

The CFC to HFA Transition and Its Impact on Pulmonary Drug Development

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Summary

The terms of the Montreal Protocol have eliminated chlorofluorocarbons (CFCs) and other ozone-depleting agents from commercial use, with the exemption of their use as propellants in metered-dose inhalers. Two new propellants have been approved for CFC substitutes: hydrofluoroalkane (HFA)-134a and HFA-227. An extensive safety program was conducted by the International Pharmaceutical Aerosol Consortium for Toxicity Testing (IPACT studies I and II), which found that the HFAs were as safe as or safer than the CFCs. The change from CFCs to HFAs in metered-dose inhalers was not a straightforward exchange. Indeed, substantial new technology had to be developed to make the HFAs suitable for use in metered-dose inhalers. Fortunately, with new understandings of respiratory diseases and the areas of the lungs that need to be targeted by medications, the new HFAs provided the opportunity to improve the performance of the β -agonist products and created some entirely new ability for inhaled steroids to reach all the airways, both large and small, where asthma pathology resides. The transition from CFCs also spurred novel new drug-delivery technologies, improved dry powder inhalers, and highly dispersible engineered powders. *Key words:* chlorofluorocarbon, CFC, hydrofluoroalkane, HFA, ozone, metered-dose inhaler, MDI, dry powder inhaler, DPI, Montreal Protocol. [Respir Care 2005;50(9):1201–1206. © 2005 Daedalus Enterprises]

Introduction

Ozone is present in the stratosphere, where it serves to filter out ultraviolet-B radiation. Without the ozone layer, ultraviolet-B radiation would increase the risk of skin cancer, cataracts, and infectious diseases, reduce crop yields, increase global warming, and eventually alter aquatic food chains and cause a general disruption of ecological pro-

cesses, leading to global catastrophe.¹ Chlorofluorocarbons (CFCs, also colloquially referred to by the brand name Freon) have been clearly shown to deplete ozone once they reach the stratosphere. The ozone-depletion issue caused governments to enter into treaties to reduce CFC emissions and private organizations to seek CFC alternatives and new technologies. The Montreal Protocol,²

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adopted in 1987, along with its subsequent modifications, requires a complete phase-out of the CFCs, although there continues to be a medical exemption for metered-dose inhalers (MDIs), renewable on a yearly basis. CFCs provide the chemical energy within an MDI to disperse and deliver the medication. The pharmaceutical industry responded by forming the International Pharmaceutical Aerosol Consortium for Toxicity Testing (IPACT studies I and II) and subsequently developing the alternative replacement propellants hydrofluoroalkanes (HFAs), specifically HFA-134a and HFA-227, for use in MDIs.³ Large safety studies conducted with animals and humans showed that the new HFA propellants were as safe as or safer than the CFCs they were intended to replace. The new HFA propellants, however, presented new technical challenges, and many problems needed to be resolved prior to receiving marketing authorizations.⁴ In addition, new understandings of respiratory diseases such as asthma, coupled with new ways to more appropriately target those diseases, led to better MDIs. The ban on CFCs has also spurred new dry powder inhaler technology as well as many other classes of specialty inhalers. There are many HFA MDIs currently coexisting with CFC MDIs, but the CFC MDIs will eventually be eliminated. The goal is to provide the best therapy to patients while at the same time making inhalers intuitively easy to use and, where propellant substitutions are present, to make the switch-over to HFA propellants as seamless as possible for physicians and patients.

CFCs and HFAs

CFCs are made up of carbon, chlorine, and fluorine atoms. The 3 common CFCs used in MDIs are CFC-11 (CCl₃F), CFC-12 (CCl₂F₂), and CFC-114 (CCl₂F₄). The CFCs were originally synthesized in the 1890s, but substantial use did not occur until the 1930s, when they began to be used in refrigerators, air conditioners, foam blowing, solvents, fire suppressants, and as propellants for various aerosols in medical as well as consumer products.¹ The global consumption of CFCs grew to 10⁹ kg per year.⁵ In the United States alone, CFC-related goods and services reached \$28 billion a year in 1990, with related jobs estimated at 700,000. The CFCs are remarkably simple molecules and they exhibit great stability. The carbon-chlorine and carbon-fluorine chemical bonds are very strong. Consequently, the CFCs are not metabolized by the environment or by biological systems to any great extent. It is this simplicity and stability that make them extremely safe for pharmaceutical MDI use. The great majority of the CFCs are rapidly exhaled. Ironically, it is this very stability that causes the problem with the ozone layer. That is, the CFCs are so stable that they are able to reach the stratosphere intact. The atmospheric lifespan of the CFCs is 50–500

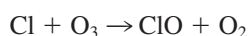
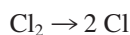
years. The CFCs contain chlorine, which is the atom responsible for their ozone-depleting potential.⁵

Hydrofluorocarbons (HFAs) are made up of carbon, fluorine, and hydrogen atoms. The 2 major alternative propellants are HFA-134a (C₂H₂F₄) and HFA-227 (C₃HF₇). The HFAs were also synthesized in the 1930s, but their commercial use was small compared to the CFCs. Because these molecules contain hydrogen atoms, they are more readily metabolized by the environment, but their main feature is that they do not contain chlorine and thus they have no potential to deplete the ozone layer.

The Ozone Layer

The ozone layer is a thin layer of ozone (O₃) in the stratosphere that protects the earth from deadly ultraviolet radiation. It filters out most of the ultraviolet-B radiation coming from the sun. Without this filtering almost all of the world's ecosystems and biological organisms would perish. It is the chlorine from CFCs, as well as many other chlorine sources, such as volcanic eruptions and possibly even chlorine from the ocean's salt sprays, that upsets the photolytic cycle. Chlorine reacts with ozone and forms chlorine oxide, thus depleting the ozone concentration. It has been estimated that one chlorine radical can destroy approximately 100,000 molecules of ozone.⁶

The following is the mechanism whereby chlorine destroys ozone:



The first evidence that ozone depletion was occurring was reported by the British Antarctic Survey, which collected atmospheric ozone data over Antarctica from 1957 to 1985. There was a marked decrease in ozone concentration beginning in the early 1970s. Later, the United States National Aeronautics and Space Administration (NASA) collected more detailed data, using satellites and U2 airplanes. Strong data emerged showing an inverse relationship between chloride oxide and ozone concentration. The "ozone hole" (formally named in 1985) developed in the lower latitudes and was seasonal in nature, with the largest ozone holes developing in winter over the Antarctic. Furthermore, the data indicated that the ozone concentrations were trending downward on a nearly yearly basis.⁷

The Global Response to Ozone Depletion

The global response to this issue reached a turning point after the research by Molina and Rowland was published

in 1974.⁸ Ironically, it received little attention until Rowland and Molina held a press conference and *The New York Times* published several articles on their work. The United States formed the Inadvertent Modification of the Stratosphere task force with the involvement of the United States Environmental Protection Agency and Food and Drug Administration as well as the Consumer Product Safety Commission. Interestingly, the whole question of emissions from industry and their effect on the environment played a major role in the United States Congress's passage of the Toxic Substances Control Act in 1976, which profoundly affected most of the major industries in the United States. The ozone-depletion issue struck such a strong note that state and local governments passed their own laws, beginning in 1975, including action taken by the state of Oregon, which banned CFC aerosols from consumer products, effective in 1997. Perhaps the most important step scientifically was the National Academy report in 1976, which concluded, among other things, that regulation of CFC uses and releases is almost certain to be necessary at some time. The response from Western Europe was even stronger, with countries such as Denmark, Switzerland, Norway, and the Netherlands passing restrictive laws on the use of CFCs in consumer products.

The culmination of the recognized need for global regulation occurred in 1987, with the adoption of the Montreal Protocol.² It restricted the production and consumption of CFCs as well as other compounds, such as the hydrochlorofluorocarbons and bromine oxides. The Montreal Protocol has been ratified by over 140 countries. It has also been modified several times since it was discovered that under the original agreement, atmospheric chlorine would continue to rise indefinitely. The revisions adopted in 1990 would not have had atmospheric chlorine return to a reasonable level until the year 2080, so the agreement was further modified in 1992, resulting in a predicted return to normal (2 ppb) in 2050.

The CFCs and HFAs, as well as ozone itself, are all "greenhouse gases," meaning that they contribute to global warming. The whole issue of global warming is very controversial, and the consequences of greenhouse gases are not nearly as clear as the consequences of CFCs and ozone depletion. Nonetheless, many international agreements have been made surrounding global warming. Most notably, the Kyoto protocol was adopted by many countries in 1997. It called for a reduction of greenhouse gas emissions to 8% below the 1990 level. The European Union has ratified the protocol but the United States has not. The Clinton administration did not submit it to Congress for ratification, and the Bush administration has withdrawn it from consideration.

There were many government, private, and industrial organizations formed to look at the CFC issue, including the Alternative Fluorocarbons Environmental Acceptabil-

ity Study and the European Collaborative Project on Atmospheric Degradation. The Program for Alternative Fluorocarbon Toxicology Testing was formed by industry to find CFC replacements and associated technology, primarily for replacement of the CFCs in air conditioners, such as in cars. They conducted many of the initial safety studies on HFA-134a, as well as others.

The first consortium to examine the replacement of CFCs in medical use, the International Pharmaceutical Aerosol Consortium for the study of HFA-134a (IPACT-1), was formed by 3M Corporation and included, at various times, 8–12 of some of the world's largest pharmaceutical companies. Later, a second consortium, IPACT-2, was formed to study HFA-227 for use in MDIs. Its membership was slightly different at times from IPACT-1, but the core companies remained the same. The cost for each of the 2 HFA safety programs was \$15–20 million. Of course, the cost for then redeveloping the new drug formulation was much more than the cost for the individual HFA. The original Montreal Protocol allowed for the essential use of CFCs to continue until appropriate alternatives were available. Those 2 uses were for MDIs and the United States space shuttle program. However, their exempt status was reviewed annually. The pharmaceutical use of CFCs accounted for less than 0.5% of the global consumption. There were many factors that influenced the continued use of CFCs in MDIs, such as the increasing prevalence of asthma and chronic obstructive pulmonary disease, new diagnosis-and-treatment guidelines encouraging MDI use, and changes in health-care coverage. In addition few technologies could match the low price per dose of the CFC MDIs for asthma and rhinitis. This cost issue would continue to keep the CFC MDIs on the market long after HFA and dry powder replacements were available.

IPACT-1 first examined the safety of HFA-134a for use in MDIs. They examined the existing literature and database generated by the Program for Alternative Fluorocarbon Toxicology Testing. IPACT-1 representatives visited the world's health authorities and eventually developed a strategy that would in one program satisfy the requirement to generate a single excipient master file that all member companies could reference for their specific drug applications. The health authorities took a very conservative approach, and while they usually expressed a desire to help the environment, they clearly stated that their primary legal obligation was to ensure the safety of drug products to patients. The CFCs had a well known 40-year record of excellent safety for patients. Everyone acknowledged that this human safety profile was going to be difficult to match, and the fact that patients (including children) would potentially be using HFAs for decades made for a daunting challenge. The phrase "HFAs must be shown to be squeaky clean" was used a great deal by the authorities. In addition,

there was a deadline in some countries that CFC exemption, even for MDIs, was going to be eliminated by 1995.

There was a great deal of protest by environmental groups not to switch to HFA, because of HFA's greenhouse gas potential, even though the greenhouse-gas potential of the HFAs is less than that of the CFCs. The contribution of the HFAs from medical use is negligible, but that message was somewhat hard to get across to the nontechnical people who questioned the greenhouse-gas contribution of the HFAs. It is true that a molecule of HFA-134a is approximately 1,000-fold more potent as a greenhouse-gas than one molecule of methane gas, but there is such an overwhelming amount of methane gas emitted from other sources that the contribution by HFA is very small. A comparison example was developed in order to put the greenhouse-gas question in perspective. A typical dairy cow passes approximately 450 L of methane gas per day, and dairy barns must be well ventilated to prevent explosions from buildup of cow gas. Calculations show that one cow contributes more greenhouse gas per day than 10 asthmatics each inhaling 2 puffs of Proventil-HFA 4 times a day. Thus one less cow would allow 10 asthmatics to receive their medications and have no net greenhouse gas contribution. That comparison seemed to quell some of the protests.

Safety Programs for the HFAs

IPACT determined that a safety program more extensive than that required for most new chemical entities had to be conducted, even though there was a long history with the HFAs and it was known that the HFAs were not biologically reactive, not carcinogenic, not mutagenic, and there was no target organ or tissue accumulation. In fact, greater than 99% of the inhaled HFA was exhaled intact within seconds. Nonetheless, IPACT and/or the Program for Alternative Fluorocarbon Toxicology Testing conducted the safety studies outlined in Table 1. The results of these extensive programs showed that HFA-134a and HFA-227 are as safe as or safer than CFCs.^{9,10}

The HFA Challenges to Pharmaceutical Drug Development

The switch from 40 years of MDI technical understanding with the CFCs was simple on the surface but scientifically very challenging.¹¹ The conventional surfactants used in CFC MDIs were not soluble in HFAs. The conventional seal materials used in CFC MDIs were not compatible with HFAs, and indeed, the seals leaked unacceptably with the HFAs. Because of the HFAs' different thermodynamic properties, the actuator (ie, boot) design was much more critical to obtaining the correct particle size and plume geometry. There was no high-boiling HFA replacement

Table 1. Outline of Safety Studies Conducted for Hydrofluoroalkane 134a and Hydrofluoroalkane 227

Genetic toxicology studies
Ames assay
Chromosome aberration
Cell mutation
Micronucleus
Acute inhalation studies with rats, mice, and dogs
Subchronic inhalation studies
14-day inhalation study with rats, mice, and dogs
90-day inhalation study with rats, mice, and dogs
6-month inhalation study with rats, mice, and dogs
Chronic inhalation studies
1-year inhalation study with dog
2-year oncogenicity studies with rats and mice
Reproductive studies
Segment I, II, and III studies in rats and rabbits
Absorption, distribution, metabolism, and excretion studies with rats, mice, and dogs
Special studies, including cardiac sensitization studies with dogs
Human clinical studies
Single and multiple dose-escalation studies

for CFC-11, so new formulation concepts had to be developed. Manufacturing facilities had to be substantially modified to accommodate the HFAs, especially to accommodate the flammability of cosolvents such as ethanol. Despite the above drawbacks, the replacement of the CFCs forced everyone to reconsider approaches and develop new and better ways to deliver inhalable medications.

The First CFC-Free MDIs

Because of the ban on CFCs, the \$7-billion inhaler market was going to completely turn over, and this represented new opportunities for inhaler improvement. The matter of how to replace existing products within the same company was very interesting. The marketing people generally wanted the same drug with the identical dose and the same particle size distribution as their existing products. From their point of view these were the products currently selling very well, and that market needed to be protected. The research-and-development people knew that new technology and better understanding of the diseases could lead to better therapy. The regulatory people generally agreed with the marketing people, in that the same product aspects meant an easier route for regulatory approval. But what was equivalence? No one knew, and with different specifications throughout the world and different ways of measuring the important variables (eg, particle size distribution), making a new HFA MDI the "same" as the old CFC MDI was problematic. The term "comparable" emerged, which allowed for some subtle differences but still enabled it to be called the "same" as the original CFC product. The

term “the same only better” was also adopted. At present there are a mix of products, some resembling the original and some quite different from that which they replaced. HFA albuterol sulfate (Airomir in Europe [3M Health Care Ltd, Loughborough, United Kingdom], Proventil-HFA in the United States [3M Pharmaceuticals, St Paul, Minnesota]) was the first CFC-free MDI, and it was introduced in 1994 and gained approval in over 40 countries.¹² It fell into the category of being comparable to the CFC albuterol inhalers. However, the researchers did find ways to improve on the old inhaler by redesigning the formulation, valve, and actuator. For example, Proventil-HFA has the same emitted dose and same particle size distribution as the CFC albuterol inhalers, but it has a warmer spray temperature and less impact force at the back of the throat. This warmer, softer spray presumably reduces the potential for the “cold Freon effect” (the propellant causes a cold sensation in the pharynx, causing the patient to stop inhaling). In addition the new HFA albuterol does not suffer a loss of dose when the inhaler is stored inverted, it is not subject to loss of dose in a cold climate, and there is much less dose variability at the end of the canister’s life. Other HFA albuterol products have now been introduced, with varying degrees of similarity to and difference from the old CFC inhalers. Interestingly, most of the CFC albuterol products, along with the generic CFC albuterol inhalers, are still on the market, and in many cases the CFC albuterol products dominate the market because they are the least expensive of the albuterol inhalers. The Food and Drug Administration recently announced that all CFC albuterol MDIs must be removed from the market by 2008.¹³

The situation for steroid inhalers in the treatment of asthma was quite different from that of albuterol. The albuterol inhalers are thought to be most effective when the drug particles are deposited at the smooth-muscle receptors in the large and intermediate airways. This was relatively easy to achieve with the CFC and HFA albuterol inhalers. However, this was not the case with respect to treatment with inhaled steroids. For many years, clinicians considered asthma primarily a disease of the large airways. Because of that assumption and limited technical options, the CFC steroid inhalers produced aerosols with relatively large particles (3.5 μm mass median aerodynamic diameter), targeted to the large airways. However, research emerged that showed that asthma was a disease of the entire respiratory tract, including the small airways (ie, ≤ 2 mm in diameter).¹⁴ Research showed that the CFC steroid MDIs did not reach the small airways to any great extent. Thus, with this knowledge and new technology available for the HFA products to decrease the particle size, many of the HFA steroid inhalers were engineered to generate aerosol particles with an average size of 1.2 μm and a particle size distribution of 2 geometric standard

Table 2. Comparison of Inhaled Steroids

Inhaled Steroid	MMAD (μm)	Lung Deposition (%)
Fluticasone Rotadisk	> 4	15
Triamcinolone	4.5	14
CFC flunisolide	3.8	15–20
CFC beclomethasone	3.5	10–15
CFC fluticasone	2.5	20
HFA flunisolide	1.2	68
HFA beclomethasone	1.1	56
HFA ciclesonide	1.0	52

MMAD = mass median aerodynamic diameter
CFC = chlorofluorocarbon
HFA = hydrofluoroalkane

deviations, which more effectively reach the entire respiratory tract, large and small airways.^{15,16}

Another consideration was the large amount of oropharyngeal deposition with the CFC steroid inhalers, which led to adverse effects, such as candidiasis and thrush,¹⁷ as well as contributing to systemic absorption and the consequent adverse effects on the hypothalamic-pituitary-adrenal axis. Table 2 depicts the relationship of particle size and lung deposition with the CFC and HFA steroid inhalers. Clearly, achieving a particle size of approximately 1.5 μm resulted in lung deposition > 50%, compared with $\leq 20\%$ with the CFC steroid MDIs. There were also other benefits from the HFA steroid inhalers producing smaller particles, such as reduced dependence on coordination of inhaling and firing the MDI, and relative independence of lung deposition from inspiratory airflow. These advances have improved clinical outcomes.^{18,19}

The CFC Ban and Its Effect on Other Inhaler Technology

Again, with the complete turnover and growth of the \$7-billion inhaler market, many new technologies emerged in the 1990s. The number of inhaler patents went from less than 5 per year up to 1985, to over 350 patents granted in the 1990s. The explosion of patents included MDIs, DPIs, and other novel technologies. However, the number of MDIs produced in the world is well over 400 million, and the MDI remains the most dominant inhaler technology. It also remains the least expensive technology, with the manufacturing cost of some asthma medications being as low as 2 cents per dose. It is unlikely that any other inhaler will match that low cost, and this is a consideration for the 40 million uninsured Americans as well as most of the world’s developing countries, where just a few pennies make the

difference in affordability for millions of otherwise untreated people.

Dry powder technology has also come of age, with combination products becoming the financially dominant player in the asthma inhalers, and with the soon-anticipated approval of inhaled insulin. Inhaled insulin will break an important barrier in that it will be the first commercial inhaled peptide for systemic application.

Dry powder technology can be thought of having 3 major evolutionary steps. The first-generation dry powder inhalers (DPIs) were small, capsule-based, passive devices, such as the Rotahaler. The second-generation DPIs relied on more sophisticated devices, such as reservoirs and micronized powders (eg, Turbohaler). The third-generation and yet-to-be approved DPI technology is that of the engineered powders, which are highly dispersible and may utilize very simple, inexpensive devices from which the powders will be delivered. Generally, the evolution of efficiency of DPIs has followed the same pattern as that of MDIs, in that there are low-density, porous powder technologies in development that show increased lung deposition, from 5–20% to 40–60%. Some of the DPI technology can also deliver as much as 50 mg of powder per inhalation. MDIs are not yet capable of delivering these high quantities, yet MDIs can more consistently deliver smaller doses of < 500 μg per puff. There are other distinct advantages and disadvantages to DPIs and MDIs, but the drug, disease state, and economics will dictate which technology is best. It is likely that both technologies will continue to flourish for some time.

Summary

The change from CFC MDIs has brought about new understanding and application of improved technology to MDIs as well as DPIs. All CFC MDIs will eventually disappear, if not through government regulation then by the sheer economic and political price being paid for continuing to use CFCs. However, the CFC and HFA MDIs will coexist for some time. The new HFA MDIs will superficially resemble existing MDIs, and hopefully, the differences will be somewhat transparent to patients, making the transition easier. Technically, however, the HFA MDIs are very different. There has been an explosion of new and exciting inhaler technologies^{20,21} that not only improved delivery of existing β agonists and steroids but also opened the door for inhaled peptides such as insulin, proteins, antibodies, oligonucleotides, hormones, nicotine substitutes, antibiotics, pain relievers, anticancer drugs, new targeted drugs for chronic obstructive pulmonary disease, vaccines, and a host of other applications.

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Discussion

Hess: It strikes me that clinicians—and I think I've been guilty of this—teach patients to use MDIs without distinguishing between HFA and CFC devices.

Leach: It does matter in some cases. We try not to confuse people, but the truth is, for example, they don't need a breath-hold with most CFC MDIs. A lot of patients resist the breath-hold and they don't understand the need. They tend to think they hold their breath for 10 seconds, but it's actually more like 4 or 5 seconds. Some people suggest that we confuse people who are taking albuterol, by saying just take a breath in and you don't have to breath-hold, whereas the inhaled steroids require a breath-hold for optimum deposition.

Hess: And what about priming the device?

Leach: The priming issue is different. You just have to know what you're dealing with. There's no problem with priming if you want to bring inhaler use to the lowest common denominator. None of the inhalers suffers from performance problems when you prime them, though you may be wasting doses. Some of them do suffer with respect to consistent drug output if you don't prime them. For patient education you might just want to keep it simple and instruct patients to prime all inhalers.

Smaldone: Regarding patient education, I think that, in general, very few pulmonologists or other physicians educate their patients in any way as to how to use an MDI. I just doubt anybody does. On another subject, when CFC was banned, what led to the choice of HFA as the replacement? Why not other types of pressurized devices, such as CO₂? Why did we have to go to the HFAs and HFCs?

What are the advantages of the modern MDI over just a pressurized can?

Leach: We and others have talked about that in detail. There are alternative propellants, such as propane and butane. They all have the stored energy, because they are in a 2-phase (ie, liquid/gas) state at room temperature and relatively low pressure. We considered a propane or butane propellant, but our marketing people said that our competitors would say "Ours clears you out; theirs blows you up." and that was the end of that story. And blowing up of patients is not as far-fetched as it might sound, because some people actually smoke between doses from their inhalers. HFAs are good because they have all that useful stored energy at low pressure, without depleting the ozone as the CFCs do.

Smaldone: Why not use a propellant that's in a single-phase state?

Leach: Because you can't have the reservoir of liquid energy. You can't compress carbon dioxide at low pressure. To use nitrogen, for example, you would have to compress it to more than 2,000 psi (today's MDIs are at about 70 psi), so you would have a massive manufacturing issue; you wouldn't be able to have a 400-dose unit. These and other options for propellant gases were examined in excruciating detail.

Newman: Regarding breath-holding, sedimentation is one of the main mechanisms of aerosol-particle deposition, so breath-holding is important. I don't think it's a good idea to leave out the breath-hold instruction. There's the possibility of confusing patients with one set of instructions for one device and another set of instructions for another device, so I advocate leaving in the breath-hold instruction for all MDIs and DPIs.

Regarding CO₂, the trouble with most compressed gases such as CO₂ is that, unless you've got some very

sophisticated type of device, the pressure changes during the lifetime of the canister, so it wouldn't give consistent dosing, whereas with CFCs and HFAs the pressure remains the same throughout the life of the canister, so the dose stays consistent.

Atkins: It's the difference between liquified gas and compressed gas. Fundamentally, you're going to get a change in performance over time if you use CO₂ or many other gases. People have tried to use CO₂ as a driver with liquified systems, but it's difficult to achieve the pressures needed to get the droplets small enough that they can reach the lung. You can get particles in the 5–7 μm range, but you can't get down to 2–3 μm.

Regarding the Montreal Protocol, I have not seen the transcript, but apparently United Nations Secretary General Kofi Annan said the Montreal Protocol was the best example ever of international cooperation.

Getting back to the science, there is apparently a hydrocarbon-propellant MDI available in Germany. It is clear that the density differences may have been overcome. I still have concerns about priming and consistent dosing, but apparently somebody has actually done it.

Dhand: How is this changed by the fact that HFA formulations don't contain surfactant? In the CFC MDI the drug particles are coated with propellant and surfactant. Although the propellant evaporates rapidly after emission of the aerosol, the patient is exposed to the surfactant coating the drug. If I am not mistaken, surfactant constituted about 10% of the CFC MDI formulation.

Leach: No, it's not that much. Oleic acid is still present in some HFA albuterol inhalers, in relatively small amounts. We tried hard to get it out of there, because it causes pulmonary dysplasia and bronchoprovocation in very high doses (ie, doses many times

higher than a patient would receive from normal use of an inhaler). But we couldn't get it out without sacrificing a lot of performance. It's in there for valve function with HFA formulations; it lubricates the valve and helps consistently suspend the drug inside the can.

Dhand: So it does not coat the drug particles?

Leach: It does go along with the drug to some extent, but we don't really know if it totally coats the drug. The hypothesis is that the oleic acid is so soluble in lung fluids that it does not alter drug particle behavior once deposited in the lungs.

Dhand: The question is that the drug is depositing on the airway epithelium, so the surfactant of interest would primarily be that lining the bronchial epithelium. In contrast to surfactant lining the alveoli, surfactant might be patchy over the airway epithelium. So it may be worthwhile to determine if

serum levels of drug (ie, clearance into the circulation) are different between CFC and HFA MDIs.

Leach: I'm not aware of any published research on Ventolin HFA versus Proventil HFA. I've heard, and I suspect it's true—though I have not seen it published—that there is no pharmacokinetic difference and no difference in efficacy. I wouldn't think there would be a difference.

Dhand: I'm not aware of any published data that have addressed this question.

Atkins: I've not seen anybody say there's any difference between the two. There are certainly differences in terms of the formulation. There's no surfactant in at least some of the GlaxoSmithKline formulations of albuterol.

Laube: Lung deposition is higher with the HFA product than with the CFC product. Does this mean that pa-

tients are being overdosed? And what about increased systemic absorption with the HFA product, since it appears to penetrate more deeply into the lung, with the possibility of higher alveolar deposition?

Leach: The higher lung deposition of the HFA beclomethasone (QVAR) led to clinical studies that showed equivalent efficacy, at lower doses, to the original CFC beclomethasone inhaler, so the change to HFA meant that patients switching from the CFC inhaler should use half the CFC dose. The HFA dose had no more, and perhaps less, adverse effect than the CFC dose. Several reasons were hypothesized for the lesser adverse effects, but a major reason was that with the CFC dose there was a lot of oral deposition and, therefore, systemic absorption and adverse effects, without contributing substantially to the efficacy, whereas with the HFA dose more of the beclomethasone reaches the lungs, increasing efficacy, so the therapeutic window may be more favorable.