Supplemental Joint IPAC/IPAC-RS Comments on
"PFAS REACH Annex XV Restriction (Public Consultation)"

Requests for Derogation of MDI Propellants HFC-134a and HFC-227ea, and Permanent Exemption or Time-Unlimited Derogation of HFO-1234ze(E) from PFAS REACH Restriction Proposal

Topic: Information on Alternatives and Socio-Economic Implications of Proposed Bans of Medical Propellants in Metered Dose Inhalers (MDIs).

As detailed in our prior submission and supplemented herein, the proposed near-term bans of three medical propellants (HFC-134a, HFC-227ea, and HFO-1234ze(E)) are unsupported by the REACH proposal, inconsistent with conclusions of the European Medicines Agency (EMA) and other regulatory agencies and could represent serious risks for patient care.

1. Brief Summary

- IPAC and IPAC-RS respectfully submit further data and evidence supplementing our 10 May 2023 submission[1] and in support of two requests:
    - **12-year derogation** for HFC-134a (CAS number 811-97-2) and HFC-227ea (CAS number 431-89-0) as medical propellants ("existing medical propellants") **and**
    - **a permanent exemption or time-unlimited derogation from the proposal** of HFO-1234ze(E) (CAS number 29118-24-9) as a medical propellant ("future medical propellant").

  Please note that this submission addresses two categories of propellants – *existing and future*. The issues and considerations are similar in some aspects, but distinguishable in others, as we outline below. One important distinction is that the two existing medical propellants – HFC-134a and HFC-227ea – are already subject to policies and regulations aimed at phasing them down over the next several years in light of their carbon footprint and impacts to climate[2, 3]. Therefore, their use by 2030 should be substantially reduced in the European Union and on the decline, globally. HFO-1234ze(E) and HFC-152a (CAS number 75-37-6) are new propellants and are potentially important solutions to delivering lower carbon footprint respiratory care for the foreseeable future[4, 5]. HFC-152a is not in the scope of the ECHA REACH PFAS proposal.

- The ECHA REACH proposal states in Table 8 (pages 100-101) that alternatives/substitutes are readily available for MDIs (also known as pressurised MDIs, or pMDIs) and the ban of medical propellants would have "likely very small costs" and would not lead to "additional administrative costs for industry or authorities." The proposal further concludes that "drop in substitute[s]" exist for HFC-134a and HFC-227ea as medical propellants in pMDIs (page 100). These statements and conclusions are not supported by experience, evidence or data. The two future alternative propellants (HFO 1234ze(E) and HFC-152a) are not currently available for patient use. Further, pMDIs are complex devices and medical propellants must meet a specific range of technical performance characteristics to be safe and effectively deliver consistent doses of life-saving medicines for patients. A new propellant cannot simply be "dropped in." As indicated by the number and complexity of the studies discussed in Section 2, significant development work is required in order to use alternative propellants. This results in regulatory burden for which sufficient time and certainty must be given. Developing pMDIs to use a new propellant requires careful review and testing of a range of several aspects and is subject to comprehensive preclinical and clinical studies, extensive product development studies inclusive of product stability and product characterisation tests as well as regulatory review and approval by the EMA and other regulatory agencies. In addition, a comprehensive package of several toxicological studies on propellant should be provided to exclude safety issues and should be part of the application for marketing authorisation of new drugs. Finally, the approach outlined in the proposal is inconsistent with the direct experience of the European Commission in the earlier propellant transition due to phase out of chlorofluorocarbon (CFC) MDIs[1, 6].

- To reiterate, the current proposal recommends a 12-year derogation for MDI coatings given "the lack of technically feasible alternatives and the high societal value of the medicinal products indicates that a full ban would be associated with high socio-economic costs." Table 8 of the proposal further states: "Sufficiently strong evidence that technically and economically feasible alternatives are not generally available." The precise same rationale applies to the existing medical propellants for MDIs and an inconsistent conclusion is not justified. In addition, although commercially available alternatives are present, since the type of material is different, a broad series of screening experiments should be planned to find compatible materials providing suitable drug product profile in terms of chemical and physical stability. In the worst case scenario, new materials or customised ones should be developed impacting development time and costs.

- In this submission, we detail technical and performance characteristics, regulatory requirements and other considerations for medical propellants for pMDIs with supporting literature and documentation. These data and evidence demonstrate the importance of having a minimum of two options for medical propellants (i.e., HFC-152a and HFO-1234ze(E)) to ensure flexibility so that a range of medicines with varying physiochemical and clinical properties remain available for patients. It is also important to note that moving to one medical propellant would reduce supply options to a single source of pharmaceutical-grade medical propellant for Europe, the United States, Canada, and the

UK. This presents significant supply risks[7]. These data and information supports why it takes several years (typically 6-10) to develop pMDIs with future propellants and time is also required to enable multiple products to transition as there will be a staggered process. It must be understood, as detailed herein, that this transition impacts a **significant** portfolio of products around the world (perhaps in the hundreds). Not all products will be submitted to or approved at once by EMA and other global regulatory authorities. Note that HFC-152a is not in scope of the ECHA REACH proposal.

- We also elaborate on the points made in our initial submission regarding respiratory patient care considerations and socio-economic impacts. Switching patients to new medicines is not a trivial matter and must be handled carefully and driven by clinical factors. For certain patient groups a pMDI device is the only means of effectively delivering an inhaled medicine to the lungs. Moreover, changing a patient's prescribed inhaler when their condition is stable on their current device risks loss of disease control and is inconsistent with clinical guidelines[8, 9]. Evidence demonstrates it can have variable clinical consequences. These points are supported by peer-reviewed literature (see below and reference list) and data collected in a recent industry survey conducted by IPAC and IPAC-RS (see Appendix C).

2. Process for Research, Development, and Approval of pMDIs Using New Medical Propellants (HFC-152a and HFO-1234ze(E)) Requires Time and Technical Options

Figure 1 provides a high-level overview of required stages that must be fulfilled in developing pMDIs that use any alternative propellants. The overall process typically takes about 6-10 years, assuming no significant issues arise related to supply chain quality and security, device development, formulation, performance, non-clinical, and clinical studies, scale up and manufacturing. The timing can be unpredictable and also depends on the resources and time constraints of health regulatory agencies. Appendix C illustrates that companies struggle to predict timing given the uncertainties of the development journey. At earliest, companies expect to launch products in 2025 to 2026. For MDIs with alternative propellants, industry is currently operating in stages 1-4 of Figure 1 conducting a number of development studies relevant to these steps.

Figure 2 elaborates on Figure 1 by outlining several key tests and studies for stages 1-5 that are required by regulatory health/medicines agencies in review and approval of any pMDIs. Select tests and studies are shown. A full list of studies required by, e.g., EMA is included in Table 1, Appendix A.

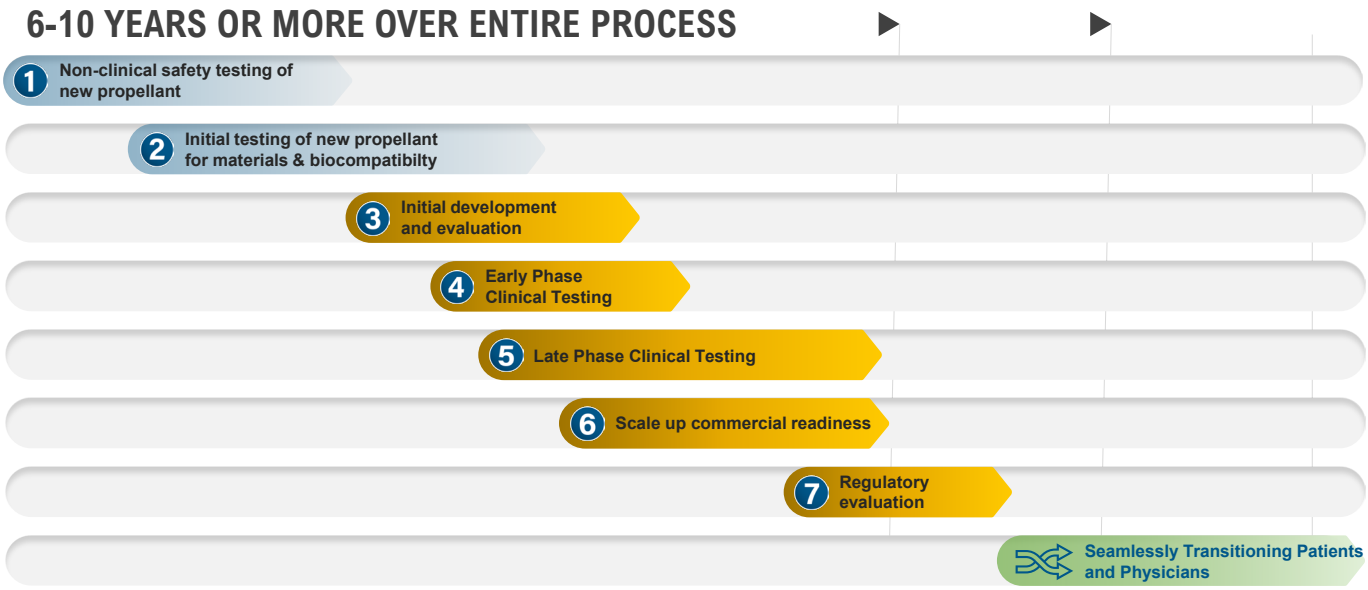


Figure 1. Key steps in development of metered dose inhalers using alternative propellants. Note that stages 3 through 7 (yellow) must be done for every drug product in a portfolio, e.g., different products, different product strengths, different dosages, other.

Non-clinical safety testing of propellant	Inital compatibility and biocompatibility testing	Quality, performance testing and non-clinical safety	Clinical studies
• Carcinogenicity studies • Cardiovascular studies •Sensitisation (in humans)	• Collection of container closure system and device composition and compatibility information from suppliers • Compatibility testing • Biocompatibility testing	• Delivered dose uniformity • Particle size distribution • Extractables and leachables •Plume characterisation	• Safety • Therapeutic equivalence •PK •PD • Potential for full Phase 1-3 clinical studies for safety and efficacy depending on regional requirements

Figure 2. Shown is a subset of key tests and studies that are required by regional regulatory agencies in review and approval of any pMDIs. A full list of studies required by, e.g., EMA is included in Appendix A.

In the following, we describe the types of risk assessments and studies required, at a minimum, for several of these key tests.

Toxicology studies. A thorough understanding of propellant toxicology including evidence from a panel of non-clinical toxicology studies is required for any propellant used in pMDIs. This

understanding of toxicology often requires studies on acute toxicity, repeat dose toxicity, genetic toxicity, carcinogenicity, safety pharmacology (such as cardiovascular functional assessments), and reproductive and developmental toxicity[38, 10]. Individual studies (depending on type) may take more than 1 year to complete, with carcinogenicity studies each typically taking up to 3 years to complete. Overall, a robust non-clinical package may take up to 10 years.

Ideally, these studies will be conducted in Organisation of Economic Co-operation and Development (OECD) member countries, in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP), and according to relevant International Conference on Harmonisation (ICH) guidelines

Biocompatibility and compatibility. Biocompatibility evaluation, also known as biological reactivity, is required by regulatory agencies to provide supportive information on potential irritation and/or cytotoxicity effects of the packaging and device material in contact with patients. These studies generally require in vitro and in some cases in vivo animal studies, although as the science and regulatory bodies progress away from animal studies, additional requirements are now in place for comprehensive chemical characterisation of extractable and leachable chemicals from container closure systems, packaging and device materials and components. Suppliers of materials and components as well as pMDI developers must conduct these studies according to pharmacopeial and medical device standards[11, 12, 13, 14, 15, 16, 17]. Typically, pMDI developers must also obtain information from these studies from their supply chain partners, along with any other materials composition information, to conduct initial hazard assessments[18]. Biocompatibility studies and composition information are especially required in the case of introducing new propellants due to their solvating and extracting properties, which will yield potentially unique extractable/leachable profiles (i.e., different from mixtures obtained using current propellants); with these results informing the need for additional toxicology studies and/or the need for new construction materials because of the introduction of new propellants.

Compatibility studies are required in order to understand the functionality over time, physico-chemical properties, swelling propensities, and any absorption issues related to new materials and components, or existing materials/components used in the presence of new propellants. These studies are done by propellant suppliers as well as material/component suppliers to the pMDI industry[19, 20, 21], and will also need to be repeated by the pMDI developers to test components with respect to the propellants mixed with surfactants and co-solvents, which are needed to meet performance, quality and efficacy requirements for the drug formulation and final drug product.

Extractables and leachables (E&L). Leachables are chemicals that migrate from device components and/or packaging of the pharmaceutical or medical device product under conditions of use. Some leachables may present toxicity concerns at certain human exposures, and thus leachables are considered a critical quality attribute for pharmaceutical products and in particular, orally inhaled and nasal drug products (OINDP). Since pMDIs use organic propellants that are in contact with the device (e.g., valves, actuators) and other container closure system components, leachables are likely. The introduction of a new propellant may change the leachables profile in significant ways. Thus, regulatory agencies require that industry mitigate

leachables risk by understanding and controlling target leachables that may appear at relevant concentrations, and in the case of propellant changes. To do this, industry must evaluate materials and components sourced from upstream suppliers for potential leachables (known as extractables), and also conduct extensive and comprehensive laboratory testing for extractables upon receipt of component batches prior to their incorporation into drug product. Developers must also conduct leachables studies to monitor leachates that may appear over time under use conditions. During development, these studies may be done under accelerated conditions as well as long-term conditions which may extend to 2-3 years. The range of extractables from components is potentially large and diverse, and a suite of complex analytical technologies is required to perform these investigations. As a result, this testing further complicates and extends development. E&L are scrutinised by regulatory agencies and requirements, including considerations for MDIs and propellant, are described in a number of regional guidelines, pharmacopoeia, and industry best practices[22, 23, 24, 25, 26, 27, 28, 29, 30, 31]. In some cases, repeat dose non-clinical safety data may need to be generated to support safety qualification of a new leachable compound.

Delivered dose uniformity (DDU). The medicine inhaled by a patient must be carefully dosed to ensure clinical effectiveness and safety. For a pMDI, the dose is generated by the device from the formulation in the canister when the user presses down the actuator. The consistency, or uniformity, of dose delivered with each and every instance of pMDI use is a critical quality attribute that must be tightly controlled for every batch (both within a single batch and across batches), and moreover must be maintained upon product's storage[22, 23, 32, 33, 34 38]. To achieve appropriate DDU in compliance with specifications required by health authorities and pharmacopoeias, the sponsor must often adjust design of the device (e.g., nozzle/valve dimensions, volume of the actuator chamber, materials of construction, and other variables) as well as fine-tune the formulation's chemical composition (e.g., to increase solubility of the active pharmaceutical ingredient, improve its stability to prevent agglomeration or caking upon storage, reduce adherence of formulation deposits on the walls of the container or the actuator, etc.). This work may take months of exploration and characterisation of various combinations involving a new propellant, which represents a significant change in the formulation composition as well as formulation-device interactions. Further complexity lies in the interplay of various critical performance parameters, which all need to be optimized simultaneously. For example, changes in device design materials to improve DDU may impact the leachables and extractable profile and/or aerodynamic particle size distribution. A successful product design, which takes all of these concerns into consideration, may take many months to years to achieve.

Aerodynamic particle size distribution (APSD). In order for the puff of medicine to be inhalable and capable of reaching the target areas in the deep lung, the size of particles generated by a pMDI has to be tightly controlled within the 1-5 micron range. The size of aerosolised particles strongly depends on the physico-chemical properties of the formulation (including its density, viscosity, vapor pressure, among many other parameters) as well as device design (including dimensions and geometries of the actuator, electrostatic properties of the materials in the pathway of the puff, and other variables). Furthermore, these inhalable particles have to be generated consistently puff to puff, container to container, and batch to batch. This engineering feat is achieved by adjusting the device design and formulation's composition while keeping all

other critical parameters within their optimal ranges. The search for such an optimised solution takes many months to years. APSD is one of the critical quality attributes of pMDIs, with recommended specifications included in guidance documents from health authorities (e.g., EMA, US FDA, Health Canada), international standards bodies, and pharmacopoeias[22, 23, 32, 33, 34 38].

Plume characterisation. Plume characterisation includes spray pattern and plume geometry evaluation. Spray pattern is evaluated during development and is usually required as part of bioequivalence evaluations in the United States[35, 36]. New propellants can produce different formulation spray patterns and plume geometry results compared to those from existing propellant formulations[37]. Industry must therefore conduct comparison studies to evaluate how new propellants in formulation (i.e., mixed with co-solvents, surfactants and active pharmaceutical ingredient) might affect plume characterisation parameters. Results may require changes to formulation and/or new plume characterisation methods, and thus further evaluations.

Clinical studies. Potential requirements for clinical studies needed to transition from existing HFC propellants (also known as hydrofluoroalkane, or HFA propellants) to any alternative propellants in pMDIs are still being considered by most global regulatory health authorities. Of note, the EMA issued its draft current thinking on what the Agency expects from companies transitioning to new propellants[38]. These expectations include a range of studies on human subjects using the "Test" product (i.e., a new product with an alternative propellant) and the "Reference" product (an existing, already authorised product):

- For propellant only:
    - local tolerance comparison studies between existing and new propellants, consisting of ciliary function studies in healthy volunteers, and airway sensitivity reactions in asthmatic patients. In the latter it is recommended to do an initial pilot study to inform the choice of study size and non-inferiority margin;
- For products under development:
    - clinical safety evaluation using placebo (no active ingredient(s)) addressing adverse events, e.g., bronchoconstriction, hoarseness, cough;
    - therapeutic equivalence testing: pharmacokinetic (PK) studies to investigate safety and efficacy; pharmacodynamic (PD) studies only if Test and Reference are not equivalent via PK studies. If not equivalent by PK or PD then reformulation could be considered. Specific considerations may be needed for extrapolation of any PK results in adults to paediatric patients.

      Reformulation may result in the need for novel excipients which must be developed and scaled to commercial volumes and will require additional safety testing before clinical efficacy can begin. If reformulation does not yield a therapeutically equivalent product, then the entire clinical development program will need to be repeated to demonstrate safety and efficacy of the 'new' product, which will require significantly extended development timelines.

It must be considered that all of the studies and other development work outlined above will need to be conducted on a large range of individual pMDIs, including different dosages and varying strengths. The IPAC/IPAC-RS survey illustrates that several companies manufacture numerous pMDIs in the European Union (at least 349 million units, and as many as 250 different types of pMDIs). See Appendix C, Section II.

This reformulation effort will incur a substantial cost, in the billions of Euros.

3. **Ensuring Access and Choice for Patients & Minimising Risk of Shortages of Essential Medicines**

As noted in our prior submission, pMDIs deliver life-saving medicines to millions of patients in the EU and worldwide. Reliever MDIs are listed on the WHO list of essential medicines[39]. Globally, it is estimated that 97% of all reliever inhaler prescriptions are pMDIs[40]. Any initiative to ban life-saving medicines must carefully and thoroughly assess the impacts on patient care. ECHA's PFAS proposal does not include adequate evidence or justification for banning medical use of the three propellants HFC-134a and HFC-227ea and HFO-1234ze(E). We urge in-depth consultation with clinical experts and regulatory health authorities to ensure patient care and access to essential medicines. Alternative delivery of the inhaled medicine, e.g., via Dry Powder Inhalers (DPIs) are not available for all currently marketed products and are not appropriate options for all patients.

Selecting a treatment regimen for patients with asthma, COPD, and other comorbidities is complex[41, 42, 43,44, 45, 46, 47, 48, 49]. "Several patient-, medication- and device-related variables contribute to determining the most appropriate treatment for an individual patient, and the benefits of individualised training in device handling are testament to the complexities of promoting good adherence in this field."[50] Device selection can also be impacted by practical considerations such as cost, health care culture and availability[51, 52, 53]. Figure 3 illustrates the range of considerations in treating patients. Before switching inhalers, ability to use the device must be seriously considered, including the following factors:

- physical dexterity,
- coordination,
- inspiratory flow,
- cognitive status,
- reliance on training and physical aids[54, 55].

Once patients are stable and their disease is well-controlled, changes in medication should only be done when warranted by clinical considerations[56, 57]. Switching inhaler regimens can have a significant impact on disease control and may be associated with negative impacts such as exacerbations and associated need for hospitalisation, increased demand on health care resources, patient discontent, declining quality of life, and reduced confidence in care plan[9, 58, 59].

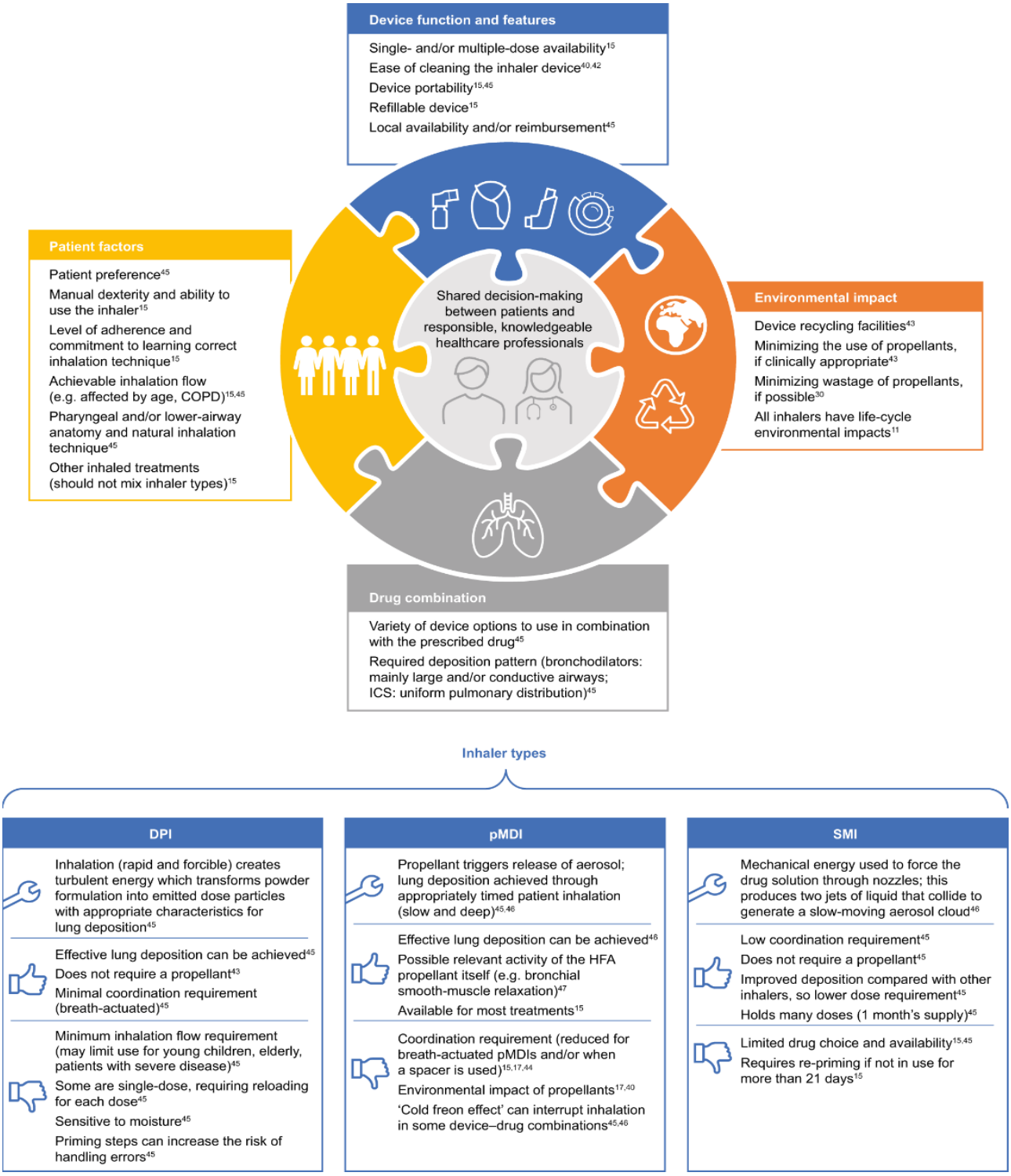


Figure 3: Considerations for selecting a particular inhaler device and drug combination. From: Omar Usmani & Mark Levy, Effective respiratory management of asthma and COPD and the environmental impacts of inhalers, *Nature, Primary Care Respiratory Medicine* (2023) http://creativecommons.org/licenses/by/4.0/. No changes were made to the original figure. COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; DPI = drug powder inhaler; pMDI = pressurised metered dose inhaler; SMI = soft mist inhaler; HFA = hydrofluroalkane.

4. Medical propellants are non-toxic and are not persistent over the long term in the environment

HFC 134a and HFC 227ea

It is well-established through preclinical and clinical studies that propellants HFC 134a and 227ea used in existing pMDIs are non-toxic. These have undergone extensive preclinical and clinical safety tests and have been used safely by patients for many years at levels that far exceed any environmental exposure [60, 61, 62, 63, 64, 65].

HFC 134a and HFC 227ea have atmospheric lifetimes of 14 years and approximately 36 years, respectively[66]. For these substances, HFC atmospheric degradation is initiated via hydroxyl radicals; breakdown products include carbon dioxide, hydrogen fluoride and trifluoroacetic acid (TFA)[67, 68, 69]. Although HFC 134a and HFC 227ea have relatively long lifetimes, their main impact is on global warming.

Since HFC 134a and HFC 227ea have a high global warming potential (GWP), their use is being phased down by climate change policies around the world[70, 71, 72]. IPAC members and other sources have estimated that the transition away from HFC-134a and HFC-227ea as medical propellants can be substantially completed in the EU by 2030[73].

HFO 1234ze(E)

Similarly, with respect to safety, new propellants that the MDI industry is transitioning to, including both HFO 1234ze(E) – which is in scope of the proposal – and HFC-152a – which is out of scope, have undergone preclinical toxicology testing that support safe patient exposure in short and long-term scenarios. Both propellants are also undergoing clinical studies as part of the final product, as required by regulatory agencies, to further support safe human exposure.

Data on HFO1234ze(E) Breakdown

HFO-1234ze(E) has a very low global warming potential, with a ***much shorter atmospheric lifetime*** (19 days) than HFC-134a (14 years) (**Table 1**).

Table 1. Properties of pMDIs propellants[51] (Pritchard, 2020, Kigali Amendment to the Montreal Protocol)

Propellant	**Chemical formula**	**GWP 100 (AR4[74])**	**Atmospheric lifetime**	**Boiling point, degrees C**	**Density at 20°C, g/mL**	**Solubility of water in propellant at 20°C, ppm**
HFA-227ea	CF_3-CHF-CF_3	3220	36 years	-16.5	1.41	610
HFA-134a	CF_3-CFH_2	1430	14 years	-26.2	1.23	2200
HFA-152a	CF_2H-CH_3	124	1.6 years	-24.7	0.91	2200
HFO-1234ze(E)	CF_3CH=CHF	1.37	19 days	-18.9	1.29	225

GWP 100, global warming potential based on a 100-year time horizon; HFA, hydrofluoroalkane; HFO, hydrofluoroolefin; pMDI, pressurised metered-dose inhalers.

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. For comparison, HFC-134a reacts with OH radicals more than 240 times slower than HFO-1234ze(E)[75]. **Further information is available in Appendix D**. IPAC acknowledges that the science and data on TFA is evolving. We would plan to supplement this data in future public consultations as further information is available. We are also happy to answer any questions.

5. Adoption of the Bans, as Proposed, Would Lead to Significant Negative Socioeconomic Impacts: Overview of Results of IPAC/IPAC-RS Survey

In order to provide data for the ECHA REACH process, IPAC and IPAC -RS undertook a survey on the socioeconomic impacts of the proposed bans. The results are summarised in Appendix C. The cost of the effort to reformulate the range of pMDIs from existing propellants to future propellants is estimated at well over 3 billion Euros, total. IPAC and IPAC-RS members have at least 13,000 employees devoted to pMDI research, development, manufacture and commercialisation, globally, and raw material and service suppliers. If the ECHA REACH restrictions impacting pMDIs were implemented as proposed, three companies would exit the market and three companies would reduce their operations by 50 to 80%. Five companies were not even able to estimate the impact on their operations. **See Appendix C, Section V.**

The ECHA REACH proposal to ban HFO-1234ze(E) may stifle innovation in next generation pMDIs with this propellant which could have negative implications for patient access to essential medicines and for the planet given the significantly lower global warming potential. Eight companies have indicated that they are investing in HFO-1234ze(E) and/or HFC-152a.

Eight companies indicated that they are not investing in developing pMDIs with an alternative to the existing propellant. **See Appendix C, Section IV**. The key reasons for this decision include expense, uncertainty about the future availability and permissibility of alternative propellants, and uncertainty about regulatory requirements for approval of products with future propellants. See Appendix C, Section IV.

The pMDI industry predicts a major economic impact if the proposal is adopted. The survey results estimate more than 1 billion Euros in annual losses.

The proposal impacts several parts of the supply chain, manufacturing, testing and packaging for pMDIs as well as DPIs, SMIs, nasal sprays and nebulisers. A number of concerns were expressed regarding the socioeconomic impacts of the proposed bans, including major supply chain disruptions and cost increases. **See Appendix C, Sections IV and V**. Respondents noted the possible negative impacts to countries outside the EU as the EU is a global hub for manufacture of pMDIs.

APPENDIX A

Table 1: Studies and tests required to fulfil stages in Figure 1. All studies included here are recommended for consideration by EMA[22, 38]

Propellant safety testing (non-clinical) **Up to 50 months**	**Materials, device and biocompatibility testing** **6-12 months[1]**	**Development and Evaluation studies** **24-36 months**	**Early and late phase clinical testing** **3-24 months[1]**	**Scale-up and commercial readiness** **Up to 36 months**
▪ Acute toxicity testing ▪ Repeat dose toxicity testing (sub-chronic, chronic) ▪ Cardiovascular safety ▪ Genetic toxicity testing ▪ Carcinogenicity testing (chronic) ▪ Reproductive and development toxicity testing ▪ Local tolerance testing (irritation, sensitisation)	▪ Biocompatibility testing ▪ Compatibility testing (e.g., functionality, swelling, performance) ▪ Collection of composition information for container closure system components; compliance with standards	▪ Physical characterisation ▪ Minimum fill justification ▪ Extractables and leachables ▪ Delivered dose uniformity and fine particle mass through container life ▪ Fine particle mass with spacer use (if spacer required) ▪ Single dose fine particle mass ▪ Particle size distribution ▪ Actuator / mouthpiece deposition ▪ Shaking requirements (for suspensions) ▪ Initial and repriming requirements ▪ Cleaning requirements ▪ Low temperature performance ▪ Performance after temperature cycling	▪ Local tolerance (of propellant) between new and reference – Ciliary function in healthy volunteers – Airway sensitivity reactions in asthmatic patients; recommended to do initial pilot study to inform choice of study size and non-inferiority margin ▪ Clinical safety addressing adverse events, e.g., bronchoconstriction, hoarseness, cough ▪ Therapeutic equivalence testing – PK studies to investigate safety and efficacy – PD studies only if test and reference are not equivalent via PK studies	▪ Adequate manufacturing method validation and stability data ▪ Stability data for at least two batches, packed in the commercial container closure system, stored at long-term conditions and in different orientations for a sufficient time should be provided. Batches should preferable be of production scale

Propellant safety testing (non-clinical) Up to 50 months	Materials, device and biocompatibility testing 6-12 months[1]	Development and Evaluation studies 24-36 months	Early and late phase clinical testing 3-24 months[1]	Scale-up and commercial readiness Up to 36 months
		▪ Effect of environmental moisture ▪ Robustness ▪ Delivery device development (description of device development; description of device changes; scale-up in tooling etc). Includes changes to valves and canister and any other components affected by propellant change ▪ Therapeutic equivalence testing; In vitro equivalence	▪ Full clinical testing potentially needed for some other world regions	

APPENDIX B

Authors	Title	Publication, Year	Summary Points
European Medicines Agency	Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers	2023	Selected sections: 3.1 What are the quality data requirements? 3.2 What are the non-clinical data requirements? 3.3 What are the data requirements to address safety/tolerance aspects of a novel propellant? 3.4 What are the data requirements to address possible changes to the exposure to the active substance(s)? 3.5 What are the data requirements for children and adolescents? 3.6 Are there any specific considerations related to the product information following a change in propellant?
European Medicines Agency	Guideline on the pharmaceutical quality of inhalation and nasal products	2006	
European Medicines Agency	Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents	2009	
European Medicines Agency	Guideline on plastic immediate packaging materials	2005	
US Food and Drug Administration	Draft Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products—Quality Considerations	2018	

Authors	Title	Publication, Year	Summary Points
US Food and Drug Administration	Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics	1999	
European Pharmacopoeia (Ph.Eur.)	Section 3, Materials for containers and containers		Tests and methods regarding quality of materials and containers
United States Pharmacopoeia	*Chapter ⟨87⟩ Biological Reactivity Tests, In Vitro*		In vitro biological reactivity test methods and specifications
United States Pharmacopoeia	*Chapter ⟨88⟩ Biological Reactivity Tests, In Vivo*		In vivo biological reactivity test methods and specifications
United States Pharmacopoeia	*Chapter <1031> The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants*		Guideline on biocompatibility and application of <87> and <88>
United States Pharmacopoeia	*Chapter <661> Plastic Packaging Systems and Their Materials of Construction*		Tests and methods to ensure quality of plastic packaging and materials of construction
United States Pharmacopoeia	*Chapter <661.1> Plastic Materials of Construction*		Tests and methods to ensure quality plastic materials of construction
United States Pharmacopoeia	*Chapter <661.2> Plastic Packaging Systems for Pharmaceutical Use*		Tests and methods to ensure quality of plastic packaging systems
International Organization for Standardization	*ISO 10993 (series)* *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process* And associated chapters	2018 and others	Process, chemical and safety tests and methods for biological evaluation of medical devices

Authors	Title	Publication, Year	Summary Points
Le Corre B, Sarrailh S, Ferrao J; Aptar Pharma	Investigation of Leachables from pMDIs Containing Propellants HFA 134a, HFA 152a and HFO 1234ze	Proceedings of Respiratory Drug Delivery 2022	Comparison of select leachables from POM, PBT, EPDM, COC in 3 propellants. Data presented for THF and formaldehyde (only). "152a is known to be a slightly stronger solvent as compared to both 134a and 1234ze(E)… "
Product Quality Research Institute (PQRI)	Safety thresholds and best practices for extractables and leachables in orally inhaled and nasal drug products Regulatory Submissions – Product Quality Research Institute (pqri.org)	2006	Best practices to manage extractables and leachables in orally inhaled and nasal drug products Document developed by PQRI members including FDA, USP, industry organizations and academia
Extractables and Leachables Safety Information Exchange Consortium (ELSIE)	Concepts in Leachables Risk Management: Screening and Materials Selection E&L Concepts | ELSIE (elsiedata.org) Screening and Materials Selection | ELSIE (elsiedata.org)	2020	Overview and description of approaches to leachables risk management for pharmaceutical lifecycle
Honeywell International, Inc.	SOLSTICE® AIRHFO-1234ze(E), cGMP, Technical Bulletin	2022	Overview of physical chemical properties of HFO 1234ze(E)
Honeywell Belgium N.V.	Solstice ze Refrigerant (HFO-1234ze); The Environmental Alternative to Traditional Refrigerants	Brochure, 2015	Contains material compatibility table for a large list of plastics and elastomers with 1234ze. Measured change in hardness, change in weight, change in volume. Includes other general information (flammability, toxicity, etc.) "Solstice ze is not subject to quota phase down in F-gas Regulation ..."

Authors	Title	Publication, Year	Summary Points
Corr S, Noakes T; Koura, The Health Technical Center UK	Compatibility of P152a with pressurized metered dose inhaler materials	2019	An example of comparability testing to establish new propellant. Shows graphs of changes in volume, hardness, weight for 152a vs 134a. Also shows graphs of permeation loss from EPDM- or nitrile-sealed containers (complete description of CCS not provided). Also has results from "rudimentary assessment of chemical stability" for salbutamol - comparison of degradation at 40/75 for 6 mo.
Koura; UK	152a Physical Properties	Brochure 2020	Tables containing physical properties such as BP, vapor density, dielectric constant, dipole moment, solubility of water in 152a, vapor pressure and vapor density as a function of temperature, etc.
Daikin Refrigerants Europe	SOLKANE 227 pharma and 134a pharma	Brochure	Extensive information on physical properties, tox data, materials compatibility tables for 134a and 227ea. Source of some physicochemical properties data in Propellants Physical Properties word document. Summary table of impurity limits per gas.
Honeywell	Solstice ze Refrigerant (HFO-1234ze (E)), The Environmental Alternative to Traditional Refrigerants	Brochure, 2018	Another version of the Honeywell 1234ze brochure, similar content -- material compatibility table, other general information (flammability, toxicity, etc.) "Solstice ze is not subject to quota phase down in F-gas Regulation ..."
Majurin JA, Gilles W, Staats SJ; Trane/Ingersoll Rand USA	Materials Compatibility of HVACR System Materials with Low GWP Refrigerant	International Refrigeration and Air Conditioning Conference, Purdue University, 2014	Evaluated compatibility of 9 types of elastomers, five polymers with R1234ze(E). Measured changes in weight, volume, appearance, hardness, tensile strength after exposure to 90C for 21 days.
Decaire B, Conviser S, Sarrailh S, Le Corre B, Baron C	Materials Compatibility Testing of Honeywell's New Low Global Warming Potential Propellants	Poster	Joint poster from Honeywell & Aptar; materials physical properties for typical pMDI valve elastomers, plastics, and metals comparing 1234yf and 1234ze to HFA 134a and 227ea -- mechanical resistance and swelling for elastomers, force resistance for plastics, corrosion and compression

Authors	Title	Publication, Year	Summary Points
			for SS springs. Conclusion - no incompatibility of 1234 propellants with Aptar valve components.
Industrial Products: Honeywell Belgium N.V.	Solstice Propellant Technical Bulletin	2017	Another version of the Honeywell 1234ze brochure with an emphasis on use as a propellant (rather than as a refrigerant); physical properties, flammability, miscibility with other propellants / organic solvents, environmental properties, materials compatibility, stability, toxicity, and storage & handling
Hulse R, Boldt E, Decaire B & Smith G; Honeywell Int. Buffalo NY	A Journey to Net Zero Using Solstice Air	Proceedings of Respiratory Drug Delivery, 2022	"Preliminary formulation studies show good compatibility with common excipients and APIs" for 1234ze. "toxicology studies have been reviewed by FDA and CHMP." Addresses environmental fate in atmosphere, physical properties, compatibility with albuterol, fluticasone, and ipratroprium, flammability, and tox.
Le Corre B, Sarrailh S & Ferrao J; Aptar Pharma	Investigation of Leachables from pMDIs Containing Propellants HFA 134a, HFA 152a and HFO 1234ze	Proceedings of Respiratory Drug Delivery 2022	Duplicate of RDD A (line 2). Comparison of select leachables from POM, PBT, EPDM, COC in 3 propellants. Data presented for THF and formaldehyde (only). "152a is known to be a slightly stronger solvent as compared to both 134a and 1234ze … "

Authors	Title	Publication, Year	Summary Points
Pritchard JN; Inspiring Strategies; UK	Is the Climate Right for a New pMDI Propellant?	Proceedings of Respiratory Drug Delivery 2022	Update on RDD 2020 commentary article, discussing medical, economic, and regulatory implications of HFA transition. Contains prescription data for MDI/DPI, costing comparisons; reviews regulatory environment
Slowey A, Hayes A; Kindeva Drug Delivery UK	Use of Accelerated Stability Storage to Fast-Track the Development of a New Metered Dose Inhaler Incorporating the Greener Propellant HFA-152a	Proceedings of Respiratory Drug Delivery 2022	Tested content, APSD, and impurities of beclomethasone diproprionate in four CCS variants following accelerated storage at 40/75 and 50/75. Used impurities results to down-select to two CCS variants after only 2 weeks of storage at 50/75.
Close J, Makar M, Boldt E, Smith G, Hulse R; Honeywell int. Buffalo NY	HFO-1234ze(E): Flammability Characterization for metered Dose Inhaler Manufacturing	Proceedings of Respiratory Drug Delivery 2023	HFO-1234ze(E) is classified as nonflammable by GHS,DOT, IATA and IMDG (measured by ASTM E 681, ISO 10156 and EC A.11. When temperature is ≥30°C, and relative humidity is ≥50%, and a high energy ignition source or open flame is present, a very narrow flammable range can be observed.
Mao L, Johnson S, Pant N, Murray J, Ellis D, Zechinati B, Carr J, Cruttenden V; Recipharm NC / Koura UK	Albuterol Sulfate Metered Dose Inhaler Feasibility Using an Environment Friendly Propellant HFA152a and Novel Valves	Proceedings of Respiratory Drug Delivery 2023	Study evaluated the feasibility of formulation an albuterol sulfate suspension with an alternative low GWP and short atmospheric life propellant HFA152a using novel MDI valves being developed at Bespak by Recipharm to match the key performance of the marketed product ProAir®, an albuterol sulfate suspension MDI. The study shows that formulation with 8% EtOH delivered more consistent doses and better matched ProAir in terms of percentage deposition and APSD by NGI as well as spray patten and force to actuate. Ethanol content is critical in modulating the delivery performance. Requires further optimization to match plume geometry. Three values were evaluated, the 25 µL hybrid valve showed the least weight loss after one month storage at 40°C/75% RH.

Authors	Title	Publication, Year	Summary Points
Murray J, Doidge W, Moseley A; Koura UK/ Herd mundy Richardson UK	Anti-Microbial Properties of Low-GWP pMDI Propellant P-152a	Proceedings of Respiratory Drug Delivery 2023	Existing pharmacopeial methodology is applicable to P-152a. Anti-microbial property of p-152a was demonstrated with inoculated canisters, yielding no recovery for all microbes at concentrations of $<10^3$ CFU/mL and a drastic log reduction in populations at concentrations > 10^6 CFU/mL. P-152a shows similar properties with respect to microbial activity to the existing medical propellants.
Lachacz K, Taylor M, Morgan B, Archbell J, Craver J, Morris T, Carrigy NB, Ivatury S, Lechuga-Ballesteros D, Joshi V; AstraZeneca	Comparative Aerosol Performance of an HFA-134a Based Fixed-Dose Triple Combination pMDI to One Made with a near-Zero Carbon Footprint Propellant	Proceedings of Respiratory Drug Delivery 2023	The test product formulated with HFO-1234ze displays aerosol performance statistically equivalent to that of the reference product formulated with HFA-134a (BREZTRI AEROSPHERE). Tests include delivered dose, fine particle mass, plume geometry and spray pattern.
Jordan L, Johnson S, Chand R, Thurston G, Jones D, Webster V, Stanford S. Proveris MA/ Koura UK	Comparison of Spray Characteristics of P-134a and Low GWP P-152a pMDIs With and Without Ethanol	Poster; Proceedings of Respiratory Drug Delivery 2023	The study evaluated propellants P134a and P-152a with varying percentages of ethanol co-solvent. The metered shot weight across all formulations was well within the FDA Guidance for pMDI products. The addition of EtOH caused an increase in variation and median plume angles and width at 60 mm in P134a formulations; the effect was diminished for P152a variations. The addition of EtOH also caused the p134a plume to become more continuous and intense. A separate spray pattern method will be needed for p152a propellant.
Baxter S, Myatt B, Stein, S. *et al.*	Spray Pattern and Plume Geometry Testing and Methodology: An IPAC-RS Working Group Overview	*AAPS PharmSciTech* **23**, 145 (2022). https://doi.org/10.1208/s12249-022-02278-w	Review and assessment of global regulatory requirements, and evaluation of the value, use and application of plume characterization in orally inhaled and nasal drug products

Authors	Title	Publication, Year	Summary Points
Lewis DA, Green JL, Turner R, Johnson RD, Lewis DI. Oz-UK UK; H&T Presspart Manufacturing, UK	Towards Pharmaceutical Equivalence: A Comparison of Three MDIs: HFA152a, HFA134a, and HFA227ea	Proceedings of Respiratory Drug Delivery 2023	Three MDI formulations 1 (152a), 2 (134a) and 3 (227ea) were evaluated for the impact of sampling flow rate, Q (30 L/Min)upon drug delivery metrics for each MDI used in conjunction with an AeroChamber Plus (spacer mode). Q = 30 L/min, 60 L/min and 90 L/min.
Wang H, Ordoubadi M, Leal J, Minootan A, Lachacz K, Carrigy N, Lechuga-Ballesteros D, Vehring R; University of Alberta, AstraZeneca	Droplet Characteristics of Low Global Warming Potential Propellants at Different Humidities	Proceedings of Respiratory Drug Delivery 2023	134a, 227es, 1234ze, 1234yf, 152a: Content equivalent diameters of HFC and low global warming potential (LGWP) propellants were experimentally measured and found to be in a relatively narrow range of 10 - 15µm. All showed similar dependence on EtOH resulting in comparable fine particle sizes. all five display similar aerosol performance under elevated relative humidities, 0 %RH, 50% RH and 95% RH.
Brittain OM, Clay J, Riley D; Kindeva Drug Delivery UK	An Evaluation of Solution and Suspension pMDIs Containing HFA152a and HFO1234ze Using Clinically Relevant Test Methods	Proceedings of Respiratory Drug Delivery 2023	There was an influence of firing angle and flow rate on fine particle mass for the solution and suspension formulations for both propellants. The difference in degree of change was not observed when change the anatomical throat model for throat size for suspension-based formulations with both propellants behaving the same. The solution - based formation with 152a did follow a similar trend to the suspension-based formulations, the solution-based 1234ze did not follow similar trends.
Willoughby A, Tank PS, Stevens N; Team Consulting UK	Evolving Strategies for Designing a Sustainable Inhaler	Proceedings of Respiratory Drug Delivery 2023	plan for sustainability from the start, with benign propellants and a simplified design.
Deraime G, Ferrao J, Bueno LC, Alix E, Williams G; Aptar France	Filling and Dose Performance of pMDIs with New Low Global Warming Potential Propellants	Proceedings of Respiratory Drug Delivery 2023	Both 152a and 1234ze were successful used to fill optimised MDIs accurately and reproducibly on pilot scale filling equipment. Static leakage was found to be within current regulatory limits and acceptable dose delivery performance was achieved for up to 6 months of shelf life using

Authors	Title	Publication, Year	Summary Points
			novel pMDI valves. These new pMDIs were equal to or superior to the currently used HFA pMDIs.
Faucard P, Fontaine I, Rives S, Le Corre B, Cannette C, Ferrao J; Aptar France	Leachables Assessment from a New Generation of pMDI Using Low Global Warming Potential Propellants	Proceedings of Respiratory Drug Delivery 2023	A new generation DF316 valve tested with 152a, 1234ze and 134a, at t0, t1, t3 and t6 months. 134a and 152a very similar, 1234ze more aggressive. THF and PBT dimer need to be considered for 152a based on the DNEL there should be a reasonable safety factor for these.
Lewis DA, Green JL, Turner R, Johnson RD, Lewis DI; Oz-UK UK; H&T Presspart Manufacturing, UK	HFA152a MDI Design: Matching the *In-vitro* Performance of HFA227ea and HFA134a MDIs	Proceedings of Respiratory Drug Delivery 2023	MDI formulations with ethanol and 152a (formulation 1) 134a (formulation 2) and 227ea (formulation 3) were evaluated at 30 L/min sampling flow rate for metered dose, delivered dose, fine particle dose, fine particle fraction. MMAD and shot weight. Consistent metrics using an NGI with USP apparatus 6; delivered dose - 223 ± 8 µg, MMAD = 2.0 ± 0.1 µg, FPD = 66 ± 5 µg.
Lechuga-Ballesteros D, Lachacz K, Joshi V, Riebe M; AstraZeneca	Quadruple Combination in a Pressurized Metered Dose Inhaler with Reduced Environmental Impact for the Treatment of COPD	Proceedings of Respiratory Drug Delivery 2023	4 APIs, 134a or 1234ze, 14L aluminum canisters, 50 µL metering valve, approximately 261 µg porous particles. Demonstrated equivalent APSD using NGI at 30 L/min with both propellants.
Buttini F, Glieca S, Carretta G, Quarta E, Motta G, Carrara M, Colombo A; University of Parma, RxPack Italy	A Roadmap for Constructing a Beclomethasone pMDI Solution Using HFA152a	Proceedings of Respiratory Drug Delivery 2023	new valve KHFA-RxPack 50 µL with an ethanol based formulation of beclomethasone and 152a showed high precision in product delivery with no initial priming or repriming.
Myrdal PB, Sheth P, Stein SW. University of Arizona, 3M Drug Delivery USA	Advances in Metered Dose Inhaler Technology: Formulation Development	AAPS PharmSciTech. Vol.15, No. 2, April 2014	pMDI formulation response to transition from CFC to HFA, impact of EtOH on spray attributes, stability of solution or suspensions. Excipients including surfactants, bulking agents and phospholipid microparticles evaluated. Engineering approaches to particle generation to optimize pMDI efficiencies discussed.

Authors	Title	Publication, Year	Summary Points
Knopeck G, Decaire B, Ghelani K; Honeywell	A New Generation of Aerosol Propellants for Metered Dose Inhalers	Proceedings of Respiratory Drug Delivery 2010	HMP-1, HMP-2 and HMP-3 being developed by Honeywell with Global Warming Potential (GWP)< 10. General properties are provided compared to 134a and CFCs. Excipient solubilities included. Selection criteria include; ultra-low GWP, suitable physical properties such as BP, VP, non-flammability or moderate flammability and stability. Candidates identified were then submitted to rigorous toxicity testing to confirm their suitability for expected applications.
Decaire G, Ghelai K, Conviser S, Sarrailh S, Le Corre B, Baron C; Honeywell USA/ Aptar France	Materials Compatibility Testing of New Low Global Warming Potential Propellants	Proceedings of Respiratory Drug Delivery 2011	Assessed mechanical material compatibility with HFO propellants 1234ze€ and 1234yf. Propellants are comparable to 134a and 227, and appear compatible with Aptar delivery devices.

Appendix C
IPAC and IPAC-RS Survey on Impact of PFAS Restrictions on OINDPs:
Survey Results Summary

I. INTRODUCTION

This document summarises the results from the IPAC and IPAC-RS survey on the pressurized metered dose inhaler (pMDI) industry's current and projected use of HFA 134a, 227ea and new low-GWP propellants, HFO 1234ez(E) and HFA 152a. The goal of the survey was to gather information responsive to the socio-economic and risk assessments being conducted by ECHA REACH relevant to the PFAS REACH Annex XV Restriction proposal and we had in mind the specific questions posed by ECHA REACH on this file. The survey focuses on pMDIs and other orally inhaled and nasal drug products (OINDPs). The survey included questions on investments and regulatory challenges in developing pMDIs/OINDPs, potential impacts to patients due to product availability/unavailability, and socio-economic impacts.

II. DEMOGRAPHICS AND MARKET INFORMATION

The survey was completed by 18 companies, including 14 responses from pMDI developers/manufacturers and 4 responses companies in the pMDI supply chain (device and container closure system developers, testing instrument developers). The survey supplements data collected earlier in 2023 by IPAC regarding the European manufacture and export of HFC MDIs. That survey (submitted to ECHA REACH in May) found:

Total IPAC Member Company MDIs in EU: **88,170,000***

For the current survey, about half of the respondents indicated that they manufacture or hold marketing authorisations for pMDIs, and supply pMDIs to the market. A majority of respondents noted that they manufacture or hold marketing authorisations, and supply to the market in both non-European Union (EU) and EU regions. A majority of respondents (about 70-80%) manufacture, hold marketing authorisations, and/or supply branded (including authorised generics) pMDIs.

The survey indicated that companies currently manufacture in the EU, anywhere from 1 to 250 different types of pMDI products using HFCs 134a or 227ea. These can also include different product strengths and dosages. Similar results were obtained for the number of different types

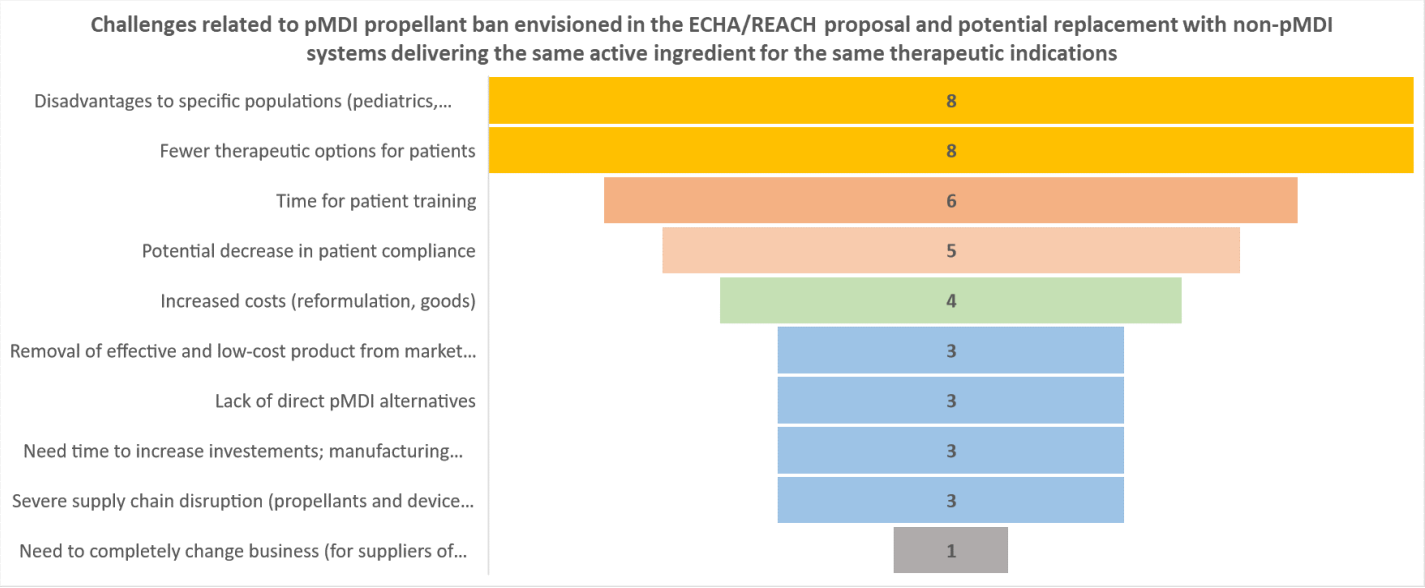
of 134a or 227ea pMDI products for which companies have EU marketing authorisations. Similar numbers were found for different types of these products manufactured outside of the EU that are imported into the EU; and for products that have marketing authorisations outside of the EU but are manufactured in the EU. Several companies reported that they have anywhere from 1 to 15 pMDI HFCs in development that will require repeat development work.

III. CHALLENGES OF BANS PROPOSED BY ECHA PFAS RESTRICTION

Respondents noted that main challenges due to the ban proposed in the ECHA PFAS restriction, and potential replacement with non-pMDI systems delivering the same active ingredient for the same therapeutic indications, are negative impacts on patients and patient access, e.g.,

- Disadvantages to specific populations (pediatrics, geriatrics, emergency use)
- Fewer therapeutic options for patients;
- Lack of time for patient training;
- Potential decrease in patient compliance;
- Increased costs (reformulation, goods);
- Removal of effective and low-cost product from market (pMDIs);
- Lack of direct pMDI alternatives;
- Need time to increase investments and manufacturing capacity for non-MDI systems;
- Severe supply chain disruption (propellants and device parts); and
- Need to completely change business (for suppliers of MDI system parts)

This is seen graphically below with direct patient access issues being mentioned the most.



IV. INVESTING IN ALTERNATIVE PROPELLANTS AND TECHNOLOGIES

Approximately half of respondents indicated that they are investing in developing pMDIs with alternative propellants to HFCs 134a and 227ea, i.e., HFC-152a and HFO-1234ze(E). Companies that develop and manufacture HFC pMDIs indicated that they collectively have about 11 to 18 products in late-stage development (Phase 2 or 3) that require substantial in vitro or in vivo studies.

For the 8 companies that are not investing in alternative propellant products, the main reasons roughly evenly noted were,

- Expense
- Uncertainty about regulatory requirements for approval of alternative propellant products
- Uncertainty about future availability and permissibility of alternative propellant products
- Overarching business decisions (e.g., decision to move away from MDI sector entirely)

The companies that are investing in alternative propellant product development indicated plans to utilise HFC 152a, HFO 1234ze(E), or both. These respondents include developers and producers of pMDIs as well as other inhalation and spray products, developers and producers of device/container closure system components, and CDMOs, illustrating the variety and depth of investment.

Some respondents further noted that the latest timeframe for transition of all of their products to a replacement propellant in the EU and outside of the EU, will be 2029 – 2030, and several others (an equivalent number) noted that timeframes cannot be estimated at this time due to current uncertainties.

As detailed in Table C-1, several uncertainties and concerns about the supply chain for propellants and overall product related goods were identified if the ECHA/REACH proposal was adopted as proposed with HFC-134a, HFC-227ea, and HFO-1234ze(E) banned effective within 18 months of adoption.

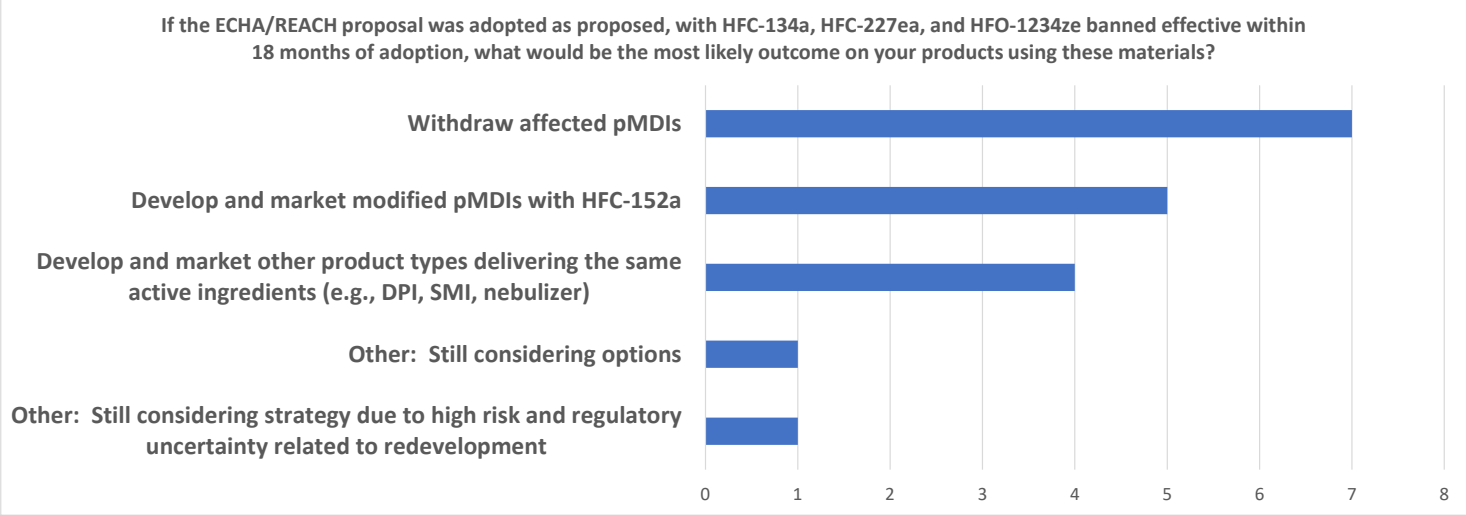
Table C-1. If the ECHA/REACH proposal was adopted as proposed, with HFC-134a, HFC-227ea, and HFO-1234ze banned effective within 18 months of adoption, what significant impacts on the supply chain are expected and why.

Significant Impacts	Considerations
Product shortages due to significantly reduced or no availability of propellants, leading to significantly reduced patient access	• Long lead time needed for reformulation; stored propellant stocks will not cover reformulation timeframe; transition to non-PFAS propellants (e.g., HFA152a) will most likely not be completed across all products and geographies leading to a shortage or a withdrawal of MDIs from markets. This is even more probable in non-EU countries supplied with MDIs manufactured in EU but with different and often longer regulatory procedures • If a significant patient population transitions from MDI to DPIs within a short timeframe (as proposed), then the supply chain would be constrained as it adjusts to meet the increased patient demand • Supply chain disruption as some products are potentially discontinued from the markets or transitioned to low carbon alternatives leading to limited product availability • Health consequences for patients unable to use dry powder inhalers (DPIs) and/or other alternatives
Significant increase in costs of propellants	Ahead of a proposed ban, the economic impact of purchasing propellants could rise and prove prohibitive to companies moving forward with product development and planned launch activities.
Significant increase in costs of all product-related goods; Detrimental impacts on all inhalation product types (shortages; supply disruption; etc)	• Increased costs of pMDIs, DPIs and any other alternatives due to propellant shortages; suppliers of product components and other related industries leaving the therapeutic area • Expected shortages in existing and new alternative therapies due to subsequent demand and lack of lead time for development and/or reformulation
Suppliers and final product companies leaving the market	Difficulty in finding alternate source of supply for canisters, device components and other inhalation and nasal product components

Respondents noted that other impacts would include potentially higher reliance on supply of product related goods from non-EU countries for products to be provided to non-EU (and EU) countries; and effect on API and manufacturing processes due to general proposed ECHA ban of

PFAS used in those areas (these latter impacts are also noted in Table C-2, below for all orally inhaled and nasal drug products).

With respect to outcomes of the ECHA restriction as proposed, respondents noted the most likely outcome to be withdrawal of affected pMDIs, with reformulation a possibility (although noting that any such reformulation requires lengthy lead times (beyond 18 months). These results are shown graphically in the figure below:



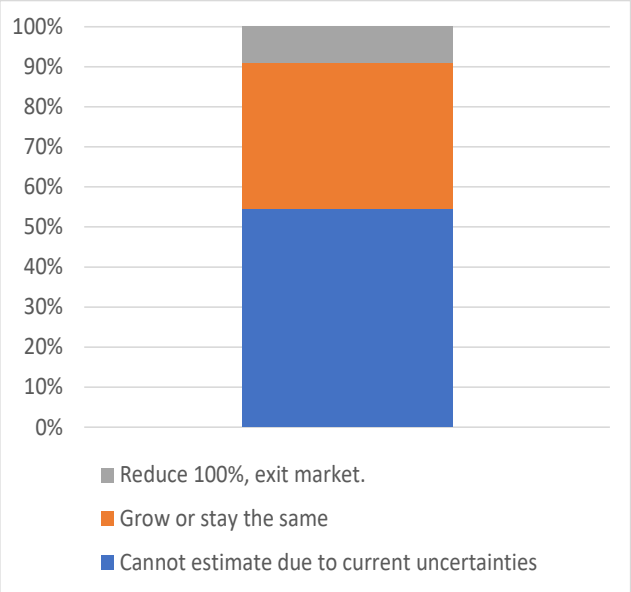
Regarding the estimated total cost of reformulation in switching to either or both alternative propellants, including clinical development, manufacturing capacity and infrastructure development, launch, etc., the costs would be many millions and perhaps more than 500 million Euros. In a few cases, switching a specific product was noted to be on the high end of this range. It was also noted that in at least one example, the cost reflected switching of multiple product families prioritising those used mostly by patients and where there is no suitable non-MDI alternative. A few respondents mentioned that estimates could not be made at this time due to uncertainties. The total costs of reformulating can be estimated to be 3 to 5 billion Euros.

V. SOCIO-ECONOMIC IMPACTS

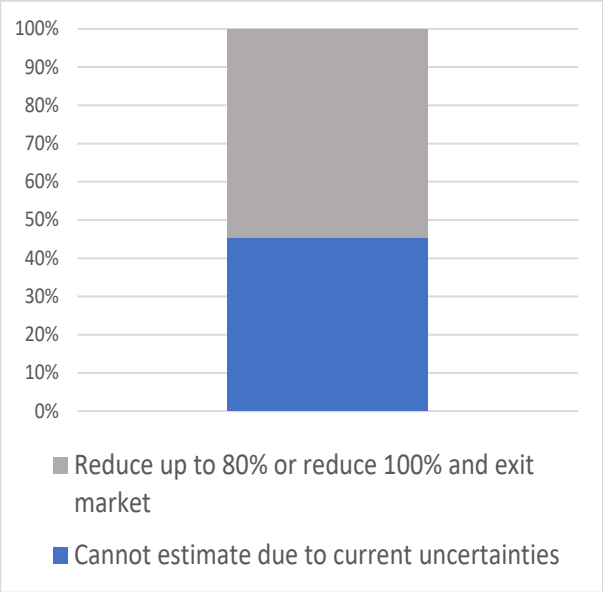
The number of employees involved with pMDI or HFC propellant related inhalation/nasal spray research, development, manufacture and/or commercialization at individual companies that responded to the survey, is in the range of single digits to approximately 8,000 people. This includes individuals at small, mid-size and large pharmaceutical companies, supplier and instrument/analytical companies, and contract development and manufacturing organisations (CDMOs). For those companies with employees working with propellant related inhalation/nasal products, this represents approximately 7-10% of total employees in those companies taken together, globally. Note that there is a large range of company total employee sizes, i.e., small to tens of thousands, and this overall average percentage includes several companies where percentage of employees (out of total employees) involved with pMDI and similar products can be as high as 80 – 100%.

Most respondents noted that they have company locations both in the EU and outside of the EU. Non-EU locations include the United States, the United Kingdom, and a several other global regions (i.e., “world-wide”). Several respondents noted that they only have company locations in the EU, while a few others noted locations only in the United States, the United Kingdom, and/or China.

Regarding company locations in the EU, respondents provided the following groups of information regarding impacts and changes in number of employees:

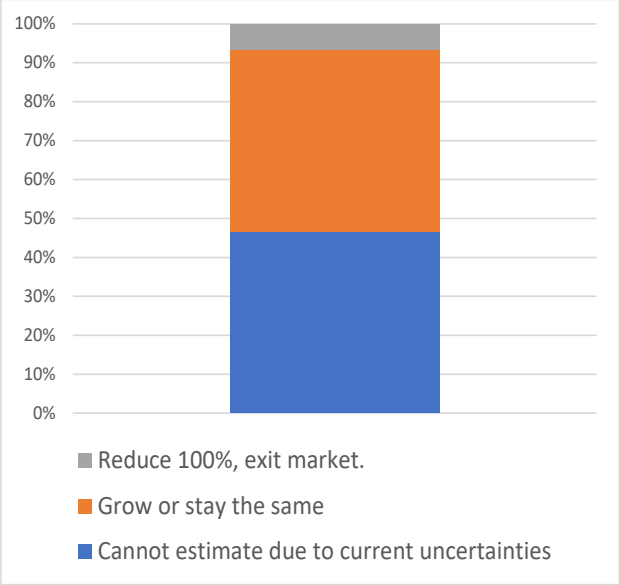


For company locations in the EU, if the potential ECHA PFAS restrictions that affect pMDIs **are NOT** implemented, how would you anticipate the number of employees (involved with pMDIs) in the EU to evolve over the next 10 years (starting with 2023)?

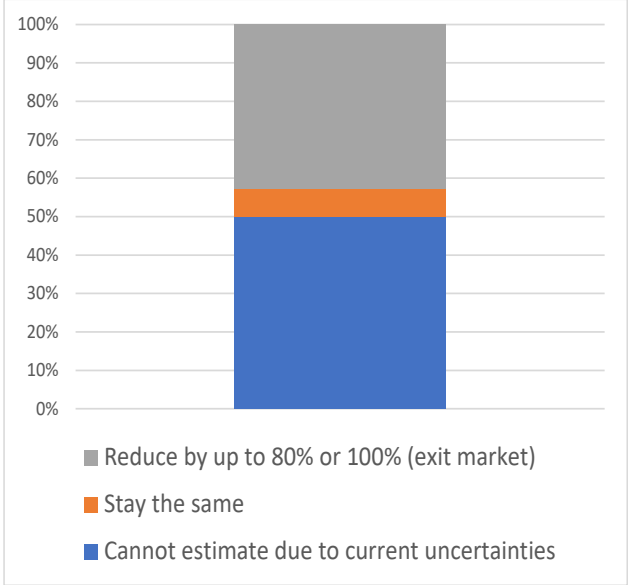


For company locations in the EU, if the potential ECHA PFAS restrictions that affect pMDIs **ARE** implemented, how would you anticipate the number of employees (involved with pMDIs) in the EU to evolve over the next 10 years (starting with 2023)?

For company locations anywhere, respondents provided the following information regarding anticipated EU income from pMDI sales:



Regardless of your company location(s), if the potential ECHA PFAS restrictions that affect pMDIs **are NOT** implemented -- anticipation of EU income from sales of pMDIs globally to evolve over the next 10 years (starting with 2023)? Growth has been estimated from 10-150%



Regardless of your company location(s), if the potential ECHA PFAS restrictions that affect pMDIs **ARE** implemented – anticipation of EU income from sales of pMDIs globally to evolve over the next 10 years (starting with 2023)?

Regarding estimated annual losses for EU income from sales of pMDIs globally, the companies who chose to respond indicated 50 million to up to 1 billion Euros in losses annually, as well as potential losses of up to 50% of total income when HFC-134a and HFC-227ea become unavailable or prohibited for use in pMDIs

All companies that indicated that they currently do not have EU locations, indicated that they would not seek to open an EU company location in the next 10 years, whether or not the ECHA PFAS proposed restrictions are implemented.

Because the ban as proposed could significantly reduce the availability of some pMDIs due to propellant type, we also surveyed the impact on other types of inhalation and nasal drug products that have been discussed as potential alternatives in some cases (depending on therapy needed, the specific patient and condition, etc.). The questions and responses are summarized in Table C-2. For all types of orally inhaled and nasal drug product surveyed, i.e., pMDIs, DPIs, soft mist inhalers, nasal sprays, and nebulizers and solutions/suspensions for nebulization, responses similarly noted the significant impact of the ECHA PFAS restriction proposal on broader PFAS applications (beyond propellant), leading to critical manufacturing, testing and supply chain losses and shortages.

Table C-2. For any pMDIs (besides propellants and canister coatings), dry powder inhalers (DPIs), soft mist inhalers, nasal sprays, nebulizers and solutions/suspensions for nebulization, what parts of supply chain/manufacturing/testing/packaging or final product is expected to be impacted by the ECHA proposed restrictions on PFAS

Key impact for pMDIs (besides propellants and canister coatings)	Examples
PFAS restrictions will impact manufacturing equipment, quality and safety testing and analysis. This will thus impact manufacturing of active pharmaceutical ingredients, excipients and final product. Alternate manufacturing equipment would need to be found and qualified.	• Lack of availability of PTFE coated materials in manufacturing storage. • Filters, seals, chemicals, coatings, components, tubing, lubricants, and maintenance sprays for manufacturing instruments and equipment • Engineering components and spares • Lubricants, foil, lab reagents and analytical equipment components and spares, filters, seals, chemicals, coatings, tubing, and PTFE materials used in testing, and potentially QC and synthesis reagents (e.g., TFA)
Development and manufacture of device parts. Any materials and components containing PFAS would need to be redesigned and/or alternate sources of components found and qualified	• Reduce or eliminate availability of valves and valve components (e.g., PTFE seals) • Reduce or eliminate availability of primary, secondary packaging materials and container closure system components. • Will impact release agents for moulding plastic materials and cleaning materials for components
Electronics for the factory, supply chain, offices, lab equipment, etc. may be more difficult to source as PFAS are used within the manufacture of electronics (the systems require very pure materials) therefore with no EU manufacturing potential, alternate markets may not be able to supply the components/end products.	

Appendix D
HFO-1234ze(E) Oxidation Pathways Information and Discussion

The OH radical initiated oxidation of HFO-1234ze(E) is summarised in **Figure 4,** 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 stable intermediates, trifluoroacetaldehyde (CF_3CHO) and formyl fluoride (HC(O)F). Ultimately, HFO-1234ze(E) degrades in the lower atmosphere rapidly and almost entirely to hydrogen fluoride (HF) and CO_2[76, 77]. The final yields of atmospheric breakdown products are dependent on pressure, temperature, and abundances of reactants such as nitrogen oxides, and hydroxyl radicals; each of these factors vary across different altitudes across Europe.

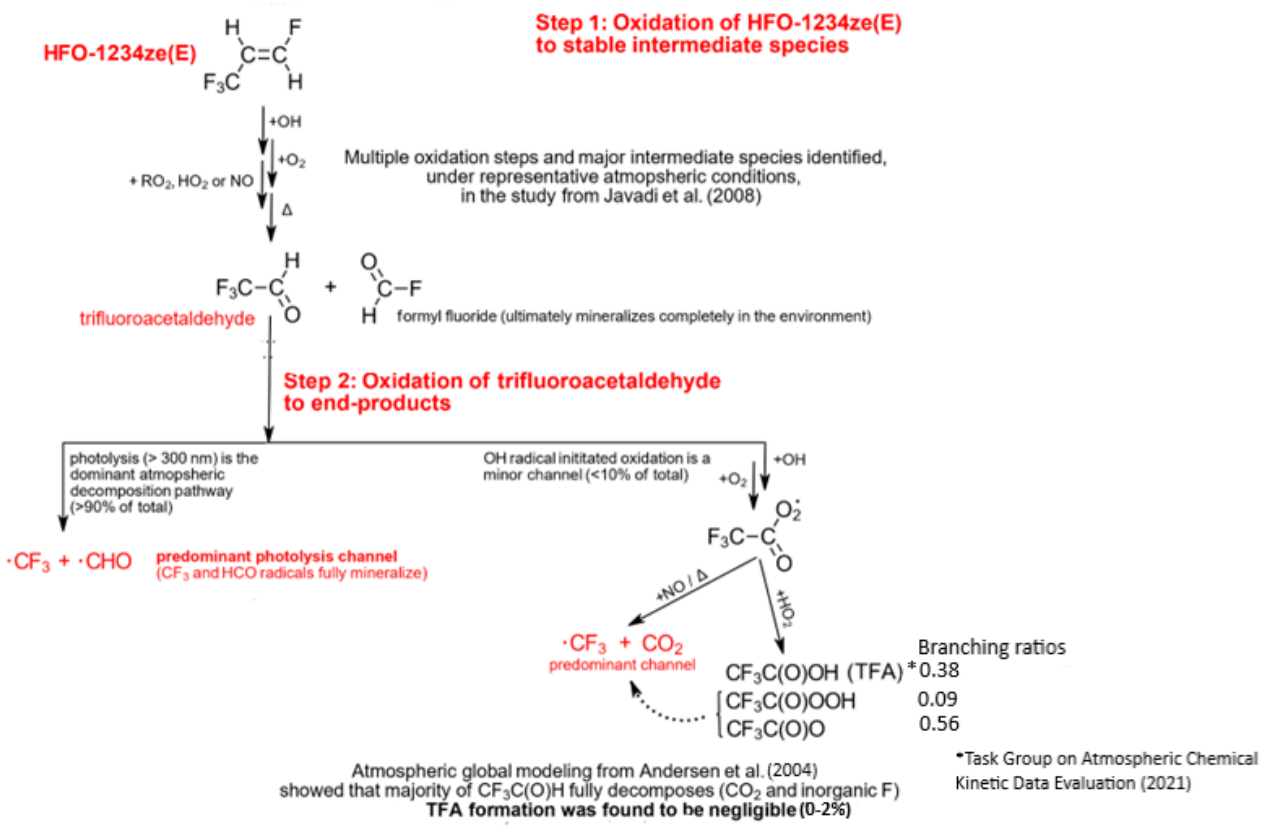


Figure 4. Atmospheric Oxidation and Photolysis of HFO1234ze(E). Based on published rate constants, the breakdown of HFO1234ze(E) will predominately result in its complete mineralisation, and between 0 to 2% forming trifluoroacetic acid, depending on abundance of oxidative species (NO, NO_2, HO, HO^*_2), in addition to the pressure and temperature of the atmosphere, through a series of minor side reactions. Higher NOx concentrations will reduce the TFA yield[78] [Figure source Javadi, et al.][77]

With regard to environmental persistence or bioaccumulation of HFO-1234ze(E), it was concluded in a European Chemicals Agency dossier that HFO-1234ze(E) does not meet P (persistent) or vP (very persistent) criteria, nor was it considered to meet B (bioaccumulative) or vB (very bioaccumulative) criteria *(European Chemicals Agency (ECHA reference TBC))*. Additionally, animal toxicology studies have demonstrated that HFO-1234ze(E) has an overall low level of toxicity[79].

One aspect of HFO 1234ze(E) degradation is the yield of small amounts of TFA. TFA has been identified as a PFAS arrowhead chemical. However, the Environmental Effects Assessment Panel under the Montreal Protocol recently concluded that TFA is considered non-toxic, with concentrations in the environment currently deemed too low to be a concern for human health or the environment.[80] It has been estimated by an IUPAC Task Group that the amount of TFA formed over time is below "the threshold for concern for human and environmental health."[81] Utilizing the underlying physico-chemical data (rate coefficients, quantum yields etc.) from evaluations performed by the IUPAC expert committee[82] the yield of trifluoracetic acid from HFO-1234ze(E) will likely be in the range between 0 to 2%, lower than the percentage yield given in the PFAS restriction proposal (page 49)[83].

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About Organizations

IPAC was formed in 1989 in response to the mandates of the Montreal Protocol and fully supported a timely and effective transition away from chlorofluorocarbons (CFCs) under the Montreal Protocol that balanced patient health and environmental concerns. IPAC's mission is to ensure that environmental policies relevant to inhaled therapies are patient-centric and appropriately balance both patient care and sustainability objectives. IPAC's members: AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Kindeva, Organon, and Teva. Further information available at www.ipacinhaler.org. *EU Transparency Register No. 602537137644-70.*

IPAC-RS is an international association that seeks to advance the science, and especially the regulatory science, of orally inhaled and nasal drug products (OINDPs) by collecting and analyzing data, and conducting joint research and development projects. Representing the OINDP industry since 2000, IPAC-RS aims to build consensus and contribute to effective regulations and standards by sharing the results of its research through conferences, technical journals, webinars, and discussions with regulatory bodies. IPAC-RS members are listed at www.ipacrs.org/about.

Both organizations are global in focus and engage in consultations around the world.