# SOLSTICE® AIR (HFO-1234ZE(E), CGMP)
# PROPELLING TOWARDS CARBON NEUTRALITY

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## Introduction

- Pressurized metered dose inhalers (pMDIs) treat respiratory conditions
  - Asthma
  - Chronic Obstructive Pulmonary Disease (COPD)
- Current propellants (HFA-134a, HFA-227ea) have high global warming potentials (GWPs)
- Countries have begun disincentivizing use of pMDIs [1]
- To reduce carbon footprint, industry leaders have committed to converting their products

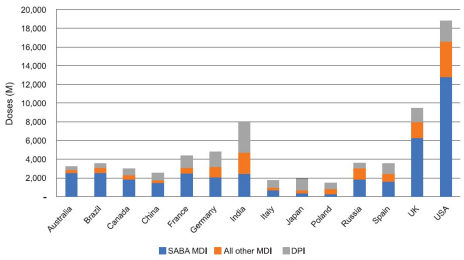


**Figure 1.** Analysis of SABA MDIs, other MDIs, and DPI doses prescribed in the top 14 markets. Adopted from Pritchard (2022) [2].

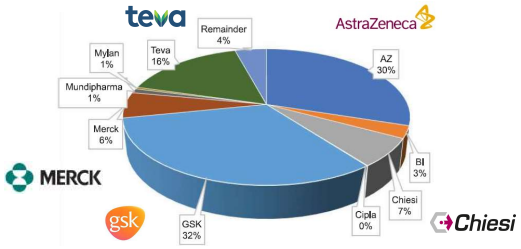


**Figure 2.** pMDI market share (by value) in Europe and the US (Q2, 2019). Adopted from Pritchard (2022) [2]

## Physical Properties

- HFO-1234ze(E) has similar physical properties when compared to HFA-134a, the most used medical propellant today.

| Properties | CFC-12 | HFA-134a | HFA-227ea | HFA-152a | HFO-1234ze(E) |
|---|---|---|---|---|---|
| Molecular Weight, g/mol | 120.9 | 102.0 | 170.0 | 66.1 | 114.0 |
| Boiling Point, °C | -29.8 | -26.1 | -16.3 | -24.0 | -19.0 |
| Liquid Density (20 °C), g/mL | 1.33 | 1.23 | 1.41 | 0.91 | 1.18 |
| Vapor Pressure (20 °C), bar | 5.67 | 5.72 | 3.89 | 5.13 | 4.27 |
| Water Solubility, ppm | 130 | 2200 | 610 | 1700 | 225 |
| Flame Limits (20 °C) | None | None | None | 3.7–16.9 vol% | None |

**Table 1.** Physical properties of CFC, HFA, and HFO propellants

- HFO-1234ze(E) is nonflammable per ASTM E-681, ISO 10156, and EU A11


**Figure 3.** Flame propagation of propellant streams a) through a burner, and b) after removing the burner

## Environmental Properties

- HFO-1234ze(E) is non-ozone depleting and does not significantly contribute to global warming.

| | HFO-1234ze(E) | HFA-152a | HFA-134a | HFA-227ea |
|---|---|---|---|---|
| GWP (versus $CO_2$, 100 year ITH) | <1 | 138 | 1300 | 3350 |
| Atmospheric Lifetime (years) | 0.04 | 1.4 | 13.8 | 33 |
| VOC Status | Exempt | Exempt | Exempt | Exempt |

**Table 2.** Environmental properties of current medical propellants

- The alkene functional group rapidly reacts with oxygen radicals, resulting in carbon dioxide and hydrofluoric acid
  - Noted to have negligible environmental impact [3,4]
- Estimated carbon emissions for HFO-1234ze(E) inhalers is 3-7 g $CO_2$ eq.

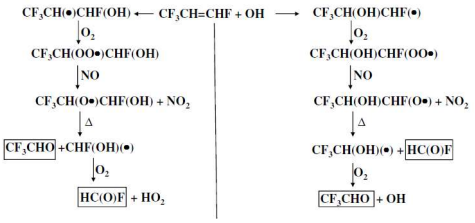


**Figure 4.**
Decomposition pathway of HFO-1234ze(E) in the atmosphere. Adopted from Javadi et al., 2008 [3]

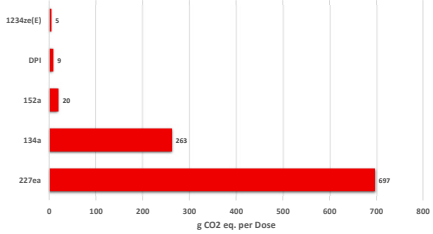


**Figure 5.** Illustrated estimates of carbon emissions of inhalers using various propellants. One dose is equivalent to 1 actuation of a DPI or 2 actuations of a pMDI. Data adopted from Jeswani, 2019 [5]

## Toxicology

- HFO-1234ze(E) has been extensively studied for toxicological effects

| Toxicology package component | Species (duration) | GLP status | Ongoing / Complete | Data support progression? |
|---|---|---|---|---|
| Genetic toxicology | In-vitro, in-vivo | GLP | Complete | ✓ |
| Acute toxicology | Rodent | GLP | Complete | ✓ |
| Chronic toxicology | Rodent (6M) & Non-rodent (9M) | GLP | Complete | ✓ |
| Safety pharmacology | Rodent & non-rodent | GLP | Complete | ✓ |
| Toxicokinetics | Rodent & non-rodent | GLP | Complete | ✓ |
| Reproductive toxicology | Rodent & non-rodent | GLP | Complete | ✓ |
| Carcinogenicity | 2 x rodent (2Y) | GLP | Ongoing | Report 2024 |
| Dermal | Rabbit | GLP | Complete | Not applicable |

**Table 3.** Toxicology tests conducted on HFO-1234ze(E)

- A Phase 1 trial by AstraZeneca showed similar safety and tolerability to the currently marketed product [6].

## Performance

- Three APIs were formulated in HFO-1234ze(E) and sedimentation rates were shown to be comparable for APIs in HFA-134a

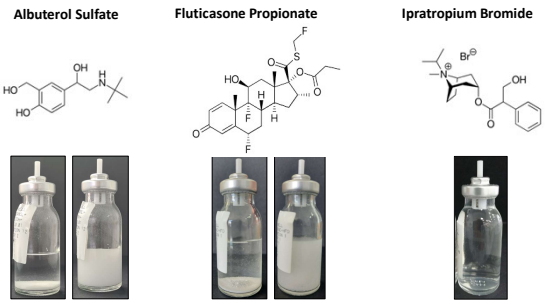


**Figure 6.** APIs formulated in HFO-1234ze(E). Suspension formulations are shown prior and post agitation

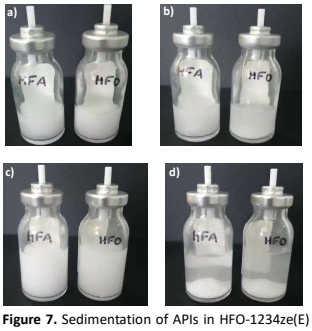


**Figure 7.** Sedimentation of APIs in HFO-1234ze(E) and HFA-134a. a) Albuterol sulfate at T = 0 and, b) T = 120 seconds, c) Fluticasone propionate at T = 0 and, d) T = 60 seconds

- Performance and stability testing is currently ongoing

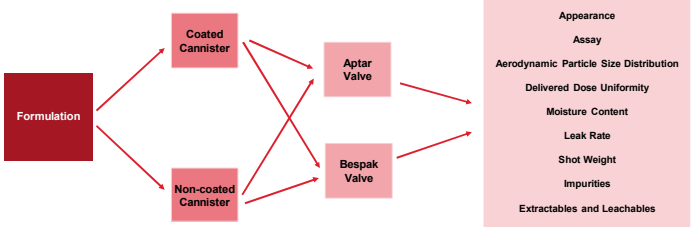


**Figure 8.** Design of experiments for performance and stability testing procedure over 6 months at 40 °C and 75% relative humidity

## Commercial-Scale Manufacturing

- cGMP distillation of HFO-1234ze(E) to ≥99.99% purity
- Pilot scale cGMP manufacturing began in Q2 2020 in Buffalo, NY
- Commercial scale cGMP production began in Q3 2022 in Baton Rouge, LA

**Figure 9.** The Buffalo Research Lab's Pilot Plant (left) and Baton Rouge's Commercial Plant (right)

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**Citations**

[1] National Health Services, England: Primary Care Networks – plans for 2021/22 and 2022/23.

[2] Pritchard JN: Is the Climate Right for a New pMDI Propellant? Respiratory Drug Delivery 2022

[3] Javadi MS, Søndergaard R, Nielsen OJ, Hurley MD, Wallington TJ: Atmospheric chemistry of trans-CF3CH=CHF: Products and mechanisms of hydroxyl radical and chlorine atom-initiated oxidation. Atmos Chem Phys 2008, 8: 3141–3147

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[6] Aurivillius M, Dunsire L, Bednarczyk A, Kokot M, Madriaga J, Mei J, Collison K, Surujbally R, Gillen M: Reducing environmental impact of pressurized metered dose inhalers: relative bioavailability of budesonide/glycopyrronium/formoterol with novel propellant formulations in healthy subjects. American Thoracic Society International Conference, 2022