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SOCIO-ECONOMIC ANALYSIS

Of the potential restriction of the per- and polyfluoroalkyl substances (PFAS) used in the production, packaging and delivery of human medicinal products

SUBSTANCES: per- and polyfluoroalkyl substances (PFAS) used for medicinal products

FROM: European Federation of Pharmaceutical Industries and Associations (EFPIA)

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DISCLAIMER:

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ABBREVIATIONS

AML	Acute Myeloid Leukaemia
AoA	Analysis of Alternatives
API	Active Pharmaceutical Ingredient
BIO	Biotechnology Innovation Organization
C2F6	Hexafluoroethane
C3F8	Octafluoropropane
CA	Competent Authority
CAGR	Compound Annual Growth Rate
CCDS	Container/Closure and Delivery Systems
C-F	Carbon–Fluorine
CFDA	China Food and Drug Administration
CFF	Cold Form Foil
CFR	Code of Federal Regulations
CLL	Chronic Lymphocytic Leukaemia
CMO	Contract Manufacturing Organisation
COC	Cyclic Olefin Copolymer
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organisations
d.r.	Discount Rate
DMR	Device Master Record
DPI	Dry Powder Inhaler
EBIT	Earnings Before Interest and Taxes
EC	European Commission
ECHA	European Chemicals Agency
ECTFE	Ethylenechlorotrifluoroethylene
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHM	Extrahepatic Manifestations
EMA	European Medicines Agency
EPDM	Ethylene Propylene Diene Monomer
ETFE	Ethylene Tetrafluoroethylene
EU	European Union
EUR	Euro (currency)
EVOH	Ethylene-Vinyl Alcohol Copolymer
FDA	U.S. Food and Drug Administration
FEP	Fluorinated Ethylene Propylene
FEPM	Tetrafluoroethylene Propylene
FKM	Fluorine Kautschuk Material
FVMQ	Fluorosilicone
GMP	Good Manufacturing Practices
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HEOR	Health Economics Outcomes Research
HFPO-DA	Hexafluoropropylene Oxide Dimer Acid
HPLC	High-Performance Liquid Chromatography
MDR	Medical Devices Regulation
MHRA	U.K. Medicines and Healthcare Products Regulatory Agency
MSCA	Member State Competent Authority
NMR	Nuclear Magnetic Resonance
NPV	Net Present Value
OECD	Organization for Economic Co-operation and Development
P&ID	Piping and Instrumentation Diagram
PCTFE	Polychlorotrifluoroethylene

PE	Polyethylene
PFA	Perfluoroalkoxy Alkane
PFAS	Per- and Polyfluoroalkyl Substances
PFBS	Perfluorobutane Sulfonate
PFCA	Perfluoroalkyl Carboxylic Acids
PFD	Perfluorodecalin
PFDA	Perfluorodecanoic Acid
PFHxA	Perfluorohexanoic Acid
PFHxS	Perfluorohexanesulfonic Acid
PFM	Fluorinated Propylene Monomer
PFNA	Perfluorononanoic Acid
PFO	Perfluorooctane
PFOA	Perfluorooctanoic Acid
PFPME	Perfluoromethylvinyl Ether
PIC	Prior Informed Consent Regulation
pKa	-log of the acid dissociation constant
pMDI	Pressurised Metered Dose Inhalers
POP	Persistent Organic Pollutants Regulation
PPORD	Product and Process Orientated Research & Development
PPQ	Process performance qualification
PTFE	Polytetrafluoroethylene
PVC	Polyvinyl Chloride
PVdC	Polyvinylidene Chloride
PVDF	Polyvinylidenefluoride
R&D	Research and Development
RAC	Committee for Risk Assessment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RO	Restriction Scenario
ROI	Return on Investment
ROW	Rest of the World
SAGA	Suitable Alternative Generally Available
SEA	Socio-Economic Analysis
SEAC	Socio-Economic Assessment Committee
SVHC	Substance of Very High Concern
TFA	Trifluoroacetic Acid
USD	US Dollar (currency)
VMQ	Silicone Rubber
vP	Very Persistent
WHO	World Health Organization

DEFINITIONS

Active Pharmaceutical Ingredient:	**"***Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the medicinal product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body*" (European Medicines Agency)
Medical Device:	"*Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:* - *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,* - *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,* - *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,* - *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,* *and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.*" (Medical Devices Regulation (EU) 2017/745)
Medicinal (Drug) Product:	"*A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action*" (European Medicines Agency)
Drug Delivery Device:	*1. "Devices that when placed on the market or put into service incorporate, as an integral part, a substance that, if used separately, would be considered as a medicinal product, provided that the action of the substance is principal (Article 1(8) MDR). (European Medicines Agency)* *2. Devices intended to administer a medicinal product, where they form a single integral product intended exclusively for use in the given combination and which is not reusable (Article 1(9) MDR). Typically, these devices have measuring, metering or delivery functions.*" (European Medicines Agency)
Excipient:	"*A constituent of a medicine other than the active substance*" (European Medicines Agency)

Immediate Packaging:	"*The container or other form of packaging immediately in contact with the medicinal product*" (Directive 2001/83/EC)
Intermediate:	**"***A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated"* (European Medicines Agency)
Processing Aid:	**"***Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc)."* (European Medicines Agency)
Quality Assurance:	**"***The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained."*
Quality Control:	**"***Checking or testing that specifications are met."* (European Medicines Agency)
Raw Material:	"*A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or APIs*" (European Medicines Agency) A raw material is a substance or mixture of substances that is used at early non-GMP stages of the production process of an API, or which is not incorporated as a significant structural fragment into the structure of the API (e.g., solvent, catalyst, reagent, processing aid)
Solvent:	**"***An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.*" (European Medicines Agency)
Starting Materials & Intermediates:	"*A substance, intermediate, or API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure"* (it meets the definition of Intermediate as defined in REACH Article 3(15)) (European Medicines Agency)

1. EXECUTIVE SUMMARY OF SOCIO-ECONOMIC ANALYSIS

Topic	Answer	Source
Market share of the EEA prescription medicines market covered by this SEA Study	40%	See SEA p.17
% of Global Pharma Production in EEA	22%	EFPIA - Pharma Industry in Figures 2023
Value (EURs) of EU Pharma Manufacturing impacted by the Restriction (i.e., social impacts from unemployment in the EEA, and economic impacts (loss of EBIT) for manufacturers)	328 Billion EUR	See SEA p.14 & p.82
Value (EURs) of PFAS APIs impacted by the Restriction	40 Billion EUR	See SEA p.14
Value (EURs) of Medical Devices impacted by the Restriction	12 Billion EUR	See SEA p.14 & p.63
Value (EURs) of Immediate Packaging (Blisters & Elastomers) impacted by the Restriction	39 Billion EUR	See SEA p.14 & p.62
# of People employed directly in the EU Pharma Industry	700,000 (based on 2022 data)	EFPIA - Pharma Industry in Figures 2023
# of People employed indirectly in the EU Pharma Industry	x3 directly employed (based on 2019 data)	EFPIA - Pharma Industry in Figures 2023 - (PwC, Economic and societal footprint of the pharmaceutical industry in Europe, June 2019)
# of People employed directly in EU Pharma R&D	130,000 (based on 2022 data)	EFPIA - Pharma Industry in Figures 2023
# of registered pharmaceutical manufacturing sites in the EU	Italy (185), France (149), Germany (92), Spain (87), and Poland (84) - top 5 Member States	Source: European Commission

On 13 January 2023, the Competent Authorities (CAs) of Germany, the Netherlands, Sweden, Denmark and Norway submitted a joint REACH restriction proposal for a broad group of fluorinated substances. The proposed restriction under REACH aims to limit the risks to the environment and human health from the manufacture and use of a wide range of Per- and Polyfluoroalkyl Substances (PFAS).[1]

Notably, two restriction options (ROs) have been put forward. A full ban with no derogations and a transition period of 18 months (RO1), and a full ban with use-specific time-limited derogations (18-month transition period plus either a five- or 12-year derogation period) (RO2). RO2 also includes a few time-unlimited, more general derogations, including for PFAS used as active substances in human and veterinary Medicinal Products, as these are addressed under their respective regulations.

The submission proposal has been sent to the European Chemicals Agency (ECHA) and both the Committee for Risk Assessment (RAC) and the Socio-Economic Assessment Committee (SEAC) will provide an opinion. Once this phase is finalised, the proposal and the opinions of RAC and SEAC will be forwarded to the Commission for decision-making with the Member States in the REACH committee. The entry into force of a potential restriction is currently anticipated to take place at the earliest in 2025.

PFAS are a group of more than 10,000 synthetic (i.e., man-made) chemicals that are ingredients in various consumer, professional and industrial products. Many PFAS are efficient surfactants or surface protectors because of the perfluoroalkyl moiety's high chemical and thermal stability as well as its ability to repel water and oil. As a result, they have been produced in large quantities and used in a variety of industrial, commercial, healthcare and consumer applications since the late 1940s.[2, 3, 4]

The main concern of the lead Member State Competent Authorities (MSCAs) regarding PFAS is their high environmental persistence, significantly exceeding the very persistent (vP) threshold set out in Annex XIII of the REACH Regulation. Additional concerns emphasised by ECHA are mobility (M) of compounds or (bio)accumulation potential and toxicity, as well as long-range transport potential, accumulation in plants, and global warming potential.

This socio-economic analysis (SEA) focuses on the relevance of PFAS for the pharmaceutical industry in the manufacture of medicinal products. In addition to the many active pharmaceutical ingredients (APIs) captured within the definition used by the European Union in its proposed restriction, process chemicals and equipment used within chemical syntheses of PFAS and non-PFAS medicines would also fall within the scope.

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[1] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

[2] Banks, R.E., Smart, B.E., Tatlow, J.C., 1994. Organofluorine chemistry: Principles and commercial applications. New York (NY): Plenum. ISBN 978-1-4899-1202-2.

[3] Kissa, E., 2001. Fluorinated Surfactants and Repellents, 2nd Edition, CRC Press. ISBN 9780824704728.

[4] Buck, R.C., Franklin, J., Berger, U., Conder, J.M., Cousins, I.T., De Voogt, P., Jensen, A.A., Kannan, K., Mabury, S.A. and van Leeuwen, S.P., 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. *Integrated environmental assessment and management*, *7*(4), 513-541.

The report has been performed by EPPA[5] at the request of European Federation of Pharmaceutical Industries and Associations (EFPIA), with the intention of providing regulators with strong evidence-based findings on social and economic impacts that are expected to occur should this group of substances be restricted under REACH.

The assessment has been conducted in accordance with the existing official guidance from ECHA under REACH,[6] and it is based on information and data gathered from the manufacturers of human medicines that use PFAS in the manufacture of medicinal products and the suppliers of PFAS containing equipment, consumables, immediate packaging, and drug delivery devices.

Major manufacturers of medicinal products and drug delivery devices have participated in the survey, covering a market share of approximately 40% of the whole European Economic Area (EEA) prescription drugs market.[7] The assessment is, therefore, representative and can serve as a basis for defining the anticipated socio-economic impacts resulting from a restriction of PFAS chemicals for human medicines.

This 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.

Main findings and considerations

This SEA-Analysis of Alternatives (AoA) report concludes that:

- **Under the two restriction options (RO1 and RO2), a broad restriction of PFAS used in the production of human medicines will have disproportionate negative impacts on the European economy and society.**

- **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. As a result, the production will be moved out of the EEA.**

- **If global capacity is not available, medicine shortages would become a realistic possibility.**

[5] www.eppa.com

[6] The ECHA Guideline for an SEA to be used in REACH Application for Authorisation is available at: https://echa.europa.eu/documents/10162/23036412/sea_authorisation_en.pdf/aadf96ec-fbfa-4bc7-9740-a3f6ceb68e6e

[7] Estimated market share of the 14 companies that participated in the survey.

Conversely, the prospect that non-EEA production could provide for the loss of EEA production of medicinal products is to be considered totally unrealistic.

- **As a result, the PFAS restriction will have severe impacts on human health of patients in Europe and outside of Europe, but also on European competitiveness, on the competition in the internal market, on innovation, and on the overall trade balance.**

- **The replacement of PFAS is however limited by availability, technical applicability, and environmental trade-offs of alternatives which are to date not (readily) available. Finding alternatives is not guaranteed, and substitution (if possible) is a time-consuming process due to the legal requirements for quality, safety and efficacy in the sectoral legislation and guidelines. Additionally, fluorinated moieties continue to be critical components in development of new active pharmaceutical ingredients.**

- **The analysis reasonably justifies a time unlimited derogation of the whole process of human medicines developing and manufacturing – not just APIs – from the scope of the upcoming REACH restriction proposal, to avoid shortages of medicines which would lead to a detrimental impact on human health of millions of patients within and outside of the EEA.**

- A **time-unlimited derogation of PFAS chemicals is strongly recommended, covering the following uses**:

  i. **EU approved APIs manufactured for the EEA market**
  ii. **APIs manufactured for export without EU registration**
  iii. **APIs under development, prior to registration (PPORD) including non-EU regulated products**
  iv. **Non-active ingredients (excipients)**
  v. **Starting materials and chemical intermediates**
  vi. **Process Chemicals (Reagents, solvents, catalysts, auxiliaries in production and Quality Control)**
  vii. **Industrial Manufacturing Equipment including spare and replacement parts**
  viii. **Single or multi-use Consumables**
  ix. **Immediate packaging materials**
  x. **Drug delivery devices**
  xi. **Medical devices (as per EU MDR 2017)**

The above-mentioned statements are reasonably founded on the following evidence-based results:

- **Many decades of scientific research and innovation have focused on finding the optimal efficiency of APIs in human medicines, with the PFAS-moiety delivering unique properties including proven efficacy and safety (positive benefit-risk ratio).** Because they have received regulatory approval either centrally at the level of the EU (via the European Medicines Agency and through the European Commission), or in the Member States, APIs which fall under the proposed PFAS REACH definition have been used in the EEA

pharmaceutical industry as the most suitable API for a large spectrum of health benefits to patients (used in diverse indications).

- **The whole process of discovering, developing and manufacturing medicinal products, independently of whether the API would be classified as a PFAS, depends heavily on a number of PFAS chemicals in a wide variety of inter-related applications.** Although not all European medicinal product production depends on PFAS process chemicals (e.g., reagents, solvents, catalysts, auxiliaries in production and in Quality Control activities), the latter underpin a considerable number of medicinal products. The same applies to immediate packaging materials, drug delivery devices and medical devices. The situation is different for equipment: the entire manufacturing of medicines relies on fixed and consumable equipment containing PFAS materials. Thus, the entire portfolio of products placed on the EEA market (or exported) and produced within Europe is in danger of being impacted by the PFAS restriction.

- **There is no evidence of currently technically suitable and readily available alternatives which can substitute PFAS APIs.** No single "drop in" replacement exists, given that each API is not only treating a certain medical condition, but has individual properties like efficacy, side-effects, incompatibilities or drug interactions. Any replacement reduces therapeutic options, even if alternatives exist for any given condition.

- **Similarly, the Analysis of Alternatives shows that there are no appropriate chemical alternatives to PFAS chemicals across their uses in the manufacturing process including process chemicals, in equipment and ultimately in immediate packaging, devices and quality control**.

- Thus, **a replacement is not technically and economically feasible for all the following uses:**

  i. EU approved APIs manufactured for the EEA market
  ii. **APIs manufactured** for export without EU registration
  iii. APIs under development, prior to registration (PPORD) including non-EU regulated products
  iv. Non-active ingredients (excipients)
  v. Starting materials and chemical intermediates;
  vi. Process Chemicals (reagents, solvents, catalysts, auxiliaries in production and Quality Control)
  vii. Equipment and consumables
  viii. Immediate packaging materials.
  ix. Drug delivery devices
  x. Medical devices

- **Overall, when (and if) a PFAS substitute were ever to be found and implemented in the synthetic route of a commercial medicine, it may need to undergo an entire successful innovation cycle. As it is a new molecule, it would therefore require a whole development, from discovery to launch to the market:**

- **Creating, manufacturing, and obtaining approval for a new medicine to replace one falling under the PFAS definition** (PFAS APIs manufactured for the EEA market, for export, and for R&D purposes), as well as the substitution of intermediates, starting materials and process chemicals (including reagents, solvents, catalysts, auxiliaries in production and Quality Control) **would require between 12 years in the best case and 22 years in the worst case**, **from the moment a suitable alternative is identified**.

- **At the same time, substitution will also take place for all other uses of PFAS, including in the production process** (e.g., the replacement of PFAS in fixed and consumable equipment at pharmaceutical sites in the EEA can easily take decades), in immediate packaging materials of medicinal products that rely on PFAS (~7-12 years from general availability of a viable alternative) as well as in drug delivery devices and other medical devices (~5-7 years minimum, provided a viable alternative is available).

- These timescales are subject to a high degree of uncertainty considering that upstream suppliers and pharmaceutical companies would be dealing with completely novel – not yet available – materials with no history of use. **As all these substitution efforts cannot happen at once, but have to be phased in, they may take decades in total. Given the scale of the substitution, and the time and resources required to adapt all production processes in parallel, bottlenecks in the production flow must be considered a real possibility that cannot be ignored.**

- **Both RO1 and RO2 would have disproportionate socio-economic implications on the EEA pharmaceutical sector. The reader should bear in mind that although RO2 is a subset of RO1, the EEA impact would be the same because even with a derogation for PFAS APIs, without derogations for manufacturing in the EEA the effects would be the same.**

As virtually all medicines manufacturing within the EEA depends on the use of PFAS, the whole pharmaceutical industry will no longer be able to manufacture any APIs or associated medicinal products

- **At the level of the pharmaceutical industry, the total socio-economic impact of a REACH restriction of PFAS materials used in the manufacturing process (particularly equipment and consumables) is monetised at over <u>328 billion EUR</u>** (conservative estimates of net losses), consisting of: social impacts from unemployment in the EEA, and economic impacts (loss of EBIT) for manufacturers.

- Based on the data collected, it was also possible to derive sub-categories of impacts for individual key uses, including:

  - **> <u>40 billion EUR</u> (impact of restricting PFAS APIs alone)**
  - **> <u>12 billion EUR</u> (impact of restricting PFAS used in medical devices and drug delivery devices)**

- **> <u>39 billion EUR</u> (impact of restricting PFAS used in immediate packaging of medicinal products)**

The estimates reported in this socio-economic analysis should be considered as a minimum (lower boundary) of the expected impacts.

- From a broader perspective, the PFAS restriction is expected to have **severe impacts on human health**. The prospect that non-EEA production could provide for the loss of EEA production of medicinal products (≅ ¼ of global production) is to be considered totally unrealistic. **If global capacity is not available, medicine shortages would become a realistic possibility.** A sudden shortage of medicinal products in the EEA will reduce the number of available medicinal products resulting in **severe human health impacts.** This risk would be even more serious in the event of a PFAS restriction for the entire production process of medicinal products.

- From an EEA macroeconomic standpoint, the PFAS restriction will have impacts on the competitiveness, on the competition in the internal market, on innovation, and on the overall EU trade balance**.**

2. AIMS AND SCOPE OF THE SEA

2.1 Purpose, scope and methodology of SEA under REACH

On 13 January 2023, the CAs of Germany, the Netherlands, Sweden, Denmark, and Norway submitted a joint REACH restriction proposal to limit the risks to the environment and human health from the manufacture and use of a wide range of PFAS in Annex XVII of REACH.[8]

Substances and products can be derogated when they have a clearly defined legal status, such as in paragraph 4, where active ingredients for regulated products are listed. This derogation is extremely important to avoid negative impacts on human health, as any change to the molecular structure of an active pharmaceutical ingredient or composition of the medicinal product voids 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.

Given that medicinal products are not generally exempt from restrictions under Title VIII of REACH, APIs manufactured using PFAS starting materials, PFAS intermediates or PFAS process chemicals, are potentially in the scope of the PFAS restriction unless a derogation is included in the final Restriction.

Although in the currently preferred restriction option 2 (RO2) APIs are derogated indefinitely (time-unlimited derogation),[9] no derogation is envisaged for medicinal products and related manufacturing:

- APIs manufactured for export without EU registration
- APIs under development, prior to registration (PPORD) including non-EU regulated products
- Process chemicals (reagents, solvents, catalysts, auxiliaries in production and Quality Control)
- Equipment and consumables
- Medical devices
- Drug delivery devices
- Immediate packaging materials

Without the derogations suggested under Main Findings above, the manufacturing and supply of medicines would be effectively banned.

This REACH Restriction aims to ban the manufacture, use and placing on the market of PFAS, and is the most complex restriction ever proposed in the EU with significant impact and unintended consequences across various industries, including the pharmaceutical sector. In the proposed restriction, PFAS are defined as any substance containing at least one fully fluorinated methyl (CF3-)

[8] https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/72301/term

[9] Paragraph 4 c of the draft restriction proposal.

or methylene (-CF2-) carbon atom (without any hydrogen, chlorine, bromine, or iodine attached to it). The definition is based on the OECD definition of PFAS published in 2021 and covers over 10,000 PFAS, including some fully degradable subgroups. However, these fully degradable subgroups, which are defined by their key structural elements and do not display the high persistence that is the main concern with PFAS, are excluded from the scope of the restriction proposal.

Certain compounds that fall within the PFAS definition have already been (or are currently in the process of being) restricted under REACH: PFOA, PFHxA, PFHxS, C9-C14 PFCA. Other members of the group are under authorisation procedures (e.g., HFPO-DA, PFDA, PFNA), or recognised as Substance of Very High Concern (SVHC) (e.g., PFBS). Further applicable measures on certain compounds of the group stem from the POPs Regulation, PIC Regulation, Food Contact Materials Legislation, and new Drinking Water Legislation.

This *ex-ante* Socio-Economic Analysis aims to identify and to assess in both qualitative and quantitative (when feasible) terms the socio-economic impacts on the pharmaceutical industry that are expected to occur in case of a REACH restriction to this group of substances, covering the generalised use and importance of PFAS used at different stages of the manufacturing process of medicinal products, in quality control or fluoropolymers used in manufacturing equipment, immediate packaging materials and drug delivery devices.

A survey has been conducted using a detailed questionnaire to gather information and data from 14 major manufacturers of human medicines, members of EFPIA, likely to be affected by a PFAS restriction in the EEA. The participating companies have provided socio-economic data in view of extrapolating (based on a large total market share) the impacts for the whole market in a conservative approach, as further detailed below. Based on the estimated total EEA market for medicinal products, the market share covered by this survey represents approximately 40% of the EEA prescription medicines market. **The estimates reported in this socio-economic analysis should be considered as a minimum of the expected impacts (lower boundary).**

The assessment has been conducted in accordance with the existing official guidance on SEA from ECHA under REACH Restrictions.[10] ECHA has developed a solid methodology for conducting socioeconomic assessments in the context of the REACH Regulation, with the support of a dedicated committee (i.e., SEAC). More specifically, this methodology is consistently applied for REACH applications for authorisation of SVHC, and REACH restrictions for certain hazardous substances with a view of forecasting through the SEA the impacts of the different regulatory options.

10 The ECHA Guideline for an SEA to be used in REACH Restrictions is available at: https://echa.europa.eu/documents/10162/2324906/sea_restrictions_en.pdf/2d7c8e06-b5dd-40fc-b646-3467b5082a9

From a geographical perspective, this analysis focuses on the EEA territory, comprising of the European Union (EU-27), Iceland, Liechtenstein, and Norway. 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).[11, 12]

In other terms, the SEA accounts for the benefits to the EEA society in the event PFAS are prohibited from being manufactured, used, and placed on the market, and/or for the socio-economic costs of a complete ban (REACH restriction) starting from the year 2027 (year of the estimated entry into force of the proposed restriction including 18 months of transition period).

Future monetary values have been estimated by using the concept of net present value (NPV), adopting a 3% annual discount rate (d.r.), which is the standard discount rate, adopted by the European Commission and European agencies (e.g., ECHA) in impact assessments.[13] All monetised values have been adjusted to a base year, assumed to be 2027. Information and data have been aggregated and anonymised. Statements and estimations from the participating companies are as close to real data or perception of future changes as possible.

2.2 Overview of human medicinal products and their value chain

The EFPIA member companies are manufacturers of APIs and/or medicinal products (which are packaged into sachets, blisters, bottles, vials, cartridges or drug delivery devices). The pharmaceutical companies perform research and development activities, manufacture, prepare and submit regulatory dossiers to receive marketing authorisation and then supply and sell medicinal products, and/or drug delivery devices, in the EEA and non-EEA markets.

The human medicines industry plays a critical role in improving and maintaining public health with medicines being essential for preventing, treating, curing and diagnosing a wide range of diseases and medical conditions including but not limited to: cardiology, diabetes, metabolism, infectious diseases, oncology, haematology, human growth hormone disorders, pulmonary hypertension, renal, endocrine diseases, ophthalmology, radiology, haemophilia, respiratory, obesity, immunology, and neurology.

Human medicines can be administered orally, topically, intravenously or through inhalation and exist in a wide range of forms, including pills, tablets, capsules, injections, and liquids. In order to handle new health concerns such as, for example, antibiotic resistance, pandemics, HIV or cancer, the development of novel drugs and treatments is also essential. In recent decades, the pharmaceutical industry has made great achievements, introducing cutting-edge new medications that have revolutionized the way many diseases are treated and controlled.

11 https://echa.europa.eu/documents/10162/13637/ec_note_suitable_alternative_in_general.pdf/5d0f551b-92b5-3157-8fdf-f2507cf071c1

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

13 European Commission, 2021. Better Regulation Guidelines and Toolbox. https://commission.europa.eu/document/download/9c8d2189-8abd-4f29-84e9-abc843cc68e0_en?filename=br_toolbox-nov_2021_en.pdf

The pharmaceutical companies either directly produce APIs and medicinal products themselves in their own manufacturing sites, located within and outside the EEA, or these are produced and supplied by external contract manufacturing organisations (CMOs) in the context of a global supply chain. Contract manufacturers are based inside and outside the EEA and work under long-term manufacturing and supply agreements. These manufacturing sites in third countries need to comply with EU Good Manufacturing Practices (GMP) requirements and are subject to regulatory inspection by European Member State Authorities.

APIs are used in the formulation step of the final medicinal products. Generally, one API can result in different medicinal products, formulated either alone or in combination. As finished products can contain several combinations of different APIs, some of the medicines end up containing multiple APIs, both responding or not to the PFAS definition. Thus, the number of medicines impacted is expected to be much higher than the number of PFAS APIs. APIs might have an exclusive European marketing authorisation or an exclusive non-European marketing authorisation, or both.

The EFPIA participating companies are also manufacturers and/or importers of chemical intermediates and excipients. The companies utilise starting materials, chemical intermediates to build in PFAS moiety in the API, process chemicals (i.e., chemicals used in the API synthesis process for other purposes than introducing a PFAS moiety in the API; for example, reagent, solvent, catalyst, processing aid), immediate packaging, and drug delivery devices in addition to a wide range of consumables and fixed equipment parts and materials/reagents used in Quality Control activities.

These components and materials are manufactured or sourced from within and outside of the EEA. The participating companies have their own R&D facilities (within and outside of the EEA) and are also involved in the supply and sale of medicinal products and medical devices. Depending on the final medicinal product or device concerned, it is distributed to countries within the EEA or in Rest of the World (ROW).

These companies, or the contract manufacturers on behalf of these companies, usually source transported isolated intermediates falling under the definition of PFAS, raw materials, packaging materials, device parts and/or equipment and consumables containing PFAS from third-party suppliers. In doing so they ensure quality controls according to Quality Agreements between the entities, GMP and other regulations. They then manufacture the API, formulate the medicine, including the filling, packaging and labelling, ready for final use. This entire process must comply with the marketing authorisation granted for the product by the European Medicines Agency (or individual Member State Health Regulatory Authorities). Pharmaceutical manufacturers typically own the intellectual property and the marketing authorisation of the medicines, even when manufactured by external CMOs.

In addition, **PFAS are present in various stages of the manufacturing, R&D, and control processes of the participating companies' products**. Throughout their supply chains, materials, consumables, and equipment are used that contain or are made of PFAS. A significant number of the APIs that the companies manufacture is considered PFAS. As such, upstream starting materials and chemical intermediates, that are building blocks for the PFAS API, will also be PFAS owing to the need to introduce the requisite fluorine groups into the final PFAS API molecule. The solid or liquid medicinal products formulated using those PFAS APIs will therefore also contain PFAS.

PFAS reagents are also used in the chemical synthesis of non-PFAS APIs. PFAS-containing immediate packaging materials, that are mainly manufactured by suppliers, include coated plungers and injection stoppers (coated with either ETFE or PTFE films), PCTFE-containing blisters for tablet immediate packaging (contains layers of PVC/PE/EVOH/PCTFE), sachet foils (contains PFAS/PE co-extruded), and lacquered aluminium tubes. PFAS are also essential components of medical devices and sterile product closures. The manufacturing equipment of the companies also extensively use PFAS. Teflon-lined pipes, for example, are widely used in API manufacturing facilities due to their unique chemical properties (cf. Section 3.1.2 for details).

Essentially all the companies' manufacturing sites will either manufacture PFAS APIs or use PFAS materials during the medicinal product manufacturing, formulation and packaging processes. Production sites that manufacture or use PFAS are located in numerous countries within the EEA; these include but are not limited to Ireland, Belgium, France, Italy, Germany, Spain, Sweden, and the Netherlands. External CMOs operate in various sites across numerous EEA countries.

Following regulatory approval, medicinal products are distributed through a network of subsidiaries and distributors, to finally reach patients through pharmacies, public and private hospitals and clinics, ambulatories, and trade channels (i.e., wholesalers).

Accordingly, the typical supply chain for medicinal products is as follows:

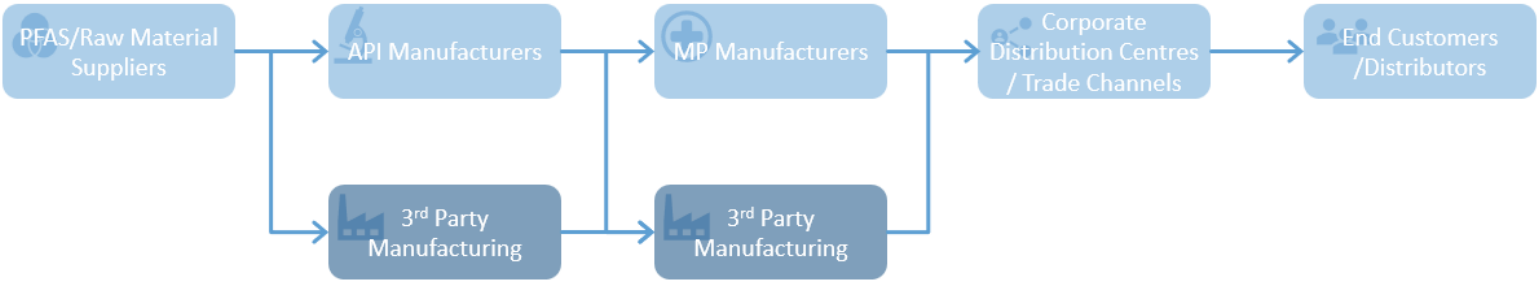


Figure 1. Typical pharmaceutical supply chain (simplified version)

In summary, the participating companies have a large network of internal manufacturing sites that span the entire supply chain, end-to-end, from API synthesis through to medicinal product manufacturing to packaging and assembly/filling of drug delivery devices. The internal manufacturing networks are complemented by a large network of external manufacturing sites. Many of the key R&D facilities and manufacturing sites of the participating companies are located in the EEA.

3. ANALYSIS OF ALTERNATIVES

This section provides a closer look at the **use, function, and requirements of PFAS chemicals used in the manufacturing of medicinal products. It covers PFAS APIs (manufactured for the EEA market, for export, and APIs under development), as well as PFAS in non-active ingredients (excipients), starting materials and chemical intermediates, process chemicals (including reagents, solvents, catalysts, auxiliaries in production and Quality Control), equipment and consumables, fluoropolymer-containing immediate packaging materials, drug delivery devices and other medical devices.**

This section examines the technical obstacles that prevent substitution via potential alternatives to PFAS, the timelines related to the development and launch of new APIs/medicinal products and the challenges related to a transition away from PFAS in the manufacture of medicines.

The analysis of alternatives concludes that there are no available substitutes for the PFAS used in the manufacture of medicines, of the APIs themselves and in immediate packaging materials. The replacement of PFAS is limited by availability, technical applicability, and environmental trade-offs of alternatives which are to date not (readily) available. Finding alternatives is not guaranteed, and substitution (if possible) is a time-consuming process due to the legal requirements for quality, safety and efficacy in the sectoral legislation and guidelines.

Unless clearly specified, all below information are sourced from participant companies' replies to the survey conducted in the context of this Socio-Economic Analysis.

3.1. Function and technical performance of PFAS in the manufacture, packaging and delivery of medicinal products

PFAS are typically extremely stable and non-reactive substances which are used in a wide range of consumer products and industrial applications because of their unique chemical and physical properties.

At present, active substances in medicinal products approved under EU pharmaceutical law are derogated, as currently worded under RO2 of the REACH restriction proposal. Nonetheless, this derogation does not achieve its aim of allowing the manufacturing of these active substances, which are considered PFAS, nor of those non-PFAS active substances and associated medicinal products in general. Except from PFAS APIs and related intermediates, none of the uses of PFAS chemicals shown below are currently listed as specific uses in the restriction dossier nor derogated under the current wording.

The following paragraphs describe the function and technological advantages of PFAS for all these uses.

3.1.1 PFAS Active Pharmaceutical Ingredients

More than 300 fluorinated compounds have been launched as medicinal products over the last few decades. Over 500 substances are in late-stage clinical trials (see Figure 3 on innovation timelines).[14] At present, **it is estimated that approximately 30% of all commercially available APIs and new APIs currently under development, contain fluorine and thus might fall within the scope of a restriction**.[15] Hence, the importance of fluorine in pharmaceutical compounds, both for existing drugs as well as for a growing number of potential future candidates.

Among fluorine-containing APIs, a number are PFAS by virtue of them containing per- and polyfluoroalkyl substructures.[16] These substructures can confer multiple desired properties onto an API when incorporated into the molecular structure.

Many decades of scientific research and innovation have focused on optimising medicinal products. To be effective, a drug needs to (a) have bioavailability so that it can reach the therapeutic targets in the body at the proper concentrations; (b) demonstrate safety so that it does not cause undesirable side effects or toxicities; (c) exhibit sufficient efficacy to alter the course of a disease or exhibit a therapeutic effect; (d) sustain a targeted concentration in the body over time.

The success of a medicine in achieving the above relies on the structure of the API molecule, and it is an exceedingly complex process to finally arrive at a suitable API molecule. To identify a suitable API, thousands of compounds are typically synthesised and tested in order to find one that will meet the criteria. **Once identified it takes several years to develop manufacturing processes to supply clinical trials and that are suitable for commercial manufacture.**

In this context, **PFAS continue to be a critical component in new drug developments for humans.** The benefits provided by the use of fluorine, and thus PFAS, include: (i) an extended biological shelf-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.**

In particular, the extensive application of fluorine in drug research and development is related to the unique properties of this element.[17] These properties enable it to have a profound effect on the biological properties of APIs. Notably, fluorine is the most electronegative atom of the periodic table, and it has a very strong bond to carbon atoms (C-F bonds).

Due to fluorine's electronegativity, the introduction of fluorine serves to attract electrons, making a molecule more acidic or less basic (modulating its pKa). This finetuning of acidity and basicity of drug

[14] https://www.efpia.eu/media/636866/pfas-position-_-efpia-and-animalhealtheurope-january-2022.pdf

[15] https://www.solvay.com/en/chemical-categories/fluorine-chemicals/organic-fluorinated-compounds

[16] Although the opposite does not hold true, i.e., not all APIs are PFAS.

[17] See, for example, H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, ChemBioChem 2004, 5, 637-643.; b) E. Gillis, K. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell J. Med. Chem. 2005, 58, 8315-8359.

candidates may be crucial in the discovery process of novel APIs. This will subsequently impact key parameters required for a successful drug.

Moreover, even though fluorine is comparably small in size, the stability that a C-F bond can provide is much greater than that of a C-H bond. Therefore, replacing hydrogen by fluorine - on e.g., alkyl substituents but it can impact key properties required to make a drug efficacious and safe, leading to reduced clearance in the human body. Lipophilicity (i.e., the ability to be dissolved in fats, lipids, oils, and non-polar solvents) can also be modulated by the introduction of fluorine. The latter, when modulated appropriately can increase the binding affinity of the API to the target, and affect other physicochemical properties positively.

The introduction of fluorine atoms into molecules is often non-trivial, and so this is only done when there is a disproportionate benefit to the performance of the API.

For all these reasons, **the introduction of fluorine is often an essential part of achieving an optimally balanced profile, and fluorine atoms have been widely used by medicinal chemists in the pharmaceutical industry to evolve a molecule into a potent and safe drug.**

3.1.2 PFAS used in the Manufacturing Process

Independent of the nature of the API (whether PFAS or non-PFAS), PFAS are widely used throughout the production activities, starting from the earliest stages of pharmaceutical supply chains all the way through to the finished/packaged product. The API synthesis itself can be very long, involving multiple chemical steps and multiple production sites.

From the early research phase of drug development to the later scaling-up of processes or during commercial production processes, a wide range of PFAS chemicals are utilised. Besides the raw materials and process chemicals used for manufacturing of APIs, **PFAS-containing materials are used as/in (not an exhaustive list) gaskets, tubes, lined piping and fittings, chemical reactor and storage tank linings, preparative chromatography equipment for purification, tape for mechanical fittings, instruments, valves, pump housings and impellors, filters and other commercial manufacturing equipment and analytical equipment**. This includes machinery such as centrifuges, coaters, driers, granulators, refrigerating, and packing and filling equipment.

The whole process of manufacturing and developing medicinal products, depends heavily on a number of PFAS chemicals in a wide variety of applications.

The different use scenarios identified as being part of the PFAS API Manufacturing Process are discussed below in more detail.

Starting material and chemical intermediates

API synthesis is the core part of the API production process, involving multiple chemical steps and multiple production sites. It begins with the raw materials, proceeds through multiple steps, isolating different chemical intermediates, and then finally results in the API molecule.[18]

The chemical intermediates often contain a CF_2 or CF_3 group. 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.

Multiple PFAS starting materials and intermediates have been identified in the production of APIs for medicines. **The impacts of their potential removal could be substantial at the level of production capability.**

Due to the limited diversity and availability of PFAS starting materials, introduction of PFAS containing substructures represents a manufacturing challenge, their use is therefore generally restricted to essential use scenarios (i.e., when they are considered essential to achieve an optimally balanced profile of the API) rather than added as a default/easy option.

Without use of fluorinated starting materials and intermediates, fluorinated APIs cannot be produced. Replacing the necessary synthetic building blocks with alternatives that are outside of the scope of the restriction proposal is not possible, as alternatives would result in a different molecule and not the required API. Therefore, **the use of PFAS-containing materials is the only practical option for the production of these PFAS API molecules as well as other fluorinated non-PFAS APIs**

Hence, either restriction option 1 or 2 in the published draft proposal, will result in the cessation of API and drug manufacture in the EEA that currently use intermediates and/or starting materials that are defined as PFAS, and the relocation outside of the EEA territory.

Process Chemicals (reagents, solvents, catalysts, auxiliaries in production and Quality Control)

The synthesis of APIs also depends on the availability of both auxiliaries and production materials. Production materials include solvents, catalysts, synthetic and analytical reagents, and processing aids. Multiple production materials also contain PFAS owing to their unique properties.

For example, **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 (e.g., Trifluoracetic acid, Trifluoromethanesulfonic anhydride, and nonaflate). PFAS such as Trifluoracetic acid,

[18] This is particularly valid for Small Molecule (Synthetic) APIs.

Trifluoromethanesulfonic anhydride, hexafluoro isopropanol and trifluoro ethanol are indispensable in solid phase peptide synthesis and analytical testing.[19]

As regards analytical chemistry, Trifluoromethanesulfonic anhydride is used for pharmaceutical 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.

Equipment and Consumables

PFAS materials are widely used in the manufacturing environment for their specific properties as this group of substance exhibits an **outstanding resistance and inertness against aggressive chemicals and mechanical impact** and maintain these favourable material properties over a very wide temperature range (i.e., from -30 °C up to +200 °C). Both the chemical and temperature durability are highly essential in production equipment and manufacturing plants, including the supporting laboratory activities.

The chemical and physical inertness, chemical and physical stability, low permeability to gasses, heat-resistance, and low friction properties offered by PFAS materials make them uniquely suited for aseptic processing in fixed and consumable equipment. PFAS lined equipment, piping and instrumentation are essential for their chemical compatibility and robustness in harsh process conditions (aggressive solvents, chemicals, extremes of temperature and pH) and necessary to avoid product contamination.

Manufacturers of human medicines rely heavily on PFAS-coated equipment in their manufacturing sites. PFAS materials used for analytical and/or production equipment are extremely robust against temperature, with a much wider usable temperature range compared to other polymers. The same applies for mechanical or chemical robustness: PFAS materials present a higher level of robustness than any metal against corrosion or other chemical degradation. These properties give rise to a long equipment lifecycle which benefits from reduced maintenance requirements.

All polymer materials are chosen for use in production equipment and processes via a thorough and standardized evaluation process for the following criteria during pharmaceutical production:

[19] Martin, V., Egelund, P.H., Johansson, H., Le Quement, S.T., Wojcik, F. and Pedersen, D.S., 2020. Greening the synthesis of peptide therapeutics: an industrial perspective. *RSC advances*, *10*(69), 42457-42492.

Table 1. Polymer Evaluation Criteria

Criteria	Scope
Chemical Resistance & Compatibility	Can the polymer withstand the exposure to a given media (or medias) – including reaction products and potential leachability to the product. This is done for all media the polymer is exposed to during production and/or maintenance activities. Parameters include: • pH – including potential pH changes in the product caused by the polymer surface • Solution type (organic solvent content) • Chemical change in product caused by polymer surface or reactive leachables
Physical Resistance & Compatibility	Does the polymer retain its form, function, and strength during repeated stressors (such as heat and/or pressure) during production activities Parameters include: • Contact time • Contact temperature • Contact pressure • Physical change in product caused by polymer surface or reactive leachables
Exposure Time & Area	Are all parts of the polymer in contact with the product or media? (This is performed for all media the polymer is potentially exposed to) Parameters include: • Contact surface area per administered dose of drug product • Proximity to finished drug product
Yield Loss	Will the polymer result in product adherence to equipment or result in clogging of filters and membranes?

The evaluation process is built upon current best available knowledge from polymer suppliers, industry standards, and decades of experience in pharmaceutical production. This ensures that the selected polymer is fit for its intended use during GMP production.

For several pharmaceutical production processes, only PFAS polymers are suitable for intended use as per the criteria set forth in Table 1 – other non-fluorinated polymer formulations such as such as Ethylene propylene (EPDM) or Silicone rubber (VMQ) are unable to meet the aforementioned criteria for use and can pose a significant risk to product quality and patient safety.

PFAS-containing polymers are most common in the following production equipment:

- Wearable parts or plastic surfaces in pumps, agitators, valves, centrifuges, etc.
- Hoses, tubing, and gaskets
- Single use equipment
- Bags, liners, membranes, and other plastic types
- Storage tanks and piping
- Filters (both particle reducing and sterile)

In addition to the examples above, PFAS-containing polymers such as FEP and PFA are also essential for use in electronics – these are used for encapsulating sensitive electrical components and instrumentation used in pharmaceutical production.

These fluoropolymers are standard materials for multipurpose API/medicinal product manufacturing equipment.

Manufacturing equipment such as storage vessels, piping, pumps, reactors, filters and tubing can either be coated with, or constructed from fluoropolymers such as Polyvinylidene fluoride (PVDF).

Overall, the usage of PFAS in fixed and consumable equipment is expected to occur along in the whole manufacturing process of medicines in general.

Examples of crucial functions provided by PFAS in equipment applications include non-sticking of product to equipment (i.e., to enable cleaning and maintenance), no chemical reaction with the product, no leaching of equipment component substances into the product, no yield loss or clogging of membrane filters, maintenance of form and function under stress (heat/pressure) to avoid in-process material leakages, and reduced friction between product and equipment.

Due to its corrosion resistance and mechanical properties, in medicinal product manufacturing equipment, fluoropolymer types (e.g., PTFE, PFA, PVDF, FEP, FEPM, ETFE, ECTFE, PCTFE, PFPME, FVMQ, TFE-P, FPM, FFKM, FKM) are widely used for coating applications in (e.g.,) lined pipework and process equipment, including (but not limited to) membrane sealings, filters, tubing, pressure reducers, pump components. There are kilometres of lined piping, valves, check valves and sight glasses in GMP process systems and utility systems which use PFA, PTFE, PVDF and ETFE lined components, where they provide corrosion protection against aggressive process solutions.

There is also a significant process safety element driving the use of PFAS in pharmaceutical manufacturing. These materials minimise the risk of leakage/release of aggressive substances/materials from closed manufacturing systems, thus minimising the risk of injury to pharmaceutical industry employees.

In this context, the main technical function of the fluoropolymers used in sealing of (multipurpose) manufacturing equipment is to prevent leakages between parts of the equipment (closures, connections). These fluoropolymer seals (e.g., PTFE seals used in valves and pipes) must be compatible with solvents, chemicals, wide temperature ranges (material must cope with thermal tensions) and pH conditions. In this respect, fluoropolymer seals and coatings are unique in their properties.

At formulation sites, some examples of equipment made using PFAS include:

- **PVDF sterilization filter**: used in several steps in the medicinal product formulation process, in product clarification, reduction of the total microbial count and ultimately, for product sterilization.
- **PTFE filling tubing**: used in the last step of the medicinal product filling process, where product is transferred into the container/closure system (cartridge, vial etc).
- **PVDF connectors**: used for connection of the formulation tubing (tubes used in the formulation process, moving product from one tank to another etc).
- **PTFE valve membrane**: used in the bottom valve of the formulation tanks.
- **PFA tubing and fittings**: used to connect the formulation tubes.

Further examples to those listed above include lubricants (containing PTFE and similar PFAS), replacements parts like gaskets (PTFE), single use disposables such as filters (PVDF), as well as PVDF membrane filters used for sterilising filtration of injectable medicinal products. O-rings, fittings, pipework, pumps, electronics, and other instrumentation used for pharmaceutical manufacturing also contain PFAS fluoropolymers.

More generally, any components that come into contact with a wide range of synthesis-related chemicals and process streams are coated with PFAS to provide superior corrosion resistance, safety, and quality.

During the R&D and production stage, the analysis of the synthesized APIs and intermediates is a mandatory step to ensure the product meets the required specifications. This can be done by different analytical methods, such as HPLC, GC, Nuclear Magnetic Resonance (NMR) to name a few. The analytical detectors employed are extremely sensitive to impurities. PFAS materials are used in this context to (e.g.,) seal samples, protect tubes because they are inert to other chemicals and do not leach out during their lifetime. Conversely, the leaching out process known from other materials would cause difficult interpretation of analytical results due to "background noise" coming from this wash-out effect. Yet, replacing these equipment parts with fluorine-free alternatives would disable a vast number of the aforementioned analytical models and analyses. They are therefore also important in this context in the manufacturing of both PFAS containing and non-PFAS containing APIs of participating companies.

Thus, fluoropolymers are standard materials for multipurpose API/medicinal product manufacturing equipment. They are essential components used in pharmaceutical manufacturing plants worldwide. Alternative or replacement materials are neither approved for use nor available to manage the corrosion resistance, safety, and quality processing requirements of thousands of medicines available today.

In comparison to chemicals "consumed" in the manufacturing process, these PFAS based production materials often have long lifetimes within equipment (or are replaced infrequently with long maintenance intervals) as PFAS coatings protect the underlying material much better than any potential alternatives. Hence, equipment and consumables containing PFAS have been a vital part of the production environment for decades. This is particularly true for pharmaceutical manufacturing where PFAS reduces impurities resulting from leachables, improves stability and shelf life, therefore reduces manufacturing waste (not only from the API but also from the equipment).

Overall, the usage of PFAS in fixed and consumable equipment ensures both product quality, safety and longevity of the whole pharmaceutical manufacturing process.

3.1.3 PFAS used in Immediate Packaging Materials of Medicinal Products

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.

In addition to the survey data collected as part of this report among manufacturers of human medicines, information was collected **on the function and alternatives from upstream suppliers of PFAS containing immediate packaging**.

Blister packaging

Some pharmaceutical (solid) oral drugs can be sensitive to moisture and other environmental parameters and can experience undesirable chemical reactions known as degradation. Inadequate barrier properties will render a medicinal product unstable, ineffective, and potentially unsafe.

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**.[20]. PFAS containing blisters deliver a medium to high moisture barrier while preserving transparency of the blister.

For example, PCTFE based immediate packaging provides cost effective commercialisation and administration of moisture sensitive solid oral dosage forms, in a transparent, lightweight mode of drug administration preferred by patients due to convenience and receptiveness. Clear packaging (transparency) helps to ensure proper dosing by making colour of the medicinal product visible to patients. Additionally, laminated thermoform films containing PCTFE allow companies to optimise the sizes of all packaging.

PCTFE offers medium to high moisture barrier properties. Many of the other attributes are shared by lower or higher barrier PFAS alternatives. In general, PCTFE and other PFAS are critical and essential packaging materials used by multiple therapeutic entities for disease management, prevention, and curative drug treatment regimens. **The efficacy and preservation of moisture sensitive drug API is inextricably linked to the barrier performance of immediate drug packaging.**

Injectables medicinal products not contained in drug delivery devices e.g., vials

High-performance fluoropolymers (especially PCTFE and ETFE) are vital to the containment, storage, and delivery of injectable medicinal products. Injectable medicinal products cover a wide spectrum of treatments (e.g., various illnesses, preventing infections, managing pain, treating allergic reactions, etc.).

Parenteral medicinal products are packaged in container closure systems such as vials that are made of an assembly of immediate packaging components. These are commonly made of glass or plastics (vials), and elastomers (stoppers, seals).

The immediate container/closure and delivery systems (CCDS) are integral to medicinal products which are authorized by European Medicines Agency (EMA).[21] In this context, the high inertness of

[20] Moisture sensitive solid oral formulations must be packaged in moisture resistant immediate packaging materials to avoid the negative impact of high relative humidity (see EMA guideline on plastic immediate packaging materials, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-plastic-immediate-packaging-materials_en.pdf).

[21] High-performance fluoropolymers are used to coat the elastomeric closure component (including rubber stoppers and plungers) of injectable CCDS and is subject to general EMA requirements.

the ETFE-/PCTFE-film coated elastomeric components provide an effective barrier, thus ensuring increased product safety over the medicinal product shelf life.[22, 23]

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,[24] by:

(i) 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;[25]

(ii) 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;

(iii) 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.

(iv) Providing a smooth surface with low surface energy to avoid potential for adsorption of medicine onto the closure surface;

(v) 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.

(vi) 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.[26]

3.1.4 PFAS used in Drug Delivery Devices and other Medical Devices

[22] The importance of coated rubber stoppers for some products (e.g., for biologics) was shown and described in literature (See, for example, Boven, K., Stryker, S., Knight, J., Thomas, A., van Regenmortel, M., Kemeny, D.M., Power, D., Rossert, J. and Casadevall, N., 2005. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. *Kidney international*, *67*(6), 2346-2353.)

[23] Requirements on leachables are e.g., described in the FDA Guidance for Industry (Food and Drug Administration, 1999. Guidance for industry. Container Closure Systems for Packaging Human Drugs and Biologics. https://www.fda.gov/media/70788/download

[24] The importance of coated rubber stoppers for some products (e.g., for biologics) was shown and described in literature (See, for example, Boven, K., Stryker, S., Knight, J., Thomas, A., van Regenmortel, M., Kemeny, D.M., Power, D., Rossert, J. and Casadevall, N., 2005. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. *Kidney international*, *67*(6), 2346-2353.)

[25] Pilchik, R., 2000. Pharmaceutical blister packaging, Part I. *Pharmaceutical technology*, 24(11), 68-68.

[26] As an example, biotherapeutics are usually administered sub-cutaneous (e.g., via an injection pen). Biotherapeutics can be contained in glass vial, which can be sealed with rubber stopper. Rubber stoppers are coated with ETFE to avoid leakage and extraction.

In this section we will discuss Drug Delivery Devices (in the scope of this SEA study) and Medical Devices (the vast majority of which are not in the scope of this study) – both are discussed to show the differences between the two from a regulatory and technical perspective.

Drug Delivery Devices

Drug delivery devices are devices which are combined with medicinal products. There are several illustrative examples of drug delivery device using PFAS:

- **Prefilled Syringes**: Prefilled syringes can be used as a stand-alone drug delivery device or can be part of a prefilled pen product. Stand-alone Prefilled syringes are today widely used within the European market for a large number of medicines like vaccines and biologics.
- **Prefilled Pens:** Prefilled pens combine a prefilled syringe or prefilled cartridge within a plastic pen which is simple to use for patients with a variety of conditions such as diabetes, anti-inflammatory etc. Prefilled pens generally require the patient to attach a needle prior to each dose. Prefilled pens provide 1-5 doses (depending upon the quantity of medicines required per dose) and so are disposable by nature
- **Autoinjectors:** Autoinjectors are self-injectable devices; they are important class of medical devices which can deliver drugs through subcutaneous or intramuscular route. The prefilled syringes or cartridges are driven by a spring system. The major benefits of this device are easy self-administration, improved patient compliance, combats dexterity challenges, alleviates some patient concerns relating to needle phobia, and improves dosage accuracy. Subcutaneous autoinjectors are designed to automatically retract the syringe and needle into the device upon delivery of the dose.
- **Reusable Pens:** Reusable pens are not prefilled with medicine – a reusable device requires a cartridge or other container of medicinal product to be loaded into the device by the patient and then reloaded again with a 'new' cartridge/container once the original cartridge/container was empty.
- **Pressurised Meter Dose Inhalers (pMDIs):** pMDIs are used for the treatment of respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD). This case example is further illustrated in Section 4.2.3.
- **Drug eluting transdermal patches**. PFAS are used in the release liners for silicone based adhesive transdermal patches. PFAS containing release liners have specific performance characteristics that make them compatible with the silicone adhesive matrix that contains the active medicinal product. Changes to the release liner will force (or trigger or prompt) evaluation and potential change to the silicone adhesive matrix, resulting in a full reformulation and redesign e.g., pain relief, hormonal patches

PFAS substances can be found in seals, silicones, lubricants, filters, barriers and propellants, 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 provides 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. 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 syringe being retracted by the syringe retraction system.

- Fluoropolymers used in a prefilled syringes would be the elastomer closure within the syringe (the coated elastomer protects the medicine from the elastomer thereby minimising two-way interaction with the drug).

- Prefilled pens contain components made with a PFAS containing thermoplastic resin as well as PFAS coatings used as dry lubricant.

- 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.

Other Medical devices

A medical device can be a simple part or a highly complex machine. A complex medical device consists of hundreds of different parts and even more homogenous materials.

Pharmaceutical companies rely heavily on the medical technologies sector to first identify the uses/ parts which contain PFAS, and to determine which of those can be substituted with less critical materials while ensuring the same level of clinical and diagnostic performance. It should be highlighted that the relevant supply chain is highly complex and global, involving thousands of suppliers around the globe. Currently, suppliers are not obligated to disclose most PFAS.

Medical devices use specific substances, including PFAS, to provide a critical function (e.g., heat and water resistance). Fluoropolymers provide lubricity and durability. The durability of PTFE can allow for the device to be used multiple times during their lifetime. PFAS parts are an essential component of medical devices and can be found in seals, lubricants, silicones, filters, surface treatment or other working parts.

A 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.[27]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.

3.1.5 PFAS Functional Excipients

Excipients may be constituted into a medicine to confer specific physicochemical properties or functionality that is crucial to targeted drug delivery and overall efficacy.

For example, in pMDIs, hydrofluorocarbons act as safe propellants to aerosolize the API and to achieve the therapeutic benefit to the patient ensuring the delivery the of the medicine to the lungs. The advantage of fluorinated propellants is that they are in the liquid phase inside the can and vaporize when the pMDI is actuated to aerosolize the active ingredients with a constant pressure/force for each dose, making them available for inhalation. This case example is further illustrated in Section 4.2.3.

In general, the same considerations for manufacturing equipment, reagents and processing aids for APIs are also relevant for excipients.

If substitution of an excipient is necessary, if this is a well-established alternative approximately 5-7 years would be required (see Table 2 in Section 3.3.3 for details). If a completely novel alternative is required, the additional development needed could take up to 12 years depending on the type of medicinal product.

[27] 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.

3.2. Challenges of substituting with alternatives

3.2.1 PFAS used as an API

As outlined in Section 3.1.1, **the unique properties of the fluorine atoms offer the possibility to influence and optimize key properties of active ingredients** such as spatial conformation, physicochemical properties, intrinsic potency, membrane permeability, metabolic pathways, and pharmacokinetic properties. This renders targeted introduction of fluorinated substituents into drug candidates an unparalleled tool for drug design. **This leads to improved drug efficacy compared to non-fluorinated alternatives.**

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. Given the inherent properties of PFAS, replacement of APIs in medicines would require the development of a new medicinal product, with all the resource that would be required to discover, develop, manufacture and register this successfully.

Other structural groups have electron withdrawing capability similar to $-CF_2-$ or $-CF_3-$. These include carboxylic esters, amides, nitro, or cyano. Nonetheless, they differ in the other properties they confer on a molecule such as stability, permeability, toxicity and other properties. A replacement of fluoro-alkyl by other halo-alkyl groups such as chloro-alkyl can lead to reactive agents with serious toxicity issues.

Overall, **a restriction that applies to the use of PFAS APIs (RO1) would remove these molecules from the EEA market. This would have severe consequences for the human health of hundreds of thousands of patients which rely on these medicines.** Even for those therapeutic areas where medicines containing PFAS APIs coexist with non-fluorinated drugs, 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, complications with other prescribed medication or individual response. **Limiting the options in a therapeutic class, because some have fluorinated groups, would have a profound impact on the ability to treat patients with the most safe and efficacious medicine.**

3.2.2 PFAS used in the Manufacturing Process

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.**

Process Chemicals (reagents, solvents, catalysts, auxiliaries in production and Quality Control)

According to the surveyed companies, the use of alternative materials 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. The time required for regulatory processes must be added to the transition period required for technical substitution, and should take into regard the available capacity of managing approvals both by companies and authorities.

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.

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 - e.g., for cyano with formation of cyanide ions).

Therefore, replacing the current auxiliaries and production materials containing PFAS is not feasible in the short term, and alternative solutions will need to be investigated over time. Hence, restriction of PFAS will result in the cessation of API and drug manufacture in the EEA that currently use PFAS process chemicals, and the relocation outside of the EEA territory.

In chemical synthesis, the reactivity of select PFAS-containing reagents is typically several orders of magnitude higher compared to other alternatives. **Substituting these reagents could affect the efficiency and waste ratio of the medicinal product synthesis**. Therefore, while seeking alternative solutions is desirable, it may not be practical or feasible to replace the current synthetic reagents in the short term.

Equipment and Consumables

For all surveyed chemical API manufacturing processes, there are no alternatives to PFAS that would enable the manufacturing of pharmaceutical APIs capable of meeting the quality and safety requirements of health authorities and minimizing the physical safety risk inherent in chemical API synthesis to levels acceptable to safety authorities.

There are some alternatives to PTFE that are used in lined pipework and process equipment, such as **glass** or **certain metals**. All available alternatives, however, are not compatible with a multipurpose

manufacturing facility. In general, **none of the alternatives provide a broad-spectrum corrosion resistance and their mechanical properties are limited.** Taking sealing applications as an example, **ceramic seals** can also be very inert, but contain fibres that can be released into the medicinal product. Similarly, **graphite seals** (e.g., gaskets) are not suitable for pharmaceutical processing due to the risk of carbon debris in the final medicinal product. Other materials, such as **tantalum** or **gold** can be used in connections between equipment parts but are extremely expensive (many orders of magnitude more expensive than PFAS).

Some companies indicated that for some applications, where the process conditions are not that harsh in terms of pH, temperature and chemicals, PTFE can be replaced by (e.g.,) **EPDM rubber**. However, where process conditions are harsh, the technical feasibility of these alternative substances decreases considerably.

Chemical compatibility for non-PFAS-made equipment may be very limited, bringing safety and quality issues into a multipurpose manufacturing facility. Ultimately, other alternative materials would limit the use of solvents, chemicals, and process conditions (temperature range, pH values). Additionally, this will involve significant capital investment to make the designated changes, which will severely impact the product cost or even availability of production capacity, ultimately limiting patients' access to medicine.

Any alternative will require several time-consuming activities such as:

1. Toxicology studies:
    a. Extended material characterization reports to determine suitability and durability (three months)
    b. Extractable and Leachable studies – to establish targets and acceptance criteria (six months)
2. Equipment requalification:
    a. Assuming a direct 1:1 polymer switch for gaskets and O-rings in existing components, instruments, and equipment is possible:
        i. New polymer(s) - would require updating thousands of design documents such as Piping and Instrumentation Diagrams (P&IDs) and revalidation of all process equipment and production lines containing the new polymers (at least three years with several production stops at the production facility).
    b. If a direct 1:1 polymer switch for gaskets and O-rings in existing components, instruments and equipment is **not** possible:
        i. The existing components, instruments and equipment must be removed and replaced with another model with the non-pfas polymer, and the impacted production lines must be revalidated (four years).
    c. Production equipment for hazardous media (tanks, pumps, valves and other equipment) constructed using a pfas-containing polymer – such as PVDF – would require complete replacement and revalidation (three years).
    d. Changes to process media to accommodate less resistant polymers would result in new process validation and regulatory filings in multiple countries.

Overall, all EEA pharmaceutical manufacturing sites are expected to make use of fixed and consumable equipment. For example, Teflon-lined pipes are used throughout EEA production facilities. This means that **an (unrealistic) replacement plan would cost millions of EUR,[28] and require many years to re-build and/or re-validate the entire manufacturing equipment system**.
Hence, the restriction of PFAS will result in the cessation of API and drug manufacture in the EEA and the relocation outside of the EEA territory.

3.2.3 PFAS used in Immediate Packaging Materials of Medicinal Products

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.

Blister packaging

For solid dose applications, the most realistic alternative available is the use of **Polyvinylidene Chloride (PVdC)**, when a medium-high moisture barrier protection is required. PVdC is relatively cheaper in purely material cost per surface unit but there are other costs associated with the use of this alternative that may significantly increase the whole cost of a medicinal product (process efficiency, logistics, etc). A concern however of PVdC is that, similar to PCTFE, the material may be not recyclable in practice and at scale,[29] and may have upstream environmental drawbacks.

A second alternative is aluminium-aluminium blisters, which is known as **cold form foil (CFF)**. Alu-Alu blisters provide the necessary barrier protection but are non-transparent, potentially impacting drug treatment adherence;[30] many patients prefer transparent presentations. Another drawback is the

[28] Ranging from 30 to 200 million EUR depending on the plant size.

[29] PVdC could be alternative in case of thicker film but they will not be allowed under recently proposed Packaging and Packaging Waste Regulation, because the material is not considered recyclable.

[30] Based on the input provided by upstream suppliers of immediate packaging which participated to the survey.

increase size of the packaging: CFF films require bigger pockets to contain the same product compared to standard thermoforming materials. This leads to larger blister cards and the need for more material surface when using cold forming foil during packaging operations, triggering logistics impacts.

Other potential (not feasible) alternatives include:

- **Polyvinyl chloride (PVC)** without a PCTFE layer does not have the same technical advantages for medicines that require a higher level of moisture protection. Even if PVC were to provide the required moisture protection without the PCTFE layer, ECHA is proposing to limit the use of PVC in EU. This may also impact any future PVC developments in blister packaging and thereby causing a regrettable substitution.[31]
- **Cyclic olefin copolymer (COC)** is also suitable for applications of blisters that require a low barrier of moisture protection. Yet, it has limitations in terms of market accessibility, forming challenges, and limited use in the packaging of pharmaceuticals.
- **Mono-material blisters** are still largely experimental and limited in scope. This material relies largely on structural crystallinity in their formulations to provide barrier properties, which results in a severe performance degradation as draw depth and wall thickness decrease. Additional major challenges of mono-material packaging are the material clarity, ageing, and overall stability.

During upstream manufacturing of flexible materials in general, PFAS may be present in raw materials often used as processing aids. A full review of all raw materials and likelihood of replacement would additionally have to be considered.

Hence, thermoformable films containing PCTFE have been reliably and consistently used in the EEA and is the preferred material of choice for medium to high moisture barriers in solid dose blisters.

Injectables medicinal products not contained in drug delivery devices e.g., vials

Concerning parenteral medicinal products (coated elastomeric stoppers): closure coatings for vials containing materials other than PFAS exist, however they are more likely to react demonstrating a lack of inertness. **Poor stoppering or inadequate closures may lead to an adulterated medicinal product, as contaminants can leach into the medicinal product**.

Similarly, the use of uncoated stoppers can give rise to unknown consequences with a potential high risk for patient safety due to the leachable profile, which is highly medicinal product specific. There is a risk to exceed toxicological thresholds and/or influence medicinal product stability (e.g., leachable-induced particle generation in finished product, which requires investigation).[32]

[31] Currently, PVC is under investigation by ECHA under European Commission mandate to understand whether regulatory measures are needed at the EU level to reduce potential risks from the substance.

[32] A study from 2005 investigated the increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes (i.e., exposure to the product form containing leachates than for leachate-free product forms). The study concluded that leachates from uncoated rubber syringe stoppers caused the increased incidence of pure red cell aplasia associated with Eprex (Boven, K., Stryker, S., Knight, J., Thomas, A., van Regenmortel, M., Kemeny, D.M., Power, D., Rossert, J. and Casadevall, N., 2005. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. *Kidney international*, 67(6), 2346-2353)

Thus, elastomeric closures made of fluoropolymers combine resilient and elastic properties which make them the preferred options for these immediate packaging materials. The materials should be compatible and provide adequate protection to the medicinal product throughout its intended shelf life.

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).[33]
- **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).

3.2.4 PFAS used in Drug Delivery Devices and Other Medical Devices

Drug delivery devices

According to the information that manufacturers received from upstream suppliers of medical and drug delivery 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 currently used (PFAS) materials have been extensively tested to maintain product quality throughout the shelf life.

[33] See, Figure 4 in Section 3.3.3.

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).

Other medical devices

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.[34]

3.3. Timelines for substitution in the pharmaceutical sector

3.3.1 Typical Innovation Process and Timing of a Medicinal Product

In the pharmaceutical sector, Research and Development refers to the systematic and investigative processes undertaken by pharmaceutical companies and organizations to discover, develop, and test new drugs, therapies, and medical treatments. It involves a range of scientific activities, including basic research, preclinical studies, clinical trials, and regulatory approval processes.

Pharmaceutical R&D is a resource-intensive and time-consuming process, often taking several years or even decades from initial discovery to final market availability. Success in R&D leads to the introduction of new medicines that can significantly improve healthcare and patient outcomes. However, the process also involves challenges such as high costs, uncertainty, and a risk of failure for many experimental medicines.

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

The cost of producing a new medicinal product, as well as total R&D spending, has been rising over the past years.[35] On average, only one to two of every 10,000 compounds created in labs will successfully pass through all the stages of development necessary to become an authorized marketable medicine.[36]

Generally speaking, the probability of success for each stage of drug development has declined over the past decades.[37] At the same time, the average innovation cycle, from patenting to product commercialisation, has been lengthening for those more recent medicinal products. The trend of longer trial timelines is likely to continue.[38] A study on the productivity crisis in pharmaceutical R&D documented an increasing focus of research activities in the development of selective drugs in complex research areas that are characterized by a low probability of success.[39]

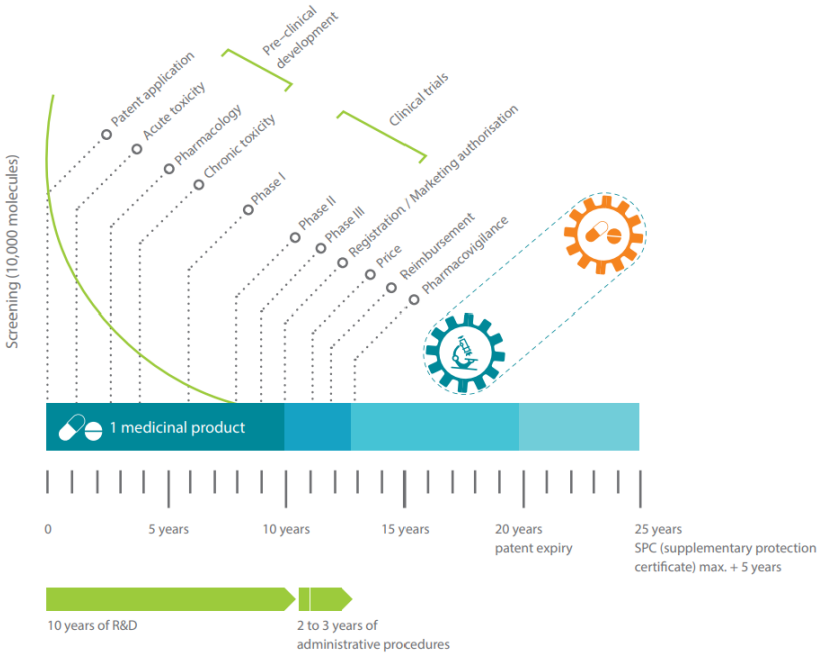


Figure 2. Stages of the Research and Development process

35 Paul, S.M., Mytelka, D.S., Dunwiddie, C.T., Persinger, C.C., Munos, B.H., Lindborg, S.R. and Schacht, A.L., 2010. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature reviews Drug discovery*, *9*(3), 203-214.

36 EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 6. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf

37 See, for example, Di Martino, R.M.C., Maxwell, B.D. and Pirali, T., 2023. Deuterium in drug discovery: progress, opportunities and challenges. *Nature Reviews Drug Discovery*, 1-23.

38 Clinical trial timelines have been lengthening since 2014 and with COVID-19 conditions forcing adaptation and adoption of new technologies and processes, the trend is likely to continue, if not accelerate. Indeed, clinical research for drug development has experienced an increase in duration compared to previous years. According to a study conducted by the Tufts Center for the Study of Drug Development (CSDD) in 2018, FDA-approved drugs and biologics, on average, spent approximately 89.8 months in clinical trials between 2014 and 2018. This duration represents a notable increase when compared to the average of 83.1 months between 2008 and 2013. The extended time spent in clinical trials reflects the growing complexity of drug development processes and the need for more extensive testing and evaluation to ensure the safety and efficacy of new treatments. (See, CSDD, 2018. Available at https://www.centerwatch.com/articles/25033-trend-of-longer-trial-timelines-is-likely-to-continue)

39 Pammolli, F., Magazzini, L. and Riccaboni, M., 2011. The productivity crisis in pharmaceutical R&D. *Nature reviews Drug discovery*, *10*(6), 428-438.

To replace a medicinal product, all the development steps for pharmaceutical development would need to be carried out. The rate of new substance introduction is rather low in the industry. This is due to the many obstacles and challenges faced by companies when trying to bring new products to market including extensive regulatory requirements.

On average, it takes around 10 to 15 years for a new medicine to go from initial discovery to market launch.[40, 41, 42]

However, the disease area of a medicines significantly affects the time it takes for it to reach the market. Some medicines may take longer due to challenges in research or clinical development, while others may have expedited development pathways for conditions with high unmet medical needs. Foer example, drugs targeting allergic, metabolic, and infectious diseases tend to have shorter development timelines. On the other hand, medicines focused on neurological, cardiovascular, and urologic diseases have the longest development timelines, indicating that bringing these drugs to market may require more time and resources compared to drugs for other disease areas. These variations in development timelines highlight the complexities and challenges associated with developing treatments for different medical conditions.

As a result, the **duration of an innovation cycle can vary from 12 years up to 22 years in the worst-case scenarios**.

The typical innovation cycle in the sector consists of the main following steps:

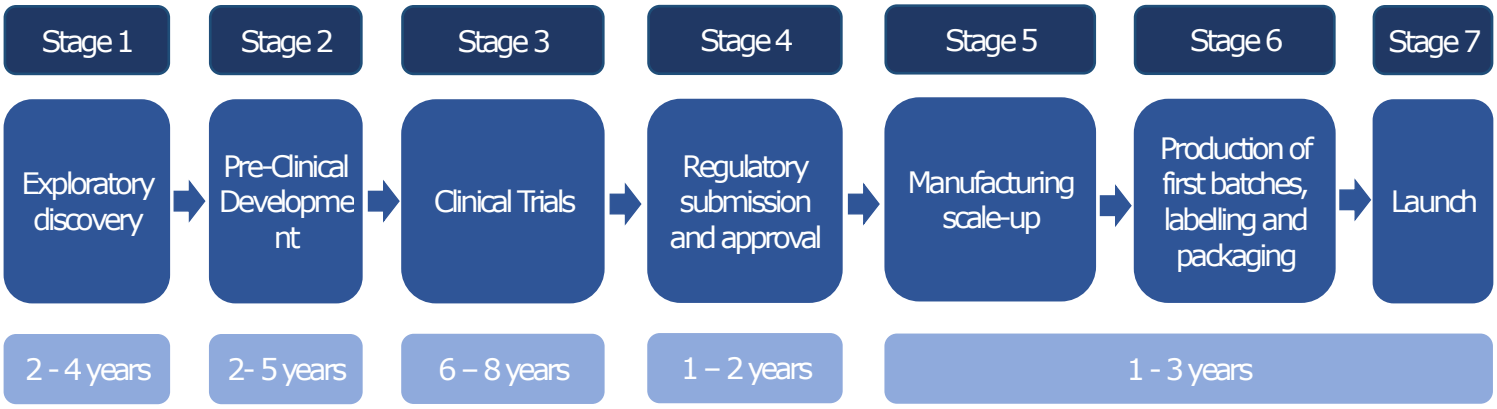


Figure 3. Typical innovation steps in the pharmaceutical sector

[40] DiMasi, J. A., Grabowski, H. G., & Hansen, R. W., 2016. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics*, *47*, 20-33.

[41] This time span is corroborated by several sources. For example, the Biotechnology Innovation Organization (BIO), the world's largest biotech trade association, has analysed more than 9,000 clinical development programs from January 2011 to November 2020, and found that, on average, it took 10.5 years for a medicinal product to get from Phase I of clinical development to regulatory approval. See BIO, 2021. Available at https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf

[42] According to Paul et al. (2010), R&D across all therapeutic areas takes on average 14 years. Paul, S. M., Mytelka, D. S., Dunwiddie, C. T., Persinger, C. C., Munos, B. H., Lindborg, S. R., & Schacht, A. L., 2010. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature reviews Drug discovery*, *9*(3), 203-214.

Once a new medicine successfully completes the necessary clinical trials and obtains regulatory approval, it can be launched onto the market. Pharmaceutical companies typically aim to bring innovative medicines to market regularly to address various therapeutic areas and patient needs. However, the number of new product launches can fluctuate from year to year. The few products that pass the four first stages then have to be manufactured on an industrial scale and launched on the market.

Stage 1. Exploratory discovery

The initial stage of drug discovery typically lasts between 2 to 4 years, and generally starts with the screening of potentially bioactive compounds against drug targets of interest. The first stage in the development of a new product consists of the design, synthesis, and evaluation of potential APIs, which involves extensive research on over 10,000 molecules, with the goal of identifying potential candidates for a new medicine. Usually, around 2,000 compounds of interest are identified in the discovery stage.

This step of the process typically involves animal testing, target identification and validation, assay development, and lead generation.[43] To increase the probability to find suitable starting points for drug development, the screening routinely starts with hundreds of thousands of molecules, only few of which may initially pass. Both approaches are designed to identify individual molecules or larger sets of compounds showing initial potential that after optimization could result in the desired therapeutic effect, commonly known as '*hits*'. Subsequently, hit exploration and optimization is initiated to a) validate and increase the often-weak effects and b) select the most promising compound classes (hit classes) for further optimization in the next research stages.

The iterative process of design, synthesis and testing of new derivatives of the initial hits aims at identifying active molecule(s) with pharmaceutical-like properties (leads). Detailed lead profiling is performed to find the optimal combination of biological efficacy as well as human, and environmental safety. Rigorous candidate selection during the lengthy process results in high attrition rates, as most lead compounds do not meet the required characteristics. Thus, pre-development work is only initiated on very few/single compounds.

During the discovery stage of medicinal product development, the choice of solvent for API synthesis is typically based on chemical expertise and literature. However, as development progresses, the selection of solvent becomes critical to optimizing process reactions, improving yield, reducing API impurities, and enhancing workplace safety. Also, during the discovery stage a decision is taken on the potential incorporation of a PFAS moiety (-CF_3, -CF_2-) in the API molecular structure in order to increase and optimize the efficacy of the medicine being developed.

Stage 2. Pre-clinical development

[43] A patent application may be submitted during this phase, which can provide rights to the New Chemical Entity (NCE) patent for 20 years. Nevertheless, up to 5 years of additional exclusivity can be applied, which is called a Supplementary Protection Certificate (SPC).

The pre-clinical development stage involves the synthesis of the API for the clinical trials and conducting toxicity studies to determine dosing levels. Details of the clinical trials are submitted to regulatory agencies to obtain permission to proceed with the clinical trials.

In the pre-clinical development stage, the API's good manufacturing practice sequence is established, including the choice of solvent used for optimal API manufacturing. Changing the solvent can alter the impurity profile of the API, necessitating re-qualification of new unique impurities, additional animal studies, and potentially exposing patients to higher levels of existing or new unique impurities. This could lead to additional human clinical trials to prove the safety of the new API. The impact of these changes is proportionally greater at later stages of the development program. In case of a marketed drug, any alterations to the solvent choice would require amendments to the marketing authorization.

During this stage, further chemical optimization within the selected classes will take place. Various laboratory trials are conducted during the discovery stage. This stage involves formula validation (stability, sourcing, industrial process) and clinical trial protocols including dose determination and first residue profile. Thus, overall, the whole stage can last up to five years.

Generally, various steps are performed at this stage of the process, including assay method finalization for API; to establish absorption, distribution, metabolism, excretion and toxicity; development of laboratory scale manufacturing and development of a formulation ready for further studies.

Before testing on humans, several preclinical tests are performed. This means that the potential pharmaceutical compounds are tested in the test tube using bacteria, cell and tissue structures, isolated organs, and in the whole organism.

Preliminary formulation work is started to enable pilot experiments in animals, explore API stability and behaviour in various formulations, determine preferable route of administration, potential effective dose, and begin to characterize the API hazard profile. Further work includes initial chemical process development and pilot manufacturing set up. Ultimately, only one API is subsequently progressed through the development stage.

Stage 3. Clinical Trials

API development begins with Route Design where the sequence of intermediates is identified followed by Process Design which clarifies specific operations and materials to manufacture those intermediates and the resulting API. The evolving manufacturing process is trialled during clinical manufacture with feedback into the Process Design activity. This sequence of activities will require the entire clinical stage to deliver effectively and the timing of significant changes may require repeat of stability, validation and regulatory approval submission activities to introduce.

The clinical development phases concern human and environmental safety, as well as all the pivotal and required studies. Clinical trials are research studies conducted to determine the safety and efficacy of experimental products, including medications, vaccines, medical devices, procedures, diagnostics, and other health-related products. They involve human subjects to determine whether these experimental products are safer and more effective than currently approved products. At this point, a final formulation will be developed and testing for regulatory purposes will begin, together with the full development and validation of the manufacturing process of both the API and the finished product. The time needed for this stage is partly dependent on the number of studies required (e.g., chronic toxicity studies) to obtain marketing authorisation. The ultimate objectives of these studies are to demonstrate the quality, safety, and efficacy of the final medicinal product.

The clinical trial process is divided into three phases:

- **Phase I:** This is the first phase of clinical trials. Usually, small group of 20 to 100 healthy volunteers, who have given informed consent, are dosed with a single ascending dose and multiple ascending doses to establish safety, with the focus on safety and proof of concept. The goal of Phase I trials is to determine the **safety** of a treatment and the appropriate dosage. This phase typically lasts 1 to 3 years.

- **Phase II:** If a treatment is found to be safe in Phase I trials, it moves on to Phase II trials, which usually involve a larger group of patients. In the second phase of the clinical trials, up to 200 people are dosed in the clinic. However, now the focus is both on safety and efficacy of the medicinal product is determined. The doses are ranging to determine the optimum therapeutic dose. The goal of Phase II trials is to determine the **effectiveness** of the treatment for a specific condition and to further assess its safety. On average, this phase lasts 2 to 4 years.

- **Phase III:** If a treatment is found to be effective and safe in Phase II trials, it moves on to Phase III trials, which involve an even larger group of patients (thousands of patients): up to 10,000 people are dosed in the clinic with a focus on long-term safety and efficacy of commercial dose. The goal of this phase is to gather enough data to **confirm the effectiveness and safety of the treatment** and compare it to existing treatments or a placebo in order to support submission for a new drug. The third and last phase generally consists of 2 to 5 years.

In the recent years, attrition rates in the sector have increased throughout all phases, but particularly in Phase II and Phase III clinical trials.[44] After the first phase of clinical trials, the dosage form of a drug is decided. Common dosage forms are tablets, capsules, syringes, solutions for infusion, nebulizers, and ointments. The formulation of a drug plays a crucial role in determining its efficacy, safety, and patient compliance. Firstly, the formulation of a drug can affect its efficacy by influencing the rate of onset and duration of the effect. For example, the drug may have a delayed or rapid onset of action depending on how it is formulated. The formulation may also influence the distribution of the drug within the body, resulting in a systemic or local effect. Additionally, the formulation can determine the concentration of the active substance in the blood, which may be constant or decreasing over time. Secondly, the safety of a drug can be impacted by its formulation. For example, certain formulation can help avoid gastrointestinal problems or side effects associated with injections and patches may provide a controlled release of the drug while minimizing side effects associated with oral or injectable formulations. Finally, the formulation may influence patients' compliance, as the formulation may influence the frequency of the application, the flavour, and the ease of portioning.

Overall, a large amount of documentation must be submitted to the regulatory authorities.[45] As such, given the body of work required for regulatory compliance, this stage is the most cost-intensive and time-consuming. Even in this third stage, compounds may fail, usually on efficacy or safety issues. Thus, it typically lasts up to 8 years (or more) and requires important resources from companies.

Stage 4. Regulatory submission and approval

After the clinical trials have successfully been completed, the registration, launch and commercialisation take place. As specified by the participating companies, and in accordance with the provisions set out in the Directive 2001/83/EC,[46] and the detailed guidelines developed by the EMA,[47] **the information about the manufacturing process for an active substance must include details about the process itself and the materials used, their quality control, and how they meet appropriate standards.** Additionally, quality control tests and acceptance criteria at each critical step, information about intermediates and process validation studies, as well as validation data for analytical methods must be provided. Information about predictable and observed impurities, as well as their safety, must also be included. A retest period and storage conditions for the active substance must be specified except when the manufacturer of the finished product fully retests the active substance immediately before its use in the manufacture of the finished product. Further, stability data must be provided to demonstrate how the quality of the active substance changes over time and to support the retest period and storage conditions. Safety of the active substance must be demonstrated through toxicological data.

[44] Pammolli, F., Magazzini, L. and Riccaboni, M., 2011. The productivity crisis in pharmaceutical R&D. *Nature reviews Drug discovery*, *10*(6), 428-438.

[45] The EMA has an extensive list of detailed studies required to complete this documentation.

[46] https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32001L0083

[47] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/quality-guidelines

A medicinal product is not to be marketed without a marketing authorisation, a certificate of registration, or a certificate of traditional-use registration (depending on the type of medicinal product). The granting of such an authorisation / certificate indicates that the product complies with the required standards of quality, safety, and efficacy. It is the responsibility of companies marketing medicinal products to comply with the relevant legislation and to ensure that such products are only marketed in accordance with legislation.

On average, this process takes approximately from 14 months to 2 years and involves submitting a registration dossier to regulatory agencies for market authorization and global launch of the medicine. The dossier is a comprehensive document that includes all the results of the clinical trials. The specific requirements for the dossier may vary depending on the country to which it is submitted, but there have been efforts to harmonize these requirements to speed up drug development. The EMA evaluates applications for centralised marketing authorisation within the EEA. This authorisation process enables pharmaceutical companies to apply for a single marketing authorisation with EMA, allowing them to market and distribute their medicine to patients and healthcare professionals throughout the EEA with a single authorisation.

Regulatory approvals for a drug, medicinal product formulation, and approved detailed manufacturing processes are based on the exact molecular structure, and on extensive clinical and safety data that were generated using only that exact molecule. The safety and efficacy profile of a drug inherently relies on an exact molecular structure of an API molecule which has been extensively studied in clinical trials. Any change to an API molecule would essentially require the development of a completely new medication, including new regulatory submission and approval.

Stages 5 to 7. Manufacturing scale up, labelling, packaging, and launch

As noted above, innovation in the pharmaceutical market is hindered by the many obstacles and challenges faced by companies when trying to bring new products to market. Regulatory compliance contributes to these challenges.

Once a new substance is authorised, the manufacturing stage can start. This stage includes the manufacturing scale-up, production of first batches, QA test and release, labelling and packaging, and launch. The manufacturing scale-up usually parallels the regulatory submission. Once the approval is received, 3 to 6 months are needed before the launch.

Stage 8. Post-Market Monitoring

Once the drug is launched, the safety of the patients is monitored through pharmacovigilance. Healthcare professionals, pharmaceutical companies, and regulatory authorities continuously monitor the use of the drug in daily routine or according to special risk management plans to record any adverse events or interactions with other drugs. It ought to be mentioned that more than 11% of the R&D budget of the manufacturers is invested in pharmacovigilance, namely activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.[48] Further clinical trials may also be conducted, and line extensions may be pursued to expand the drug's uses.

Post-market monitoring trials are clinical studies that continue to gather information on the side effects, risks, benefits, and optimal usage of a product after it has received EMA approval and is available for consumer use. Typically, these trials involve the participation of several hundred to a few thousand individuals.

3.3.2 Replacing PFAS APIs and associated medicinal products

The development of the API is the first step of the research for new medicines. Once the API is established, the rest of the development of processes is designed in function of the API. It is therefore practically impossible to substitute PFAS APIs in existing drugs.

Substituting one PFAS API for another one that does not bear any perfluoroalkyl substituents would require the design, synthesis and evaluation of a novel non-PFAS API. Indeed, when a new active ingredient is sought in a certain therapeutic area – which is the case if one needs to substitute a product that would be banned under a PFAS restriction – that process will need to start with the very first stage. The duration of the initial four innovation stages, from exploratory discovery to regulatory submission and approval, is variable and depends on the intended therapeutic indication and studies required. When looking to replace a product with certain therapeutic use, in practice it may take several failed innovation cycles (and many more years) before a true replacement can be found.

Therefore, when (and if) a PFAS substitute were ever to be found and implemented in the synthetic route of a commercial medicine, it may need to undergo an entire successful innovation cycle.

As visually displayed below, the research and development of (bio)pharmaceutical products is a lengthy and expensive process that can span more than 10 years. **Promising candidates are typically developed to become API in a process which takes about 10 to 15 years**.[49, 50] The process includes numerous studies to evaluate a product's efficacy and safety, followed by submission to regulatory bodies who review the data and decide whether to grant marketing approval. Only a limited selection of therapeutic candidates successfully navigates through such rigorous scrutiny and ultimately become available for use in clinical treatment. Upon obtaining approval, continual research

[48] https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview

[49] See, for example, Schuhmacher, A., Gassmann, O. and Hinder, M., 2016. Changing R&D models in research-based pharmaceutical companies. *Journal of translational medicine*, *14*(1), 1-11.

[50] DiMasi, J. A., Grabowski, H. G., & Hansen, R. W., 2016. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics*, *47*, 20-33.

and development efforts are devoted to marketed medicinal products, including life-cycle management, medical affairs, and various investments.

As a result, **creating, manufacturing, and obtaining approval for a new medicine to replace one which falls under the PFAS definition would require between 12 years in the best-case scenario (industry average) and 22 years in the worst-case scenario** where repeated failed studies and several iterations may be required.

Certain medicines may experience extended timelines due to research or clinical development challenges, whereas others may follow faster development pathways to address conditions with significant unmet medical requirements.

Given the importance of PFAS for the pharmaceutical industry, their replacement is anticipated to pose significant challenges, involving extensive research, preclinical studies, clinical trials, and regulatory approvals. **It is likely that it will necessitate longer timelines, thus falling closer to the upper range**. Like the time requirements for Research & Development of a new API, the resulting costs also vary depending on the project and/or therapeutic area.

In conclusion, the estimated total development time for a new API/medicinal product can be proxy by the timelines for a successful innovation cycle from discovery, development, authorisation of a new medicine to launch to the market, and estimated in the range of 12 (industry average) to 22 years from the moment a suitable candidate (alternative) is identified, and average costs of an approved medicine amounting to 2.3 billion EUR in investment.

However, multiple factors will most likely extend this timeline even further. Perfluorinated substituents and their use in drug discovery have been studied in industry and academia for decades, so their unique role is very well understood and thus can be exploited to precisely alter important drug properties during the optimization process. To accumulate the same knowledge about potential replacements that offer comparable properties would require years of extensive research. Considering the current lack of knowledge about any equivalent to fluorinated alkyl group in APIs, the risk of late project failure is much higher for not achieving the necessary profile for efficacy and safety.

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.**

These timeframes are not unrealistic, given previous cases of reformulation and re-adjustment of production processes, albeit on a much smaller scale than in the case of PFAS (e.g., the industry-wide cases of Triton X-100 and TiO_2).[51] For example, regarding the replacement of TiO_2, according to EMA, the industry estimated up to 12 years, and indicated that "*a transition period of 10 years or even longer would be required for the phasing out of TiO_2 in medicines*".

[51] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2017.150.01.0007.01.ENG&toc=OJ:L:2017:150:TOC

Finally, it should be noted that all the above-mentioned tasks do not necessarily constitute concurrent phases of the implementation process, but rather some phases are consecutive. This means that for some cases, each step must be completed before moving on to the next one. In the meantime, however, the medicinal products will not be available in the market, besides those that are already produced outside of the EEA and imported under derogation.[52]

Alternative: moving production of an API

As indicated above, APIs cannot be substituted and if there is no derogation for process chemicals that leaves the choice of either abandoning the products completely or relocating API production out of the EEA.

Manufacturers indicated that **the estimated timeline to transfer an API process out of the EEA can take 10+ years plus additional time to get the medicine re-approved and marketing authorisations amended**. Indeed, if a medicinal product were to be reformulated with a substitute starting material, intermediate or reagent, companies would also need to amend the Registration or Marketing Authorisation. This can take up to five years depending on the national health regulator (e.g., MHRA, EMA, FDA, CFDA).

3.3.3 Timelines for substitution of PFAS in the Manufacturing Process, in Packaging Materials of Medicinal Products, and in Drug Delivery Devices

Substitution of starting materials, chemical intermediates and process chemicals

In a similar manner, and in line with the timelines presented in detail in the previous chapter, after identification of an alternative, several tasks must also be accomplished for implementing an alternative to PFAS as starting materials, chemical intermediates, auxiliaries, solvent, catalysts, synthetic and analytical reagents, and processing aids. The technical implementation of a substitute is a challenging task requiring extensive validation and testing in order not to compromise the safety and capacity of the current processes, and thus spanning several years.

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.**

Broadly speaking, some uses highly dependent on suppliers and their capability of substitution; for some others, no alternatives may be possible based on the current state of the art**.**

[52] 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.

The table 2 below lists the substitution activities that can take place together with the time required to execute them once (and if) an alternative has been identified. The tasks shown constitute the major actions that will need to be carried out in order to find and implement a feasible alternative in each of the products.

These substitution activities would be necessary for a number of APIs and medicinal products and cannot be done all at once. They need to be staged and together can take decades from the general availability of suitable alternatives, as outlined above. Therefore, longer transition times than those stated in the table would be required.

Table 2. Substitution activities of raw material, intermediate or auxiliaries included in the registration

Milestone	Description	Substitution Timeline *(i.e., time after alternative has been identified)*
Identification of raw material	Develop alternative synthetic route, check suppliers, approve raw material and supplier	Up to 6 years
Testing at laboratory for key functionalities and qualification of alternative	Testing for key functionalities, check for technical issues, verification of compatibility Investigate supplier including supply chain analysis. Identify critical material attributes. Identify and validate suitable raw material analyses in-house	48 months
Change control activities	Preparation of functional and user requirements specifications, quality plans and validation plans	Up to 12 months
Equipment readiness	Installation, operational and process qualifications, including cleaning validation	12 months
Large-scale Validation	Process performance qualification (PPQ) including medicinal product production and stability	12 months
Shelf-life stability studies	Investigate impact of change on stability using PPQ batches.	48 months. When approximately 12 months data are available, update of registration – step 2 can be performed
Update of Registration Step 1: Scientific review/advice from health authorities on scope of change	Preparation of the application and response by health authorities	12 months (EU and non-EU)
Update of Registration Step 2: Preparation and submission of updated regulatory documentation to health authorities	All documentation is prepared by the subject experts in conjunction with regulatory affairs, and, in some cases, affiliates.	Up to 1 year
Update of Registration Step 3:	Review of submitted documents by health authorities	Up to 4 years

Milestone	Description	Substitution Timeline *(i.e., time after alternative has been identified)*
Approval of change by health authorities		

Finally, PFAS play important roles in drug discovery as reagents or materials in laboratory, analytic or production equipment. Thus, finding replacements for these applications of PFAS will require additional work and time in almost all phases of drug discovery. For example, for identifying alternative reagents in early chemical research, process research and scale up.

Equipment and Consumables

In the case of both fixed and consumable equipment based on PFAS materials, pharmaceutical companies are heavily dependent on the development of alternatives in other sectors (upstream global supply chain). A direct replacement for PFAS, providing the corrosion resistance, safety, and quality characteristics of PFAS does not exist at this point in time and manufacturers of the potentially impacted fixed and consumable equipment are not in a position to estimate the time requirements for discovering and developing alternative materials. In addition, one needs to consider that supply chain is highly complex and global, involving thousands of suppliers worldwide. Moreover, at the time being, no disclosure of PFAS (e.g., fluoropolymers) is required for suppliers as no mandatory disclosure of PFAS (e.g., fluoropolymers) is required by suppliers.

Thus, companies are unable to calculate accurate timelines for substitution. In terms of costs, the **substitution costs for refurbishing the current EEA plants to substitute all PFAS coated equipment would likely be in the same order to magnitude investment costs for a full new built plant (hundreds of millions of EUR). Furthermore, the use of inferior materials may cause the unintended consequences of increased equipment downtime and higher maintenance costs.**

Concerning consumable equipment in production, the timelines depend significantly on the consumable in question. For example, consumables that are part of the drug registration will require a new/updated registration.

For example, from a legal and technical standards perspective, significant efforts must be put into updating the manufacturing information in the countries where products are registered. National authorities must evaluate the substitution and give their approval for commercialization of the products once a change is made, such as:

i. Find replacement sterile filter and tubes
ii. Treatment & sterilisation of sourced materials
iii. Perform compatibility tests incl. extractables/leachable testing
iv. Bacterial retention studies on new filters
v. Stop-time validation studies on filling lines implementing new sterile filters
vi. Regulatory submission of change

As an example, in the case of a potential substitution of sterile filters and tubes at several production lines with multiple products, once a suitable alternative is identified, much effort is required for assessing its suitability and implementing it in all processes. Each process must be evaluated separately, irrespective if the alternative is the same.

From a technical perspective, efforts will focus on testing the compatibility of a potential alternative with the current processes to minimize any impacts on the final product. A scale-up must be carried out and extensive analyses and trial runs are necessary to guarantee the safety of the new process. Furthermore, an analytical method for measuring the concentration of an alternative throughout the process must also be developed and put in place. Validation of the new process will then be required to ensure that it is robust and consistent. This step requires multiple trial runs along with the corresponding equipment preparation, updating of procedures and protocols, planning of tests and compilation of data.

Immediate Packaging Materials of Medicinal Products

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 product development and validation, followed by verification and validation of the new component 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 in 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.

For solid dose blisters containing a PFAS layer, these would include:

1. Component qualification by pharmaceutical company (~1 years as a minimum).
2. Equipment qualification/verification at packaging site. Determination of critical process parameters and assessment of performance of the new material and protection of the new container closure system (~6 months as a minimum).
3. Stability studies to assess safety and compatibility of the new material with all oral products (3 years as a minimum).
4. Regulatory activity to change the immediate material for all the impacted products (~1 year as a minimum).
5. Packaging process validation with commercial batches (~3 months as a minimum).

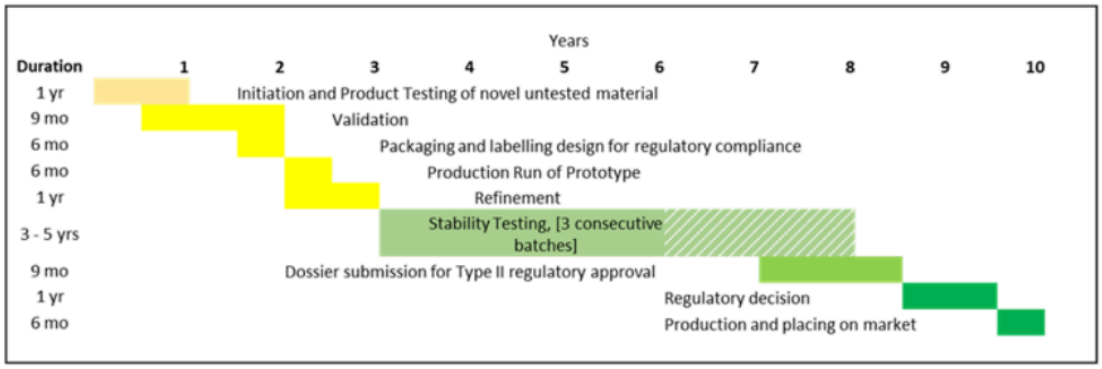
Once an alternative is available, and under the assumption the alternative shows similar inertness and does not impact negatively the impurity profile or stability, the estimated time for a new immediate packaging material is estimated at more than 6 years (minimum) and up to 12 years, in addition to the medicinal product authorisation process.

Similarly, for elastomers in vials and prefilled syringes coated with a PFAS materials, manufacturers will need to undergo several activities, including:

1. Candidates screening and characterization (~1 year as a minimum)
2. Formal qualification – implementation in pharmaceutical process (~1 year as a minimum)
3. Fill finish and device qualification and registration stabilities (~2 years as a minimum)
4. Registration process (3 years as a minimum)

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.**

Figure 4. Typical process flow for introduction of a new Immediate Packaging Material in the first market; additional markets require up to 2 years more.



Drug Delivery Devices and Other Medical Devices

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

- 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

- 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

- 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

- 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

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.

3.4. Overall conclusion on substitution of PFAS via alternatives

In conclusion, the human medicines sector manufactures a variety of APIs that classify as PFAS. In particular, the introduction of fluorine is an essential part of achieving an optimally balanced profile and is key to increase of the drug's efficacy. At the same time, independent of the nature of the API, PFAS are widely used throughout the production activities, starting from the earliest stages of pharmaceutical supply chains (e.g., the importance of fluoropolymers in equipment) all the way through finished/packaged product.

The whole process of manufacturing and developing medicinal products depends heavily on PFAS chemicals in a wide variety of applications. Consequently, it can be expected that all medicines manufactured in the EEA are reliant on PFAS materials at a certain stage of the production.

The analysis of alternatives shows that there are no appropriate chemical alternatives to PFAS in the different manufacturing phases of medicinal products, including:

- **EU approved APIs manufactured for the EEA market, for export and APIs under development**
- **Non-active ingredients (excipients)**
- **Starting materials and chemical intermediates**
- **Process Chemicals (reagents, solvents, catalysts, auxiliaries in production and Quality Control)**
- **Equipment and consumables**
- **Drug delivery devices**
- **Immediate packaging materials**

Once (and if) a PFAS substitute were ever to be found and implemented in the synthetic route of a commercial medicine, it may need to undergo an entire successful innovation cycle.[53] As a matter of fact, it would be a new molecule and therefore would require a whole development, from discovery to launch to the market. Promising candidates are typically developed to become API in a process which takes about 10 to 15 years.[54]

However, from practical experience, to find a suitable candidate can take considerably longer as it may require repeated failed cycles. In each phase, compounds fail the process and several iterations may be required, prolonging the duration of the whole cycle. Therefore, **creating, manufacturing, and obtaining approval for a new medicine to replace one which falls under the PFAS definition would require between 12 years in the best-case scenario and 22 years in the worst case**.

Simultaneously, should the restriction materialise, pharmaceutical companies would be forced to replace PFAS from all above-mentioned non-API uses. These include, for example, fixed and consumable equipment (based on previous cases, it can be expected that at least 15 to 20 years from the general availability of compliant equipment will be required), medical devices and drug delivery devices (~5-7 years once a feasible alternative is available), immediate packaging materials of medicinal products (up to 12 years from general availability of a viable alternative).

All these substitution efforts cannot be done all at once, due to development and regulatory capacity reasons, but need to be staged and together can take decades. Therefore, timelines are very likely to increase accordingly.

In conclusion, a balance needs to be found between toxicological limits of known substances and toxicological and environmental concern of PFAS substances. In this context, APIs, medicinal products, immediate packaging materials and drug delivery devices undergo rigorous registration and market authorization schemes, proving their beneficial health effects and safety of use. **Losing these uses of PFAS in human medicines would undermine the ability to manufacture and would result in the lack of effective treatment for millions of patients in the short-term and undermine the confidence in the long-term performance of medicines**.

[53] In other words, substituting PFAS APIs manufactured for the EEA market, for export, and for R&D purposes, as well intermediates, starting materials and process chemicals (incl. solvents, catalysts, synthetic and analytical reagents, and processing aids) would require an entire successful innovation cycle from discovery to launch to the market

[54] See, for example, Schuhmacher, A., Gassmann, O. and Hinder, M., 2016. Changing R&D models in research-based pharmaceutical companies. *Journal of translational medicine*, *14*(1), 1-11.

4. ANALYSIS OF IMPACTS

At present, active substances in medicinal products are derogated from the scope of the REACH restriction proposal under reporting obligations, as currently worded under restriction option 2. The derogation for active substances is justified in the restriction dossier because (i) the use of these substances is specifically regulated in the EU with extensive evaluations and approval processes by designated bodies; (ii) because of the importance for human health; and (iii) to ensure the security of supply of medicinal products.

Nonetheless, as worded, this derogation does not achieve its very aim of allowing manufacturing of these active substances, which are considered PFAS, nor of the remaining non-PFAS active substances and associated medicinal products in general in the EEA.

The pharmaceutical industry is crucial to the development and production of the drugs and treatments needed for the diagnosis, prevention, treatment, and cure of a wide range of illnesses and ailments. To meet the changing healthcare demands of individuals throughout the world, the pharmaceutical industry is continually producing novel treatments and cures. As such, the sector is a key driver of medical innovation and has a significant impact on public health outcomes.[55] The COVID-19 pandemic has also drawn attention to the vital role that the pharmaceutical industry plays in reacting to public health emergencies and advancing the development of vaccinations and therapies.

The therapy areas with the highest forecast spending in 2027 are oncology, immunology, and anti-diabetics, followed by cardiovascular. The biggest contributors to the growth in the next five years are immunology, anti-diabetics and obesity, result of a continuous influx of innovative products. By 2027, specialty medicines are projected to account for approximately 43% of global expenditure and 56% of total spending in developed markets. These medicines are specifically designed to address chronic, complex, and rare diseases.[56]

The sections below provide a general overview of the social and economic impacts, considering business impacts for the pharmaceutical industry, market impacts (on the product market), substitution costs, and broader EU macroeconomic consequences resulting from a potential REACH restriction of PFAS used for medicines.

4.1 Economic impacts on manufacturers of human medicines

[55] DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Econ. 2016; 47:20-33.

[56] EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 11. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf

A survey of **major manufacturers of human medicines** was performed in the preparation of this report. The participating companies are among the biggest producers in the EEA pharmaceutical market. The market share covered by this questionnaire is approximately 40% of the whole EEA human medicines market. The assessment is, therefore, representative. This fairly large share can be used to obtain reliable estimates for the EU market via extrapolation, as detailed below for the assessment of the economic impacts.

The core business of the participating companies is the production of medicinal products used to prevent, diagnose, treat or cure a wide range of diseases. Nevertheless, as outlined above (cf. Section 2.2), some of these companies are also active at different levels of the value chain (vertically integrated) and directly produce the active pharmaceutical ingredients used in pharmaceutical drugs as well as drug delivery devices.

In 2022, the industry employed more than 700,000 employees directly engaged in the manufacturing, and supply chain of PFAS APIs and/or medicines containing PFAS APIs across the EEA, including 130,000 involved in R&D activities related to medicinal products.[57]

In the business-as-usual scenario (i.e., assuming no PFAS restriction), the demand for human medicines is growing consistently. The growth of the pharmaceutical market value (at ex-factory prices) averaged 5% from 2000 until 2020, reaching a market value (at ex-factory prices) of 194 billion EUR in 2021.[58] The trends are upgoing as there are several new medicinal products in the pipeline. Accordingly, **the annual sales of medicinal products are projected to grow at a comparable CAGR in the period 2027-2030**.

In 2022, the European market was the second world's largest market with a 22.4% share, behind the North American market (USA plus Canada). The EEA production of medicinal products amounted to approximately 226.4 billion EUR.[59] These data were taken from a typical sales year and the sales are considered representative for annual sales.

Given the broader definition of PFAS, and under the assumption that all PFAS uses would be eventually restricted in the EEA, it is estimated that the vast majority of the overall company turnover in the EEA will be lost. **Virtually, all pharmaceutical manufacturing within the EEA depends on activities that currently rely on the use of PFAS.**

4.1.1 Economic impacts of a restriction of PFAS used as an API

[57] Employment in the pharmaceutical industry, excluding Russia, Serbia, Switzerland, Turkey, and U.K. (EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 12. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf)

[58] Pharmaceutical market value (at ex-factory prices), excluding Russia, Serbia, Switzerland, Turkey, and U.K. (EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 15. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf)

[59] Value of pharmaceutical production, excluding Russia, Serbia, Switzerland, Turkey, and U.K. (EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 11. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf)

Under RO2, the derogation in the current restriction proposal does exclude APIs. However, API manufacturers located in the EEA use PFAS process chemicals during manufacture of PFAS and non PFAS APIs. As only the API is exempted from the PFAS restriction but not PFAS chemicals used for synthesis of the APIs, corresponding APIs cannot be supplied from European manufacturers and manufacturing and development activities could only take place outside the EEA.

The APIs utilised in human medicines can be either PFAS or non-PFAS based. PFAS APIs represent a smaller fraction of the API - product portfolios of these manufacturers: approximately 5% of the APIs used in medicinal products are PFAS.[60] The pharmaceutical companies receive or manufacture PFAS (active ingredients) to produce human medicinal products. These relatively small volumes underpin much larger turnovers – and most pre-eminently importance for society – when considering the medical products containing different combinations of PFAS and non-PFAS APIs.

The medicinal products containing PFAS APIs cover a wide range of diseases, including AIDS, malaria, depression, cancer, diabetes, multiple sclerosis, and inflammation. Many of these diseases are indicated in the WHO's List of Essential Medicines.[61]

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. Developing a new "non-PFAS" API would be costly and time-consuming: the research and development of biopharmaceutical products is a lengthy and expensive process that can span more than 10-15 years, without any certainty on the final outcome, as outlined in Section 3.3.

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).[62] 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).

The direct cost of a PFAS restriction on the API is represented by the loss of the contribution to the EEA economy of the Earnings Before Interest and Taxes (EBIT) generated by manufacturers using PFAS APIs. In other words, the relevant economic measure to quantify this economic impact is given by EBIT. The monetization (NPV, with 3% discount rate)[63] of this economic impact (lost EBIT) is reported below.

[60] Volume-weighted average of the number of PFAS APIs in companies' portfolio.

[61] https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists

[62] The lost commercial value of the production (i.e., loss in sales of medicinal products containing PFAS APIs) and the lost EBIT are derived from the aggregation of data from seven companies out of 14 participants.

[63] In accordance with European Commission, 2021. Better Regulation Guidelines and Toolbox. https://commission.europa.eu/document/download/9c8d2189-8abd-4f29-84e9-abc843cc68e0_en?filename=br_toolbox-nov_2021_en.pdf

Therefore, if the PFAS restriction proposal would materialize, and PFAS were to be restricted from use as active pharmaceutical ingredient,[64] it is estimated that **manufacturers of medicines would experience a net EBIT loss of nearly 3.4 billion EUR/year** (rounded).[65]

Over four years, **the total economic impact amounts to approximately 12.6 billion EUR** (NPV, 3% d.r.) **for participating pharmaceutical companies**.[66]

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).[67]

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.

Because the REACH restrictions would affect equally the whole EEA pharmaceutical industry, the corresponding loss in value added (i.e., loss in EBIT) can be considered as a lower bound estimate of the net impact (EEA industry-wide impact).[68]

It must be noted that the estimate does not take into account API/medicinal products under development. A PFAS API development product is not derogated, and in case clinical trials are ongoing in 2027, they cannot be continued nor manufactured in the EEA with copious wasted (past and future) investments.

4.1.2 Economic impacts of a restriction of PFAS used in the manufacturing process, immediate packaging, drug delivery devices and quality control

For both non-PFAS APIs and PFAS APIs, PFAS are required as auxiliaries and production materials, including solvents, synthetic and analytical reagents and processing aids, in fixed and consumable equipment, in drug delivery devices, and in immediate packaging materials. Without any of these derogations, the development and production would be simply infeasible in the EEA.

A PFAS restriction would result in prohibiting the import, manufacture, sale, and export of PFAS materials in the EEA. If this restriction is implemented without any derogations, it would have significant consequences for companies in various aspects of their operations.

64 Companies were asked to project lost sales and EBIT under the assumption that a PFAS restriction were to be fully adopted as of 2027.

65 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.

66 Using the Excel function =PV(3%,4,-3400000000,0,0).

67 Result of the extrapolation: 12.6 billion EUR / 40% = 31 billion EUR.

68 In other words, we are assuming that the companies that may benefit from a negative regulatory outcome for PFAS are competitors based outside the EEA (where the REACH requirements, especially in the manufacturing process, do not apply.

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. The following sections report on the economic impact of a restriction of PFAS used in medical and drug delivery devices, in packaging materials (both blisters and elastomers), and ultimately in production equipment.

Immediate Packaging Materials of Medicinal Products

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,[69, 70] and 39 billion EUR (result of the extrapolation via the 40% market share).

Medical Devices and Drug Delivery Devices

Similarly, using the same methodology, we repeated the same analysis for the use of PFAS in medical and drug delivery devices.

Based on the data received in the context of this survey, 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.[71, 72] 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.

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[69] 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).

[70] Data from six 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 4.23 billion EUR/year. Total over four years is calculated using the Excel function =PV(3%,4,-4230000000,0,0).

[71] 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).

[72] 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).

Equipment and Consumables

Based on preliminary investigation, and as described in earlier sections, manufacturers of medicinal products expect that close to 100% of the medicines manufactured in the EEA (including those medicinal products that do not contain any PFAS APIs) are reliant on PFAS materials at a certain stage of the production. In other words, their entire portfolio of products placed on the EEA market, or produced in EEA for export, is potentially impacted by the PFAS restriction.

Precisely, companies declared that, without a derogation for the whole manufacturing process of medicines or for use of PFAS at industrial sites from the proposed PFAS restriction, at present it is not possible to manufacture one single medicinal product in the EEA.

Therefore, a broad restriction of PFAS in the EEA would have significant impacts on the business of the medicinal product manufacturers and, most importantly, to their customers and patients.

If one applies the estimated growth rate, **the expected loss in income generated through the sale of prescription medicinal products in 2027 is estimated at approximately 303 billion EUR/year** (rounded).[73] Future values are expected to grow at the same CAGR of 5%.

The direct cost of a PFAS restriction is represented once again by the loss of the contribution to the EEA economy of the EBIT generated by manufacturers using PFAS chemicals in the production of medicinal products. **If PFAS were to be restricted from use in the different stages of the manufacturing process, the estimated loss of contribution to the EEA economy (i.e., net EBIT loss) at the level of the pharmaceutical industry would be therefore estimated at 60.7 billion EUR/year (rounded).[74]**

Over four years, the total impact amounts approximately to 226 billion EUR (NPV, 3% d.r.) for the EEA pharmaceutical industry.[75]

4.1.3 Substitution costs for the pharmaceutical industry

PFAS APIs are also widely used in R&D activities. Generally, for research and development activities, intermediates are used on a mg to g scale in the research phases. For reagents with more general purposes, kg quantities might be necessary even during research. In case drug candidates are identified where such intermediates or reagents are used for synthesis, development activities routinely require kg up to ton quantities (e.g., in chemical process development, scale-up, API supply for advanced efficacy or safety studies, or launch support).

[73] Based on the value of pharmaceutical production, excluding Russia, Serbia, Switzerland, Turkey, and U.K. (EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 11. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf)

[74] For the purpose of estimating the lost EBIT, it was assumed that EBIT = 20% of the turnover (sales).

[75] Using the Excel function =PV(3%,4,-60700000000,0,0).

The main challenge that has been raised by participating companies is the fact that deadlines provided by authorities are considered too tight for business adaptability and to develop alternative products. There are various challenges associated with substitution. As outlined in the previous sections, a transition towards PFAS free API and manufacturing process would involve various players in the steps to redevelop a new medicinal product.

Given the importance of PFAS for these companies' portfolios (i.e., close to 100% of all medicinal products manufactured in the EEA), implementing a new manufacturing process and the associated regulatory submissions require longer timelines to convert the entire portfolio and significant cost increases.

The EU pharmaceutical industry is highly innovative, in the sense that innovation focuses on development of new medicinal products rather than on the reformulation of currently available medicinal products. Surveyed companies are committed to the research and development of innovative medicinal products. On average, these companies invest approximately 15% of their turnover on R&D budget. In the EEA, the R&D expenditures peaked more than 41.5 billion EUR in 2021.

Most of the R&D is invested in developing new, alternative medicinal products for consumer use.[76] Precisely, more than half of the R&D budget is allocated for pre-clinical and clinical trials (phase 2 and phase 3 of the typical innovation process), and especially in Phase III trials.

On the one hand, the search for alternatives to PFAS has so far borne no fruit, as outlined in the Analysis of alternatives (cf. Chapter 3). On the other hand, a reformulation of the entire product portfolio of these companies would not only divert significant resources from R&D (with associated impacts on innovation), but also entail considerable costs for the companies in terms of resources.

On aggregate, for PFAS APIs one can take the typical innovation cycle as a proxy. As illustrated in Section 3.3, timelines for successful innovation cycles range between 12 to 22 years in more complex cases (like PFAS), with **average costs of an approved medicine amounting to 2.3 billion EUR per medicinal product**.

This can be considered as a minimum, because replacing products with certain therapeutic indications, in practice it may take several failed innovation cycles (and many more years) before a true replacement can be found. The costs would accordingly increase (i.e., limited access to medicines for patients).

Moreover, the supply chain is in discovery phase of presence of PFAS and not at all ready with substitution plan. Thus, **these estimates are certainly optimistic**.

[76] EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 6. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf

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.

It must be noted that this estimate does not take into account the cost of transitioning towards PFAS-free manufacturing equipment, immediate packaging and delivery devices.

Taking into account the large number of medicinal products that would have to be reformulated, and the production processes re-designed, the total cost of a substitution would easily reach an order of magnitude of hundreds of billions of EUR for the whole industry. Obviously, the reformulation of the entire medicines' portfolio is not a realistic scenario as companies would more likely transfer the production outside of the EEA.

4.2 Social impacts: unemployment

The restriction of PFAS will have a direct impact on the headcount of the manufacturer companies. However, to what extent these impacts will be felt on the employment is difficult to be predicted for surveyed companies. Indeed, all participating companies highlighted that the unemployment effect of a PFAS ban on sales will likely depend on the adaption of the supply chain to non-PFAS based materials required for the development and manufacture of medicinal products or imports of PFAS-containing medicines from outside of the EEA.

Due to the broad and extensive use of PFAS chemicals/components/materials throughout the whole value chain, should the restriction apply as it is currently drafted, all manufacturing would be extensively impacted and unable to operate properly.

If there were not specific derogations assigned to all critical applications which included the ability to continue manufacturing the products with the EEA, the amount of revenue at risk could force the closure of EU based manufacturing sites and relocation to non-EU based locations where the product could be imported under derogation, otherwise distributed globally.

4.2.1 PFAS used as an API

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. Here we report the monetization of the likely social costs of unemployment for these workers.

The average annual salary across these European workers (including the employer's social security contributions) is approximately 83,000 EUR per worker.[77]

A well-known guideline in monetising the social impact of unemployment has been developed by ECHA for evaluating such impact in different regulatory processes.

Estimates have been made in accordance with the ECHA document on the evaluation of unemployment (SEAC/32/2016/04)[78] and the paper of Dubourg (2016)[79] endorsed by ECHA. Therefore:

- Using Table A7 (column G, considering the gross wages including the employer's social security contributions) in Dubourg's paper, the total social cost of unemployment in EU is equal to 2.16 times the annual gross salary.[80]
- Table 3 presents the statistics from Eurostat (data for 2022-Q1) on the average duration of unemployment for both men and women in the age of 15-64 years in EU-27.[81]
- Only 75% of the average duration of employment is considered, to reflect the fact that some affected workers are highly skilled and could find employment sooner.

Table 3. Duration of unemployment in EU-27

Duration Grouping	Thousand units	Proportion (A)	Assumed duration (B)	Weighted average (A*B)
Less than 1 month	1643.2	0.121421710	0.5	0.060710855
From 1 to 2 months	2424.4	0.179147270	1.5	0.268720904
From 3 to 5 months	2126.5	0.157134412	4.5	0.707104855
From 6 to 11 months	1890.1	0.139666002	8.5	1.187161014
From 12 to 17 months	1441.2	0.106495234	14.5	1.544180891
From 18 to 23 months	830.8	0.061390675	20.5	1.258508830
From 24 to 47 months	1601.0	0.118303406	35.5	4.199770930
48 months or over	1575.8	0.116441292	48	5.589182000
Total	13533.0	1		**14.815340279**

The social costs of unemployment would therefore be equal to:

[77] Weighted average of the average annual salary (including the employer's social security contributions) weighed by the number of impacted workers.

[78] ECHA (2016). The Social Cost of Unemployment. Available at: https://echa.europa.eu/documents/10162/13555/seac_unemployment_evaluation_en.pdf/af3a487e-65e5-49bb-84a3-2c1bcbc35d25

[79] Richard Dubourg, 2016. Valuing the Social Costs of Job Losses in Applications for Authorisation. The Economics Interface Limited.

[80] This value is greater than one (1) because it takes into account the following components: lost wage, costs of job searching, recruitment costs, the impact of unemployment status on future wages (scarring effect) and employment possibilities, and leisure time (which is a benefit and therefore subtracted from the previous components).

[81] Data extracted from https://ec.europa.eu/eurostat/web/products-datasets/-/lfsq_ugad

83,000 EUR x 22,500 people x 2.16 x 14.826475584/12 x 75% = 3.9 billion EUR (rounded).

Although companies along the supply chain would face a reduction in sales over the years, we assume for simplicity that the entire workforce will continue working for the other three years. Therefore, one discounts the monetised impact derived above by three years due to the assumed delay in the layoff, using discount rate of 3% per year, as follows: 3.9 billion EUR x $(1 + 0.03)^{-3}$ = 3.6 billion EUR (rounded).

One can use the market share to extrapolate the total social impact of the unemployment in the EEA across all medicinal product manufacturers: 3.6 billion EUR / 0.75 = 9 billion EUR (rounded).

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.

Other workers would be likely impacted, even though the participating companies are not in a position today to quantify the unemployment effect. Due to the impact on turnover, R&D capabilities would be reduced as well, since the R&D budget is a rather fixed percentage of sales and will not be increased because of the restriction, but the contrary will happen also in terms of employment.

Moreover, as a progressive result and due to the expected reduction in sales**, job creation is also expected to be negatively affected**. Manufacturers anticipated that eventually they would inevitably reduce new recruitment as all manufacturing and R&D activities would relocate outside the EEA.

4.2.2 PFAS used in the manufacturing process, immediate packaging, medical and drug delivery devices and quality control

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.[82] **The social costs of unemployment associated with this scenario is estimated in the order of magnitude of one hundred billion EUR.**

[82] Employment in the pharmaceutical industry, excluding Russia, Serbia, Switzerland, Turkey, and U.K. (EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 12. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf

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.[83]

4.2.3 Broader consequences on the human health: patients

A restriction of PFAS in the manufacture of human medicines would have serious consequences on human health of millions of patients in the EEA. Due to extensive research and innovation, the pharmaceutical industry has evolved and has driven medical progresses. A result of these developments is that European citizens can expect to live up to 30 years longer as well as living a better-quality life than they did a century ago.[84]

Restrictions on intermediates, auxiliaries, and other production materials used in the manufacturing process will significantly affect the production of several human medicinal products.

Many of these treat a wide range of diseases which are included in the World Health Organization's List of Essential Medicines.[85, 86] **Any sudden discontinuation of supply of these critical materials will affect production and result in sudden shortages of medicines in the EEA and abroad.**

The ban of PFAS based medicinal products in the EEA will **reduce the number of available human health medicinal products in the EEA** – and beyond. **As such, EEA-based patients can no longer access the treatment they need.**

In this regard, it must be noted that the prospect that non-EEA production could provide for the loss of EEA production of medicinal products is to be considered totally unrealistic. Even assuming that non-EEA production could step in and mitigate these shortages, at present, the non-EEA production capacity would not be able to cope with the current EEA demand. **The EEA is current net exporter of medicinal products**. There is currently no 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.**

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83 PricewaterhouseCoopers (PwC), 2019. The economic and societal footprint of the pharmaceutical industry in Europe. Technical Report. Available at https://www.efpia.eu/media/412939/efpia-economic-societal-footprint-industry-final-report-250619.pdf

84 EFPIA, 2023. The Pharmaceutical Industry in Figures. Available at: https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf

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

86 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.

The limited availability of pharmaceutical options in a specific therapeutic or diagnostic class would greatly impact the ability to treat and diagnose patients effectively and safely. Ultimately, this puts additional pressure on healthcare systems that are already overheated in several European countries. All in all, **this results in a higher likelihood of increased healthcare costs, increased health complications, and even an increased risk of excess mortality** compared to the status quo.

The aforementioned consequences on human health inevitably have widespread social impacts. For instance, if people are desperately in need of certain medicines that are not available anymore, or at increased prices, this may even increase the risk of **adverse health outcomes due to the use and trade of unsafe or substandard products**. This, in turn, would lead to even more health complications and have severe impact on human health.

Beyond the direct monetised economic and social impacts, there is a broader economic impact in terms of overall public health. The case study below illustrates how a restriction of PFAS would potentially have important impacts on the availability and importance of life saving medicines for Hepatitis C virus (HCV), and in turn on the human health of patients in the EEA.

Case studies

In order to assess the socio-economic impacts of restricting PFAS on the pharmaceutical sector, it is essential to examine real-world case examples. By delving into specific instances, it is possible to gain valuable insights into the potential consequences on the human health of millions of patients. These case examples shed light on the consequences of a potential REACH restriction of PFAS on single examples of products that would be impacted, and contribute to our understanding of the socio-economic implications of restricting PFAS in the pharmaceutical sector.

One should bear in mind that these are only few examples of APIs/products potentially falling in scope of a REACH PFAS restriction and there are many more medicinal products on the market potentially affected. Potentially, if, as explained above, there should be shortages in the supply of medicines in Europe, one could possibly take every medicine on the market as an example.

Hepatitis C medicinal product (Glecaprevir/Pibrentasvir - Maviret)

Maviret contains one API categorized as a PFAS, Glecaprivirm and one API which is fluorinated, but not categorized as PFAS. Both APIs in this medicinal product are manufactured at EU sites, and the final medicinal product is manufactured at other EU sites. All of the manufacturing sites use process equipment and consumables containing PFAS substances.

HCV infection is a chronic disease that affects approximately 58 million people worldwide with approximately 1.5 million new infections occurring each year. Over time, the chronic infection will cause increasing levels of hepatic fibrosis, which may ultimately result in cirrhosis. Complications of cirrhosis include hepatic decompensation, hepatocellular carcinoma (HCC), liver transplantation, and

death.[87, 88, 89, 90, 91] Both cirrhosis and HCC are rare in children, although liver disease can progress early in life.[92, 93] Hepatitis C virus infection is the leading cause of liver transplantation in the developed world. Without liver transplantation, decompensated cirrhosis leads to death in 50% to 72% of patients after five years.[94]

Patients with HCV infection may additionally develop extrahepatic manifestations (EHMs) attributable to the body's altered immune response from chronic HCV infection. EHMs of chronic HCV infection occur in up to 40-74% of patients with HCV infection during their lifetime.[95] EHMs can pose a high clinical burden on patients, and the prevalence of EHMs in patients with HCV has been found to be higher than in patients without HCV. Reau et al. (2017) also found that mean annualized all cause medical costs were significantly higher for patients with HCV compared with patients without HCV (43,891 USD vs 17,989 USD; P<0.05).[96]

The prevalence of chronic HCV infection in the European Union (across all genotypes) is estimated to be over 1.6 million people.[97] Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy (AASLD/IDSA, 2019).[98] In 2016, the World Health Assembly approved the Global Health Sector Strategy to eliminate viral hepatitis by 2030, and the World Health Organization (WHO) published targets that countries must meet to achieve the elimination goals of reducing incidence of viral hepatitis'. In a study of 45 high-income countries, only

87 European Centre for Disease Prevention and Control. Hepatitis C. In: ECDC. Annual epidemiological report for 2019. Stockholm: ECDC; 2021.

88 Sangiovanni, A., Prati, G.M., Fasani, P., Ronchi, G., Romeo, R., Manini, M., Del Ninno, E., Morabito, A. and Colombo, M., 2006. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. *Hepatology*, *43*(6), 1303-1310.

89 El-Serag, H.B., 2004. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology*, *127*(5), S27-S34.

90 Serfaty, L., Aumaître, H., Chazouillères, O., Bonnand, A.M., Rosmorduc, O., Poupon, R.E. and Poupon, R., 1998. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology*, *27*(5), 1435-1440.

91 Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens, F., Solinas, A., Mura, D., Brouwer, J.T. and Thomas, H., 1997. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112(2):463-72.

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93 Mohan, P., Barton, B.A., Narkewicz, M.R., Molleston, J.P., Gonzalez-Peralta, R.P., Rosenthal, P., Murray, K.F., Haber, B., Schwarz, K.B. and Goodman, Z.D., 2013. Evaluating progression of liver disease from repeat liver biopsies in children with chronic hepatitis C: a retrospective study. *Hepatology*, *58*(5), 1580-1586.

94 Fattovich, G., Pantalena, M., Zagni, I., Realdi, G., Schalm, S.W., Christensen, E. and European Concerted Action on Viral Hepatitis (EUROHEP, 2002. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. *The American journal of gastroenterology*, *97*(11), 2886-2895.

95 Maasoumy, B. and Wedemeyer, H., 2012. Natural history of acute and chronic hepatitis C. *Best practice & research Clinical gastroenterology*, *26*(4), 401-412.

96 Reau, N., Vekeman, F., Wu, E., Bao, Y. and Gonzalez, Y.S., 2017. Prevalence and economic burden of extrahepatic manifestations of hepatitis C virus are underestimated but can be improved with therapy. *Hepatology Communications*, *1*(5), 439-452.

97 The CDA Foundation. Hepatitis C — [multiple countries]. Lafayette, CO: CDA Foundation, 2022. Available from http://cdafound.org/polaris/ (Accessed November 2022)

98 Ghany, M.G., Morgan, T.R. and AASLD-IDSA hepatitis C guidance panel, 2020. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases–Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. *Hepatology*, *71*(2), 686-721.

eleven countries were on target towards eliminating HCV by 2030, of which 5 countries were in the European Union: France, Germany, Italy, Spain, and Sweden.[99] Elimination of HCV treatments would further compromise the ability of any country in the European Union to achieve these goals.

Hepatitis C is a preventable viral infection that damages the liver. Chronic hepatitis C can lead to serious complications such as cirrhosis, liver cancer and liver-related death. HCV is transmitted through contact with the blood of an infected person; as a result of unsafe injections or other invasive medical and nonmedical practices (such as tattooing and piercing) when the skin is damaged; and, where blood safety measures are suboptimal, as a result of transfusion of unscreened blood and blood products. Hepatitis C is curable; new direct acting antiviral medicines can achieve a sustain viral response in more than 95% of infected people, reducing the risk of complications and death. There is currently no vaccine for hepatitis C. Prevention should therefore focus on reducing the risk of exposure to the virus. It is possible to eliminate hepatitis C as a public health threat by 2030.[100] Without direct acting antivirals available, HCV incidence and prevalence would continue to rise.

Glecaprevir/pibrentasvir (Maviret) is the only 8-week pan-genotypic direct acting antiviral indicated for the treatment of adult and pediatric patients three years and older or weighing at least 45 kg with chronic Hepatis C in the European Union. Both clinical trials and real-world studies have demonstrated glecaprevir/pibrentasvir efficacy rates at 95% or better.

The population of the European Union exceeds 450 million individuals, of which 0.37% (1,667,010) have HCV infection. It is estimated that approximately 50,000 new individuals contract HCV each year. If there were no HCV treatments available, patient's liver function would progressively get worse leading to decompensated cirrhosis, hepatic cellular carcinoma, liver transplant, and death; extrahepatic manifestations would rise in this population; and the virus would spread.

Using a Markov population model to forecast HCV disease burden and cascade of care in the EU, we can estimate the number of patients progressing to end stage liver disease (decompensated cirrhosis, hepatic cellular carcinoma, and liver transplant), total deaths, and healthcare spending over a set period.[101]Costs include total spending on liver-related complications, extra-hepatic complications, HCV care, and HCV Screening. Using this model, we explored three scenarios: no treatment, maintain current treatment rate, and delay treatment for 3 years.

- Using this model, Scenario 1, if no treatments were available for HCV; there would be 214,773 individuals progressing to end stage liver disease; 125,348 deaths; costing the healthcare systems 140,894,613,497 USD over a ten-year period.

99 Gamkrelidze, I., Pawlotsky, J.M., Lazarus, J.V., Feld, J.J., Zeuzem, S., Bao, Y., Gabriela Pires dos Santos, A., Sanchez Gonzalez, Y. and Razavi, H., 2021. Progress towards hepatitis C virus elimination in high-income countries: an updated analysis. *Liver International*, *41*(3), 456-463.

100 https://www.who.int/docs/librariesprovider2/default-document-library/hepatitis-c-in-the-who-european-region-factsheet-july-2022.pdf?sfvrsn=1e330371_3&download=true

101 Razavi, H., Sanchez Gonzalez, Y., Yuen, C. and Cornberg, M., 2020. Global timing of hepatitis C virus elimination in high-income countries. *Liver International*, *40*(3), 522-529.

- Scenario 2, if HCV treatments were available and the same number of patients were treated each year; 163,393 patient's progression to end stage liver disease would be averted (compared to no treatment); 102,348 total deaths would be averted (compared to no treatment); and 6,804,199,845 USD would be saved (compared to no treatment) over ten-years.

- Scenario 3, if it took 3 years to develop a new treatment for HCV and no treatments were available during the development period; only 117,966 end stage liver disease would be averted, 80,988 total deaths averted, and 343,377,868 USD would be saved over ten-years.

Based on these model results, hundreds of thousands of patients would be negatively impacted and healthcare spending would dramatically rise if no HCV treatments were available in the European Union. The ability to achieve the World Health Organization target of eliminating Hepatitis C by 2030 would be significantly impaired, having a major impact on HCV incidence and the HCV epidemic.

Venclyxto, Oncology medicinal product

Another case in point is the example of Venclyxto. Venclyxto contains the active substance venetoclax, which is not, in and of itself, a PFAS substance. Venclyxto is impacted, however, in that this final medicinal product is packaged in blisters containing PCTFE, and both the API and final medicinal product are manufactured in EU plants whose equipment and process consumables contain PFAS. As such, it would be impacted by a restriction of PFAS and companies would be forced to withdraw it from the market.

According to the European Medicines Agency, Venclyxto is a cancer medicine used to treat adults with two severe forms of blood cancers: the chronic lymphocytic leukaemia (CLL) and the acute myeloid leukaemia (AML).[102]

For CLL, it is used either in combination with other cancer medicines or on its own. Venclyxto can be used with obinutuzumab in patients who have not previously been treated for CLL or with rituximab in patients who have received at least one previous treatment. Obinutuzumab and rituximab are immunotherapy medicines (medicines that act through the body's defence system).

It can also be used on its own in patients with particular genetic changes (17p deletion or TP53 mutation) who cannot be treated with medicines known as B-cell receptor pathway inhibitors (ibrutinib and idelalisib) or if these medicines have stopped working. Likewise, in patients who do not have these genetic changes, after treatments with chemotherapy combined with immunotherapy as well as a B-cell receptor pathway inhibitor have both not worked.

For AML, Venclyxto is used in combination with either azacitidine or decitabine in adults who cannot have intensive chemotherapy

Observed effects in studies of Venclyxto in CLL

102 https://www.ema.europa.eu/en/medicines/human/EPAR/venclyxto#authorisation-details-section

Studies have shown that a high proportion of patients have their cancer cells partially or completely cleared following treatment with Venclyxto on its own. In a main study of 107 previously treated patients with CLL and 17p deletion, 75% responded partially or completely to Venclyxto. In another study of 127 patients with or without 17p deletion or TP53 mutation, the response rate was 70%. Patients in this second study had all previously taken B-cell receptor pathway inhibitors. A third study in 389 patients with CLL who received at least one previous treatment showed that patients treated with Venclyxto plus rituximab lived longer without their disease getting worse (progression-free survival) than patients treated with rituximab and bendamustine (another cancer medicine). Another study involving 432 patients with CLL who had not previously been treated for the disease found that patients treated with Venclyxto plus obinutuzumab lived longer without their disease getting worse compared with patients treated with chlorambucil (a chemotherapy medicine) plus obinutuzumab.[103]

Observed effects in studies of Venclyxto in Acute Myeloid Leukaemia

A study involving 431 patients with AML who had not previously been treated for the disease found that 65% of patients treated with Venclyxto plus azacitidine had no sign of the disease (complete response), with or without recovery of blood cells compared with 25% of patients treated with azacitidine alone. Patients lived an average of 15 months with Venclyxto plus azacitidine compared with 10 months with azacitidine alone.[104]

In the AML indication, Venclyxto is considered to be part of the standard of care where it cannot be replaced by another drug. The addition of venetoclax to the standard of care improved clinical response from 28.3% to 66.4% and the overall survival from 9.6 to 14.7 months.[105]

Empowering Respiratory Health: Unravelling the importance of fluorinated molecules in medical inhalers

Respiratory diseases such as COPD and asthma are challenging to manage and have a profound impact on affected individuals.[106,107,108] COPD is a progressive, chronic disease that obstructs airflow in the

[103] Venclyxto (venetoclax) An overview of Venclyxto and why it is authorised in the EU. EMA/249539/2020. European Medicines Agency. Accessed April 12, 2023. https://www.ema.europa.eu/en/documents/overview/venclyxto-epar-medicine-overview_en.pdf

[104] Ibid.

[105] Döhner, H., Wei, A.H., Appelbaum, F.R., Craddock, C., DiNardo, C.D., Dombret, H., Ebert, B.L., Fenaux, P., Godley, L.A., Hasserjian, R.P. and Larson, R.A., 2022. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood, The Journal of the American Society of Hematology*, *140*(12), 1345-1377.

[106] GOLD, 2023. Global Strategy for the Diagnosis, Management and Prevention of COPD. *Global Initiative for Chronic Obstructive Lung Disease (GOLD)*. Available at: https://goldcopd.org/2023-gold-report-2/. Accessed in June 2023.

[107] The Global Asthma Report, 2022. Available at: http://globalasthmareport.org/. Accessed in June 2023.

[108] National Asthma Education and Prevention Program, 2007. Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Available at: https://www.ncbi.nlm.nih.gov/books/NBK7223/. Accessed in June 2023.

lungs, leading to debilitating bouts of breathlessness.[109] As the third leading cause of death worldwide in 2019, COPD affects 1 in 10 adults over the age of 40 in the EU.[110,111]

The prevalence of chronic respiratory diseases, including asthma and COPD, is on the rise, with an incidence of 84.8 million people in Europe of both conditions and a total of 366,000 people in Europe passing away from the diseases in 2019.[112]

pMDIs play a crucial role in delivering inhaled medicines to the lungs of patients with respiratory diseases such as asthma and COPD. Improving lung function, minimizing exacerbations, and effectively managing daily symptoms such as breathlessness are fundamental objectives in the treatment of COPD.[113] In this treatment, inhaled medicines aim to control symptoms, prevent disease progression, reduce mortality and improve patient outcomes overall. Several factors should be considered when selecting the most suitable inhaler type for a patient, including their familiarity with the device, limited lung function, and age.[114,115,116,117] In 2021, 70% of all individual inhalations of respiratory medicines delivered in the EU-5 countries (France, Germany, Italy, Spain and Poland) were provided via pMDIs.[118]

In this context, fluorinated propellants, such as HFA/HFC aerosols, act as approved excipients and form part of the drug formulation in pMDIs. These **propellants serve the crucial role of aerosolizing the active substance, facilitating its delivery to the lungs and ensuring therapeutic benefits.** The advantage of fluorinated propellants is that they are in a liquid phase in the can and can vaporize when the pMDI is actuated. The vaporization process, coupled with a constant pressure or force for each dose, enables the aerosolization of the active therapeutic ingredients. The current proposed definition of PFAS includes HFAS propellants and canister coatings within the PFAS category and aims to ban them without allowing derogation periods.

Without the propellant, a diverse range of respiratory medicines cannot be delivered to the lung. Maintaining propellant options for pMDIs is, therefore, critical to ensuring the flexibility to formulate

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[109] GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023. Available at: https://goldcopd.org/2023-gold-report-2/. Accessed: May 2023.

[110] World Health Organization, 2020. The top 10 causes of death. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed in June 2023.

[111] Song, P., Rudan, D., Zhu, Y., Fowkes, F.J., Rahimi, K., Fowkes, F.G.R. and Rudan, I., 2019. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *The Lancet Global Health*, *7*(8), e1020-e1030.

[112] International Respiratory Coalition. Diseases: Asthma and COPD. Available at: https://international-respiratory-coalition.org/lung-facts/diseases/ [Last accessed: June 2022].

[113] GOLD, 2023. Global Strategy for the Diagnosis, Management and Prevention of COPD. *Global Initiative for Chronic Obstructive Lung Disease (GOLD)*. Available at: https://goldcopd.org/2023-gold-report-2/. Accessed in June 2023.

[114] Lavorini, F., 2013. The challenge of delivering therapeutic aerosols to asthma patients. *International Scholarly Research Notices*, *2013*.

[115] Roche, N. and Dekhuijzen, P.R., 2016. The evolution of pressurized metered-dose inhalers from early to modern devices. *Journal of aerosol medicine and pulmonary drug delivery*, *29*(4), 311-327.

[116] Laube, B.L., et al., 2011. What the pulmonary specialist should know about the new inhalation therapies.

[117] Lavorini, F., Mannini, C., Chellini, E. and Fontana, G.A., 2016. Optimising inhaled pharmacotherapy for elderly patients with chronic obstructive pulmonary disease: the importance of delivery devices. *Drugs & aging*, *33*, 461-473.

[118] AstraZeneca Data on File - REF-154642. Using Respiratory Disease Prevalence and Global Sales of Inhalers to Estimate pMDI User Populations in Europe. [June 2022].

the APIs whose varying physical properties secure the efficacy and safety of a medicine whilst being compatible with the various device component materials that constitute the device.[119]

Currently, there are two alternative propellants under development for medical use in pMDIs. One of these alternatives is HFC-152a, which does not fall under the proposed PFAS definition in the current draft restriction. Nevertheless, it is subject to a phase-down process under the Kigali Amendment and EU F-Gas regulation.[120] The second alternative being explored is HFO-1234ze(E), which falls within the scope of the PFAS restriction. The PFAS restriction proposal would therefore preclude the use of HFO-1234ze as a viable alternative to reformulate existing pMDI medicines, or for the development of new low global warming potential pMDIs in the future. While other alternatives have been examined, they have been deemed unsuitable for use in pMDIs.[121]

Another essential component is the coating, consisting of fluoropolymers, which are applied to the canisters of the pMDIs. The coated canisters are then filled with medicinal product and assembled with the other parts of the pMDI device. **The presence of the PFAS-containing coating is crucial for maintaining the medicine's required standards and preventing degradation during the shelf life of the product**. Furthermore, the coating prevents APIs and other excipients from sticking to the canister's surface, **ensuring accurate doses are delivered to the patient**.

It is important to note that any loss of access to a patient's preferred inhaler necessitates a switch to alternative options. Switching patients to alternative inhalers, such as Dry Powder Inhalers (DPI), should not be seen as a solution to potential medication shortages. Medicines are not interchangeable, and switching should be based on clinical need and individual patient assessment.[122, 123] **Switching without proper clinical justification may result in poor health outcomes**.[124, 125, 126, 127] Even amongst the patients where switch to an alternative may be safely achieved, t**he current supply and manufacturing capacity of DPIs are unlikely to fully compensate for the expected shortfall of pMDIs within the timelines outlined in the current restriction proposal**.

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[119] EMA - Questions and answers on data requirements when replacing hydrofluorocarbons as propellants in oral 6 pressurised metered dose inhalers. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-data-requirements-when-replacing-hydrofluorocarbons-propellants-oral-pressurised_en.pdf. Accessed May 2023.

[120] Kigali amendment 2016. Available at: https://ozone.unep.org/treaties/montreal-protocol/amendments/kigali-amendment-2016-amendment-montreal-protocol-agreed. Accessed May 2023.

[121] United Nations Environment Programme: Medical and Chemicals Technical Options Committee 2018 Assessment Report. Page 25. Available at: https://ozone.unep.org/system/files/documents/MCTOC%20Assessment%20Report%202018.pdf. Accessed May 2023.

[122] Bjermer, L., 2014. The importance of continuity in inhaler device choice for asthma and chronic obstructive pulmonary disease. *Respiration*, *88*(4), 346-352.

[123] Doyle, S., et al., 2010. What happens to patients who have their asthma device switched without their consent? *Primary Care Respiratory Journal*, *19*(2), 131-139.

[124] WHO. Noncommunicable diseases, 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases. Accessed in June 2023.

[125] World Health Organization, 2020. The top 10 causes of death. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed in June 2023.

[126] Song, P., et al., 2019. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *The Lancet Global Health*, *7*(8), e1020-e1030

[127] Bell, J.P., Ringall, A., Khezrian, M., Kocks, J.W. and Usmani, O.S., 2023. An Assessment of Pressurized Metered-dose Inhaler Use in Countries in Europe and the Rest of the World. American Thoracic Society.

The submitted draft restriction proposal on PFAS and the current challenges of switching to an alternative for these specific applications raises concerns about the availability of these life-saving inhaled medicines and devices in the EEA. **This situation creates significant uncertainty for manufacturers, healthcare professionals, and eventually individuals living with respiratory diseases**.

In conclusion, this case study sheds light on the pivotal role of pMDIs in managing respiratory diseases such as asthma and COPD. PFAS, including fluorinated propellants and coatings, play a vital role in ensuring effective drug delivery and maintaining medication quality. However, the proposed restriction of PFAS raises concerns about the availability of these essential inhalers. The current supply and manufacturing capacity of alternative inhalers may not fully compensate for the expected shortfall of pMDIs within proposed timelines**. Thus, it is imperative to strike a balance between therapeutic benefits and environmental considerations to ensure optimal respiratory care for individuals in need.**

4.3 Wider economic impacts

It is also important to consider the wider macroeconomic impacts and consequences on the EU society at large, by focusing on the expected consequences for the EEA market. In particular, there are concerns on the overall EU trade balance (increase of imported medicinal products) and on the competitiveness of the EEA market.

Impacts on the market – Competitiveness and competition

Currently, by driving medical progress that improve the health and quality of life for patients around the world, the research-based pharmaceutical industry is one of Europe's top performing sectors.[128] Because REACH Restrictions apply to all producers equally when placing products on the EEA market, **a potential broad restriction of PFAS would disadvantage the EEA-based manufacturing versus non-EEA one.** Non-EEA manufacturing sites would have a considerable advantage compared to EEA manufacturing, both in European and international markets. Indeed, they would not be subject to a restriction of PFAS used in the different stages of production. As such, they would be able to supply and place on the market a wider range of products, currently preferred and purchased by consumers without bearing any reformulation costs.[129]

Clearly, **the EEA market for pharmaceutical manufacturing would be subject to significant hurdles as compared to the non-EEA market.** Ultimately, the EEA would **face a further loss of competitiveness** compared to the rest of the world, in opposition to the EU strategy to boost domestic industry and cut dependencies on foreign suppliers (i.e., EU industrial strategy for 2030).

In the medium to long run, as a result of this decreased competitiveness, surveyed companies have indicated that **their manufacturing activities in the pharmaceutical industry would likely experience**

[128] EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 3. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf

[129] **It must be noted that at present 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.**

a significant shift from EEA locations to non-EEA locations, in case of a negative regulatory decision and export non-PFAS containing drugs to Europe.[130]

This scenario has been depicted as the most likely (and inevitable) option to a restriction of this group of substances.

Should the pharmaceutical industry move out of the EEA to service the rest of the world, it would thus result in a significant downsize for manufacturing in Europe. This shift from EU pharmaceutical manufacturing to non-EU manufacturing would result in layoffs, site closures, decreased capital investments, and a general loss of economic activity in the EEA. This will also have negative spillover effects to other industries in the EEA that provide services or goods to the EEA pharmaceutical industry.

This is particularly challenging since Europe, at this point, is already facing increased competition from emerging economies. Rapid growth in market and research environments in countries such as China and Korea are already contributing to the move of economic and research activities to non-European markets.[131]

Impacts on the market – Trade

A broad restriction of PFAS would disadvantage European companies in their trade with the rest of the world. Indeed, just as the production of human medicines would turn to non-EEA markets, exports of these products would decrease considerably. On the other hand, imports are projected to grow in importance. The EU pharmaceutical industry will have to source products from outside of the EU.

This will increase the technological and manufacturing dependency of the EU on foreign countries and thereby also affect EU export and import flows. As a result, the **overall EEA trade balance would be adversely impacted by the restriction**.

Importantly, many European economies have been trying to be **more self-reliant and domesticate the manufacturing of medicines** following the COVID-19 pandemic shutdowns and the difficulties in importing medicines from foreign manufacturers. At present, pharmaceutical exports play a key role for the EEA economy. **The EEA is a net exporter of medicinal product**, with a positive trade balance estimated at 123 billion EUR in 2021.[132] The widespread ban of PFAS would have the opposite effect and **force the EEA to be much more, or even completely reliant, on foreign manufacturers of medicines**.

Impacts on the market – Innovation and R&D

130 This option would still be permitted by law as long as PFAS are only used in the production process and no traces of PFAS remain in the final products exported to the EEA.

131 EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 9. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf

132 Trade balance, excluding Russia, Serbia, Switzerland, Turkey, and U.K. (EFPIA, 2023. The Pharmaceutical Industry in Figures. Key Data 2023, p. 20. Available at https://efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf)

Overall R&D activities for product manufacturing would therefore be largely affected by the current restriction proposal. With a broad PFAS-restriction, investments already made in the development of these molecules would be wasted. This would **further impact the resources available for innovation**.

R&D investments have been made by medicinal product manufacturers as a function of both new market technology opportunities and the companies' financial health. **Assuming that R&D is proportional to revenue, the loss of sales to the EEA market will have an inevitable negative impact on R&D investments and spending.** In a broader context, the current geopolitical situation, supply chain disruptions, and inflated cost of materials have already taken a toll on R&D funding.

The **current R&D efforts and resources would inevitably be redirected towards re-formulating, re-qualifying, and re-certifying the portfolios of the participating companies** (or to move their production outside of the EEA). This will require R&D resources to support efforts to redevelop portfolios, stalling innovation and new product development.

For R&D, PFAS are mostly used in API and process development, in consumable equipment as well as for analytical use. The quantity of PFAS used depends on the stage of development of the medicinal product. Some APIs in the R&D pipelines of the participating companies are PFAS (thus, they would be banned)[133]. These APIs will have PFAS starting materials and chemical intermediates used in multiple manufacturing steps upstream of the API formulation and will also have used PFAS reagents or solvents. Additionally, the R&D pipelines of the participating companies also contain multiple non-PFAS APIs that utilise PFAS reagents in the manufacturing synthesis; a common example is Trifluoroacetic acid (TFA). Synthetic and analytical lab equipment and consumables used in the development of these manufacturing processes will also commonly contain PFAS (e.g., piping, filters, tubing, lubricants, sealings, etc.). A PFAS restriction with no derogation would mean that none of these R&D activities could take place in the EEA.

A large proportion of ongoing and future research projects rely on the aforementioned building blocks and reagents, highlighting the importance of poly- and perfluorinated substituents in R&D activities for new APIs. [134]

[133] These APIs are not derogated as they do not have marketing authorization yet (in accordance with Directive 2001/83/EC). Therefore, according to the current proposal, they would be banned from both manufacture and clinical testing.

[134] The participating companies have a significant number of compounds classified as PFAS present as APIs and in their compound collections. Various suppliers and contract research organisations offer a wide range of other synthesis building blocks that meet the definition of PFAS in the current restriction proposal. Even if these building blocks are currently not in stock in the repositories of the participating companies, they could be relevant for future research projects. This is also true for custom-made intermediates that have not yet been described in the literature and are not available off-the-shelf (as is commonly the case in the drug discovery phases). In case drug candidates are identified where such intermediates or reagents are used for synthesis, development activities routinely require these entities for chemical process development, scale-up, API supply for advanced efficacy or safety studies, or launch support.

Several of the key manufacturing sites of the participating companies located in the EEA have been designated as sites which also perform late-stage process development activities, in advance of product filing and launch (both API and medicinal product manufacturing sites). Key to the mission of these sites is being adaptable and flexible to accommodate the development needs of a dynamic and evolving product pipeline and being able to supply initial launch quantities of medicines for global markets. **If these sites were unable to use PFAS materials during manufacturing, this would significantly reduce their flexibility, and therefore reduce the usefulness of these sites in accommodating a dynamic development pipeline.** As a result, the associated development and manufacturing activities performed by these sites would be shifted to non-EEA locations.

More generally, **broad regulatory restrictions, such as the PFAS restriction proposal, have a negative impact on the attractiveness of the EEA for investment**, including investments in innovation and R&D.

Every high tech/high purity industry relies on fluoropolymers in industrial use. Even with a time-limited derogation, both investors (looking at long term investments in plant lifetimes of 15-25 years) as well as manufacturers or importers of fluoropolymers will probably turn away from the EEA market with immediate effect.

Typically, innovation is made for global markets, including EEA, and not for specific regions. The Return on investment (ROI) for research and innovation around non-PFAS medicinal products for EEA only is rather limited and the development costs expensive, lengthy and complex for one single region. **A ban on PFAS chemicals would impact discovery research activities in the EEA and slow down drug discovery timelines, and potentially lead to less-than-ideal drug candidates. As such, the EEA risks to jeopardize an important field of innovation.**

The current restriction proposal does not contain a derogation for product and process orientated research and development (PPORD). Manufacturing pipeline drugs containing PFAS-type APIs within the EEA would be unfeasible under the current restriction text, putting EEA manufacturing sites at a disadvantage compared to options outside the EEA with regard to innovation. This will result in a barrier for innovation and R&D in the EEA. It is common for EU pharmaceutical sites to undertake late-stage testing of PFAS APIs with >1 ton/year of the API and its associated isolated PFAS intermediates. This and other R&D activities would no longer be possible if not derogated.

Therefore, the decision to adapt manufacturing, move outside of Europe, or stop producing drugs will come with large costs for the companies, potentially slowing down investment in new treatments for patients.

Impacts on the market – Sub-contractors

Various sub-contractors and suppliers, such as CMOs and CROs, will be negatively affected by the restriction scenario. Therefore, they may discontinue manufacturing parts containing PFAS or cease importing PFAS-containing materials into the EEA, which could adversely impact manufacturing efforts. The **(bio)pharmaceutical companies mainly or even exclusively rely on CMOs and suppliers of starting materials and immediate packaging materials that are located in the EEA,** which means they are heavily impacted by the restriction. One participating company indicated that in 2022, their direct spending towards EEA based suppliers and CMOs was over 800 million EUR and that this amount was only increasing over the past years. In case of the restriction proposal, they stated their manufacturing activities would be shifted outside the EEA area to countries like India, China, UK, or USA, or cease operations altogether. Similarly, contract manufacturers producing PFAS APIs or PFAS intermediates may face similar challenges.

Some companies have mentioned that they are exploring replacement options for PFAS-containing auxiliaries with alternative materials whenever possible, although some materials like filters may not have readily available substitutes. Some starting materials suppliers, particularly those operating in Asian countries, may not be impacted by the PFAS restriction, as indicated by certain companies. Additionally, while some companies do purchase fluoropolymer-coated rubber closures as part of their final product, they do not solely rely on PFAS for immediate packaging materials. **Filter suppliers anticipate investing in research and development efforts and may only supply materials to non-EEA customers if located outside the EEA.**

Thus, a PFAS restriction would lead to **income losses in both the short- and long-term for sub-contractors** and could also lead to the **stop of some CMO API production in the EEA**. This also conflicts with EU strategies to reduce dependency on supply chains located mainly outside of the EU.
Accordingly, as an indirect result of such consequences for subcontractors, a **restriction would affect API development processes, resulting in longer production cycles, inefficiencies, and higher prices for the whole supply chain.**

5. CONCLUSION

This SEA identifies the main potential negative consequences that the EU society at large would face in the framework of the potential REACH restriction of PFAS used in the production of human medicines. It has been performed in line with existing ECHA guidance under REACH and the results are based on a survey focused on the EU pharmaceutical industry, with an expected market share coverage of approximately 40% of EEA human medicines market. It therefore provided sufficiently reliable data for a representative extrapolation of the EU market.

The evidence-based findings of this report reasonably justify the exclusion of the whole process of pharmaceutical (medicines) manufacturing from the scope of the upcoming REACH restriction proposal, on the basis that a broad restriction of PFAS in the manufacturing of medicinal products will have disproportionate negative impacts on the European economy and society, impacting the security of supply of all medicinal products.

The above statement is founded on the following:

- **The whole process of developing and manufacturing medicinal products, independent of containing PFAS APIs or not, depends heavily on a number of PFAS chemicals in a wide variety of inter-related applications.**

- **The replacement of PFAS is limited by availability, technical applicability, and environmental trade-offs of alternatives which are to date not (readily) available. Finding alternatives is not guaranteed, and substitution (if possible) is a time-consuming process due to the legal requirements for quality, safety and efficacy in the sectoral legislation and guidelines.**

- **Similarly, the Analysis of Alternatives shows that there are no appropriate chemical alternatives to PFAS chemicals across their uses in the manufacturing process, including process chemicals, equipment components, and ultimately, in packaging, devices and quality control**.

- Thus, at present, **a replacement is not technically and economically feasible for all the following uses:**

    a. EU approved APIs manufactured for the EEA market,
    b. APIs manufactured for export without EU registration
    c. APIs under development, prior to registration (PPORD) including non-EU regulated products
    d. Non-active ingredients (excipients);
    e. Starting materials and chemical intermediates;
    f. Process Chemicals (Reagents, solvents, catalysts, auxiliaries in production and Quality Control);
    g. Industrial Manufacturing Equipment including spare and replacement parts;
    h. Single or multi-use Consumables;

i. Immediate packaging materials.
j. Drug delivery devices;
k. Medical devices (as per EU MDR 2017);

- **Overall, when (and if) a PFAS substitute were ever to be found and implemented in the synthetic route of a commercial medicine, it may need to undergo an entire successful innovation cycle (it is a new molecule and therefore would require the entire development, from discovery to launch to the market):**

  - **Creating, manufacturing, and obtaining approval for a new medicine to replace one which falls under the PFAS definition would require between 12 years in the best-case scenario and 22 years in the worst cases, from the moment a suitable candidate (alternative) is identified**.

  - **At the same time, substitution will also take place for all other uses of PFAS, including in the production process, in immediate packaging materials of medicinal products, and in drug delivery devices and other medical devices.**

  - These timescales are subject to a high degree of uncertainty considering that upstream suppliers and pharmaceutical companies would be dealing with completely novel – not yet available – materials with no history of use. As all these substitution efforts cannot happen at once, but have to be phased in, they may take decades in total. **Given the scale of the substitution, and the time and resources required to adapt all production processes in parallel, bottlenecks in the production flow must be considered a real possibility that cannot be ignored.**

- **Both RO1 and RO2 would have disproportionate socio-economic implications on the EEA pharmaceutical sector. The total socio-economic impact of a REACH restriction of PFAS materials used in the manufacturing process (particularly equipment and consumables) is monetised at over <u>328 billion EUR</u>** (conservative estimates of net losses), consisting of: social impacts from unemployment in the EEA, and economic impacts (loss of EBIT) for manufacturers. **The reader should bear in mind that although RO2 is a subset of RO1, the EEA impact would be the same because even with a derogation for PFAS APIs, without derogations for manufacturing in the EEA the effects would be the same.**

- **Non-EEA manufacturers would have a considerable competitive advantage compared to EEA manufacturers.** Hence, a PFAS restriction in the EEA will have impacts on the competitiveness of the EEA markets, on the competition in the EEA, on innovation, and on the overall EU trade balance, as EEA companies will be forced to relocate production and research and development out of Europe.

- From a broader perspective, the PFAS restriction is expected to have **severe impacts on human health**. The prospect that non-EEA production could compensate for the loss of EEA production of medicinal products is to be considered totally unrealistic. **If global capacity is not available, medicine shortages would become an unfortunate reality.** A sudden shortage of medicinal products in the EEA will reduce the number of available medicinal products resulting in **severe human health impacts.** This risk would be even more serious in the event of a PFAS restriction for the entire production process of medicinal products.

Based on the above evidence-based considerations, this report concludes that a broad restriction of PFAS for pharmaceutical manufacturing would not be warranted and will have disproportionate negative impacts on the European economy and society.

The use of medicines is highly regulated in the EU with extensive generation of data along with evaluations and approval processes by European Regulatory Authorities. **The analysis supports the proposed time unlimited derogation for active substances in human medicinal products** on the basis of the importance for the protection of human health.

Nevertheless, without additional inter-related derogations, the whole pharmaceutical industry will no longer be able to manufacture any API (both, classifying as PFAS or non-PFAS APIs) or associated medicines in the EEA. This would necessitate moving production out of the EEA as the only option, which would require years in itself, plus years of regulatory inspections and approvals. As a result, the supply and availability of medicines in the EEA will be substantially impacted even in the longer term with new and extensive dependencies on non-EEA manufacturing.

Thus, the analysis reasonably justifies the introduction of a time-unlimited derogation of PFAS chemicals as substances required for the chemical synthesis of active pharmaceutical ingredients, excipients and medicinal products for human use. The derogation should apply to these substances on their own, in mixtures or in an article, and cover the following uses:

i. **EU approved APIs manufactured for the EEA market**
ii. **APIs manufactured for export without EU registration**
iii. **APIs under development, prior to registration (PPORD) including non-EU regulated products**
iv. **Non-active ingredients (excipients)**
v. **Starting materials and chemical intermediates**
vi. **Process Chemicals (Reagents, solvents, catalysts, auxiliaries in production and Quality Control)**
vii. **Industrial Manufacturing Equipment including spare and replacement parts**
viii. **Single or multi-use Consumables**
ix. **Immediate packaging materials**
x. **Drug delivery devices**
xi. **Medical devices (as per EU MDR 2017)**

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