THE PHYSICS OF THE SWITCH: OPTIMISING pMDI DESIGN FOR LOW-CARBON LUNG DELIVERY

Thomas Daly and **Tony Mallett** of **Bespak** discuss the transition to low-global warming potential propellants, examining the vital adjustments to the whole inhalation system necessary to support effective and safe dosing without hydrofluorocarbons.

As the industry accelerates its transition away from hydrofluorocarbon propellants, the focus is no longer whether change will happen, but how to deliver it without compromising clinical performance or patient care. The 10th anniversary of the Kigali Amendment to the Montreal Protocol marks this defining moment for the inhalation sector.

Low-global warming potential (GWP) propellants exhibit distinct physicochemical properties that directly affect aerosolisation, formulation stability and lung deposition in pressurised metered dose inhalers (pMDIs). Achieving equivalent clinical performance therefore demands a detailed understanding of these differences, alongside targeted design interventions to manage the resulting changes in fluid dynamics within the device.

This transition represents one of the most significant operational shifts in inhalation therapy in decades. While comparable in scale to the chlorofluorocarbon-to-hydrofluoroalkane transition of the 1990s, today's challenge is distinct in its engineering impediments and design constraints. To ensure consistent dose delivery, critical hardware components

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must be precisely matched to the vapour pressure, density, viscosity and solvency of a propellant. Optimising these elements requires a rigorous, system-level approach to device design, ensuring that progress towards low-carbon solutions is achieved without compromising clinical performance or the quality of patient care.

THE PHYSICS OF THE SWITCH

The two primary candidates for next-generation low-GWP propellants are HFA-152a and HFO-1234ze(E). While both significantly reduce the carbon footprint compared with legacy propellants, offering a reduction in GWP of approximately 90% and 99.9% respectively, they behave differently inside a canister.[1]

The pMDI aerosol generation process consists of two distinct phases: droplet formation (Phase I) and aerosol maturation (Phase II). Both phases are heavily influenced by the physicochemical properties of the propellant, meaning that a change in propellant necessitates a re-evaluation of the entire system.

The critical factors driving these differences are saturated vapour pressure, liquid density, viscosity and surface tension. The new propellants exhibit distinct physical profiles. HFA-152a has lower density but operates at similar vapour pressure to current standards. HFO-1234ze(E) has similar density to existing propellants, but requires careful tuning to maintain dose consistency.

These properties ultimately influence the atomisation process. When the metering valve opens, the propellant flashes, blasting the liquid formulation into droplets. Research indicates that, because HFA-152a possesses relatively lower vapour pressure and higher surface tension, it tends to deliver larger initial droplets. This alteration in Phase I droplet formation can cascade into Phase II aerosol maturation, shifting the aerodynamic particle size distribution of the drug.

Furthermore, the thermal properties of the plume have an influence. Recent studies have measured the plume temperature at the position representing the tongue surface. HFA-152a was found to be the coldest, reaching temperatures as low as –27°C due to its specific boiling point and evaporation characteristics. This is significantly colder than legacy plumes. Without design intervention, such a cold plume could trigger the "cold Freon" effect in patients, leading to breath-holding or poor inhalation technique.[1]

> "FOR SUSPENSION FORMULATIONS, THE DENSITY DIFFERENCE BETWEEN THE DRUG PARTICLES AND THE LIQUID PROPELLANT IS CRITICAL."

Beyond the mechanics of the spray, the interaction between the propellant and the drug formulation inside the canister is governed by distinct interactions. For suspension-based formulations, the density difference between the drug particles and the liquid propellant is critical. According to Stokes' law, this difference drives the rate of sedimentation (settling) or creaming (floating). As such, the lower liquid density of HFA-152a presents unique stability challenges.

This low density appears to be problematic for suspension stability, as most micronised drug particles are denser than the propellant. However, HFA-152a also exhibits higher viscosity, which helps to mitigate this effect. Experimental data suggest that sedimentation times in HFA-152a can actually be longer than in legacy propellants, aiding dose uniformity. Conversely, formulations designed for denser propellants will require reformulation to maintain dose consistency.

For solution-based pMDIs, the chemical interaction is equally critical. HFA-152a acts as a stronger solvent for many lipophilic drugs and excipients than traditional propellants. This enhanced solvency enables higher drug loading but increases the risk of extractables and leachables from valve components.

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ADAPTING VALVES FOR THE LOW-CARBON ERA

Bespak is at the forefront of this optimisation, conducting extensive research to adapt the market-leading BK357 valve platform for the low-carbon era.

One of the immediate challenges with HFA-152a is its compatibility with elastomeric seals. Due to its solvency profile, HFA-152a can interact with certain polymers, leading to the extraction of material components. Recent studies have highlighted that levels of specific leachables can be higher with HFA-152a if incompatible gaskets are used.[1]

Bespak has addressed this by optimising the BK357 valve with robust material configurations. Through rigorous material screening, specific elastomers – such as ethylene propylene diene monomer and bromobutyl – have been validated for use with these new propellants. These materials ensure robust seal integrity, preventing leakage and moisture ingress that could degrade the formulation over the product's shelf life.

Beyond materials, the physical dimensions of the valve and actuator often require adjustments. The aerosol performance, specifically the emitted mass and particle size distribution, is directly influenced by the expansion of the propellant as it exits the actuator opening.

Since the new propellants expand differently to their legacy counterparts, the actuator sump volume, orifice diameter and length may need modification to match the spray pattern and fine particle fraction of a reference product. For instance, studies have shown that HFA-152a, with its lower vapour pressure, may require a smaller orifice diameter to increase jet turbulence and form droplets more effectively, thereby matching the respirable dose of a legacy propellant. Bespak uses proprietary empirical models to tune these parameters, helping to ensure equivalent lung deposition to legacy propellants.

VISUALISING THE INVISIBLE

The refill event, when the metering chamber refills immediately after actuation, is a critical yet often overlooked facet of inhaler design. If the chamber does not refill completely or consistently, the next dose delivered to the patient may be inconsistent. Historically difficult to observe, this internal flow has now been modelled using computational fluid dynamics (CFD) and captured experimentally with unprecedented temporal and spatial resolution using high-speed X-ray synchrotron imaging.[2]

This high-speed X-ray imaging, conducted at the European Synchrotron Radiation Facility (Grenoble, France), has revealed that the refill process is far more chaotic than previously understood. When ethanol is used as a co-solvent – common in solution -based pMDIs – the flow behaviour becomes significantly more complex. The X-ray imaging revealed that ethanol-based formulations create a chaotic flow with high vapour bubble number density inside the metering chamber.

If a larger proportion of vapour remains in the metering chamber before the next actuation, it may result in a lower dose than intended for the patient. This insight is crucial for the propellant transition, because HFA-152a/ethanol mixtures have different properties to legacy mixtures.

Complementing the physical imaging, Bespak presented a study at DDL 2025 using CFD to simulate the refill dynamics of a metering valve using four different propellants. The results highlighted a divergence in performance driven by the physics of each propellant:

- HFA-152a exhibited the fastest refill, achieving an 88.3% liquid fill level within 300 ms. Its lower density allows it to flow rapidly into the chamber, compensating for pressure differentials.
- HFO-1234ze(E), by contrast, demonstrated a slower refill rate, reaching only 75.9% in the same timeframe, largely due to its higher density and lower saturation pressure.

The simulation confirmed that this variance can be compensated for by modifying the metering valve inlet diameter. By tuning this specific geometric feature, engineers can equalise the refill performance, ensuring consistent dosing regardless of the propellant chosen.

MAPPING THE DESIGN SPACE FOR SUSTAINABILITY

The utility of digital simulation extends beyond just fluid dynamics. In typical development programmes, tolerance limits are established through a labour-intensive process of trial and error. This is not only costly, but can also generate significant material waste.

Bespak has moved towards a "digital-first" approach by mapping the product design space *in silico*. By combining finite element analysis with statistical techniques, engineers can virtually adjust over 100 design inputs to predict device performance under thousands of tolerance combinations.[3] This approach allows the team to identify a safe zone where manufacturing variability will not compromise critical quality attributes such as leakage or shot weight.

The sustainability impact of this digital shift is measurable. In a recent proof-of-concept project, Bespak used this method to avoid approximately 5 tonnes of plastic waste that would have otherwise been generated through physical prototyping and testing.[3]

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While the propellant accounts for the majority of a pMDI's carbon footprint, a truly holistic approach to sustainability must also consider the embodied carbon of the device hardware. The green transition is not just about what is inside the canister, but the canister and valve themselves.

Bespak has achieved a significant sustainability milestone by completing the first lifecycle assessment for a pMDI valve – specifically for its BK357 platform.[4] This assessment has enabled engineers to pinpoint carbon hotspots within the componentry, specifically identifying the energy-intensive metal components as primary drivers of embodied carbon.

Based on this assessment, Bespak is actively investing in a decarbonisation strategy focused on the supply chain. By exploring the substitution of standard alloys with high-quality recycled grades, the aim is to significantly lower the embodied carbon of the valve without altering component geometry or compromising assembly processes.

When combined with the transition to low-GWP propellants, this hardware optimisation offers a credible pathway to a truly low-carbon product. Furthermore, Bespak's manufacturing sites in the UK at Holmes Chapel and King's Lynn now obtain 97.5% of their electricity from renewable sources, further reducing the Scope 2 emissions associated with production.[5]

INDUSTRIALISING THE GREEN TRANSITION

Beyond technical considerations, this transition requires significant operational changes. HFA-152a is classified as a flammable gas, which necessitates crucial upgrades to manufacturing infrastructure, including ATEX-certified filling lines and specialised safety handling procedures. This requirement has created a bottleneck in the industry, as few legacy facilities are equipped to handle flammable aerosols at pharmaceutical standards.[5,6]

"THE FUTURE OF DRUG DELIVERY TO THE LUNGS IS LOW CARBON, AND THROUGH PRECISE ENGINEERING AND COLLABORATION, THE INDUSTRY IS READY TO DELIVER IT."

Bespak has positioned itself as a specialist inhalation CDMO capable of guiding partners through this complex landscape. The company has invested heavily in commercial-scale filling lines for both HFA-152a and HFO-1234ze(E) – an investment that is underpinned by a culture of safety and collaboration with suppliers and manufacturers to define best practices.

Advanced simulation of refill dynamics, robust seal materials and optimised actuator geometry enable devices to be both sustainable and clinically robust. The future of drug delivery to the lungs is low carbon, and through precise engineering and collaboration, the industry is ready to deliver it.

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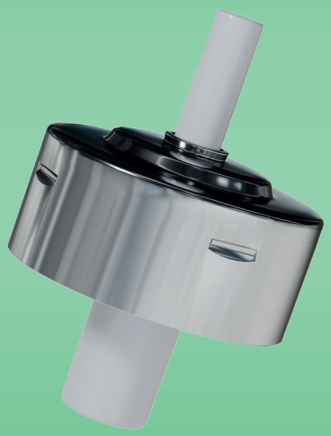

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