



A BREATH OF FRESH AIR: PHARMA'S PUSH FOR SUSTAINABLE pMDIs



Andy Burns of **Kindeva** considers the driving factors for the transition to more sustainable propellants, as well as explaining the benefits and challenges of these next-generation propellants in terms of compatibility, performance, safety and global warming potential.

The pharmaceutical industry is in the midst of a green revolution, with a growing emphasis on sustainability and environmentally conscious manufacturing. A key area of focus for this transformation is the development of pulmonary and nasal drug delivery devices. For decades, pressurised metered-dose inhalers (pMDIs) have been a cornerstone of respiratory therapy, however, the propellants that power them are currently under legislative scrutiny for their environmental impact.

The change is driven by global and national regulations across Europe, the UK and the US stemming from the Kigali Amendment to the Montreal Protocol. This mandates a phasedown of the current generation of high global warming

potential (GWP) hydrofluorocarbons (HFCs) to 85% of present levels in terms of tonnes of carbon dioxide equivalent. Building on this, the EU in particular has included a phaseout of HFCs by 2050 in its own regulations written to achieve the goals of the Amendment.

As these legislative changes come into effect worldwide, they are driving a period of focused innovation in inhalation drug development. Pharmaceutical companies must now reformulate their products to remain efficacious for patients while making them compliant with these new regulations and sustainable for the planet. This challenge requires a fundamental re-evaluation of the pMDI as an entire system, from its formulation and device components to its manufacturing.

This industry-wide shift, propelled by an evolving regulatory landscape and a shared commitment to sustainability, presents significant technical hurdles. This article will explore these challenges, the pivotal role expert CMDO partners play in navigating the transition and what these vital changes mean for the future of sustainable respiratory drug delivery.

THE GLOBAL MANDATE FOR GREENER PROPELLANTS

The driving force behind the transition to greener propellants is the Kigali Amendment to the Montreal Protocol – a global agreement that compels signatory nations to phase down the production and consumption of HFCs, such as HFA 134a and HFA 227, which are potent greenhouse gases with high GWP. The agreement sets an ambitious schedule, requiring a first group of nations (including the US, UK and all EU member states) to achieve an 85% phasedown by 2036.¹

This international treaty is now being implemented through national and regional laws:

- **European Legislation:** The EU's updated F-Gas Regulation (EU 2024/573), which took effect in March 2024, is a primary driver. It accelerates the HFC phasedown and will eventually remove the previous medical-use exemption for pMDIs.
- **UK Legislation:** Post-Brexit, the UK has retained and continues to enforce its own F-gas regulations that align with the goals of the Kigali Amendment, pushing the industry toward lower-GWP alternatives.²
- **US Legislation:** The American Innovation and Manufacturing Act directs the Environmental Protection Agency (EPA) to phase down HFCs in line with the Kigali schedule. The EPA is now establishing a framework for this transition, which includes managing HFCs for essential uses such as pMDIs while encouraging the shift to next-generation technologies.³

To understand the drive for change, it is crucial to consider the scale of the impact. The use of some traditional pMDIs can have a carbon footprint equivalent

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to a car journey of over 100 miles.⁴ This is due to the high GWP of HFC propellants, which disproportionately contribute to global warming when released into the atmosphere. For pharmaceutical companies, the implications are clear – to keep pMDI products on the market, they must find and validate next-generation propellants (NGPs) with lower GWPs to replace traditional gases and reformulate their products to be both safe and efficacious.

NAVIGATING NEXT-GENERATION PROPELLANTS

Finding a replacement for established HFCs in pMDIs is far more than a simple swap of the propellant gas, as it is in non-pharmaceutical applications, such as in heating, ventilation and air conditioning systems. This transition presents a unique set of technical challenges, including:

- **Compatibility with pMDI Devices:** The new propellant must be chemically and physically compatible with all device components, from the metal canister to the elastomer valve seals. This includes a thorough assessment of extractables and leachables to ensure that the propellant's unique properties do not introduce new impurities that could compromise the stability of the formulation.
- **Compatibility with Drug Formulations:** The propellant is a critical part of the drug formulation itself. It must be compatible with the API and any excipients, ensuring that the drug remains stable and deliverable over the product's shelf life.

- **Patient Safety:** Any new propellant must undergo rigorous toxicological testing to prove that it is safe for inhalation. This safety assessment must also extend to any new compounds identified during compatibility testing, ensuring that the final delivered dose is free from potentially harmful impurities.

- **Administration Performance:** The reformulated product must demonstrate bioequivalence to the original, meaning that it delivers the same therapeutic effect to the patient. This requires extensive testing to ensure that metrics such as particle size and plume geometry result in the correct drug deposition in the lungs.

- **Manufacturing and Safety:** While leading candidates such as HFA-152a are classified as flammable, this is a manageable engineering challenge. It can be addressed through the implementation of expert safety protocols and the use of specialised, ATEX-compliant manufacturing facilities.

- **Regulatory Approval:** Switching propellants will require a thorough assessment and approval by regulatory authorities, necessitating the generation and submission of a comprehensive package of technical data, and possibly clinical data, on the reformulated product.

The search has narrowed to two primary low-GWP NGP candidates: HFA-152a from Orbia Fluor & Energy

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Materials (Boston, MA, US) and HFO-1234ze from Honeywell (Charlotte, NC, US). Both offer environmental benefits and have potential as near-term solutions for reformulating many existing pMDI products.

The choice comes down to a trade-off between formulation science and key factors such as manufacturing safety and environmental performance. HFO-1234ze has an exceptionally low GWP and is non-flammable, but its chemical properties may make it a poor solvent for some respiratory drugs, creating challenges with reformulation – particularly for solution-based formulations. In contrast, HFA-152a has a higher GWP and is flammable, but is more similar chemically to the currently used HFA-134a, which may provide a more direct route to achieving a stable and effective product.

WHO IS PROPELLING THE TRANSITION TO NGPS?

The scale and complexity of the propellant transition mean that many pharmaceutical companies will turn to expert partners for support. A CDMO with specialised expertise in inhalation and sustainable propellants can significantly de-risk and accelerate the transition to NGPs.

An expert CDMO can offer several key advantages to its partners:

- **Legacy of Inhaled Innovation:** A long history of formulating and developing complex inhalation products can provide the scientific foundation needed to tackle reformulation challenges.
- **Purpose-Built Infrastructure:** A proactive CDMO partner will have already invested in the specialised infrastructure needed to safely handle flammable propellants such as HFA-152a. This can save pharmaceutical companies significant time and capital expenditure, removing a major barrier to entry.
- **Regulatory Expertise:** Decades of experience in bringing inhalation products to market can provide the regulatory insight needed to navigate the complex filing process for reformulated pMDI products across global agencies.

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- **Integrated Combination Product Development:** A pMDI is a combination product, and its success will depend on the seamless integration of the drug formulation, the components and the device. A CDMO with in-house expertise in both areas can co-optimize the entire system, ensuring consistent, effective drug delivery while accelerating the overall development timeline.

Successfully integrating this deep scientific knowledge, regulatory insight and application-specific infrastructure is where working with an experienced partner becomes essential.

Kindeva brings a legacy of pMDI innovation that stretches from inventing the world's first pMDI in 1956 to leading the industry's last major environmental

shift with the first chlorofluorocarbon-free inhaler. This deep heritage, particularly the expertise gained during that first propellant transition, provides an unmatched understanding of the intricate interplay between formulation, device and manufacturing. Today, this expertise is focused on the next generation of sustainable inhalers, with significant investment in new commercial-scale manufacturing lines to support the transition to green propellants.

GREENER TOMORROWS ARE IN THE MAKING

The mandated phasedown of high-GWP propellants marks a pivotal moment for respiratory medicine. The journey is not merely about compliance but about fundamentally re-engineering a cost-



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effective, critical and patient-preferred drug delivery platform for a sustainable future. The pMDI platform remains the ideal pulmonary platform from a cost-efficiency point of view, so it is essential to address this propellant issue as quickly as possible.

While the transition to NGPs presents significant technical and manufacturing challenges, it is also a powerful catalyst for innovation. This transition is driving change across the entire pMDI system, demanding a more integrated approach to formulation, device compatibility and

manufacturing. The long-term impact of this shift will be substantial. It will dramatically reduce the carbon footprint of these inhaled therapeutics and align the pharmaceutical industry with global climate goals. Most importantly, this will be accomplished without sacrificing the high standards of patient safety and efficacy that have made pMDIs a cornerstone of respiratory care.

Successfully navigating this complex landscape requires both deep technical capability and a new level of collaboration.

The journey to the next generation of pMDIs will be built on strategic partnerships between pharmaceutical innovators and experienced CDMOs who have the scientific legacy and the purpose-built infrastructure to turn these new propellants into approved, life-sustaining products. This shared commitment is both a regulatory necessity and the foundation for the future of sustainable respiratory care.

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