24 September 2023

# Global Initiative for Asthma (GINA) submission to ECHA REACH on proposal to restrict PFAS

**GINA response to consultation on proposed restriction on the manufacture, placing on the market and use of per- and polyfluoroalkyl substances (PFAS)**

## Use sector: Medical devices. Sub-use: Propellants in metered dose inhalers (MDIs)

## About GINA

The Global Initiative for Asthma (GINA) is an international non-profit organisation that works with healthcare professionals, health officials and the general public to raise awareness of asthma and improve its management asthma worldwide. GINA is an independent organisation with no financial links to industry, funded solely through sale and licensing of its educational publications. Members of the GINA Board of Directors are drawn globally from leaders with an outstanding demonstrated commitment to asthma research, asthma clinical management, public health and patient advocacy. GINA Science Committee members are highly experienced asthma experts from around the world, who continually review and synthesise scientific evidence to provide guidance on asthma prevention, diagnosis and management.

GINA shares concerns about global environmental health and supports efforts to reduce exposure to per- and polyfluoroalkyl substances (PFAS), but we warn about serious unintended medical consequences of the proposed banning of propellants that are essential for survival and safety of patients with respiratory conditions.

## Comments on Annex XV restriction report

Our comments focus on PFAS applications in metered-dose inhalers used to deliver respiratory medicines.

**Coatings of Metered Dose Inhalers (MDIs):** We welcome the proposed 12-year derogation for coatings of metered-dose inhalers.

**Propellants in Metered Dose Inhalers (MDIs):** We request a change in the status of three PFAS propellants in pressurised metered-dose inhalers (pMDIs). These propellants (HFC-134a, HFC-227ea and HFO-1234ze(E)) are essential for the delivery to the patient of the medications contained in the pMDI. However, all three are currently classified as Restriction Option 1 (RO1) status, i.e. they would be subject to a full ban with no derogations and a transition period of only 18 months.

**For the *current* propellants HFC-134a and HFC-227ea**, we request a change from RO1 to RO2 status, providing a 12-year derogation, with the same considerations as for coatings of metered dose inhalers; that is:

- Technically and economically feasible alternatives are **NOT** generally available.
- Substitution potential at entry into force is **VERY LIMITED**.
- The lack of technically feasible alternatives and the high societal value of the medicinal product indicates that **a full ban would be associated with high socio-economic costs in the EU and also especially in persons with lung diseases in poorly resourced countries**.
- A 12-year derogation is warranted because **identification, development and certification of alternatives would take more than five years to complete**.

**For the future propellant HFO-1234ze(E)**, we request exemption from the ban, or a time-unlimited derogation because:

- Technically and economically feasible alternatives are **NOT** available.
- There is **NO** substitution potential at entry into force.
- The lack of technically feasible alternatives and the high societal value of the medicinal product indicates that a full ban or even 12-year derogation **would be associated with high socio-economic costs in the EU, and also especially in persons with lung diseases in poorly resourced countries**.
- Exemption or time-unlimited derogation is warranted for this propellant because **identification, development and certification of alternatives would take more than 12 years** to complete.

**Key points**

**Pressurised metered-dose inhalers (pMDIs) are used to deliver essential medicines for patients with asthma and COPD.** In these inhalers, **a propellant is essential to deliver the medicine to the patient's lungs.** For many patients, **particularly children and the elderly,** pMDIs cannot be substituted with any other devices, and some regions of the world do not have access to alternative types of inhalers.

Three propellants for use in pMDIs would be affected by the proposed RO1 ban. Two of them (HFC-134a and HFC-227ea) are currently in widespread use in pMDIs around the world and the other (HFO-1234ze(E)), which has very low global warming potential (GWP), is being developed to replace the current propellants.

**A ban on these three propellants would have serious unintended medical consequences**, putting patients' health and lives at significant risk.

**A different propellant cannot simply be substituted in medical devices**. Many years are required to develop devices containing new propellants because they must pass stringent clinical tests and regulatory processes.

**Delayed implementation of PFAS restrictions should apply to pMDI propellants**, to allow time for new devices with new propellants to be tested for efficacy and safety, approved for use, and manufactured in sufficient quantity to meet needs of patients, both in Europe and in global export markets.

## Impossibility of substitution with alternatives for medical needs within the proposed timeframe

The propellants in currently available pMDIs are hydrofluoroalkanes HFC-134a and HFC-227ea. These will be phased out under proposed fluorinated gas restrictions[1] in the transition to alternatives with low GWP. Both of these propellants are also classified as PFAS.

However, pMDIs using alternative propellant will not become available for several years. As International Pharmaceutical Aerosol Consortium (IPAC), and International Pharmaceutical Aerosol Consortium on Regulation and Sciences (IPAC-RS) have explained:[2]

*It is not possible to simply "drop in" an alternative medical propellant to MDIs. Propellants for medical uses must be non-toxic and must have specific physico-chemical characteristics to enable appropriate*

[1] European Commission. Proposal for a regulation of the European Parliament and of the Council on fluorinated greenhouse gases, amending Directive (EU) 2019/1937 and repealing Regulation (EU) No 517/2014. COM(2022) 150 final. European Commission, 2022. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52022PC0150

European Parliament. P9_TA(2023)0092. Fluorinated gases regulation. Fluorinated gases regulation Amendments adopted by the European Parliament on 30 March 2023 on the proposal for a regulation of the European Parliament and of the Council on fluorinated greenhouse gases, amending Directive (EU) 2019/1937 and repealing Regulation (EU) No 517/2014 (COM(2022)0150 – C9-0142/2022 – 2022/0099(COD)). (Ordinary legislative procedure: first reading): European Parliament; 2023. Available at: https://www.europarl.europa.eu/doceo/document/TA-9-2023- 0092_EN.pdf

[2] International Pharmaceutical Aerosol Consortium (IPAC), International Pharmaceutical Aerosol Consortium on Regulation and Sciences (IPAC-RS). Preliminary joint comments to ECHA REACH on proposal to restrict PFAS. May 2023.

*performance, meeting high standards of safety and efficacy; they cannot be replaced easily. Ensuring that a new propellant is safe for patients, compatible with the device components and formulation, and supports required particle size distributions and delivered dose uniformity, is an extensive, resource-intensive process. The change in propellants also impacts many elements of the supply chain, including elastomers, valves, and any other device components in the drug delivery pathway. Many of these must be tested and/or redesigned with the new propellant for compatibility and final product tested for leachables. New manufacturing equipment must be developed and built to adapt to the characteristics of any new medical propellants (e.g., flammability). It is also important to understand that these changes involve regulatory assessment, and depend on regulatory approval, by the European Medicines Agency (EMA) and national regulatory authorities.*

EMA has advised the pharmaceutical industry that: *propellant replacement constitutes a major change to the finished product formulation with potential impact also on the construction of the inhaler; therefore, data confirming maintenance of adequate finished product performance need to be provided for each modified product. In addition, data addressing possible toxicity and local tolerance of novel propellants need to be provided*.[3] The EMA guide sets out rigorous data requirements.

Substitution of current propellants within 18 months of finalising the proposed restrictions is therefore not technically or economically feasible – this would risk the health of patients in Europe and elsewhere.

IPAC/IPAC-RS have explained that:[4] *[p]rematurely banning these essential products could lead to drug shortages of essential, life-saving medicines. A significant proportion of medicines manufactured in Europe are exported around the world. Adequate time must be provided to allow replacement products to be developed, tested, and approved by medicines regulators and for patients to be safely and seamlessly transitioned.*

pMDIs using new, lower-GWP propellants are under development[5] to replace the current high-GWP propellants (HFC-134a and HFC-227ea). Although the new propellants are already available for other industrial applications, pMDIs containing them will not be available for several years. Moreover, one of the only two future pMDIs announced to date contains a propellant (HFC-152A) that is subject to phase-down under EU F-gas legislation.[6]

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[3] European Medicines Agency Committee for Medicinal Products for Human Use. Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers. EMA/CHMP/83033/2023. European Medicines Agency, 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-data-requirements-when-replacing-hydrofluorocarbons-propellants-oral-pressurised_en.pdf

[4] International Pharmaceutical Aerosol Consortium (IPAC), International Pharmaceutical Aerosol Consortium on Regulation and Sciences (IPAC-RS). Preliminary joint comments to ECHA REACH on proposal to restrict PFAS. May 2023.

[5] Honeywell. Honeywell teams with AstraZeneca to develop next-generation respiratory inhalers that use near-zero global warming potential propellant. Honeywell, 2022. https://www.honeywell.com/us/en/press/2022/02/honeywell-teams-with-astrazeneca-to-develop-next-generation-respiratory-inhalers-that-use-near-zero-global-warming-potential-propellant ; Chiesi. Chiesi outlines €350 million investment and announces the development of the first carbon minimal pressurised Metered Dose Inhaler (pMDI) for Asthma and COPD: Chiesi, 2019. https://www.chiesi.uk.com/img/news/613_final-021219_chiesi-investment-in-carbon-minimal-pmdis-december-2019.pdf

[6] European Commission. ANNEXES to the Proposal for a Regulation of the European Parliament and of the Council on fluorinated greenhouse gases, amending Directive (EU) 2019/1937 and repealing Regulation (EU) No 517/2014. Annex to: European Commission. Proposal for a regulation of the European Parliament and of the Council on fluorinated greenhouse gases, amending Directive (EU) 2019/1937 and repealing Regulation (EU) No 517/2014. COM(2022) 150 final. European Commission, 2022. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52022PC0150

The other new propellant, HFO-1234ze(E) (trans- 1,3,3,3-tetrafluoroprop-1- ene; tetrafluoropropene, Honeywell),[7] is reported to have extremely low GWP, but it is currently classified as a PFAS. An immediate ban on this propellant would set back by many years efforts to reduce global warming associated with respiratory treatments, and leave no potential replacement for delivery of essential medicines.

GINA is concerned by inconsistency in the ECHA regulations proposed for inhalers, compared with that for other medications; derogation is provided for active medications and for the lining of the pMDI canister, but not for the ingredient that is essential for the delivery of the active medication (the propellant) and without which patients will be denied essential and life-saving medications.

## The medicinal product has a high societal value

Inhalation remains the optimal mode of medication delivery for patients with asthma and chronic obstructive pulmonary disease (COPD).

**pMDIs with spacers are essential for young children and for many older patients**, as they are unable to use the alternative inhaled drug delivery devices such as dry-powder inhalers (DPIs).[8] For all age groups, selecting the right inhaler for the individual patient is crucial to reduce patients' symptom burden and risk of severe attacks requiring emergency treatment and hospitalization, and even death. Furthermore, **not all treatments required for the management of asthma and COPD are available in DPI formulations**, nor are they likely to be in the next five years. In addition, **DPIs are not widely available or used in low-income countries**, owing to their greater cost.[9]

Therefore, **global access to pMDIs remains crucial for people with asthma and COPD**. The potential harm to persons with asthma and COPD, if access to pMDIs is even temporally restricted, may be gauged from the following facts:

- In 2019, 3.20 million persons died from COPD and 455,000 from asthma.[10] Ninety-five per cent of deaths from asthma and 84% of deaths from COPD were in low- and middle-income countries (LMICs),[11] and the heterogeneity of mortality rates is strongly associated with socio-economic factors.[10]
- The widening gap between morbidity and mortality from asthma in high- versus lower-income countries is attributable to the lack of access to medications in inhaler form, as treatments in oral forms have little efficacy.[12]

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[7] Honeywell. Honeywell teams with AstraZeneca to develop next-generation respiratory inhalers that use near-zero global warming potential propellant. Honeywell, 2022. https://www.honeywell.com/us/en/press/2022/02/honeywell-teams-with-astrazeneca-to-develop-next-generation-respiratory-inhalers-that-use-near-zero-global-warming-potential-propellant

[8] Levy ML, Bateman ED, Allan K, et al. Global access and patient safety in the transition to environmentally friendly respiratory inhalers: the Global Initiative for Asthma perspective. *Lancet*. 2023;402(10406):1012-1016. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01358-2/fulltext

[9] Kponee-Shovein K, Marvel J, Ishikawa R, et al. Impact of choice of inhalers for asthma care on global carbon footprint and societal costs: a long-term economic evaluation. J Med Econ. 2022;25(1):940-953. doi:10.1080/13696998.2022.2088196 https://www.tandfonline.com/doi/full/10.1080/13696998.2022.2088196

[10] Li X, Cao X, Guo M, Xie M, Liu X. Trends and risk factors of mortality and disability adjusted life years for chronic respiratory diseases from 1990 to 2017: systematic analysis for the Global Burden of Disease Study 2017 [published correction appears in BMJ. 2020 Aug 6;370:m3150]. BMJ. 2020;368:m234. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7190065

[11] WHO Global Health Estimates 2019 https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death

[12] Meghji J, Mortimer K, Agusti A, Allwood BW, Asher I, Bateman ED, et al. Improving lung health in low-income and middle-income countries: from challenges to solutions. Lancet. 2021;397:928-40. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00458-X/fulltext

- **pMDIs are the main inhalation device used in LMICs** as they are less costly, especially when in generic formulations.[13]
- However, the **production of generic pMDIs in LMICs is made possible through the import of essential components (for example, the dosing mechanism) and the propellant from high-income countries.** The generic inhalers, like the original ethical devices, require approval from regulators in each country in which they are used. The regulatory process involves numerous steps, and it is estimated that transition to novel MDI propellants would likely take at least a decade based on the timeline for the transition from chlorofluorocarbon-based MDIs.[13, 14]

Despite the efforts of the World Health Organization (WHO) and several United Nations resolutions to improve access to inhalers for all,[15] access to inhalers remains the major barrier to reducing asthma and COPD mortality in LMICs.[16] Improving access to inhalers is a priority in recent WHO resolutions, for example WHA66.10 of 2013, the global action plan for the prevention and control of non-communicable diseases 2013–2020, subsequently extended to 2030 (WHA72(11) (2019) and the WHO's Implementation Roadmap 2023–2030 for the Global Action Plan on the Prevention and Control of NCDs (75th World Health Assembly 2022).

With the planned phasing-out of currently used high-GWP propellants beginning in 2028,[17] GINA is concerned that the supply of pMDIs and propellants for LMIC will diminish or stop, owing to inevitable price increases for developing the new products, competing demand from other sectors for propellant gases for other uses, and lengthy delays associated with obtaining regulatory approval for new medical products within the EU and each country globally (referred to in the IPAC/IPAC-RS submission[18]).

Thus, GINA, as an international non-profit organisation with a global perspective, while fully supporting actions to replace harmful propellants and devices, wishes to draw attention to the serious unintended consequences of the proposed PFAS restrictions for patients both within and outside the EU, particularly for LMICs, given the potential to exacerbate serious global inequities in health care through major disruption of the availability and affordability of essential inhaled medicines.

As stated in the United Nations commentary on the Sustainable Development Goals: *[e]nding poverty and other deprivations must go hand in hand with strategies that improve health and education, reduce inequality and spur economic growth – all while tackling climate change and working to preserve our oceans and forests.*[19]

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[13] Woodcock A, Beeh KM, Sagara H, et al. The environmental impact of inhaled therapy: making informed treatment choices. Eur Respir J. 2022;60(1):2102106. https://erj.ersjournals.com/content/erj/60/1/2102106.full.pdf

[14] Wilkinson AJ, Braggins R, Steinbach I, et al. Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. BMJ Open. 2019;9(10):e028763.

[15] United Nations General Assembly Resolution 66/2 of 2011. Political Declaration of the High-level Meeting of the General Assembly of the Prevention and Control of Non-communicable Diseases.; United Nations General Assembly Resolution 70/01 of 2015. Transforming our world: the 2030 Agenda for Sustainable Development. 3. United Nations General Assembly Resolution 74/2 of 2019. Political Declaration of the High-Level Plenary Meeting on Universal Health Coverage: resolution adopted by the General Assembly.

[16] Stolbrink M, Thomson H, Hadfield RM, et al. The availability, cost, and affordability of essential medicines for asthma and COPD in low-income and middle-income countries: a systematic review. Lancet Global Health 2022;10:e1423-42.

[17] European Commission. Proposal for a regulation of the European Parliament and of the Council on fluorinated greenhouse gases, amending Directive (EU) 2019/1937 and repealing Regulation (EU) No 517/2014. COM(2022) 150 final. European Commission, 2022. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52022PC0150

[18] International Pharmaceutical Aerosol Consortium (IPAC), International Pharmaceutical Aerosol Consortium on Regulation and Sciences (IPAC-RS). Preliminary joint comments to ECHA REACH on proposal to restrict PFAS. May 2023.

[19] The United Nations Sustainable Development Goals Project. https://www.unsdgproject.com/unpacking-the-goals.html

## Conclusion

GINA submits that the proposed ban on propellants which are essential for function of pMDIs will have a profoundly negative effect on patients with asthma (particularly young children and the elderly) or COPD who rely on this treatment, and will severely exacerbate inequalities in healthcare globally.

For these reasons, we request 12-year derogation for the current high-GWP propellants (HFC-134a and HFC-227ea) and exemption or indefinite derogation for the future low-GWP propellant HFO-1234ze(E)), because of the lack of currently available alternatives and the long time to develop, test, regulate and manufacture new options for safe delivery of essential medicines.

We urge all involved in regulatory discussions relevant to medical inhalers to prioritise the health of those within and beyond Europe – including people with asthma in LMICs, who already bear the brunt of impact of environmental degradation.