EFPIA response to the ECHA consultation on the Annex XV restriction report on Per- and polyfluoroalkyl substances (PFAS) - Restriction on the manufacture, placing on the market and use of PFAS

Introduction

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the biopharmaceutical industry operating in Europe. We advance the availability and accessibility of medicines, while fostering a competitive environment in Europe. While we support the need to restrict certain PFAS, we need to find the right approach for ensuring the continued manufacturing and availability of medicines in Europe. We have serious concerns that measures within the proposal for a universal ban on PFAS will accelerate the erosion of innovation in EU, discourage medicine manufacturing, jeopardise jobs and growth as well as negatively impacting patients' access to medicines.

The human pharmaceutical sector manufactures a variety of medicines which includes materials meeting the broad definition of PFAS. In addition to active pharmaceutical ingredients (API) captured within the definition used by the European Union in its proposed restriction, it applies for instance to building blocks and the raw materials used within chemical synthesis of PFAS and non-PFAS medicines, but also to reagents and equipment falling within the scope of the restriction. It would apply to packaging materials using fluoropolymers, or combination products such as pre-filled syringes. In addition, the whole process of manufacturing and developing medicines depends heavily on a number of PFAS materials in a wide variety of applications, and we would therefore not be able to manufacture medicines in Europe if the current proposal is maintained.

If the proposed restriction is implemented, a large number of important medicines will no longer be available. This is not only based on unavailability of replacement materials, but also because the time needed for regulatory processes to re-acquire approvals exceeds the given transition periods. In addition, the supply chain of pharmaceuticals is targeted by the restriction at many stages. Shortages of medicines lead to severe impact on human health of millions of patients within and outside of the EEA.

Paragraph 4.c. of the draft restriction proposal derogates active substances used in human and veterinary medicinal products. EFPIA welcomes the proposed time-unlimited derogations for API in the preferred Restriction Option 2 (RO2), recognising the essential role of fluorinated compounds in medicinal products. Any change to the molecular structure of an API or composition of the medicinal product would void regulatory approval and marketing authorisation. Human medicine manufacturing and development is a highly regulated environment where all parts of a process including environmental impact are assessed. The application of Title VIII of REACH and the consequences for marketing authorisations increase the risk of supply disruption, ultimately affecting the provision of medicines to patients. Though paragraph 4.c. includes a derogation for the API in human medicinal products, the Annex XV dossier as published would have an immense impact on human healthcare in Europe. However, we observe that the restriction text proposal has not identified the (bio)pharmaceutical health industry as sector. Indeed, some derogations set in paragraph 5 and 6 specifically address the use of PFAS by certain industry sectors such as paragraph 6.f. (petroleum and mining). This is problematic in the light of fair competition rules as promoted by the EU. Beyond that, we strongly support that authorised products such as APIs but also finished medicinal products be

derogated from the Restriction. Nevertheless, supply chain and development of medicinal products need also be taken into account.

The following uses of materials matching the wider PFAS definition were identified in the pharmaceutical supply chain:

- API meeting the PFAS definition according to 2001/83/EC as derogated, but also API for export without EU registration
- API in development stages (PPORD)
- Starting materials and chemical intermediates required to introduce the fluorinated function in API meeting the PFAS definition
- Ingredients other than API (excipients), such as propellants in inhalers
- Reagents, catalysts, solvents or auxiliaries used for the synthesis, purification or analysis of pharmaceutical ingredients
- Fluoropolymers in immediate packaging of finished pharmaceuticals such as tablet blisters or coated vial stoppers for injectables, or as sterile barriers
- Fluoropolymers in drug application devices such as pre-filled syringes or pens, either as coatings with pharma contact or as parts with mechanical function
- Fluoropolymers in production equipment such as reactors or pipework, seals or gaskets, or in laboratory equipment used in analysis or quality control
- Fluoropolymer containing consumables such as filters or gaskets in production or laboratories
- Manufacturing, storage and transport: non-polymeric PFAS in equipment, such as electrical components, refrigerants in HVACR equipment and low temperature refrigeration, refrigerants in storage and transport, including spare or replacement parts

A ban of these uses as drafted would not allow continued manufacturing of many APIs and ultimately medicinal products in the EEA, which conflicts with recent EU strategies to reduce dependency on supply chains located mainly outside of the EEA, and seems out of proportion. As the only common property of PFAS as claimed is persistence, their emission should be restricted rather than the use of the substances. If emission control is in place and covers the waste stage, a ban is neither justified nor proportionate, regardless of transition periods. This would be the case for industrial use under management plans as outlined by paragraph 8 of the restriction proposal.

API, medicinal products and medical devices are placed on the market under rigorous registration and market authorisation schemes, proving their beneficial health effects and safety of use. API also undergo an Environmental Risk Assessment (ERA). Environmental sustainability policies need to be consistent with sector-specific regulatory requirements and support the availability of safe medicinal products for patients and users. We encourage the adoption of evidence-based and proportionate policies taking into account the impact on patient access to medicines and medical technologies and foreseeing appropriate timelines to allow the highly regulated healthcare sector to implement any potential changes to its products and packaging.

To allow for the continued research, development and manufacturing of innovative medicines including biopharmaceuticals and vaccines, the products in scope of specific regulations should generally be derogated from a universal PFAS restriction, including all steps which are necessary for their manufacturing, packaging and delivery devices, in the EEA. While there is need to minimise emissions of PFAS, the chosen approach must ensure the availability of medicines in Europe, and their production here. The pharmaceutical industry is committed to building a healthier and more environmentally sustainable future. We do this by driving an agile, innovative, evidence-based sustainability strategy to enable the pharmaceutical industry to evolve in science, technology and society. Integrating sustainability across our entire value chain delivers quality-based, healthy and green outcomes while positively impacting the lives of patients. Industry is investing in partnerships to

develop[1] new and effective technologies, products and innovations that generate minimal waste throughout their lifetime of use in healthcare systems. Such innovations may include[2] environmentally friendly packaging materials and methods, increasingly reusable and recyclable medical devices, digital products and practices, among others[3,4,5].

EFPIA Response to the ECHA consultation on the Restriction Proposal

General Comments Section

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the innovative pharmaceutical sector in Europe. We welcome the proposed time unlimited derogation for active substances in human medicinal products within the scope of Directive 2001/83. The proposed derogation for active substances is part of necessary mitigation measures to prevent medicine shortage.

We are concerned that development and/or supply of medicines in the EU will be severely impacted by the PFAS Restriction as presently drafted, based on a broadened definition of "PFAS" and the wide applicability across many different uses. If implemented as proposed, production may become impossible in the long run. This concern is not only based on "missing uses" in the proposal, but rather on the scope of the restriction. It appears unbalanced and out of proportion in the following aspects:

Regulatory scope: the restriction proposal aims at substances and articles without derogating products where marketing is subject to specific regulations. For medicinal products and medical devices, these are granted market authorisations under Directive 2001/83, or permissions under the EU Medical Device Regulation (MDR) or EU In Vitro Device Regulation (IVDR), respectively. Restricting products under marketing authorisation or permission causes regulatory conflicts.

Substance scope: the substance group PFAS as defined in the regulation has no common hazardous properties. Fluoropolymers, for example, are non-hazardous, most are considered polymers of low concern by the OECD and some have food contact approval. Persistence of either the substance itself or its degradation products is the property of concern, but PFAS with demonstrated degradability are not derogated as such, so it cannot be claimed to be a common property of the regulated group.

Definition: the long-term goal of reducing emissions can only be achieved by a global restriction of PFAS, such as under the Stockholm convention. To facilitate this process, the definition of "PFAS" should be aligned as much as possible. The U.S. EPA working definition published in the fifth contaminant candidate list (CCL5) may serve as a blueprint.

Restriction Scope: the current proposal restricts the use of materials with certain structural properties, while the goal should be to reduce emissions of persistent chemicals. A re-adjustment of the scope from use to emissions would allow for innovative concepts, such as fostering circularity in the industrial use of fluoropolymers.

Restriction Options: if Restriction Option 1 (RO1) is applied, all chemical, pharmaceutical and biopharmaceutical manufacturing will have to move out of the EEA, as production and development depend on fluoropolymers and replacements are not available. Supply of medicines will be severely

[1] https://www.ihi.europa.eu/apply-funding/ihi-call-4
[2] https://www.efpia.eu/media/636524/efpia-eps-brochure_care-for-people-our-environment.pdf
[3] https://www.efpia.eu/media/554663/circular-economy.pdf
[4] https://www.efpia.eu/media/sydk5acr/white-paper-on-climate-change.pdf
[5] https://www.efpia.eu/media/gtbncsjc/survey.pdf

impacted, as approved active pharmaceutical ingredients (API) and medicines delivered within packaging and/or with drug delivery devices used to administer the medicinal products under market authorization are in scope of the restriction.

The same is true, to a lesser degree, for Restriction Option 2 (RO2). A socio-economic analysis (SEA) for the pharmaceutical industry/EFPIA prepared by EPPA[6] is provided in Annex 1.

Emissions depend on the use of the PFAS

In case of fluoropolymer in industrial use, PFAS are still part of the equipment at its end of life, and emissions could be controlled. In case of use of PFAS as chemicals or auxiliaries in Manufacture/Storage/Transport and Quality Control, substances can be used under controlled conditions to minimise exposure to the lowest level possible. The use of substances should not be restricted if the goal of the restriction can be reached by other means. This would apply, for instance, to fluoropolymers in industrial use under inventory and end-of-life management as outlined in Article 8 of the Restriction Proposal.

For packaging of medicinal products or medical devices, the emissions depend on local waste management. Most European countries have implemented incineration of medical or municipal waste or are moving towards this goal. The typical packaging use is a thin fluoropolymer film (PCTFE, ETFE or other) laminated with other plastics or elastomers, facilitating incineration. As published, PFAS could be mineralised when incinerated[7]. It is recognised however that the member companies of EFPIA do not operate incineration installations and therefore defer to the information provided by the waste sector federation(s) on the effectiveness of incineration methods.

In the case of PFAS API, the emission resulting from patient use is assessed as part of the marketing authorisation of medicinal products in an Environmental Risk Assessment (ERA). Pharmaceutical initiatives (Pharmaceuticals in the Environment, Innovative Medicines Initiative PREMIER[8]) aim at increasing the environmental compatibility of all API. In the case of unused PFAS API, disposal schemes are established and continually improved[9].

Alternatives do not exist for API. Introduction of fluorine in the API molecule is an essential part of developing efficacious and safe candidates. Any changes to an API molecule would essentially require the development of a completely new candidate. Due to the unique properties of individual molecular structures containing fluorine, alternatives for API, development products and their starting materials and intermediates do not exist, as the function of the substances is on the chemical molecular level.

Alternatives for fluoropolymers in production, packaging and devices may exist in some cases. However, the sought-after properties are outstanding resistance against heat, light, chemicals, time and abrasion, which is naturally linked to persistence. This means that close evaluation of alternatives is needed, as they may result in unintended consequences within the production process and may be persistent, too. In manufacturing and packaging, the use of fluoropolymers is closely linked to other sustainability considerations (recyclability, long service life or shelf life, production or transport resources/emissions, energy considerations etc.). These environmental trade-offs are not regarded when only the chemical nature of the material is regulated.

Benefits of fluoropolymers in production, packaging and devices include thermal and chemical stability, smooth hard surfaces that are easily cleaned and disinfected, and outstanding barrier

[6] www.eppa.com
[7] https://www.sciencedirect.com/science/article/pii/S0045653519306435
[8] https://imi-premier.eu/
[9] https://medsdisposal.eu/about-us/

properties protecting products from air, moisture, impurities, extractables and particles. This safeguards the safety and quality of products throughout their shelf life.

Other SEA topics: the ban of PFAS API as proposed in Restriction Option 1 has an expected impact on the industry of tens of billion Euros. The ban on manufacturing materials as outlined in both Restriction Option has an industry impact of hundreds of billion Euros (EFPIA SEA (Annex 1)).

Transitional period: the established substitution timelines (5 or 12 years) are tailored to technical substitution. They do not factor in regulatory timelines such as mandatory stability testing or re-submission of market authorisations for regulated products.

Requests for exemption or derogation

- A time-unlimited derogation for PFAS API as laid out in Restriction Option 2, to keep the products in question on the EEA market. Note: A ban would restrict patients' access to safe and approved medicine in Europe, for which there is no alternative. This would result in a shortage of medicinal products.
- A time-unlimited derogation of non-EU API (not registered under 2001/83) for export and development products (PPORD) to the scope of this derogation. A ban at any point in time moves production and/or R&D out of the EEA, and has patient impact when the supply chain is disrupted or clinical trials cannot be conducted in the EEA.
- A time-unlimited derogation of fluoropolymers in industrial use, under management plans (Article 8). Fluoropolymer presence is unknown in more complex products and devices, as no information, labeling, registration or disclosure requirements exists along the supply chain. Limiting the derogation to industry sectors (food and feed in 6a, petroleum and mining 6f) causes issues with definitions and justification. Emission can be controlled in the industry, and are limited to the waste stage.
- A time-unlimited derogation for packaging material of medicinal products and sterile barrier systems for drug delivery devices as in 6.l in Restriction Option 2, containing any fluoropolymers with approval instead of PCTFE only. Any substitution requires regulatory efforts in addition to the technical implementation, which must be regarded in the timeline to avoid disruption in the availability of medicines, and cannot be handled within 13.5 years.
- Additional derogations for identified specific PFAS uses in the pharmaceutical supply chain. These include starting materials, intermediates, reagents, solvents, catalysts and single or multiple use equipment necessary for the manufacture of pharmaceuticals or related processes such as quality control or diagnostic testing. They can be time-limited only if replacement materials are available and implementation throughout the supply chain in sufficient quality and quantity within the given time frame is safeguarded. Details are submitted under 6: Missing Uses.
- Exemption of all approved medicinal products from the scope of the restriction to avoid regulatory conflicts. This would include pharmaceuticals or medicinal products under valid market authorisations under Directive 2001/83.

Specific Information Requests

1: Sectors and (sub-)uses

Sector: pharmaceutical and biopharmaceutical industry.

This sector is missing from Table 9 of the Annex XV restriction report. Only the use as active ingredient, and coating of pMDI and PCTFE packaging materials are covered in Restriction Option 2 of the draft restriction. All (sub-)uses are missing for this sector, and are listed in 6: Missing Uses

2: Emissions in the end-of-life phase

As emissions depend on the use, information is included in the section 6: Missing Uses

Furthermore, close partnership across supply chains for medicinal products is needed to identify all sources of PFAS, to sufficiently manage emissions from waste streams, and where possible, to develop suitable alternatives that maintain the highly controlled environment required for efficacy and patient safety.

General overview on a medicines environmental risk assessment

In the EU a prospective Environmental Risk Assessment (ERA) is required since 2006 (CPMP/SWP/4447/00, 2006) when a marketing authorisation application (MAA) is submitted for a new Medicinal Product to be placed on the market or where there is potential for significant increase in environmental concentrations as a result of modifications to existing marketing authorisations (MAs), such as the addition of new indications. The EMA has scientific guidance on Environmental risk assessment of medicinal products for human use[10]

On the 26 April, the Commission adopted a proposal for a new Directive (Directive on the Union code relating to medicinal products for human use) and a new Regulation (Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) NO 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006), which revise and replace the existing general pharmaceutical legislation.
As part of this revision, the Commission proposes to strengthen the ERA requirements by:

- Refusal of a Marketing Authorisation based on environment concerns
- Manufacturing included in the environmental risk assessment of antimicrobials
- Prioritisation of ERA for legacy active pharmaceutical ingredients, which were placed on the market before 2006
- Increased interlinkage across non-pharma legislations
- Restrictions on hazardous medicinal products

As part of the revision, the industry (trade associations EFPIA, AESGP and Medicines for Europe) has proposed an extended environmental risk assessment (eERA)[11]. In summary the eERA aims to provide the following benefits:

- An API based ERA which better reflects the risks posed to environment from patient use
- Strengthen the industry's commitment to conduct robust and risk-based ERAs without compromising environmental protection or patient access to medicines

[10] https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use-scientific-guideline
[11] https://www.efpia.eu/media/677261/interassociation-paper-on-extended-environmental-risk-assessment.pdf

- Provision for the ability to automatically cross-reference ERA data in marketing authorisation applications
- Provide a mechanism for risk identification, refinement, and management during the MAA evaluation process
- Provide clarity on appropriate well-defined follow-up responsibilities for ERAs with no need for independent and duplicative risk identification and prioritisation processes under different legislations (e.g. Water Framework Directive)
- Updates to the ERA across the life cycle of the API in each MP in which it is contained that will ensure that each ERA reflects the latest environmental information
- A focus on risk that reduces the burden on regulators (i.e. oversight) and industry
- Reduction in the duplication of testing, delivering improved ERA consistency, proportionate use of testing resource, and bioethical benefits
- Suggestions for mechanisms to increase the transparency of, and access to, ERA data

3: Emissions in the end-of-life phase

Effectiveness of incineration under normal operating conditions

The member companies of EFPIA do not operate incineration installations and therefore defer to the information provided by the waste sector federation(s) on the effectiveness of incineration methods.

Collaboration

The pharmaceutical industry is open to continued collaborations and is investing in partnerships to develop new and effective technologies, products and innovations that generate minimal waste throughout their lifetime of use in healthcare systems. These include pilot take back schemes and the @Medsdisposal[12] campaign which raises awareness on how to dispose of unused or expired medicines appropriately in Europe.

4: Impacts on the recycling industry

EFPIA does not have information on this topic.

5: Proposed derogations

As tonnage and emissions depend on the material and use, this information is included in the section 6: *Missing Uses.*

6: Missing uses

Below in the tables, EFPIA provides information on the analysis of alternatives and socio-economic impacts on several PFAS uses that we identified as not covered in detail in the Annex XV restriction report. As part of the preparation of this work, EFPIA carried our various analyses which are detailed in the Annexes attached to our submission. These include:

Annex 1: **EFPIA Socio-economic analysis report prepared by EPPA**

> This analysis looks at the potential impacts of the restriction of the PFAS used in the production, packaging and delivery of human medicinal products. The report has been prepared by EPPA at our request, with the intention of providing regulators with strong evidence-based findings

[12] https://medsdisposal.eu/

on social and economic impacts that are expected to occur should PFAS be restricted under REACH. The SEA gathers technical and economic information to describe ex-ante in both qualitative and, where feasible, quantitative terms, the (orders of magnitude of) socio-economic impacts the pharmaceutical industry as well as the relevant EEA supply chain and society are expected to face as a result of a ban on PFAS. In particular, this SEA covers the function of PFAS APIs in human medicines as well as the crucial importance of PFAS at the different stages of the manufacturing process of medicinal products, and for immediate packaging and drug delivery devices. It will also describe the lack of available technologically suitable and economically viable alternatives, the technical difficulties associated with the substitution of PFAS via alternatives, the social and economic impacts from their restriction, and the broader impacts on society.

Annex 2: **Human Health Medicinal Products Sector Survey - Impact of Proposed PFAS Restriction on Patient Access to Medicines and EU Strategic Autonomy**

As part of the preparation of a submission to the ECHA consultation on the proposal for a universal ban on PFAS, the European based human pharmaceutical trade associations carried out a survey across their memberships to outline how the proposed PFAS Restriction could impact patient access to medicines and hinder the utilisation of pharmaceutical manufacturing capacity in the EU. The objective of this work was to gather evidence to justify derogations, to prevent medicine shortages to inform ECHA and the Commission of the potential impact of the PFAS Restriction on medicinal product supply chains.

The SEAC guidance (SEAC-52 of 15 September 20213)[13] on the preparation of the potential impact of a proposed restriction on consumers, notes an exception for medicinal products, where patients stand to lose the corresponding health benefit. It is our interpretation that the most important socio-economic impact to evaluate, is non-availability of medicinal products on patients. This was the basis behind our survey and preparation of this report.

Evidence suggests that for the continued research, development and marketing of medicines (biopharmaceuticals and vaccines), including all steps which are necessary for their manufacturing, packaging and delivery devices of medicines in the EEA, they should generally be derogated from a universal PFAS restriction. Furthermore, as currently for all PFAS use scenarios associated with the development, manufacture, and supply of medicinal products there are no suitable alternatives. This further strengthens the need for a derogation that encompasses all parts of the supply chain as this is a necessary medicine shortage mitigation measure.

The extensive raw data received can be made available to the ECHA scientific committees on request.

Annex 3: **Industrial Use of Fluoropolymers & Fluoro-Elastomers in Pharmaceutical Manufacturing Facilities (in collaboration with ISPE)**

Medicinal product manufacturing facilities are heavily dependent upon fluoropolymer components present in utilities, piping, equipment (process/utilities), & single use systems. While some alternatives exist, these materials are widely used to maintain safe working environments and enable the production of safe and effective medicines.

[13] https://echa.europa.eu/documents/10162/0/afa_seac_surplus-loss_seac-52_en.pdf/5e24c796-d6fa-d8cc-882c-df887c6cf6be?t=1633422139138

EFPIA worked in coordination with the International Society of Pharmaceutical Engineers (ISPE)[14] to compile a report on the industrial use of fluoropolymers & fluoro-elastomers in pharmaceutical manufacturing facilities. This included information gathered in a survey (August 2023) where the objective was to identify the impact of the proposed restriction on PFAS on various sectors of the pharmaceutical industry during the production and packaging stages. Responses were received from 130 companies of varying sizes with a very wide spread of activity such as supply of materials and manufacture of drug substance (small molecule and biologics), supply of materials and manufacture and package drug product (sterile and non-sterile), provision of analytical and manufacturing materials and equipment. The report also includes case studies/infographics identifying the various uses of fluoropolymers & fluoro-elastomers across medicinal product manufacturing facilities.

[14] https://ispe.org/

The drug development and commercial portfolio of medicinal products and starting materials used in manufacture has been investigated, and several substances meeting the proposed PFAS definition are currently used by EFPIA members. These substances can be categorised in the following groups e.g.:

Table: Active Pharmaceutical Ingredients (API)

- EU API that are PFAS by definition, and downstream products containing them (medicinal products) as derogated in Restriction Option 2 – **NOT** a missing use (paragraph 4.c.)
- API that are PFAS by definition, and downstream products containing them (medicinal products) intended for export, without EU API approval according to Regulation (EC) No 726/2004 or Directive 2001/83/EC
- Development products under product and process orientated research and development (PPORD) for API that are covered by the PFAS definition, and downstream products containing them (medicinal products); their manufacturing, medicinal product manufacture and application (e.g., clinical testing)

a) annual tonnage and emissions	Cumulated PFAS API tonnage or emissions not available in the SEA report	
b) The key functionalities provided by PFAS for the relevant use	Annex 1, SEA, Section 3.1.1, p. 22-23	Fluorine is the most electronegative element and being of small size and molecular weight is unique in the periodic table. These features mean it elicits powerful impacts on molecular properties of potential drug molecule in a precise and highly efficient way The benefits provided by the use of fluorine, and thus PFAS, include: (i) an extended biological half-life resulting in a significant reduction of the dose and dosing frequency of medicinal products; (ii) increasing permeability, binding affinity to the target and reducing drug efflux; (iii) reducing undesired side effects. Fluorination is typically employed to modulate and optimise all these properties in parallel. The modulation of pKa is also enabled by the introduction of fluorine. Its electronegativity attracts electrons allowing molecules to be made more acidic or basic depending on their overall structure and the precise location of fluorine atoms. This fine tuning of acidity and basicity may be crucial in the discovery of novel APIs.
c) number of companies in the sector affected	Annex 1, SEA, Section 2.2 p. 18-20 Annex 1, SEA, Section 3.1.2 p.28	All companies are affected. Essentially all the companies' manufacturing sites will either manufacture PFAS APIs or use PFAS materials during the medicinal product manufacturing, formulation and packaging processes. Fluoropolymers are standard materials for multipurpose API/medicinal product manufacturing equipment. They are essential components used in pharmaceutical manufacturing plants worldwide

d) The availability, technical and economic feasibility, hazards and risks of alternatives	Annex 1, SEA, Section 3.2.1, p. 34	Restricting drug design such that PFAS structure elements cannot be used in an API molecule would lead to less effective alternatives and complex or impractical development. All participating companies indicated that there are no suitable alternatives to PFAS APIs. Replacement of PFAS APIs in medicines would require the development of a new medicinal product, with all the time, cost and resource that would be required to discover, develop, manufacture and register a new medicine. Some structural groups have some of the features of fluorine containing substructures. For example, electron withdrawing capability similar to -CF2- or -CF3- groups can be found in carboxylic esters, amides, nitro, or cyano groups. Nonetheless, they differ in the other properties they confer on a molecule such as stability, permeability that can be problematic in achieving dose, potency and safety requirements. Replacement of stable fluoro-alkyl groups with other halo-alkyl groups such as chloro-alkyl can lead to reactive compounds with serious toxicity issues.
e) Where alternatives are not yet available, information on the status of R&D processes for finding suitable alternatives	Annex 1, SEA, Section 3.3.2, p.49	Creating, manufacturing, and obtaining approval for a new medicine to replace one which falls under the PFAS definition would require between 12 years (industry average) and 22 years in the worst-case scenario where repeated failed studies and several iterations may be required. The lack of ability to use PFAS containing features in medicinal chemistry (discovery phase) will likely lead to further extended development times owing to the increased challenge of discovering a medicine using a reduced medicinal chemistry tool kit. Perfluorinated substituents and their use in drug discovery have been studied in industry and academia for decades since the first use of fluorine in a drug molecule in the 1950s. Their unique role is very well understood and thus can be exploited to precisely alter important drug properties during the optimization process. Given the maturity of medicinal chemistry as a science it is considered extremely unlikely that direct replacements for, for example -CF3 and -CF2- substructures, will be found. This will lead to the requirement for more wholesale redesign of individual APIs to achieve the desired molecular properties with no guarantee of success, and likely with compromises in efficacy, safety and/or other environmental impacts.

f) Cases in which substitution is technically and economically feasible but more time is required	Answers in I-IV below	
I. the type and magnitude of costs (at company level and, if available, at sector level) associated with substitution	Annex 1, SEA, Section 3.3.2, p.48-50	The anticipated cost would be at least EU2.3 billion per API where PFAS API replacement proves feasible. This is based on average development time which could be longer given the reduced tool kit in the discovery phase (see e. above). The impact per company will vary dependent on the specific product portfolio, but a large pharmaceutical company may have several marketed pharmaceuticals containing PFAS substructures and more in development
II. the time required for completing the substitution process	Annex 1, SEA, Section 3.3.1, p.42, Figure 3 Annex 1, SEA, Section 3.3.2, p.48-50	As indicated in e. above replacement of single API would require between 12 years in the best-case scenario (industry average) and 22 years. Discovery and development of multiple replacement APIs concurrently would bring additional challenges for pharmaceutical companies, given the available resources. This will likely be leading to discovery and development of some replacement API being prioritised ahead of As a result, the manufacturers of medicinal products which participated to the survey highlighted that in the case of a PFAS restriction, the timelines are likely going to be longer, if we also take into consideration the time to re-adapt all production processes that rely on PFAS. As all these substitution efforts would need to be done in parallel, timelines are very likely to increase accordingly.
III. information on possible differences in functionality and the consequences for downstream users and consumers	Annex 1, SEA, Section 3.2.1, p.34	The impact on patients of removing PFAS containing APIs from the EEA would be significant, affecting the health of hundreds of thousands of patients. Replacement medicines, if they can be found would have different efficacy and safety profiles to the medicine being replaced, with no guarantee of their suitability for all patients. Currently, in therapeutic areas where medicines containing PFAS APIs coexist with non-fluorinated medicines, the two are not interchangeable. Due to their pharmacology and side effect profiles, a medical professional will select between them based on the unique circumstances of the patient such as health status, interaction with other prescribed

		medication or individual response. Limiting the options in a therapeutic class, would have a profound impact on the ability to treat patients with the most safe and efficacious medicine.
IV. information on the benefits for alternative providers.		
g) If substitution is not technically or economically feasible, information on what the socio-economic impacts	**<u>Patient Impact:</u>** Annex 2: Human Health Medicinal Products Sector Survey, Section 5.3.1 (R&D PPORD), Section 5.3.4 (APIs with PFAS moiety) + Section 5.4 (Patient Impact) Annex 1, SEA, **EEA manufacturers: 31 billion EUR** lost revenue (rounded, annually, 2027; 4.1.1, p.6) Annex 1, SEA, Plus 9 billion from unemployment (4.2.1., p. 67) Annex 1, SEA, Section 4.1.1, p.59-61 Annex 1, SEA, Section 4.2.1, p.65-67 Annex 1, SEA, Section 3.3.2, p.50 Footnote 52	169 APIs were reported to be undergoing process development, at an EU manufacturing facility. A PPORD derogation is necessary to support the research and development of new medicinal products containing both fluorinated and non-fluorinated APIs. In this way material manufactured in EU facilities can be used to supply clinical trials been conducted to meet unmet medical needs. PFAS containing APIs are approximately 5% of the API portfolios of the participating companies. While the product volumes (tonnes of API) are relatively small, these underpin much larger turnovers – and most importantly significant societal impact. […] The medicinal products containing PFAS APIs cover a wide range of diseases, including AIDS, malaria, depression, cancer, diabetes, multiple sclerosis, and inflammation. Many ... are indicated in the WHO's List of Essential Medicines. […] The participating companies indicated that a restriction on PFAS would require them to largely shut down the (PFAS) API production in the EEA and transfer production outside the EEA to continue supplying medicines. […] The companies emphasized that without a derogation for PFAS APIs (RO1), sales of medicines containing PFAS APIs would be cancelled in the EEA, reducing treatment options for patients and causing substantial economic impacts. The expected income generated through the sale of medicinal products containing PFAS API in 2027 (year of the entry into force of the proposed restriction plus 18 months of transition period) likely to be affected by a REACH restriction of PFAS used as an active pharmaceutical ingredient, is estimated at approximately 9.1 billion EUR/year (rounded). These

		medicinal products are produced in the EEA for the European and non-EEA markets (it must be noted that the EEA is a net exporter of medicinal products). […] As mentioned before, the survey does not cover the whole EEA pharmaceutical market. The market share covered by this survey represents approximately 40% of the whole EEA prescription drugs market. One can use the market share of the manufacturer companies which participated to the survey to extrapolate the total economic impact in the EEA across the whole EEA global prescription drugs market: 31 billion EUR (rounded). Accordingly, in the event of RO1, the economic fallout of a broad REACH restriction of PFAS APIs in the EEA would be therefore equal to at least 31 billion EUR. […] With the loss of business, action would be deemed necessary to reduce workforce. It is estimated that, assuming a PFAS restriction is implemented on PFAS APIs (i.e., assuming that equipment and other uses of PFAS in production of medicines containing non-PFAS APIs could continue unaltered), approximately 22,500 workers in the companies participating in the survey will face layoff in the EEA. […] At the level of manufacturers of human medicines, the total impact from unemployment in the EEA caused by a restriction of PFAS APIs is estimated at 9 billion EUR. […] It is important to note that the non-EEA production capacity would not be able to cope with the current EEA demand. There is not a readily available production capacity at biotechnology and chemical synthesis manufacturing facilities outside of EU-27. If global capacity is not available medicine shortages would become a realistic possibility.

Table Non-Active Ingredients (including Excipients)

- Excipients in pharmaceutical products containing PFAS residues
- Excipients in pharmaceutical products manufactured on equipment that utilises PFAS materials in its construction
- Propellants for metered dose inhalers (MDI) - not a missing use (mentioned in Table 2), but missing derogation

a. annual tonnage and emissions	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC)	According to the European Environmental Agency (EEA) Data reported to the United Nations Framework Convention on Climate Change, (Category 2.F.4a Metered Dose Inhalers), in 2021 the annual tonnage for medical HFA-134a and HFA-227ea was 984 tonnes and 59 tonnes respectively with reported GHG emissions 1280 KT and 198 kt CO2 equivalents respectively (Source: UNFCCC GHG Inventory, available at https://di.unfccc.int/time_series Accessed 110923)
	Excipients information aligned with the submission and analysis carried out by IPEC (International Pharmaceutical Excipient Council)	All drug products on the market contain excipients of which IPEC Europe members reported that up to 73% of which are likely to have been made on equipment that contains PFAS materials in its construction. The tonnage of the excipient industry is unknown as excipients come from many different industries chemical, foods and agriculture for example.
b. The key functionalities provided by PFAS for the relevant use	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC)	Fluorinated medical grade propellants used in MDIs , act as approved excipients and form part of the drug formulation. These propellants serve the crucial role of aerosolizing the active substance(s), facilitating delivery to the lung and ensuring therapeutic benefit. The advantage of fluorinated propellants is that they are in the liquid phase in the can when pressurised, and can vaporize when the MDI is actuated. The vaporization process, coupled with a constant pressure or force for each dose, enables consistent aerosolization of the active substance(s).
	Excipients information aligned with the submission and analysis carried out by IPEC (International Pharmaceutical Excipient Council)	In excipient manufacture PFAS materials are used widely in the manufacturing installation where they are used as seals, gaskets, pipelinings etc. For example: PTFE Seals for sample ports in stainless steel vessels– selected as they are water resistant, chemical resistant and hard wearing. PTFE lined tubing for liquid delivery – selected as they are water resistant, chemical resistant and hard wearing. PVDF rotors in mills selected for hard wearing nature and water resistance, alternative materials expand over time.

c. number of companies in the sector affected	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC) Excipients information aligned with the submission and analysis carried out by IPEC (International Pharmaceutical Excipient Council)	All companies who manufacture or import MDIs in the EU will be affected. Including wholesalers, in 2022 within the European Union it is estimated that over 70 companies provided MDIs to the patients that needed them. The majority of excipient manufacturing companies are affected, in a recent survey by IPEC Europe 55% of companies confirmed PFAS materials used in plant construction with a further 18% still investigating.
d. The availability, technical and economic feasibility, hazards and risks of alternatives	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC) Excipients information aligned with the submission and analysis carried out by IPEC (International Pharmaceutical Excipient Council)	Alternatives may not be available across all medicines or markets and are not appropriate for all patients. The Medical and Technical Options Committee to the Montreal protocol (MTOC) state that "Complex considerations are necessary when patients and healthcare professionals make an informed choice about a patient's inhaled therapy, taking into account therapeutic options, patient history, patient preference, ability (e.g., dexterity, inspiratory flow, vision) and adherence, patient-borne costs, as well as environmental implications, with the overall goal of ensuring patient health." (Source: 10.2 Technology options for treatment by inhalation, MCTOC 2022 Quadrennial Assessment Report. Available at https://ozone.unep.org/system/files/documents/MCTOC-Assessment-Report-2022.pdf). From IPEC Europe member feedback the potential replacement materials for the PFAS items used in construction of manufacturing equipment tend to be more reactive to chemicals and water, they are less hard wearing which could make them a potential contaminant in excipient and therefore drug product manufacture. This then becomes a GMP issue as "construction materials shall not be absorbative or additive to the excipient"
e. Where alternatives are not yet available, information on the status of R&D processes for finding suitable alternatives	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC) Excipients information aligned with the submission and analysis carried out by IPEC	The R&D process has identified two alternative MDI propellants HFA-152a and HFO-1234ze for further evaluation and product development, with a focus on decreasing global warming potential (GWP). The investigation into alternative materials for use in the construction of excipient manufacturing installations has not really started, much of it is outside our direct control

	(International Pharmaceutical Excipient Council)	and is the material used by equipment manufacturers and suppliers to the chemical and food industries.
f. Cases in which substitution is technically and economically feasible but more time is required	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC)	The development process for a MDI using an alternative propellant can typically take 6-10 years, encompassing formulation development, device development, non-clinical and clinical studies, manufacturing process development and scale up/establishment of the commercial supply chain. Taking the sequential nature of these activities into account, along with the need to complete them for each marketed product globally, more time is required.
I. the type and magnitude of costs (at company level and, if available, at sector level) associated with substitution	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC) Excipients information aligned with the submission and analysis carried out by IPEC	The company level cost of transitioning from current propellants is dependent on the number of products being transitioned and the number of regions where each product is marketed. It is also dependent on the complexity of the MDI, the extent of reformulation, and the associated safety and clinical development programmes required. The cost of replacing these materials in the excipient industry will be significant and cannot be easily estimated at this time.
II. the time required for completing the substitution process	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC)	Many companies are targeting 2030 for portfolio transformation but it is difficult to be definitive due to the normal uncertainties associated with medicines development, in particular if additional development studies are required. Take into account this target, along with the associated development uncertainties associated with portfolio transformation, a 12-year derogation for HFA-134a and HFA-227ea is required. Given the widespread use of these materials and the current lack of alternatives it will take a significant amount of time to evaluate potential replacements and make the substitution if at all viable.
III. information on possible differences in functionality and the consequences for downstream users and consumers	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC)	All changes made to a licensed medicine are reviewed and approved by the European Medicines Agency in accordance with their specific requirements. Performance must be compared between current and updated products (for example refer to 'Q&A on data requirements when replacing hydrofluorocarbons as propellants in oral pressurised metered dose inhalers', 30 March 2023, EMA/CHMP/83033/2023[15]). This will ensure that any updated products are fully assessed.

[15] https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-data-requirements-when-replacing-hydrofluorocarbons-propellants-oral-pressurised_en.pdf

		Excipients information aligned with the submission and analysis carried out by IPEC (International Pharmaceutical Excipient Council)	The use of more reactive and softer materials in the construction of excipient production equipment may lead to contamination of the excipient and more frequent replacement of these alternatives increasing the waste coming from the industry.
IV.	information on the benefits for alternative providers.	Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC)	The new propellants HFA-152a and HFO-1234ze both have considerably lower GWP compared with currently used medical propellants (124 and <1 for HFA-152a and HFO-1234ze compared with 1430 and 3220 for HFA-134a and HFA-227ea respectively). These properties are of benefit in the context of climate change and will support regional net zero emissions targets and compliance with local and global HFA phasedown under the Kigali Amendment to the Montreal Protocol.
g.	If substitution is not technically or economically feasible, information on what the socio-economic impacts	Annex 2: Human Health Medicinal Products Sector Survey, Section 5.3.5 (Excipients with PFAS moiety) + Section 5.4 (Patient Impact) Aligned to the position of the International Pharmaceutical Aerosol Consortium (IPAC)	All cases of PFAS use for excipients are related with the manufacture of small molecule based medicinal products and will affect at least 38 medicinal product manufacturing facilities which reported use of PFAS excipients during production of drug product. 86% are located in EU (Italy, France, Germany, Poland and Spain). Assuming potential lack of derogation or partial derogation in the near future, transition to new non-PFAS excipient will most likely not be completed across products and geographies. The consequence will be a shortage or a withdrawal of medicinal products from markets. As the current restriction proposal for medical HFA-134a and HFA-227ea would come into effect during the global portfolio transition period for European based MDI manufacturers and non-EU based MDI importers, this will impact the supply of currently marketed MDIs to both EU and non-EU patients who currently rely on these medicines. EU patients would not be able to access MDIs and supply of MDIs to non-EU patients would also cease until manufacturing could be relocated outside of the EU.

Table: **Fluoropolymers in Industrial Use: equipment and consumables**

- Chemical, pharmaceutical, biopharma, sterile production: fluoropolymers in production equipment (reactor lining, seals, gaskets, piping, anti-stick coating, surfaces, filtration units etc.) – fluoropolymers with product contact and quality impact, including spare or replacement parts
- Chemical, pharmaceutical, biopharma production: PFAS consumables and single-use material (filters, bags, tubes, etc.) – fluoropolymers with product contact and quality impact
- Production: fluoropolymers in complex equipment, such as insulation material, mechanical parts, including spare or replacement parts
- Analytical laboratory equipment, e.g., Teflon tubing, valves, gaskets, filters …

a) annual tonnage and emissions	See Annex 3 ISPE_Industrial Use of Fluoropolymers & Fluoro-Elastomers in Pharmaceutical Manufacturing Facilities	Annex 3 contains an explanation for the widespread use of fluoropolymer types associated with the manufacturing operations is provided for: - Small molecule & peptide manufacturing - chemical synthesis of an active substance - Bioprocessing facility - manufacture of an active substance using biological processes - Sterile manufacturing - aseptic processing of a parenteral medicinal product - Tableting process – dry product formulation of a solid dosage form
b) The key functionalities provided by PFAS for the relevant use	See Annex 3 ISPE_Industrial Use of Fluoropolymers & Fluoro-Elastomers in Pharmaceutical Manufacturing Facilities	Chemical Synthesis Manufacturing Facilities & Bioprocessing Facilities & Aseptic Processing Chemical / Corrosion Resistance Temperature resistance, Mechancial strength; Repellence properties / low coefficient of friction
c) number of companies in the sector affected	See Annex 3 ISPE_Industrial Use of Fluoropolymers & Fluoro-Elastomers in Pharmaceutical Manufacturing Facilities	A survey of ISPE members conducted in August 2023 indicated that at least 157 companies have manufacturing and/or packaging operations in the EU. Based on the membership of the trade associations representing actors in the human pharmaceutical sector, there at least 200 companies who depend on the use of fluoropolymers in manufacturing operations and are affected by the proposed Restriction.
d) The availability, technical and economic feasibility, hazards and risks of alternatives	See Annex 3 ISPE_Industrial Use of Fluoropolymers & Fluoro-Elastomers in Pharmaceutical Manufacturing Facilities	Chemical Synthesis Manufacturing - In certain applications, rather than use PTFE lined pipework and process equipment high nickel alloys and glass lined carbon steel pipe work could be used instead. However, pipework flanges will require PTFE sealing and gasket material. - A potential replacement that provides all key functionalities provided by fluoropolymers in particular PTFE will be hard to find. Any alternative with

		comparable chemical stability, corrosion resistance may be persistent in the environment, a case of regrettable substitution. Bioprocessing & Sterile Manufacturing - There are some alternatives in certain aspects of manufacturing (i.e. EDPM gaskets, silicone tubing) but they come with other risks (worker safety, product protection) that need careful management. PES is cited in the literature as a potential alternative filter MOC (material of construction) to PVDF, which is used in all low bioburden and sterile manufacturing processes. If re-execution of filtration studies was successful, ISPE member companies surveyed indicated that a complete replacement program could be in the order of 20 years. The industry moved away from stainless steel equipment trains to single-use systems that contain some fluoropolymer components to optimize yield and decrease waste from cleaning. Single use technology exhibits a lower environmental impact due to a reduction in demand for WFI, process water, steam and less requirement for cleaning and sanitization in place.
e) Where alternatives are not yet available, information on the status of R&D processes for finding suitable alternatives	See Annex 3 ISPE_Industrial Use of Fluoropolymers & Fluoro-Elastomers in Pharmaceutical Manufacturing Facilities	A potential replacement that provides all key functionalities provided by fluoropolymers in particular PTFE will be hard to find. The C-F chemical bond is one of the most stable bonds in organic chemistry leading to superior chemical resistance against acids, caustics, solvents, oxidizing materials etc. It is possible that any future alternative with the comparable chemical stability and corrosion resistance could be very persistent in the environment, leading to cases of regrettable substitution
f) Cases in which substitution is technically and economically feasible but more time is required	See Annex 3 ISPE_Industrial Use of Fluoropolymers & Fluoro-Elastomers in Pharmaceutical Manufacturing Facilities	
i. the type and magnitude of costs (at company level and, if available, at sector level)		Not evaluated

associated with substitution		
ii. the time required for completing the substitution process		Taking the PES filtration example described above - If re-execution of filtration studies was successful, ISPE member companies surveyed indicated that a complete replacement program could be in the order of 20 years.
iii. information on possible differences in functionality and the consequences for downstream users and consumers		In chemical synthesis facilities, non-fluoropolymer materials with inferior functionality, would increase the risk of leakage/release of aggressive substances/materials from closed manufacturing systems, thus creating risk of injury to employees. Biological active substances are more labile and sensitive to product quality impact, e.g. adsorption, aggregation, degradation, etc. when using non-fluoropolymer containing filters. Additionally, other filter materials have higher leachables which pose a greater risk to patient safety.
iv. information on the benefits for alternative providers.		Not evaluated
g) If substitution is not technically or economically feasible, information on what the socio-economic impacts	<u>Patient Impact:</u> Annex 2: Human Health Medicinal Products Sector Survey, Section 5.3.2 (Fluoropolymers used in the plant, equipment and single use systems within manufacturing facilities) + Section 5.4 (Patient Impact) See Annex 3 ISPE_Industrial Use of Fluoropolymers & Fluoro-	Supply chains of 93% of active substances involve EU manufacturing operations, which depend on fluoropolymers, within plant, equipment and single use systems. If the proposed PFAS restriction prohibits the supply of these critical raw materials, manufacturing operations at EU facilities will cease when contingency stock levels are depleted An alternative that exhibits all the properties of the fluoropolymers used in medicinal product manufacturing facilities is not available. If the proposed PFAS restriction prohibits the supply of these critical raw materials, manufacturing operations at EU facilities will cease when contingency stock levels are depleted. The number of active substances associated with manufacturing operations that are dependent on

	Elastomers in Pharmaceutical Manufacturing Facilities	fluoropolymer components in equipment and single-use systems is estimated to be at least 1794. These active substances are intended to treat conditions cancer, cardiovascular disease, diabetes, mental health disorders. A time unlimited derogation for the industrial use of fluoropolymers in medicinal product manufacturing facilities is a necessary medicine shortage mitigation measure

Table **Raw and Starting Materials, Chemical Intermediates, Reagents, Solvents, Auxiliaries in Manufacturing including Storage and Transport, Quality Control**

- Chemical and biopharma production of PFAS and non-PFAS APIs: PFAS reagents, catalysts and ligands or solvents, not becoming part of the API molecule – for example homogeneous catalysts like Crabtree-Pfaltz-type catalyst or other precious metal catalysts that feature CF_3-substituted ligands, TFA, hexafluoroisopropanol, trifluoromethanesulphonic anhydride, trifluorotoluene, …
- Chemical production of PFAS APIs: PFAS raw and starting materials and intermediates (building blocks of the API molecule).
- Chemical production of excipients: PFAS used as processing aid in the production of functional excipients
- PFAS materials and reagents used in quality control activities mandated by product licenses or regulations such as European Pharmacopoeia monographs. They include for example trifluoro acetic acid (TFA) in the mobile phase of high-performance liquid chromatography (HPLC), perfluoro butanoic acid (PFBA) as ion pair reagent in chromatography; N-methyl-bis(trifluoroacetamide) (MB-TFA), N,O-bis-trimethylsilyl-trifluoroacetamide (BS-TFA), and N-methyl-N-trimethylsilyl-trifluoroacetamide (MS-TFA) to derive silyl derivatives in gas chromatography or other methods.
- Manufacturing, storage and transport: non-polymeric PFAS in equipment, such as electrical components, refrigerants in HVACR equipment and low temperature refrigeration, refrigerants in storage and transport, including spare or replacement parts
- Quality control and research and development: PFAS other than fluoropolymers in equipment, such as electrical components, diagnostic laboratory testing, refrigerants in laboratory equipment such as temperature-controlled centrifuges

a) annual tonnage and emissions	Cumulated PFAS API tonnage or emissions not available in the SEA report. A cumulative quantative assessment is not possible for the pharmaceutical industry .	
b) The key functionalities provided by PFAS for the relevant use	Annex 1, SEA, Section 3.1.2, p.24	PFAS starting materials and intermediates are necessary to introduce fluorine into the PFAS API molecules. Direct late-stage fluorination of the API would not be selective and lead to APIs with substantial levels of other fluorinated impurities.

		In the manufacture of non-PFAS APIs, the use of PFAS as transient intermediates, such as triflates, for joining chemical substances together, can be advantageous. The highly electron withdrawing nature of some PFAS groups can effectively activate chemicals to reaction. There are alternative groups with similar electron-withdrawing properties (e.g., carboxylic esters, amides, nitro, or cyano), but due to their nature they can either be incompatible with chemistry or pose an elevated safety risk compared with PFAS (in some cases, substitution can have safety implications) PFAS used as reagents and processing aids have very specific properties that are required to achieve the desired quality during manufacture of medicinal products, but are not part of the final medicinal product. They are therefore important in the manufacturing of both PFAS containing and non-PFAS containing APIs. For example perfluorinated reagents are effective in the development of new chemical manufacturing processes as both activating reagents and catalysts .... PFAS such as Trifluoroacetic acid , trifluoromethanesulfonic anhydride, hexafluoro isopropanol and trifluoro ethanol are indispensable in solid phase peptide synthesis and analytical testing. … as well as an essential reagent in numerous Quality Control analytical procedures, such as high-performance liquid chromatography (HPLC). In these analytical laboratories, instruments as well as equipment that consist of or contain fluoropolymers is used.
c) number of companies in the sector affected	Annex 1, SEA, Section 2.2 p. 18-20	All EFPIA member companies are affected representing a market share of approximately 40% of the whole European Economic Area (EEA) prescription drugs market. PFAS are present in various stages of the manufacturing, R&D, and control processes of the participating companies' products. Essentially all the companies' manufacturing sites will either manufacture PFAS APIs or use PFAS materials during the medicinal product manufacturing, formulation and packaging processes.
d) The availability, technical and economic feasibility, hazards and risks of alternatives	Annex 1, SEA, Section 3.2.2 p.34	Manufacturers of human medicines which participated to the survey highlighted the complete lack of alternatives for the wide range of applications of PFAS used in the manufacturing process. A PFAS restriction would have a severe impact on the manufacturing of medicinal products in the EEA since chemicals falling under the current definition of PFAS are used throughout the manufacturing process.

		There are no alternatives to PFAS containing raw materials and intermediates where these contribute a PFAS substructure to the API. Direct late-stage perfluorination of the API would not be selective and lead to APIs with substantial levels of other fluorinated impurities Where not contributing a PFAS substructure to the API the use of alternative materials, where these could be identified, would result in lower yields for the synthesis of an API and increased waste, as well as significant costs and time for the development of new chemistry processes and obtaining necessary regulatory approvals. Each use case would require a separate evaluation within the specific chemical synthesis process, which would involve extensive testing and qualification procedures. There is no guarantee that comparable product quality levels could be maintained with any alternative materials, and this could lead to potential product safety concerns.
e) Where alternatives are not yet available, information on the status of R&D processes for finding suitable alternatives	Annex 1, SEA, Section 3.2.2 p.35	Identifying suitable alternatives for the auxiliaries and production materials that contain PFAS would require significant time and effort to investigate the functional specifications of potential replacements (see section 3.3.3). At present, companies have not been able to identify suitable alternatives. Each use case would require a separate evaluation within the specific chemical synthesis process, which would involve extensive testing and qualification procedures. There is no guarantee that comparable product quality levels could be maintained with any alternative materials, and this could lead to potential product safety concerns. For example In the manufacture of non-PFAS APIs, the use of PFAS as transient intermediates, such as triflates, for joining chemical substances together, can be advantageous. The highly electron withdrawing nature of some PFAS groups can effectively activate chemicals to reaction. There are alternative groups with similar electron-withdrawing properties (e.g., carboxylic esters, amides, nitro, or cyano), but due to their nature they can either be incompatible with chemistry or pose an elevated safety risk compared with PFAS
f) Cases in which substitution is technically and economically feasible	Annex 1, SEA, Section 3.3.3 p.50	It must be noted that for PFAS API and related raw materials, starting materials and intermediates no substitution is currently possible, as outlined in the Analysis of Alternatives (section 3.2). Thus, the time to find alternatives is unpredictable.

but more time is required		
I. the type and magnitude of costs (at company level and, if available, at sector level) associated with substitution	Annex 1, SEA, Section 4.1.3 p.64	There are no alternatives to PFAS containing raw materials and intermediates where these contribute a PFAS substructure to the API thus, in a conservative approach, the expected costs to switch to a PFAS-free alternative medicinal products can be conservatively estimated to be 2.3 billion EUR per medicinal product (rounded) due to additional investments in regulatory dossiers and manufacturing processes, including "developmental costs" to identify suitable alternatives, costs for reformulation and quality assurance, and costs for the transition to a full-scale production using the alternatives or altered formulations.
II. the time required for completing the substitution process	Annex 1, SEA, Section 3.3.3 p.51	These substitution activities ... need to be staged and together can take decades from the general availability of suitable alternatives. Therefore, longer transition times than those stated in the table [Table 2 on p51 of the Annex I SEA] would be required.
III. information on possible differences in functionality and the consequences for downstream users and consumers	Not available in the SEA Report	Assessment not possible yet, as alternatives have not yet been identified.
IV. information on the benefits for alternative providers.	Not available in the SEA Report	
g) If substitution is not technically or economically feasible, information on what the socio-economic impacts	Patient Impact: Annex 2: Human Health Medicinal Products Sector Survey, Section 5.3.3 (process chemicals) + Section 5.4 (Patient Impact)	There is a specified substance with a PFAS moiety in the medicinal product marketing authorisation filed for 18% of the active substances with EU manufacturing operations. These included raw materials, starting materials, intermediates, APIs and excipients. Only 139 APIs with PFAS moiety have been reported by the companies and would therefore fall under the proposed derogation for APIs.

	Annex 1, SEA, Section 4.2.2 p.67	Without additional derogations, the whole pharmaceutical industry will no longer be able to manufacture any APIs (whether classified as PFAS or non-PFAS APIs) or associated medicinal products in the EEA. Thus, the production will be moved out of the EEA. Accordingly, with the relocation outside of the EEA, action would be deemed necessary to reduce workforce, especially for those directly engaged in the manufacturing of medicines in the EEA. Therefore, it is estimated that, assuming a PFAS restriction is implemented on PFAS, even with derogation for active ingredients, but assuming that equipment and other uses of PFAS in production of medicines are no longer allowed as of 2027 (year of the entry into force of the proposed restriction plus 18 months of transition period), approximately 700,000 workers will face layoff in the EEA, which is equivalent to 100% of the current EEA employment. The social costs of unemployment associated with this scenario is estimated in the order of magnitude of one hundred billion EUR. Nevertheless, there is a high likelihood that the total social impact of a restriction of PFAS along the whole supply chain would be much larger than this, once all other economic operators having business linked to medicinal products are considered. Indeed, the pharmaceutical industry generates approximately three times as many indirect jobs, both upstream and downstream, compared to the number of jobs it directly generates. A considerable portion of these jobs are highly skilled (e.g., academia or clinical science). Thus, these jobs contribute to maintaining a robust knowledge base in the EEA and serve as a deterrent against a "brain drain" in Europe.

Table: Packaging of Medicinal Products or Pharmaceuticals: immediate packaging and barrier films

- Immediate packaging of medicinal products and API's such as containers or closures with product contact, using approved fluoropolymer materials or coatings such as PCTFE, ETFE or PTFE. Applies to blisters, sachets, tubes or other metal or plastic containers, vial stoppers or other coated elastomers. – NOT a missing use (§ 6. l), if "medicinal preparations" include pharmaceuticals (clarification on terminology required) and also limited to PCTFE
- Packaging containing fluoropolymer film for the protection of medicinal products or medical devices from air, moisture, other contaminants or to maintain sterility or stability as in § 6. m and n, but not restricted to individual products or materials - not a missing use (mentioned in Table 2), but missing a general derogation

a) annual tonnage and emissions	Cumulated tonnage or emissions not available in the SEA Report	
b) The key functionalities provided by PFAS for the relevant use	Annex 1, SEA, Section 3.1.3., p.29 - 30	Pharmaceutical API efficacy and performance are protected and guaranteed by the use of highly effective barrier materials. To ensure the drug remains stable and efficacious over registered shelf-life, tablets are packaged in 'blister' packaging to preserve and protect sensitive APIs in medicinal products. PFAS containing blisters deliver a medium to high moisture barrier while preserving transparency of the blister. The efficacy and preservation of moisture sensitive drug API is inextricably linked to the barrier performance of immediate drug packaging. High-performance fluoropolymers (especially PCTFE and ETFE) are vital to the containment, storage, and delivery of injectable medicinal products. The purpose of fluoropolymer coated elastomeric closures is to form a protective barrier to the elastomer in contact with the medicinal product, which is key to ensure product quality and patient safety, by: - Creating a barrier layer to inhibit the migration of elastomer chemicals into the medical product (leachables) that can potentially compromise medicinal product quality, stability and/or safety; - Creating a barrier layer to inhibit the absorption (i.e., loss) of constituents of the medicine into the elastomer and potentially leading to physical degradation of the elastomer and loss of functionality;

		- Creating a barrier layer to prevent the absorption of water into a stopper during steam sterilisation, which is important for the shelf-life of lyophilised injectable products. - Providing a smooth surface with low surface energy to avoid potential for adsorption of medicine onto the closure surface; - Enabling manufacturing and delivery of medicines by creating a protective and lubricious layer that will not delaminate, flake off, become a source of particles or deteriorate. - Facilitating sterilisation according to required GMP standards of fully coated stoppers due to the smooth hard surface The unique properties of fluoropolymers provide resistance to biological, chemical, and physical degradation. It is not plausible for a single non-fluoropolymer coating to achieve all the same benefits. In conclusion, fluoropolymer coated elastomeric closures are still state-of-the-art when it comes to the protection of highly sensitive parenteral medicinal product formulations, especially in the biotech field.
c) number of companies in the sector affected	Annex 1, SEA, Section 3.1.3, p.28	The manufacturers of human medicines do not produce immediate packaging but are instead downstream users. These materials are sourced from third parties (upstream suppliers) and then used in the packaging of a wide number of medicinal products.
d) The availability, technical and economic feasibility, hazards and risks of alternatives	Annex 1, SEA, Section 3.2.3, p. 37-38-39	According to major suppliers of packaging materials which contributed to this analysis, and the manufacturers of human medicines, i.e., downstream users of immediate packaging components, there are no alternatives that completely meet the performance and safety considerations of PFAS, such as PCTFE, ETFE and PTFE, in immediate pharmaceutical packaging applications. R&D efforts undertaken by major suppliers to develop products suitable for medicinal products have thus far been unsuccessful. All currently identified substances present several issues and concerns. The main key issues related to the lower performance of alternatives, include but are not limited to:

		- Alternatives have not been shown to provide an effective barrier to prevent chemicals from leaching into pharmaceutical products; - Alternatives have not been shown to provide required surface lubricity for functionality and effective performance of containment products; - Alternatives have been shown to have higher surface energy which negatively impacts biological product adsorption onto the containment products; - Alternatives have been shown to have a higher risk for particles/particulates in medicinal products. […] In summary, a change in immediate packaging components could have a number of potential impacts, including: - **Medicinal product stability**. PFAS coating is qualified as a low interacting direct medicinal product contact material. A medicinal product / new material of construction interaction may affect product critical characteristics over time (shelf life), that would require stability testing (2-5 years). - **Leachables**. The benefit of PFAS coating is to minimize elastomer leachables' migration into the medicinal product. A new material of construction may increase potential leachables quantitatively and qualitatively. Chemical species may migrate into the medicinal product over time, potentially impacting patient safety. - **Component functionality**. New materials of construction may affect the component functionality in its packaging system. Critical functions such as container sealing/integrity, coring/fragmentation/re-sealability may be affected over time (shelf-life). - **Manufacturing operations**. PFAS coating lubricity is beneficial to component storage and processing by mitigating stickiness/high friction during the manufacturing process. New materials of construction may affect the component's ability to be washed, sterilized and properly handled during fill/finish process. - **Regulatory constraints**. Immediate component materials of construction are registered with individual national/regional health authorities. Any change will require a registration update (long timelines).

e) Where alternatives are not yet available, information on the status of R&D processes for finding suitable alternatives	Annex 1, SEA, Section 3.3.3, p.53	PFAS containing packaging materials are in direct contact with the medicinal product. As such, they are part of the medicinal product qualification and authorisation. Replacement of fluoropolymer containing immediate packaging materials will involve long-term timelines based on: (i) upstream supplier innovation and material development; (ii) compatibility trials, verification/validation of lamination/coating processes, scale-up production, and distribution; (iii) qualification by pharmaceutical companies for use with pipeline and marketed medicinal products, manufacturing validation and subsequent review by the health authorities. Assuming a suitable alternative can be found, it would take multiple years of packaging development and validation, followed by verification and validation of the new packaging materials by pharmaceutical companies, compounded with time required for regulatory approval of the final product. Compatibility, as demonstrated by the drug stability, is required to be granted a marketing authorization for a medicinal product. Therefore, packaging material requirements are defined in mandatory technical specifications approved by the health authorities such as EMA for each drug. Changes in immediate packaging materials can affect stability characteristics will therefore require new stability testing. Hence, alternatives will require additional testing to demonstrate they meet mandatory specifications established before reapproval by global authorities. In general, any replacement of an immediate packaging material of medicine in the market triggers a full requalification with the relevant national/regional health authorities. Alternative materials for fluoropolymers would need to meet the strict requirements for medicinal products approval: extractable and leachable studies as well as stability and safety studies will be required for each product for which the replacements would be used. This process would take many years depending upon which global markets the products are licensed for patient use. There are several activities that would need to be performed by manufacturers, once a feasible non-PFAS alternative has been identified, to replace PFAS in immediate packaging components.

f) Cases in which substitution is technically and economically feasible but more time is required	Answers in I-IV below	
I. the type and magnitude of costs (at company level and, if available, at sector level) associated with substitution	Not available in the SEA Report for this use	
II. the time required for completing the substitution process	Annex 1, SEA, Section 3.3.3, p.54	Accordingly, the estimated time for a new immediate packaging material is estimated between 7 to 12 years (or more) from validation and commercial availability of a feasible alternative (as visually displayed in Figure 4). These timelines are subject to high uncertainty considering that upstream suppliers and pharmaceutical companies would be dealing with a completely novel – not yet available – material with no history of use. Moreover, every (bio)pharmaceutical company will be required to change many products at the same time. Bottlenecks for packaging related testing capacities during medicine production and impacts to continuous manufacturing volumes cannot be disregarded.
III. information on possible differences in functionality and the consequences for downstream users and consumers	Annex 1, SEA, Section 3.2.3, p. 37	The main key issues related to the lower performance of alternatives, include but are not limited to: - Alternatives have not been shown to provide an effective barrier to prevent chemicals from leaching into pharmaceutical products; - Alternatives have not been shown to provide required surface lubricity for functionality and effective performance of containment products; - Alternatives have been shown to have higher surface energy which negatively impacts biological product adsorption onto the containment products; - Alternatives have been shown to have a higher risk for particles/particulates in medicinal products.
IV. information on the benefits for	Not specified in the SEA Report	

alternative providers.		
g) If substitution is not technically or economically feasible, information on what the socio-economic impacts	Patient Impact: Annex 2: Human Health Medicinal Products Sector Survey, Section 5.3.6 (Packaging containing PFAS constituents or components) + Section 5.4 (Patient Impact) Annex 1, SEA, Section 4.1.2, p.62	There is currently no technically viable alternative for packaging. Packaging is part of registered medicines, therefore the regulatory environment requires toxicological evaluations, extractive and leachable studies and product stability to ensure the continued quality of the product. In addition, child resistance and patient usability studies may be required. All this takes over 10 years. This data will form part of a regulatory assessment and approval processes taking between 6 months to 2 years. According to the investigated supply chain, including major suppliers of packaging materials and their downstream users (i.e., pharmaceutical companies which participated to the survey), it may be necessary to evaluate the cost-effectiveness of substituting immediate packaging. If a substitution would not be feasible in the short term, as described in the earlier section on alternatives and timelines, sales of medicinal products containing packaging materials made using PFAS chemicals would likely cease in the EEA. Consequently, in the event of RO2, the economic cost of a REACH restriction of PFAS used in immediate packaging of medicinal products produced in the EEA is estimated at 11.6 billion EUR/year (loss in sales). Therefore, the total economic impact of a restriction of PFAS used in immediate packaging of medicinal products, measured by the loss of the contribution to the EEA economy is estimated to be in the range of 15.7 billion EUR, and 39 billion EUR (result of the extrapolation via the 40% market share).

Table : Drug Delivery Devices

- Fluoropolymer substances used in the functioning and components of devices used in single integral medicinal products regulated by Medicinal Product Directive 2001/83/EC, and EU MDR 2017/745 Annex I (General Safety and Performance Requirements) for the device component, as per MDR Art 117. Under this, it is accepted that the device component is compliant with EU MDR 2017/745 ('CE' marked), or conformance to EU MDR 2017/745 Annex I is evaluated and confirmed by a Notified Body if not 'CE' marked, or it is grandfathered under previous regulations (e.g., prefilled syringes, prefilled auto-injector pens, prefilled on-body delivery systems). NOT a missing use when the device component is coated (§ 6 d. coatings of Metered Dose Inhalers (MDIs) and § 6 j. coating applications for medical devices other than Metered Dose Inhalers), but a missing use for other applications (parts, membranes etc.)
- Fluoropolymer substances used in the functioning and components of medical devices used for designated medicinal products, packed separately or co-packaged with medicinal products, that are in compliance with EU MDR 2017/745 ('CE' marked) (e.g., reloadable injector pens, or empty syringes which may be packed with injectable pharmaceutical vial). NOT a missing use when the device component is coated (§ 6 d. coatings of Metered Dose Inhalers (MDIs) and § 6 j. coating applications for medical devices other than Metered Dose Inhalers), but a missing use for other applications (parts, membranes etc.)
- Fluoropolymer substances where their use is justified for the functioning and components of drug delivery devices in development of medical devices compliant with EU MDR 2017/745

a) annual tonnage and emissions	Cumulated PFAS API tonnage or emissions not available in the SEA report	
b) The key functionalities provided by PFAS for the relevant use	Annex 1, SEA, Section 3.1.4 (p31-34) PFAS used in Drug Delivery Devices and other Medical Devices	PFAS substances can be found in seals, silicones, lubricants, filters, barriers and coatings, which, are vital to the containment, storage, function and performance of the drug delivery device and administration of medicine to patients. - Fluoropolymers (generally PTFE and ETFE) minimise friction which allows smaller volumes to be accurately dosed from prefilled pens. Fluoropolymers provide for reduced user activation forces allowing device design specification and ISO requirements to be fulfilled. This allows for easy hand operation by most of the user population thereby enabling at home administration of specific therapies e.g., diabetes medicines, anti-inflammatory etc. Dosing accuracy is especially important for highly concentrated drugs and/or for paediatric dosing. Without

		the fluoropolymers the dose accuracy and device actitation force requirements cannot be met. - For particular devices, fluoropolymers form a barrier between the medicine and the walls of the container thereby minimising two-way interaction with the drug. - PFAS-containing silicone grease is used in autoinjectors to allow a delay function which ensures that the complete, accurate dose is delivered prior to the needle and syringe being retracted by the syringe retraction system. - Fluoropolymers are also used in prefilled syringes – this would be the coating on the elastomer closure within the syringe (the coated elastomer protects the medicine from the elastomer thereby minimising two-way interaction with the drug). - Drug delivery devices (Prefilled pens) and Reusable pens contain components made with a PFAS containing thermoplastic resin as well as PFAS coatings used as dry lubricant. The latter is key to minimise wear inside device. Without this, wear would occur at a much faster rate, reducing the expected lifetime of the reusable pen device. - pMDI canisters use a fluorinated coating; this is essential to avoid APIs and other excipients sticking to the surface, to preserve the quality of the medicinal product and to ensure the correct dose is delivered to the patient. It would also be more susceptible to chemical degradation by contact, which would also increase the dosage variability. Changing the canister coating would require reformulation, stability studies and regulatory approval by health authorities In conclusion, PFAS is widely used in drug delivery devices ensuring quality and accuracy in the delivered dosing, as well as increasing the lifetime in multi-use devices. Another relevant example of medical devices made of substances containing PFAS as an active principle are the ocular endotamponades for the cure of retinal diseases by surgery. Continued access to these substances as intraoperative tools is outstandingly important because without them, patients will suffer much poorer operative outcomes and worse vision. Liquid endotamponades like perfluorodecalin (PFD) and perfluorooctane (PFO) as well as gaseous endotamponades like perfluorocarbon, hexafluoroethane (C2F6), and octafluoropropane (C3F8) have become indispensable

		curative tools in the surgical therapy of serious and severe retinal diseases during the last few decades. They are used because of their unique physical parameters (high density) and the excellent biocompatibility by their inertness. The introduction of these substances in retinal surgery was in fact a genuine paradigm shift, and modern vitreoretinal surgery cannot be imagined without them. The introduction of intravitreal liquid perfluorocarbons as intraoperative devices in the 1990s proved to be a milestone in the development of surgery of the retina and vitreous body for complex eye diseases, as until then, it was not possible to adequately treat surgically. Their intraoperative application is vital to help cure (or at least alleviate) these eye diseases sufficiently. Back before these effective substances became available for intraocular tamponades, there were much higher rates of blinded patients. Their abolition would lead to a dramatic and incalculable rise in permanent severe vision impairments and even total blindness. Retinologists would be unable to handle the rising numbers of vitreous body interventions without relying on PFAS.
c) number of companies in the sector affected		
d) The availability, technical and economic feasibility, hazards and risks of alternatives	Annex 1, SEA, Section 3.2.4 (p39-40) PFAS used in Drug Delivery Devices and Other Medical Devices	**<u>Drug delivery devices</u>** According to the information that EFPIA's members received from upstream suppliers of drug delivery and medical devices regarding the alternatives and the possibility to transition to the alternatives, at present there are no commercially available drop-in replacements. Alternatives require more investigation and development to establish them as pharma grade materials (see Section 3.3.3 for details on substitution timelines). The PFAS materials currently in use have been extensively tested to ensure product quality is maintained throughout the shelf life. New materials of construction may affect the component functionality. Critical functions such as container sealing/integrity, dosing efficiency (break, loose/glide force/stiffness) coring/fragmentation/re-sealability may be affected over time (shelf-life). Changes of

		medicinal product immediate contact materials would require reformulation, stability studies and regulatory approval by health authorities. **Key issues with a potential replacement of PFAS include suitability with other materials, durability (some medical devices have longer lifetimes and the wear resistance of PFAS has added a level of durability), and component functionality (new materials may affect the component functionality, reducing mechanical properties).** **<u>Other medical devices</u>** Regarding the example of eye surgery products for retinology, materials (perfluoroctane, perfluordecaline, C2F6, C3F8) have currently no alternatives. For the last 40 years, gaseous tamponades like C2F6 and C3F8 have become indispensable, and there is to date no alternative to using them as tamponade substances in about half of vitreoretinal interventions. Without such tamponades, the surgeon's operative concept is incomplete and doomed to fail with the result that the affected eye will very probably go blind. Heavy oil, with per- and polyfluorinated components like perfluorohexyloctane or perfluorooctyl-2-methyl-4-ene, is employed as a short-term tamponade to treat the most severe types of retinal detachments, and there is no substitute for it to alleviate this particular condition[16].
e) Where alternatives are not yet available, information on the status of R&D processes for finding suitable alternatives	No reference as this is 'free text' that was not in the original SEA	PFAS substances can be found in seals, silicones, lubricants, filters, barriers, propellants and other parts, which, are vital to the containment, storage, function and performance of the drug product and the drug delivery device and administration of medicine to patients. These PFAS seals, silicones, parts etc. are mostly provided by external suppliers. EFPIA's members who are impacted by the Restriction have been working with their external suppliers since at least 2021 to find suitable alternatives which are technically and economically feasible. In many cases, alternative materials may be available however the alternatives may be suitable/applicable for some applications but not others. Additionally, any alternative would need to be assessed for compatibility and long-term stability with the unique product formulation prior to implementation.

[16] eltgen, N. and Hoerauf, H., 2019. Aktueller Stellenwert von schweren Flüssigkeiten als intraoperative Hilfsmittel bei vitreoretinalen Eingriffen. Der Ophthalmologe, 10(116), 919-924.

		No suitable alternatives have been identified, particularly in the manufacture of biologicals which are more labile and sensitive to product quality impact, e.g., adsorption, aggregation, degradation, etc. when using non-fluoropolymer containing filters and stoppers. If PFAS free materials are not commercially available, the sector could be faced with a 5–7-year process (SEA, Section 3.3.3 (p55-56) Timelines for substitution of PFAS in the Manufacturing Process, in Packaging Materials of Medicinal Products, and in Drug Delivery Devices) to develop a new drug delivery device with PFAS free materials for different uses and applications; additional testing time is also then required to assess compatibility of the new device with a medicinal product. If PFAS free materials could be identified, there would be numerous challenges to identifying a commercial supply of material and then to also qualify those materials. During this 'transition period' (if it is possible), costs will ultimately increase, there would be impacts on manufacturing process performance, reduced productivity, and no doubt delays in production, leading then to supply issues. With a change in material, Market Authorisation/Notified Bodies updates may be required, which could lead to a delay due to the increased number of change requests to the regulatory authorities. In the end, such delays could impact the manufacture and supply of drug delivery devices. Looking ahead, as our industry develops new devices, there is a concerted effort to specify and use PFAS free materials where technically feasible (e.g., Silicone lubricated or polyolefin lubricated grades are in development). At this stage, the timelines of bringing these alternative materials in sufficient commercial quantities to the market may not align with the timeframes in the Restriction proposal and definitely doesn't align with the timeframes set out in SEA Section 3.3.3.
f) Cases in which substitution is technically and economically feasible but more time is required	Answers in I-IV below	

I. the type and magnitude of costs (at company level and, if available, at sector level) associated with substitution	Not specified in the SEA Report	
II. the time required for completing the substitution process	Annex 1, SEA, Section 3.3.3 (p55-56) Timelines for substitution of PFAS in the Manufacturing Process, in Packaging Materials of Medicinal Products, and in Drug Delivery Devices	The estimated total development time for a new standalone medical device can vary. On average this takes approximately between 5 to 7 years from commercial availability of a feasible alternative. Additional testing time is required to assess compatibility of the new device with a medicinal product. When developing a new drug delivery or other medical device, there are several International Standards for [Medical] Device Development that must be considered as part of the device design and development process (US – 21 CFR, Part 820; EU – Medical Devices Regulation (EU) 2017/45 Annex I; ISO 13485). Device design development and commercialization occurs through several phases before it is launched 1. Phase 0 (Proof of Concept): - Demonstrated device performance with conceptual devices - User risk management (is the patient risk/benefit margin sufficient to proceed) - Initial PHA (preliminary hazard assessment) - Phase 1 (Planning): - Scope Statement: Resource/Timing estimates - Development Quality agreements - Design Inputs (based on stakeholder needs and requirements as well as system requirements) - Risk management plan - Shipping distribution master planning - Supply chain design

		2. Phase 2 (Design): - Master test plan, trace matrix - Purchased component/sub-assembly specifications/bill-of-material - Test method development - Container closure system - Device stability - Clinical trials - Label content, User manual - Shipping screening studies/max stress - Design iterations 3. Phase 3 (Verification & Validation): - Test method transfer - Specifications (including Materials, Lot release, and Packaging) - Design verification/"in-use" conditions - Shipping verification & validation - Process assembly control plan - Process validation - Design validation/Human Factors studies 4. Phase 4 (Design Transfer): - Transfer to Manufacturing Site - Specifications for components/sub-assemblies - Label content/IFU - Commercial Quality agreements - Project verification closure (Asset Delivery completion) - Process validation report - Site Quality plan (open Quality issue list) - Device Master Record (DMR) - Risk management
III. information on possible differences in functionality and	Annex 1, SEA, Section 3.2.4 (p40) PFAS used in Drug	Key issues with a potential replacement of PFAS include (a) suitability with other materials [in the device], (b) durability (some medical devices have longer lifetimes; the wear resistance of PFAS adds durability), and (c) component functionality (new materials

the consequences for downstream users and consumers	Delivery Devices and Other Medical Devices	may affect the component functionality, reducing mechanical properties). Additionally, alternative stoppers for container-closure integrity may impact device functionality, resulting in increased product quality complaints and possible missed doses for patients.
IV. information on the benefits for alternative providers.	Not specified in the SEA Report	
g) If substitution is not technically or economically feasible, information on what the socio-economic impacts	<u>Patient Impact:</u> Annex 2: Human Health Medicinal Products Sector Survey, Section 5.3.7 (PFAS constituents or components present in drug delivery devices) + Section 5.4 (Patient Impact) Annex 1, SEA, Section 4.1.2 (p62) Economic impacts of a restriction of PFAS used in the manufacturing process, immediate packaging, drug delivery devices and quality control Annex 1, SEA, Section 4.2.3 (p68) Broader consequences on the human health: patients	There is currently no technically viable alternative for drug delivery device, which are part of registered medicines, therefore the regulatory environment requires toxicological evaluations, extractive and leachable studies and product stability to ensure the continued quality of the product. In addition, child resistance and patient usability studies may be required. All this takes over 10 years. This data will form part of a regulatory assessment and approval processes taking between 6 months to 2 years. A PFAS restriction would result in prohibiting the import, manufacture, sale, and export of PFAS materials in drug delivery devices and other medical devices. If this restriction is implemented without any derogations, it would have significant consequences for patients access to those medicines in the drug delivery devices, to patient's using other medical devices and to companies in various aspects of their operations. It is complicated for manufacturers to make an accurate estimate as they currently do not have a complete visibility from their supply chain of all PFAS which are used in their production. <u>Economic Impact:</u> Based on the data received in the context of the Pharma Sector SEA Report relating to Medical Devices and Drug Delivery Devices, the total economic impact in terms of lost EBIT for pharmaceutical companies covering a 40% market share would be about 5 billion

		EUR over four years[17,18].Extrapolating to the whole market, a restriction of PFAS would have economic impacts in the magnitude of 12.3 billion EUR (lower bound estimate). In case of a restriction (both RO1 and RO2), the economic consequences of a REACH restriction of PFAS used in medical devices and drug delivery devices in the EEA is estimated at > 12.3 billion EUR. For this study, it has been decided to use a 4-year time horizon to estimate the socio-economic impacts, which is the time period suggested by SEAC when there is no suitable alternative available in general (SAGA). Data from seven companies out of 14 participants. For the purpose of estimating the lost EBIT, it was assumed that EBIT = 20% of the turnover (sales) for those companies who did not provide this information. The net EBIT loss is estimated at approximately 1.3 billion EUR/year. Total over four years is calculated using the Excel function =PV(3%,4,-1329000000,0,0). Patient Impact: Until alternatives are identified, tested and designed into Medical and Drug Delivery Devices, a Restriction on PFAS materials used in Devices will significantly affect the production, import and export of several human medicinal products in EEA and therefore would have serious consequences on the health of a significant number of patients in the EEA. Medical Devices and Drug Delivery Devices are used to treat a wide range of diseases which are included in the World Health Organization's List of Essential Medicines. Any sudden discontinuation of supply of these devices will affect production and result in sudden shortages of medicines in the EEA and abroad.

[17] World Health Organization, 2021. WHO Model list of essential medicines – 22nd list. https://www.who.int/medicines/publications/essentialmedicines/en/

[18] EFPIA and AnimalhealthEurope, 2022. EFPIA (Representing European Pharmaceutical industry) and AnimalhealthEurope (representing Animal Health Industry) position on use and risk of "per- and Polyfluorinated alkyl substances". https://www.efpia.eu/media/636866/pfas-position-_-efpia-and-animalhealtheurope-january-2022.pdf.

7: Potential derogations marked for reconsideration

As socio-economic impact and potential alternatives depend on material and use, this information is included in the section *6: Missing Uses*

8: Other identified uses

Although there is a time-unlimited derogation for the specific use of active substances used in human medicinal products in the EU, the sector was not identified in the restriction, including Table 8 and Table 9 of the draft proposal. Derogations for substances which do not cover their manufacture and development in Europe will initiate relocation outside of Europe. The current European share of global pharmaceutical revenue is 23.4%, and the estimated Research and Development spending is 41.5 bn Euro (2021, statista.com). The socio-economic impact analysis prepared for the innovative (bio)pharma industry (Annex 1) substantiates the consequences of the proposed restriction on the pharmaceutical industry and the availability of medicines.

9: Degradation potential of specific PFAS sub-groups

EFPIA does not have information to submit for this section

10:Analytical methods

Greater than 90% of all analytical testing on pharmaceutical ingredients and drug products utilize PFAS. These are present as reagents, consumables and in the instruments utilized throughout R&D, Manufacturing and Quality Control.

As currently drafted the PFAS restriction would limit the availability of replacement parts, necessary consumables, and reagents and would cause significant disruption to pharmaceutical company's legal obligations to analyze and release its registered medicines. This would result in the disruption of the supply of approved medicines to patients and the progression of future medicines in clinical trials.

An example of the impact to analytical testing would be the multiple components of an HPLC (High Performance Liquid Chromatography) system that are made of polymeric PFAS that enable analyses to be executed in a way that minimizes loss of compounds during analysis. In addition, there are a significant number of developmental, registered, and compendial HPLC methods (European pharmacopeia and other global compendia) that utilize trifluoroacetic acid as part of the mobile phase used for analysis. A primary source of PFAS in analytical are in the instruments and the vendors need to define and implement alternatives. Additionally, the amount of time and personnel to successfully navigate any post-approval changes for registered methods would be significant to enable the development of new medicines as well as ensuring adequate supply of approved medicines.

Therefore, any restrictions that do not include appropriate derogations either, time unlimited, or if time limited with a sufficient grace period to allow discovery, testing, validation and registration of alternatives to allow continued European and Global delivery of medicines to patients.

SECTION IV. Non-confidential attachment

- **Report:** EFPIA response to the ECHA consultation on the proposal for a universal ban on PFAS
- **Annex 1**: EFPIA SEA report prepared by EPPA
- **Annex 2**: Human Health Medicinal Products Sector Survey - Impact of Proposed PFAS Restriction on Patient Access to Medicines and EU Strategic Autonomy
- **Annex 3**: Industrial Use of Fluoropolymers & Fluoro-Elastomers in Pharmaceutical Manufacturing Facilities (in collaboration with ISPE)
- **Annex 4**: EFPIA information provided during the Call for evidence (2021)

SECTION V. Confidential Attachment

EFPIA did not submit confidential information to the consultation.