Interview: The Transition to Lower-Global-Warming-Potential Propellants in pMDIs

The transition to lower-global-warming-potential (GWP) propellants in pressurised metered dose inhalers (pMDIs) will play a significant role in reducing the carbon footprint of inhaled asthma and chronic obstructive pulmonary disease medications – a key factor for meeting the environmental goals of pharmaceutical companies with a large respiratory pMDI portfolio. The hydrofluoroalkanes (HFAs) currently used as propellants have a high GWP rating and produce significant CO_2 emissions. Reducing emissions from all sources, including medicines and their delivery systems, is essential to meeting climate change goals.

Aptar Pharma's Chris Baron discusses how, in response to this challenge, the company has developed a new metering valve technology platform – ZEN30 Futurity™ – that is compatible with leading lower-GWP propellants. By collaborating with drug developers, regulators and the pMDI supply chain, Aptar Pharma aims to support the reduction of the CO_2 footprint of pMDIs while ensuring that the pharmaceutical industry's strict regulatory requirements are met or exceeded.

Q What are lower-GWP propellants and why are they needed for pMDI applications?

A Formulations for pMDIs typically consist of a defined amount of API combined with a propellant and a number of excipients, which can include surfactants, co-solvents and stabilisation systems. The propellant expels the formulation from the cannister via the metering valve, creating an aerosolised spray that is then inhaled by the patient and delivered to the lungs. The most common class of propellants currently used in pMDIs are HFAs, such as HFA134a and HFA227ea.

However, these propellants have a high GWP, leading to an undesirable CO_2 footprint. New lower-GWP propellants are being used to develop the next generation of pMDIs, which, according to current estimates, will reduce the CO_2 footprint pMDIs generate by over 90% compared with existing propellants. As pMDIs are an important and widely used technology for delivering a variety of inhaled drugs around the world, especially for rescue therapies, the adoption of these new propellants is critical for organisations that want to reach their climate goals.

Chris Baron
Director Business Development
T: +33 6 3095 5331
E: chris.baron@aptar.com

Chris Baron is Director of Business Development, Pulmonary Category at Aptar Pharma. In this role, he is responsible for the global business development activities for Aptar Pharma's inhalation drug delivery devices, as well as their respective services pertaining to the application fields of asthma and COPD. With a degree in Mechanical Engineering, Mr Baron has over 28 years' industry experience in the field of inhalation drug delivery, specifically metering valve technologies for pMDIs and their accessory peripheral device technologies, including dose indicators and breath-activated inhalers.

Q Which lower-GWP propellants are being used in pMDI development projects and what makes them different from the current HFA propellants?

A There are two main frontrunners with respect to lower-GWP propellants – Koura's (Waltham, MA, US) HFA152a and Honeywell's (Charlotte, NC, US) HFO1234ze, each offering significantly reduced CO_2 footprints. There are a number of differences between the two new propellants, including their flammability, density, vapour pressure, boiling point and dipole moments. These differences may impact the final solubility and stability of any given pMDI formulation in conjunction with any additional excipients selected.

Q How do the propellants impact pMDIs and their components?

A The use of the new propellants in pMDIs requires close attention to all aspects of the container closure system (CCS). This includes the metering valve, canister and actuator. In some cases, drug delivery device manufacturers can even integrate digital technologies, such as dose counters or breath-actuated mechanisms, to provide additional levels of patient convenience. Each component of a pMDI's CCS that comes into contact with the formulation must be strictly evaluated for

its chemical compatibility. The resulting components must also deliver the functionality and mechanical performance required for dose consistency over the entire shelf-life of the medication.

We must also consider the impact on manufacturing processes and analytical testing methods. For example, HFA152a is considered a higher risk material from a flammability perspective compared with its counterparts. Therefore, formulation mixing and filling suites must be capable of handling such materials.

Q Are there any concerns about the move to convert pMDIs to use lower-GWP propellants?

A Compatibility with existing pMDI components is a concern that should be addressed during product design. New propellants, including HFA152a and HFO1234ze, will require extensive testing and may even require the optimisation or potential redesign of the CCS' key critical quality attributes so that they can maintain product performance similar to current HFA-based formulations. The materials currently used in the construction of pMDI components, including metering valves, may or may not be compatible with the new lower-GWP propellants, so each component needs to be re-evaluated.

Any incompatibility could necessitate substantial modifications to the metering valve or other pMDI components to ensure the pMDI product's continued performance and efficacy. As some lower-GWP propellants have greater flammability risks than current propellants, the manufacturing and filling processes need to be reviewed to ensure that they are safely handled at every step of the process.

Additionally, regulatory compliance is always a major consideration when making any changes to complex drug-device combination products. One needs to assess material selection not only against today's regulations but also against anticipated or new potential regulations that could impact the future compliance of a new part or component. Ignoring these risks in the short term could result in the need for a costly and time-consuming redesign and revalidation of pMDI components in just a few years.

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Finally, patient acceptance and adherence are critical concerns. Changes in propellants can affect the patient experience, which, if not handled appropriately, could lead to lower patient compliance and poorer health outcomes.

Q How did Aptar Pharma initially get involved in the transition to lower-GWP propellants in pMDIs?

A Aptar Pharma is a well-established and trusted global developer and supplier of metering valves that have been reliably used in many leading pMDI products for decades. Realising that addressing global sustainability concerns and meeting corresponding objectives for pMDIs would require a collaborative, industry-wide effort, the company took the initiative to work alongside drug developers, drug delivery device companies, equipment manufacturers, chemical suppliers, key opinion leaders and regulators to find practical solutions.

For example, Aptar Pharma organised an event in conjunction with Pharmaserve Northwest back in September 2021 that was attended by device developers, pharmaceutical companies, CDMOs and the two lower-GWP propellant suppliers to discuss common objectives and share knowledge. For some time, Aptar Pharma has been initiating developmental collaborations with customers regarding the advancement of their next-generation pMDIs using lower-GWP propellants.

This has resulted in Aptar Pharma engineering the new ZEN30 Futurity™ metering valve technology platform, designed specifically to be compatible with leading lower-GWP propellants. However, developing a new metering valve was only part of the process. Our customers led the necessary reformulation and testing effort in parallel with Aptar Pharma's development of the new metering valve to shorten the overall transition timelines for their reformulated products.

Q What are the new or pending regulations driving this change?

A Global climate change objectives are driving new regulations to help reduce CO_2 emissions. For example, the EU's new F-Gas legislation was adopted in March 2024. These regulations will impact pMDIs as they will be partially combined with the wider F-gas quota system, requiring a 15% reduction in F-gas use by 2026/27 and a complete 100% elimination of hydrofluorocarbons by 2050. These reductions are relative to a 2023/24 baseline. There are also potential future restrictions stemming from the European Union's "Registration, Evaluation, Authorisation and Restriction of Chemicals" (REACH) regulations, which aim to eliminate materials determined to pose an unacceptable risk.

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These anticipated changes could eliminate the ability to use certain materials in pMDI components. As many of the materials that may be subject to a ban are already known, it is important to future-proof new pMDI part or component designs today to avoid costly redesigns later. Aptar Pharma took this into consideration when designing the new ZEN30 Futurity valve, selecting only materials that provide the required performance and that are also unlikely to fall inside the upcoming REACH elimination criteria.

In December 2024, the US FDA held a series of collaborative industry workshops with an aim of developing guidance for the implementation of new pMDIs intended for the US market using lower-GWP propellants. Aptar has been monitoring and participating in these developments to stay engaged in the latest regulations impacting pMDIs. These considerations were implemented throughout the design of the ZEN30 Futurity valve, including its material selection, to ensure compatibility with lower-GWP propellants.

Q What are the challenges and opportunities associated with transitioning to lower-GWP propellants, including supply chain restrictions? How is Aptar Pharma planning to overcome these challenges?

A Although the transition to lower-GWP propellant use in pMDIs presents a variety of challenges, including new supply chain restrictions, updated manufacturing and filling capability requirements, reformulation complications and the need for optimised device designs, this transition also offers significant new opportunities to reduce the environmental impact of pMDIs. Aptar Pharma applies ecodesign tools and lifecycle assessment approaches to design new products and services with lower environmental impacts.

Aptar Pharma's main contribution to moving pMDIs to lower-GWP propellants comes in the form of the ZEN30 Futurity metering valve. This valve was designed for compatibility and performance when used with the new lower-GWP propellants. The additional support provided by Aptar Pharma helps to accelerate the transition process for our customers. We also offer end-to-end supply chain control with the valves. This can help pharmaceutical companies avoid disruptions to business continuity and protect patients' access to potentially life-saving medicines.

"APTAR PHARMA CREATED THE NEW ZEN30 FUTURITY METERING VALVE SPECIFICALLY FOR LOWER-GWP PROPELLANTS AND RELATED FORMULATIONS."

Q Did you have to modify existing pMDI metering valves or develop new valves in order to be compatible with the new lower-GWP propellants?

A Aptar Pharma created the new ZEN30 Futurity metering valve specifically for lower-GWP propellants and related formulations. We assessed every material and critical quality attribute to ensure that the ZEN30 Futurity could stand up to the demands of new formulations that contain either of the new HFA152a or HFO1234ze propellants. As a result, we selected materials that were compatible with the new formulations and lower-GWP propellants, as well as providing the mechanical and chemical performance needed over the entire lifespan of the product.

This was supported by the data generated in multiple accelerated stability studies. We decided to eliminate some of the existing materials used in our current DF30 metering valves because they were not compatible with the new propellants. We also future-proofed the ZEN30 Futurity metering valve design against future anticipated EU REACH restrictions. Aptar Pharma was able to do this quickly based on our decades of experience as a leading pMDI metering valve developer and supplier and because of our specialised R&D capabilities located in both our Le Vaudreuil (France) and Nanopharm (Cwmbran, UK) operations. Ultimately, we were able to produce a practical, manufacturable and scalable design that is regulation-compliant and compatible with the demands of both lower-GWP propellants.

Q What is Aptar Pharma's Futurity platform and what are its objectives?

A Aptar Pharma created the Futurity platform to represent products that bring enhanced sustainability and circularity features. This includes products such as mono-material drug delivery systems designed for greater recyclability, multiuse delivery systems that reduce plastic use and the new ZEN30 Futurity metering valve as discussed earlier. All of the Futurity product lines contribute to the enhanced sustainability of critical drug products that can have an impact on patient's lives.

Q Can you tell us more about the design of the ZEN30 Futurity valve and the benefits it brings to customers?

A Our internal R&D teams worked collaboratively with customers to develop the ZEN30 Futurity metering valve. First off, we ensured that it was compatible with the needs of formulations containing HFA152a and HFO1234ze.

"THESE MATERIALS ARE DEVELOPED AND MANUFACTURED AT APTAR PHARMA'S OWN STATE-OF-THE-ART ELASTOMER FACILITY IN FRANCE TO ENSURE THE HIGHEST QUALITY, AS WELL AS TO SAFEGUARD THE SUPPLY CHAIN OF THESE CRITICAL MATERIALS."

We selected valve component materials that demonstrated chemical compatibility and enhanced mechanical performance that could provide reproducible dosing over the entire shelf-life of the pMDI.

For example, the static gasket is made from a cyclic olefin copolymer elastomer for a strong and durable seal that is resistant to degradation and provides a best-in-class moisture protection barrier, maintaining product stability. The dynamic elastomers are made from proprietary formulations of ethylene propylene diene monomer because of its durability, flexibility and resistance to degradation in various climatic zones.

These materials are developed and manufactured at Aptar Pharma's own state-of-the-art elastomer facility in France to ensure the highest quality, as well as to safeguard the supply chain of these critical materials. We also use a polybutylene terephthalate polymer for some components because of its insulative and chemically resistant properties. This combination of newly selected materials resulted in a high-performance metering valve that is compatible with both of the leading lower GWP propellants.

Q How does Aptar support its customers through the development of the ZEN30 Futurity valve and incorporating it into their pMDI products?

A Aptar has built an extensive list of additional support services that can help customers to advance their pMDI products to market in the shortest possible timeframe. Aptar Pharma's Nanopharm team provides sophisticated inhaled drug development services, including highly specialised *in vitro*, *in silico*, physiologically-based pharmacokinetic and deposition modelling, uniquely applied to pMDI and inhaled drug products. Furthermore, offering the ATEX-rated R&D pilot filling facility to support the development of customer pMDI products has meant that our customers could move their development programmes forward, avoiding the wait time to secure access to their own suitably scaled manufacturing and testing capabilities.

As experts in pMDI drug delivery, Aptar Pharma also provides extensive regulatory support, including some of the documentation our clients are expected to include in their submissions to regulatory bodies. Aptar provides customers with full Combination Packages and Art117 dossiers for our ZEN30 Futurity metering valves. Aptar's Noble group (Orlando, FL, US) provides sophisticated patient onboarding services and training kits, along with human factors studies, to get new devices into the hands of patients sooner. Aptar Pharma also provides in-person support for the integration of our drug delivery systems on to their manufacturing and filling lines for seamless implementation of technology changes.

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Q What are the expected impacts of the new lower-GWP propellants on patients?

A At Aptar Pharma, we try to consider the needs of the end user, the patient, as our key driver. Our products and services are designed to help our customers derisk and accelerate their pMDI development programmes. Our company's mind-set is always focused on taking customers from "formulation to patient". We see the ZEN30 Futurity metering valve as enabling patients to maintain the same convenient, preferred pMDI delivery platform and methodology to deliver their treatments.

Although there are alternative inhaled drug delivery systems, such as dry powder inhalers (DPIs), many of them require a minimal level of inhalation capability from the patient to ensure that the drug is adequately delivered. Administering drugs via some DPIs can also require the co-ordination of different preparation and inhalation steps by the patient, which can be challenging for some. Instead, the continued use of newer pMDIs driven by lower-GWP propellants means that patients can maintain their established drug administration practices while also contributing to the reduction of CO_2 emissions associated with traditional propellants.

"ONE OF THE FACTORS IMPACTING pMDI VOLUMES WILL BE THE RELATIVE ECONOMICS ASSOCIATED WITH THE TRANSITION TO NEW LOWER-GWP pMDIs AS COMPARED WITH ALTERNATIVE DELIVERY TECHNOLOGIES."

Q What future do you see for pMDIs and how does Aptar's ZEN30 Futurity valve fit into that future?

A It is expected that the new lower-GWP pMDIs will be able to maintain their place as one of the world's most widely used orally inhaled drug delivery systems. Alternative inhalation delivery technologies, such as DPIs and non-propellant liquids inhalers are available, but their combined commercial volumes still do not approach those of pMDIs.

One of the factors impacting pMDI volumes will be the relative economics associated with the transition to new lower-GWP pMDIs as compared with alternative delivery technologies. Historically, pMDIs have been one of the most cost-effective respiratory drug delivery platforms based on cost per dose. However, the cost to purchase new propellants relative to the current propellants will also become an important factor. Pharmaceutical companies must also consider the investment costs associated with upgrading mixing and filling capacity to meet the required ATEX safety guidelines for the more flammable lower-GWP propellants – HFA152a in particular.

In summary, the speed of change in a given region will depend on both market regulations and economics, which will be impacted by the levies and taxes applied to the older HFA propellants during their phase out. Ultimately, pMDIs will continue to serve the critical medical function of delivering inhaled drug products to patients in a convenient and portable package. Now, the next generation of pMDIs will be able to do so while contributing to a reduced carbon footprint with every inhalation. Designed specifically for a seamless transition to lower-GWP propellants and ensuring reliable and robust performance, the ZEN30 Futurity valve will be at the forefront of this transformation.

Aptar pharma

Aptar Pharma
Avenue des Falaises
27100 Le Vaudreuil
France
www.aptar.com/pharma

The Future starts now

LOW GWP

ZEN30 Futurity™: A valve designed for a seamless transition to low GWP pMDIs, ensuring reliable, robust performance

The shift to low GWP pMDIs does not have to be complex. Aptar Pharma's ZEN30 Futurity™ valve for pMDIs supports both HFA 152a and HFO 1234ze propellants, simplifying formulation transition while maintaining consistent delivery.

Aptar Pharma's **in-house elastomer production and valve gasket manufacturing** enhances supply chain security and ensures full and transparent change control. Our SmartTrack™ modeling platform helps you demonstrate the bioequivalence of inhaled products to reference drugs without conducting a comparative clinical endpoint (CCEP) study.

This combination of supply chain control, advanced bioequivalence validation, and **regulatory expertise and U.S. FDA understanding** helps to derisk your product submission and approval process.

Backed by over **35 years of expertise in pMDI valve development, manufacturing, and performance**, our ZEN30 Futurity™ helps you derisk your transition and accelerate development of your next-generation pMDI.

Discover what your future holds with ZEN30 Futurity™

- **Engineered for a smooth transition to low GWP propellants**
- **One valve, two propellants**
- **In-house elastomer production**
- **Navigate regulatory complexity with confidence.**

To start your next generation pMDI project, contact Chris Baron, Director of Business Development Pulmonary Category, at: chris.baron@aptar.com or +33 6 3095 5331.

futurity™

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GWP, global warming potential; **HFA**, hydrofluoroalkane; **HFO**, hydrofluoroolefin; **pMDI**, pressurized metered dose inhaler.