

MDI propellants

A Q&A with experts from 3M Drug Delivery Systems on the changeover from CFCs to HFA

As the FDA's deadline for conversion from chlorofluorocarbons (CFCs) to hydrofluoroalkane (HFA) in MDIs approaches, we ask 3M's Barbara Davidson, Georgina Fradley, and Simon Cawthorne how the transition is going.



Q *What kind of cooperation has there been from suppliers and regulatory agencies?*

A **Barbara Davidson, EU Regulatory Manager:** Two groups of metered dose inhaler manufacturers, IPACT-I and IPACT-II, collaborated on the unique challenge posed by the Montreal Protocol on Substances that Deplete the Ozone Layer, which was adopted in 1987. These consortia cooperated on rapid and cost-effective toxicity testing of HFA-134a and HFA-227 and the establishment of unique regulatory procedures for obtaining speedy approval of the compounds.

The IPACT teams took up the challenge to define and conduct the required toxicological testing necessary to satisfy the global regulatory authorities, including the US FDA and the European Medicines Agency (EMA) Committee for Proprietary Medicinal Products

(CPMP). The process included compiling and filing the data generated with the regulatory authorities in order to secure the regulators' agreement that the data were sufficient to support applications for reformulated MDIs.

The US and EU regulations do not permit the registration of excipients *per se*; but given the need to gain speedy regulatory approval, the consortia decided to submit one regulatory data package on behalf of all members, and the regulatory authorities agreed to the deviation from normal regulatory procedures. In the EU, the CPMP agreed to carry out a single "co-ordinated" review, resulting in positive endorsement for HFA-134a in July, 1994 and for HFA-227 in September 1995. In the US, the FDA agreed to carry out a single review of the Drug Master Files (DMFs), submitted in installments as data became available, to support clinical work undertaken by consortia members. Although DMFs do not receive formal approvals, the FDA reviewed the submissions to its apparent satisfaction.

Q *What have been the greatest challenges for formulation in the conversion to HFA?*

A **Georgina Fradley, Development Specialist:** The conversion to HFA propellants posed significant challenges for the inhalation industry. First, considerable searching and testing was required to identify potentially suitable non-CFC propellants. Once HFA-134a and, later, HFA-227 were identified, extensive studies were required to ensure safety of the new propellants in the lung. That meant that the pharmaceutical industry needed to assess the requirements for these studies, to conduct the necessary safety testing, and to ensure that the results were endorsed by the CPMP.

Although promising, the new HFA propellants differed from CFCs in a number of ways that significantly impacted both formulations

and container closure system components. Excipients that had been suitable for the old CFC formulations were no longer suitable because many surfactants soluble in CFCs do not dissolve well in HFA. In order to produce homogeneous dispersions, novel approaches such as using ethanol as a co-solvent were required. However, adding ethanol can cause problems with suspension formulations, so some companies looked to increase the amounts of ethanol in order to form solution formulations. This approach benefited performance because the solution products demonstrated improved efficiencies, and the small particle sizes led to peripheral deposition, which is thought to be beneficial for some therapies.

Q *How has the transition affected device design?*

A **GF:** The transition to HFA propellants significantly impacted container closure systems, particularly the metering valves. A pMDI must remain a closed system in order to prevent leakage of the formulation and to reduce ingress of moisture, which can significantly impact product performance. Many of the valve sealing materials which had been used for CFC formulations were no longer suitable because they displayed different swell characteristics in HFA than in CFCs. Seals are key components in valves, and seemingly trivial changes can have significant impact on performance. The differences in characteristics with the new HFA formulations lead to propellant leakage; and without lubrication from the surfactants that had traditionally been used, valve sticking became a

problem. Designers needed to find new materials that would seal the unit while still enabling the valve to actuate freely and without requiring excessive forces. Consequently, it took many years to optimize valve performance with HFA formulations.

Q *What are the major challenges for the use of HFA in new product MDIs?*

A **Simon Cawthorne, Formulation Group Leader:** The great challenges associated with obtaining container closure systems

that are compatible with HFAs are now largely resolved. Most CFC-containing products have become available in CFC-free alternatives. We learned how to design metering valves and canisters for use with HFA during the early transition period. However, many challenges remain for new product development.

For one thing, only two HFAs, 134a and 227, are widely accepted as appropriate propellants, restricting the palette from which to select components for a formulation. In the event of incompatibility between the active pharmaceutical ingredient and one of the HFA propellants, the formulator has only one other option available. The limited choice can make it difficult to achieve the desired type of formulation. If the formulator wants to create a solution with the drug dissolved in the propellant, that may not be possible if the drug is not soluble in HFA; the only choice may be to create a suspension instead. The selection of excipients compatible with the HFAs and at the same time safe for inhalation use is limited also, further reducing the approaches to the

formulation and the options available when technical problems arise.

For APIs that are very soluble in the propellant and co-solvent, solution formulations are the easy choice; likewise, very insoluble APIs can be formulated as suspensions. For HFAs, as well as for CFCs, the real challenge lies with those APIs that are intermediately soluble. New surfactants, such as oligolactic acids, are now being developed to address this need, but they have yet to reach the market.

Challenges also exist in designing container closure systems for new products. Solutions to these problems may require new metering valve designs, non-stick coating materials, metering valve elastomer materials, and product manufacturing processes. Many patent protected technologies have been born out of the need to solve technical problems associated with the way the API behaves in the HFA propellants or with incompatibility of the excipients and/or elastomers used in the CFC propellants. Continual investment in new technologies through the transition has been necessary; 3M and other companies now offer the technology for licensing or co-development services which grant access to these technologies.

Q *Have clinicians and patients accepted HFA-based products?*

A **GF:** The switch to HFA products has been interesting for the inhalation industry. With the reformulation of existing molecules, manufacturers had to choose between designing entirely new HFA products and making them equivalent

to the familiar CFC products. Companies that have decided to improve performance during the new product development have had the opportunity to differentiate their products; for example, increasing the lung deposition and product efficiency, which can be attractive attributes to doctors and clinicians, may help a new product gain acceptance.

Most companies, however, chose to reformulate equivalent products, facilitating seamless transitions for patients and prescribers. However, due to the cost of development, HFA products tend to be more expensive than their CFC counterparts, so the payer, whether patient, government or insurer, has little incentive to switch to the non-CFC option. The patient may also encounter small changes in the inhalation experience when switching to an HFA product; a number of patients have noted differences in taste and sensation in the mouth when using HFA products for the first time. However, these differences do not

seem to pose significant problems and, especially in markets where HFA products are now the norm, patients have become comfortable with the feel of the new products.

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How far along is the conversion?

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SC: The transition is going well. The vast majority of devices now sold in Europe are CFC-free, and the same will soon be true in the US, especially after the FDA institutes its ban on sales of CFC-containing albuterol (salbutamol sulfate) pMDIs, which is slated to begin on December 31, 2008. Regulations in Europe and the US now restrict inhaler product development to HFA propellants only, and the US FDA recently issued a proposed rule seeking to ban the sale of all CFC-based

MDIs starting December 31, 2009. That proposed rule is currently open for public written comment. A total withdrawal of CFC-based pMDIs in the US and Europe is likely to occur at some point, but predicting exactly when is difficult.

Manufacturers of CFC propellants have seen, and will continue to see, a downward trend in CFC volume, and there will come a point when selling CFC propellants at commercial prices and volumes for pMDI manufacture will cease being economically viable. At that point, manufacturers of pMDIs will no longer be able to obtain CFC propellants and, as a result, they will no longer be able to produce CFC-containing pMDIs. Predicting what will happen in developing countries that may not have signed up to the same environmental agreements as the developed countries is more difficult. In those cases, CFC production may continue, and CFC-containing pMDIs may continue to be produced on a relatively small scale in the future.