem Fluor, United Kingdom, personal communications, 2014. HFC consumption data derived from this HFC industry source differs from that derived from IMS Health market data. For the purposes of this report, the “top-down” industry data has been used to derive HFC consumption.

⁵² *Assessment for Decision-Makers: Scientific Assessment of Ozone Depletion: 2014*, World Meteorological Organization, Global Ozone Research and Monitoring Project—Report No. 56, Geneva, Switzerland, 2014. Global GWP-weighted emissions of HFCs used as ODS replacements (0.5 Gt CO₂-equivalent) specifically exclude HFC-23 emissions. These emissions are currently growing at a rate of about 7% per year and are projected to continue to grow.

⁵³ WRI, CAIT 2.0. 2014. Climate Analysis Indicators Tool: WRI's Climate Data Explorer. Washington, DC: World Resources Institute. <http://cait2.wri.org>. Accessed February 2014. Total greenhouse gas emissions (~43

Under a business as usual model, global HFC demand in MDI manufacture (HFCs -134a and -227ea) has been estimated by industry for the period to 2025 (Figure 2-5). It is worthwhile noting that accuracy is likely to decline from 2018 onwards. This modelling does not allow, other than in the flattening of demand for HFC-227ea due to the European Union F-gas regulations⁵⁵, for any other regulatory impact. Neither does it allow for the on-going trend towards smaller metering chambers⁵⁶, which may have a net effect of a 25-30 per cent reduction in future HFC demand. Nevertheless, based on these predictions, global HFC demand for MDI manufacture is estimated to increase annually by 2 per cent over the period.

HFC-134a accounts for 95 per cent or more of total global demand for MDI manufacture over the period, with annual growth of 2 per cent. Global HFC-227ea demand is likely to remain flat, with its proportion of total HFC demand declining slightly over time to less than 5 per cent. As such, HFC-227ea MDIs are likely to remain niche products. They are unlikely to expand significantly beyond current products due to expected increasing HFC-227ea prices and uncertainty in the long-term viability of the industrial HFC-227ea business as a result of HFC regulations.

Under a business as usual model, for the period 2014 to 2025, the total cumulative HFC consumption in MDI manufacture is estimated as 124,500 tonnes (119,000 tonnes HFC-134a; 5,500 tonnes HFC-227ea), corresponding to direct emissions with a climate impact of approximately 0.173 Gtonnes CO₂-equivalent, which would be significantly less than the climate impact of CFC MDIs had they not been replaced.

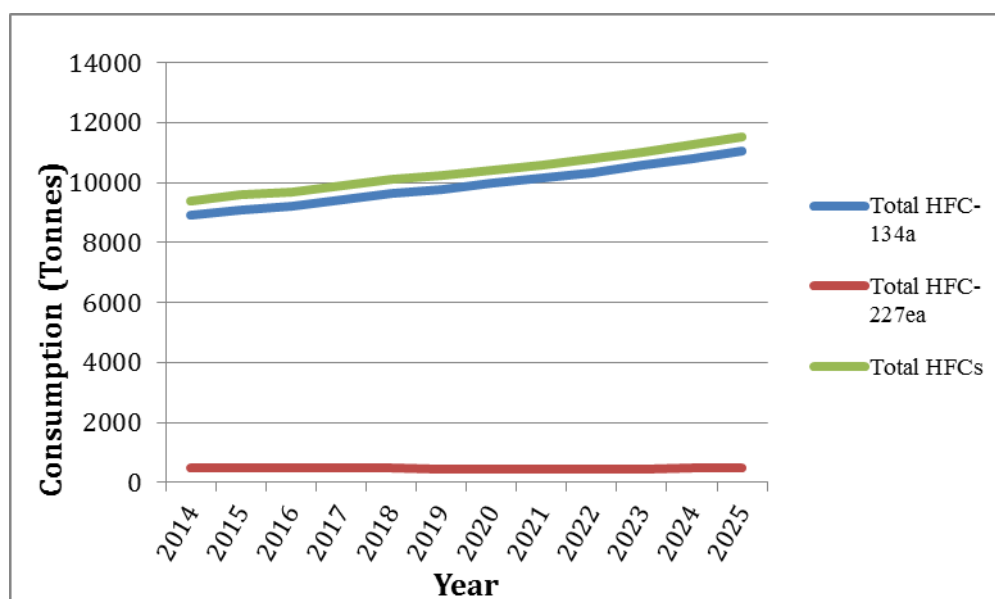
GtCO₂-equivalent in 2011) exclude land use change and forestry. Total HFC consumption in MDIs was estimated based on data from Noakes⁵¹ for 2011, and used as a surrogate for emissions. GWP-weighted HFC emissions from MDIs in 2011 are estimated as 0.011 GtCO₂-equivalent.

⁵⁴ D. Price, E. Valovirta, and J. Fischer, The Importance of preserving choice in inhalation therapy: the CFC transition and beyond, *Journal of Drug Assessment* 2004; 7: 45-61.

⁵⁵ The European Union F-gas regulations prescribe, *inter alia*, reductions in HFCs permitted on the market in the European Union from 2015 onwards. Reductions will apply to MDIs until 2018 onwards, after which MDIs are currently exempted from on-going HFC reductions.

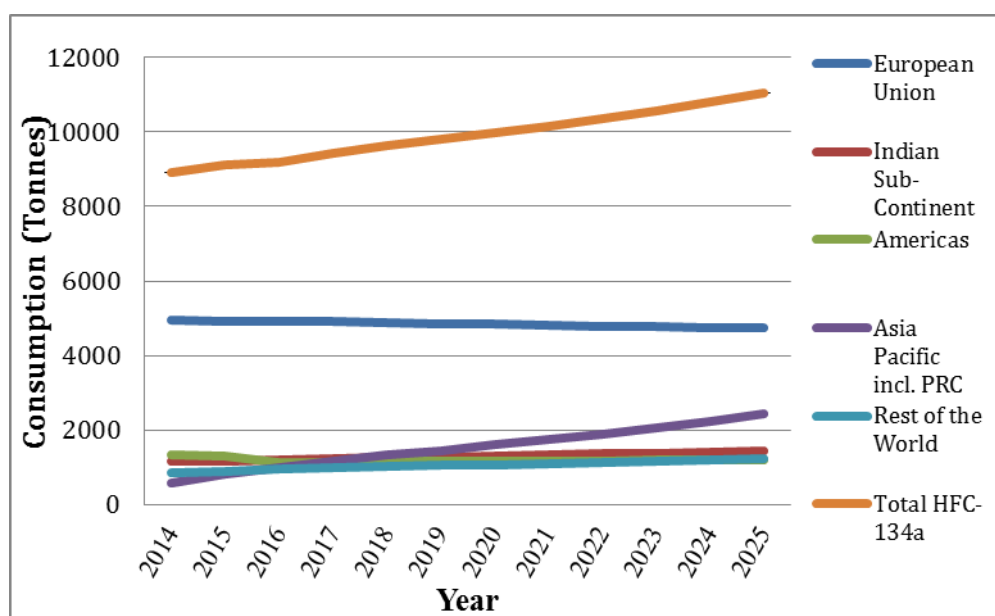
⁵⁶ Some companies have reduced the size of the metering values on the canisters (to ~25 or 30µl) from an historically larger size (50-65µl) to deliver the same dose, allowing a reduction in the amount of propellant used per can and per dose. Many companies have also reduced the number of doses in each inhaler (from 200 to 120), which reduces the amount of propellant used per can. Both of these changes will increase the number of inhalers made per tonne of HFCs.

Figure 2-5 Global HFC demand for MDI manufacture, 2014-2025⁵⁷



Regional demand for HFC-134a in MDI manufacture is variable, with demand in the European Union and the Americas flat or declining, and demand increasing in the Indian sub-continent (India, Bangladesh and Pakistan), Asia Pacific (including China), and the rest of the world (including Russian Federation and the Middle East). Figure 2-6 shows the various trends. Major growth in HFC-134a MDI manufacture is expected to occur in China, with HFC-134a demand in the Asia Pacific region estimated to increase three-fold by 2025. The majority of MDI exports occur from the European Union, China, and India.

Figure 2-6 Regional HFC-134a demand for MDI manufacture, 2014-2025



⁵⁷ Based on data provided by T.J. Noakes, Mexichem Fluor, United Kingdom, personal communications, 2014.

3 Other Medical Aerosols

3.1 Background

This section describes the medical aerosol products that are not metered dose inhalers (MDIs) for the treatment of asthma and chronic obstructive pulmonary disease (COPD), identifies the propellants available, and estimates the order of magnitude of the volumes of hydrochlorofluorocarbons (HCFCs) and hydrofluorocarbons (HFCs) they might use. In most cases, the device does not contain a metering mechanism and so the amount of material dispensed is entirely dependent on the duration for which the spray is activated.

The term aerosol product describes a product *pressurized* with a propellant that expels its content from a canister through a nozzle. In many cases the product delivered is not a true aerosol⁵⁸, for instance foams and gels are dispensed in products considered aerosols. The wide variety of articles that are sold as aerosol products has been made possible by the development of different containers, valves and propellants.

Containers can be made of tin plate, aluminium, coated glass and even plastic. Valves and actuators can be designed to deliver different types of products at different rates and distances. Propellants can be compressed gases (nitrogen, nitrous oxide, carbon dioxide), or can be liquefied gases that are a liquid inside the pressurized container; these liquefied gas propellants include chlorofluorocarbons (CFCs). CFC propellants were replaced mostly by hydrocarbons (butane, propane, isobutane, dimethyl ether (DME)), but also by HCFCs and HFCs, in specific applications. For treatments where there is a significant risk of inhalation into the respiratory tract, HFCs are preferred, as their safety is well proven through use in MDIs. In addition, propane or isobutane (and their blends) tend to cause an "oily" or slightly stinging taste.

The versatility of the aerosol package has enabled the marketing of a wide variety of products that are sold worldwide. Total production is above 14 billion cans per year. The economies of scale have resulted in very competitive packaging and production costs, and as a result consumers are familiar with aerosol products.

CFCs in MDIs used to treat asthma and COPD presented a significant challenge to the Montreal Protocol and forced the pharmaceutical industry to totally redesign MDIs to use HFC propellants, DPIs or other devices. However, there are many other medical aerosol products that did not require Essential Use Exemptions and were reformulated to use propellants that do not damage the ozone layer. Their volumes of production can be estimated from the reports of Aerosol Associations that list production figures by product category in their regions or countries. In other cases, the products were not reformulated as an aerosol, but instead replaced with aqueous sprays that are created by a mechanical pumping action.

3.2 Inhalers and non-inhalation medical aerosols

Medical aerosols are used to deliver topical medication mostly onto the skin, but also to the mouth, and other body cavities. Aerosols products are an efficient means of dispensing medication in finely dispersed droplets, solutions, foams, gels, and powders. The group of medical aerosols can be expanded to include some products that are not sprayed directly to the body, such as sterile saline solutions for soft contact lenses.

⁵⁸ An aerosol is a colloid of fine solid particles or liquid droplets in air or another gas.

The majority of aerosol products are dispensed with valves that deliver product while they are depressed, but for deposition of an active ingredient in the lungs it is important that the amount of product delivered is carefully controlled, hence inhalers use valves designed to meter a specific dose or volume to ensure constant delivery with every actuation or puff. This is why these products are commonly known as metered dose inhalers or MDIs. There are other metered dose aerosol products that are not inhalers, for instance some topical sprays for the throat and mouth, and sublingual nitroglycerin used to treat episodes of angina (chest pain) in people who have coronary artery disease.

When the Montreal Protocol had to identify critical uses for CFCs, it differentiated oral inhalation from nasal inhalation. Oral inhalation allows the delivery of drugs through the mouth directly to the airways. The precise particle size control required to target the drug to the relevant part of the airway is only possible when the aerosol puff travels unhindered through the oropharyngeal cavity. MDIs for the treatment of asthma and COPD are oral inhalers.

Administration of a medicine to the nose with an aerosol is not very different to the use of drops or ointments because the particle size is not important for therapeutic efficacy. Nasal aerosol products using HFC-134a are commercialized and they offer the benefits of hermetic containment, and precise dosing when deposited into the nose. Aqueous *non-pressurized* formulations (“sprays”) are also used for the treatment of rhinitis; although by definition these “sprays” are not aerosol products, they still deliver a metered dose to the nose. They use a manual pumping action, and so the dose is discrete and related to each stroke of the pump. Aqueous sprays and drops are well-established not-in-kind alternatives to nasal aerosol products. Aqueous formulations in general and other not-in-kind alternatives, such as creams, can also be used in many medical aerosol applications and are not considered further here when discussing (*pressurised*) aerosol alternatives to the use of ozone-depleting substance (ODS) propellants, unless specified.

The other medical aerosols that are not inhalers cover a wide range of uses that go from the simple numbing of pain by the cold produced when a low temperature boiling solvent evaporates over the skin, to the dosage of corticosteroids for the treatment of colitis. It is also likely that some traditional Chinese medicines are also administered using aerosol products. Therefore, it is impossible to make an all-inclusive list of medical products that are not oral inhalers, but the following section presents the most common applications of this group of products.

There are also aerosol products that are associated with medical use, such as lubricants for dentist’s drills or fixatives for microscopy. It is likely that there are many such uses for medical equipment that are hard to track and represent low volume niche markets. These products are not covered in this report.

The availability and number of different medical aerosol products varies within countries and regions, and is closely related to the development of the local aerosol industries. Similarly, the degree to which these products are regulated depends on the country, on the active ingredient, and the specific product application. Sunscreen sprays, for instance, are regulated by the FDA in the United States when they claim protection against UV radiation, but will not be considered as part of the medical sector in this report even though they will be listed in some tables for illustrative purposes.

3.3 Other medical aerosol products and their propellants

The availability of other medical aerosol products that are not oral inhalers seems to be specific to each country. Inquiries made to MTOC members identified uses in Argentina, Australia, Canada, China, Japan, the European Union and other European countries, Mexico, the United States and Venezuela. Apparently these products are rare in most of Africa, the Indian subcontinent and the

Middle East. Table 3-1 below lists the main medical aerosols other than MDIs for oral inhalation and the propellants they commonly use after CFC phase-out⁵⁹ (non-pressurised not-in-kind alternatives to aerosols, such as aqueous sprays are excluded).

Table 3-1 Other medical aerosols and their propellants

| Product | Propellant |
|---|---|
| Metered-dose corticosteroid nasal sprays | HFC-134a |
| Throat / mouth topical sprays (disinfectants, anti-inflammatories, anaesthetics)* | HFC-134a, Nitrogen |
| Anaesthetic, analgesic, calamine sprays for minor blunt injury or itches** | Propane /butane blends, DME, CO ₂ HFCs |
| Cut or wound sprays | A-46*** |
| Sprays to prevent bedsores | A-46*** |
| Sprays for diaper rash for babies | HFC-152a |
| Foot sprays | A-46*** |
| Other anti-fungal products | A-46***, DME |
| Vaginal hygiene sprays | A-46 or higher pressure |
| Nitroglycerin sublingual sprays | HFC-152a, HFC-134a |
| Sterile saline solutions | Nitrogen |
| Rectal foams for treatment of colitis | A-46 or lower pressure |
| Foams for scalp hair loss | A-46 or lower pressure |
| Sunscreen sprays | A-46***, DME, HFC-152a |

* In the United States and other countries where use of CFCs from pre-1996 stockpiles is not prohibited, some products still are filled with CFCs; these are being phased out as final revisions to US regulations are underway to address remaining products.

⁵⁹ Dr. M. A. Johnsen and Geno Nardini, personal communications, 2014, and input by MTOC experts.

** In Article 5 Parties where the use of HCFCs in aerosols is not prohibited, the HCFC-141b cooling effect as it evaporates is used to numb pain, but the same result can be achieved with hydrocarbon blends. It is unlikely that other HCFCs are used in other medical aerosols. In the United States, sale and distribution of aerosols using HCFCs was banned in 1994 with few exceptions.

*** A-46 is the name given in the United States to a blend of hydrocarbons that may contain propane, normal butane and isobutane and has a pressure of 46 pounds per square inch gauge (317 kPa) at 130°F (54.4°C). Other hydrocarbon blends can also be used.

Medical aerosol products for use on or near nose or mouth, and also on babies, tend to use HFCs or nitrogen. All other pressurised medical aerosol products tend to use propane / butane mixtures or DME and compressed gases to a lesser extent. Many external factors affect the selection of a given propellant, such as regulatory approval of products, Volatile Organic Compounds (VOC) controls, and supplier controls of HFC-134a, among others. Table 3-1 provides for a qualitative perspective of aerosol propellant options.

3.4 Impact of regulations

There are still some residual uses of ODS in the sector of other medical aerosols. These uses are not in contravention of the Montreal Protocol (that regulates production of new ODS) and remain where no specific regulations to ban the use of ODS as aerosol propellants have been enacted. It is likely that the stockpiles from which these ODS are drawn will be depleted soon.

In most countries, there are no rules or regulations that require the use of specific propellants for medical aerosols. A change in propellant for products approved for a medical use (like the nasal MDIs) would necessitate a new development programme and regulatory approval, much like that required for MDIs for asthma and COPD. In the United States some of these products, whilst regulated by FDA, may not require prior approval following the over-the-counter (OTC) monograph system (also known as “grandfather clause” for products with a long time of use), provided they do not change propellant. In Japan, propellants for medical aerosols are limited by the Japanese pharmacopoeia codex for additives, and other official compendia. If a pharmaceutical company uses a new propellant in an aerosol product, necessary toxicity data on both propellant and the aerosol product are required for registration.

In locations like California, stringent VOC controls will have an impact on the choice of propellant, although up until now medical products have been largely exempted. Further, manufacturers of HFC-134a exert a certain control on where their propellant can be used, and they can refuse to sell HFC-134a for some applications because of global warming concerns. The US EPA is currently considering which aerosol product types may continue to use HFC-134a.

All aerosols in the European Union are regulated, especially with regard to flammability, under Aerosol Dispensers Directive 75/324/EEC and subsequent amendments. The European Aerosol Federation (FEA) has adopted a code of conduct that restricts the use of HFC propellants which should only be “...used in the aerosol industry in applications where there are:

- *No other safe, practical, economic or environmentally acceptable alternatives.*

- *No other safe solution: where the alternatives would represent a serious health and safety risk for the users:*

- a) *Where the presence of potential ignition sources is unavoidable;*
- b) *Where the application has to be performed in confined spaces where sufficient ventilation cannot be guaranteed;*
- c) *Where quantities applied could create an explosive gas mixture;*
- d) *Where national or international regulations impose non-flammable requirements;*
- e) *Where products have to be applied on hot surfaces;*

- f) Where products have to be applied in areas susceptible to static electricity;
- g) Where the product has to be applied on equipment under voltage.

- No other practical alternatives: where the alternative solution would present significant operational issues e.g. availability of air-compressors or high pressure cylinders on difficult to reach places.

-No other economic alternatives: where the alternative product would be too expensive or only available in very limited quantities.

-No other environmentally acceptable alternative: where new demands are made for products currently on the market with respect to their impact on the environment, particularly as far as their VOC content is concerned.

*The only use of HFC in the aerosol industry should be intended for applications which fit within the above-mentioned conditions. Preference would be given to substances with a lower global warming potential, where this was compatible with the desired objective and safety considerations.*⁶⁰

HFCs are used in the aerosol industry as propellants in MDIs for the treatment of asthma/COPD, in some other medical aerosols, and in some industrial products where flammability is a major concern. Although the volume of HFC used in aerosol products is minor compared with refrigeration or foam blowing, propellant use is totally emissive.

3.5 Production figures and consumption estimates

Although aerosol associations provide regional production figures for the different aerosol categories, there is not a single classification that has been adopted globally; therefore any analysis has to be interpreted with caution. Furthermore, products can be quite different in size, typically ranging anywhere from 10 to 300 ml, so production units cannot be readily translated to volumes of propellant. In 2010, global HFC consumption for all aerosol products was estimated at 54 million tonnes CO₂-equivalent. Seventy-six per cent of this amount was used for medical aerosols. The total amount of HFCs used for aerosols was equivalent to 5 per cent of global HFC consumption in 2010.⁶¹ Nonetheless, the use of HFCs is considered by the US aerosol industry to be flat to declining⁶² and it is likely that global figures are growing very slowly, if at all.

For North America, the Consumer Specialty Products Association CSPA prepares the Aerosol Pressurized Products Survey every year that reports aerosol production classified in eight categories, one of which is Personal Products. Personal Products includes eight subcategories, of which subcategory 404 is defined as “Medicinal and Pharmaceutical (vaporizers, fungicides, burn treatments, antiseptics, contraceptives, saline, etc.) (not inhalers)”. Subcategory 407 includes Sun Care products. The specific instructions for the survey questionnaire used to prepare the report say “Do not report medical inhalers in Subcategory 404; if you would like to report them in this or future surveys, inform CSPA.”

FEA reports on the European Aerosol Production, but in its report pharmaceutical and veterinary products are in one category. This report also provides aerosol production estimates for the rest of the

⁶⁰ http://www.aerosol.org/uploads/Modules/Publications/20140422-fea-code-of-practice-on-hfc-use-in-aerosols_update.pdf. Accessed January 2015.

⁶¹ U.S. Environmental Protection Agency, EPA 430-F-13-013, www.epa.gov, April 2013.

⁶² Market Characterization of the U.S. Aerosols Industry. ICF International May 2014 for the Stratospheric Protection Division, Office of Air and Radiation, US EPA.

world. The British Aerosol Manufacturers' Association (BAMA) provides production figures that separately specify medical aerosols excluding inhalers, and suntan/bronzing products, whereas in the case of the Aerosol Industry Association of Japan (AIJA) it is not clear whether inhalers or sunscreen products are included as medicinal.

These figures can be summarized in Table 3-2.

Table 3-2 Regional production volumes for different aerosol categories

| Country | Year | Category | Units Filled |
|----------------|-------------|-----------------|---------------------|
| Japan | 2011 | Medicinal | 12,532,000 |
| United States | 2013 | Medicinal | 50,957,000 |
| United States | 2013 | Sunscreen | 79,916,000 |
| United Kingdom | 2013 | Medical | 21,000,000 |
| United Kingdom | 2013 | Suntan/bronzing | 2,200,000 |

Numbers for the production of medical aerosols have been relatively stable in the last years, specifically in the case of Japan, the number has been around 12 million units since 2007, and therefore it is not unreasonable to assume that production there remains unchanged. Sunscreen products are listed to illustrate the relative size of their production. Sunscreens largely use hydrocarbon propellants.

MTOC is aware that medical aerosol products are common in China where the production has been growing rapidly. For the group of other medical aerosols, a production between 120 and 130 million units was given for 2014. This number is large when compared to the total 1.5 billion aerosols produced in China in 2013.

For the countries listed in Table 3-2, it is also possible to compare the production figures of other medical aerosols to their industry totals in order to calculate a market share as shown in

Table 3-3.

Table 3-3 Proportion of other medical aerosols of total aerosol production by region

| Country | Year | Total Aerosol Production units | Medical as a percentage of Production |
|-------------------|------|--------------------------------|---------------------------------------|
| Japan | 2013 | 509,740,000 | 2.46 |
| United States | 2013 | 3,767,567,000 | 1.35 |
| United Kingdom | 2013 | 1,466,500,000 | 1.43 |
| World Production* | 2013 | 14,000,000,000 | |

*The FEA report provides production figures for Argentina, Brazil, China, Europe, Japan, Mexico, South Africa and the United States; the total of these figures is 13,654,680,000 units. Since the production of ASEAN, Indian subcontinent and Middle East countries are not included in the calculation above, the figure of 14 billion is probably an underestimate that is in agreement with other aerosol market analysis⁶³.

It is quite likely that in the case of Japan the numbers for medical aerosols might include inhalers or sunscreen products, hence the slightly larger percentage of medical products. However, it is safe to assume that the percentage of medical products will be smaller in most other countries, particularly in Article 5 Parties, where the insecticide sector is very large and where products tend to be less specialized because of the smaller markets. Assuming that, globally, other medical aerosols represent around 1 per cent of total production, the resulting estimate for the sector would be approximately 250-300 million cans per year (the one per cent figure is calculated by noting that Europe, Japan, and the United States represent close to 70 per cent of the world aerosol production; multiplying 70 per cent times a market share of 1.4 per cent of other medical aerosols results in an estimate of at least 1 per cent share of other medical aerosols from total production).

This estimate has been derived using CSPA and BAMA figures that exclude all inhalers. However, nasal inhalers, which for this report are a part of other medical aerosols that are not oral inhalers, are not a large market segment (probably limited to the United States) and it is very likely that their production is already accounted in the industry numbers for MDIs. Regardless of this limitation, if one compares the estimated figure of 630 million HFC MDIs currently produced worldwide with the estimated 250-300 million for other medical aerosols, it becomes clear that inhalers are the main medical application for aerosol products.

Trying to estimate the amount of ODS that are used in other medical aerosols is even more difficult than estimating total production of the sector. As it was mentioned above, small productions of aerosol products using CFCs and HCFCs have been reported for some products like topical anaesthetic sprays and coolants to numb pain respectively. HCFC use is about 100 ODP tonnes or less worldwide (HCFC-22 and HCFC-141b), with the majority used in China. ODS-free alternatives are available for all other medical aerosols.

⁶³ <http://www.grandviewresearch.com/industry-analysis/aerosol-market> Aerosol Market Analysis By Application (Personal Care, Household, Paint, Medical) And Segment Forecasts To 2020. Published December 2014, ISBN Code: 978-1-68038-288-4.

With regard to HFCs an educated guess is that less than 10 per cent of all other medical aerosols use HFC propellants, close to 25-30 million cans per year, of which the majority would be for nasal inhalation, throat topical medication, and nitroglycerin sublingual application. The average HFC content per can is estimated around 30 grams for a total HFC requirement of less than 1,000 tonnes per year.

This consumption is not likely to grow in the near future, since production figures from CSPA, BAMA and AIAJ reflect a mature market. It seems possible to find alternatives to the use of HFCs either by the use of nitrogen or not-in-kind metered pumps. Registration of new HFC-free formulations will be costly and require time. The Montreal Protocol considered none of these uses essential.

4 Sterilants

4.1 Background

The provision of good quality health services requires effective disinfection and/or sterilization of health care products to prevent transmission of infection. Sterilization, in particular, 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 facilities ranging from industrial settings with large outputs of similar items (such as manufacturers of sterile medical devices such as single-use syringes or specialist contractors offering a sterilization service to medical device manufacturers) and dissimilar items (such as procedure packs and kits), to smaller facilities including hospitals with much smaller outputs but great diversity of items. Process requirements for these two settings are similar but the types of sterilization processes used and the challenges presented to assuring sterility differ.

There is a range of commercially available sterilization methods including: heat (moist heat or dry heat), ionizing radiation (such as gamma, electron beam, x-ray radiation), alkylating processes (such as ethylene oxide (EO), formaldehyde) and oxidative processes (including hydrogen peroxide gas, gas plasma systems, liquid or gaseous peracetic acid, and ozone). Further sterilization methods based on these and other chemicals are now available or are under investigation for commercialization.

Sterilization using humidified EO under controlled cycle conditions is used to treat heat and moisture sensitive medical devices, which are packaged in breathable materials that maintain sterility once the product is removed from the sterilization chamber. The EO gas processes can be used to penetrate many types of packaging materials and internal areas of medical devices, destroy micro-organisms and then diffuse away from the product through the package. Following exposure, adequate aeration is essential after processing to achieve acceptable levels of residues. EO is toxic, mutagenic, carcinogenic, flammable and explosive, and increasingly more stringent regulations are applied to protect the environment and ensure worker safety. 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, and its use growing in the industrial sector, is evidence that for 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 (CO₂) 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 Parties, but this also will be phased out over time. Hydrofluorocarbons (HFCs) were investigated as alternative replacement diluents but were not widely adopted for technical reasons and the environmental impact of the use of HFCs.

Some hospitals and other healthcare facilities 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 under controlled conditions and thereby reducing sterilant consumption. Furthermore, improvements in validation practices have enabled the use of processes at lower EO concentrations, reducing sterilant usage, and decreasing levels of residues in products. It is common to use abatement equipment in conjunction with an EO sterilizer in order to reduce emissions to acceptable levels.

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 Parties, and in many Article 5 Parties. Although it is difficult to be certain, global total use of CFCs for this application is believed to be 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 is less than 500-700 metric tonnes, which amounts to less than 25 ODP tonnes worldwide. EO/HCFC use in Article 5 Parties is estimated to be less than 200-400 tonnes. EO/HCFC use has been significantly reduced by using less gas per sterilizer load, 100 per cent ethylene oxide, and by hospital conversion to other technologies.

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 was phased out on 31 December 2014⁶⁴. 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 applied until 31 December 2014. It was expected that only a small amount of HCFC-22 would be used for sterilant applications under this exception. There are very few reasons, excluding financial limitations, for not converting sterilization equipment in hospitals. Medical device manufacturers that use EO/HCFC are also converting to alternatives, with the major providers in the United States now exclusively using 100 per cent EO-based processes.

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

The complete phase-out of HCFCs in sterilization uses is readily achievable in Article 5 Parties to meet the Montreal Protocol schedule. In addition, the useful lifetime of existing EO/HCFC sterilizers is about 20 years when well maintained. Therefore, by 2030, current sterilizers 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.

4.3 Available options for replacing ozone-depleting substances

Methods for sterilization of medical devices had traditionally 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. Over time, these differences have become less due to international standardization and harmonization.

An effective infection control strategy requires the availability of sterile medical devices. Validation of sterilization processes is important to ensure product safety and functionality including the attainment of sterility, lack of toxicity, and avoidance of material compatibility problems. No single sterilant or sterilization process is compatible with the range of potential products, be they designed for single or multiple (reusable) use in healthcare facilities. The nature and complexity of items and

⁶⁴ 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).

loads to be sterilized will vary according to the user requirements. Some items are more robust than others with regard to pressure, temperature, moisture and radiation. Therefore a number of different processes are available for use and each will offer specific advantages depending on the need.

Opportunities and technologies that can be considered to avoid processes using ozone-depleting EO/HCFC blends include: use of alternative heat-sterilizable devices, use of single-use devices, use of 100 per cent EO sterilization processes, and a range of other methods that will sterilize most of the heat sensitive medical devices used in healthcare or industrial settings. Alternative low temperature processes for disinfection and particularly sterilization that have been commercialised include hydrogen peroxide gas (used with or without the generation of plasma during the process), humidified ozone gas, nitrogen dioxide gas, liquid phase peracetic acid formulation and low temperature steam-formaldehyde processes. Other 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 do not represent an exhaustive list of such developments. This summary updates information included in the 2010 *Assessment Report of the Medical Technical Options Committee*⁶⁵.

4.3.1 Heat

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

Moist heat (e.g. steam) – This process is non-toxic and relatively safe. Pressurized steam is a particularly effective and well-used sterilization method. Available sterilizing equipment ranges from small self-contained pressure vessels to large installations requiring supporting utilities. Devices must be able to tolerate a temperature greater than 115°C, very high moisture levels and changes in pressure in order to use the process.

4.3.2 Radiation

Ionising radiation – Ionising radiations (gamma rays, accelerated electrons, X-rays) are widely used for sterilization, but only in large, industrial facilities; governments operate these facilities in many Article 5 Parties. Operation of ionising radiation facilities is not generally appropriate for hospitals or centralised sterilization facilities supplying hospitals, due to complexity, costs and safety implications. 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 used as radiation sources. Systems using low energy electron beams have been introduced for in-line treatment of certain materials such as those being introduced into the aseptic processing of pharmaceuticals, thereby reducing the need for treatment with gaseous sterilants. *X-ray* sterilization equipment and facilities are also commercially available on a limited basis.

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

⁶⁵ 2010 Report of the UNEP Medical Technical Options Committee, 2010 Assessment Report.

4.3.3 Alkylating agents

Aldehydes – Formaldehyde, in combination with steam at sub-atmospheric pressure, is used mainly in Europe and parts of South America for materials that are able to withstand temperatures of up to 80-85°C and high levels of moisture, although uses at 60-65°C have also been reported. Sterilization processes include humidification, formaldehyde exposure and aeration. Formaldehyde is toxic and a suspected carcinogen, and this technology has not been widely accepted in many countries due to these concerns. Other aldehydes, such as glutaraldehyde and ortho-phthalaldehyde (OPA), are widely used for high level disinfection purposes, but the use of these is also decreasing due to concerns with operator safety and bacterial resistance.

100 per cent EO – Despite being a flammable and hazardous gas, 100 per cent EO can be effectively used when proper safety requirements are met (such as installation requirements, ventilation, personal protection equipment, etc.). Equipment ranges from large industrial sterilizers to small sterilizers used in healthcare facilities. On an industrial scale, the use of deep vacuum cycles and/or nitrogen may also be used or added to the sterilizer chamber during the sterilization process to render the process non-flammable. 100 per cent EO processes typically operate at sub-atmospheric pressures to ensure adequate penetration of EO. The increased safety measures employed when using 100 per cent EO, and updated technologies to limit worker exposure and environmental issues, have been major factors in the increased use and resurgence of pure EO in the industrial marketplace.

Blends of EO and CO₂ – Carbon dioxide (CO₂) is used to produce flammable and non-flammable mixtures with EO. Those containing more than 8.5 per cent by weight EO are flammable. In the past, EO/CO₂ mixes were generally not used to replace other non-flammable mixes, but more recently, due to the declining use of other EO blends, there is a renewed interest in considering CO₂ blends. Sterilant container pressures are about ten times higher than for 12/88 EO/CFC mixtures, and chamber pressures are about three times higher. Additionally, processes include phases operating both below atmospheric pressure (to ensure penetration of EO) and pressure in excess of 3 atmospheres (to achieve the required EO concentration⁶⁶). Use of EO/CO₂ blends has other disadvantages, such as composition changes during the use of a single tank or cylinder, potential for increased EO polymerization, and compatibility and corrosion problems caused by the acidity of CO₂.

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. 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 was permitted, but by 2010 no new HCFC blends could be sold. Reclamation and reuse of HCFCs was permitted until the end of 2014. In the United States, 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 initially tested in the United States. Technical problems were identified that would require re-engineering, perhaps new equipment, in addition to process revalidation. 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 rebuilt. New HFC blends have not been broadly adopted or used worldwide, although some sterilization service providers in Asia continue to explore the potential application. In the European Union, there are restrictions on certain uses of HFCs, for

⁶⁶ These are also necessary for blends of EO/HCFCs, and blends of EO/HFCs.

example as refrigerants. The use of HFCs in sterilizing equipment is not currently explicitly excluded. One company in Poland supplies EO/HFC-134a (5.6 per cent by weight EO and 94.4 per cent HFC-134a) for use in hospital sterilizers⁶⁷. EO/HFC blends have also been investigated to replace EO/methyl bromide blends to fumigate, *inter alia*, archives and antiquities⁶⁸.

4.3.4 Oxidising agents

Hydrogen peroxide gas – Sterilization processes based on hydrogen peroxide gas are commercially available. These are vacuum-based processes that use hydrogen peroxide gas for sterilization. Some of these systems use plasma generation during the process for the removal of residual gas/liquid from the load. Low energy plasma may also be used for heating or gas generation purposes, depending on the specific sterilizer design. A wide variety of sterilization processes are in commercial use with many sterilizers sold worldwide, mostly to healthcare facilities, and these systems continue to be used extensively. They offer shorter cycle times in comparison to traditional EO systems, depending on the sterilization cycle design.

Liquid peracetic acid – Available equipment uses cassettes in which items to be sterilized (e.g. endoscopes) are placed. The cassette is designed to provide a chamber for exposure to a peracetic acid containing solution (with dedicated flow to internal components) for sterilization, followed by rinsing with sterile (or extensively treated) water, followed by draining. Sterilized items are not, to date, packaged for storage. It is recommended that they be used immediately after removal from the cassette in order to ensure safety at point of use. Gaseous peracetic acid systems have also been described.

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 that 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 – One process operating at less than 30°C has become recently available for use in hospitals, but, to date, has had limited commercial success. Ozone is generated within the sterilizer from an oxygen source. The humidified process must be carefully controlled to ensure efficacy, and it can also 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.

Chlorine dioxide – A system for sterilizing medical devices using humidified chlorine dioxide was initially developed and patented but was not successful commercially. Chlorine dioxide is generated in situ, for example from sodium chlorite and chlorine gas in a nitrogen carrier. Gaseous chlorine

⁶⁷ <http://www.sterylgez.com.pl/en/main.php?k0=PRODUCTS&k1=GS-1z>. Accessed January 2015.

⁶⁸ Methyl bromide or mixtures of methyl bromide and EO are used for de-infestation 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.

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 and now developed, but have had limited commercial success to date.

Supercritical carbon dioxide – Carbon dioxide in a supercritical state⁶⁹ has been reported as having activity against vegetative micro-organisms. However it has little activity against 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 at this time.

4.4 Conclusions

Sterilization is an important process in the provision of good quality healthcare 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. It is legal requirement in pharmaceutical and medical devices industries that any change in manufacturing processes, including sterilization, must be validated using appropriate guidelines before implementation.

CFC-12 use in the sterilization sector has been phased out in non-Article 5 Parties, and in many Article 5 Parties. EO/HCFC blends have small ozone depletion potentials (ODP) (0.03) and have been used as virtual drop-in replacements for EO/CFC blends. There are a number of viable ODS-free alternatives, based on high or low temperature technologies. Many of these alternative technologies provided significant advances, such as better safety profiles and turn-around times, and reduced cost per cycle. The complete phase-out of HCFCs in sterilization uses to meet the Montreal Protocol schedule is readily achievable.

⁶⁹ 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.

5 MTOC Membership Information

Medical Technical Options Committee (MTOC)

| Co-chairs | Affiliation | Country |
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| You Yizhong | Journal of Aerosol Communication | China |