A Pioneer's Path to Transition: *How HFO-1234ze(E) Is Shaping the Future of Sustainable Pressurised Metered Dose Inhalers*

The pharmaceutical respiratory inhalation sector is entering its second major propellant transition. In response to the Montreal Protocol requirements, the first transition moved pressurised metered-dose inhalers (pMDIs) away from ozone-depleting chlorofluorocarbons (CFCs such as CFC-11) to hydrofluoroalkanes (HFAs), principally HFA-134a and HFA-227ea. These HFAs eliminated the ozone-depletion concern but unfortunately retained high global warming potential (GWP).

Climate change regulation is now driving a further transition. Following the Montreal Protocol, the Kyoto Protocol and the related Kigali Amendment established a global hydrofluorocarbon phasedown trajectory, implemented regionally in the EU through Regulation (EU) 2024/573, which removed the previous quota exemption for HFA-based pMDIs, and in the United States through the American Innovation and Manufacturing (AIM) Act and its implementing allowance programme at 40 CFR Part 84.[1,2,3] For pMDIs, the challenge is to decarbonise without compromising patient access, inhaler performance, or therapeutic continuity.

This review summarises HFO-1234ze(E) as a successfully approved next-generation propellant, assessing its physical properties, formulation compatibility, toxicological profile, clinical evidence, and regulatory readiness.

Physical Property Comparison of Common pMDI Propellants

Property	HFO-1234ze(E)	HFA-134a	HFA-152a
Chemical formula	CF3-CH=CHF	CF3-CFH2	CHF2 -CH3
Molecular weight (g/mol)	114.0	102.0	66.1
Boiling point (°C)	-19.0	-26.1	-24.0
Density at 21.1 °C (g/mL)	1.17	1.22	0.91
Vapour pressure at 21°C (psia/bar)	64.2 / 4.42	85.8 / 5.92	77.0 / 5.31
Vapour pressure at 54°C (psia/bar)	161.7 / 11.15	213.4 / 14.71	190.6 / 13.14
Water solubility (ppm)	225	2200	1700
Flame limits in air at 20°C (vol%)	None	None	3.7-16.9
GWP (100-year ITH, AR6)	1.37	1530	164
Atmospheric lifetime	19 days	14 years	1.6 years
Manufacturing requirements	No ATEX required	No ATEX required	ATEX required

Table 1. Physicochemical, environmental, and manufacturing properties of common pMDI propellants. The data presented in Table 1 are drawn from the supplier's technical data sheet and product literature and the propellant property comparison presented at Respiratory Drug Delivery 2022.[4,5,6]

Technical and Formulation Considerations

Medical Propellant HFO-1234ze(E), GMP is a hydrofluoroolefin propellant for pMDIs, reducing propellant greenhouse gas emissions by up to 99.9% relative to the incumbent HFAs.[4,5] Its liquid density of 1.17 g/mL is comparable to HFA-134a at 1.22 g/mL so that suspension sedimentation and creaming behaviour carry across the transition without wholesale reformulation, in contrast to the substantially less dense HFA-152a.4,5 HFO-1234ze(E) exhibits no vapor flame limits under standard test conditions and is classified non-flammable under EC Testing Method A11, ISO 10156 and the US DOT standard (ASTM E681), and in the ASTM flame projection, ignition distance and enclosed-space ignition tests.[4] A narrow flammable range can be observed only where temperature is at or above 30°C, relative humidity at or above 50%, and a high-energy ignition source is present.[7] The propellant is thermally and hydrolytically stable, showing no breakdown and no effect on metals after two weeks at 200°C in the presence of water and metals, and remaining within specification after several years of storage in steel cylinders. Compatibility has been demonstrated with aluminium, tin plate and PET-lined canisters and with common valve gasket materials including grades of butyl rubber, Buna and neoprene, with pMDI valve compatibility testing conducted by Aptar Pharma.[4] Nonetheless, the best approach is to conduct confirmatory testing with the specific container closure system used.

Formulation studies further demonstrate the suitability of HFO-1234ze(E) across both suspension and solution pMDI formulations. Using static multiple light scattering, salbutamol sulphate suspensions in HFO-1234ze(E) were more physically stable than the equivalent HFA-134a suspensions, with lower migration rates (52 versus 64 mm/hour propellant-only, and 40 versus 53 mm/hour at 5% ethanol); ethanol addition reduced both flocculation and sedimentation, with the benefit plateauing above approximately 5% w/w.[8] In higher drug-load suspension work, ethanol at 2–5% w/w brought mean delivered dose onto a 180-microgram target with acceptable uniformity and fine particle doses of 89–114 micrograms per actuation, exceeding marketed comparators, while 15% ethanol reduced fine particle dose to 49 micrograms through increased throat deposition.[9] Solution formulations of beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide delivered doses at or above their reference listed drugs with dose uniformity meeting USP 601, and reducing actuator orifice diameter to 0.22 mm raised beclomethasone fine particle dose from 44.1 to 80.2 micrograms and fine particle fraction from 48.0 to 83.7% while lowering MMAD and geometric standard deviation; storage at 40 degrees C/75% RH for 12 weeks produced no statistically significant change in delivered dose and little change in aerodynamic particle size distribution.[10]

Compatibility extends beyond simple substitution. Budesonide, marketed only as a suspension because of solubility limits in HFA propellants, formed clear solutions in HFO-1234ze(E) at 14–16% w/w ethanol, meeting USP 601 dose uniformity criteria with higher fine particle dose (51.1 versus 40.6 micrograms), higher fine particle fraction (46.5 versus 36.3%) and markedly finer mass median aerodynamic diameter (MMAD) 1.48–1.56 versus 3.75 micrometres than the suspension

reference product.[11] Fluticasone propionate, previously the least characterised active in this propellant because of its hydrophobicity and aggregation tendency, was successfully formulated as a suspension at 2% ethanol with either oleic acid or magnesium stearate, delivering 94.9–105.9% of label claim against the reference at 85.4% with acceptable uniformity and comparable aerodynamic performance.[12] Standard excipients including ethanol, oleic acid, magnesium stearate, citric acid and propylene glycol perform as expected in these systems.[6]

Taken together, the combination of near-zero GWP, non-flammability, HFA-134a-like density and demonstrated container closure compatibility, alongside formulation profiles closely comparable to existing HFA-based products supports HFO-1234ze(E) as a technically viable near drop-in replacement for HFA-134a that can often be implemented using similar materials, excipients, device platforms, and manufacturing approaches. Modest cosolvent adjustment and actuator orifice selection are the principal levers for aligning in vitro performance, and in the case of poorly HFA-soluble actives, HFO-1234ze(E) offers formulation opportunities that were previously difficult to achieve with conventional HFAs.

Toxicology and Safety Assessment

A comprehensive toxicological programme has been conducted for HFO-1234ze(E), covering repeated-dose toxicity, safety pharmacology, genetic toxicology, carcinogenicity, reproductive and developmental toxicity, and local tolerance.[13, 14, 15, 16]

Pharmacokinetic investigations showed very limited metabolism (below 1% of the administered dose) and rapid systemic clearance following inhalation exposure, with peak blood concentrations occurring immediately after dosing and declining rapidly thereafter.[13] Safety pharmacology evaluations demonstrated no adverse effects on cardiovascular, respiratory or central nervous system function in rats or dogs, and a cardiac sensitisation study in dogs was negative.[14]

HFO-1234ze(E) was generally well tolerated in repeat-dose inhalation studies of up to 3 months in mice, 6 months in rats, and 9 months in dogs.[14] In repeat-dose rat studies, the propellant exacerbated progressive cardiomyopathy, a known spontaneous background lesion in this species.[15] These effects were observed principally at exposures of approximately 15,000 ppm, did not increase in severity with longer treatment duration, and were not seen in mice or dogs. The 6-month rat study established a NOAEL of 5,180 ppm (4,280 mg/kg/day).[14]

A multigeneration reproductive toxicity study identified deaths and neurological findings in lactating female rats exposed to 19,400 ppm (approximately 23,000 mg/kg/day). These events were confined to the late lactation period and were not observed in males, non-lactating females, or in any other repeat-dose study.[14] The parental toxicity NOEL was 4,820 ppm, while reproductive performance and offspring development were unaffected at all tested exposure levels. Embryo-foetal development studies in rats and rabbits demonstrated no maternal, reproductive, developmental or teratogenic effects.[14]

The propellant showed no genotoxic potential across a complete battery of *in vitro* and *in vivo* studies, including bacterial reverse mutation assays, chromosomal aberration assays, micronucleus tests, and unscheduled DNA synthesis assessments.[15] Two-year inhalation carcinogenicity studies in mice and rats showed no treatment-related neoplastic or non-neoplastic findings, indicating that HFO-1234ze(E) is not carcinogenic under the OECD test conditions of those studies.[16]

The non-clinical data support a favourable safety profile.[14,16] The compound exhibits low systemic toxicity, rapid clearance, negative genotoxicity and carcinogenicity findings, and no adverse effects on fertility or development. The effects observed were limited to high-dose rat studies at exposure levels substantially exceeding those anticipated in clinical use. Key NOAELs were 29,000 mg/kg/day in mice (3 months), 4,280 mg/kg/day in rats (6 months), 5,760 mg/kg/day in the rat reproductive study, and 3,620 mg/kg/day in dogs (3 months).[14]

Clinical Experience

Clinical characterisation of HFO-1234ze(E) advanced during 2025 with two randomised, double-blind studies.[17, 18] Both were designed around the same premise: because non-clinical work showed the propellant appears in blood only transiently and produced no risk at pMDI exposure levels, its effects were expected to be primarily airway-based, making the potential for bronchospasm the key tolerability consideration for a new inhaled excipient.[14, 17, 18]

Pleasants *et al.* addressed airway sensitivity directly in a Phase IIIb, randomised, double-blind, single-dose crossover study in adults with well-controlled or partially controlled asthma (NCT05850494), using propellant-only inhalers containing no active drug at four inhalations per dose, twice the exposure anticipated for a combination product. HFO-1234ze(E) met non-inferiority to HFA-134a for change from baseline in FEV1 AUC0-15 min against a margin set at the minimum FEV1 change classifiable as reversible and consistent with asthma, and no bronchospasm event occurred in either arm in a study powered to detect such events at a rate of 5% or greater. Both propellants were well tolerated, with no serious adverse events, no adverse events of special interest, and no discontinuations.[17]

Usmani *et al.* then evaluated the propellant in its intended commercial configuration in a Phase 3, randomised, double-blind, parallel-group, active-comparator study at 92 sites across nine countries (NCT05573464), comparing budesonide/glycopyrronium/formoterol fumarate dihydrate delivered by HFO-1234ze(E) or HFA-134a in moderate-to-very-severe COPD over 12 weeks, with a prespecified cohort continuing to 52 weeks. Adverse event incidence was balanced at both timepoints, and respiratory adverse events of special interest, selected as most relevant to an inhaled propellant with very limited systemic exposure, showed no difference between groups. Continuous Holter monitoring covering the first inhaled dose, serial ECGs, clinical laboratory tests and vital signs showed no clinically meaningful differences; exploratory lung function and health status indicated comparable therapeutic effect; and no new or unexpected safety signals emerged.[18]

The two studies are complementary. The crossover isolates the propellant in a susceptible airway population at supra-therapeutic dosing and finds no effect on lung function and no bronchospasm.[17] The Phase 3 study confirms that this neutrality holds in the finished product across chronic dosing to 52 weeks in an older, comorbid population, consistent with earlier Phase 1 findings of systemic and lung bioequivalence for the active ingredients formulated with either propellant.[19] Taken together, the evidence indicates a similar benefit-risk profile for both propellants and supports substitution of HFO-1234ze(E) for HFA-134a, with real-world evaluation identified as the next step.[18]

Regulatory Approval Journey and Timeline

The regulatory pathway for HFO-1234ze(E) in pMDIs reflects a progression of international environmental agreements, agency-level scientific engagement, and initial product approvals spanning nearly four decades.

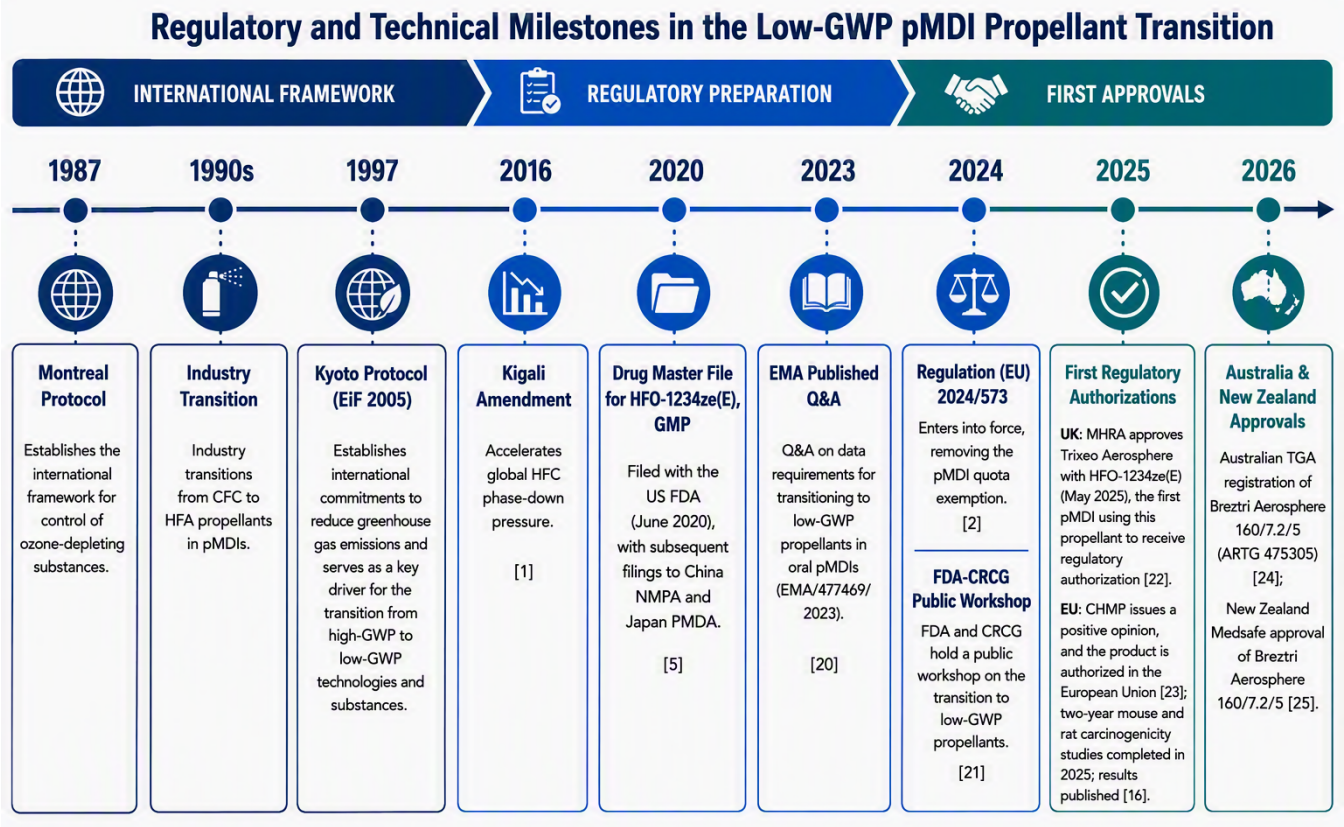


Figure 1. Transition and regulatory approval journey for HFO-1234ze(E): environmental agreements, agency engagement and first pMDI product approvals, 1987 to 2026.

Figure 1 above traces this journey, mapping the key environmental, scientific and regulatory milestones from the 1987 Montreal Protocol through to the first pMDI approvals containing HFO-1234ze(E) in 2025 and 2026.

The 2025 MHRA approval of Trixeo Aerosphere with HFO-1234ze(E) in the United Kingdom represents the first regulatory authorisation of a pMDI product using this next-generation ultra-low-GWP propellant, establishing a precedent for subsequent EU and global submissions.[22] As of mid-2026 the propellant is approved for patient use in the United Kingdom, the European Union, Australia and New Zealand.[23,24,25]

Evolving Regulatory Landscape

In the United States, the FDA 2018 draft quality guidance for MDIs and DPIs remains the primary reference for CMC expectations, covering delivered dose uniformity, aerodynamic particle size distribution, spray pattern, leachables and related critical quality attributes.[26] The Agency has not yet issued dedicated final guidance for the low-GWP propellant transition. The 2024 FDA and CRCG public workshop addressed scientific understanding of low-GWP propellants, product performance considerations, and data requirements for both innovator and generic transition programmes, but binding regulatory pathways remain product-specific.[21] FDA supports the transition to low-GWP propellants while expecting a science-based demonstration of safety, quality and performance, and has signalled interest in reducing unnecessary testing where confidence in reformulated product safety and effectiveness can be maintained.

The EU and UK framework is more developed. The EMA Q&A on data requirements for transitioning to low-GWP propellants sets expectations for a novel propellant, comprising full novel excipient quality, toxicology and pharmacokinetic data, local tolerance assessment covering ciliary function and airway sensitivity, clinical safety evaluation, and pharmacokinetic bioequivalence demonstrating therapeutic equivalence. Once a propellant has been used in an approved product, the package for subsequent applicants narrows to product quality and demonstration of therapeutic equivalence.[20] The EMA draft guideline on the pharmaceutical quality of inhalation and nasal medicinal products (EMA/CHMP/20607/2024) consolidates inhalation product quality expectations and incorporates the Medical Device Regulation, requiring risk-based demonstration of quality, safety and performance comparability, including consideration of therapeutic equivalence and device changes.[27] International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) has published proposed pathways for US FDA approval of low-GWP propellant transitions, providing an industry reference in the absence of dedicated FDA guidance.[28]

HFO-1234ze(E) is now supported by a coherent scientific and regulatory evidence base: an AR6 GWP of 1.37, an atmospheric lifetime of approximately 19 days, non-flammable classification under recognised international test methods, a comprehensive non-clinical safety package including two-year carcinogenicity studies in mice and rats, demonstrated formulation compatibility across suspension and solution systems, clinical tolerability data in asthma and COPD populations, and regulatory approval of the first pMDI products incorporating this propellant in four jurisdictions.

Adoption should nonetheless proceed through disciplined product-specific comparability, quality-by-design development, and early regulatory engagement. Sponsors must generate evidence across formulation performance, container closure compatibility, extractables and leachables, stability, delivered dose uniformity, aerodynamic particle size distribution, and clinical bridging where required.

The strongest case for HFO-1234ze(E) rests on its combined ability to reduce inhaler climate impact while preserving the clinical utility, usability, and patient access advantages that define the pMDI platform.

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