

# Expert Insight:

## Adapting Valves for Greener Propellants

**Sustainability initiatives have brought the problematic carbon footprint of propellants in pressurised Metered Dose Inhalers (pMDIs) into sharp relief. A shift to low carbon pMDIs that incorporate alternative, low Global Warming Potential (GWP) propellants is underway. However, successfully transitioning to new propellants is not as simple as swapping one ingredient out for another. Drug formulations and device components go hand in hand and must be considered holistically to ensure Critical Quality Attributes (CQAs) for the product are met.**

This is especially true for the metering valve, which is crucial for delivering consistent doses and protecting the formulation. Optimising valve design for compatibility with low GWP propellants is a key step in the industry's green transition, and one that can be significantly accelerated by an experienced partner. Bepak, a CDMO with a long legacy of developing and manufacturing pMDIs, has been working hard to optimise its valve technology ahead of the transition.

### Learning from the Past

Valves are at the heart of a pMDI device, ensuring accurate doses of therapeutically effective drug are administered throughout the shelf life of the product and across the label claim number of doses. At the same time, because valves are effectively a weak point in a closed, pressurised container, they must be developed carefully to minimise propellant leakage and ingress of atmospheric moisture. Additionally, as a component that comes into direct contact with the formulation, valve materials must be designed to keep extractables and leachables within product specifications.

Due to their integral role in the pMDI device, updating valve design and materials for compatibility with new low GWP propellants requires careful consideration. Fortunately, the current green transition is not the first time the pharma industry has faced this challenge. In 1987, the global adoption of the Montreal Protocol resulted in the discontinuation of industry-standard chlorofluorocarbon (CFC)

propellants due to their potential to deplete the ozone layer. Subsequently, Bepak's BK356 valve evolved into the BK357 platform valves that we know today, which are compatible with the hydrofluoroalkane (HFA) propellants that came to replace CFCs. The main adaptation required for the CFC-HFA propellant transition was a change to the elastomers used for the chamber seats and neck gaskets in the valve. Black nitrile components in the BK356 were swapped for a cleaner nitrile and ethylene propylene diene monomer (EPDM) – a synthetic rubber – in the BK357 design.

Since then and until the current green transition, Bepak valves have changed remarkably little – a testament to the effectiveness and robustness of the design.

### Preparing for New Propellants

While the standard design of pMDI valves is consistent, minor changes to components, such as core side hole sizes, seat dimensions, spring strengths and chamber volumes, are made on a case-by-case basis to meet the needs of different drug formulations. Because propellants make up a significant proportion of the formulation, evolving the BK357 valve for compatibility with HFA-152a and HFO-1234ze goes a step further, necessitating an update to the elastomers in the device. These changes are essential to reduce propellant leakage from the inhaler, presenting a good barrier internally and also externally to moisture ingress. A further benefit that can be achieved is a reduction in the extractables and leachables burden.

When selecting a new elastomer material, compatibility with the physical properties of the low GWP propellant is a key factor. For example, HFA-152a has a relatively low molecular size that can penetrate plastic and rubber components more easily than existing propellants. This means that in an all-EPDM valve, leakage rates for HFA-152a could be expected to exceed those of the same valve with HFA-134a – the current industry-standard propellant – and the leachables burden would be higher. Additionally, due to its higher dipole moment, moisture ingress for HFA-152a exceeds that seen for HFA-134a. In the context of valve design, the higher observed leakage and moisture ingress rates mean that, in order to be compatible with HFA-152a,

the valve neck gasket needs to be made of a good barrier material, such as bromobutyl.

On the other hand, the near-zero GWP propellant option, HFO-1234ze, has physical properties such as density, boiling point, and vapour pressure that are much closer to the currently used HFA-134a than those of HFA-152a. This allows greater flexibility in the choice of elastomer materials when using this propellant.

Bepak has developed a new hybrid BK357 valve with EPDM seats and a bromobutyl neck gasket that has been found to work particularly well with the new low GWP propellants.

### Exploring Valve Performance

Bepak has been leading the way towards making low carbon pMDIs a reality, including by leveraging advanced simulation technology. Virtual simulations were critical in the development of the hybrid EPDM/bromobutyl BK357 valve for low GWP propellants. To verify the simulation data and better understand the performance of the hybrid valve, it was tested in the lab with placebo propellant only and placebo propellant / 15% ethanol mixtures.

The hybrid valve exhibited good shot weight reproducibility, low leakage and low moisture ingress throughout the study for both novel propellants. As a result, Bepak recommends the use of the hybrid EPDM/bromobutyl BK357 valve for compatibility with HFA-152a and HFO-1234ze propellant systems. It has already progressed outside of the lab, with BK357 hybrid valve samples currently under evaluation with industry partners developing their own low GWP propellant formulations, as well as Bepak's pMDI formulation team. Bepak has also developed pilot plant filling and clinical manufacturing capabilities for pMDIs incorporating low GWP propellants and optimised valves, setting the stage for further uptake.

### Seeking a Partner with End-to-end Expertise

Now that valve technology has evolved and manufacturing infrastructure is in place, the next step for pharma companies embarking on the transition to low carbon pMDIs is

to select a partner who can guide them effectively. When seeking out a valve supplier, a partner with end-to-end capabilities across pMDI development from formulation to manufacture is of great benefit to ensure the device performs well holistically.

From a formulation perspective, an expert understanding of how to tailor valves to solutions or suspensions is beneficial. Which formulation type is chosen – solution or suspension – is a choice driven at the outset by the drug's solubility in the propellant. Solutions confer enhanced dose-to-dose reproducibility, since the drug is completely dissolved in the propellant in these cases. On the other hand, suspensions often deliver improved fine particle mass or, in other words, a greater proportion of drug that is therapeutically effective in the lungs.

However, suspensions may cause more issues than solutions as the suspended, insoluble drug particles can become trapped in low flow areas of the valve or canister. The valve design, therefore, needs to allow for this possibility. Partnering with an expert can help you to select and tailor your valve according to the needs of your formulation, whether solution or suspension.

### Applying Expertise Across Device Design

The valve can be thought of as the engine of the pMDI device – it is absolutely integral. However, the valve does not work in isolation. Expertise across the other components of the pMDI device – such as the actuator, dose counter, and canister – should also be sought, as components can interact, and

the best result is achieved when all device components work well together in a system. For instance, the valve influences drug particle size distribution, which ensures particles are of the correct size for deposition in the therapeutically effective areas of the lung. However, optimisation of actuator dimensions, such as the jet orifice diameter, also impact the resultant fine particle mass from a delivered dose. Bespak can offer expertise in matching actuator dimensions to the desired product performance. Advanced models are of assistance here too. A 1D model developed by Bespak allows the team to not only predict the performance of the formulation and the expected particle size distribution, but also to identify a specific actuator that will perform well with the constituents of the formulation.

Additionally, the presence of a dose counter on some products can slightly increase the force needed to fire the inhaler. The spring strength, level of silicone oil lubrication used, elastomer materials and dimensions must ensure that the finished inhaler, complete with dose counter, does not require excessive force to actuate and that the return of the valve to rest after firing is not too slow. Meanwhile, most canisters are made of aluminium or occasionally stainless steel. Internal canister coatings may be applied to prevent too much drug depositing on the can walls from the formulation, which in turn could have a detrimental effect on the delivered drug dose.

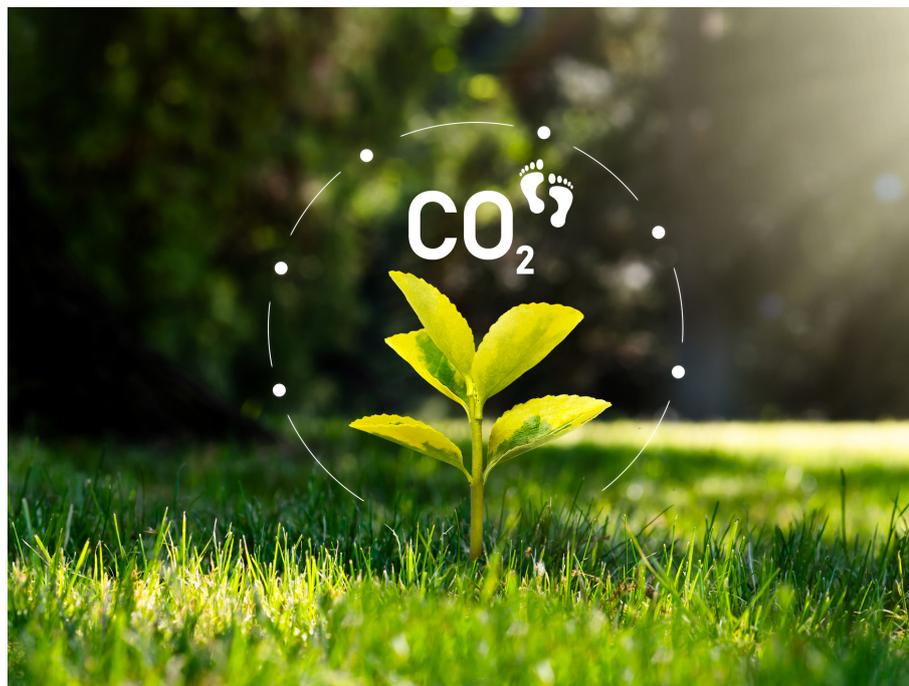
Every component has an important role to play and can interact in ways that impact the

final product performance, so seeking out a partner with end-to-end expertise for device and system development will help to ensure high performance against CQAs.

### Preparing for the Future

Low GWP propellants mark a new chapter in pMDI development, and the industry is gearing up to fully transition in the coming years. However, the work is not over after updating valves for compatibility with the new propellants.

There is also potential to innovate further with more sustainable materials and to make greater use of virtual simulation technologies to streamline development. Device design is fluid and evolves according to industry needs, so keeping an eye on new valve design opportunities that can enhance performance or reduce the carbon footprint of the product even further, is a must. Moving forward, it is clear that there will be many exciting possibilities to refine low carbon pMDI device components and product development. Valves work holistically in pMDI devices, so seeking out a partner with end-to-end development and industrialisation expertise and a demonstrated track record of success will be crucial in making the switch to low carbon pMDIs.



**Tony Mallett**

Tony Mallett is a Platform Development Group Manager at Bespak with over 23 years of experience within medical device development. Tony's expertise encompasses pMDIs, dose counters, DPIs, IVDs, patch pumps, gas and spring powered auto injectors, and NRT devices.



**Andy Sapsford**

Andy Sapsford is a Technical Advisor at Bespak who guides the development of Bespak's pMDI valves, with reference to their interaction with active formulations and low GWP propellants. Andy's prior experience includes 32 years in pharmaceutical R&D at GSK, where he played a leading role in developing GSK's HFA pMDI portfolio.