Is the transition to low global warming propellants in metered dose inhalers on track?

A review of predictions made five years ago and what might happen next

John N. Pritchard, PhD
Inspiring Strategies

Climate change and global warming continue to be at the forefront of public and political discussions. Consequently, legislation has been introduced to phase down the emission of gases with significant global warming potential (GWP), which includes specific regulation of F-gases, i.e., hydrofluorocarbons (HFCs), perfluorocarbons, sulphur hexafluoride and nitrogen trifluoride. Despite accounting for only ~0.03% of all GWP gases [1], the propellants used in metered dose inhalers (pMDIs) are HFCs, and so must comply with this regulatory framework. In a paper published in 2020, I described a clear need for alternatives to the current pMDIs that remained both affordable and had a lower GWP [2]. I also suggested that 2025 could be a tipping point, due to a significant increase in the cost of existing propellants, which might particularly impact reliever medications. Given that it takes several years to bring a new product to market, it was therefore necessary to begin the development of lower-GWP alternatives to ensure an adequate choice of life-saving medication for patients with asthma and chronic obstructive pulmonary disease (COPD). This article takes the opportunity to review the last five years and project how things might change in the future.

Phase-down targets

The process began with the European Union (EU) F-gas regulations, first introduced in 2006, and last updated in 2024 [3]. It was subsequently agreed that the phase-down in usage of these gases should be managed under the Montreal Protocol, following an amendment agreed upon in Kigali, Rwanda in 2016 [4]. As of September 2025, 168 sovereign states together with the EU have ratified this amendment. Parties to the agreement commit to a phased reduction, with different timelines for different member states (Figure 1). It should be noted that targets relate to a baseline usage, which is still to be set for India over the period of 2024-2026. HFCs account for 97% of all F-gas emissions, although their use in medical aerosols accounts for a relatively small proportion. However, as other uses are phased out, the role of HFCs is increasing; for example, pMDIs accounted for 11% of equivalent greenhouse gas (GHG) consumption of F-gases in the UK in 2022, compared to 8% a decade ago [5].

The latest EU regulations represent a significant shift from the situation in 2020. Not only is the phase-down of F-gases further accelerated, the exemption for use in pMDIs is reduced from 2027, eliminated in 2030, and ultimately there will be a complete phase-out by 2050. When the pMDI exemption is removed, if the status quo remained in terms of the amount of propellants in use today, pMDI usage would account for one-third of consumption in 2029 and five-sixths in 2030 [6]. As discussed below, there will be some product launches of low-GWP pMDIs to reduce these proportions. Nevertheless, as a safeguard, the EU is committed to a review in 2028 of the impact of this latest legislation on healthcare. Following its exit from the EU, the United Kingdom (UK) has yet to enact similar proposals, which is of importance, given the number of multinational pharmaceutical companies and propellant manufacturers with production capability based there.

While the United States has implemented legislation to follow the Montreal Protocol phase-down schedule, it should be noted that individual states are at liberty to set their own laws for a faster transition. In

one example, the California Senate passed bill 1206 in 2022 that bans the sale of pMDIs containing HFC-227ea after the end of 2030, and those containing HFC-134a from the end of 2032 [7].

Furthermore, the situation may not be clear cut for those countries designated as "developing countries" (Article 5) under the Montreal Protocol, including India and China. Taking India as an example, it has been estimated that the significant growth in F-gas uses for refrigeration and room air conditioning could lead to India exceeding their commitment under the Kigali amendment when the first reduction from baseline occurs in 2032 [8]. This analysis did not include any contribution from domestic pMDIs, which could add approximately 4% to that from other uses in India [6]. Indian pMDI manufacturers now also have a significant presence in Western markets. In response to global warming, the proportion of households with an air conditioner is projected to grow from one-third today to two-thirds by 2050—more than a billion new air conditioning units across the world [9], leading to difficult decisions in policy-making as to which uses of F-gases to prioritize as phase-down targets increase in impact.

Therefore, the situation has evolved over the last five years. The environmental pressures to transition to a lower-GWP product, or risk losing market access have increased significantly both in the EU and elsewhere and now present a potential risk to manufacturers globally within the next ten years.

HFC propellant supply

In 2020, I proposed that there were also commercial drivers for change. When other applications of F-gases are phased out in favor of materials with lower GWP, the price of pharmaceutical-grade propellant will rise. This is due to falling demand leading either to a move from continuous to campaign manufacturing or complete closure of a production facility. Currently, pharmaceutical-grade HFC-134a represents just over 5% of the total industrial production [10]. However, over the last ten years, industrial demand has fallen from 110,000 tonnes in 2015 to around 50,000 tonnes in 2025 and is predicted to drop by a further 35,000 tonnes by 2030. This is expected to lead to plant closures, such that 95% of the global HFC-134a manufacturing capacity may be in China by 2030. This is likely to then be the major source of bulk propellant for purification to pharmaceutical-grade material [10].

As can be seen from Figure 2, when the first reduction in EU consumption came into force in 2017, the cost of propellant rose more than 6-fold, although it fell back when imports provided cheaper alternatives for industrial applications [11]. Refrigerant-grade HFC-134a has been increasing in price over the last three years, and is once again, more than six times the price it was in 2014. In 2020, I estimated that a 6-fold increase in propellant price could lead to a 3-fold increase in the cost to manufacture a pMDI containing HFC-134a and a 4-fold increase for HFC-227ea

Figure 1

Schedule for the phase-down in F-gas use by selected countries. (Adapted from references 3, 4.)

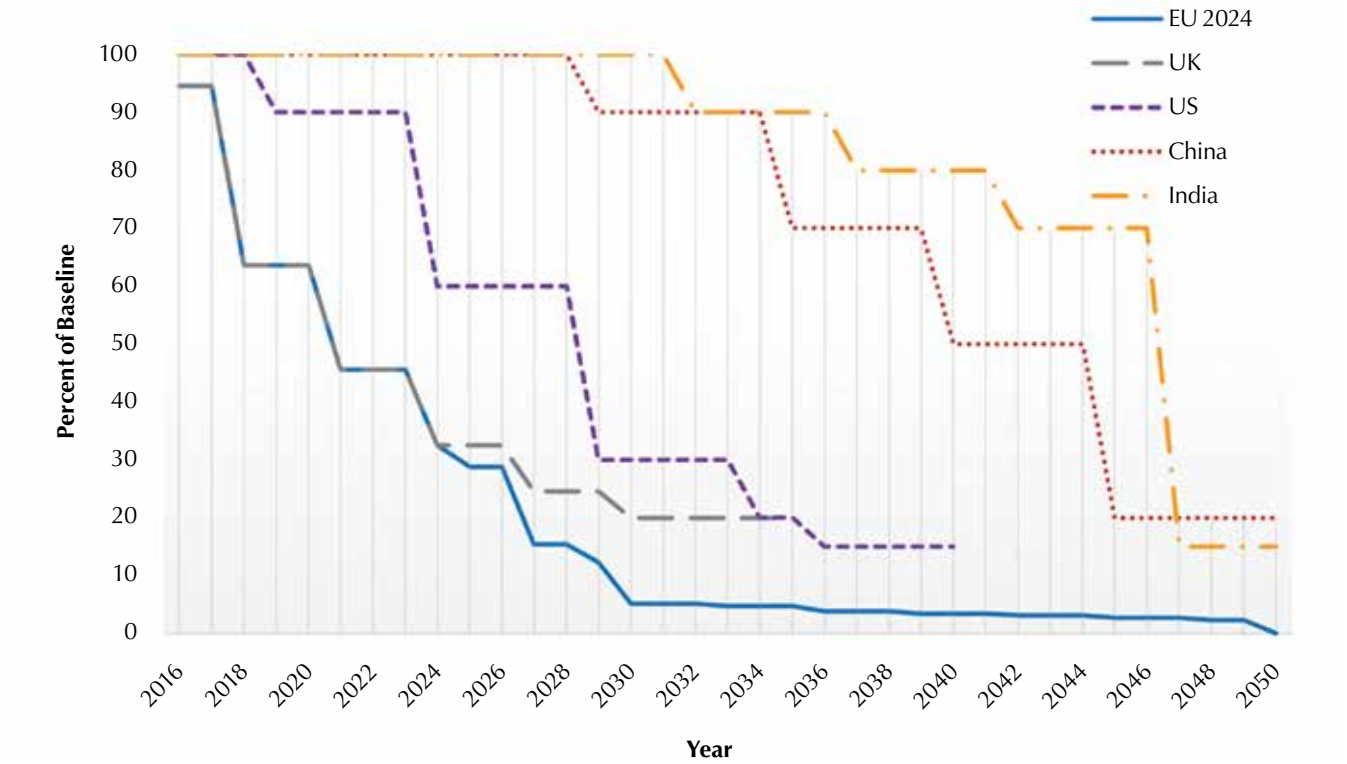
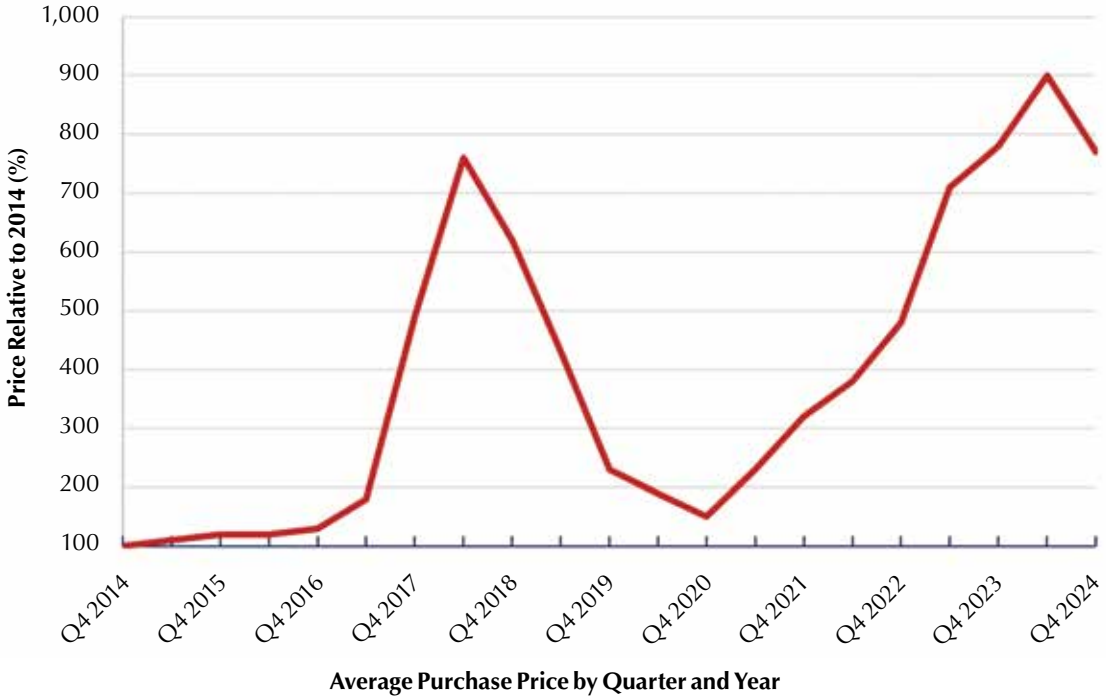


Figure 2

Evolution of the price of industrial-grade HFC-134a in the EU. (Adapted from reference 11.)



pMDIs [2]. In the past five years, the cost of pharmaceutical-grade propellant has risen as predicted. For example, a 3-fold increase in the cost of bulk HFC-227ea led Cipla in 2021 to apply for price increases in India for inhalers using this propellant [12].

It should also be noted that price increases impact the affordability and usage of life-saving medication. As an illustration of price sensitivity in the US, it was found that a $10 increase in out-of-pocket costs of an albuterol (salbutamol) pMDI after the chlorofluorocarbon (CFC) to HFC transition led to a 1% reduction in utilization [13]. Furthermore, in the US in 2022, for the generally poorer patients receiving Medicare or Medicaid support, cheaper pMDIs accounted for 70% of claims but only 38% of total spend, compared to more expensive dry powder inhalers (DPIs), where 50% of spend was associated with only 25% of claims [14].

Where it is not possible to raise the price, companies are faced with the choice of finding an alternative propellant, or discontinuation of the product if it becomes unprofitable. Given the wholesale price for a generic salbutamol pMDI in the UK is still only £1.50, it is hard to believe this product is currently sold at a profit, providing a powerful incentive to reformulate (or discontinue!). As an example, it has been estimated the payback period from investing in a low-GWP propellant pMDI could be as little as 4 years [2].

Progress in development of new products

As in 2020, two alternate propellants are in development, HFC-152a (Koura (Orbia), Runcorn, Cheshire, United Kingdom) and hydrofluoroolefin (HFO)-1234ze(E) (Honeywell, Charlotte, North Carolina, United States). These were discussed in detail in a recent article addressing the technical and regulatory aspects of replacing current HFCs in existing products [15]. In the past five years, both have become available in pharmaceutical grade at commercial scale. In parallel, there has also been significant progress in the development programs. An HFO-based triple combination of budesonide/glycopyrronium/formoterol fumarate has been approved for use by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and has received a positive opinion endorsing it for use from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency. It is also under review in China and other countries [16]. Progress with HFC-152a is slightly slower, with a salbutamol product on track to be launched in 2026 [17], and a triple combination of beclomethasone/glycopyrronium/formoterol fumarate completed Phase III clinical trials in September 2025 [18].

Five years ago, the data requirements for a market authorization submission were unclear. Key to aid in the progress of these programs in Europe has been the publication of clear guidance on requirements for the introduction of products containing a new propellant [19]. In addition to the usual controls expected

Table 1

Clinical studies for the development of a triple combination pMDI (budesonide, formoterol fumarate, glycopyrronium, (BGF)) utilizing a low-GWP propellant. HFO=HFO-1234ze(E); HFC=HFC-134a. (Adapted from reference 6.)

CT.GOV ID	Design	Number of Patients	Outcomes
NCT05573464	Phase III COPD 12-week Safety. 52-week Follow-up.	558	Safety and tolerability of BGF HFO vs. BGF HFC
NCT05755932	Phase IIIb Mucociliary Clearance	35	Mucociliary clearance after administration of HFO pMDI vs. HFC
NCT05850494	Phase IIIb Bronchospasm Study	52	Changes in forced expiratory volume over 1 second (FEV_1) and symptoms of bronchospasm induced by HFO vs. HFC
NCT05569421	Phase I Systemic Bioequivalence	108	Bioequivalence of systemic exposure to all active ingredients in BGF for HFO vs. HFC
NCT05477108	Phase I Lung Bioequivalence	108	Bioequivalence of lung exposure to all active ingredients in BGF HFO vs. HFC using charcoal block of oral absorption
NCT06297668	Phase I Systemic Bioequivalence with a Spacer	42	Total systemic exposure (without charcoal block) of BGF HFO pMDI with a spacer does not exceed that with HFC

of a new excipient (e.g., identification, boiling point, vapor pressure, relative density, acidity, moisture content, related impurities and unrelated impurities), and all product performance requirements including stability, the EMA specifically requests:

- Data on any impact upon ciliary function, for example by gamma scintigraphy
- Potential for airway sensitivity reactions, using a supratherapeutic dose of propellant
- At least one 3-month safety study of adverse events preferably compared to the marketed version of the same product. Recognizing the need to do this in patients, maintenance treatment is acceptable, although a placebo would be ideal.
- Therapeutic equivalence (TE) as set out in the EMA guideline on the requirements for clinical documentation for orally inhaled products [20]. This was recently updated to a new version coming into effect in February 2026. TE may be demonstrated *in vitro* if all requirements are fulfilled. Otherwise, TE is preferably demonstrated by pharmacokinetics (PK) if equivalent systemic exposure (as a surrogate marker for safety) and equivalent lung absorption/deposition (as a surrogate marker for efficacy) are achieved. Pharmacodynamic or clinical endpoints are not recommended as these are deemed insensitive.

Table 1 illustrates the clinical approach taken by AstraZeneca to comply with this guidance. Of note, the EMA states that if a certain propellant has already been used in an approved medicinal product for the same route of administration, the data requirements for including the said propellant in another medicinal product can be reduced when sufficient data, including pharmacovigilance data, have been collected. This suggests that companies who are later in development may be able to reduce their safety data requirements if the pharmacovigilance data on a low-GWP propellant are publicly available.

The situation is somewhat different in the US, where the development of guidance has not progressed as quickly. For generic pMDIs, the FDA has produced many Product Specific Guidance documents (PSGs) to show equivalence between test and reference products. For example, taking the triple combination listed in Table 2, the FDA has proposed in a draft PSG that equivalence can be demonstrated by meeting endpoints either a) across seven different types of *in vitro* tests, plus b) one study comparing the morphology of emitted drug particles, together with c) two PK studies, or alternatively, all of i) five *in vitro* bioequivalence tests, ii) one comparative morphology study, iii) one study with PK endpoints and iv) one comparative clinical endpoint bioequivalence study [21]. The FDA has indicated it may be possible to approve pMDIs with low-GWP propellants using an abbreviated clinical program along the lines of the appropriate PSG, but this will be decided on a case-by-case basis [15]. As a result, none of the products in development five years ago have yet been filed for approval in the US.

Furthermore, in the last five years, only six other companies have announced programs to develop low-GWP pMDIs (Beximco, Cipla, DevPro Biopharma, Glenmark, Lupin and Mundipharma) [22] to join the original three companies that had established programs in 2020 (AstraZeneca, Chiesi

Table 2

Status of key low-GWP pMDI development programs. HFO=HFO-1234ze(E); HFC=HFC-134a.

Company	Product	Propellant	Status
AstraZeneca	Breztri/Trixeo Aerosphere® (Budesonide/Glycopyrronium/Formoterol)	HFO	Approved UK, endorsed EU. Filed China, other countries [16]. Plan for all products to be transitioned by 2030.
Beximco	Various	HFC	Early stage [22]
Chiesi Farmaceutici	Trimbow® (Beclometasone/Formoterol/ Glycopyrronium)	HFC	Phase 3 trial completed September 2025 [18]. Plan to enter US market with this product.
Cipla	Various	HFC	Early stage [22]
DevPro Biopharma	Salbutamol/Albuterol	HFO	Plan to start Phase 1 trial in 2025. Launch projected 2027 [22].
GlaxoSmithKline	Ventolin® (Salbutamol/Albuterol)	HFC	Phase 3 trials successfully concluded. Launch expected in 2026 [17]. Future of other products is not stated.
Glenmark	Various	HFC	Early stage [22]
Lupin	Various	HFC or HFO	Development work to be completed in 2026 [23]
Mundipharma	Flutiform ® (Fluticasone propionate/ Formoterol)	HFC or HFO	Development started 2024 [22]

and GlaxoSmithKline). These six companies are significantly further behind in progress (Table 2).

Barriers to progress

One of the biggest challenges during the transition from chlorofluorocarbons (CFCs) to HFCs was the lack of HFCs with similar physicochemical properties, meaning that formulations, componentry and manufacturing methods all had to be radically altered. This time around, there are fewer significant differences between current and low-GWP propellants, such that potentially less than half of the key constituents of a pMDI would be affected [15]. Five years ago, a pharmaceutical grade of these new propellants had yet to be qualified, but this has proven relatively straightforward [22]. Flammability was identified as a risk that would need to be mitigated during manufacture, but not considered insurmountable, given the many millions of conventional aerosol cans that are filled with isobutane every year.

Less clear five years ago was the role that intellectual property protection could play. It is clear from a recent review that different strategies have been employed by the developers of these pharmaceutical-grade propellants [6]. For HFO-1234ze(E), as a relatively new propellant, patents still exist on the method of production so relatively few inhaler product patents including this HFO have been filed. Pharmaceutical companies who wish to use this propellant will have to obtain a supply agreement with the manufacturer until such time as a different route of synthesis is developed by a competitor. However, for HFC-152a, the production method was developed decades ago and there are already at least two suppliers of pharmaceutical-grade propellant. Therefore, the lead company who developed pharmaceutical-grade HFC-152a has filed multiple patents covering almost all commonly prescribed drugs and combinations in order to encourage pharmaceutical companies to use them as their supplier. Some have been granted, but many are still under review. They may either not be granted, only granted in certain countries, be granted with limited claims or overturned when tested in the courts. For companies who are still considering whether to develop a low-GWP pMDI, this forms a major consideration. Either they take a view that the patent landscape will not affect the markets they intend to enter, or they must negotiate a commercially acceptable licence and supply agreement with one of the propellant manufacturers.

On top of these considerations—and the key factor—is whether there is an adequate return on investment. As mentioned above, there is a positive business case in today's markets due to the increasing price of current propellants. However, this assumes the markets remain largely the same. Five years ago, there were calls to switch patients to inhalers with lower impact on global warming. Furthermore, international asthma guidelines now recommend the use of a long-acting β-agonist /inhaled corticosteroid (LABA/ICS) combination as first-line therapy in preference to a short-acting reliever [24], which cur-

rently represents around 70% of all pMDI usage. An analysis of sales data from 2024 suggests the growth in pMDI sales is slowing in comparison to the total respiratory market [6]. Such calls persist today, suggesting that *most* patients on pMDIs can be switched to an equivalent DPI, with significant reduction in the GWP emissions [25].

Key then to creating a business case to develop a low-GWP pMDI is an assumption of how many of those sales will remain when development is complete. But how big is the proportion that describes most patients who can use a DPI? DPIs are not approved for use in children less than 4 years of age. While there is no consensus as to the number of older patients for whom there is no alternative to a pMDI, there is a useful indicator from a clinical study in primary care [26], where a cohort of 1,081 asthma patients were switched from their current care to an inhaled, once-daily, long-acting, combination of LABA/ICS, delivered from a DPI. Despite the proven efficacy of this combination and the convenience of once-daily administration, 12% of the patients reverted to a pMDI over the 12-month study duration. In addition, 11% of patients in the standard-of-care group also switched from a DPI to a pMDI, whereas only 2% switched the other way. Given the pediatric asthma market was US$ 11.2 Bn in 2022, of which approximately one-fourth was for inhalers [27], and that the total asthma drug market was US$ 37.2 Bn of which 73% was inhaled [28], pediatric pMDIs might add a further 10%, suggesting that around 20% of all patients will still require a pMDI.

However, the business case also needs to make assumptions about pricing. Five years ago, the US represented almost three-quarters of the value of the top 15 markets around the world. Since that time, there have been a number of changes, including the introduction of a $35 monthly price cap on inhalers [29]. More recently, there have been threats to impose significant tariffs on pharmaceutical products imported into the US. Specific details regarding the exact rates and implementation timeline remain subject to change at the time of writing but are part of an overall goal to lower drug prices and increase domestic manufacturing, which includes potential investigations into foreign drug pricing policies and whether imports pose a national security risk [30]. This could then impact decisions on whether to modify existing pMDI production facilities outside of the US or invest in new plants within the US at extra capital cost. Furthermore, the current requirement of at least one clinical endpoint study adds significant cost to a development program. Uncertainty over the ability to recoup these costs in the US market may deter companies from launching a low-GWP pMDI there.

Of note, one technical solution has been proposed that addresses many of the issues above, namely to add the formulation directly to the canister in the form of a self-dispersing tablet, crimp the valve and then add liquefied pure propellant as a second step [31]. This is directly analogous to the methods used today in the manufacture of aerosol cans containing flammable propellants. There are advantages in safety, in that the formulation concentration within the batching vessel does not need to be adjusted during a filling run, as well as in development time, since the only scale-up is of the tableting process, allowing faster access to the clinic. This approach clearly results in additional differences in product formulation and manufacture from those products currently marketed, which may result in additional studies to obtain regulatory approval in Europe. However, if a clinical endpoint study is already required in the US, then this study could address these differences as well. Furthermore, with the current pressures on drug pricing and foreign manufacture in the US, it may be a way of introducing a partly-finished product into the country, with final manufacture and release taking place at a filling plant there.

There is one further consideration, that of other environmental regulation that could impact the introduction of low-GWP propellants. In the last five years, considerable attention has been drawn to the role of per- and poly-fluorinated alkyl substances (PFAS) following the publication of a draft amendment to EU regulations that would result in a ban on almost all uses [32]. In this draft, PFAS are defined as any compound containing a fully fluorinated carbon atom (i.e., either -CF3 or -CF2- groups), that would include HFC-134a, HFC-227ea and HFO-1234ze(E). HFC-152a is not in itself a PFAS, but the proposals also capture products containing a single PFAS impurity at a level above 25 ppb. Given that current propellants set a total impurity level at < 1,000 ppm, and are typically in the range of 17 ppm [33], controlling an individual impurity at levels three orders of magnitude less might be problematic for HFC-152a production as well. Clearly this would have a major impact on patient access to medicines within the EU. This draft is in the post-consultation phase, having received more than 5,600 comments, with a likely revision published in early 2026. In the US, the Environmental Protection Agency (EPA) uses a narrower definition of PFAS, which excludes current and future propellants used in pMDIs. Nevertheless, certain states have enacted their own PFAS legislation, including Maine and Minnesota. Defining a molecule containing at least one fully fluorinated carbon atom, thereby capturing all pMDI propellants except HFC-152a, Maine has nevertheless exempted pMDI use until 2040 and Minnesota similarly until 2032, although in the latter, additional future exemptions may be allowed. Other states are developing legislation that follows one of these two approaches.

It is hard to see why legislation that is aimed at preventing the accumulation of persistent chemicals in living tissues should apply to compounds that are emitted into the upper atmosphere. However, there is a potential degradation pathway leading to the formation of trifluoroacetic acid (TFA), a PFAS that returns to earth primarily in rainwater [34]. There are still many unknowns relating to any possible risks to health from TFA and legislation will undoubtedly evolve as more data become available.

Furthermore, each inhaler is a disposable item, often containing multiple types of plastic. Attempts to recycle these items have met with very limited success. A recent campaign involving collection of used inhalers at pharmacies only resulted in about 2% returned [35]. For those inhalers that are not recycled, it has been estimated that among 14 separate environmental impact categories, DPIs exceed pMDIs in six, including freshwater and marine ecotoxicity [36]. The overall conclusion is that while there may be an immediate focus on the global warming impact of an inhaler, companies must not lose sight of the other environmental impacts deriving from the use of both pMDIs and DPIs.

Future directions

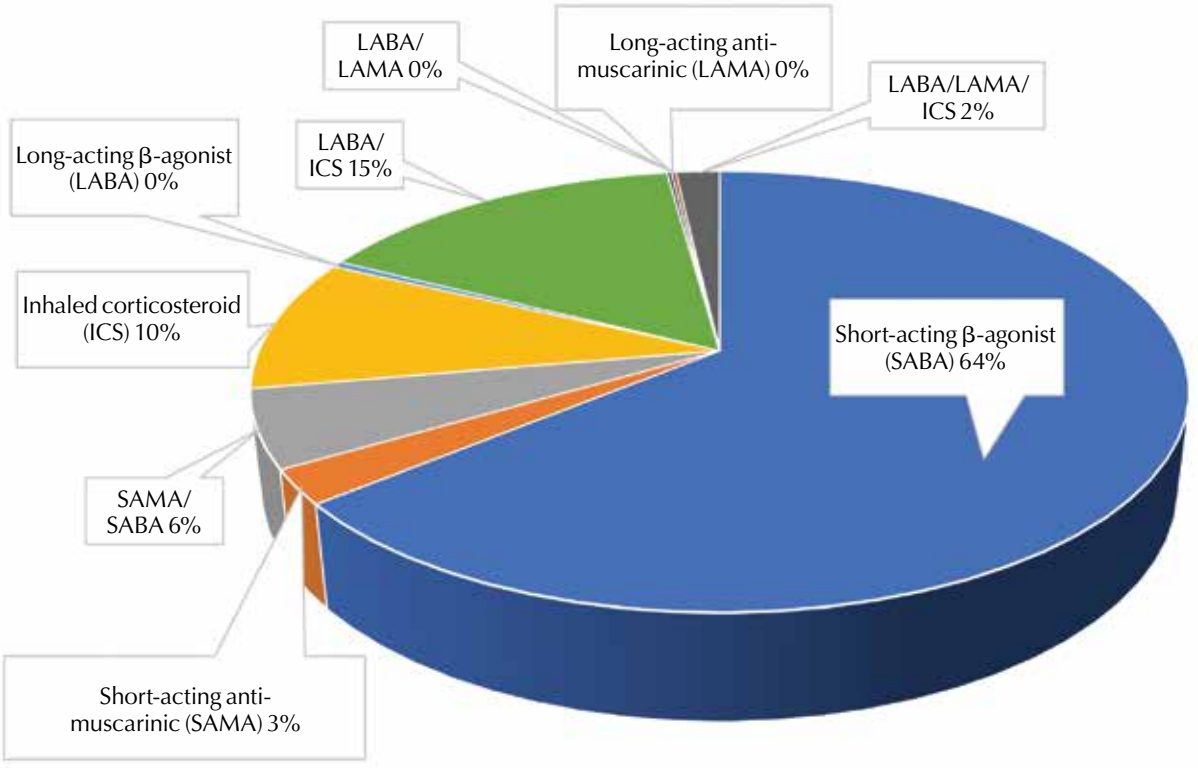
There are around 70 pMDI companies across the world who are now facing these issues. While development programs are expensive, commercial returns could be attractive due to potential patent protection for the first entrants, together with the potential removal of corresponding generic products as regulation and current propellant supply issues become more significant. Against that, the uncertainties described above may leave companies either undecided or having taken the view that it is not commercially viable now to invest in a low-GWP pMDI development.

Of the companies with stated active programs, the three companies who were underway five years ago have all made significant progress. Together, in 2024, they accounted for over 60% of the market value of all pMDIs sold in North America plus the top five European markets, (France, Germany, Italy, Spain and the UK) although for only 40% of the units sold [6]. These proportions are similar if the global market is analyzed. Correspondingly, in 2024, the six newer entrants in the last five years had global market share of 16% of the units sold, but only 5% of the value, reflecting the generally lower price of the products they sell. Of some concern then, is that 44% of pMDIs sold today have no publicly declared intent to replace them with low-GWP alternatives.

Looking further, the most advanced development programs are centred around two drug classes, two triple combinations and one reliever (Table 2). However, taking the prescriptions dispensed in England in May 2025 as an example of a country with high pMDI usage, these only accounted for 28% of all pMDIs [37]. Although at 10%, the triple combinations have risen significantly in market share com-

Figure 3

Annual sales of pMDIs by drug class in Q2 2023. (Source: IQVIA Quarterly MIDAS® Database, Durham, North Carolina, US.)



pared to 2023 (Figure 3), inhaled corticosteroids, alone or in combination with a LABA are significantly behind in progress. Given this combination is now recommended as first line therapy in asthma [24], this leaves a significant gap currently. Furthermore, in the reliever segment, having only one supplier does not offer the manufacturing capacity to supply the world nor security of supply, nor the commercial competition to influence pricing.

Other than the three late stage developments listed in Table 2, no other program has reached the stage of Phase I trials, so it is hard to see any other products being launched into the market before 2030. This brings into play several of the factors discussed above. For products containing HFC-227ea and HFC-134a, medical-grade propellant will likely need to rely on purification of industrial-grade propellant sourced from China. This will require the necessary work to get regulatory approvals for a new supplier in place, something in which one HFC-134a supplier has already made significant progress [10]. Then referring to the discussion of the EU F-gas regulations above, if only three pMDIs have transitioned to low-GWP propellants, this sector could still account for over half of the allowable consumption in 2030. At the same time, China and other countries will see their first reductions under the Montreal Protocol, closely followed by India in 2032. All may lead to competing demands among different industrial sectors that in total exceed the amounts allowable under the Kigali Amendment, forcing governing bodies to prioritize their most essential uses. Consequential to reduced consumption, the prices of bulk propellant will rise again, and coupled with downward price pressures, at some point pMDIs will become uneconomic to sell in those markets with lower prices, potentially leaving healthcare professionals with a limited selection of available medicines to prescribe.

Final thoughts

I suggested five years ago that 2025 could be a tipping point for the pMDI. Much of what was described has indeed come to pass, but more has happened that was not foreseen. Nonetheless, it appears that the situation has crystallized. Some companies have elected, deliberately or otherwise, that they will exit the pMDI market in due course. Others have seized the opportunity and stand to benefit from reduced competition and additional patent protection in the future. Provided those active in the field can successfully complete their development programs, there should be products available in all the main drug classes, albeit the timing remains of concern, both in Europe and elsewhere. Whether, given the reduced competition, smaller market size and the higher costs of manufacture, these products are affordable to all remains to be seen, but it is very encouraging that several of these manufacturers have a tradition of supplying products with lower prices.

References

1. United National Environment Programme (2014). Assessment report of the Technology and Economic Assessment Panel; 2014. https://ozone.unep.org/sites/default/files/2019-05/TEAP_Assessment_report_2014.pdf

2. Pritchard JN (2020). The climate is changing for metered-dose inhalers and action is needed. Drug Des Devel Ther 14: 3043-3055. doi:10.2147/DDDT.S262141

3. European Union (2024). Regulation (EU) 2024/573 of the European Parliament of 7 February 2024 on fluorinated greenhouse gases, amending Directive (EU) 2019/1937 and repealing Regulation (EU) No 517/2014. https://eur-lex.europa.eu/eli/reg/2024/573/oj

4. United Nations Environment Program (2016). The Kigali Amendment to the Montreal Protocol: HFC Phase-down. OzonAction Fact sheet OZFS/16/11_1, UNEP, Paris, France. https://wedocs.unep.org/bitstream/handle/20.500.11822/26589/HFC_Phasedown_EN.pdf?sequence=1&isAllowed=y

5. National Atmospheric Emissions Inventory (2024). Greenhouse gas emissions data. https://naei.energysecurity.gov.uk/greenhouse-gases/greenhouse-gas-emissions-data

6. Pritchard JN (2024). A global warning for MDI propellants: Clinical, regulatory and economic factors driving the transition. In Dalby RN, Byron PR, Peart J et al (Eds). Respiratory Drug Delivery Asia 2024, 1-17. Virginia Commonwealth University, VA, US

7. Skinner N (2022). State of California Senate Bill 1206, Hydrofluorocarbon Gases: Sale or Distribution. https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=202120220SB1206

8. Hillbrand A, Madan P, Singh M, McNamara M, Andersen SO, Mathur A, Shende R, Jaiswal A (2022). Scenarios for future Indian HFC demand compared to the Kigali Amendment. Environ Res Lett 17(7):074019

9. Woodcock A (2023). Hydrofluorocarbons, climate, and health—Moving the Montreal Protocol beyond ozone-layer recovery. NEJM 388:2404-2406

10. Watkinson P, Bromley-Davenport D (2025). Technical challenges in sustaining medical propellant supply during the low GWP transition. May 7, 2025 Workshop presentation at Respiratory Drug Delivery 2025, Estoril, Portugal

11. Oko-Recherche (2025). Monitoring of refrigerant prices on the EU market. Results of quarterly survey: Quarter 4/2024. https://climate.ec.europa.eu/

document/download/08ac662a-6582-4379-8d1e-0fb0048c5fa7_en?filename=Excerpt_Price%20monitoring%20Q2%202024_remake%20%28003%29.pdf

12. Pilla V (2021). Cipla seeks price hike for certain respiratory medications, writes to NPPA. https://www.moneycontrol.com/news/business/companies/cipla-seeks-price-hike-for-certain-respiratory-medications-writes-to-nppa-7442041.html

13. Jena AB, Ho O, Goldman DP, Karaca-Mandic P (2015). The impact of the US Food and Drug Administration chlorofluorocarbon ban on out-of-pocket costs and use of albuterol inhalers among individuals with asthma. JAMA Intern Med 175(7):1171-1179

14. Tirumalasetty J, Miller SA, Prescott HC, DeTata S, Arroyo AC, Wilkinson AJ, Rabin AS (2024). Greenhouse gas emissions and costs of inhaler devices in the US. JAMA 332(12):1017-1019

15. Singh GJP, Ivatury S (2025). Point of view: Product development considerations for transition to the lower global warming potential propellants use in metered dose inhalers: Status quo versus scientifically rationalized approach. Inhalation 19(3):22-35. https://www.inhalationmag.com/wp-content/uploads/pdf/inh_20250601_0022.pdf

16. AstraZeneca plc (2025). Trixeo Aerosphere receives positive EU CHMP Opinion as first inhaled medicine using next-generation propellant with near-zero global warming potential. https://www.astrazeneca.com/media-centre/press-releases/2025/trixeo-aerosphere-receives-positive-eu-chmp-opinion-first-inhaled-medicine-using-next-generation-propellant-with-near-zero-global-warming-potential.html

17. GSK plc (2025). GSK announces positive pivotal phase III data for next-generation low carbon version of Ventolin (salbutamol) metered dose inhaler. https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-pivotal-phase-iii-data-for-next-generation-low-carbon-version-of-ventolin-salbutamol-metered-dose-inhaler

18. Chiesi Group (2025). Chiesi carbon minimal inhalers reach new milestone with clinical phase III initiation. Chiesi completes clinical development program for carbon-minimal pressurized metered-dose inhalers (pMDIs), paving the way for regulatory submissions. https://www.chiesi.com/en/pmdi-carbon-minimal-clinical-development-regulatory-submissions/

19. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) (2023). Questions and Answers on Data Requirements when Replacing Hydrofluorocarbons as Propellants in Oral Pressurised Metered Dose Inhalers, EMA/CHMP/83033/2023, https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-data-requirements-when-transitioning-low-global-warming-potential-lgwp-propellants-oral-pressurised-metered-dose-inhalers_en.pdf

20. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) (2025). Guideline on the Requirements for Demonstrating Therapeutic Equivalence Between Orally Inhaled Products (OIP) for Asthma and Chronic Obstructive Pulmonary Disease (COPD). CHMP/EWP/4151/00 Rev.2. www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-demonstrating-therapeutic-equivalence-between-orally-inhaled-products-oip-asthma-chronic-obstructive-pulmonary-disease-copd-revision-2_en.pdf

21. US FDA Draft Guidance (2024). Draft Guidance on Budesonide; Formoterol Fumarate; Glycopyrrolate. PSG 212122 February 2024. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_212122.pdf

22. United National Environment Programme (2025). Progress report of the Technology and Economic Assessment Panel; May 2025. https://ozone.unep.org/system/files/documents/TEAP-May2025-Progress-Report-vol1.pdf

23. Lupin Healthcare (2024). Lupin Healthcare UK Ltd. announce the development of respiratory inhalers with near-zero global warming potential propellants, as part of their net zero plans. https://www.lupinhealthcare.co.uk/wp-content/uploads/2024/09/Press-Release-Lupin-LGW-Potential-Propellant-development-UK-RESP-2408-00001.pdf

24. Global Initiative for Asthma (2024) Global Strategy for Asthma Management and Prevention. 2024 Report. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf

25. Vartiainen V, Woodcock AA, Wilkinson A, Janson C, Björnsdóttir U, Haahtela T, Lehtimäki L (2024). Thoughtful prescription of inhaled medication has the potential to reduce inhaler-related greenhouse gas emissions by 85%: BMJ Open Respir Res 11:e001782. https://doi.org/10.1136/bmjresp-2023-001782

26. Woodcock A, Janson C, Rees J, Frith L, Löfdahl M, Moore A, Hedberg M, Leather D (2022). Effects of switching from a metered dose inhaler to a dry powder inhaler on climate emissions and asthma control: Post-hoc analysis. Thorax 77(12):1187-1192

27. Transparency Market Research (2023). Pediatric asthma treatment market. https://www.transparencymarketresearch.com/pediatric-asthma-treatment-market.html

28. Towards Healthcare (2024). Asthma and COPD drugs market size and segmentations report. https://

www.biospace.com/asthma-and-copd-drugs-market-size-and-segmentations-report-5-01-percent-cagr-2023-2032

29. GlobalData Healthcare (2024). Impact and implications of the $35 monthly price cap on asthma inhalers. Pharm Technol. June 26, 2024. https://www.pharmaceutical-technology.com/analyst-comment/impact-implications-monthly-price-cap-asthma-inhalers/?cf-view

30. Thiery F (2025). New measures announced by Trump to hit the pharma sector. https://credendo.com/en/knowledge-hub/pharma-sector-changing-us-landscape-will-prove-disruptive-entire-sector

31. Warren S, Zheng C, Fowler S, Obirek A, Kay R, Tran C (2023). Stability evaluations of salbutamol sulphate propellant-dispersible tablets (Respitab™) for formulation with HFA-152a. In Drug Delivery to the Lungs 2023 (DDL2023).The Aerosol Society, Bristol, UK: 34. https://ddl-conference.com/wp-content/uploads/2023/10/Gerallt.Warren.docx

32. European Chemicals Agency (2023). Proposal for a Restriction on Per- and Polyfluoroalkyl Substances (PFAS). https://echa.europa.eu/documents/10162/f605d4b5-7c17-7414-8823-b49b9fd43aea

33. US Environmental Protection Agency (2024). Draft Review of Applications in the American Innovation and Manufacturing (AIM) Act Subsection (e)(4)(B)(4). https://www.epa.gov/system/files/documents/2024-10/nprm-technical-support-document.pdf

34. Lim XZ (2025). There's a new acid in our rain – should we be worried? Nat 643:894-897

35. Murphy A, Howlett D, Gowson A, Lewis H (2023). Understanding the feasibility and environmental effectiveness of a pilot postal inhaler recovery and recycling scheme. NPJ Prim Care Respir Med 33(1):1-6

36. Fulford B, Mezzi K, Aumônier S, Finkbeiner M (2022): Carbon footprints and life cycle assessments of inhalers: A review of published evidence. Sustainability 14(12):7106. https://doi.org/10.3390/su14127106

37. NHS Business Service Authority (2025). Prescription cost analysis (PCA) monthly administrative data; May 2025. https://opendata.nhsbsa.net/dataset/prescription-cost-analysis-pca-monthly-data/resource/20e8c84d-ef2c-4bb9-889c-48517024e5eb

John N. Pritchard, PhD, is an independent consultant, trading as Inspiring Strategies and is also Chair of the Boards of Cardiff Scintigraphics and Nebu-Flow. For more than 20 years, he has served on the Medical & Chemical Technical Options Committee that advises the parties to the Montreal Protocol on issues relating to the treatment of respiratory diseases. The views expressed here are his own and do not necessarily represent those of this Committee. john@jnpinspiring.com.