HFA propellants

How manufacturers insure that hydrofluoroalkanes used in metered dose inhalers meet purity and performance specifications

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Excipients used in the vast majority of medications consist of materials such as sweeteners, flavorings, binders, fillers, and, in the case of injections, water. These materials, which often only make up a minority of a finished formulation, are usually simple, well-understood, low risk, and easily tested and controlled.

HFA (hydrofluoroalkane) propellants, on the other hand, whose manufacture involves complex, aggressive chemistry, make up the majority of the inhaled dose (often over 99%) from a metered dose inhaler (MDI). Patients inspire these chemicals into an organ, often a diseased organ, that is designed to pass inhaled gases efficiently into the bloodstream, and many patients take in doses several times a day for life.

Small wonder then that among all of the various types of excipients, HFAs are subject to some of the tightest controls and specifications. As HFAs have now replaced chlorofluorocarbons (CFCs) in most parts of the world, it is useful to take a look at how manufacturers produce these gases, the controls used to assure high levels of product quality, and the contrast between the stringent requirements for their manufacture with the simpler standards that were applied to CFCs.

What are HFAs?

HFA propellants are low-boiling liquids made up of carbon, fluorine, and hydrogen that represent highly purified versions of refrigerant gases, also known as hydrofluorocarbons (HFCs), used in a wide variety of

technical applications, including refrigeration, air conditioning, foam blowing, and fire fighting. Beginning in the late 1980s, manufacturers developed the five HFAs in common use today to replace chlorofluorocarbon refrigerant gases when CFCs became implicated in the depletion of stratospheric ozone. Although chemically inert, the presence of hydrogen in the molecule provides a point of weakness that allows the gas to degrade harmlessly in the atmosphere after use.

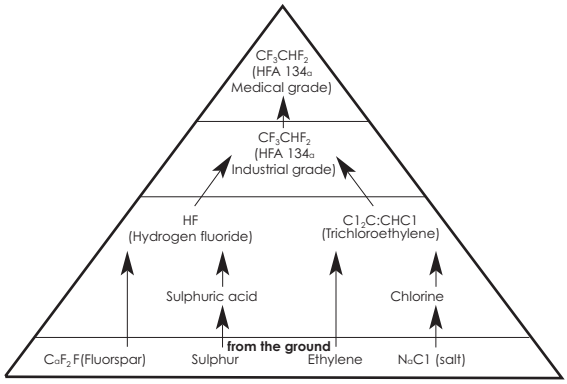
HFAs used as medical propellants include two variants: HFA 134a (1,1,1,2-tetrafluoroethane) and HFA 227ea (1,1,1,2,3,3,3-heptafluoropropane). HFA 134a accounts for the vast majority of inhaler propellants, roughly 95% of the HFA MDIs manufactured. HFA 227ea's higher cost restricts its use to the minority of applications that require its greater liquid density.

The manufacturing process

HFA manufacturing begins with simple starting materials that include salt, sulfur, ethylene, and fluorite (or fluorspar), all of which originally come out of the ground in one form or another. Processing transforms these feedstocks into chemicals that react to create industrial grade HFA. Obtaining medical grade HFA requires a further purification step (Fig. 1). The inevitable impurities found in the natural, quarried starting materials vary in both range and concentration, requiring producers to take great care towards the top of the processing pyramid to allow for the variability at its base.

Figure 1

Steps to make medical HFA 134a from extracted starting materials



The more common of the two routes for producing industrial grade HFA 134a uses trichloroethylene as feedstock and follows the overall reaction:

$Cl_2C = CHCl + 3HF \rightarrow CF_3CH_2Cl$ (133a) + HF → CF_3CH2F (HFA 134a)

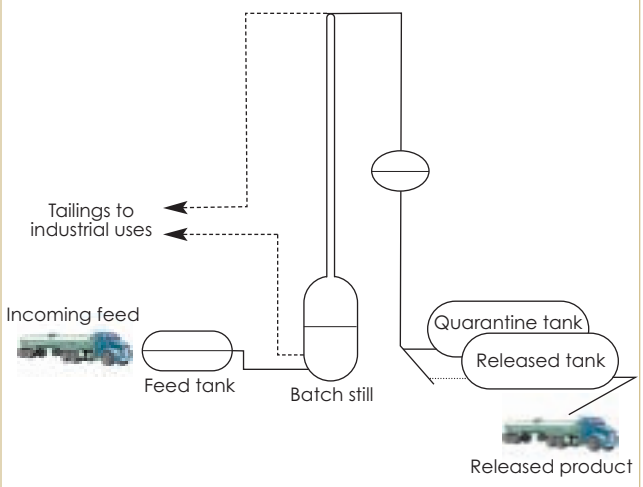
The second step of the reaction involves an equilibrium lying heavily on the side of the reactants. Forcing the reaction requires the use of heat and catalysis, and these conditions produce a number of byproduct impurities, ranging from the toxicologically inert such as HFA 134 (1,1,2,2-tetrafluoroethane, the other isomer of HFA 134a) through to some very unpleasant compounds such as HCFC 31 (chlorofluoromethane), a known carcinogen. From the beginning of the development of MDI propellant HFAs, it was clear that for these industrial refrigerants to be elevated to a medical grade, all aspects of purification would require very careful design and control.

Making medical HFAs

The conversion of industrial HFAs to medical HFAs takes place in purification process that often occurs in two stages, with a classic batch distillation at the heart of the process. The middle of the distillation, which offers the purest material, produces the main cut, while the early and late distillate material returns to industrial sales (Fig. 2).

Figure 2

HFA purification plant schematic



In many ways, the level of quality standard compares to that applied to water for injections, although the quality control process differs in the critical parameters monitored and controlled. A "medical island" operated strictly to the pharmaceutical industry's code of Good Manufacturing Practice (GMP) segregates the purification asset from other chemical manufacturing activities in the facility (Fig. 3), and every activity in the process, from distillation to analysis to packing, is meticulously validated.

This process stands in stark contrast to the manufacturing techniques used to manufacture CFCs for inhalation purposes, where the selection of medical

Figure 3

A typical medical HFA purification facility in the foreground. Note the stainless steel isotank for transporting the propellant to the MDI manufacturer.

CFC batches relies on analytical results that may or may not derive from validated methods, depending on the manufacturer. CFC production facilities have no segregated plants and produce the medical CFCs on the same assets as the industrial grade.

Demonstrating safety

In the early 1990s, when the industry realized that it would have to abandon the use of CFCs in all applications, little was known about the proposed replacement gases. Because the complex chemistry required to make HFAs resulted in a wide range of additional impurities, the chemical industry first had to assess these gases for their safety in general use, then additionally for their safety as respiratory excipients.

In order to allay any concerns about their products, a number of fluorochemical producers formed a technical consortium (Programme for Alternative Fluorocarbon Toxicology, PAFT-1) to investigate the toxicology of a number of CFC alternatives, including HFA 134a. This thorough study gave HFA 134a a clean bill of health, setting the maximum workplace exposure limit of 1000 ppm.

A subsequent, more rigorous study by a consortium of pharmaceutical companies (International Pharmaceutical Aerosol Consortium Tox Study 1, IPACT), using PAFT-1 as a foundation, demonstrated the suitability of HFA 134a in respiratory use and defined a minimum purity specification of 99.8%. The consortium later carried out a similar exercise (IPACT-2) for HFA 227ea. Since then, all respiratory grades for the two HFAs have complied with the IPACT recommendations and nowadays often have purities greater than those initial specified.

Overcoming formulation challenges

As a consequence of the change from CFC to HFA in the MDI package, as well as the opportunistic regulatory tightening up that took place at the same time, pharmaceutical companies had to completely rebuild their MDIs, with no parts left unchanged. Formulation chemistry differed significantly from the old CFC products, with formulations usually consisting of either drug suspended in HFA alone or drug suspended in a solution containing a HFA/ethanol mixture. Reliable handling of the new formulations required redesigned metering valves, different cans to ensure that the suspensions did not stick to them, and new actuators to cope with higher atomization pressures.

All of these changes took time, and from the moment the CFC phase-out became a certainty with the publication of the Montreal Protocol in 1988, seven years passed before the first HFA MDI (3M's Airomir) came to market in 1995. Several more years went by before the first real volume HFA product hit the market with the launch of GSK's Ventolin Evohaler in 1997. Even today, the MDI industry continues to expend tremendous effort to educate patients regarding this change.

The taste issue

Although manufacturers make HFA aerosols to much tighter specifications and to perform better than CFCs, patients have resisted the switch due in part to a fear of any change in an essential asthma attack relief medication, plus a particularly strong reaction to changes in taste. The patient population has largely become accustomed to the taste of CFC MDIs, sometimes described as "cabbagey" or "rubbery," that sometimes results from impurities in the CFC propellant. HFA propellants have very little taste, but the alcohol used in many HFA formulations is often contaminated with traces of oxidation products such as aldehydes, which have a pungent unpleasant odor. In addition, patients often experience a physiological reaction, or alcohol burn at the back of the throat.

The regulatory community has yet to take the taste issue fully to heart, and requirements to control this attribute remain very rare, although substantial anecdotal evidence suggests that an unpleasant taste

will have a major impact on the way that patients relate to their MDIs. Patients will likely tolerate some taste in relief medications; however, an unpleasant or bitter taste in a preventer-type medication such as a corticosteroid can have a substantial effect on patient compliance, especially in pediatrics.

The future

We have arrived at the tail end of the conversion to HFA-propelled inhalers, as the US banned CFC-propelled MDIs at the end of 2008. Probably about 20% of MDIs worldwide still use CFCs, largely in developing countries, but chlorofluorocarbons should be phased out completely by around 2012.

At this time, it appears that no other gases are set to challenge HFA as propellants for MDIs. Although manufacturers are developing alternative low global warming, low flammable refrigerants called hydrofluoroolefins such as $CF_3(F)C=CH_2$, also known as HFO 1234yf, for some industrial applications, the reactivity of the double bond in these gases tends to create more toxicology concerns than do the existing HFAs. Further work remains, but the current published toxicological data makes it extremely unlikely that any propellants from this class of gases will ever be developed and approved for inhalation use.

However, the problem of global warming now looms large over the future of HFAs as some industrial uses of the gases already face regulatory control related to global warming, even though HFAs are much weaker global warming gases than CFCs, which also deplete ozone. For example, after Jan 1, 2011, the European Union will not permit auto makers to launch new car models onto the European market with HFA 134a in the air conditioning.

While there is no sign that regulation will spill over into the MDI world in the foreseeable future, non-medical uses of HFAs with higher potential for global warming, such as HFA 134a, will likely fall under progressively increasing regulatory control. In time, reduction in demand may leave HFAs for medical aerosols as one of the major remaining uses of these gases, and the lower demand will no doubt lead to shakeouts in the fluorochemicals industry. With that possibility in mind, users should take the probability of a manufacturer's longevity into consideration when selecting a supplier.

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