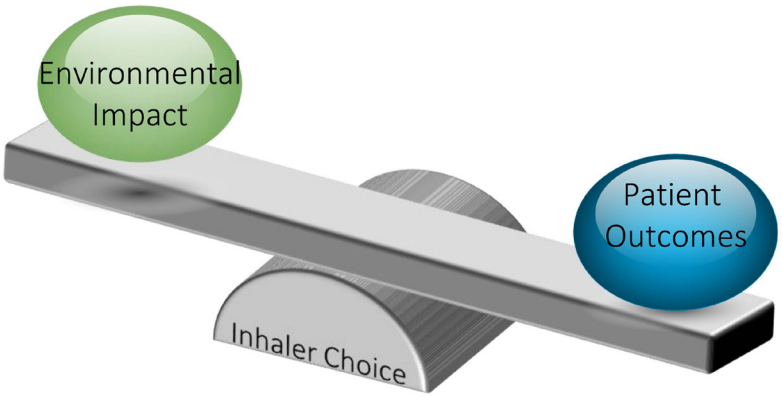
PEER REVIEWED

Under Pressure: Finding a More Sustainable Future for pMDIs

The transition away from the use of ozone-damaging chlorofluorocarbon (CFC) gases has been one of the major environmental achievements of modern times.

Today, hindsight affords us the ability to see how this transition enabled the Earth's protective ozone layer to heal itself over several decades. An unintended consequence, however, was that the withdrawal of CFCs (Chloro-fluorocarbons) ushered in greater use of hydrofluorocarbons, known as F-gases, which introduced their own environmental challenges.



While this family of gases might not pose a risk to the atmospheric ozone layer, they were found to contribute to the greenhouse effect. Compared with carbon dioxide (CO_2), F-gases have a far higher global-warming potential (GWP), based on attributes including infrared radiation absorption and atmospheric lifetime. These characteristics mean F-gases are now also subject to a phasing down, impacting a variety of processes and applications where they currently play an essential role.[1]

In medicine, the use of F-gases is widespread across the globe, with HFC-134a and HFC-227ea relied upon as safe and effective propellants within inhalation devices, helping millions of patients manage respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). As the negative environmental impact of these gases becomes more understood, there are implications for every stakeholder in the chain, from device manufacturers and pharmaceutical companies to healthcare professionals (HCPs) and patients.

The phasing down of F-gases is already well underway, with global efforts falling in line with the Montreal Protocol of the Vienna Convention on Substances that Deplete the Ozone Layer. The Montreal Protocol has provided a framework for safeguarding the ozone layer since it went into effect in 1989 to define the transition away from CFCs.[2] This framework was expanded on January 1, 2019, through the Kigali Amendment, which binds all 198 signatories to also take action to reduce the production and use of F-gases, including the HFCs used in medical devices.

Of all territories across the world, Europe has historically implemented the most stringent targets for HFC reduction. On April 5, 2022, The European Commission set out proposals for two new regulations that would strengthen F-gas legislation and pave the way for a series of changes to accelerate the phasing down process. In announcing the proposals, Frans Timmermans, Executive Vice-President for the European Green Deal, said that while the EU's current ambitious policies have been successful, "science urges us to go further and faster now".[3]

Currently, F-gases account for 2.5% of total greenhouse gas emissions across Europe. The European Commission (EC) said the proposals to accelerate their phasing down would contribute to reducing these emissions by at least 55% by 2030 and support the continent's overarching plan to be climate-neutral by 2050.

In the United States, the world's largest market for pressurised metered dose inhalers (pMDIs), the phase-down programme is scheduled to follow behind Europe through the American Innovation and Manufacturing Act, which came into effect in December 2020. While pMDIs are encompassed within 'set-aside' allocations to ease the transition in the region, these are only in place for a period of five years and the US is expected to achieve a phase-down level of 15% by 2035. Other territories across the rest of the world, including India and countries across the Middle East, are expected to follow behind the US by a period of around 15 years.

Although these robust environmental targets are fixed in place, less certainty surrounds the knock-on effects of meeting them. Of primary concern here are patients, whose ongoing needs must be met in terms of consistent access to relief and prevention medication – something that can only be achieved through the transition either to alternative inhalation devices with lower GWP, such as dry powder inhalers (DPIs), or to pMDIs using lower GWP propellants.

While it would be hoped that such a transition would follow some of the precedent set by the move away from CFCs, it is clear that the phasing down of F-gases must overcome a different set of complex hurdles to ensure device and drug are optimised in a way that satisfies patient need.

In the most acute circumstances, patient need can manifest itself as the administration of life-saving medicine to a potentially incapacitated individual who might not have the respiratory force required to deliver the necessary dose via a DPI. Over decades, pMDIs have proved their worth in this scenario, with the force of a propellant driving successful drug deposition and, therefore, patient outcomes when used in tandem with a spacer or nebuliser. As an indication of their importance to patients, pMDIs account for 77% of inhaled device doses in the world's top 15 markets.

Dry powder inhalers, while highly effective, do not represent a like-for-like 'swap'

in this regard. For elderly populations, drug delivery can be impaired when respiratory muscle weakness limits a patient's inhalation action, while younger children can struggle to comply with the technique required for optimal dose delivery. As such, the use of DPIs as a rescue medication remains limited, accounting for only 3% of prescriptions containing a short-acting beta-agonist (SABA).

Running in parallel with the requirement to answer patient need is the need to consider limiting the disruption to the current economic models that successfully underpin pMDI use. It cannot be ignored that delivering medication via HFC-based pMDIs is both highly efficient and highly cost-effective, with the average cost per dose of salbutamol estimated at $0.06.

However, analysis of the global economic impact of switching from pMDIs to DPIs, using prescribing data sourced from the IQVIA database, has revealed that in all the world's top 15 markets for respiratory drugs by value, costs would rise if SABA pMDIs were replaced with DPIs. The only exception is Brazil, where there is no equivalent DPI registered.[4]

That is not to say that the economics for existing pMDIs are fixed. As regulations drive down volumes of industrial-grade F-gases, from which medical-grade propellants are manufactured, prices are likely to increase. Indeed, the market has already experienced this dynamic in recent years, with escalating propellant cost pressures only eased by the allowance of imports under the 'exempted' classification.

The answer to providing patients with device continuity therefore rests on the development of a new era of pMDIs using propellants with lower GWP than existing options. Of the candidate gases being evaluated across the sector, HFA-152a and HFO-1234ze show promise in terms of balancing high performance and environmental credentials with low toxicity.

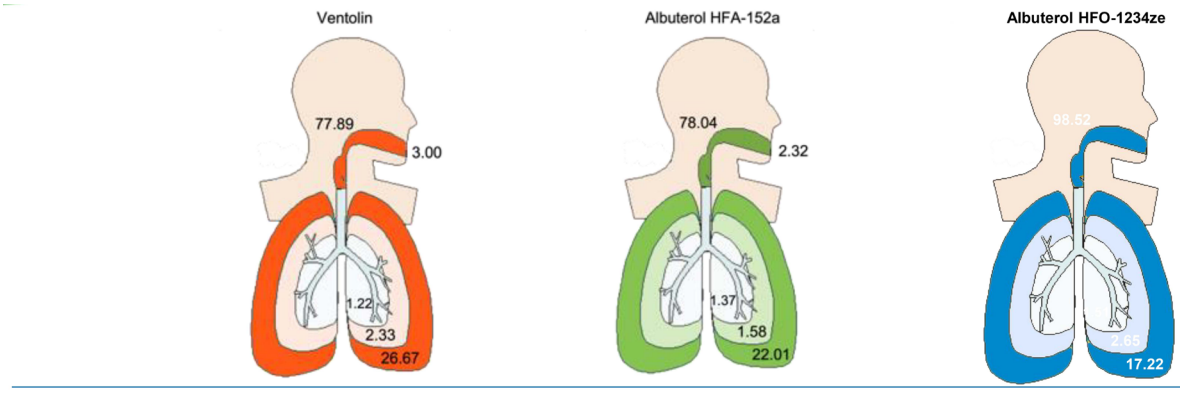
Simply switching to these new propellants might be an appealing notion, but, of course, their potential must first be fully evaluated via an assessment of their characteristics to ensure device performance, clinical efficacy, toxicology and patient safety are all satisfied. Nanopharm, an Aptar Pharma company, has conducted extensive testing in this area, revealing the influence of variable propellant attributes, such as solubility, and their interaction with the drug formulation. During their research, Nanopharm has uncovered, for example, that the electrostatic charge for HFA-152a is comparatively higher than HFO-1234ze, and that the two gases impact on particle dynamics differently, with higher oropharyngeal deposition observed for HFO-1234ze.

As well as overcoming any formulation and aerosolisation challenges for devices using new propellants, regulatory hurdles must also be cleared to ensure patient safety is guaranteed in the final marketed product. As urgency builds around the accelerated phase down of F-gases, any transition will require stakeholders to engage closely with regulatory bodies to facilitate approval with the requisite clinical data. Pathways may be available to expedite this process. The US Food & Drug Administration (FDA), for example, points to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act as an option for providing an abbreviated route for approval, potentially opening the door to applications being augmented with data from bioequivalence studies.

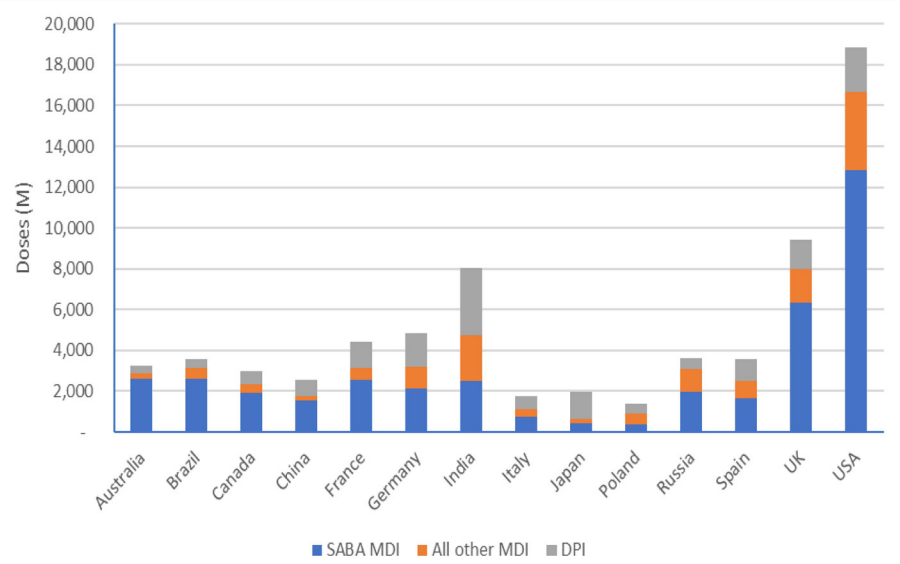
Particularly in light of the compressed development timeframe presented by the EU's recent proposals, the emphasis on accelerating the transition to low-GWP propellants has intensified. It could also be said, however, that this has constricted the potential for wider reflection and innovation around inhalation devices. Tighter controls on imports and the removal of exemptions for medical use mean that by 2027, F-gas levels are projected to be at just 10% lower than the baseline and, without significant change, almost all that allowance would be consumed by MDIs.

Considering these figures, it is understandable that healthcare professionals (HCPs) are being encouraged to move patients to DPIs. However, there is also the risk that such an isolated switch does not take into account the realities of human behaviours and therefore does not fit into a holistic healthcare strategy for controlling the serious risks associated with respiratory conditions.

For example, if patients have difficulty in self-managing their condition, it is possible that they will require additional support within primary or secondary care settings. Aside from the health risk involved, this places an unnecessary burden on the health system while also carrying an additional carbon cost.

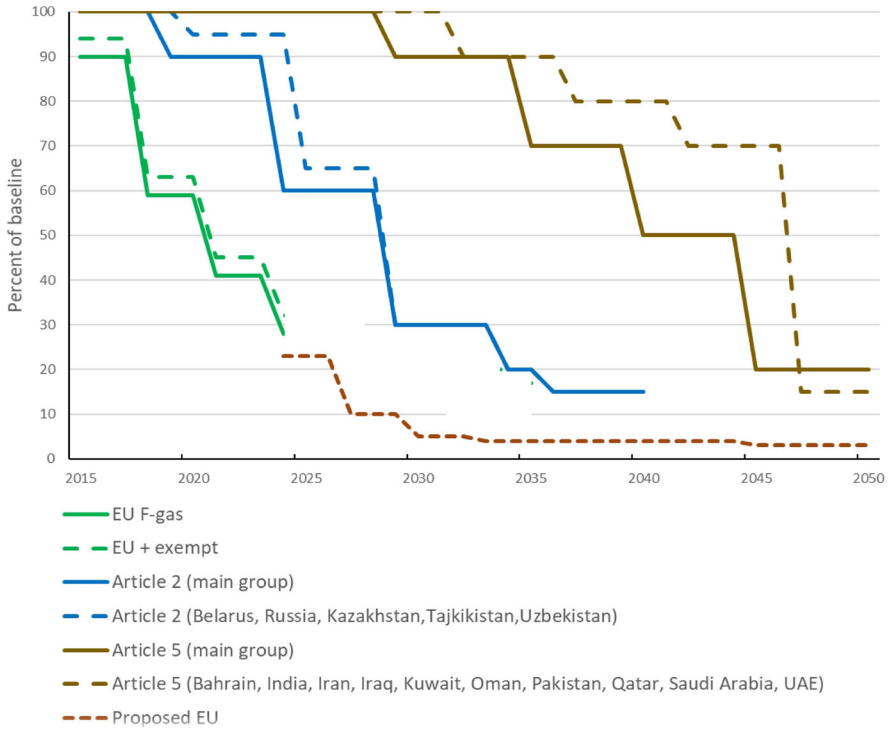


Formulation	ET (µg)	BB (0-8) (µg)	Bb (9-15) (µg)	AL (16-23) (µg)	EX (µg)
Ventolin	77.89	1.22	2.33	26.67	3.00
Albuterol HFA-152a	78.04	1.37	1.58	22.01	2.32
Albuterol HFO-1234ze	98.52	1.51	2.65	17.22	1.03



Data from the SABINA CARBON UK study found that excess greenhouse gas emissions per capita were eight times higher for patients with uncontrolled asthma (as defined by one or more exacerbations in the past 12 months or being prescribed three or more SABA inhalers per year) compared with patients with controlled asthma (defined by no exacerbations and being prescribed up to two SABA inhalers per year).[5] In addition, a single hospitalisation for a respiratory patient has been found to have a larger carbon footprint than 1.5 years of daily pMDI use.[6]

Findings like the above show that there is a wider picture to be considered when tackling the global challenge of climate change. It is essential that the use of F-gases is controlled, but it is also critical that this process is managed within a holistic approach to the future of pMDIs, and that the contribution of associated factors such as dose efficiency, adherence and compliance are all equally considered. Within a managed transition to low-GWP alternatives, pMDI devices can not only continue to fulfil their vital purpose in delivering rescue and relief medication for patients with respiratory conditions, but they can also fulfil their potential in areas such as nasal drug delivery and as a platform for sensitive biologics, where low-GWP propellants show promise in supporting formulation stability and the delivery of high payloads.



Within the EU in particular, the drive to phase down F-gases and switch to DPIs means opportunities for more holistic reflection and innovation might be limited. In other territories, however, the elongated phase-down schedule could allow companies in these regions to leverage their position, using the introduction of low-GWP propellants to also usher in complementary device innovation.

One of the important lessons from the phasing out of CFCs via the Montreal Protocol was collaboration: all stakeholders were aligned on a singular vision, taking action to support a common goal. Today, however, we are faced with different circumstances in the challenge to deliver a sustainable strategy for the future of managing respiratory conditions. Converging on a collective vision must involve a comprehensive assessment of the changing role of different device formats within a multi-layered ecosystem over time.

Simpler strategies might hold more immediate appeal, but arguably come with risk attached.

Targets to reduce greenhouse gas emissions are of immediate interest to many across the globe but trying to make progress by exclusively focusing efforts on certain directions may carry consequences that are not immediately visible. From policymakers to healthcare providers, drug companies and device manufacturers, it is incumbent to find the right balance on the path to delivering better outcomes for patients and the planet long into the future.

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Dr. Jag Shur

Dr. Jag Shur, Vice-President, Science & Technology, Nanopharm, an Aptar Pharma company, and Co-Founder of Nanopharm is an internationally recognised expert in the investigation of bioequivalence of OINDPs. Holding a BSc (Hons) in Chemistry, he completed his PhD entitled 'Formulated Muco-Regulatory Agents in the Airways of Patients with Cystic Fibrosis' from Portsmouth School of Pharmacy in the UK. Dr. Shur is also a post-doctoral fellow at the London School of Pharmacy, having investigated the fabrication of micro particles for vaccine delivery using supercritical fluid technology.

Dr. John N. Pritchard

Dr. John N. Pritchard, PhD is a private consultant specialising in strategic approaches for developing respiratory devices, drugs and digital health. He sits on several Scientific Advisory Boards as well as the UN Committee that makes recommendations on the medical uses of propellants covered by the Montreal Protocol and is Director for a number of SMEs. Having worked previously at GSK, 3M, AZ and Philips, he has worked on MDIs, DPIs and nebulized products, and was associated with the launch of 11 major products. At RDD 2018, John received the Charles Thiel award for outstanding research and discovery in respiratory drug delivery.

Omar Usmani

Professor Omar Usmani is Professor of Respiratory Medicine at the National Heart and Lung Institute (NHLI), Imperial College London and Consultant Physician at the Royal Brompton Hospital and St Mary's Hospital London. He is currently Head of the ERS (European Respiratory Society) Assembly 5 Airway Diseases. His clinical research themes are Inhaled Drug Delivery, Airways Physiology, Lung Imaging and Biomarkers, and Digital E-health. He was co-investigator and lead Clinical PI, on an EU HORIZON 2020 grant, myaircoach, to investigate the role of E-health in asthma self-management. In 2015, he received, the Thomas T Mercer Award from the American Association of Aerosol Research (AAAR) and ISAM, recognizing his international research excellence in pharmaceutical aerosols and inhalable materials.