PEER REVIEWED

The Next Frontier for Inhaled Therapies:
Low Global Warming Propellants and the Future of pMDI Development

The pharmaceutical inhalation industry stands at a pivotal crossroads. After decades of relative stability following the phase-out of CFCs in the 1990s, a second major transition is underway — this time driven by the urgent need to mitigate climate change. The move toward low-global-warming-potential (LGWP) propellants such as HFA152a and HFO-1234ze(E) represents not just an environmental imperative, but also an enormous opportunity to rethink how we develop, evaluate, and deliver pressurised metered-dose inhalers (pMDIs) to patients worldwide.

This article explores the significance of the shift to LGWP propellants, early performance data generated through the pioneering work of Proveris Laboratories and H&T Presspart, and the broader implications for product development, regulatory strategies, and patient access.

A Turning Point for pMDIs

pMDIs have long been a cornerstone of respiratory care, offering portable, fast-acting relief for asthma and chronic obstructive pulmonary disease (COPD) patients. However, their environmental impact, stemming primarily from their hydrofluoroalkane (HFA) propellants – notably HFA134a and HFA227 – has come under increased scrutiny. These HFAs, although ozone-safe compared to CFCs, have high global warming potentials (GWP >1300), far exceeding carbon dioxide.

Enter the next generation: LGWP propellants, such as HFA152a and HFO1234ze, have GWPs below 150, making them eco-friendly alternatives for inhalers. While they address critical environmental concerns, their adoption demands careful evaluation of their physical properties and effects on inhaler performance to ensure effectiveness and safety.

These new propellants have distinct physicochemical profiles compared to legacy HFAs. As a result, they influence critical pMDI attributes, including aerosol generation, droplet size distribution, spray force, and patient deposition patterns, all of which directly impact drug delivery efficiency and therapeutic outcomes.

The Challenges of LGWP Propellants

Despite promising data, transitioning to LGWP propellants presents real technical hurdles, including increased volatility. HFA152a has a boiling point of -24.7°C, compared to -26.2°C for HFA134a, but its lower molecular weight (~66 g/mol vs. ~102 g/mol) affects vapour pressure and aerosolization behaviour. This can influence Plume Geometry, droplet velocity, and drug particle size – factors critical for efficient lung deposition.[1]

In making the transition to the LGWP inhaler, it is important to consider material compatibility and the propellant's safety profile, as well as to understand the regulatory uncertainty. Swelling behaviour refers to how certain materials, particularly elastomers (rubber-like materials used in gaskets, seals, and valve components of inhalers), interact with propellants. When exposed to a propellant, elastomeric materials can absorb it, causing them to swell, soften, or change in physical properties. This can affect the integrity of seals, leading to potential leaks, or alter the performance of valve components, which are critical for consistent drug delivery in metered-dose inhalers (MDIs). Different propellants, such as HFA152a or HFO1234ze, have unique chemical properties (*e.g.*, polarity and solubility) that may cause more or less swelling compared to traditional propellants like HFA134a. This necessitates rigorous testing to ensure that all components remain compatible and maintain performance over the inhaler's shelf life.

Although HFA152a is safe for inhalation at intended doses, its flammability at certain volumes – unlike the non-flammable HFA134a – requires enhanced safety measures in the manufacturing process, such as explosion-proof manufacturing equipment, inert gas storage systems, and compliance with hazardous material transport regulations. These measures, while feasible, increase operational costs. In contrast, HFO1234ze is a non-flammable LGWP propellant with a GWP of less than 1, offering significant advantages for manufacturing and logistics. Its non-flammability aligns with HFA134a's safety profile, allowing manufacturers to leverage existing facilities without costly upgrades for spark-proof environments or specialised transport protocols. Additionally, in Europe, HFO1234ze faces potential classification as a per- and polyfluoroalkyl substance (PFAS) under REACH regulations due to its environmental persistence, which could lead to regulatory restrictions and impact its adoption. While HFA152a avoids PFAS concerns, its flammability makes HFO1234ze an attractive alternative for manufacturers prioritising operational simplicity, provided regulatory hurdles are resolved.[2]

Understanding how LGWP propellants behave in real-world inhalers is crucial for successful transition. Proveris Laboratories and H&T Presspart have been at the forefront of this effort, deploying innovative as well as traditional evaluation methods to study the performance of HFA152a and HFO1234ze formulations compared to standard HFA134a.

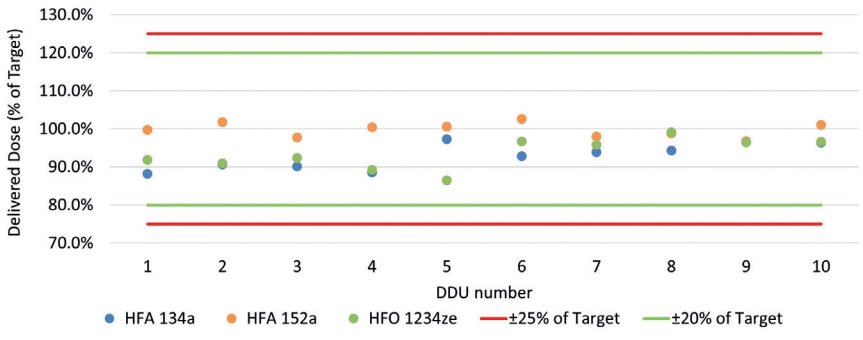

Figure 1: Delivered Dose Uniformity Data of Ipratropium Bromide pMDI by Propellant Type

In recent studies, both Proveris and H&T Presspart labs evaluated[3]:

- Delivered Dose Uniformity (DDU) testing
- Nozzle Design Assessments (orifice diameter and jet length)
- Aerodynamic Particle Size Distribution (APSD) using Next Generation Impactor (NGI)
- Inhalation Deposition with a human-realistic breathing simulator

During the DDU study, the impact of three propellants – HFA134a, HFA152a, and HFO1234ze – on the DDU of an Ipratropium Bromide solution formulation was assessed. Figure 1 shows the DDU for all three formulations. The DDU is calculated as a percentage of the target value of 18 µg/dose. The results for all three propellants were consistent through-life and within allowable limits for each pMDI.

In an initial study done jointly between H&T Presspart and Proveris Laboratories, a comparison of the commercially available Atrovent was made to an inhaler of Ipratropium Bromide 20 µg/actuation with a 15 % w/w ethanol cosolvent and a citric acid excipient with HFA152a propellant.[4] Three different actuator geometries were examined for inhaler deposition testing and APSD. Actuator geometries tested looked at varying the Orifice Diameter (0.25, 0.26 and 0.29mm OD) and Jet Length, (0.35, and 0.75mm), as shown in Table 1.

APSD testing revealed comparable aerodynamic profiles between the HFA134a and HFA152a propellants, with most deposition occurring in the induction port – a behaviour typical of pMDIs as shown in Figure 2. The effect of actuator geometry is illustrated in the levels of drug deposition measured in the NGI. Actuator 3 with a larger Orifice Diameter gave a higher Induction Port and a lower inter-stage deposition than A1 and A2 actuators. The Fine Particle Mass (FPM) of actuator A3 showed an agreement with Atrovent (p=0.857) while actuators A1 and A2 had higher FPM results than Atrovent.

Regional deposition of the inhalers was performed using the *In Vitro* Inhaled Drug Analysis Platform (INVIDA® Platform), (Proveris Laboratories, USA). INVIDA is a groundbreaking, human-realistic inhalation deposition simulation testing service offered through Proveris Laboratories that mimics human-realistic testing of aerodynamic deposition, shown in Figure 3.

Drug deposition was measured across four anatomical regions using a realistic airway model: the mouthpiece adapter, mouth-throat, tracheobronchial region, and deep lung (captured by a downstream filter). INVIDA, offered as a service by Proveris Laboratories, pairs with the Proveris

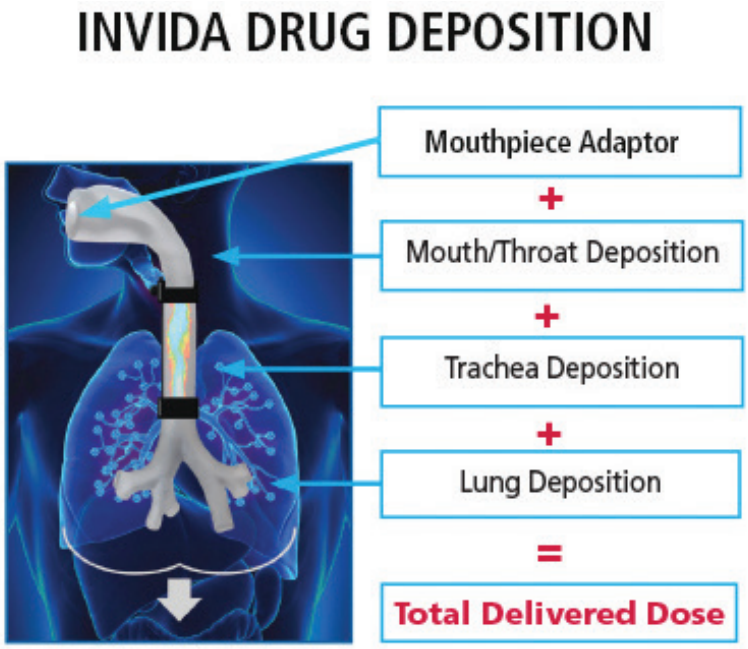

Figure 3: In Vitro Inhaled Drug Analysis Platform

Tests Performed	Sample	Actuator Ref.	Orifice Diameter (OD) (mm)	Jet Length (JL) (mm)
Regional Deposition, APSD, and SP/PG	Atrovent	Atrovent	-	-
	Ipratropium Bromide HFA152a	A1	0.25	0.35
		A2	0.26	0.75
		A3	0.29	0.75

Table 1: Actuator Geometries and Tests Performed

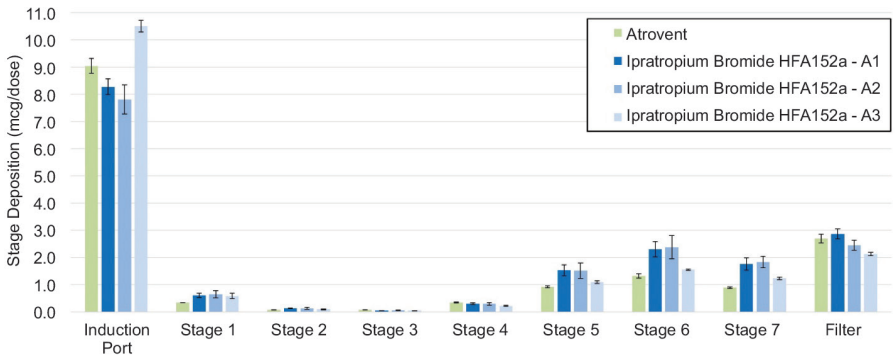

Figure 2: APSD – Atrovent Versus Ipratropium Bromide HFA152a

Human Breathing Simulator to replicate a human flow rate vs. time profile during inhalation. Three inhalers were tested per group – Atrovent and Ipratropium Bromide HFA-152a formulations – with six actuations per inhaler.

The inhalers were manually actuated into the INVIDA mouthpiece adaptor with one inhalation cycle and a peak inspiratory flow rate of 74.71 LPM, with an inhaled volume of 1.5L. The regional deposition stages were extracted, and Ipratropium Bromide was quantified by HPLC. Deposition results for all 4 regions of the mouth-throat, trachea, and lungs indicated similar regional distribution between HFA134a and HFA152a. Results showed no statistically significant difference ($p>0.05$) for total drug delivered for any of the 3 HFA152a actuators tested. Slight differences in deposition were observed in the mouth/throat and lung regions (Figure 4).

Most notably, the INVIDA platform delivered performance insights comparable to traditional APSD testing, but in one-fifth of the time – demonstrating a powerful path toward faster and more efficient inhalation product development.

A key regulatory question for the pharmaceutical industry is whether transitioning an approved pMDI from HFA-134a to an LGWP propellant like HFA-152a requires submission of a new drug application (NDA), or whether the change can be managed through a Prior Approval Supplement (PAS).

Requiring full NDAs could lead to drug shortages, delay patient access to environmentally friendly inhalers, and significantly increase development costs. The PAS pathway, supported by robust analytical, performance, and clinical data, offers a scientifically sound and patient-centered approach to facilitate the transition to low global warming potential propellants like HFA152a.

A related question arises when developing a generic version of a previously approved product: can an LGWP propellant be used, and what regulatory pathway would that entail? According to the FDA's draft guidance on quality considerations for metered dose and dry powder inhalers, and insights from industry experts, a PAS may be sufficient for reformulated pMDIs – provided the new formulation meets specific criteria[5]:

- Demonstrates equivalence in critical quality attributes (CQAs) such as delivered dose, particle size, Spray Pattern, and Plume Geometry.
- Establishes bioequivalence through pharmacokinetic bridging studies or *in vitro – in vivo* correlations (IVIVC).

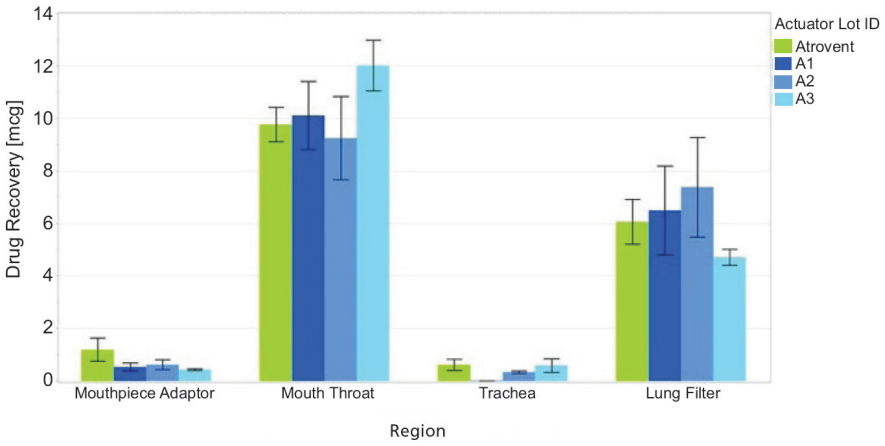

Figure 4: Regional Deposition – Atrovent and Ipratropium Bromide HFA152a Inhalers

- Confirms no new safety concerns arise from changes in formulation or device.

While regulators like the FDA have signalled support for science-driven approaches, definitive guidance on equivalence testing, clinical bridging requirements, and reformulation pathways continue to evolve. This creates ambiguity for sponsors planning their transition strategies.

Conclusion

The Future is LGWP, Human-Realistic, and rapid analysis. The pharmaceutical inhalation industry is poised for a once-in-a-generation shift. LGWP propellants like HFA152a and HFO1234ze are essential for meeting global climate goals, but their adoption demands innovation across formulation science, device engineering, analytical testing, and regulatory strategy. Early evidence – work combining DDU, APSD, and INVIDA testing – shows that performance equivalence is achievable, albeit with a need for careful optimisation. Human-realistic testing platforms, faster workflows, and data-driven development models are not just desirable – they are now essential. Companies that embrace this change proactively will not only deliver better environmental outcomes but also emerge as leaders in respiratory care for the next decade and beyond.

The future of pMDIs is lighter, faster, greener – and above all, better for patients and the planet.

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