AstraZeneca PLC response to ECHA public consultation on PFAS REACH Restriction Proposal

This document has been prepared by AstraZeneca for the European Chemicals Agency (ECHA), following a public consultation on the proposed restriction of per- and polyfluoroalkyl substances (PFAS*).*

Table of Contents

7 June 2023

1- Executive summary

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology.

AstraZeneca supports the EU's goal to protect the environment and public health.[1,2] We comply with regulations and ethical and sustainability standards across our manufacturing chain to mitigate risks to people and the environment.[3] We are an industry leader in accelerating sustainable healthcare innovation while lowering the environmental burden of healthcare.[4]

We welcome the chance to respond to the European Chemicals Agency (ECHA) public consultation on the per- and polyfluoroalkyl substances (PFAS) REACH restriction proposal,[5] (hereafter 'restriction proposal'), because PFAS are used across many medicines' lifespans and play a role in the research, development, and manufacturing of life-saving medicines.[6,7]

Our first response to the consultation focuses on the application of PFAS in respiratory medicines, in particular the use of fluorinated substance HFO-1234ze(E), a novel propellant under development for use in pressurised metered-dose inhalers (pMDIs) that has near-zero Global Warming Potential (GWP).[8,9] pMDIs are an important therapeutic option for the millions of patients globally with respiratory diseases, as these inhaled medicines reduce chronic obstructive pulmonary disease (COPD) exacerbations and asthma attacks, which are potentially life-threatening events.[10,11] These diseases are difficult and complex to manage and carry a heavy burden for patients, healthcare systems and society.[10,11,12]

AstraZeneca notes that HFO-1234ze(E) has been classified as a PFAS within the restriction proposal based purely on its chemical structure. However, HFO-1234ze(E) is backed by comprehensive evidence demonstrating that this substance is non-persistent, non-bio accumulative and non-toxic.[13,14]

AstraZeneca, therefore, recommends exempting/excluding from the restriction proposal substances such as the novel pMDI propellant HFO-1234ze(E), as it does not fulfil the criteria of persistence, bioaccumulation and toxicity, and to ensure patient access to life-saving and essential pMDI medicines is maintained.

Please consider further information below.

2- Detailed rationale

I. pMDIs deliver life-saving medicines with essential socio-economic benefits.

pMDIs are an important therapeutic option for patients with respiratory illnesses recommended by international guidelines.[15] These products answer to specific medical needs and include several medicines listed as essential by the World Health Organization.[16]

Nearly 550 million people globally and nearly 60 million people in Europe live with complex chronic respiratory diseases,[17,18,19] including asthma and COPD, with increasing prevalence. In 2016, 339,000 people in the EU died from respiratory diseases.[19] These diseases account for approximately 4.1 million deaths per year globally.[20]

Respiratory diseases such as COPD are serious, complex to manage and can take a significant toll on individuals.[10,11,12] COPD is a long-term, progressive disease which can cause obstruction of airflow in the lungs resulting in debilitating bouts of breathlessness.[10] COPD is the third leading cause of death worldwide and is estimated to affect up to one in 10 adults over the age of 40 in the EU.[21,22] Improving lung function, reducing exacerbations and managing daily symptoms such as breathlessness are important treatment goals in the management of COPD.[10] Inhaled medicines aim to control symptoms, prevent disease progression, reduce mortality and improve patient outcomes overall.[10]

Inhaled medicines delivered to patients by pMDIs are the most used medicines in respiratory care in Europe and worldwide. In 2021, pMDIs accounted for 76% of all inhaler use in Europe, and 78% of global use.[23] pMDIs are an important therapeutic option for patients, particularly where familiarity with the device, limited lung function, young or advanced age or reduced dexterity or cognition are considerations.[24,25,26,27] These medicines are not interchangeable and switching should only be based on clinical need and individual patient assessment. [28,29]

pMDIs contain an active pharmaceutical ingredient (API) either suspended or solubilised in a propellant which delivers the medicine to the lungs of the patient.[30] APIs, which are exempt from the restriction proposal, cannot be delivered without the propellant. Maintaining propellant options for pMDIs therefore, is critical to ensuring the flexibility to formulate APIs whose varying physical properties secure the efficacy and safety of a medicine whilst being compatible with the various device component materials that constitute the device.[31]

The delivery of the therapeutic ingredient relies on the propellant in the pMDI. There are currently two fluorinated greenhouse gases (F-Gases) used as propellants – HFA-227ea and HFA-134a. Both are subject to production and consumption phase-down following the Kigali Amendment to the Montreal Protocol and the soon to-be-adopted EU F-Gas Regulation, and in accordance with appropriate transition timelines.[32,33] Maintaining propellant options for pMDIs has been important to ensure flexibility in formulating APIs with widely varying physical properties. In the same vein, it remains important to maintain options for next-generation hydrofluoroolefins (HFO) propellants transitioning away from current hydrofluorocarbons (HFC) gases with high GWP.[34]

There are, currently, two alternative propellants in development for medical use in pMDIs – HFC-152a (which does not fall in the proposed PFAS definition of this draft restriction but is subject to phase down under the Kigali Amendment and EU F-Gas Regulation, see section III), and HFO-1234ze(E) (which falls

within the scope of this restriction proposal, but not subject to phase down under the Kigali Amendment and EU F-Gas Regulation).[35] Other alternatives have been investigated by the industry but are considered unsuitable for use in pMDIs.[36]

In accordance with AstraZeneca's climate ambitions and global and EU regulation phasing down use of F-Gases, AstraZeneca has committed to transitioning its portfolio of inhaled respiratory medicines to the next-generation propellant HFO-1234ze(E) with an ultra-low GWP of 1.37. It has up to 99.9% less GWP than propellants currently used in respiratory medicines, and therefore presents a viable alternative for long-term respiratory patient care with pMDIs.[8,9]

Adoption of these near-zero GWP propellants will enable healthcare providers and patients to be able to contribute to reduced carbon emissions without having to accept a less effective and safe approach to therapy.[37] The proposed restriction proposal, however, could have the unintended consequence of limiting patient options for essential life-saving and innovative medicines.[15]

II. AstraZeneca's position on PFAS restriction aligns with the United Nations Environment Programme, recognising that not all classed PFAS should be grouped together to assess human health risk.
The universal EU PFAS restriction proposal does not take into account that PFAS substances do not all exhibit the same properties or risks to human health and the environment, nor industry-wide efforts to deliver non-persistent, non-bio accumulative and non-toxic substances.

The 2022 Assessment Report from the United Nations Environment Programme supports the AstraZeneca position with a statement from a majority panel of experts who agreed that "*all PFAS should not be grouped together, chemical structure and persistence alone are not sufficient for grouping PFAS for the purposes of assessing human health risk,"* and furthermore that "*it is inappropriate to assume equal toxicity/potency across the diverse class of PFAS*."[38]

While the next-generation propellant for pMDIs, HFO-1234ze(E), falls under the OECD PFAS definition because of its chemical structure, it is classified according to the ECHA dossier assessment as non-persistent, non-bio accumulative and non-toxic, and its breakdown does not present a risk to the environment.[13,39,40] It is a well-studied and a fully REACH-registered substance, which should not be grouped with all other PFAS for hazard, exposure and risks characterisation purposes.

A) **Evidence that HFO-1234ze(E) is not persistent**: HFO-1234ze(E) has a short atmospheric lifetime of 19 days. The short atmospheric lifetime of HFO-1234ze(E) is a result of the alkene (>C=C<) functional group which enables rapid reaction with OH radicals, a common atmospheric oxidant. The atmospheric breakdown by OH radical initiated oxidation of HFO-1234ze(E) is summarised below. The initial addition of OH radicals to the olefinic double bond, followed by addition of O_2 and subsequent peroxy radical chemistry results in the formation of the intermediates, trifluoroacetaldehyde (CF_3CHO) and formyl fluoride (HC(O)F).[41,42]

   While formyl fluoride decomposes via aqueous-phase chemistry in clouds or water droplets, to CO_2 and hydrogen fluoride (HF), the atmospheric chemistry of trifluoroacetaldehyde is more complex, with multiple decomposition pathways being active. Photolysis of CF_3CHO leads predominantly to

trifluoromethyl (CF_3) and HCO radicals which eventually form HF and CO_2 as end products.[43] Besides photolysis, a minor fraction of CF_3CHO decomposes via OH radical initiated oxidation, which leads to HF and CO_2 as end products. It is worth noting here, that while fluorocarbons degrade to HF, which subsequently is deposited via rain, they do not contribute to environmental acidification as compared with other much larger acid sources (natural or anthropogenic).[39] In regions remote from urbanisation, where HO_2 radicals dominate the organic peroxy radical chemistry, trifluoracetic acid (TFA) may also be formed via OH-initiated oxidation of CF_3CHO. Based on atmospheric global modelling, 2% of HFO-1234ze(E) is expected to be converted to TFA through atmospheric decomposition.[44]

As described below, HFO-1234ze(E) was evaluated in a range of toxicology studies whereby animals were directly exposed to HFO-1234ze(E), at high concentrations in the breathable air. In these studies, HFO-1234ze(E) was rapidly cleared from the blood of treated animals demonstrating that it is not persistent.[45,46,47,48]

HFO-1234ze(E) is an excellent example of why a broad PFAS definition and a class-based approach is not appropriate. Based on all the evidence and decision criteria for persistence, it is concluded in the ECHA dossier that HFO-1234ze(E) does not meet P (persistent) or vP (very persistent) criteria of ECHA. The last point to address is whether any of the environmental degradation products of HFO-1234ze(E) justify inclusion in the proposed REACH legislation.[49] As discussed above, studies have shown that HFO-1234ze(E) degrades in the lower atmosphere rapidly and almost entirely (>98%) to HF and CO_2.[44] Overall, the evidence is clear that HFO-1234ze(E) is not persistent.

B) **Evidence that HFO-1234ze(E) does not-bioaccumulate:** The systemic exposure of HFO-1234ze(E) was evaluated following single and repeat administration in mice, rats and dogs. To achieve this, blood samples were collected at a series of timepoints after inhalation and analysed for HFO-1234ze(E) concentration. In all species, and on all occasions, the highest blood concentration of HFO-1234ze(E) was determined in samples collected immediately after dosing. Thereafter, blood HFO-1234ze(E) concentrations declined very rapidly. In general, HFO1234ze(E) was quantifiable in samples collected within 30 minutes post exposure, except at very high dose levels whereby HFO-1234ze(E) was occasionally quantifiable at low levels for a short period thereafter. There were no notable differences in blood HFO-1234ze(E) concentrations following single or repeat exposures. Overall, these data provide strong evidence- that HFO-1234ze(E) is rapidly removed from the body following exposure and does not accumulate even at exposure levels which are several thousand-fold higher than expected in humans given typical MDI usage (2 x 2 inhalations/day). Taking this into account, the evidence strongly supports that HFO-1234ze(E) does not bio accumulate.[45,46,47,48]

C) **Evidence that HFO-1234ze(E) is not of toxicological concern:** To support its use as a medical grade propellant in pMDI medicines, HFO-1234ze(E) has been evaluated in a series of single and repeat dose inhalation toxicology studies as well as reproductive toxicology (including exposure of juvenile animals), safety pharmacology and genetic toxicology assessments. These studies are summarised in Table 1.[45,46,47,48]

Across the toxicology studies, HFO-1234ze(E) was evaluated at a range of exposure. To achieve this, separate groups of animals were exposed to different air concentrations of HFO-1234ze(E) for

defined periods of time on single or repeated occasions. The achieved exposures in the toxicology studies (based on the HFO-1234ze(E) concentration, duration of exposure and animal body weight), were up to several thousand-fold greater than those expected in humans given typical MDI usage (2 x 2 inhalations/day). These studies included endpoints such as the analysis of blood (haematology and clinical pathology) and pathology evaluation of tissues. There were no findings of toxicological concern in these studies. Further, there was an absence of any findings which could be considered to reflect the typical toxicology of PFAS molecules, which are well reported and may include increases in cholesterol, alterations in liver enzymes, complications related to fertility and pregnancy, immune alterations, and cancer.[45,46,47,48]

The development path required to support use or include a propellant such as HFO-1234ze(E) in a medicine involves process validation, pre-clinical and clinical studies to ensure their safety and efficacy and will be subject to regulatory review and approval by the European Medicines Agency (EMA).[50] The non-clinical package has been reviewed thoroughly by EMA and other global regulatory authorities inclusive of FDA (US), MHRA (UK), CDE (China), and PMDA (Japan). These regulators have reviewed the package and approved usage of HFO-1234ze(E) in late-stage Phase III clinical trials.[51]

The above also demonstrates that HFO-1234ze(E) risks are already adequately controlled through other regulatory measures. Introducing horizontal legislation which does not account for existing regulatory frameworks may create barriers for pharmaceutical innovation in the EU.

Table 1: Non-clinical toxicology studies with HFO-1234ze(E)

Study type	Route of administration	Species
Genetic toxicology	In-vitro or inhalation (in-vivo)	Bacteria and human lymphocyte cultures and in-vivo (mice and rats)
Acute toxicology	Inhalation	Mouse and Rat
Sub-chronic and chronic toxicology [1]	Inhalation	Mouse (to 3 months) Rat (to 6 months) Dog (to 9 months)
Safety pharmacology • **Central nervous system function** • **Cardiovascular function** • **Respiratory function**	Inhalation	 Rat (repeat dose) Dog (single and repeat dose) Rat and Dog (repeat dose)
Toxicokinetics	Inhalation	Mouse Rat Dog
Reproductive toxicology • **Pre and postnatal development** [2] • **Embryofetal development** • **Juvenile toxicity** [2]	Inhalation	 Rat Rabbit and Rat Rat
Carcinogenicity (2 years repeat dose)[3]	Inhalation	Mouse and Rat (studies ongoing)
Dermal Irritancy	Dermal	Rabbit

1 Animals were exposed to HFO-1234ze(E) by daily inhalation for up to 2 hours/day (mice and dogs) or 4 or 6 hours/day (rats)
2 Conducted as part of a multigeneration toxicology study
3 Carcinogenicity study designs agreed with the US Food and Drug Administration (FDA). Carcinogenicity Advisory Committee. Carcinogenicity studies are ongoing (reports in early 2024).

III. A lack of viable alternatives creates significant uncertainty for manufacturers, healthcare professionals and people living with respiratory diseases.

EU pMDI manufacturers estimate that the safe, global transition of inhaled medicines to low-GWP pMDIs will take at least until 2030.[52] With a novel propellant for use in pMDIs yet to be approved by regulators, the proposed restriction on HFO-1234ze(E) creates significant uncertainty for manufacturers, supply chains, healthcare professionals and people living with respiratory diseases in the EU and globally. Overly broad definitions of PFAS within the restriction proposal risk the transition to next-generation respiratory medicines. All patients with respiratory diseases including asthma and COPD have a right to high quality of care.[53]

Analysis of alternatives

A. Dry powder inhalers (DPIs):

Assessment of the proposed PFAS restriction on DPIs is still ongoing.

While there have been calls to switch patients to low carbon, propellant-free alternatives, such as DPIs, it is important to note that inhaler medicines are not interchangeable.[54] These are complex and difficult to treat diseases[10,11] and non-consensual inhaler device switching has been shown to be associated with lower therapeutic adherence and reduced disease control. A systematic review of the real-world consequences of switching inhaler regimens for non-clinical reasons reported that switching inhaler regimens is a complex issue that can have variable clinical consequences and can harm the patient-doctor relationship and worsen respiratory disease.[54]

pMDIs remain the mainstay inhaler for patients with asthma or COPD in most countries, particularly for those with limited lung function, such as the elderly, the very young, or those undergoing an acute exacerbation.[24,25,26,27] In addition to patient preference, cost is an important factor in considering a wholesale switch from pMDIs to DPIs, as DPIs are more expensive than pMDIs, in addition to costs incurred to healthcare systems such as retraining of healthcare professionals.[55]

Even if mass switching could be achieved, manufacturing capacity of DPI may not be scalable to a level that would serve the 76% of patients in the EU currently relying on pMDIs, if no exemption or exclusion for HFO-1234ze(E) is granted and HFC-152a is phased-out due to F-Gas regulations by the mid-2030s.[23]

Switching from pMDIs to DPIs could cause a significant worsening of other environmental impacts, including human toxicity, marine eutrophication and fossil depletion, likely due to the higher plastic and aluminium content of some DPIs.[56,57]

B. HFC-152a:

HFC-152a is the only potential alternative propellant for use in inhaled medicines, however it is subject to phase-down under the Kigali Amendment, EU F-Gas Regulation and the American Innovation and Manufacturing (AIM) Act, which will see a significant reduction in the production and consumption of the propellant.[33,58] Whereas HFO-1234ze(E) is not subject to this phase down as a result of its reduced environmental impact.

HFC-152a is less technically compatible with certain pMDI formulations, APIs, and/or excipients. The EMA is considering a flammability warning for HFC-152a as the propellant can make the inhaled medicine flammable near an open flame, lit cigarette, or other sources of heat (e.g., hairdryers).[31] Any transition to HFC-152a would require significant investment (hundreds of millions of Euros) to build new HFC-152a compatible manufacturing facilities, primarily related to its flammability, as well as longer transition time and further investment in order to meet the stringent requirements from regulators worldwide including the EMA.[31]

Given HFC-152a is not yet authorised, has an elevated GWP, and has a flammable hazard classification.[31] it is important to preserve HFO-1234ze(E) as an alternative novel propellant for use in respiratory medicines.

3- Proposed amendments to the restriction

Given these considerations, it is important that HFO-1234ze(E) is exempt/excluded from the PFAS restriction given the evidence to support its non-persistent, non-bio accumulative and non-toxic qualities and to ensure patient access to life-saving and essential pMDI medicines is maintained.

Specifically, there is a need for the following amendments to Annex XVII Proposed restriction entry PFAS (Restriction Option 2) column 2, paragraph 4.
By way of derogation paragraphs 1 and 2 shall not apply to:

- active substances in biocidal products within the scope of Regulation (EU) 528/2012
- active substances in plant protection products within the scope of Regulation (EC) 1107/2009
- active substances in human and veterinary medicinal products within the scope of Regulation (EC) No 726/2004, Regulation (EU) 2019/6 and Directive 2001/83/EC
- non-persistent, non-bio accumulative and non-toxic substances authorised in accordance with Regulation (EU) 2017/745, Regulation (EU) 2019/6, Regulation (EU) [COM(2023) 193] and Directive [COM(2023) 192]/EU

AstraZeneca looks forward to working with ECHA and relevant stakeholders to support sustainable and safe practices in the healthcare sector, which continue to meet patient, public health, and environmental needs.

Further considerations from AstraZeneca regarding derogations for substances used in pMDIs, reflecting appropriate timelines for transitioning such substances without risk to patient outcomes, will follow in upcoming responses to the consultation.

4- References

[1] European Parliament – Public health. Available at: https://www.europarl.europa.eu/factsheets/en/sheet/49/public-health. Accessed May 2023.
[2] European Union – towards and greener and more sustainable Europe. Available at: https://european-union.europa.eu/priorities-and-actions/actions-topic/environment_en. Accessed May 2023.
[3] AstraZeneca. Ambition Zero Carbon 2022. Available at: https://www.astrazeneca.com/sustainability/environmental-protection/ambition-zero-carbon.html. Accessed May 2023.
[4] Carbon Disclosure Project. Available at: https://www.cdp.net/en/responses?per_page=20&queries%5Bname%5D=astrazeneca&sort_by=project_year&sort_dir=desc. Accessed May 2023.
[5] ECHA / ECHA publishes PFAS restriction proposal. Available at: https://echa.europa.eu/-/echa-publishes-pfas-restriction-proposal. Accessed May 2023.
[6] American Chemistry Council. PFAS: Integral to Life-Saving Drugs. Available at: https://www.americanchemistry.com/chemistry-in-america/chemistries/fluorotechnology-per-and-polyfluoroalkyl-substances-pfas/pfas-integral-to-life-saving-drugs. Accessed May 2023.
[7] Glüge J et al. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). Environ Sci Process Impacts. 2020;22(12):2345-2373.
[8] AstraZeneca Pharmaceuticals. Data on File. Global Warming Potential of HFO-1234ze. (ID: REF-140251).
[9] AstraZeneca. AstraZeneca progresses Ambition Zero Carbon programme with Honeywell partnership to develop next-generation respiratory inhalers. Available at: https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2022/astrazeneca-progresses-ambition-zero-carbon-programme-with-honeywell-partnership-to-develop-next-generation-respiratory-inhalers.html. Accessed May 2023.
[10] GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023. Available at: https://goldcopd.org/2023-gold-report-2/. Accessed: May 2023.
[11] The Global Asthma Report 2022. Available at: http://globalasthmareport.org/. Accessed: May 2023.
[12] National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Section 2, Definition, Pathophysiology and Pathogenesis of Asthma, and Natural History of Asthma. Available at: https://www.ncbi.nlm.nih.gov/books/NBK7223/. Accessed May 2023.
[13] ECHA Dossier - 1-Propene, 1,3,3,3-tetrafluoro-. Available at: https://echa.europa.eu/registration-dossier/-/registered-dossier/31292/2/3. Accessed May 2023.
[14] Wallington TJ, Sulbaek Andersen MP, Nielsen OJ. Atmospheric chemistry of short-chain haloolefins: photochemical ozone creation potentials (POCPs), global warming potentials (GWPs), and ozone depletion potentials (ODPs). Chemosphere. 2015;129:135-141.
[15]Global Initiative for Asthma. Global strategy for asthma management and prevention, 2023. Available at: https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf. Accessed: May 2023.
[16] WHO. Model List of Essential Medicines. Available at: https://list.essentialmeds.org/?section=458&indication=&year=&age=&sex=. Accessed: May 2023.
[17] Soriano JB, Kendrick PJ, Paulson KR, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir. Med. 2020;8(6):585-96.
[18] AstraZeneca UK Ltd Data on File. ID: REF-154642. June 2022.
[19] Eurostat. Respiratory diseases statistics. Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Respiratory_diseases_%20statistics&oldid=497079#Deaths_from_diseases_of_the_respiratory_system. Accessed: May 2023.
[20] WHO. Noncommunicable diseases. Available at: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases. Accessed: May 2023.

[21] World Health Organization. The top 10 causes of death. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed May 2023.
[22] Adeloye D, Song P, Zhu Y, et al. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis [published online ahead of print, 2022 Mar 10]. Lancet Respir Med. 2022;S2213-2600(21)00511-7.
[23] Bell J, et al. An Assessment Of Pressurized Metered-dose Inhaler Use In Countries In Europe And The Rest Of The World. Poster Presentation at American Thoracic Society (ATS) international congress, 2023 19-24 May.
[24] Lavorini F. The challenge of delivering therapeutic aerosols to asthma patients. ISRN Allergy. 2013; 102418.
[25] Roche N, et al. The evolution of pressurized metered-dose inhalers from early to modern devices. J Aerosol Med Pulm Drug Deliv. 2016; 4: 311–27.
[26] Laube BL, et al. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J. 2011; 37 (6):1308-31.
[27] Lavorini F, et al. Optimising inhaled pharmacotherapy for elderly patients with chronic obstructive pulmonary disease: the importance of delivery devices. Drugs Aging. 2016; 33 (7): 461–73.
[28] Bjermer L. The Importance of continuity in inhaler device choice for asthma and chronic obstructive pulmonary. Respiration. 2014;88(4):346-52.
[29] Doyle S, et al. What happens to patients who have their asthma device switched without their consent? Prim Care Respir J. 2010; 19 (2): 131–139.
[30] Bing Z, Traini D, Lewis DA, Young P. The solid-state and morphological characteristics of particles generated from solution-based metered dose inhalers: Influence of ethanol concentration and intrinsic drug properties. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2014;443: 345–355.
[31] EMA - Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral 6 pressurised metered dose inhalers. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-data-requirements-when-replacing-hydrofluorocarbons-propellants-oral-pressurised_en.pdf. Accessed May 2023.
[32] United Nations environment programme Montreal protocol. Available at: https://ozone.unep.org/treaties/montreal-protocol. Accessed May 2023.
[33] Harvard Law – International Climate Agreements – The Kigali Amendment, COP26, and Other Agreements. Available at: https://eelp.law.harvard.edu/2022/09/international-climate-agreements-the-kigali-amendment-and-cop26-and-other-agreements/#_ftn1. Accessed May 2023.
[34] European Parliament Think Tank. https://www.europarl.europa.eu/thinktank/en/document/EPRS_BRI(2022)730323. Accessed May 2023.
[35] Kigali amendment 2016. Available at: https://ozone.unep.org/treaties/montreal-protocol/amendments/kigali-amendment-2016-amendment-montreal-protocol-agreed. Accessed May 2023.
[36] United Nations Environment Programme: Medical and Chemicals Technical Options Committee 2018 Assessment Report. Page 25. Available at: https://ozone.unep.org/system/files/documents/MCTOC%20Assessment%20Report%202018.pdf. Accessed May 2023.
[37] Pernigotti D, Stonham C, Panigone S, et al. Reducing carbon footprint of inhalers: analysis of climate and clinical implications of different scenarios in five European countries. BMJ Open Respir Res. 2021;8(1):e001071.
[38] UN environment programme. Environmental Effects of Stratospheric Ozone Depletion, UV Radiation, and Interactions with Climate Change. Available at: https://ozone.unep.org/system/files/documents/EEAP-2022-Assessment-Report-May2023.pdf. Accessed May 2023.
[39] Lindley A, McCulloch, Vink J. 2019. Contribution of Hydrofluorocarbons (HFCs) and Hydrofluoro-Olefins (HFOs) Atmospheric Breakdown Products to Acidification ("Acid Rain") in the EU at Present and in the Future. Open Journal of Air Pollution. 2019;(8)81-95.
[40] Chiappero MS, Malanca FE, Argüello GA, et al. Atmospheric chemistry of perfluoroaldehydes (CxF2x+1CHO) and fluorotelomer aldehydes (CxF2x+1CH2CHO): quantification of the important role of photolysis. J Phys Chem A. 2006;110(43):11944-11953.

[41] Javadi, M. S. et al. 2008. Atmospheric chemistry of trans-CF3CH=CHF: products and mechanisms of hydroxyl radical and chlorine atom initiated oxidation. Atmos. Chem. Phys. Discuss., 8, 1069–1088.
[42] Nilsson E.J.K., Nielsen O.J., Johnson M.S., Hurley M.D., and Wallington T.J. (2009): Atmospheric chemistry of cis-CF3CH=CHF: Kinetics of reactions with OH radicals and O3 and products of OH radical initiated oxidation. Chemical Physics Letters 473 (4-6), 233- 237.
[43] Sulbaek Andersen, P & Nielsen, OJ. Tropospheric photolysis of CF3CHO, Atmospheric Environment, Volume 272, 2022, 118935, ISSN 1352-2310.
[44] ECHA ANNEX XV restriction report. Available at: https://echa.europa.eu/documents/10162/6f4a2076-7221-67a3-64f7-c67cc307f59c. Accessed May 2023.
[45] AstraZeneca Data on File.
[46] AstraZeneca Data on File.
[47] AstraZeneca Data on File.
[48] AstraZeneca Data on File.
[49] REACH standard information requirements (ECHA). Available at: https://echa.europa.eu/standard-information-requirements-recommendations. Accessed May 2023.
[50] Wylie JL, House A, Mauser PJ, et al. Inhaled formulation and device selection: bridging the gap between preclinical species and first-in-human studies. Ther Deliv. 2018;9(5):387-404.
[51] A Study to Assess the Safety of Budesonide/Glycopyrronium/Formoterol Fumarate With the Hydrofluoroolefin Propellant in Participants With Moderate to Very Severe Chronic Obstructive Pulmonary Disease. Available at: https://clinicaltrials.gov/ct2/show/NCT05573464?term=HFO-1234ze%2C+astrazeneca&draw=2&rank=1. Accessed May 2023.
[52] European Commission. Feedback from: International Pharmaceutical Aerosol Consortium. Available at: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12479-Fluorinated-greenhouse-gases-review-of-EU-rules-2015-20-/F3317512_en. Accessed May 2023.
[53] European Federation of Allergy and Airways Diseases Patients' Association. https://www.efanet.org/news/news/4069-efa-looks-back-at-30-years-of-advocating-with-and-for-patients-with-allergy-asthma-and-copd. Accessed May 2023.
[54] Usmani OS, Bosnic-Anticevich S, Dekhuijzen R, et al. Real-World Impact of Nonclinical Inhaler Regimen Switches on Asthma or COPD: A Systematic Review. J Allergy Clin Immunol Pract. 2022;10(10):2624-2637.
[55] Keeley D, Scullion JE, Usmani OS. Minimising the environmental impact of inhaled therapies: problems with policy on low carbon inhalers. Eur Respir J. 2020;55(5):2001122.
[56] Pernigotti D, Stonham C, Panigone S, et al. Reducing carbon footprint of inhalers: analysis of climate and clinical implications of different scenarios in five European countries. BMJ Open Respir Res. 2021;8(1):e001071.
[57] Jeswani, H.K. & Azapagic, A. Life cycle environmental impacts of inhalers. Journal of Cleaner Production, 237**,** 117733.
[58] EPA – Protecting Our Climate by Reducing Use of HFCs. Available at: https://www.epa.gov/climate-hfcs-reduction. Accessed May 2023.