The International Pharmaceutical Aerosol Consortium (IPAC) is an association of companies which manufacture products for treating respiratory diseases, including metered dose inhalers (MDIs). One of IPAC’s purposes is to ensure that the vital role of the MDI is fully appreciated and accounted for in the implementation of the Montreal Protocol on Substances that Deplete the Ozone Layer and the United Nations Framework Convention on Climate Change. The members of IPAC that sponsored this Paper are AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Chiesi Farmaceutici; Glaxo Wellcome; Norton Healthcare Ltd.; Rhône-Poulenc Rorer Inc.; and 3M Pharmaceuticals.

In October 1995, IPAC established an Advisory Panel on HFC MDIs. The Panel was charged with the preparation of a document that would explain the vital role of the HFC MDI. The first edition of this Paper, published in April 1997, was the result of the Panel’s effort. The Chairmen of the Panel were Dr. William Gore and Dr. Ian Tansley. Dr. Gore is the Director of Analytical Sciences at Boehringer Ingelheim Pharmaceuticals, Inc. Dr. Tansley, now retired, was Senior Technical Manager at 3M Health Care Ltd. Other members of the Advisory Panel were Dr. Joel Sequeira, Senior Associate Director, Schering-Plough Research Institute; Dr. Aaron Taub, Consultant, Rhône-Poulenc Rorer Inc.; and Mr. Anthony Taylor, Senior Project Team Leader, Inhalation Product Development, Glaxo Wellcome.

This second edition of Ensuring Patient Care was prepared by an IPAC Editorial Panel under the direction of Dr. Gore. Members of the Editorial Panel include: Mr. Douglas Patton and Mr. Carl Dabruzi, 3M Pharmaceuticals; Ms. Lise Geduldig, Rhône-Poulenc Rorer Inc.; Mr. Ray Maginley, Norton Healthcare Ltd.; Ms. Sally Stone, Glaxo Wellcome; and Dr. Paul Wright, AstraZeneca.
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Following the initial preparation of this second edition, the Editorial Panel selected seven individuals with relevant knowledge and experience to participate in peer review of the document. Each of these individuals devoted substantial efforts to evaluating the Paper and offering comments on how it might be improved. The Editorial Panel wishes to recognise the contributions of Dr. Peter Byron, Dr. Richard Dalby, Dr. Tim Nokes, Dr. Robert Schultz, Dr. Ian Tansey, Dr. Lynn Van Campen, and Mr. Tony Vogelsberg. Opinions expressed in this Paper are those of IPAC and do not necessarily reflect those of individual reviewers.

Dr. Peter R. Byron is Professor and Chairman of Pharmaceutics, at Virginia Commonwealth University School of Pharmacy (Medical College of Virginia Campus) in Richmond, Virginia. He has a B.Sc. in Pharmacy and Ph.D. in Immunology and Immunochemistry, both from Manchester University, England (1970 and 1973). Dr. Byron performed post-doctoral work with S.S. Davis and Robert Notari in the fields of pharmaceutics, biopharmaceutics and pharmacokinetics at the University of Aston, England (1974) and Ohio State University, Columbus, Ohio (1976). Between 1975 and 1984 he held the position of Lecturer in Pharmaceutics at Aston University, Birmingham, England. He was on the faculty at the University of Kentucky College of Pharmacy between July 1984 and June 1988. He is currently also a Visiting Professor at the School of Pharmacy at the University of Bath, UK, and Virginia Commonwealth University's Distinguished Scholar (1998). Dr. Byron is a registered pharmacist in Great Britain, Fellow of the American Association of Pharmaceutical Scientists in the USA, and elected member of the USP’s Committee of Revision (Excipients and Chemistry 5 Subcommittees) where he has responsibility for Aerosols. He has made numerous invited lectures within the pharmaceutical industry and academic institutions in Europe and the USA. He has published over 100 research articles in immunology, microbiology, pharmacokinetics, pharmaceutics, analytical chemistry and aerosol science, while leading graduate students to their Ph.D. degrees. He organises and co-edits the proceedings of the biannual international meeting “Respiratory Drug Delivery.” He has a number of patents in alternative propellant formulation and is a reviewer or editorial board member for several international science journals. He has taught widely at undergraduate and graduate levels throughout the Pharmacy curriculum. He currently leads the Aerosol Research Group in Richmond, investigating physiochemical and formulation factors controlling drug aerosol generation, deposition, and chemical disposition in the lung.

Dr. Richard N. Dalby is an Associate Professor, Vice Chair for Academic Affairs and Graduate Program Director in the Department of Pharmaceutical Sciences at the University of Maryland School of Pharmacy. He was previously a Research Assistant Professor in the Department of Pharmacy and Pharmaceutics at Medical College of
Virginia / VCU (1989-1992). Dr. Dalby holds a Bachelor of Pharmacy degree (1983) from Nottingham University in England and a Ph.D. in Pharmaceutical Sciences from the University of Kentucky (1988). Dr. Dalby's aerosol research, which focuses on novel inhalation and nasal formulations and devices, is founded on both his Ph.D. work on sustained release metered-dose inhalers, and industrial experience as an Inhalation Formulation Scientist with Fisons Pharmaceuticals (1988-1989). He has over 25 published papers and 45 abstracts related to aerosol technology, has authored several chapters, and has spoken at many international meetings. He is a co-inventor on three patents concerned with novel MDI formulations, a review and editorial board member for several international journals, and acts as an industrial consultant. He is a member of the Royal Pharmaceutical Society of Great Britain and the American Association of Pharmaceutical Scientists. He is the director of an annual Inhalation Aerosol Technology Workshop, and co-organiser of a major international symposium "Respiratory Drug Delivery," now in its 11th year.

Dr. Tim Noakes is the business manager responsible for the medical propellants of ICI Klea in Runcorn, England. Dr. Noakes received a Ph.D. from Manchester University, where he studied organic fluorine chemistry. He has worked for ICI for 25 years in a number of fields, including running a wide ranging research programme on atomisation science. Since 1985 he has had special technical responsibility for the provision of pharmaceutical grade CFCs and more recently HFAs to MDI companies. His current role is both a technical and a commercial one, and has as a key component the objective of ensuring a smooth transition for the pharmaceutical industry from CFCs to HFAs.

Dr. Robert K. Schultz graduated from the University of Minnesota in 1979 with a B.S. degree in Pharmacy and completed his Ph.D. in Pharmaceutics at the University of Minnesota in 1993. In 1980, Dr. Schultz joined 3M Riker as a research pharmacist in the conventional dosage form group. He held various positions within this group and had responsibility for development of sustained release products. In 1988, Dr. Schultz transferred to the Inhalation Technology Department of 3M Pharmaceuticals serving as group leader of the Pharmaceutics and Drug Delivery section. Dr. Schultz's responsibilities included the preformulation, formulation and scale up of metered dose inhalers, with specific emphasis on the development of MDIs using non-CFC propellants. Dr. Schultz joined Durapharmaceuticals in 1994, where he is Vice President of Product Development. In his current position, Dr. Schultz has responsibility for the design, formulation, and scale-up of dry powder inhalation products utilizing the company's patented Spiros® technology. Dr. Schultz's research interests include the crystallinity and polymorphic changes which occur in solids and the study of the factors related to dose delivery of MDIs and powder aerosols. Dr. Schultz has made many presentations and published several papers in the area of aerosol technology.

Mr. F.A. (Tony) Vogelsberg is a 1956 graduate of the University of Minnesota with a bachelors degree in Chemical Engineering. Mr. Vogelsberg was with DuPont U.S. from June 1956 until retiring in December 1996 in various technical, marketing, business, and
manufacturing assignments. His experience includes over a decade of plant design and start-up, including plant manager of a new grass roots chemical complex in the U.S. Gulf Coast. Mr. Vogelsberg was in DuPont’s “Freon” Products Division (which was renamed “Fluorochemicals” in 1991) since mid-1985, and was the DuPont corporate spokesperson for chlorofluorocarbons and activities designed to protect the stratospheric ozone layer since the Fall of 1988. Mr. Vogelsberg has participated in the UNEP negotiation process as an advisor to the U.S. government team and is a frequent advisor and speaker at trade and international conferences on the global stratospheric ozone protection issue. He also is DuPont’s management representative on the PAFT international consortium for toxicity testing of alternatives for CFCs, and Chairman of AFEAS, the international consortium that is funding studies to determine the environmental effects of any fluorocarbon alternative chemicals. Mr. Vogelsberg also represented DuPont by attending as an industry NGO the International Negotiating Committee for a Framework Convention on Climate Change (INC FCCC).

Dr. Ian Tansey has recently retired from 3M, where he spent 30 years working on Inhalation Delivery. He was the leader of the team that developed the world’s first CFC-free pMDI. He continues to serve as a member of the United Nations Technical Options Committee on pMDIs and was awarded the U.S. EPA Stratospheric Ozone Award in 1997.

Dr. Lynn Van Campen is Vice President of Pharmaceutical Development at Inhale Therapeutic Systems, Inc., in San Carlos, California, whose dry powder inhalation technology is directed primarily toward the non-invasive delivery of proteins and peptides to the lung as a route to systemic delivery. Prior to joining Inhale, Dr. Van Campen was Director of Pharmaceutics at Boehringer Ingelheim Pharmaceuticals, Inc., where she was responsible for the development and clinical manufacture of MDIs, DPIs and other dosage forms. During this time she served as a member of the PhRMA Pharmaceutical Development Committee, as well as a member of the Scientific Advisory Panel for IPAC prior to departing Boehringer. Prior to obtaining her Ph.D. in Pharmaceutics at the University of Wisconsin, she was employed by Pfizer Central Research, where she first became familiar with inhalation dosage form technology.

The Editorial Panel wishes to express its deep appreciation to each of the individuals named above for participating in peer review of the second edition of Ensuring Patient Care.

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The purpose of this Paper is to inform decision makers who are involved in policy discussions on climate change about the critical role of the hydrofluorocarbon (HFC)-propelled metered dose inhaler (MDI) in the treatment of respiratory disease.

The MDI is a vital therapeutic option for the estimated 300 million people worldwide who suffer from asthma and the many millions more afflicted by a variety of other respiratory diseases. This pocket-sized, portable therapy provides patients and physicians with quick, proven delivery of pulmonary medication.

MDIs are aerosol devices that rely on propellants to deliver precisely-metered doses of medication to the patient’s lungs. For approximately forty years, MDIs have used chlorofluorocarbons (CFCs) as propellants. Due to growing awareness that CFCs contributed to the depletion of stratospheric ozone, however, in the mid-1980s the pharmaceutical industry began an intensive search for alternatives to CFC-propelled MDI. Three major initiatives resulted: testing of alternative propellants and reformulation of MDIs with these propellants; acceleration of programmes to improve existing non-propellant delivery systems, such as nebulisers and dry powder inhalers (DPIs); and expansion of efforts to develop new, innovative delivery systems. The first initiative, development of the non-CFC MDI, is the primary subject of this Paper.

This Paper begins by giving a brief overview of respiratory disease and by providing perspective on MDIs and other therapy options. Next, it discusses the impact of the Montreal Protocol and the extensive search for a CFC substitute. It then explains why, given the stringent technical criteria for MDI propellants, HFCs emerged as the only viable alternative to CFCs. It continues by outlining the processes of reformulation and regulatory approval and the ongoing research into alternative delivery systems. Finally, this Paper discusses the minimal contribution of the HFC MDI to climate change and explains the enormous health benefits provided by this device.
Principal Themes

- Asthma and other respiratory conditions impose great hardship on the millions of patients around the world who suffer from these diseases. Proper treatment makes a critical difference in these patients' ability to lead full and active lives. For some asthma patients, it may mean the difference between life and death.

- Metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulisers are all important therapy options, and all must coexist. Each possesses a unique set of characteristics that differentiates its use. Physicians must be allowed to choose the therapy that is best for the individual patient.

- The MDI has special benefits for many patients. Effective treatment of asthma and other respiratory diseases depends on the continuing availability of the MDI.

- Hydrofluorocarbons (HFCs) are the only suitable alternative to CFC propellants for MDIs. No other compounds are proven to meet the stringent criteria required for an MDI propellant.

- In addition to improving existing therapies, the pharmaceutical industry is continuously seeking new means of delivering medication to the lungs. However, there is no guarantee that any new technology would have universal application and replace the MDI in respiratory therapy.

- The projected environmental impact of the HFC MDI is extremely small. The MDI's enormous contribution to public health must be clearly understood, respected, and taken into account in all relevant policy discussions.
Summary of Paper

Respiratory Disease

Asthma is a chronic and potentially life-threatening disease which affects 300 million people around the world. Many millions more suffer from other pulmonary disorders such as chronic bronchitis and emphysema. Each year, millions of people die from these diseases. Most asthma deaths are preventable with proper treatment.

Therapy

Physicians may select from a broad range of medications for treating respiratory disease. Patient response to medication can be highly idiosyncratic; thus, the physician must attempt to determine the best available treatment for each individual patient.

There is international consensus that treatment by inhalation is the preferred form of treatment for asthma sufferers. Three types of inhalation delivery systems are available: nebulisers, MDIs, and DPIs. An examination of the characteristics of these delivery systems demonstrates that each system has particular strengths and weaknesses. It is essential to maintain each of these therapeutic options in order to meet individual patient needs.

Although no one therapy is suitable for all patients, an estimated 70 million patients in 100 countries around the world rely on MDIs for treatment of respiratory disease. MDIs assist the patient by providing the energy needed for drug delivery in the form of a propellant; they meter out doses independent of the patient’s inspiratory effort; they are adaptable to a variety of needs and situations, including use by young children and infants; they provide good protection for the drug substance from atmospheric humidity and the patient’s respiration; they can be used for all of the most commonly prescribed respiratory medications; and they are widely available. No other inhalation system provides the same range of benefits as the MDI.

Montreal Protocol and CFC MDIs

The CFC MDI for the treatment of asthma and other respiratory diseases has been declared an “essential use” of CFCs under the Montreal Protocol, because it is vital to public health and there is no other therapy that can take its place. The expert scientific panel created by the Parties to the Protocol reaffirmed the essentiality of the CFC MDI annually since 1992, with the understanding that the CFC MDI eventually will be replaced by HFC MDIs.

Transition to Non-CFC MDIs

An MDI propellant must be a gas that can be liquefied in a closed container at room temperature. It must have appropriate pressure, density, and solvency characteristics and very low toxicity. It must be chemically stable, and acceptable to patients in terms of taste and smell.

In response to the Montreal Protocol, pharmaceutical firms and others evaluated potential alternative propellants for safety and MDI performance. In the course of this review, HFCs 134a and 227 emerged as the only propellants suitable for pharmaceutical use.
The process of developing HFC MDIs has been challenging. The MDI is a complex device consisting of a canister, a valve, elastomer gaskets, and an actuator. It contains formulations of drug substances, propellants, lubricants, co-solvents, and surfactants. Most of these components and compounds must be redesigned or developed for use with HFCs to ensure the quality of the product and to meet today’s strict regulatory requirements. The new formulations must also undergo extensive safety and clinical testing, followed by extensive regulatory review. From start to finish, the process will take up to ten years or longer, depending on the product.

Potential Future Technologies

Competitive forces are driving pharmaceutical firms to intensify the search for new means of delivering medication to the lungs. It is unlikely, however, that the current mix of therapeutic options will change significantly in the near future. Considerable time is required for development, clinical studies, regulatory approval, and acceptance of a new drug delivery system by patients and the medical community. In addition, any new treatment option may not be appropriate as a universal substitute for the range of currently available therapies.

The HFC MDI

There is a large and growing need for effective treatment of respiratory disease. On a worldwide basis, the great majority of patients who receive inhalation therapy rely on the MDI for delivery of their medication. MDIs account for 70 percent of all inhalation therapy in the countries with the largest populations of patients with respiratory disease.

The quantity of HFCs needed for MDIs is extremely small. Other greenhouse gas emissions vastly overshadow expected emissions from HFC MDIs. It is estimated that the contribution to climate change of HFCs from MDIs in the year 2010 will be no more than 0.02 percent of all global greenhouse gas emissions. (See Section VIII). Unlike CFCs, HFCs do not contribute to ozone depletion, and they have significantly lower global warming potentials than the CFCs which they replace.

All manufactured devices have some impact on the environment. Medical devices are no exception. However, the environmental effects of medical devices must be viewed in the context of their critical role in patient care.

Conclusion

MDIs provide a high level of assurance to the many millions of patients who depend on them. The HFC-alternative to the CFC MDI will play a crucial role in securing the future of patient care.
This section provides an overview of respiratory disease and briefly discusses its incidence and growth.

Asthma and chronic obstructive pulmonary diseases (COPD), such as emphysema and chronic bronchitis, reduce the capacity for respiration. They inflame the human airway, which becomes hyperreactive and may be subject to coughing and wheezing that disrupts breathing. These diseases can also produce obstructions such as swollen tissues and mucus plugs that impede airflow. In addition, nervous system stimulation of airway smooth muscle contributes to further airway narrowing and worsening symptoms. Finally, in the case of emphysema and chronic bronchitis, these diseases gradually destroy the surface area of the lung, reducing its capacity for the exchange of oxygen and carbon dioxide. Both asthma and COPD greatly diminish the quality of life for the patient and his or her family and, in severe cases, may cause death.

Asthma

Asthma is a chronic and debilitating respiratory disease with sudden, unpredictable and potentially life-threatening effects. The treatment of asthma requires constant vigilance and the active involvement of patients, families, physicians and other caregivers in a comprehensive programme to monitor, anticipate and promptly respond to the onset of asthmatic attacks.

The victim of asthma may be restricted from normal physical activity, limited in his or her choice of work, afflicted by the side effects of some medications and subject to unpredictable and sudden asthma attacks which disrupt his or her daily activities and may even threaten his or her life.

Asthma sufferers experience a distressing set of symptoms:

The bronchial tubes of asthma sufferers are virtually continuously inflamed and hyperreactive, sent into suffocating spasms by a broad range of provocations that may vary from one individual to another... An attack finds the victim gasping for breath as the airways become constricted, the passages inflamed and clogged with thick, sticky secretions.

John Updike, the prominent U.S. author who suffers from asthma himself, describes the experience of an asthma attack from a more personal perspective:

An asthma attack feels like two walls drawn closer and closer, until they are pressed together. Your back begins to hurt, between the shoulder blades, and you hunch... I felt immensely angry at my own body and at everyone. Like a child blind in his tantrum, I thought, serves them right, and waited to die, standing bent over and gasping, of suffocation.

Factors that may trigger asthma attacks include smoke, airborne moulds, pollens, dust, tiny scales from animal skin, exercise, cold air, household and industrial products, air pollutants, scents, and stress.

The impact of asthma on children is particularly severe:

Measurements of actual days lost from school provide only a one-dimensional view of asthma's impact on child development... To help understand
the long-term consequences, other important measurements include scholastic achievement and the attainment of age-appropriate social functioning. Children with asthma may be at higher risk of learning disability as compared with children without asthma, and among families with low incomes, children with asthma have twice the odds of grade failure compared with well children... Asthma can also affect psychological development, including self-esteem.¹¹

The incidence of asthma globally is generally accepted to be on the order of five to eight percent of the population, at least in the developed world. No fewer than 300 million people worldwide are asthma sufferers.¹² For example, in the United States alone, over 14 million people suffer from the disease, with nearly 5 million being children and youngsters under the age of 18.¹³ Between 1982 and 1994, there was a 61 percent increase in the prevalence of asthma in the U.S.¹⁴ Asthma hospitalisation rates have been highest among blacks and children, while death rates for asthma were consistently highest among blacks aged 15 to 24 years.¹⁵ Asthma mortality is on the rise: the number of deaths caused by asthma in the U.S. nearly doubled between 1979 and 1993.¹⁶

In the United Kingdom, 31.3 million prescriptions were written for asthma medications in 1993; this figure equals approximately seven percent of the total number of prescriptions written during that year.¹⁷ It is estimated that there are approximately three million asthma sufferers in the U.K.¹⁸ Asthma is the most frequently reported cause of long-standing illness among British children and is responsible for over 1,700 deaths per year among the general population.¹⁹

Asthma is also a public health problem in developing countries: India has an estimated 15 to 20 million asthmatics.²⁰ In Brazil, Costa Rica, Panama, Peru, and Uruguay, the prevalence of asthma is between 20 percent and 30 percent.²¹

On a global level:

Data from many countries suggest that both asthma morbidity and mortality are increasing, although the reasons for this are not clear. Asthma prevalence has been reported to be increasing in the United States, the United Kingdom, New Zealand, and Australia; asthma mortality rates and mortality trends vary widely but appear to be increasing in many countries where data are available...²²

**Chronic Obstructive Pulmonary Disease (COPD)**

Chronic obstructive pulmonary diseases such as emphysema and chronic bronchitis produce inflammation, swelling and mucus in the human airway and gradually destroy the surface area of the lung. COPD is inexorably progressive and generally irreversible, and severely restricts the capacity for respiration.
Emphysema is a debilitating disease:

Classic emphysema develops over many years of assault on lung tissues. The wall between the tiniest air sacs within the lungs breaks down, and those compartments become unnaturally enlarged. Elasticity of the lung tissue is lost, and the lungs become distended, unable to expand and contract normally... As emphysema progresses, the effort needed to breathe increases and, ultimately, each breath becomes a chore. Meanwhile, the patient grows progressively weaker—at first experiencing only minimal shortness of breath, soon unable to attempt even minor physical activity, in the end dependent on administration of oxygen.23

Chronic bronchitis also develops over many years, sometimes in conjunction with emphysema. It produces inflammation and clogging of the lungs and causes periodic attacks of obstructed breathing.24

Although COPD has a public health importance similar to asthma, it has previously received much less attention.25 COPD is the fifth leading cause of death worldwide, with an estimated 600 million cases and three million deaths annually.26 The mortality rate for COPD is 14 times greater than for asthma.27

The incidence of COPD is believed generally to be eight to fifteen percent of the population, at least in the developed world. For example, in the U.S., over 16 million people suffer from COPD.28 Deaths from COPD in the U.S. rose from 53,000 in 1980 to nearly 96,000 in 1993.29 In the European Union, COPD and asthma rank together with pneumonia as the third most common cause of death.30
**Overview**

A broad range of over twenty medications worldwide has been developed for treatment of asthma and COPD. These medications differ in terms of the biological influences they exert; relative potency; the speed, duration and extent of therapeutic effect; and side effect profiles. The benefits they provide may vary significantly according to a patient’s age, weight, sex, genetic make-up and physiological idiosyncrasies.

In developing a treatment programme, physicians seek to match a patient with one or more medications that will combine optimal therapeutic control with minimal side effects. In view of the many variables involved, and the changing needs of the patient, care is generally far more successful where a broad range of alternative medications and delivery systems are available. Even then, it may take several years of treatment experience to establish which medication, or combination of medications, yields consistent relief with minimal side effects for a particular patient.

The principal types of medication for treating asthma are anti-inflammatory agents (termed preventers and controllers) and bronchodilators (termed relievers):

- **Anti-inflammatory agents** may interrupt the development of bronchial inflammation and have a prophylactic and suppressive action. Bronchodilators act principally to dilate the airways by relaxing bronchial smooth muscle.

- The principal types of medication for treating COPD are bronchodilators.

Anti-inflammatory agents include corticosteroids, sodium cromoglycate (cromolyn sodium), and nedocromil sodium.

Bronchodilators include short- and long-acting beta2-agonists, methylxanthines (principally theophylline), and anticholinergics (principally ipratropium bromide).

Recently a new class of anti-asthma agents has been introduced, the leukotriene modifiers. As yet their place in asthma management is not fully established.

The rising morbidity and mortality of asthma prompted the U.S. National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI), to convene an international group of leading physicians and scientists to develop a consensus on therapy and identify areas for further research. This group produced the International Consensus Report on Diagnosis and Management of Asthma in June 1992. The report concluded:

The major factors contributing to asthma morbidity and mortality are under-diagnosis and inappropriate treatment. Most exacerbations reflect a treatment failure because they can be prevented if treatment of the disease is comprehensive and ongoing.

Ongoing from this report, the NHLBI and World Health Organisation (WHO) collaborated to produce guidelines aimed at “providing information, recommendations and tools to assist health care professionals and public health officials in designing and delivering effective asthma management and prevention programs in their communities.” The resulting report, The Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop Report, was published in 1996.
A number of national groups have developed guidelines for the management of asthma to help standardise treatment across their health care systems.\textsuperscript{36}

The latest report from the National Education and Prevention Program critically reviews and builds on the previous NHLBI and WHO reports, and concludes that “Recommendations for managing asthma exacerbations are similar to those in the 1991 Expert Panel Report. However, the treatment recommendations are now on a much firmer scientific basis because of the number of studies addressing the treatment of asthma exacerbations in children and adults in the past 6 years.”\textsuperscript{37}

The NHLBI and WHO have also collaborated to organize the Global Obstructive Lung Disease (GOLD) Initiative. Their report recommending COPD management guidelines will be published at the European Respiratory Society meeting (October 1999, Madrid, Spain).\textsuperscript{38}

\textbf{Non-Inhaled}

An early means of delivering medications for asthma and COPD was systemically, i.e., via the blood stream, through orally administered tablets, capsules or liquids, injections and suppositories. This form of delivery has serious drawbacks. First, orally delivered drugs tend to be slow-acting; the minimum onset of action for oral dosage forms is 20-30 minutes. A rapid onset of action is important to alleviate the symptoms of an acute respiratory incident. Secondly, systemic delivery is non-targeted; that is, every part of the body is exposed to medication. Relatively large doses may be required for effective treatment with systemic drugs. This is particularly true of oral medications, as medication delivered orally passes from the intestine through the liver, where it is in part metabolised and removed from the bloodstream. Thus, higher doses must be administered to ensure that sufficient amounts remain; such higher doses may lead to significant side effects.

The International Consensus Report on Diagnosis and Management of Asthma states that "treatment via inhalation is generally preferable to systemic or oral treatment."\textsuperscript{39} The Global Initiative for Asthma (GINA) guidelines describe a stepwise approach to drug treatment based on disease severity. The role of oral therapy has largely been restricted to those patients with severe asthma. "Long term oral corticosteroid therapy (daily or alternate day) may be required to control severe persistent asthma, but its use is limited by the risk of significant adverse effects."\textsuperscript{40}

It is possible that in the future oral delivery could become a preferred means of delivery for new respiratory medications. However, such treatments will be required to have a therapeutic ratio acceptable to physicians and the regulatory authorities.

\textbf{Inhaled}

Inhaled therapies are preferred over non-inhaled therapies because they deliver the active ingredient directly to the lungs. This targeted delivery of bronchodilators achieves an extremely rapid onset of action
for symptomatic relief. The patient is able to obtain relief within one or two minutes after inhalation. Another important benefit of targeted therapy is the much lower dose of medication that is used to achieve the same clinical result, compared to oral delivery. Targeted therapy avoids metabolism by the liver before the medication reaches the rest of the body, allowing effective treatment at lower dose levels.41

The GINA guidelines state that “Inhaled medications are preferred because of their high therapeutic ratio: high concentrations of drug are delivered directly to the airways with potent therapeutic effects and few systemic side effects.”42 Three types of inhaled therapies are currently available: nebulisers, metered dose inhalers (MDIs), and dry powder inhalers (DPIs). These therapies are described below in the order in which they were introduced to physicians and patients.

**Nebulisers**

Using either ultrasonic or air-jet technologies, nebulisers transform an aqueous product in which drug particles are dissolved or suspended into an aerosol cloud for inhalation by the patient. The most significant drawbacks of nebulisers include: the length of time needed for delivery of the medication, the complexity of assembling the device and filling it with a nebuliser product, and the amount of energy required for operation. In addition, only some commonly used drug substances are available as products suitable for nebulisation. Although progress is being made in developing smaller, more portable nebulisers, most existing nebulisers are costly and cumbersome. Many require an independent power source. Nebulisers typically deliver a single, high-volume dose.

Nebulisers generate a wide range of particle sizes; the largest particles are filtered out and returned to the aqueous solution. Some nebulisers run continuously for a number of minutes as the patient inhales, pauses, exhales, and repeats the cycle numerous times. As much as two-thirds of the medication may be lost to the atmosphere while the patient is exhaling or at rest. A new generation of breath-actuated nebulisers that delivers medication on...
demand and thus reduces this problem has recently been developed. The cost of these devices is still high, however, and may prohibit widespread uptake in some countries.

Use of nebulisers is generally restricted to hospitals and to home care of severely incapacitated patients and young children. The mechanics of set-up and administration can consume 10-20 minutes, and may require assistance from a caregiver. Due to the potential for bacterial contamination, nebulisers must be disassembled and cleaned after each use. The industry is seeking to improve the effectiveness of existing nebulisers through efforts to:

- make compressors more portable and more reliable;
- minimise the time for nebulisation;
- reduce the size of the particles generated;
- minimise the amount of drug remaining in the nebuliser;
- reduce environmental contamination from the active drug during administration; and
- deliver a dose in a single inhalation without refilling the device.

**Metered Dose Inhalers (MDIs)**

MDIs were introduced in the 1950s as a major advance over oral therapy and stationary nebulisers. The MDI is a pocket-sized, hand-held, pressurised multiple-dose inhalation delivery system. It delivers small, precisely measured therapeutic doses, greatly minimising the risk of adverse side effects. Unlike most nebulisers, it is portable and convenient to use. MDIs can be used for the inhalation of all commonly prescribed respiratory medications for the treatment of asthma and COPD.

The patient affected by asthma or COPD is free to pursue a variety of activities, knowing that, should an acute respiratory incident occur, rescue medication is at hand.

The MDI gained rapid acceptance among physicians and their patients as a superior means of drug delivery. It has proven safe, effective and reliable for virtually all patients, and is the mainstay of successful asthma therapy worldwide. The MDI accounts for 70 percent of all inhalation therapy in the world’s fifteen largest patient populations.

The essential components of an MDI are a storage canister; a medicinal formulation, including at least the propellant and the active ingredient(s); a metering valve to control the discharge of precise doses of formulation; and an actuator. The storage canister is placed valve-down into the actuator. In press-and-breathe MDIs, the patient pushes down on the canister to release a dose. Breath-actuated MDIs actuate automatically during inspiration.

Inside the canister is a complex formulation developed specifically for use in an MDI. The formulation may consist of several ingredients in either solution or suspension form: (1) one or more active ingredients; (2) one or more propellants; and, in some cases, (3) a co-solvent and/or surfactant.
The propellant mixture is made up of one or more liquefied gases which generate a pressure of 50-80 psig inside the canister. Upon release from the MDI, the propellant flashes to a gas. The result is a very fine mist of the drug that was suspended or dissolved in the propellant.

In DPIs, the drug substance is formulated as a dry powder. The force of inspiration lifts drug particles out of the dosing chamber, through the device, into the mouth and down into the airways. The patient need not co-ordinate drug release with inhalation.

The MDI accounts for 70% of all inhalation therapy in the world’s fifteen largest patient populations.
Single-dose DPIs became widely available in the late 1960s and early 1970s. In these devices, only one dose can be loaded at a time. The dose is contained in a gelatine capsule that is punctured or split open to make the drug available for inhalation.

Multiple unit dose DPIs contain premeasured doses, individually sealed in a blister pack or coiled blister strip. Some provide only one day’s treatment; others provide up to a month’s worth of medication. Devices in this category either puncture individual blisters or peel back a section of foil from the blister strip to release a dose.

Reservoir DPIs contain a reservoir of bulk powder. The patient meters out a dose by manipulating the device prior to inhalation.

Characteristics of Inhaled Therapies

Inhalation delivery systems can be compared with respect to the following characteristics: energy source for drug delivery; consistency of dose delivered; device operation; co-ordination requirements; protection from humidity; suitability for paediatric use; and availability. Figure 1 summarises some of the salient differences among the three types of inhalation systems.

Energy Source for Drug Delivery. All inhalation delivery systems require an energy source to move medication from the device to the lungs. The energy source may be provided mechanically, externally (e.g., electric current or batteries), by flash evaporation of liquefied gas propellants, or by the patient’s own inspiratory capacity.

Nebulisers. An external power source is required to convert the medicinal product into an aerosol for inhalation. The patient inhales the medication simply by breathing normally.

MDIs. For MDIs, the energy source is the high pressure of the propellants. The patient has to breathe slowly and deeply, at the right moment, in order to create an airflow that draws the aerosol cloud deeper into the lung.

DPIs. Current DPIs require the patient to provide the energy needed to deagglomerate the powder and move the drug into the lungs. DPIs have differing designs and individual performance characteristics, and in most cases the patient’s inspiratory effort is critical to the amount of drug delivered to the lungs. Patients whose inspiratory capacity is reduced during an acute asthma attack, e.g., infants and the elderly, may lack the inspiratory capacity to use DPIs effectively. In addition, patients with a limited manual dexterity may find the manipulation required with some DPIs difficult.

In light of these concerns, efforts are being made to develop DPIs that use mechanical devices, electrostatics, or compressed gases to improve powder delivery. Although these new devices represent promising innovations, none is yet approved for use.

Consistency of Dose Delivered. The consistency of the dose delivered may vary depending on the patient or the device.

Nebulisers. Given the wide range of nebulisers available, the dose
Figure 1: Characteristics of Inhalation Delivery Systems

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nebulisers</th>
<th>MDIs</th>
<th>DPIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy Source for Drug Delivery</td>
<td>Provided by an external source</td>
<td>Provided by the device</td>
<td>Provided by patient’s inspiratory effort</td>
</tr>
<tr>
<td>Consistency of Dose Delivered</td>
<td>Dose dependent on type of nebuliser used and duration of therapy</td>
<td>Dose independent of patient inhalation</td>
<td>Dose dependent on inspiratory effort of patient</td>
</tr>
<tr>
<td>Device Operation</td>
<td>Varies from one product to the next</td>
<td>Similar for all products provided the same type of actuator is used</td>
<td>Varies from one product to the next</td>
</tr>
<tr>
<td>Co-ordination</td>
<td>Do not need to co-ordinate inspiration with actuation</td>
<td>Must be able to co-ordinate inspiration with actuation, except when using a breath-actuated device or a spacer</td>
<td>Do not need to co-ordinate inspiration with actuation</td>
</tr>
<tr>
<td>Protection from Humidity During Use</td>
<td>Aqueous medium; protection not required</td>
<td>Good</td>
<td>Dependent on device design</td>
</tr>
<tr>
<td>Paediatric Use</td>
<td>Accepted practice</td>
<td>Accepted practice (with spacer or breath-activated device)</td>
<td>Not suitable for infants</td>
</tr>
<tr>
<td>Availability</td>
<td>Widely available</td>
<td>Widely available</td>
<td>Not widely available</td>
</tr>
</tbody>
</table>
delivered depends on the type of nebuliser and compressor used, the duration of therapy, and the patient’s breathing pattern. Some products for nebulisation are incompatible with certain types of nebulisers.

**MDIs.** The delivered dose is determined by the metering valve and the formulation. Patients must coordinate their inhalation or use a spacer or a breath-actuated device.

**DPIs.** The patient’s inspiratory effort will affect the quantity of drug that reaches the lungs from a DPI.

**Device Operation.** The technique required to operate a device may vary from one manufacturer to the next. Some devices may require maintenance to ensure their effective operation.

**Nebulisers.** With most nebulisers, medication can be administered to a completely passive or unconscious patient. Thus, operating technique is not an issue. Nebulisers do require frequent maintenance. They generally must be rinsed or cleaned and allowed to dry after each use.

**MDIs.** All press-and-breathe MDIs require a similar operating technique, because the technology differs little from one manufacturer to another. A patient who uses one company's MDI for a particular drug may use an MDI made by another company for another drug with minimal confusion.

**DPIs.** Several companies have introduced DPIs with designs that require patients to perform differing forms of manipulation to release the dose. No one design is approved for use with all commonly used respiratory drugs. Thus, a patient who requires multiple asthma medications may have to contend with a confusing variety of devices. Under these circumstances, it may be difficult for the patient to learn several operating techniques, which may reduce compliance.

**Co-ordination.** Issues relating to co-ordination include the need for manual dexterity in actuating the device and the need to co-ordinate actuation with inhalation.

**Nebulisers.** Nebulisers must be set up prior to use. This can be a time-consuming process. Elderly patients and young children may have difficulty setting up nebulisers and may require assistance from a caregiver. However, once the nebuliser is functioning, no co-ordination is required on the part of the patient.

**MDIs.** Some patients, including young children and the elderly, may have difficulty in co-ordinating inhalation with actuation of the MDI. Such patients benefit from use of a “spacer.” The spacer captures the dose as it leaves the MDI and allows the patient to breathe the medication in after a slight delay. Another option available for some drugs is a breath-actuated MDI, which automatically releases the dose at the appropriate time in the patient’s normal respiratory cycle. Similarly, for some drug products
aids are available for arthritic patients who may have trouble actuating an MDI due to reduced manual dexterity.

DPIs. Some patients who have difficulty in co-ordinating inhalation and actuation when using an MDI may be able to use a DPI more easily. DPIs eliminate the need to co-ordinate inspiration with actuation. Patients who have limited manual dexterity, however, may find certain DPIs difficult to operate. Young children and the elderly may be unable to perform all necessary steps adequately. Patients who suffer from arthritis or who have impaired vision may have difficulty loading a DPI, particularly if the drug is contained in a single dose unit that must be punctured before use. No aids are currently available to assist such patients.

Nebulisers. Because water is the delivery medium, nebulisers are not affected by humidity.

MDIs. MDIs provide a good degree of protection from atmospheric humidity. This protection is sufficient for most drug substances. Patient exhalation does not affect the drug remaining in the MDI.

DPIs. DPIs are susceptible to the effects of relative humidity if the powder is left exposed to high environmental humidity. Patients may introduce moisture by exhaling into the device during use and this may affect subsequent doses in reservoir DPIs. Certain devices have specific mechanisms to prevent this problem. Some devices incorporate a desiccant (drying agent) to mitigate the effect of water ingress. Multiple unit dose and unit dose systems are less susceptible in this instance, due to doses being individually stored.

Exposure to moisture in the air causes drug particles to agglomerate or stick together, forming larger aggregated particles which impact on the mouth, throat, and upper airways. Aggregates that exceed respirable particle size (5-10 µm) are not delivered to the lungs and reduce the effective drug dose.

Paediatric Use. The delivery system may or may not be appropriate for infants and young children.

Nebulisers. Nebulisers are well-suited for young children and
Infants. The nebulised solution may be administered through a mask, if necessary.

MDIs. The World Health Organisation (WHO) has stated: “In terms of ease of administration, availability and effectiveness, metered dose inhaler and spacer devices may be the most appropriate method for administering inhaled medication to young children at home and in outpatient facilities.” Use of the MDI in infants has recently expanded due to the introduction of small-volume spacers specifically designed for this population.

DPIs. DPIs are generally not recommended for use by children below the age of four to six years, principally because young children cannot generate sufficient inspiratory effort to deaggregate the powder and draw the medication into their lungs. Young children also may not be able to perform the mechanical manoeuvres required to load and actuate some DPIs.

Availability. Patients’ access to the delivery system may be limited by lack of regulatory approvals or unavailability of certain drugs in that format.

Nebulisers. Nebulisers are widely available. A variety of drug categories is offered in the form of nebuliser products. However, not every commonly used respiratory medication is available in this form. Additionally, the requirement for an external power source can limit the portability and universal acceptability of this system.

MDIs. MDIs are widely available worldwide for the most commonly used respiratory medications.

DPIs. Only limited combinations of DPI device and molecule are available in some countries. For example, few DPIs have been approved for use in the United States and Japan.

Preservation of Therapy Options

Each of the inhalation delivery systems described above has an important role in the treatment of respiratory disease. No single delivery system is universally acceptable for all patients. As patients’ needs change due to aging, situation or disease severity, it is vital that the most appropriate delivery system be available. This increases the likelihood that physicians will be able to prescribe appropriate medication in the optimum format for a specific patient.
MDIs possess numerous characteristics that, taken together, set them apart from other inhalation delivery systems. These characteristics can be summarised as follows. MDI propellants provide the energy needed for drug delivery independent of any external power source or extra inspiratory effort on the part of the patient. In MDIs, the delivered dose depends significantly on the metering valve and formulation, as opposed to patient inspiration. A patient who must take multiple medications can operate a variety of MDIs using the same technique. MDIs provide good protection from atmospheric humidity and patient exhalation. They can be used for the inhalation of all of the most commonly prescribed respiratory medications and are widely available around the world for use with these medications. They can be adapted to meet the needs of special patient populations, including infants, young children, and the elderly.

As this summary demonstrates, MDIs offer patients a unique combination of benefits. Thus, MDIs are a vital therapy option for patients who suffer from asthma, COPD, and other respiratory diseases.
The Montreal Protocol and CFC MDIs

For decades, CFCs have served admirably as propellants in MDIs. CFCs are non-toxic, non-reactive, and non-flammable. They have no offensive odour or taste. Mixtures of CFCs 11, 12, and 114, when stored in liquefied form in a closed, pressurised container, are an excellent vehicle for delivery of medication.

Due to their effect on the stratospheric ozone layer, however, CFCs are being replaced by alternative propellants. The history and rationale of the CFC phaseout is explained briefly below.

Ozone Science

Disparate strands of research by scientists in the early 1970s combined to give the world its first insight into stratospheric ozone depletion as a theoretical possibility.

Some of the seminal research in ozone science concerned the fate of CFCs used in aerosols and other familiar products. The work of several scientists demonstrated that CFCs released from these products eventually reach the upper atmosphere.

During this period, Richard Stolarski and Ralph Cicerone were investigating the atmospheric effects of emissions from spacecraft. In 1974, they published the theory that chlorine depletes ozone in the stratosphere.

In that same year, F.S. Rowland and Mario Molina theorised that because CFCs are exceptionally stable, these compounds are not chemically broken down in the lower atmosphere. Instead, they drift over time into the stratosphere, where they are broken down by solar radiation to release chlorine.

In combination, these theories led to the conclusion that CFCs released on earth reach the stratosphere, where they degrade to release chlorine, which reacts with ozone. Thus, the very quality that makes CFCs so commercially useful—their stability—gives them considerable potential for environmental impact.

Although there was little information available to test this hypothesis when it was first presented, it aroused great interest in industry, government, and academic circles, catalysing a massive research campaign by the scientific community. The growing awareness of this issue led ultimately to international agreements restricting the production of CFCs and other ozone depleting substances. New scientific data subsequently confirmed the link between CFCs and ozone depletion. As scientific understanding increased, controls tightened, and the decision was made to eliminate CFCs entirely.

The Montreal Protocol

In March of 1985, twenty countries and the Commission of the European Communities signed the Vienna Convention for the Protection of the Ozone Layer. The Vienna Convention imposed obligations on the signatories to conduct research and exchange scientific and technical data but did not prescribe specific control measures. In September 1987, the Convention was followed by the Montreal Protocol on Substances that Deplete the Ozone Layer (the “Protocol”). The Protocol entered into force on 1 January 1989. Unlike the Convention, it specifically set forth restrictions on the production of a variety of ozone-depleting sub-
stances, including CFCs. In 1992, the Parties to the Protocol agreed to phase out CFC production for nearly all uses in the developed world by 1 January 1996. In recognition that CFC alternatives would not be available by that date for certain important products, the Parties established a process for exempting “essential uses” from the phaseout. A use is considered essential if it “is necessary for health, safety or is critical for the functioning of society” and there are no “technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health.”

Essential use applications are reviewed by a body of experts called the Technology and Economic Assessment Panel (TEAP). The TEAP has repeatedly recognised the crucial role of the MDI in the treatment of asthma and COPD. In its 1993 report, the TEAP stated:

“There is international consensus that primary treatment of these diseases should be by the inhaled route. This permits treatment to be delivered quickly and efficiently to the airways, with minimal risk of adverse reactions... [T]here is an existing and increasing requirement for inhaled medications. This is largely met by CFC-driven metered dose inhalers (MDIs), which are cheap, reliable and effective therapy.”

In 1994, the first year during which the TEAP considered essential uses of CFCs, the TEAP reiterated these findings and recommended “that the Parties authorise production and consumption of controlled substances after 1 January 1996 for... Aerosol Metered Dose Inhalers.”

Since 1995, the TEAP has annually affirmed that CFC MDIs for the treatment of asthma and COPD will remain essential until an adequate range of alternatives become available. In its 1999 report, the TEAP stated:

“Given the current rate of introduction of alternatives, it is likely that a wide range of reformulated products will be available in many developed countries and transition will be making good progress by the year 2000. Minimal need for CFCs for MDIs is envisaged by the year 2005 for developing countries. Remaining technical, patent, safety and regulatory issues for some commonly used drugs still make it difficult to predict the schedule for full phaseout with precision.”

In summary, the Montreal Protocol provided the impetus for a shift away from CFC MDIs. Through the essential use process, the Parties to the Protocol confirmed the essentiality of the MDI and pressed MDI manufacturers to find an appropriate substitute for CFC propellants.
This section describes the process by which pharmaceutical firms and others identified suitable alternatives to CFCs and the massive reformulation effort that followed.

Criteria for an MDI Propellant

Compounds identified as potential substitutes for CFCs must meet particularly strict requirements in order to be considered for use in MDIs. The principal criteria for MDI propellants are now well established.

An MDI propellant must:

- be a liquefied gas;
- have very low toxicity;
- be non-flammable;
- be chemically stable;
- be acceptable to patients (in terms of taste and smell);
- have appropriate solvency characteristics; and
- have appropriate density.

The relative significance of these criteria may vary from one product or formulation to another. These criteria are discussed in more detail below.

- The propellant must be a gas of appropriate vapour pressure that can be liquefied at ambient temperature in a closed container. This characteristic is crucial to ensure dose reproducibility and effective delivery.

One important feature of the MDI is dose reproducibility, i.e., the consistent delivery of same-sized dose amounts. Consistent delivery is highly dependent on the pressure inside the canister remaining constant from one actuation to the next. Use of a liquefied gas ensures constant pressure throughout the life of the canister.

A second important feature related to pressure is delivery of appropriately-sized particles into the lungs. Effective delivery depends on dispersancy, i.e., break-up of the formulation into very fine particles that can penetrate into the affected portions of the lungs. The flash evaporation of the liquefied gas is essential to this process.

The pressure required to maintain a gaseous propellant in the liquid state at room temperature varies from one compound to another. A typical formulation of CFCs 11, 12, and 114 has a pressure of 50 psi at room temperature (20°C or approximately 70°F).

The maximum desirable pressure for an MDI formulation is approximately 100 psi: a pressure of greater than 100 psi could prove unacceptably forceful to the patient and be inefficient in delivery. Furthermore, such a pressure would require a stronger, thicker canister and a stronger valve than those currently available. The necessary re-engineering would pose a significant technological challenge.

For the reasons outlined above, the optimal pressure for an MDI propellant is between 40 and 100 psi at room temperature.

Compared to liquefied gases, the compressed gases (e.g., carbon dioxide, nitrous oxide, and nitrogen) are used only to a minor extent in aerosol products generally. Even though the cost of these propellants is low, they have inherent disadvantages.
has stated that “[c]ompressed gases . . . have been used as propellants for a long time but for many products produce poor quality sprays.”

In aerosol products propelled by compressed gases, spray characteristics are inferior because flash evaporation does not occur during use. Furthermore, the pressure of the product is constantly changing; accordingly, spray rate varies as the product is used. If a compressed gas were used as an MDI propellant, the pressure inside the canister would decrease with each actuation, resulting in variation in dosage and particle size range. In addition, compressed gases do not have sufficient pressure to produce particles in the appropriate size range.

Finally, particular compressed gases are associated with corrosion or reactivity. For example, carbon dioxide forms carbonic acid in the presence of moisture. In some formulations, this could lead to corrosion and other problems. Nitrous oxide is an oxidising agent. Thus, it is potentially reactive and could pose a hazard.

Therefore, compressed gases are not realistic alternatives for MDI usage.

- The propellant must have very low toxicity.

The propellant must be safe for human inhalation on a daily basis and for indefinite periods.

- The propellant must be non-flammable.

MDIs must be safe for a variety of patients, of all ages and mental abilities, in a wide range of situations. Flammability is a lesser concern with consumer aerosols, as such products are commonly used only by adults who are able to understand and minimise the associated risk. MDIs are intended for use by children as well as adults. They are frequently used in emergency rooms or operating rooms, where exposure to potentially explosive materials must be avoided.

In addition, MDIs must contain propellants that can be used safely with spacers. The use of a spacer may increase the risk of ignition or explosion, as air combines with the propellant mixture within the holding chamber.

- The propellant must be stable and non-reactive.

The propellant must not react with the canister materials or with the other components of the formulation, including the drug substance. Similarly, the propellant must not degrade and lose its essential properties.

Compounds identified as unacceptably “reactive” include those that contain a functional group or groups that can be converted through oxidation, reduction, hydrolysis or other processes to another compound, or that are capable of being polymerised to a solid or liquid.

- The propellant must have acceptable taste and smell.

This characteristic is necessary to ensure that patients are willing to use the medication as often as required.

- The propellant must possess the appropriate solvency characteristics.
Solvency may affect particle size and therapeutic efficacy. If propellant solvency is either too high or too low, this may limit the effective formulation of many drug substances. In addition, high solvency may result in an undesirable interaction between the propellant and valve elastomer components.

MDIs may be formulated so that the drug is either in solution or dispersed as a suspension in the propellant. Many drugs are not soluble in propellants and must be formulated as suspensions.

When a drug is formulated as a suspension, it must be insoluble in the propellant. If it is partially soluble, a phenomenon known as “Ostwald ripening” or “Ostwald ageing” may occur. Smaller particles may dissolve and redeposit on larger particles, or join to each other. As a result, the largest drug particles may grow too large to reach their destination in the lung.

Although the propellant must be a non-solvent for the drug, it must be able to dissolve the surfactants used in MDI formulations. Therefore, solvency characteristics appropriate to the drug and type of MDI formulation are key to the MDI product performance in delivering the drug to the lungs.

- Other considerations.

Other considerations include whether the proposed substitute is commercially available or capable of being synthesised through realistic commercial processes; whether it can be made sufficiently pure for pharmaceutical use; and whether it will continue to be available in sufficient quantities to meet patient needs.

Identification of Alternative Propellants

This section describes the difficulty of identifying compounds that fulfill all the criteria for use as MDI propellants.62

Overview

Consideration of two or three of the necessary criteria for MDI propellants quickly eliminates many compounds from consideration. For example, one threshold question is vapour pressure or volatility. As discussed above, an MDI propellant must be able to exist as a gas at room temperature and be liquefied by compression. Most compounds have higher molecular weights or other molecular characteristics that cause them to be solids or liquids at room temperature. For example, a survey of 15,000 compounds listed in the Handbook of Chemistry and Physics shows that fewer than 200 have boiling points in the required range.63

Stability concerns also eliminate many possible propellants. A relatively unstable compound may deteriorate over time and lose its essential properties, react with the other agents in a formula, or cause container corrosion. Degradation can be dangerous, as it
leads to breakdown products with unknown toxicity. Furthermore, some compounds may degrade easily in the lower atmosphere, contributing to photochemical smog (excess ground-level ozone).

More stable compounds are generally preferable because they are non-reactive and tend to be safer for use in humans. These compounds do not contribute to photochemical smog, because they do not break down in the lower atmosphere. However, they are associated with a different set of environmental impacts. Because of their stability, they rise to the upper atmosphere and may contribute to stratospheric ozone depletion or potential climate change. CFCs are a prime example of safe, stable compounds that have upper-atmosphere environmental effects.

In general, it is difficult to unite a large number of positive characteristics in a single compound without creating one or more drawbacks. A compound may possess certain characteristics due to the predominance of particular constituents, such as hydrogen or fluorine. Increases or decreases in these constituents typically improve a compound’s acceptability in one respect while lessening it in another. The following example illustrates the unavoidable trade-offs:

- High hydrogen content is desirable because it reduces the compound’s atmospheric lifetime. Hence, it tends to reduce the compound’s ozone depleting potential. However, high hydrogen content is linked to flammability.

- Flammability can be reduced by increasing the relative amounts of chlorine or fluorine.

- Higher chlorine content generally reduces flammability but increases ozone depleting potential.

- Higher fluorine content generally reduces flammability but increases atmospheric lifetime. Hence, it tends to increase the compound’s contribution to climate change.

As this example illustrates, efforts to eliminate a particular characteristic tend to result in the addition of other undesirable effects.

**Consumer Aerosols: Hydrocarbons**

The pharmaceutical industry is highly regulated, with standards significantly different to those in the food and consumer industries. This results in a high degree of constraint around the materials that may be used for ingestion by humans.

Hydrocarbons (e.g., propane and isobutane) have replaced CFCs as propellants in many commercial aerosols, such as hairsprays. Although initially considered to be potential CFC replacements, they have been found unacceptable for pharmaceutical purposes.

An efficacious pharmaceutical formulation must be physically stable for many months to satisfy the practical requirements of manufacture, distribution, and patient use. Solvency and density are critical properties of the propellant which determine the com-
patibility of the drug with the propellant, other components of the formulation, and ultimately the stability of the MDI product. While hydrocarbons differ significantly from CFCs in these key properties, exploratory studies suggested that hydrocarbon propellants could serve as potential replacements. However, to date, there have been no reports of robust commercial formulations that could overcome the solvency and density limitations of hydrocarbons.

The safety of materials for use in humans is of paramount importance to all parties concerned in the development and treatment of patients with medicinal products. Concerns were raised over the suitability of certain hydrocarbons as replacement propellants whilst reviewing the animal safety data available on isobutane. These concerns arose because the ability of isobutane to induce abnormalities in the heart rhythm under certain circumstances was greater than that for HFA 134a.

Hydrocarbons are highly flammable substances, which pose an added risk factor for the development of new medical products. Flammability was seen as an added liability for obtaining worldwide regulatory approval and acceptance.

In some regions of the world, hydrocarbons pose a concern due to photochemical oxidant formation. This process involves a series of reactions between hydrocarbons and oxides of nitrogen, which result in elevated concentrations of ozone and other harmful chemicals at ground level.

Ozone is the only naturally occurring gas in the atmosphere whose background concentration is near to its occupational exposure standard. This means that slight increases in the concentration of ground-level ozone due to photochemical reactions can cause adverse physiological effects in humans.

Hydrocarbons—particularly those known as “liquefied petroleum gases” (LPGs) or “volatile organic compounds” (VOCs)—are the subject of numerous environmental regulations in Europe and the United States. They have also received attention at the international level. In 1991, nineteen European countries, the U.S., and Canada agreed to cut their emissions of VOCs by thirty percent by 1999.

On balance, the difficulties associated with pharmaceutical development and the potential safety and environmental consequences lead to the conclusion that hydrocarbons are not viable substitutes for CFC propellants in MDIs.

The Choice of HFCs

Following the first warnings from the scientific community in the early 1970s regarding the environmental effects of CFCs, chemical manufacturers began the search for replacements.

The criteria listed above are specific to MDI propellants; somewhat different considerations had to be taken into account in finding suitable CFC replacements for refrigeration, air conditioning, and other uses. One element, however, was common to each of these efforts: the need to find a substitute that would not deplete stratospheric ozone.

With this consideration in mind, the major chemical producers concentrated their search for CFC replacements on hydrogen-
containing compounds. It was well established that if a compound contained hydrogen, it would decompose to a great measure before it reached the stratosphere. Thus, the possibility of ozone depletion would be much reduced.

In seeking a class of compounds that would provide the best possible mix of characteristics, and after review of other potential alternatives to CFCs, the chemical producers eventually began to focus on hydrofluorocarbons (HFCs) and hydrochlorofluorocarbons (HCFCs).

HCFCs have some ozone depletion potential (though less than CFCs); thus, they are not attractive as long-term CFC replacements. They are being used on an interim basis in some applications that do not require lengthy periods of testing and approval. HFCs, in contrast, have no ozone depleting potential. Therefore, HFCs are clearly better suited for uses that require a long development period, such as in MDIs.

Pharmaceutical firms and others also attempted to find suitable alternatives to CFC propellants in MDIs. In addition to HFCs, hydrocarbons, perfluorinated compounds, and dimethyl ether were also considered.

In the end, two particular HFCs emerged as substitute propellants for MDIs: HFCs 134a and 227. These HFCs fit the criteria for an MDI propellant far better than any other known compounds (apart from CFCs). Neither HFC-134a nor HFC-227 has any ozone-depleting potential. These propellants are non-flammable and have been shown to be safe for human inhalation through extensive toxicity testing. Each has a vapour pressure suitable for MDI usage. The vapour pressure of HFC-134a at 20°C is approximately 70 psi. The vapour pressure of HFC-227 at 20°C is approximately 40 psi.

No known propellant, however, can be described as environmentally neutral. Although HFCs have no ozone depleting potential, they have been identified as contributors to climate change. The minimal contribution of the HFC MDI to climate change is discussed further in Section VIII ("The HFC MDI").

A recent review of 15,000 compounds has confirmed that there are no CFC alternatives other than HFCs that now appear promising for use as MDI propellants. The results of this study are summarised in Appendix A.

The Testing Consortia

The search for CFC alternatives required extensive research into the toxicological and environmental effects of promising substitutes. As a result, key industry representatives decided to establish joint programmes to conduct the necessary studies. Chemical companies specialising in fluorocarbon technology led the initiative by establishing two international consortia, PAFT and AFEAS. The pharmaceutical industry soon followed
with the IPACT-I and II consortia, whose mission was to test the safety of CFC alternatives for pharmaceutical use.

PAFT. The Programme for Alternative Fluorocarbon Toxicity Testing (PAFT) was created in December 1987 to test CFC alternatives for industrial use. PAFT had three major goals: “to determine the potential health and environmental effects of CFC alternatives in accordance with international guidelines, to derive toxicity information through a rapid, cost-effective programme which pooled the resources of member companies and shared results, and to ensure the rapid publication of results.” PAFT built upon the initial findings of individual manufacturers, testing a variety of HFCs and HFCFs as possible CFC replacements.

AFEAS. The Alternative Fluorocarbons Environmental Acceptability Study (AFEAS) was set up by 17 chemical companies in 1988 to investigate the environmental effects of CFC alternatives.

IPACT I & II. The PAFT studies provided much needed information to the pharmaceutical industry on the safety of potential CFC substitutes. Pharmaceutical requirements, however, are much more stringent than standards for general industrial use. Thus, MDI manufacturers had to undertake their own toxicity testing to prove that the compounds they proposed to use for MDIs were safe for inhalation.

Co-operative efforts by the pharmaceutical industry began in January 1989, when a group of U.S. MDI manufacturers met to discuss the impending restrictions on the supply of CFCs. That meeting led to the formation of the Pharmaceutical Aerosol CFC Coalition (PACC). In April 1989, a consortium similar to PACC formed in Europe. This European grouping of pharmaceutical companies was called the International Pharmaceutical Aerosol Consortium (IPAC). PACC and IPAC later merged, forming a single entity known as IPAC.

In September 1989, PAFT released preliminary toxicity data on HFC-134a. Subsequently, IPAC formed a Toxicology Panel to investigate HFC-134a and make recommendations on the need for a global consortium of MDI manufacturers to organise and fund toxicity testing specifically targeted toward pharmaceutical use of this compound.

At the Toxicology Panel’s first meeting in January 1990, the members decided to take the lead in toxicity testing. In May 1990, the International Pharmaceutical Aerosol Consortium for Toxicology Testing of HFA-134a (IPACT-I) formally came into being. IPACT-I’s mission was to test HFC-134a (also called HFA-134a) for use in MDIs.

At the same time, a second potential alternative, HFC-227, was introduced to IPAC by Hoechst AG, which had performed some preliminary testing on this compound. Unlike HFC-134a, which was intended for multiple industrial uses, HFC-227 was developed primarily for use as a propellant in MDIs. In December 1990, MDI manufacturers formed a second testing consortium, IPACT-II, to conduct the necessary toxicity tests for the pharmaceutical use of HFC-227.
IPACT-I and II undertook extensive testing programmes designed to meet the most stringent regulatory requirements. HFC-134a and HFC-227 were found to be essentially biologically inert, with mild clinical effects seen only at extremely high dose levels. By the end of 1995, the Committee for Proprietary Medicinal Products (CPMP) of the European Union had issued assessments of HFC-134a and HFC-227, concluding that each represented a “...suitable alternative to CFCs currently used in the formulation of medicinal products, including metered dose inhalers for treatment of asthma.”

Thus, these two compounds were evaluated and shown to be safe for use in MDIs. As of July 1999, HFC MDIs have been approved and introduced in at least 40 countries around the world. Many more will be introduced over the next several years.

The Reformulation Effort

As described above, the pharmaceutical industry identified two non-CFC propellants suitable for use in MDIs: HFCs -134a and -227. However, the components and formulations used in CFC MDIs had to be modified for use with these new propellants. Intensive testing and research is underway to identify and develop formulations and materials that will work with HFCs. Potential formulations must undergo toxicology, stability, and clinical testing.

MDI products are also subject to extensive regulation by national health authorities to ensure product safety, product efficacy, and manufacturing quality. In virtually all countries, a company may place a product on the market only in accordance with specific licenses issued by the appropriate authority. If a company wishes to alter an MDI to a significant degree, e.g., change propellants, it must first obtain a new market authorization. A new market authorization is based on a comprehensive re-development effort including clinical and toxicology studies. The review by health authorities typically is rigorous and searching, especially when the product is intended, as here, for chronic use by millions of particularly vulnerable patients (e.g., severe asthmatics, children, and the elderly).

This section will discuss the essential elements of MDIs and the steps in the development process for HFC MDIs. Figure 2 shows the essential elements of a CFC MDI. Figure 3 indicates that all physical components and formulation ingredients except the drug substance are subject to change.

An Overview of the CFC MDI

Propellants

Propellants, which constitute more than 98% of the drug formulation, are key ingredients of MDIs. CFC MDIs typically contain as propellants various mixtures of

<table>
<thead>
<tr>
<th>Propellant</th>
<th>Vapour Pressure (20 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFC-11</td>
<td>-1.8 psi</td>
</tr>
<tr>
<td>CFC-12</td>
<td>67.6 psi</td>
</tr>
<tr>
<td>CFC-114</td>
<td>11.9 psi</td>
</tr>
<tr>
<td>HFC-134a</td>
<td>70 psi</td>
</tr>
<tr>
<td>HFC-227</td>
<td>40 psi</td>
</tr>
</tbody>
</table>

Summary of the Vapour Pressures of the CFC and HFC Propellants
Figure 2: Elements of an MDI

Figure 3: HFC MDI Development
CFC-11, CFC-12 and CFC-114 in liquid form. CFC-12 is the major component, providing most of the propellant energy.

When stored as a liquid in a closed container at room temperature, the propellant mixture has a pressure greater than one atmosphere. This pressure forces the drug formulation out of an MDI when the valve is triggered.

CFC-11 and CFC-114 are used to moderate pressure and to adjust the density and solubility of the propellant mixture. In some MDI manufacturing processes, the lower pressure CFC-11 is also used as a vehicle to manipulate formulation ingredients at ambient pressure and temperature. In some MDI manufacturing processes, the lower pressure CFC-11 is also used as a vehicle to manipulate formulation ingredients at ambient pressure and temperature.

The propellants also serve a critical role in creating a very fine mist. Upon release from the MDI, the propellant gases suddenly encounter a temperature well above their boiling point. This causes their flash-evaporation. The result is a respirable mist of the drug that was suspended or dissolved in the liquefied gas.

Surfactants and Co-Solvents

MDIs are formulated in two basic types: solutions and suspensions. In solution formulations, the medication is dissolved in the liquid contents of the MDI. In the suspension formulation, the medication is in the form of a fine particle dispersion.

HFCs themselves are poor solvents, and surfactants and/or co-solvents are frequently needed to obtain a suitable formulation. The properties of the individual drug and type of formulation are unique, and each MDI requires a specific formulation.

MDIs may contain, in addition to the drug and the propellants, a surface active agent or surfactant. Surfactants are used to create a stable suspension of drug particles, and to provide lubrication for the aerosol metering valve so that it will function effectively without sticking. The physical properties of the surfactants also allow them to control the size of the droplets in the final mist by preventing aggregation (clumping) of the small particles. The ideal particle size for the delivery of medication to the small passageways of the lungs is between 2 and 7 µm. Precise control of the drug particle size is crucial for ensuring effective deposition of the medication in patients’ lungs and consistent dosage amounts.

The choice of surfactant is an important and difficult step in designing an MDI. The surfactant must be soluble in the propellant mix. Furthermore, to ensure uniform suspension of the medication, the medication itself must be insoluble in the mixture formed by the combination of the surfactant and propellants. Any deviation from these conditions will result in unsatisfactory formulations. In practice, there are few surfactants available for use in MDIs which satisfy all the necessary criteria, including very low toxicity. All surfactants, including those as yet unidentified, require lengthy and costly toxicological and clinical evaluations before they can be used.

Depending on the capacity of the propellant vehicle to dissolve the surfactant, it may be necessary to incorporate a solubilising agent.
In CFC suspension MDIs, CFC-11 itself acts as a solubilising agent for the surfactants used in the formulation. As noted above, both CFC-12 and CFC-114 are poor solubilising agents, and many surfactants do not dissolve well in them. The addition of CFC-11 to the formulation creates a solution in which surfactants can be dissolved.

As with the CFC formulations, HFC formulations may require a co-solvent and/or a surfactant.

The Valve and Elastomers

MDIs use a “metering” valve that is designed to measure each dose precisely. The valve is equipped with a metering chamber that surrounds the valve stem.

At each end of the chamber there is a seal made of an elastomer. When the MDI is used, it is held with the valve pointing downward. This allows liquid to enter the metering chamber through its top end. On actuation of the device, the top end of the metering chamber is closed off by the elastomeric seal, an opening at the bottom end is unsealed, and the liquid held in the metering chamber is discharged from the valve due to the vapour pressure of the liquefied gas. The elastomers used to seal the chamber must be compatible (i.e., non-reactive) with the substances contained in the storage canister. In order to ensure proper MDI performance throughout the lifetime of the product, the design specifications for the valve and elastomers are demanding and narrowly defined.

An Overview of HFC MDI Development

CFC MDIs constitute a highly successful balance of complex forces. A change in one element of the system, the propellant, requires changes in varying degrees in others. Figure 4 provides a general overview of the HFC MDI development process. The major steps in the process are roughly as follows:

- Selection of HFC propellant(s) (HFC-134a and/or HFC-227)
- Formulation development using HFC propellant(s)
- Toxicology studies on alternative HFC propellant(s)
- Component and package development (valve, elastomers, etc.)
- Toxicology studies on new HFC-based formulation
- Stability testing on finished MDI product
- Clinical studies on new formulation (tests in humans)
- Regulatory review and approval
- Market introduction

Where possible, companies take certain steps in parallel. However, some steps can be begun only when others have been completed. For example, formal toxicology studies on the formulation cannot begin until the formulation and components have been identified.
Challenges Encountered in the Development Process

Once a company has identified a propellant candidate, it must determine the chemical and physical compatibility of the propellant with the other elements of the MDI—the drug, the surfactant, the co-solvent, any other propellant and excipient, and the valve elastomers. It must work to resolve any incompatibilities by experimenting with available alternatives to the other elements. Conceivably, the company might have to find a new substitute element, for instance, a new elastomer to go with the new propellants. A company might develop such a substitute itself, or might have to rely on another supplier of components.

In an unprecedented worldwide effort, the pharmaceutical industry has deployed more than 1,400 scientists and 90 laboratories in 10 countries around the world to reformulate MDIs with HFCs. This effort has proven far more difficult than initially anticipated.

The following are the main challenges which have been encountered by IPAC companies thus far in developing HFC MDIs:

- **Alternative Propellants:** The closest functional replacements for CFC-12 and CFC-114 are HFC-134a and HFC-227, respectively. To date, there is no suitable replacement candidate for CFC-11 in MDIs. Companies are evaluating the use of other solubilising agents which can be used in the formulations to dissolve surfactants.

- **Surfactants:** Studies to date indicate that HFC-134a and HFC-227 are not generally compatible with the surfactants currently used in CFC MDIs. New surfactants and co-solvents are under development.

Figure 4: HFC MDI Development Process Generic Timeline

<table>
<thead>
<tr>
<th>Stage</th>
<th>Average Duration</th>
<th>Anticipated Variation from Product to Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation Development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicology Testing on Propellants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component and Package Development</td>
<td></td>
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</tr>
<tr>
<td>Toxicology Studies on Formulation</td>
<td></td>
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</tr>
<tr>
<td>Stability Testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulatory Review and Approval</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Years: 1 2 3 4 5 6 7 8 9
- **Valve Elastomers**: A nother element in the reformulation process is the identification of elastomers which are more compatible with an HFC formulation. In some cases, elastomers from CFC MDIs function less well in HFC formulations, causing unacceptable fluctuations in the dosage amount. Alternative elastomers for use in HFC MDIs are under development.

- **Actuators**: The actuator in an MDI is a plastic device which directs the medication expelled from the valve stem into the mouth of the patient. It affects the size of drug particles and the shape of the spray resulting from activation. These two factors are critical to the delivery of precise amounts of medication to the small passageways in the patient’s lungs. Due to the differences in the formulations between CFC and HFC MDIs, there may be a need in some cases to redesign the actuator.

- **Manufacturing Process**: Companies are designing and evaluating possible changes in the manufacturing process simultaneously with reformulation. This will make it possible to begin full-scale production at the earliest possible date. It may also prompt further changes in the formulation in order to facilitate manufacture of the final product.

  CFC-11 has historically played an important role in the manufacturing process. Because CFC-11 is a liquid at room temperature, a drug dispersion in CFC-11 can be maintained at standard atmospheric pressure during product manufacture. There are significant technical advantages to manufacturing using non-pressurised systems. However, because no substitute has been found for CFC-11, manufacturing processes are being redesigned to accommodate a more volatile propellant mixture.

**Studies on the Propellant**

- **Toxicology**: In order to market a new MDI, the manufacturer must show that it is safe for human use. This requires extensive toxicity testing of each new component. The following discussion summarises the testing required for one new component: the HFC propellant.

  MDI manufacturers entered into two separate joint research ventures (IPACT-I and IPACT-II) to facilitate the rapid and efficient completion of toxicology testing on the non-CFC propellants, HFC-134a and HFC-227. The IPACT-I and II programmes were equivalent in scope to a programme for a new drug substance.

  Toxicology testing and evaluation of the new propellants consisted largely of four major types of studies, performed in three species of animals (rats, mice, and dogs). These studies were: (i) acute studies, (ii) repeated-dose studies, (iii) reproductive studies, and (iv) carcinogenicity studies. The acute studies were designed to estimate the lethal limits of toxicity of the compound. The repeated-dose studies examined the range and severity of toxic effects in all organ systems. On the basis of the repeated-dose studies, an appropriate dose was selected for carcinogenicity studies. Approximately two years were required for the carcinogenicity studies, with an additional year needed for evaluation of the data resulting from the studies.
IPACT-I began its testing programme for HFC-134a in July 1990. The IPACT-II testing programme for HFC-227 began in March 1991. In July 1994 and September 1995, respectively, both compounds were officially recognised as suitable for use in MDIs by the CPMP of the European Union.  

Pharmacokinetics

An essential part of the evaluation of a new propellant is pharmacokinetics. IPACT-I and II conducted an extensive pharmacokinetic programme to investigate absorption, distribution, metabolism, and excretion (ADME) of the HFC propellants. Results from these studies were presented to the CPMP together with the results of toxicology testing.

Clinical Studies

IPACT-I and II conducted basic clinical studies on the propellants in healthy human volunteers which established tolerability as well as absorption/elimination kinetics. These safety findings were recently confirmed through joint studies co-sponsored by IPACT-I, IPACT-II, and PAFT.  

Studies on the Formulation

Toxicology

Toxicology studies on the separate components are insufficient to show the safety of the new product. MDI companies must also perform toxicology studies on the formulation as a whole. These studies, which are being undertaken individually, are designed to ensure that no new or increased incidence of toxicity results from the interaction of components in the formulation. The toxicology protocols for formulations are product-specific and are generally less extensive than those required for the propellant.

Bioequivalence

MDI companies must also establish that the bioavailability of the new formulation is equivalent to the old. This is accomplished through studies on animals and humans, as well as additional laboratory work.

Formulation Data and Stability

The MDI company must demonstrate that the new product will meet detailed performance and quality criteria. The company must assemble data on the moisture content of the formulation; the extraction of components into the formulation from the valve or container; the need for priming shots; the amount of active ingredient delivered; the uniformity of content per actuation; the particle size distribution of the active ingredient in the aerosol; and stability.

The purpose of stability testing is to determine whether a product will remain suitable for use throughout its indicated shelf life. The tests look for any deterioration or breakdown of the medication, the storage canister, or the valve over time. Delivery consistency and, in aerosols, particle size are also monitored. These studies are especially labour-intensive for inhalation drugs. Experimental stability studies may begin in conjunction with reformulation studies, but formal, long-term stability studies are required for the final product.

Most health authorities require that a new pharmaceutical product undergo stability testing for a period of time equal to its stated shelf life before it is approved for sale. In the U.S., the FDA requires that the tests be carried out on three large-scale production batches of the product, manufactured in the actual plant that will be used for commercial production after approval is obtained.
This formal testing can begin only after reformulation and retooling of the manufacturing process is complete. The minimum practical shelf life for MDIs is two years. Thus, stability tests have to continue for at least two years. Any significant change in the formulation or canister/valve components introduced during development requires restarting stability studies. After stability testing is concluded, several months are needed for data evaluation and report generation.

Clinical Studies

Before any new drug formulation can be tested in humans, the appropriate approvals must be obtained. In some countries, an application must be filed with the health authorities. This application must include results of specified toxicology studies. In other countries, the company needs only obtain approval from the hospital ethics committee where the clinical trial will be conducted.

Clinical trials are clearly the most critical and difficult step in the drug development process. They are required to show efficacy and long-term safety. U.S. authorities also require dose-ranging studies on the formulation. Health authorities' ultimate approval decision will be based primarily upon data derived from clinical studies.

Efficacy studies for a reformulation vary in length depending on the type of drug involved. Protocols also vary from one category of drug to the next.

Regulatory authorities require controlled, randomised safety studies of at least three months' duration. In addition, at least one year's experience for 100 individual patients is required.

The specific requirements for clinical studies vary from country to country. In both Europe and the United States, health authorities have developed and issued special guidance on the types of studies and data that will be required for HFC MDIs. In general, the time required from the design of the first study to the completion of the last study report will range from two to three years.

Even after the product has been approved for marketing, post-marketing surveillance studies may be required. These studies monitor the product after its introduction to the market to ensure that no unexpected safety aspects emerge.

Regulatory Approval

Filing of a marketing application initiates formal government review of a new product. Toxicology studies on the formulation and clinical trials must be completed, and the corresponding reports prepared, prior to filing. Some stability data must also be available at this stage, though the studies do not necessarily need to be complete. The amount of time required for review of an application varies widely depending on the specific product and the country in which it is being registered. In general, approval will take between six months and two years.

Where the Industry Stands

The pharmaceutical industry has spent over US one billion dollars to reformulate CFC MDIs and considerable continued investment will be necessary to complete the transition.

This hard work and investment are now bearing fruit. In 1995, the first HFC MDI was introduced in several countries. Since that time, the industry has made significant
and continuous progress in bringing the new generation of inhalers to patients around the world. As of July 1999, HFC MDI products were available in at least 40 developed and developing countries. For example, at the time of publication, at least two salbutamol products and an inhaled corticosteroid product are available in many Member States of the European Union. At least one HFC MDI product is available in the United States, in each Member State of the European Union, in Australia, Canada, Japan, New Zealand, and in other developed countries. Likewise, many developing countries, such as Costa Rica, El Salvador, Guatemala, Malaysia, Mexico, and South Africa have at least one HFC MDI product on the market. Many additional HFC MDIs are awaiting regulatory approval and will be introduced in the coming years.

While substantial progress has been made in introducing new CFC-free MDIs, pharmaceutical companies continue their research and development efforts to introduce new inhalation delivery systems.

**Implications for Patients and the Medical Community**

Patients who depend on MDIs may be reluctant to make the transition to HFC MDIs. A considerable educational effort for both patients and physicians may be necessary to overcome this reluctance. Those who suffer from respiratory disease are extremely sensitive to even the smallest changes in medication. Some asthma patients are particularly resistant to change because they must count on their therapy to relieve sudden, unpredictable, and potentially life-threatening attacks. A doctor's recommendation may be crucial in persuading these patients to use the new products.

In addition, it is likely that patients will perceive a difference between their CFC inhalers and the reformulated inhalers. Possible differences may include the way that a puff of medicine will impact on the back of a patient's throat; slight changes in product appearance; and subtle, yet noticeable, differences in taste and odour.

All of these factors may cause the potential for anxiety in patients. As a result, comprehensive education programmes to teach doctors and patients about the new products will be of the utmost importance. Patients will need to understand that despite the superficial differences in the products, they can expect to receive the same health benefits. Some HFC MDIs may actually offer improved performance over CFC MDIs, due to technological advances.

Tens of thousands of physicians and other health care providers in over 100 countries must be educated in the use of these new products. In turn, they will be required to educate millions of patients. To this end, IPAC has implemented educational initiatives for doctors and patients through brochures, symposia, and press releases. These initiatives will help to ensure that patients continue their confidence in the MDI delivery system.

Finally, one inevitable effect of the reformulation effort has been the re-direction of time and resources to this effort and away from research into new chemical entities. In patient terms, this translates into lost opportunities to benefit from the introduction of promising new treatments. Thus, the decision to assign resources to reformulation of an existing drug product has not only environmental but medical implications.
The development of the HFC MDI is only one element of the pharmaceutical industry's efforts to develop new pulmonary delivery systems. The industry is actively engaged in research on alternative technologies for delivering medication to the lungs that use neither CFCs nor HFCs.

One area of investigation is how to produce a fine mist without the benefit of a liquefied gas propellant, by using an alternative vehicle such as water. In theory, there are various ways in which droplets of medication can be generated and delivered to the lungs. Several examples follow:

- A drug-containing solution can be forced through a nozzle with small channels, resulting in liquid jets which generate the aerosol. One of the most advanced of this new type of delivery systems is a multidose inhaler, which utilises mechanical energy to direct two opposing jets to aerosolise on impaction. A culation of the device releases a soft mist aerosol of medication. Promising results for this type of soft mist inhaler (SMI) have been reported for beta agonists, anticholinergics, inhaled corticosteroids and combination bronchodilators.

- Certain materials — referred to as “Piezoelectric”— change their shape in response to an alternating electric current. The movement of the Piezoelectric material may be transmitted to a liquid, causing droplets to be thrown off the surface of the liquid. Piezoelectric devices are now used in nebulisers to generate a fine droplet mix by means of a rapidly vibrating crystal. Development of a miniaturised portable device is technically feasible.

- A delivery device might force liquid through a break-up plate, mesh cap, or open-cell foam, resulting in an aerosol with droplets dependent on the size of the holes.

- An ultrasonic horn might be used to generate an aerosol cloud by capillary wave action.

- Other possible future initiatives include use of microelectronics in breath-actuated devices to improve accuracy and allow compliance monitoring; use of reusable delivery systems to diminish the waste stream; and development of strategies for reduction of droplet coalescence.

An alternative area of investigation focuses on how to generate and deliver medication as dry powder. Researchers are studying the manipulation of the physicochemical properties of the drug substance (e.g., size and shape of the drug substance particles using super critical fluid recrystallisation) and the use of carrier particles (e.g., large porous particles). Another area of research addresses the need to provide aerosolisation mechanisms that do not rely on the inspiratory effort of the patient. Such mechanisms may include use of a compressed gas, an electrical power source, or a mechanical hammer.

It is important to recognise that the development process for inhaled products is complex due to the interaction between the delivery system and the medicinal formulation. The physical and chemical properties of some formulations and the technology being utilised in the future may make this even more challenging. Several years will be required to demonstrate acceptable in vitro
and in vivo performance, gain regulatory approval, and achieve patient acceptance for each new product, even for a known product reformulated with HFCs. Products are subject to extensive regulation by national health authorities to ensure product safety, product efficacy, and manufacturing quality. Additional time is required for registration on a country-by-country basis. Once a new product is approved, significant time is required for uptake and evaluation by physicians and patients. Post-marketing experience will ultimately demonstrate to what extent a new product can meet the needs of patient populations and subpopulations.

It is impossible to predict to what extent new technologies might replace current delivery systems. The MDI is a nearly universal, low-cost device, applicable to virtually all asthma medications. There is no guarantee that any new technology would have more universal application than the MDI over the full spectrum of active ingredients and patient populations worldwide. Rather, new delivery systems would likely add to the mix of treatment options rather than allowing a wholesale substitution.

Asthma, once thought of as a “simple” hypersensitive reaction, is now known to be a complex condition with a spectrum of causes and contributing factors. There has been a recent explosion of research on asthma, and in the future, a better understanding of the disease process could lead to improved therapies.
The Medical Need

There is a large and increasing need for respiratory therapy. In the case of asthma, proper treatment allows the patient to engage in normal physical activities and to pursue a variety of occupations. Proper treatment improves the overall health of asthma patients and may save the lives of those who experience acute attacks.

Inhalation is generally accepted as the preferred means of delivery for respiratory medication. The current mix of inhalation delivery systems includes MDIs, DPIs, and nebulisers. A comparison of these three delivery systems shows that they are not always interchangeable. Each offers important benefits. Availability of a wide range of therapy options ensures that individual patients receive the best possible treatment.

The MDI is the mainstay of treatment for asthma and other respiratory diseases. It requires no external power source; meters out doses independent of the patient’s inspiratory effort; is available to deliver all of the most commonly prescribed asthma and COPD medications; is adaptable for use by special patient populations; and is widely available in an extensive range of drug categories. Recent data from the world’s fifteen largest populations of patients receiving respiratory medication indicate that MDIs account for 70 percent of all inhalation therapy.

Greenhouse Gases and Climate

In recent years, scientists have raised concerns about the emissions of “greenhouse gases” resulting from human activity and their impact on the earth’s climate patterns. Greenhouse gases include carbon dioxide (CO$_2$), methane, nitrous oxide, CFCs, HFCs, perfluorocarbons, and sulfur hexafluoride.

The concept of climate change is linked to a process known as the “greenhouse effect.” When radiation from the sun travels to the earth, some of it is absorbed by the earth which heats up, reflecting heat energy back into the atmosphere. Water vapor, CO$_2$, and other gases trap solar heat released from the earth and slow its escape back into space. This greenhouse effect warms the Earth’s surface.

Greenhouse gas emissions resulting from human activities have increased over time, due to industrialisation and population growth. The burning of fossil fuels is the primary source of CO$_2$ emissions (estimated to represent more than 60 percent of anthropogenic—manmade—releases of all greenhouse gases).

Many scientists now believe that this increase in anthropogenic emissions is causing an acceleration of the greenhouse effect and disrupting the balance between incoming and outgoing heat energy.

In 1992, over 160 nations signed and ratified a treaty called the United Nations Framework Convention on Climate Change (UNFCCC). This treaty calls for voluntary reductions of greenhouse gas emissions by developed countries. After official reports predicted that the voluntary
emissions reduction goals in the UNFCCC would not be met, the Parties to the UNFCCC began to negotiate mandatory greenhouse gas emission reductions.

In December 1995, a scientific advisory body to the United Nations Environment Programme stated that “the balance of evidence suggests a discernible human influence on global climate.”

In December 1997, the Parties reached agreement on the Kyoto Protocol, an historic Protocol to reduce greenhouse gas emissions. The Kyoto Protocol contains binding emission reduction targets for developed countries. If ratified, it will be implemented on an international level.

The member companies of IPAC share the Parties’ concerns about the potential effects of global warming on, among other things, human health, forests and other natural areas, freshwater supplies, and agriculture. Some scientists predict that a warming climate could, among other things, exacerbate air quality problems and lead to increased levels of airborne pollen that aggravate respiratory disease, asthma, and allergic disorders.

IPAC agrees with the Parties that the Kyoto Protocol should be implemented in such a way as to minimise any negative effects on public health and social welfare. Through educational efforts explaining the critical role of HFC MDIs in treating illness, IPAC seeks to ensure that the implementation of the Protocol does not jeopardise or impede the use or availability of medical inhalers and aerosols by patients who rely on these vital medications.

The Climate Change Impact

Among the greenhouse gases covered by the Kyoto Protocol, carbon dioxide is the most significant, accounting for well over half of all man-made greenhouse gas emissions.

It is estimated that global emissions of all greenhouse gases in the year 2010 will total approximately 59 billion tonnes of carbon dioxide equivalent emissions. In the year 2010, HFC emissions from MDIs are currently projected to make up no more than 0.02 percent of total worldwide emissions.

HFCs 134a and 227 fit the criteria for an MDI replacement propellant far better than any other known compound. These propellants are pharmaceutically acceptable and have been shown to be safe for human inhalation through extensive toxicity testing. Each has a vapour pressure suitable for MDI usage, and each is essentially biologically inert.

Neither HFC-134a nor HFC-227 has any ozone depleting potential. Moreover, these HFCs have shorter atmospheric lifetimes and lower global warming potentials than the CFCs which they replace. The chart below demonstrates the differences between these compounds.

MDIs are an indispensable therapy for over 70 million patients suffering from respiratory disease. The replacement of CFC propellants with HFCs allows for the continuation of MDI therapy with no ozone depleting potential and savings in terms of global warming potential.
The enormous medical need for the HFC MDI must be taken into account in the application of any climate change policy on both an international and national basis. Actively protecting patients and preserving responsible patient care is vitally important during this radical and comprehensive replacement of the CFC medications currently relied upon by millions of patients around the world.

Conclusion

The MDI is an essential element of respiratory care. Relying on patients worldwide, it provides quick, proven delivery of preventive therapy and rescue medication. The industry is vigorously pursuing research in inhalation delivery and may someday be able to add other options to the mix of available treatments. Nevertheless, the MDI will play an important role for a long time to come. It is imperative that patients retain access to this trusted and vital therapy.

### Comparison of CFCs and HFCs

<table>
<thead>
<tr>
<th>Propellant</th>
<th>Ozone Depletion Potential ( (\text{CFC} \ 11 = 1) )</th>
<th>Atmospheric Life (years)</th>
<th>Direct Global Warming Potential ( (\text{CO}_2 = 1)^{11} )</th>
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<tr>
<td>CFC 11</td>
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<td>CFC 114</td>
<td>1</td>
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<td>9,300</td>
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<tr>
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<td>0</td>
<td>16</td>
<td>1,300</td>
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<tr>
<td>HFC 227</td>
<td>0</td>
<td>33</td>
<td>2,900</td>
</tr>
</tbody>
</table>
2 Id.
3 It has been estimated that one million people worldwide die from asthma every decade. See “Industry Supports Global Asthma Plan,” 2103 Scrip 23 (16 Feb. 1996).
6 Figure based on information from IPAC members.
8 American Lung Association, Lung Disease Data 1996, at 3.
10 American Lung Association, Lung Disease Data 1996, at 3.
14 Id.
15 Centers for Disease Control and Prevention 1996.
16 Id. 5,167 deaths were recorded in 1993, as compared to 2,598 in 1979.
18 Spray Technology & Marketing 26, 63 (Sept. 1995).
22 International Consensus Report at vii.
24 Id.
29 Id.
31 International Consensus Report at 28.
I nhalation therapy is not limited to asthma and COPD. This form of therapy may be used in other respiratory disorders, including cystic fibrosis, bronchiectasis, and airway irritability. It is also employed in the treatment of non-respiratory disorders, e.g., for the delivery of medications whose oral bioavailability is extremely low, such as peptides.


Grossman, supra, at 62.

Id. at 61-62.


Id. at 44-45.

Decision IV/25 of the Fourth Meeting of the Parties to the Montreal Protocol.

Creation of expert panels to assess control measures is authorised by Article 6 of the Protocol.


See W. Stahlhofen et al., supra, at 385-98. Other factors influencing dispersancy are the percent of the propellant in the formulation; the valve type; the addition of low-boiling solvents to the formulation; and the amount of polymer or high viscosity ingredients.

The individual pressures of the CFCs at 20°C are as follows: CFC-11, -1.8 psi; CFC-12, 67.6 psi; CFC-114, 11.9 psi.


Appendix A contains a list of these compounds. The original list of 15,000 compounds was drawn from The Handbook of Chemistry and Physics (67th ed. 1986-87).


Deborah MacKenzie, "Europe cuts the chemicals that cause smog; agreement to cut emissions of volatile
Testing to Extremes: Industry's Cooperative Effort to Test the Health and Safety of Selected Fluorocarbon Alternatives to CFCs. PAFT (1995).

Sixteen CFC manufacturers are members of PAFT: AlliedSignal Inc. (USA); Asahi Glass Co., Ltd. (Japan); Ausimont S.p.A. (Italy); Central Glass Co., Ltd. (Japan); Daikin Industries Ltd. (Japan); E.I. Du Pont de Nemours & Co., Inc. (USA); ICI Chemicals & Polymers Ltd. (UK); La Roche Industries Inc. (USA); Shinwha Co., Ltd. (Republic of Korea); Hoechst AG (Germany); Rhône-Poulenc Chemicals Ltd.; Showa Denko K.K. (Japan); Solvay SA (Belgium); Solvay Fluor Derivate GmbH (Germany).

The term "Hydrofluoroalkane" (HFA) is used interchangeably with the term "Hydrofluorocarbon" (HFC).

Committee for Proprietary Medicinal Products, "Result of the Coordinated Review of 1,1,1,2-Tetrafluoroethane HFC-134a," 13 July 1994; and Committee for Proprietary Medicinal Products, "Result of the Coordinated Review of 1,1,1,2,3,3,3-Heptafluoropropane (HFC-227)," 13 Sept. 1995. IPACT-I and IPACT-II were asked to provide some further reassurance regarding possible effects on bronchial hyperreactivity and nasal mucociliary clearance. Studies addressing these issues have been completed and currently are undergoing review by European health authorities.

IPAC Survey (Nov. 1995).

T he results of the joint studies are available from the United States National Technical Information Service (www.ntis.gov).


Patent US 5469843.


A ne independent consulting report prepared for the European Commission concluded that: "Because of such an excessively slow product development cycle it is hard to envisage any significant market penetration of non-HFC propelled MDIs by 2010."


ALA Lung Disease Data 1997, at 7. Now under intensive study are the chemical reactions that take place in the asthmatic process the nature of cell-cell communications; the way information is conveyed from one cell or type of cell to another; and the role of the tissue lining of the airways.

Executive Office of the President, Office of Science and Technology Policy, "Climate Change: State of Knowledge" at 2.


Derived from the Inter governmental Panel on Climate Change, The Supplementary Report to the IPCC Scientific Assessment 1992, at 91-92.

IPAC projects that in the year 2010 total worldwide emissions from MDIs will be approximately 7,500 to 9,000 metric tonnes of HFCs, or 10.8 to 12.9 million metric tonnes of carbon dioxide equivalent (CDE).
In 1999, IPAC projected total worldwide HFC emissions from MDIs in the year 2010. Through a survey of its members and reference to data assembled by a Montreal Protocol panel of experts, IPAC gathered information concerning (i) the total number of MDI units manufactured worldwide by the entire MDI industry in 1998; (ii) the average amount of HFC 134a and HFC 227 that will ultimately be contained in each MDI unit; and (iii) estimated annual growth for the worldwide MDI market.

Based on this information, the total number of units that will be manufactured in the year 2010 was projected assuming (i) all CFC MDIs will be converted to HFC MDIs by 2010; and (ii) two annual MDI market growth rate scenarios, 1.5 percent and 3 percent. HFC emissions from MDIs in 2010 were calculated by multiplying the projected MDI unit data for 2010 by the average amount of HFC contained in each MDI unit.

In comparing the climate change effect of various greenhouse gases, carbon dioxide is used as the basis of comparison. Each greenhouse gas is assigned a “global warming potential” (GWP) over a given period of time to reflect its relative contribution as compared to carbon dioxide. HFC 134a has a 100 year GWP of 1300; HFC 227 has a 100 year GWP of 2900. Carbon dioxide equivalent emissions were calculated taking into account each MDI company's use of HFC 134a versus HFC 227.

Based on 1992 IPCC emission scenarios, it has been projected that total emissions of all greenhouse gases worldwide will be approximately 59 billion tonnes of carbon dioxide equivalent. HFC emissions from MDIs in the year 2010 are projected to be no more than 0.02 percent of the total impact from all greenhouse gases.

A 100 year time horizon is assumed.
Appendix A

During the preparation of this Paper, a study was conducted to determine whether any compounds other than HFCs could be identified as promising CFC alternatives for MDI usage. The study focused on a list of 15,000 compounds drawn from The Handbook of Chemistry and Physics (67th ed. 1986-1987). Compounds that did not possess a boiling point in the chosen range (-100° to +30°C) were eliminated from consideration. This range is believed to include all compounds with acceptable vapour pressures for MDI usage. Elimination of compounds with boiling points that were either too high or too low left approximately 180 compounds for further study. These compounds are shown in the table below. Characteristics that disqualify a compound from usage as an MDI propellant are noted in the right-hand column.

A review of this table demonstrates that none of the studied compounds (with the exception of HFCs) now appears to be a promising substitute for CFC propellants in MDIs.

The terms “flammable” and “reactive” are used in the table as follows:

“Flammable”: The compound forms an explosive mixture in air.

“Reactive”: The compound contains a functional group or groups that can easily be converted through oxidation, reduction, hydrolysis, etc. to another compound, or are capable of being polymerised to a solid or a liquid. Examples of these functional groups are CHO; COX where X=Cl, Br, or S; CN; NO; C=C; and C≡C.

This study was conducted by Dr. John J. Daly, Jr., a contributor in the preparation of this Paper.
Properties of Volatile Organic Compounds Selected From the Handbook of Chemistry and Physics
(Boiling Point Range: −100° to +30°C)

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Structure</th>
<th>b.p. (°C)</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>6603</td>
<td>Ethane</td>
<td>CH₃CH₃</td>
<td>-88.6</td>
<td>Flammable</td>
</tr>
<tr>
<td>443</td>
<td>Acetylene</td>
<td>H:C=CH</td>
<td>-84</td>
<td>Flammable</td>
</tr>
<tr>
<td>9089</td>
<td>Nitroso Trifluoroethane</td>
<td>CF₃NO</td>
<td>-84</td>
<td>Toxic; Reactive</td>
</tr>
<tr>
<td>4741</td>
<td>Carbonyl Fluoride</td>
<td>COF₂</td>
<td>-83</td>
<td>Reactive; Toxic</td>
</tr>
<tr>
<td>9100</td>
<td>Trifluoromethane (HFC-23)</td>
<td>CHF₃</td>
<td>-82.2</td>
<td>High pressure</td>
</tr>
<tr>
<td>9047</td>
<td>Chlorotrifluoromethane (CFC-13)</td>
<td>CClF₃</td>
<td>-81.1</td>
<td>Ozone depletor</td>
</tr>
<tr>
<td>6651</td>
<td>H exafluoroethane (FC-116)</td>
<td>CF₃CF₃</td>
<td>-79</td>
<td>High pressure</td>
</tr>
<tr>
<td>4715</td>
<td>Carbon Dioxide</td>
<td>CO₂</td>
<td>-78.6</td>
<td>Compressed gas (sublimes)</td>
</tr>
<tr>
<td>9079</td>
<td>Fluoromethane</td>
<td>CH₃F</td>
<td>-78.4</td>
<td>Flammable</td>
</tr>
<tr>
<td>6876</td>
<td>Tetrafluoroethylene (TFE)</td>
<td>CF₂=CF₂</td>
<td>-76.3</td>
<td>Reactive; possibly explosive</td>
</tr>
<tr>
<td>14934</td>
<td>Vinyl Fluoride (VF)</td>
<td>CH₂=CHF</td>
<td>-72.2</td>
<td>Reactive; flammable</td>
</tr>
<tr>
<td>14500</td>
<td>Trifluoroacetonitrile</td>
<td>CF₃CN</td>
<td>-64</td>
<td>Reactive; possibly toxic</td>
</tr>
<tr>
<td>9033</td>
<td>Bromotrifluoromethane (FE-1301)</td>
<td>CF₃Br</td>
<td>-59</td>
<td>Ozone depletor</td>
</tr>
<tr>
<td>13296</td>
<td>M ethyl Silane</td>
<td>CH₃SiH₃</td>
<td>-57</td>
<td>Flammable</td>
</tr>
<tr>
<td>8640</td>
<td>Ketene</td>
<td>CH₂=CO</td>
<td>-56</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>9067</td>
<td>Difluoromethane (HFC-32)</td>
<td>CH₂F₂</td>
<td>-51.6</td>
<td>Flammable</td>
</tr>
<tr>
<td>4742</td>
<td>Carbonyl Sulfide</td>
<td>COS</td>
<td>-50</td>
<td>Reactive; toxic</td>
</tr>
<tr>
<td>12342</td>
<td>3,3,3, Trifluoropropylene</td>
<td>CH=CCF₃</td>
<td>-48.3</td>
<td>Reactive; possibly flammable</td>
</tr>
<tr>
<td>12025</td>
<td>Propylene</td>
<td>CH₃CH=CH₂</td>
<td>-47.4</td>
<td>Flammable</td>
</tr>
<tr>
<td>6676</td>
<td>1,1,1,-Trifluoroethane (HFC-143a)</td>
<td>CF₃CH₃</td>
<td>-47.3</td>
<td>Flammable</td>
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<tr>
<td>6659</td>
<td>Pentfluoronitrosoethane</td>
<td>CF₃CF₂NO</td>
<td>-42</td>
<td>Reactive; possibly toxic</td>
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<tr>
<td>11772</td>
<td>Propane</td>
<td>CH₃CH₂CH₃</td>
<td>-42.1</td>
<td>Flammable</td>
</tr>
<tr>
<td>9037</td>
<td>Chlorodifluoromethane (HFC-22)</td>
<td>CHClF₂</td>
<td>-40.8</td>
<td>Ozone depletor</td>
</tr>
<tr>
<td>581</td>
<td>Tetrafluoroalene</td>
<td>CF₂=C=CF₂</td>
<td>-38</td>
<td>Extremely reactive</td>
</tr>
<tr>
<td>6618</td>
<td>Chloropentafluoroethane (CFC-115)</td>
<td>CF₃CF₂Cl</td>
<td>-38</td>
<td>Ozone depletor</td>
</tr>
<tr>
<td>6646</td>
<td>Fluoroethane (HFC-161)</td>
<td>CH₃CH₂F</td>
<td>-37.7</td>
<td>Flammable</td>
</tr>
<tr>
<td>11880</td>
<td>Perfluoropropane</td>
<td>C₃F₈</td>
<td>-36</td>
<td>Significantly higher GWP</td>
</tr>
<tr>
<td>6762</td>
<td>Perfluoroethylamine</td>
<td>CF₃CF₂NF₂</td>
<td>-35</td>
<td>Possibly toxic; reactive</td>
</tr>
<tr>
<td>580</td>
<td>Allenne</td>
<td>CH₂=C=CH₂</td>
<td>-34.5</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>5824</td>
<td>Cyclopropane</td>
<td>C₃H₆</td>
<td>-32.7</td>
<td>Flammable</td>
</tr>
<tr>
<td>14501</td>
<td>Trifluoromethylperoxide</td>
<td>CF₃O CF₃</td>
<td>-32</td>
<td>Reactive; possibly explosive</td>
</tr>
<tr>
<td>1585</td>
<td>H exafluoroacetone</td>
<td>CF₃N=NCF₃</td>
<td>-31.6</td>
<td>May explode in spark/flame</td>
</tr>
<tr>
<td>9088</td>
<td>N itrotrifluoromethane (fluoropictin)</td>
<td>CF₃NO₂</td>
<td>-31.1</td>
<td>May explode due to shock/friction</td>
</tr>
<tr>
<td>445</td>
<td>Chloroacetylene</td>
<td>CIC=CH</td>
<td>-30</td>
<td>Flammable; reactive; possibly explosive</td>
</tr>
<tr>
<td>9061</td>
<td>Dichlorodifluoromethane (CFC-12)</td>
<td>CCl₂F₂</td>
<td>-29.8</td>
<td>Ozone depletor</td>
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<tr>
<td>12293</td>
<td>Perfluoropropylene (HFP)</td>
<td>CF₃C=CF₂</td>
<td>-29.4</td>
<td>Reactive; toxic</td>
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<tr>
<td>324</td>
<td>H exafluoroacetone (HFA)</td>
<td>CF₃COOCF₃</td>
<td>-28</td>
<td>Powerful solvent; toxic</td>
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<tr>
<td>6668</td>
<td>1,1,1,2,-tetrafluoroethane (HFC-134a)</td>
<td>CF₃CH₂F</td>
<td>-26.5</td>
<td>Good</td>
</tr>
<tr>
<td>11379</td>
<td>Trifluoromethylphosphine</td>
<td>CF₃PH₂</td>
<td>-26.5</td>
<td>Spontaneously flammable</td>
</tr>
<tr>
<td>16847</td>
<td>1 chloro, 1,2,2,-trifluoroethylene</td>
<td>CIFC=CF₂</td>
<td>-26.2</td>
<td>Reactive; toxic</td>
</tr>
<tr>
<td>No.</td>
<td>Compound</td>
<td>Structure</td>
<td>b.p. (°C)</td>
<td>Properties</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------------------</td>
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<td>-----------</td>
<td>-------------------------------------------------</td>
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<tr>
<td>9155</td>
<td>Dimethylether</td>
<td>CH$_3$OCH$_3$</td>
<td>-25</td>
<td>Flammable</td>
</tr>
<tr>
<td>6632</td>
<td>1,1-difluoroethane (HFC-152a)</td>
<td>CH$_3$CHF$_2$</td>
<td>-24.7</td>
<td>Flammable</td>
</tr>
<tr>
<td>4211</td>
<td>Perfluorobutene-2</td>
<td>CF$_3$C=CCF$_3$</td>
<td>-24.6</td>
<td>Toxic; reactive</td>
</tr>
<tr>
<td>9035</td>
<td>Chloromethane</td>
<td>CH$_3$Cl</td>
<td>-24.2</td>
<td>Flammable</td>
</tr>
<tr>
<td>7055</td>
<td>Formylfluoride or Fluoroformaldehyde</td>
<td>FCHO</td>
<td>-24</td>
<td>Reactive; flammable</td>
</tr>
<tr>
<td>12333</td>
<td>M ethylacetylene</td>
<td>CH$_3$C=CH</td>
<td>-23.2</td>
<td>Flammable; reactive; possibly explosive</td>
</tr>
<tr>
<td>9084</td>
<td>Trifluoriodomethane</td>
<td>CF$_3$I</td>
<td>-22.5</td>
<td>Irritant</td>
</tr>
<tr>
<td>14502</td>
<td>Bis-trifluoromethysulfide</td>
<td>(CF$_3$)$_2$S</td>
<td>-22.2</td>
<td>Reactive</td>
</tr>
<tr>
<td>5429</td>
<td>Cyanogen</td>
<td>NCCN</td>
<td>-21.2</td>
<td>Lethal gas</td>
</tr>
<tr>
<td>9123</td>
<td>Trifluoromethanesulfonylfluoride</td>
<td>CF$_3$SO$_2$F</td>
<td>-21.7</td>
<td>Reactive; toxic</td>
</tr>
<tr>
<td>7047</td>
<td>Formaldehyde</td>
<td>HCHO</td>
<td>-21</td>
<td>Toxic; reactive</td>
</tr>
<tr>
<td>1415</td>
<td>Trifluoromethylarsine</td>
<td>CF$_3$AsH$_2$</td>
<td>-11.6</td>
<td>Poisonous</td>
</tr>
<tr>
<td>11374</td>
<td>Methylphosphine</td>
<td>CH$_3$PH$_2$</td>
<td>-14</td>
<td>Very reactive; flammable</td>
</tr>
<tr>
<td>3942</td>
<td>1-butene</td>
<td>CH$_3$CH$_2$CH=CH$_2$</td>
<td>-6.3</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>3981</td>
<td>Trans 2-butene</td>
<td>CH$_3$CH=CHCH$_3$</td>
<td>0.9</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>11360</td>
<td>Bistrifluoromethylphosphine</td>
<td>(CF$_3$)$_2$PH</td>
<td>1</td>
<td>Spontaneously flammable; possibly toxic; reactive</td>
</tr>
<tr>
<td>11867</td>
<td>1,1,1,2,2,3 hexafluoropropane</td>
<td>CF$_3$CF$_2$CH$_2$F</td>
<td>1.2</td>
<td>Possible (would require testing)</td>
</tr>
<tr>
<td>1584</td>
<td>Azomethane</td>
<td>CH$_3$N=NCH$_3$</td>
<td>1.5</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>1411</td>
<td>Methylarsine</td>
<td>CH$_3$AsH$_3$</td>
<td>2</td>
<td>Flammable; toxic</td>
</tr>
<tr>
<td>No.</td>
<td>Compound</td>
<td>Structure</td>
<td>b.p. (°C)</td>
<td>Properties</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------------</td>
<td>----------------------------------</td>
<td>-----------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>14514</td>
<td>Trimethylamine</td>
<td>(CH$_3$)$_2$NH</td>
<td>2.9</td>
<td>Flammable; odourous</td>
</tr>
<tr>
<td>5456</td>
<td>Perfluorocyclobutene</td>
<td>C$_4$F$_6$</td>
<td>3</td>
<td>Toxic</td>
</tr>
<tr>
<td>6628</td>
<td>1,2,2,2-Tetrafluoro1,1-Dichloroethane (CFC-114a)</td>
<td>CF$_3$CCl$_2$F</td>
<td>3.6</td>
<td>Ozone depletor</td>
</tr>
<tr>
<td>9020</td>
<td>M ethyl Bromide</td>
<td>CH$_3$Br</td>
<td>3.6</td>
<td>Flammable; ozone depletor</td>
</tr>
<tr>
<td>3980</td>
<td>Cis 2-Butene</td>
<td>CH$_3$CH =CH =CH$_3$</td>
<td>3.7</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>3715</td>
<td>Perfluorobutane</td>
<td>C$<em>4$F$</em>{10}$</td>
<td>3.96</td>
<td>Significantly higher GWP than HFCs -134a or -227</td>
</tr>
<tr>
<td>444</td>
<td>Bromoacetylene</td>
<td>BrC=CH</td>
<td>4.7</td>
<td>Reactive; flammable; ozone depletor</td>
</tr>
<tr>
<td>3972</td>
<td>Perfluoro 1-Butene</td>
<td>CF$_3$CF$_2$CF =CF$_2$</td>
<td>4.8</td>
<td>Reactive; toxic</td>
</tr>
<tr>
<td>5833</td>
<td>M ethylcyclopropane</td>
<td>CH$_3$—C$_2$H$_5$</td>
<td>4.5</td>
<td>Flammable</td>
</tr>
<tr>
<td>4065</td>
<td>Vinyl Acetylene</td>
<td>CH$_2$=CHC=C=CH</td>
<td>5.1</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>3657</td>
<td>Hexafluoro 1,3-Butadiene</td>
<td>CF$_2$=CFCF =CF$_2$</td>
<td>6</td>
<td>Reactive; toxic</td>
</tr>
<tr>
<td>9124</td>
<td>M ethyl mercaptan</td>
<td>CH$_3$SH</td>
<td>6.2</td>
<td>Odorous; flammable</td>
</tr>
<tr>
<td>4740</td>
<td>Carbon Suboxide</td>
<td>O=C—C=O</td>
<td>6.8</td>
<td>Reactive</td>
</tr>
<tr>
<td>6619</td>
<td>2 Chloro 1,1,1-Trifluoroethane (H CFC-133a)</td>
<td>CF$_3$CH$_2$Cl</td>
<td>6.93</td>
<td>Ozone depletor; toxic</td>
</tr>
<tr>
<td>6156</td>
<td>Dimethyl amine</td>
<td>(CH$_3$)$_2$NH</td>
<td>7.4</td>
<td>Odorous; flammable</td>
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<tr>
<td>11359</td>
<td>Phosgene</td>
<td>COCl$_2$</td>
<td>7.6</td>
<td>Poisonous gas</td>
</tr>
<tr>
<td>4195</td>
<td>1-Butyne</td>
<td>CH$_3$CH$_2$C=CH</td>
<td>8.1</td>
<td>Flammable; reactive</td>
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<tr>
<td>9064</td>
<td>Dichlorofluoromethane (H CFC-21)</td>
<td>CHCl$_2$F</td>
<td>9</td>
<td>Ozone depletor; toxic</td>
</tr>
<tr>
<td>9797</td>
<td>2,2-Dimethyl propane</td>
<td>(CH$_3$)$_2$C</td>
<td>9.5</td>
<td>Flammable</td>
</tr>
<tr>
<td>3668</td>
<td>Butylylene</td>
<td>CH =C —C =CH</td>
<td>10.3</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>3631</td>
<td>1,2-Butadiene</td>
<td>CH$_2$=C=CH=CH$_3$</td>
<td>10.8</td>
<td>Flammable; reactive</td>
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<tr>
<td>6859</td>
<td>Ethylmethyl ether</td>
<td>CH$_3$OCH$_2$CH$_3$</td>
<td>10.8</td>
<td>Flammable</td>
</tr>
<tr>
<td>3655</td>
<td>2-Fluoro-1,3-Butadiene</td>
<td>CH$_2$=CFCH =CH$_2$</td>
<td>12</td>
<td>Flammable; reactive; possibly toxic</td>
</tr>
<tr>
<td>5438</td>
<td>Cyclobutane</td>
<td>C$_4$H$_8$</td>
<td>12</td>
<td>Flammable</td>
</tr>
<tr>
<td>9205</td>
<td>M ethyl vinyl ether</td>
<td>CH$_3$OCH =CH$_2$</td>
<td>12</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>5389</td>
<td>Crotononitrile</td>
<td>CH$_3$CH =CH =CHCN</td>
<td>12.1</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>6614</td>
<td>Ethyl Chloride</td>
<td>CH$_3$CH$_2$Cl</td>
<td>12.3</td>
<td>Flammable</td>
</tr>
<tr>
<td>5431</td>
<td>Cyanogen Chloride</td>
<td>CNCI</td>
<td>12.7</td>
<td>Toxic gas</td>
</tr>
<tr>
<td>5980</td>
<td>1,1,1-Trifluorodiizomethane</td>
<td>CF$_3$CH$_3$N$_2$</td>
<td>13</td>
<td>Very reactive; decomposes</td>
</tr>
<tr>
<td>6920</td>
<td>Ethylene Oxide</td>
<td>C$_2$H$_5$O</td>
<td>13.2</td>
<td>Flammable</td>
</tr>
<tr>
<td>9077</td>
<td>Disilanomethane</td>
<td>(SiH$_3$)$_2$CH$_3$</td>
<td>14.7</td>
<td>Flammable</td>
</tr>
<tr>
<td>14930</td>
<td>Vinyl Bromide</td>
<td>CH$_2$=CHBr</td>
<td>15.8</td>
<td>Flammable; ozone depletor</td>
</tr>
<tr>
<td>6814</td>
<td>Ethyl Nitrite</td>
<td>CH$_3$CH$_2$ONO</td>
<td>16</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>6754</td>
<td>Ethyl Amine</td>
<td>CH$_3$CH$_2$NH$_2$</td>
<td>16.6</td>
<td>Flammable; odour</td>
</tr>
<tr>
<td>11385</td>
<td>Trifluoromethylphosphine</td>
<td>(CF$_3$)$_2$P</td>
<td>17.3</td>
<td>Spontaneously flammable</td>
</tr>
<tr>
<td>9029</td>
<td>Bromofluoromethane</td>
<td>BrCH$_2$F</td>
<td>18-20</td>
<td>Ozone depletor; possibly flammable</td>
</tr>
<tr>
<td>3576</td>
<td>Trimethylborine</td>
<td>(CH$_3$)$_3$B</td>
<td>20</td>
<td>Flammable</td>
</tr>
<tr>
<td>3971</td>
<td>3 M ethyl-1-butene</td>
<td>(CH$_3$)$_3$CHCH =CH$_2$</td>
<td>20</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>5827</td>
<td>1,1-Dimethylcyclopropane</td>
<td>(CH$_3$)$_2$—C$_2$H$_6$</td>
<td>20.6</td>
<td>Flammable</td>
</tr>
<tr>
<td>21</td>
<td>Acetaldehyde</td>
<td>CH$_3$CHO</td>
<td>20.8</td>
<td>Reactive; flammable</td>
</tr>
<tr>
<td>No.</td>
<td>Compound</td>
<td>Structure</td>
<td>b.p. (°C)</td>
<td>Properties</td>
</tr>
<tr>
<td>------</td>
<td>--------------------------------------</td>
<td>----------------------------</td>
<td>-----------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>439</td>
<td>Acetyl fluoride</td>
<td>CH$_3$COF</td>
<td>20.8</td>
<td>Very reactive; flammable</td>
</tr>
<tr>
<td>3572</td>
<td>Dimethylmethoxy borine</td>
<td>(CH$_3$)$_2$B—OCH$_3$</td>
<td>21</td>
<td>Flammable</td>
</tr>
<tr>
<td>11361</td>
<td>Bis(Trifluoromethyl)chlorophosphine</td>
<td>(CF$_3$)$_2$P—Cl</td>
<td>21</td>
<td>Spontaneously flammable</td>
</tr>
<tr>
<td>6867</td>
<td>1,2 Dichloro 1,2- Difluoroethylene</td>
<td>CHClF=CHClF</td>
<td>21.1</td>
<td>Ozone depletor; reactive; possibly toxic</td>
</tr>
<tr>
<td>9068</td>
<td>Difluorodimethane</td>
<td>CHF$_2$I</td>
<td>21.6</td>
<td>Toxic; irritant</td>
</tr>
<tr>
<td>12266</td>
<td>2-Chloro-2-propylene</td>
<td>CH$_3$C=CH=CH$_2$</td>
<td>22.6</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>5416</td>
<td>Cyanic acid</td>
<td>HOCN</td>
<td>23.5</td>
<td>Reactive; toxic</td>
</tr>
<tr>
<td>11386</td>
<td>Trifluoromethylphosphine oxide</td>
<td>(CF$_3$)$_3$PO</td>
<td>23.6</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>6225</td>
<td>Propylene carbonate</td>
<td>C$_4$H$_6$O$_3$</td>
<td>24.2</td>
<td>Flammable</td>
</tr>
<tr>
<td>9056</td>
<td>Dibromodifluoromethane</td>
<td>Br$_2$F$_2$C</td>
<td>24.5</td>
<td>Ozone depletor</td>
</tr>
<tr>
<td>5807</td>
<td>3 Chlorocyclopentene</td>
<td>Cl—C$_4$H$_7$</td>
<td>25-31</td>
<td>Flammable; possibly toxic</td>
</tr>
<tr>
<td>9038</td>
<td>Chlorodifluoronitromethane</td>
<td>ClF$_2$C—NO$_2$</td>
<td>25</td>
<td>Reactive; possibly explosive</td>
</tr>
<tr>
<td>11371</td>
<td>Dimethylphosphine</td>
<td>(CH$_3$)$_2$P—H</td>
<td>25</td>
<td>Flammable</td>
</tr>
<tr>
<td>11373</td>
<td>Ethylphosphine</td>
<td>CH$_3$CH$_2$PH$_2$</td>
<td>25</td>
<td>Flammable</td>
</tr>
<tr>
<td>11865</td>
<td>Heptofluoro-1-nitropropane</td>
<td>CF$_3$CF$_2$CF$_2$NO$_2$</td>
<td>25</td>
<td>Possibly reactive; possibly explosive</td>
</tr>
<tr>
<td>14953</td>
<td>Ethoxydithioformic acid</td>
<td>CH$_3$CH$_2$OCS$_2$H</td>
<td>25</td>
<td>Unstable, decomposes</td>
</tr>
<tr>
<td>8761</td>
<td>Hydrogen cyanide</td>
<td>HCN</td>
<td>25.7</td>
<td>Very toxic</td>
</tr>
<tr>
<td>10307</td>
<td>1,4 Pentadiene</td>
<td>CH$_2$=CHCH$_2$CH=CH$_2$</td>
<td>26</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>13323</td>
<td>Tetramethylsilane</td>
<td>(CH$_3$)$_4$Si</td>
<td>26.5</td>
<td>Flammable</td>
</tr>
<tr>
<td>4202</td>
<td>2-Butyne</td>
<td>CH$_3$=CH=CH$_3$</td>
<td>27</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>3777</td>
<td>2-Methylbutane</td>
<td>(CH$_3$)$_2$CH$_2$CH$_3$</td>
<td>27.8</td>
<td>Flammable</td>
</tr>
<tr>
<td>14932</td>
<td>Divinylether</td>
<td>(CH$_2$=CH)$_2$O</td>
<td>28</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>4199</td>
<td>3-Methyl-1-butane</td>
<td>(CH$_3$)$_2$CH=CH</td>
<td>29.5</td>
<td>Flammable; reactive</td>
</tr>
<tr>
<td>5829</td>
<td>1,2 Dimethylcyclopropane (trans, dl)</td>
<td>1,2(CH$_3$)$_2$C=CH$_4$</td>
<td>29</td>
<td>Flammable</td>
</tr>
<tr>
<td>10537</td>
<td>Perfluoropentene-1</td>
<td>CF$_3$CF$_2$CF=CF$_2$</td>
<td>29-30</td>
<td>Possibly toxic; reactive</td>
</tr>
<tr>
<td>10517</td>
<td>1-Pentene</td>
<td>CH$_3$CH$_2$CH$_2$CH=CH$_2$</td>
<td>30</td>
<td>Flammable</td>
</tr>
</tbody>
</table>