IS NOW THE TIME TO SHAKE UP THE pMDI ENVIRONMENT?

In this article, Chris Baron, Director of Business Development, Aptar Pharma, explores how the use of propellants in pressurised metered dose inhalers has evolved – and how alternative propellants could be a catalyst for greater patient adherence.

Given that humans are largely creatures of habit, it's no surprise that most of us find it uncomfortable to truly embrace change. When the 1987 Montreal Protocol initiated the phasing-out of ozone-depleting substances, including chlorofluorocarbon (CFC) propellants, those who work with pressurised metered dose inhalers (pMDIs) were naturally nervous. As it happened, the switch was beneficial not just to the ozone layer but also to the pMDI carbon footprint.

Today, the industry is faced with a similar challenge – how to move away from propellants such as hydrofluoroalkanes HFA P227 and HFA 134a and towards newer, more environmentally friendly approaches aimed at further reducing the sector's carbon footprint.

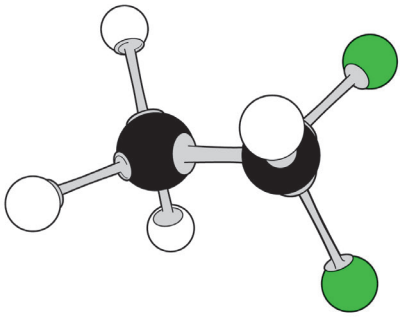
Just six months ago, experts could not say with any certainty that one such alternative – HFA 152a (1,1-difluoroethane, Figure 1) – would work. We knew it was more environmentally friendly but would it pass the technical trilogy of excellent toxicology, limited flammability and reduced environmental impact while maintaining formulation stability (Figure 2)? All without losing sight of the greatest challenge of all – ensuring patient safety and supporting regimen adherence. These are, after all, life-enhancing, life-saving treatments for many patients.

In this article we will explore how the industry's use of propellants has evolved and consider where we could end up in the drive for greater sustainability, providing some context on the impact pMDIs have on the environment today, while at the same time suggesting some areas for improvement.

We will also discuss how HFA 152a and other alternative propellants could be a catalyst for greater patient adherence, and how greater adherence could in itself be an effective route to improved sustainability.

KEEPING UP WITH CLIMATE SCIENCE

While sustainability dominates today's agenda, environmental science has not always enjoyed such prominence. Indeed, when the first pMDI was introduced in 1956,



A colorless, odorless, non-toxic low boiling liquid
In large scale industrial use (~150Ktpa), as:

- Polymer precursor
- Aerosol propellant (e.g. hairsprays, deodorants)
- Foam blowing agent
- Air conditioning and refrigeration

Figure 1: HFA 152a – a low global warming potential (GWP) medical propellant.

Chris Baron
Director of Business Development
M: +33 6 30 95 53 31
E: chris.baron@aptar.com

Aptar Pharma
Route de Falaises
27100 Le Vaudreuil
France

pharma.aptar.com

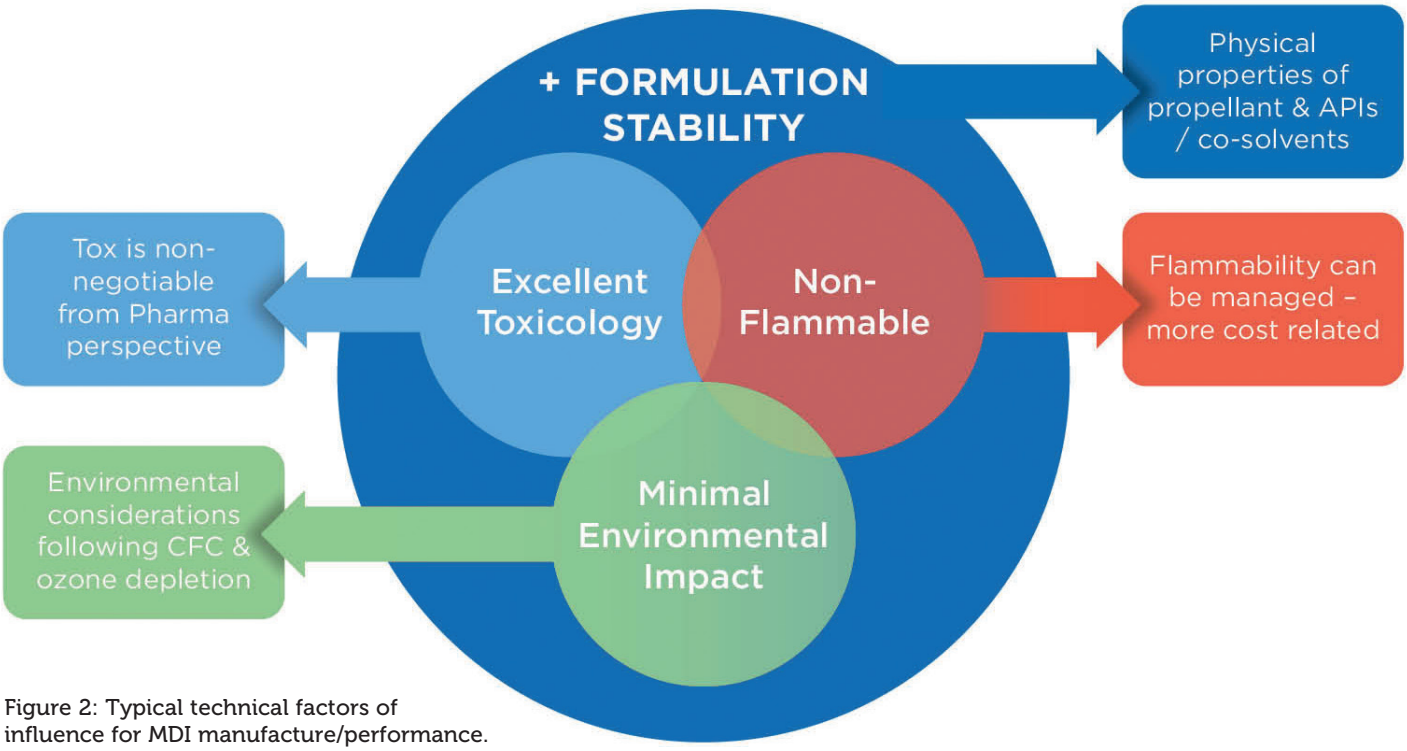


Figure 2: Typical technical factors of influence for MDI manufacture/performance.

it was almost another two decades before the term "global warming" became popularised through the publishing of a paper by US geochemist Wally Broecker in 1975.[1]

The following decade saw growth in the evidence base for the damaging impact that so-called "greenhouse gases" were having on the environment, including their contribution to the depletion of the ozone layer. This culminated in 1987 with the establishment of the Montreal Protocol, which regulated the consumption and production of compounds harmful to the ozone layer. Within the decade, CFCs – the family of gases most commonly used as a pMDI propellant – were to be phased out, although in the case of pMDIs an exemption was granted until alternative products using HFA propellants could be safely brought to market.

It was in 1995, some eight years after the signing of the Montreal Protocol, that the first HFA-based salbutamol product was launched in the UK. By 2012, the US FDA banned the manufacture and sale of CFC-based products entirely.

Given that 400 million pMDIs were sold in 2014, the result of the move from CFC to HFA has been a net reduction of around 2,600 tons of CFCs being released into the atmosphere every year.[2]

While not as significant as other CFC-heavy sectors, this reduction has helped contribute to a reversal of the depletion of the ozone layer while also ushering in a decline in the sector's carbon footprint. In October 2019, satellite measurements from NASA and NOAA registered the ozone hole at 3.9 million square miles – the smallest level since records began. While unusual weather patterns were a factor in this figure, experts suggest the ozone will be fully repaired by the 2060s.

"The move to restrict HFAs presents an ongoing challenge for those involved in the manufacture and development of pMDIs."

NOW HFAS ARE UNDER SCRUTINY

But the environmental story of pMDIs does not end there. In recent years, as the issue of sustainability has escalated to a climate emergency, the focus on limiting the use of products with the potential to impact the environment has become more acute. As a result, there is an emphasis on reducing the use of other fluorocarbons that have a global warming impact, beyond just CFCs.

Collectively known as F-gases, this family accounts for around 2% of total greenhouse gas emissions, and their use is dominated by the air-conditioning and refrigeration industry. However, F-gases also include the HFCs used as propellants in pMDIs – predominantly in the form of HFA 134a and HFA P227, albeit only accounting for a very small proportion (see Figure 3).

The restriction on F-gases has been made official through the Kigali Amendment (2016) to the Montreal Protocol, which came into effect in 2019 and seeks to phase down the use of HFCs by 85% by 2047. The situation regarding compliance is not necessarily consistent across the globe, however. In the US, despite the introduction of the Significant New Alternatives Policy (SNAP) programme and its intention to identify and evaluate substitutes for ozone-depleting substances, pMDIs remain fully exempt.

In Europe, legislation to phase down the use of F-gases restricts their use through a quota system and specific bans. Medical use exemptions are applied to pMDIs but the products are impacted by regulation linked to the phasing out of industrial HFC grades, which are used as the basis for the purified HFAs used as propellants. As these products are phased out, taxation

"The challenges of repurposing are well known, both from a manufacturing and regulatory perspective as well as in terms of efficacy and patient compliance."

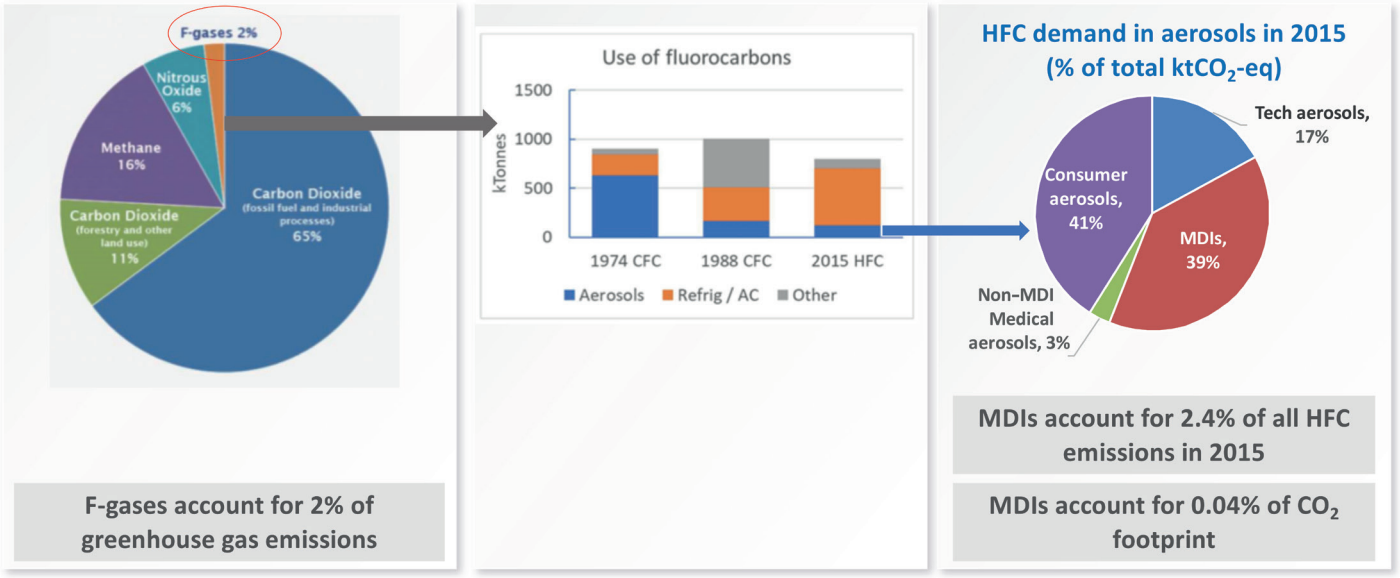


Figure 3: Use of fluorocarbons (F-gases).
Sources: US Environmental Protection Agency Web Page (https://www.epa.gov/ghgemissions/global-greenhouse-gas-emissions-data); Hauck HR, "Do Medical CFCs Threaten the Environment?" J Aerosol Med, 1991, Vol 4(3), pp 169-174; Technology & Economic Assessment Panel, Meeting of Parties, Kigali, 2016.

and inflated quota pricing are leading to significant cost increases that will no doubt be passed through to the price of medical-grade gases. With the pMDI exemptions only applied on a temporary basis, there is also a chance they will be subject to withdrawal when next reviewed in 2021 if the European Commission decides to enforce measures to accelerate the adoption of lower-carbon alternatives.

Amid the inconsistencies, it is clear that the move to restrict HFAs presents an ongoing challenge for those involved in the manufacture and development of pMDIs, who find themselves in a position similar to that experienced in 1987, when the Montreal Protocol outlined a new CFC-free future and presented a clear challenge to find a commercially viable way forward.

FINDING NEW ALTERNATIVES

In the short term, the manufacture of pMDIs will continue as normal as the supply chain recalibrates its approach. Any immediate impact is likely to be felt in a shifting dynamic between product pricing and margin, with HFA costs set to continue their rise.

In the longer term, there will have to be consideration of alternatives. In terms of drug delivery methods, options are available that have comparatively lower carbon footprints, including dry powder inhalers (DPIs), soft mist inhalers (SMIs) and portable nebulisers. However, the challenges of repurposing are well known, both from a manufacturing and regulatory perspective as well as in terms of efficacy and patient compliance.

Here at Aptar Pharma, we are already committed to defining the next phase of the pMDI market. As stocks of current propellants deplete, inevitably leading to a sustained increase in pricing, we believe now is the time for pharmaceutical companies to align themselves with more environmentally friendly propellants. HFA 152a and HFO 1234ze, for example, present significantly lower global warming potential (GWP) compared with existing HFA propellants.

With these lower-carbon alternatives, the key question that must be answered is whether they can successfully balance the required levels of toxicology and flammability, ensuring formulations remain

> "With lower-carbon alternatives, the key question that must be answered is whether they can successfully balance the required levels of toxicology and flammability, ensuring formulations remain stable and efficacy is not impaired."

stable and efficacy is not impaired. In the case of HFO 1234ze, the environmental case is incredibly strong and flammability is limited – but toxicology concerns have been raised in the context of its use as a medical propellant.[3]

In the case of HFA 152a, the environmental case is also compelling. Furthermore, an exhaustive full-inhalation propellant toxicology study is entering the final year of a two-year study, with no adverse findings raised to date. Properties such as a lower flammability limit (LFL) of 3.8% mean there are still important safety hurdles, primarily from a manufacturing perspective, that need to be overcome before HFA 152a can be introduced within a marketable product but, overall, the indications are promising. Indeed, calculations based on research presented by the University of Manchester[4] have shown that a month's worth of medication taken using a salbutamol + EtOH product – but propelled by HFA 152a – has a similar carbon footprint to a single healthy bite of a beefburger, with around 1kg of CO_2 per 100 doses.

LIMITING CARBON IMPACT THROUGH INNOVATION AND PATIENT COMPLIANCE

At Aptar Pharma, we are focused on finding more sustainable, lower-carbon propellant alternatives, and have already undertaken significant work to evaluate the compatibility of our metering valves with more environmentally friendly options, including formulations based on HFA 152a. As a company, we have committed resources to these programmes, with the support of our research and development laboratories, and filling capabilities in Le Vaudreuil (France).

Collaboration with fluoroproducts specialist Koura and a range of pharmaceutical companies is enabling Aptar Pharma to screen metering valves across multiple model formulations and optimise new valve configurations for the use of HFA 152a. This has allowed us to show that the distinct properties of this gas, such as its low liquid density, do not pose a problem in working with suspensions.

Important developments such as this, when coupled with other technical innovations targeted at optimising patient behaviour and compliance, will in time become part of the wider range of factors to support a reduction in the carbon impact associated with pMDIs. Connected devices have the potential to bring real benefit here, providing the basis to increase patient awareness around adherence and promote the sustained, correct use of inhalers. For a global population increasingly aware of their environmental impact, the benefit of reducing their carbon impact just provides an additional incentive to improved compliance.

A STEP-CHANGE IN pMDI SUSTAINABILITY

As this new generation of lower-carbon products emerges, it's important to put some of the more dramatic headlines associated with current HFA-based pMDIs into context. It must be remembered that pMDIs represent a small proportion of the overall use of HFAs, and that HFAs themselves are part of a collective family that represents 2% of greenhouse gases. In fact, MDIs account for just 0.04% of the total carbon footprint. Over the course of a year, it would take 275 million pMDIs used for maintenance therapy to create the equivalent level of CO_2 output by a single 1,000 MW coal power station.

The fact remains that pMDIs offer unique benefits as a mechanism for delivering essential medicines. Experts are unanimous in their view that asthma patients must have access to the most suitable treatments when they need them. Also, with an estimated 95% of portable rescue medications administered using pMDIs, the importance of familiarity and ease of use should not be underestimated.

Change, rightly, is coming. Having successfully risen to the challenge of eradicating CFCs from the supply chain, pharmaceutical companies and their partners are now responsible for establishing greener alternatives to HFA-based inhalers. The potential of HFA 152a, in tandem with innovation to drive greater patient compliance, presents an evolutionary pathway for the pMDI sector to continue to meet its dual commitments to patients and the planet.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, providing innovative drug delivery systems, components and active packaging solutions across a wide range of delivery routes including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early stage to commercialisation support to accelerate and derisk the development journey. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 14 manufacturing sites, Aptar Pharma provides security-of-supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc (NYSE:ATR).

REFERENCES

1. *Broecker W, "Climatic change: Are we on the brink of a pronounced global warming?". Science, 1975, Vol 189 (4201), pp 460–463.*
2. *Stein S, Thiel C, "The History of Therapeutic Aerosols: A Chronological Review". J Aerosol Med Pulm Drug Deliv, 2017, Vol 30(1), pp 20–41.*
3. *Lindley A, Noakes T, "Consideration of hydrofluoroolefins (HFOs) as potential candidate medical propellants". White Paper, Mexichem Flour (now Koura), April 2010.*
4. *Jeswani H, Azapagic A, "Life cycle environmental impacts of inhalers". J Clean Prod, 2019, Vol 237.*

ABOUT THE AUTHOR

Chris Baron is Director of Business Development in asthma and COPD at Aptar Pharma. For the last 10 years he has been located at Aptar Pharma's manufacturing facility in Le Vaudreuil, France, where he oversees global business development activities for Aptar's inhalation drug delivery devices (MDIs and DPIs) and their respective services pertaining to the application fields of asthma and COPD. Mr Baron has 29 years' experience working in the field of inhalation drug delivery, with significant expertise in metering valve technologies for pressurised metered dose inhalers and their accessory/peripheral device technologies, including dose indicators and breath-activated inhalers.

Transforming bright ideas into brilliant opportunities for decades

Aptar Pharma – the go-to drug delivery expert

When pharmaceutical companies around the world want to develop safe, efficient and compliant medicines, they turn to Aptar Pharma for proven drug delivery solutions.

Leveraging our therapeutic insights, over 25+ years of regulatory expertise and the widest portfolio of solutions and services in the industry, we accelerate and derisk our customers' drug development process, helping them transform bright ideas into new market opportunities to improve and save patients' lives.

Let's partner together on your next bright idea. Visit **www.aptar.com/pharma** to get started.

Delivering solutions, shaping the future.

Aptar pharma