Staying Ahead of Green Propellant Regulations in pMDIs

Navigating the transition to green propellants, while maintaining performance and usability

The next few years will see substantial changes for pressurised metered-dose inhalers (pMDIs).

As a result of emerging regulations such as the European Union's F-Gas legislation and the Kigali Amendment to the Montreal Protocol on Substances that Deplete the Ozone Layer, the pharmaceutical industry is working to transition to more sustainable inhalers with reduced environmental impact.

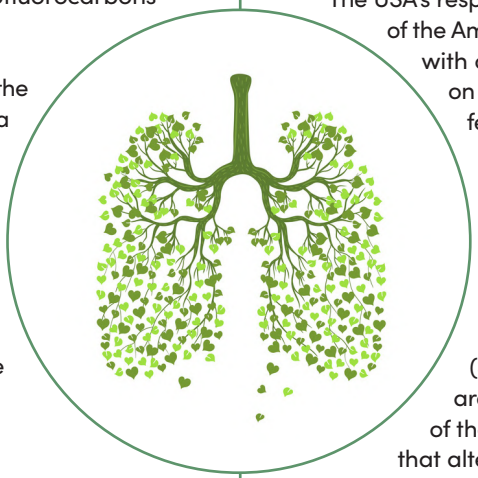
In this article, Craig Sommerville, Senior Vice President of the Metered-Dose Inhaler (MDI) business unit at Kindeva, will discuss how companies can respond to these changes without compromising performance or patient welfare, and how they can act strategically to ensure they are prepared for future opportunities and regulatory shifts.

The "Green" Focus on pMDIs

As countries around the world look to mitigate the effects of climate change, there has been a renewed focus on the propellants used in inhalers.

In 1987, the Montreal Protocol was adopted, precipitating the phasing-out of ozone-depleting substances such as chlorofluorocarbons (CFCs) worldwide. At the time, collaboration and innovation enabled the industry to navigate a transition that has left a lasting legacy.

Nearly 30 years later, in 2016, the Kigali Amendment was signed, turning the world's attention to the hydrofluorocarbons (HFCs) that effectively replaced them.



Companies are now looking to replace the current pMDI propellants – such as HFA-134a and HFA-227ea – with more environmentally friendly alternatives with a significantly reduced global warming potential (GWP). HFA-152a and HFO-1234ze have a GWP that is 90% and 99.9% lower than HFA-134a. Economics also plays a part in the shift. The price of HFA-227ea has risen considerably in recent years, and HFA-134a prices are expected to follow the same trend.

Taking a Holistic Approach

With the regulatory focus currently trained on pMDIs, it may be tempting for companies to consider a switch away to other types of inhaler devices, such as dry powder inhalers (DPIs).

However, this is where companies should take a step back and take a more holistic, strategic view. While it is imperative to reduce environmental impact, the industry must also consider the impact of any change as a whole, and plan for longer-term sustainability and compliance.

A 2024 study estimates that as many as 13.6 million patients in the five largest European Union countries required a pMDI in 2021, and any widespread change would involve a substantial time and cost investment.[1] The pMDI enables the fast and effective delivery of medication directly to the lungs, and moving patients to other inhaler options may have knock-on effects that affect patient convenience and adherence to treatment.

Furthermore, it is important for companies to anticipate regulations that may arise in the future. Europe is presently taking the lead on HFA regulation, with the European Union's F-Gas legislation aiming to phase out all such gases by 2050.[2] The USA's response is currently taking shape in the wake of the American Innovation and Manufacturing Act, with other territories such as India embarking on strategies to phase out HFCs over the next few decades.[3,4] While the goals are clear, the precise path forward is still being shaped by industry experts and regulators.

As legislators continue to work toward more environmentally friendly practices, it is safe to expect that regulations affecting inhalers such as DPIs and soft mist inhalers (SMIs) are on the horizon. While propellants are the current area of focus, a recent study of the environmental impacts of inhalers notes that alternatives such as DPIs may have room to improve on factors such as recyclability and component materials.[5]

Experience of the previous major transition away from CFCs has demonstrated that it is vital to be proactive, and to investigate potential innovations and improvements in all potential propellants. The industry risks missing out on potentially transformative breakthroughs if it abandons lines of treatment.

By remaining open to multiple products, therapies and methods of delivery, strategic companies can maximise their ability to stay ahead of regulatory changes and breakthroughs. Partnering with the right contract development and manufacturing organisation (CDMO), with extensive experience in optimising different approaches, can therefore be an important step in preparing for the future.

Achieving the Best for the Planet, and the Patient

The shift toward next-generation low-GWP propellants such as HFA-152a and HFO-1234ze is an important step. The challenge is to ensure that this can be achieved while maintaining – and even ultimately improving – the standards of efficacy, convenience and safety that patients expect.

It is therefore important to explore the ways in which changing the propellant used in pMDIs affects performance. Switching to next-generation propellants can result in changes to vapor pressure, density, surface tension, specific heat capacity and latent heat of vaporisation, all of which must be analysed and accommodated where necessary.

For example, HFA-152a and HFO-1234ze both have higher surface tension values than the currently used propellants, which can affect the size of the initial droplets formed in atomisation as well as the final size of the droplets in the lungs. Furthermore, the physical suspension stability of the low-GWP propellants could be impacted because of their lower density.

Analysing the effects of changing the propellant can be challenging due to the chaotic atomisation that takes place when the pMDI is actuated, and the propellant liquid depressurises rapidly. Nevertheless, it is crucial to develop a deeper understanding of how formulation and device are affected by the introduction of a new propellant – both inside and outside the device - so that future formulation and hardware adaptations can be made with confidence.

This will require companies to partner with experienced research partners and CDMOs, using a combination of compendial and novel methodologies. For example, initial explorations of spray performance at ultra-high-speed imaging facilities indicate that the vapor pressure of next-generation propellants is less sensitive to increased ethanol concentration than current propellants such as HFA-134a.[6] As a result, manipulation of the ethanol cosolvent in the formulation may be one option for tuning the formulation and optimising performance.

Changes in inhaler hardware could also improve outcomes. For example, studies indicate that lengthening the pMDI orifice slightly can reduce the width of the spray, which makes it a potential mitigation route for modulating plume width and mixing.[6]

Insights such as these are crucial in helping companies to integrate next-generation propellants while maintaining performance and patient safety, as well as remaining compliant with upcoming regulations. However, it is important to note that some key aspects of regulation are yet to be determined. For example, it is not yet clear whether moving to pMDIs with next-generation propellants will require a New Drug Application (NDA). Furthermore, while the HFO-1234ze next-generation propellant offers a substantially lower GWP than current propellants, it may yet fall under emerging European restrictions on per- and polyfluoroalkyl substances (PFAS).

As these regulations are shaped and refined, it is important that the industry shares its expertise to ensure that the best route forward is agreed. CDMOs with extensive experience in developing pMDIs at scale over many years are ideally placed to play a key role in this.

Ensuring a Smooth Transition

This transition will no doubt require careful planning and investment. That said, the priority must be to ensure that there is as little disruption to the patient as possible. This means working to adapt pMDIs so that there is no perceivable difference in product performance and taking all necessary steps to make this next generation of pMDIs available to patients with no impact on supply.

Any disruption to availability could result in patients moving to other options or interrupting their treatment. Therefore, companies that wish to respond to next-generation propellant regulations – and perhaps obtain a commercial advantage over competitors – should ensure that they work with partners who are sufficiently advanced in upgrading to next-generation propellants. Furthermore, partners should be able to demonstrate that they can handle, fill and manufacture pMDI products using these propellants at the required capacity to meet patient demand.

Forward-thinking CDMO partners have been investing heavily in recent years to ensure they can help this change take root. This involves scaling up both infrastructure and production lines and undertaking extensive re-designs to adapt to the unique storage needs of the new materials. Many are working with companies on more integrated drug-device development strategies, which enable them to consider formulation, device design and manufacturing in tandem. In this way, they can anticipate challenges and opportunities, avoid setbacks and make more informed choices.

Selecting proactive partners with a coherent and advanced strategy will minimise the impact on patients, and the companies themselves.

Anticipating the Future

While the move away from current propellants represents a sizable and complex challenge, companies should also keep an eye on the future. The shift to next-generation propellants is almost certainly part of an ongoing trend toward reducing environmental impact in the industry as a whole. This trend will affect different products in different ways as regulations emerge and evolve.

As such, companies that wish to prepare for the long term must consider a number of crucial factors to make sure they are prepared for what comes next.

- **Do not make decisions in haste:** Switching to next-generation propellants may be complex in the short and medium term, and it may be tempting to react by switching to other inhaler options.

However, abandoning treatment options may cause companies to miss out on potential future innovations, and the cost and impact of switching at scale may lead to larger environmental impacts.

- **Anticipate evolving regulations:** Instead of simply reacting to the immediate challenges of current and imminent legislation, companies should develop an informed strategy that observes the direction of travel of the industry, and plans based on what is expected in the future.

  This requires companies to be well-versed in current regulations, and ideally active in discussions about how regulations need to evolve in the coming years.

- **Understand your product, and how it can be optimised:** While the current focus of legislation is on propellants, it is probable that other components and practices will be discussed in future years.

  By developing a highly detailed understanding of their products, companies can start to catalogue all the potential options that are open to them for product optimisation and can react with more confidence and insight as regulations emerge.

- **Select informed and prepared partners:** The right partner can provide invaluable guidance and expertise during a complex change. For example, an experienced CDMO with a background in multiple therapies, products and delivery methods can anticipate challenges, point out the best approaches, and potentially provide access to new and innovative techniques and methodologies.

  It is also important to choose a partner who can provide the infrastructure and expertise necessary to switch to green propellants quickly, to maintain supply and minimise disruption.

- **Keep the patient in mind:** Ultimately, the aim is to provide treatments that are safe, effective, affordable and easy to use, while keeping environmental impact as low as possible.

While adapting to legislation, companies must strive to ensure that the patient is not affected. This means adapting formulation and product design to maintain efficacy, and maintaining supply so that treatments remain accessible to those who rely on them. With the phasedown of existing propellants likely to commence in 2027, it is likely that the move to next-generation propellants will dominate discussions in the industry in the near future.[7]

However, companies must resist the temptation to act reactively. By taking a wider view, the industry can put itself in a better position to adapt to future regulations. Furthermore, by continuing to explore how to optimise a variety of therapies and devices, we can maximise our chances of discovering innovative treatments which change lives down the line.

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Craig Sommerville, Senior Vice President of Kindeva's Metered-Dose Inhaler (MDI) business unit, is responsible for shaping and executing Kindeva's MDI platform's global strategy, focusing on leading the industrialisation of the green propellant transition. With over 25 years of experience in increasingly senior roles across site leadership, supply chain strategy, operations, logistics, procurement and technical functions, Craig brings a proven track record of transforming challenges into opportunities.