2023

PQRI Comments to ECHA REACH on Annex XV Restriction Report for Per- and polyfluoroalkyl substances (PFAS)

About PQRI

The Product Quality Research Institute (PQRI) (www.pqri.org) is a non-profit consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality, manufacturing, and regulation.

Contents

Glossary

AD	Alzheimer's Disease
API	Active Pharmaceutical Ingredient
CCS	Container closure system
COPD	Chronic Obstructive Pulmonary Disease
CSS	European Commission Chemicals Strategy for Sustainability
DDS	Drug delivery system
EC	European Community
ECHA	European chemicals agency
ECTFE	Ethylenechlorotrifluoroethylene
EEA	European Economic Area
EiF	Entry into Force
EMA	European Medicines Agency
EPPA SEA	European Public Policy Advisors Socioeconomic Analysis
ETFE	Ethylene tetrafluoroethylene
EU	European Union
FEP	Fluorinated ethylene propylene
FFKM	Perfluoroelastomers
FIH	First In Human
FKM	Fluoroelastomers
FVQM	Fluorosilicones
GMP	Good Manufacturing Practice
HVAC	Heating, Ventilation, Air Conditioning, Refrigeration
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IPAC	International Pharmaceutical Aerosol Consortium
IPAC-RS	International Pharmaceutical Aerosol Consortium on Regulation & Science
MAA	Marketing Authorisation Application
Mab	Monoclonal Antibodies
Mfg	Manufacturing
OECD	Organisation for Economic Co-operation and Development
OELs	Occupational Exposure Limits
PFAS	Per- and Polyfluoroalkyl substances
PFOA	Perfluorooctanoic Acid
PLC	Polymers of Low Concern
pMDI	pressurized Metered Dose Inhaler
PMT	Persistant, mobile, toxic
POC	Proof of Concept
PPE	Personal Protective Equipment
PQRI	Product Quality Research Institute
PTFE	Polytetrafluoroethylene
PVDF	Polyvinylidene fluoride
QC	Quality Control
R&D	Research and Development

REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
RO1	Restriction option 1 in Annex XV Restriction Report on PFAS
RO2	Restriction option 2 in Annex XV Restriction Report on PFAS
SBT	Science-Based Targets
SBTi	Science-Based Targets initiatives
TULAC	Textiles, Upholstery, Leather, Apparel and Carpets
UK	United Kingdom

Introduction

The Competent Authorities of Germany, The Netherlands, Sweden, Denmark, and Norway submitted a joint REACH Annex XV restriction proposal for a broad group of PFAS. The proposed restriction aims to limit the risks to the environment and human health from the manufacture and use of a wide range of PFAS for entry into REACH Annex XVII. Two restriction options were proposed in consideration of stakeholders' information [1]:

- A full ban with no derogations and a transition period of 18 months from EiF
- A full ban with use-specific time-limited derogations. (18-month transition period plus either a five- or 12-year derogation period)

It is acknowledged that a stakeholder call for PFAS evidence occurred in 2020 and 2021 which was reflected in the final proposal. Specific impact assessments for 14 sectors were documented in Annex E and PFAS data on human health and environmental hazards of alternatives was listed in Appendix E.2It was observed in the impact assessments that there were insufficient data for evaluation of human health and environmental hazards in many cases. Further, there were cases in the Annex XV restriction report, where the available evidence base is considered weak. A derogation is not supported at the moment, but derogations could potentially be warranted [1]. There was no Pharmaceutical Sector included in the Annex XV restriction report. As the call for evidence took place during the height of the pandemic, the full scope and complexity of PFAS used throughout the medicinal product (pharmaceutical) supply chain was not entirely conveyed. The intention of this paper is to provide regulators with information on the major impact that the proposed PFAS ban will have on the pharmaceutical supply chain and the risks that will be posed to the health and well-being of patients. The societal effects are expected to be severe should this restriction, as written, become effective.

The European Medicines Agency (EMA) is responsible for the authorization of safe and effective medicines [2]; however, medicinal products cannot be produced without access to PFAS and the articles containing PFAS that are used to manufacture, store, transport and deliver medicines to patients. In an effort to better understand PFAS sub-uses in the Pharmaceutical Sector, the Product Quality Research Institute (PQRI) conducted a survey among pharmaceutical companies and their suppliers. The survey was constructed in the form of a questionnaire to obtain data on PFAS uses, alternatives, and the impact of a ban on medicinal products and diseases they are used to treat. The results from this survey are provided as evidence in this document.

Background – Medicinal product lifecycle

Background on the medicinal product lifecycle is necessary to understand the full effect that the PFAS restriction would have on the Pharmaceutical Sector, and therefore patients. The medicinal product scope encompasses pharmaceuticals, biotechnology products, biological products, and vaccines. The approval of medicines requires significant time and substantial evidence for product safety and efficacy across the entire pharmaceutical supply chain prior to submission. There is a wide array of PFAS types, uses and suppliers throughout the pharmaceutical supply chain starting with the API, as well as articles used to manufacture, package, store, transport, and deliver a medicinal product to patients. As shown in Figure 1, changes to any parts of the pharmaceutical supply chain, medicinal product manufacturing processes or delivery will trigger assessments of the impact of the change within the company responsible. In the case of suppliers, notification of their customers will prompt them to also consider the impact on their product/process (as evidenced via PQRI survey responses – refer to Request #7 section of this document).

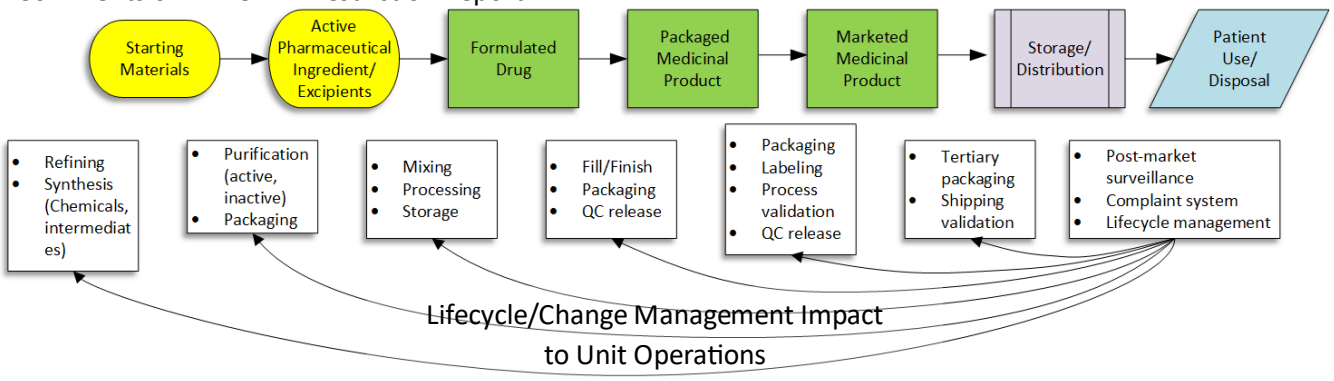

Figure 1 Points of Change Impact on Medicinal Product Manufacture and Delivery

All manufacturing and supply changes need to be evaluated and often require testing and data to be generated as part of the change. Depending on the change and the registered information, these changes could lead to the generation of additional development data or the submission of post-approval changes for marketed products. It can take years to generate sufficient data to support a change that may delay development or require approval by regulatory authorities before the change can be implemented. The lifecycle phases and estimated time frames for regulatory review and approval are illustrated in Figure 2.

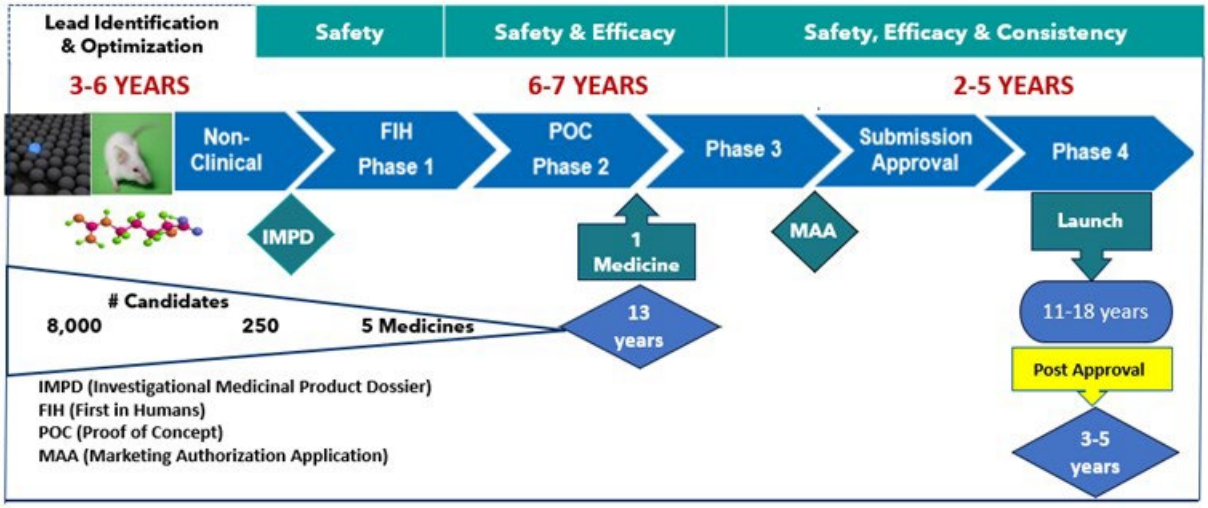

Figure 2 Medicinal Product Lifecycle

Scope of Evaluation

The focus of the evaluation presented in this document is on the societal impact on the European Union with respect to the proposed restriction submitted to ECHA as a REACH Annex XV Restriction Report on Per- and polyfluoroalkyl substances (PFAS) [1]. Qualitative data was acquired by PQRI from multinational pharmaceutical/ biopharmaceutical and vaccine companies (19 in total) and suppliers to pharmaceutical companies (15 in total) based on an anonymous questionnaire that was open for entry for just five weeks. The questions were formulated to provide information on the types, uses and interdependencies of PFAS across the pharmaceutical supply chain, the potential for alternatives, substitution times, supply of medicinal products and risk to patients who rely on lifesaving medicines every day. Additional information from literature and references to other consults already submitted are included.

Summary of Core Findings

Below is a list of core findings and resultant recommendations:

Findings	Recommendations
1. Pharmaceutical production and patient safety have unique requirements that are not captured within the 14 sectors that are defined in the proposal.	• **Include a Pharmaceutical Sector and their PFAS missing uses/sub-uses.**
2. Multiple types of PFAS are used in every phase of pharmaceutical development and some are known to have low toxicity and not expected to have adverse effects on human health.	• **Group PFAS to enable safety risk assessments as appropriate for the environment (emissions, biota, workers, and consumers) and include safety risk assessments that are suitable for patient populations.**
3. Supply chain is complex, and it is difficult to correlate all types of PFAS to sources and emissions. **4.** Potential supply chain vulnerabilities exist with highly uncertain data which can contribute to medicinal shortages. a. Shortages can drive demand for new sources of medicines and consequently, patients can be subjected to unapproved, illicit or counterfeit products compromising safety and efficacy. b. The societal cost of discontinuation or shortages of medicinal products cannot be weighed against the environmental risks of their degradation products. Lower environmental impact of medicines is increasingly in focus of pharmaceutical regulations, and not limited to "PFAS" API. c. Nearly a quarter of the EU population, who have diabetes or respiratory diseases, could be impacted if the proposal, as it stands, moves forward.	• **Invest time to understand types of PFAS, emissions, and environmental contributions from the Pharmaceutical Sector to enable justifications for derogations.**
5. The majority of PFAS applications used in the Pharmaceutical Sector have an essential combination of properties that are unmatched by any other material.	• **Reconsider time-unlimited derogation for those PFAS used in the pharmaceutical supply chain and availability of continued PFAS supply from upstream and downstream supplier inventories.**

6. Substitution of auxiliary PFAS across the pharmaceutical supply chain could have unintended consequences on human health and cause disruption to the medicinal product supply. **7.** The time to discover a PFAS alternative and implement it for each medicinal product can take anywhere from 20-60 years based on data that has been acquired from the PQRI survey of suppliers and pharmaceutical manufacturers. **8.** There is a realistic possibility that multiple lifesaving or life-sustaining medicinal products would be discontinued. A large percentage of the EU population could be impacted if the proposed derogation timelines are kept.	

ECHA-Specific Information Requests

The sections below address each of the specific information requests listed by ECHA for the purpose of organizing all consults with a similar structure.

Request #1 Sectors and Sub-uses

Although fourteen sectors were identified in which PFAS are commonly used, it seems that with respect to human health, only active pharmaceutical ingredients and medical devices have been addressed in the proposed derogations. As described in the introduction a survey of pharmaceutical manufacturers and suppliers to pharmaceutical manufacturers was conducted. The breakdown of the products represented in the survey results is shown in Figure 3 and Figure 4.

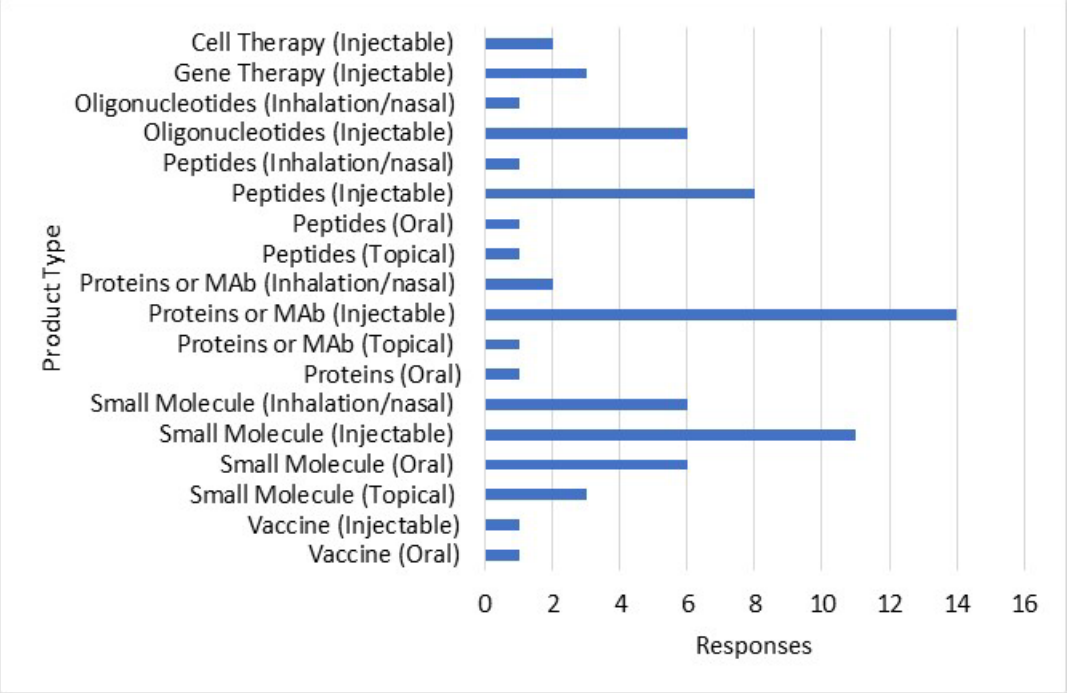

Figure 3 Medicinal product types (routes of administration) containing PFAS represented by pharmaceutical manufacturers in the PQRI survey

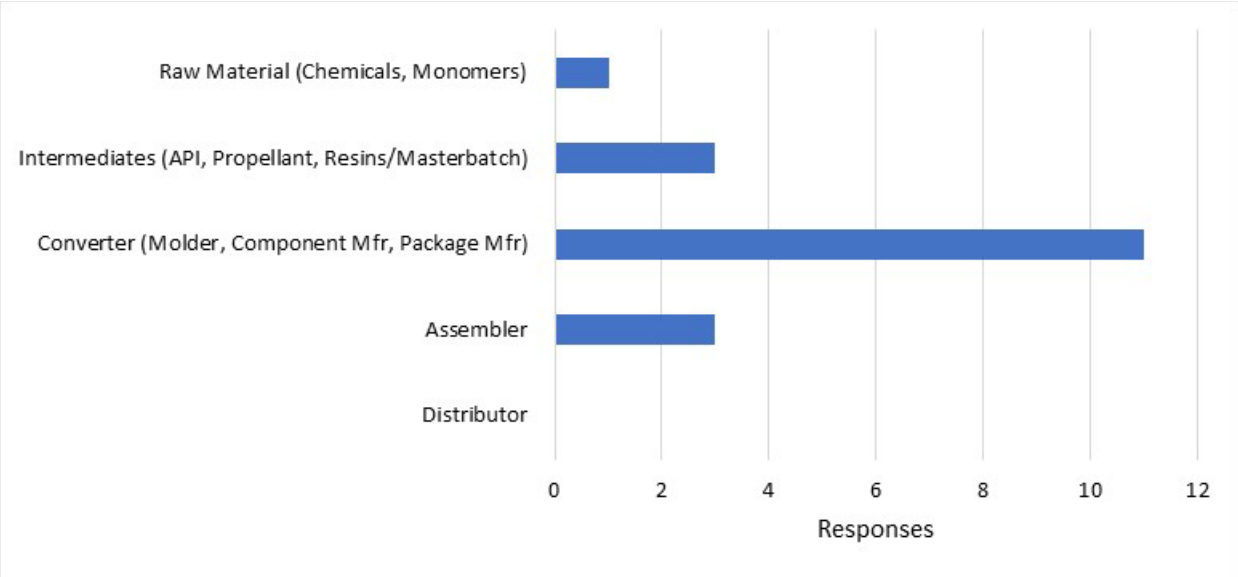

Figure 4 Role of PFAS suppliers represented in the PQRI survey

It was found from the PQRI survey that all pharmaceutical product types would be impacted in some way by a complete ban of PFAS. When compared to all of the diseases that these pharmaceutical products are used to treat (see Figure 5 and Figure 6) it is clear that all non-communicable disease treatments would be impacted at some level. Although there were fewer responses that indicated treatment for communicable diseases, all but one of the disease areas (measles, mumps, rubella) would be impacted in some way by a PFAS ban (see Figure 6). Due to the short timeframe in which the survey data was collected, it is quite possible that pharmaceutical manufacturers of treatments for any missing disease areas had not responded to the survey. It is also possible

that the results may not reflect the full scope of treatments and disease areas that might be impacted. This points to the fact that more time is needed to assess the impact on the Pharmaceutical Sector as a whole. In general, the results of the survey emphasize that many life-saving and life-sustaining treatments would be impacted by a PFAS ban.

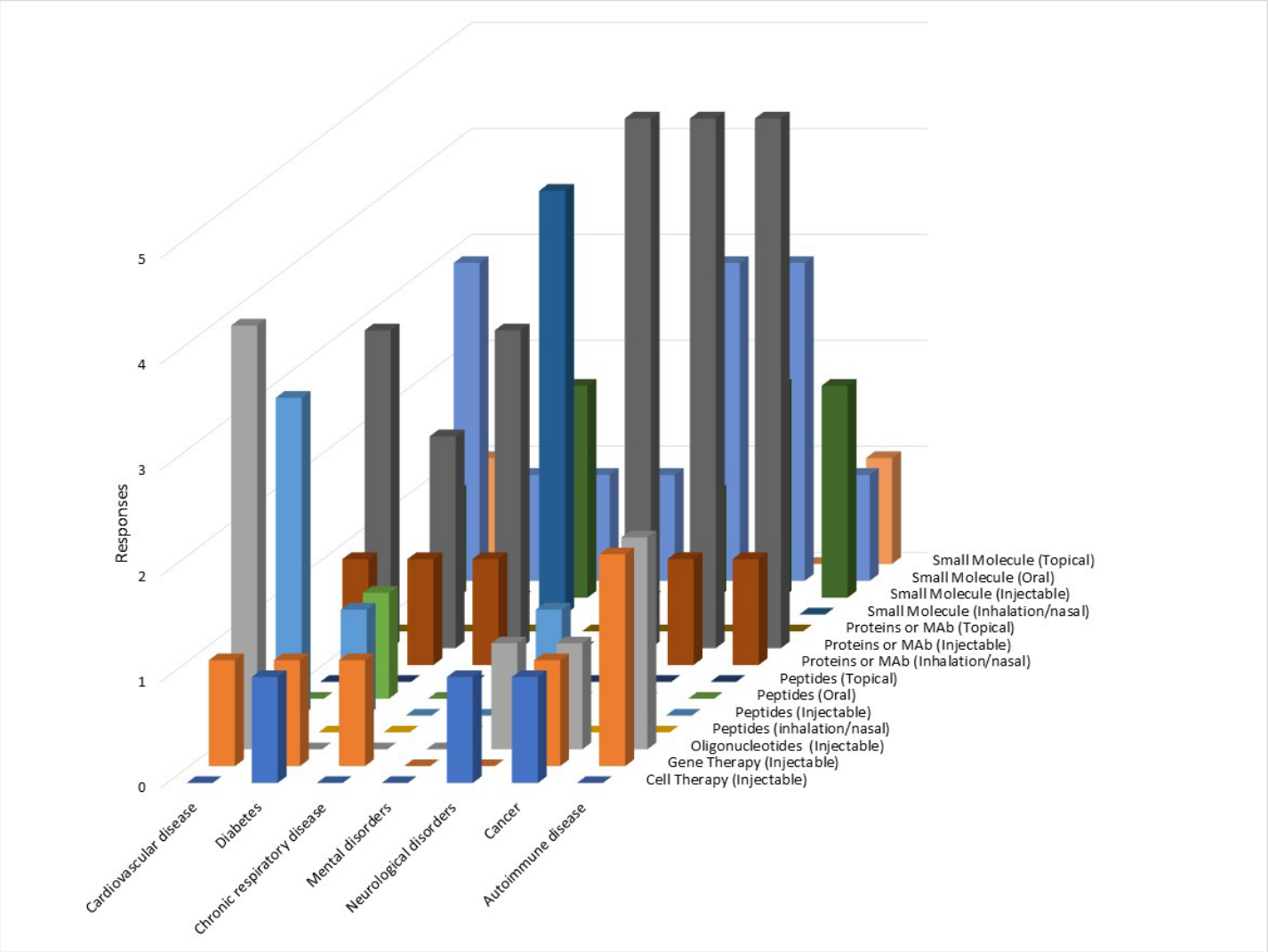

Figure 5 Product types (route of administration) impacted by a PFAS ban and non-communicable diseases treated

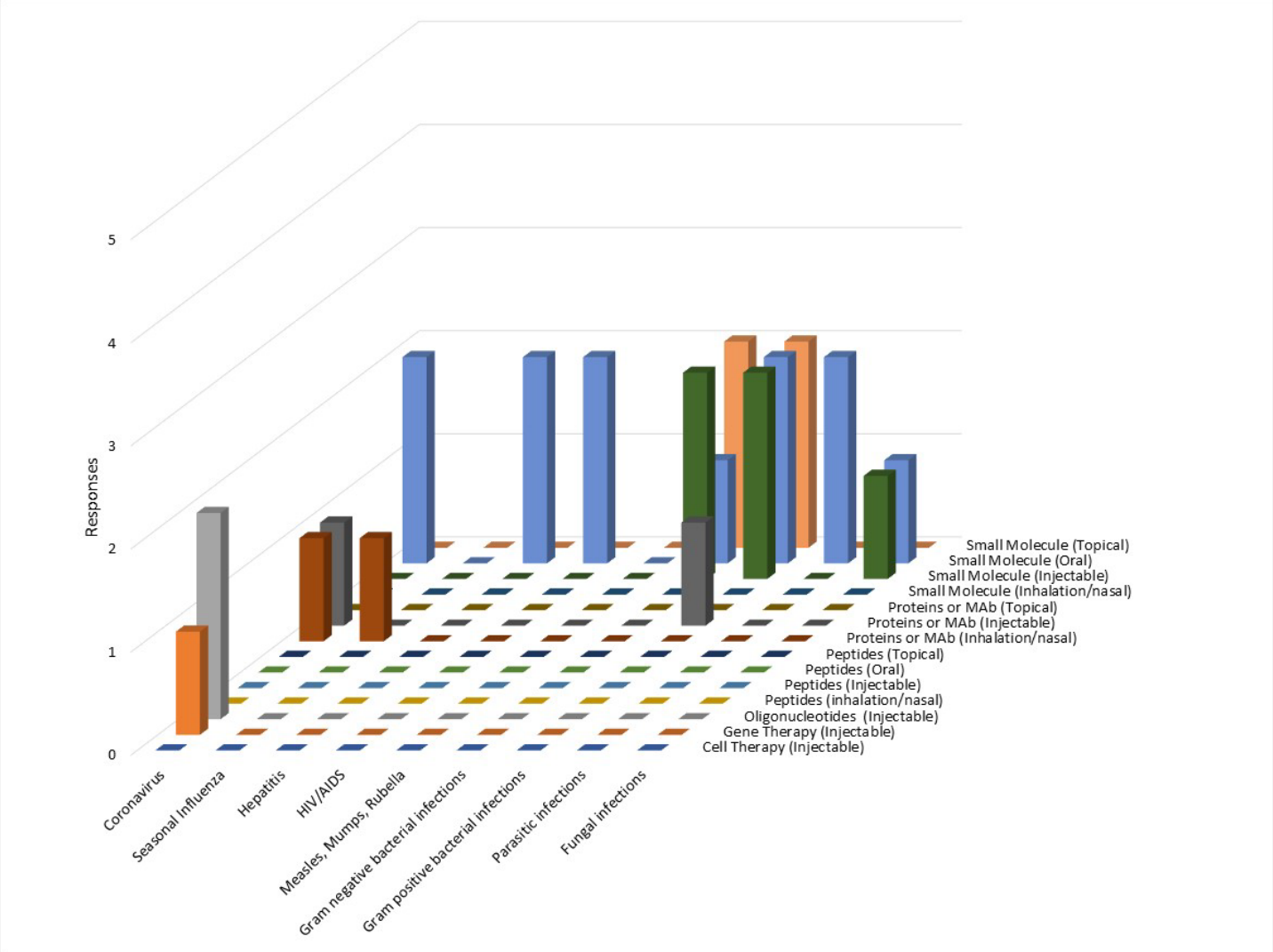

Figure 6 Product types (route of administration) impacted by the proposed PFAS ban and communicable diseases treated

To get a better understanding of PFAS sub-uses in the pharmaceutical supply chain, the survey included both pharmaceutical manufacturers and their suppliers. Based on the results of the survey it can be seen that there are several uses and sub-uses of PFAS associated with medicinal product manufacture, storage/transport, delivery and disposal. As shown in Figure 7, the primary areas of use for the Pharmaceutical Sector include drug synthesis, drug product manufacturing, container closure/drug delivery systems (CCS/DDS) and storage. It is noted, that in the event of a PFAS ban, a direct impact on active pharmaceutical ingredients (API) was indicated only for small molecule medicinal products that are administered by several routes (i.e., topical, oral, injectable). The proposed derogation for medicinal products only applies to active pharmaceutical ingredients and is a very small portion of the actual impact on pharmaceutical manufacturing and distribution processes. Therefore, it is proposed that consideration be given to the establishment of a separate Pharmaceutical Sector and that the scope of the proposed API derogation be reconsidered to include all pharmaceutical uses and sub-uses.

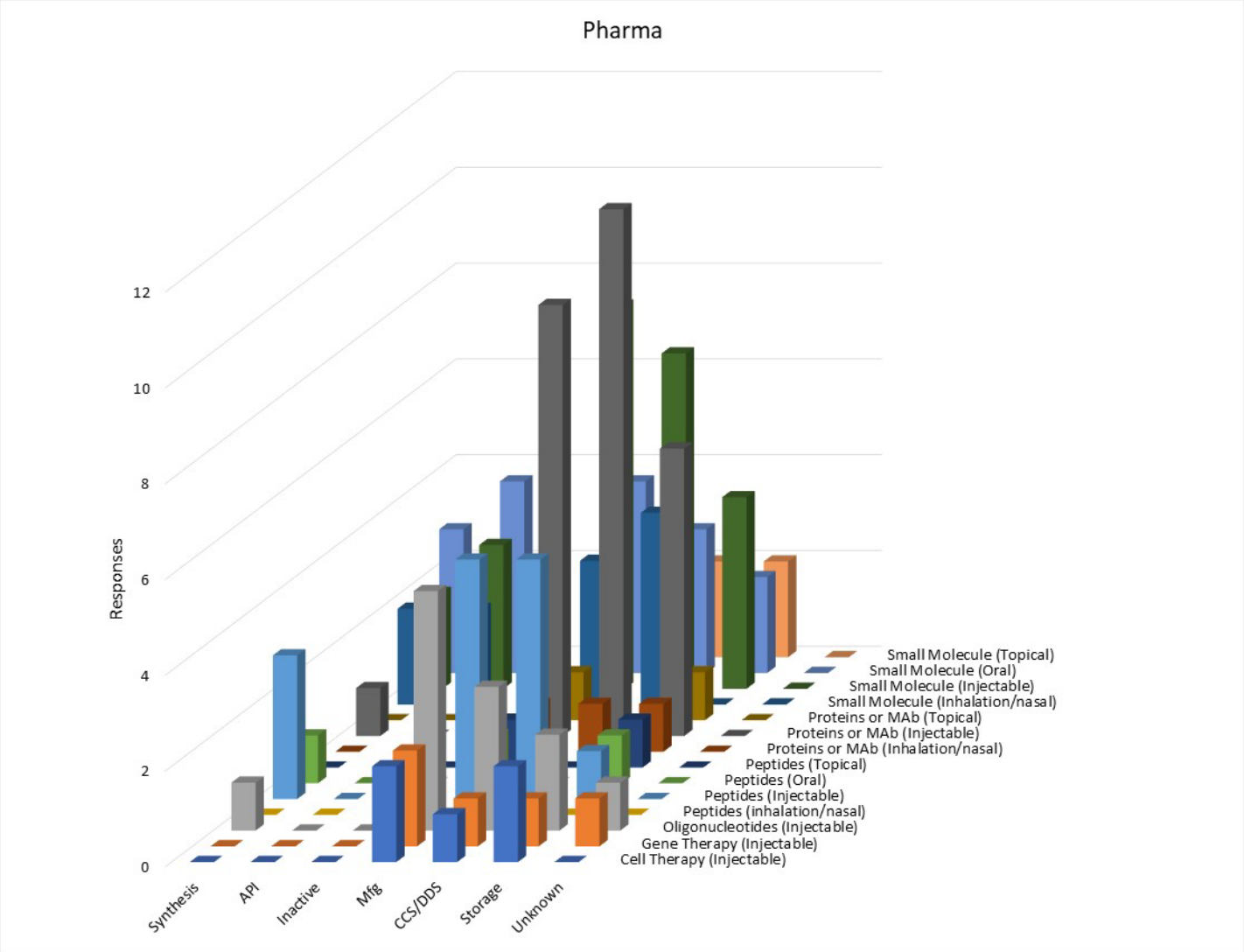

Figure 7 Proposed PFAS ban impact on pharmaceutical manufacturing and distribution

By looking at the PQRI survey results further granularity to PFAS uses and sub-uses can be understood. As shown in Figure 8, in addition to API, excipients and reagents are included when considering the drug formulation. From a manufacturing perspective in-process container closures, processing aids and lubricants were identified. From a packaging and delivery system perspective, containers, closures, coatings and functional/mechanical components as well as secondary and tertiary packaging were highlighted. Based on the noticeable differences in perceived impact of a PFAS ban between the pharmaceutical manufacturer responses and the supplier responses to the survey it is clear that more information needs to be obtained on the various types and uses of PFAS in the Pharmaceutical Sector. Since uses/sub-uses of PFAS are not always obvious, it is possible there is a lack of awareness due to the broad PFAS definition; research has shown significant gaps in understanding types and sources of PFAS [1].

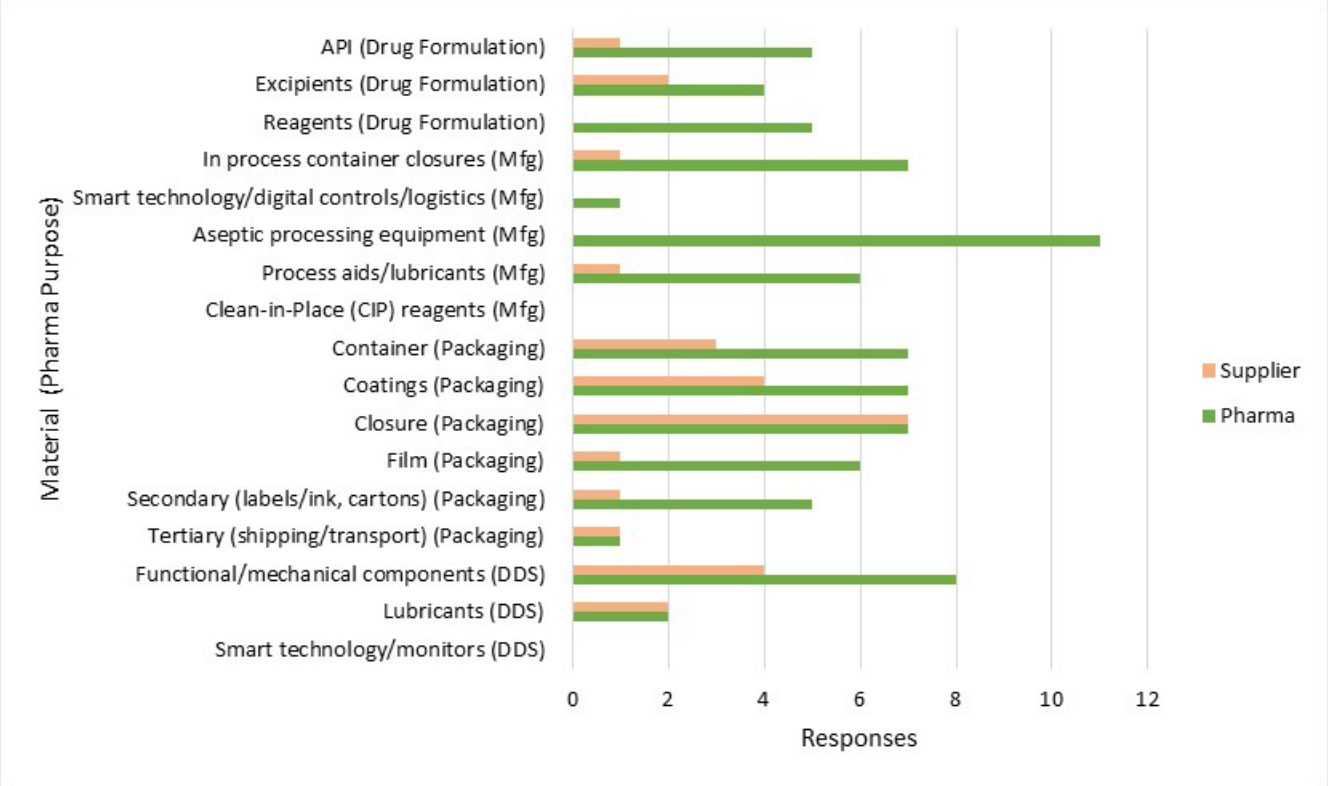

Figure 8 Proposed PFAS ban impact on materials supplied and uses in the Pharmaceutical Sector

When consideration is given to the sub-uses identified by both pharmaceutical manufacturers and their suppliers, it is possible to conceive that some of the sub-uses have already been accounted for in the 14 sectors identified in the Annex E Impact Assessment [1]. To investigate that, the Pharmaceutical Sector uses and sub-uses were compared to the main uses and sub-uses identified in Annex E and Table 2 of the Annex XV Restriction Report. The details of that comparison are discussed in detail in the Request #6 section (see Table 3). After consideration of the detail provided in Annex E Impact Assessment [1] there is very little direct overlap in uses, perhaps slightly with food packaging. Although there are some similar sub-uses, they are not the same. For example, the requirements for food contact may serve as a starting point but when materials that may be used in other consumer applications are used in medicinal applications there exist additional expectations regarding consistency of supply and quality of materials and manufacturing processes [3, 4, 5]. To summarize the outcome of the comparison, the Pharmaceutical Sector uses and sub-uses were listed in order of progression from starting materials through delivery to the patient. To complete the summary shown in Figure 9, above each set of Pharmaceutical Sector sub-uses is a list of the relevant previously identified 14 sectors that had similar sub-uses for reference. Based on the lack of synergy between the pharmaceutical uses and sub-uses and those already described in the identified 14 sectors, it is highly recommended that a separate Pharmaceutical Sector be considered.

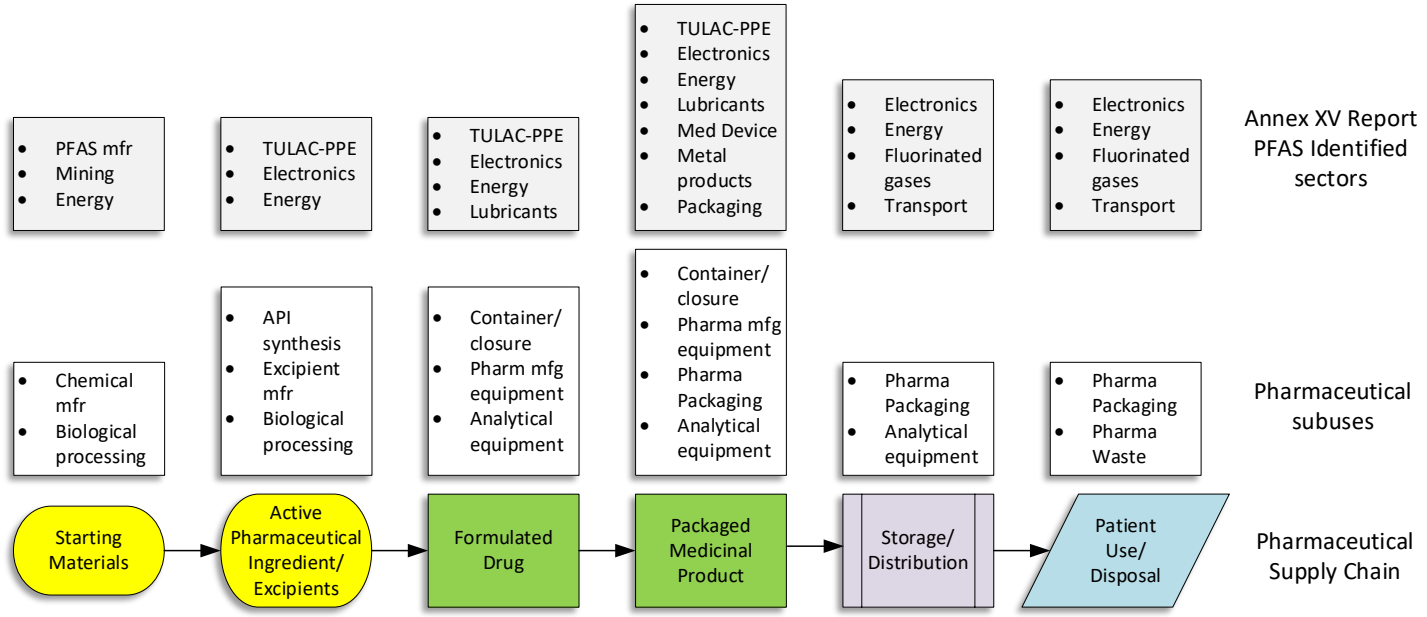

Figure 9 Mapping of Pharmaceutical Sector sub-uses to relevant 14 Sectors identified in Annex XV report.

Request #1 Summary – Sectors and Sub-uses

Based on the information provided a Pharmaceutical Sector is justified. Unlimited derogations are necessary due to the unique applications of PFAS use and sub-uses with respect to the pharmaceutical lifecycle and impact on the pharmaceutical supply chain. The intended use for PFAS in the pharmaceutical supply chain encompasses materials used from discovery through clinical studies to marketed product, for the purpose of manufacture, packaging and delivery to patients. Pharmaceutical discovery to product launch can take as long as 20 years or more. Changes over a medicinal product lifecycle can involve varying degrees of risk but could result in requirements for clinical studies adding to the time to identify and validate a replacement with the same properties. The regulatory change approval process can take 2-10 years, depending on the type and magnitude of change(s). Points to be considered regarding the health and well-being of patients include the following:

Risk to supply of medicines in the EU

1. From the range of therapies and conditions treated which have been highlighted by the survey responses, there is an opportunity to consider the potential impact that the proposed PFAS ban may have. The impact would be not just to the EU but to the global healthcare system of a wide-ranging lack of access to medication due to shortages linked to PFAS restrictions for articles within the supply chain. Shortages of materials used in manufacturing processes or other areas of the pharmaceutical manufacturing supply chain would potentially be similar to shortages recently observed during the COVID-19 pandemic, where patients unable to access routine medications would default to the healthcare system for support. The healthcare systems would potentially be overloaded. There is also a significant risk to the availability of life-saving medication in an emergency situation (medication has a shelf life and must be used or replaced by the expiry date, so a constant supply of medication is required to ensure that it is always available at the point of need).

Regulatory Challenges

2. While the proposal to ban PFAS-containing materials is driven by ECHA, the EMA and country-specific regulatory authorities are reviewing and approving submissions for new medicinal products and delivery systems, and are monitoring (via pharmacovigilance) all approved marketed pharmaceutical

products. These are both branded and generic products. Some of these products may also be for rare diseases and may be under the orphan medicine process. All of these are at risk with the progression of the proposed PFAS ban. The generation of significant amounts of data will be required to sufficiently support the changes. Preparation of the required changes for review, and the performance of the review of the changes by health authorities require significant amounts of time for the review cycle and approval to be completed. This will significantly increase workloads for regulatory agencies due to increases in variations for changes and inevitably result in product withdrawals and shortages of medicines.

Pandemic and Catastrophic Event Preparedness

3. There may be a serious public health impact if another global health emergency were to arise, and the pharmaceutical industry was not able to respond in the same way as it did to the COVID-19 pandemic due to the lack of critical materials within the supply chain, manufacturing process or other area of the pharmaceutical supply chain. Any restrictions will have an impact on patients, whether this is immediate access to current medicines, future access to novel medicines, or pandemic and catastrophic event preparedness. The COVID-19 pandemic closed down supply chains/ countries/ borders/ facilities and effectively stopped production and shipping around the globe for a period; and natural disasters such as major weather events have disrupted and destroyed manufacturing facilities around the world that provide specialist products, leading to acute shortages of the medicines or materials.

Future population

4. There is a risk to the future development of medicines as the products highlighted within the survey were both on the market and under development. Therefore, any restrictions not only affect the current products but also future products and development, potentially limiting the future availability of new life-saving medications, which could include vaccines, cancer therapies, and rare diseases. There may also be a reduction in the availability of veterinary medicines as indicated in the Animal Health EPPA SEA consult (Part 24-9530) where there is an impact on the resilience of the pharmaceutical industry. Some companies may go out of business if their sales are EU only or materials are sourced from the EU, which will reduce the quantity of medicine available in the global marketplace. Diseases that are currently well controlled may become a public health issue if there is a lack of available medicine in the EU due to restrictions and/or companies going out of business or withdrawing products.

Aging population

5. Populations globally are aging, which brings with it the complexities of treating more diseases and often multiple diseases in individuals. Neurodegenerative conditions, such as Alzheimer's Disease (AD), are more common in older people. Therefore, the incidence of AD and other similar diseases will increase with the aging population. Age is the biggest risk factor [6] and as of 2020, there were approximately 50 million people worldwide with Alzheimer's disease [7]. Alzheimer's financial burden on society is large, with an estimated global annual cost of US$1 trillion [7]. In Europe, more than one fifth of the population was aged 65 or over in 2020 (an increase of 3% compared to 2010) and the prevalence of dementia in 2018 was around 1.6% and is anticipated to double by 2050 [8]. Other diseases will also have an increased probability with age. Therefore, the demands on research and the pharmaceutical industry for treatments will increase further – there are not yet cures for many diseases (AD included) but development work is ongoing with treatments to slow the disease progress. Restrictions on the use of PFAS or fluoropolymers may have the consequence of reducing this research and the potential for new therapies in many areas.

Societal Impact and Unintended Consequences

6. The PFAS restriction can have a negative effect on the EEA due to 1) low or scarce inventory of medicinal products and 2) inhibited innovation of new and improved treatments. There will be high demand for essential medicines and shortages are known to give rise to alternative markets with inventories of unapproved, illicit or counterfeit medicinal products. This can result in serious consequences, causing hospitalizations and even death for vulnerable populations [9]. Additionally, this would contradict the EU's stated aim of shortening supply chains and bringing production to the EU: "Europe supports research and innovation in strategic areas where supply shortages persist, such as raw materials,….and increasing the resilience of industry." [10].

Request #2 Emissions in the end-of-life phase – manufacture, use, end-of-life

Data were analyzed from the PQRI survey regarding both Pharmaceutical Manufacturers' and Suppliers' end-of-life treatments for materials used or supplied to support each stage of pharmaceutical production. As shown in Figure 10 and Figure 11 there is no evidence of reuse for any of the materials. Recycling and on-site or off-site disposal are generally used by suppliers for starting materials, container closures and drug delivery systems. From the pharmaceutical manufacturers' perspective, the primary mode of end-of-life treatment is offsite disposal. Offsite disposal is generally diverted from landfill to incineration due risk and potential impact of pharmaceuticals on the environment and local regulation requirements.

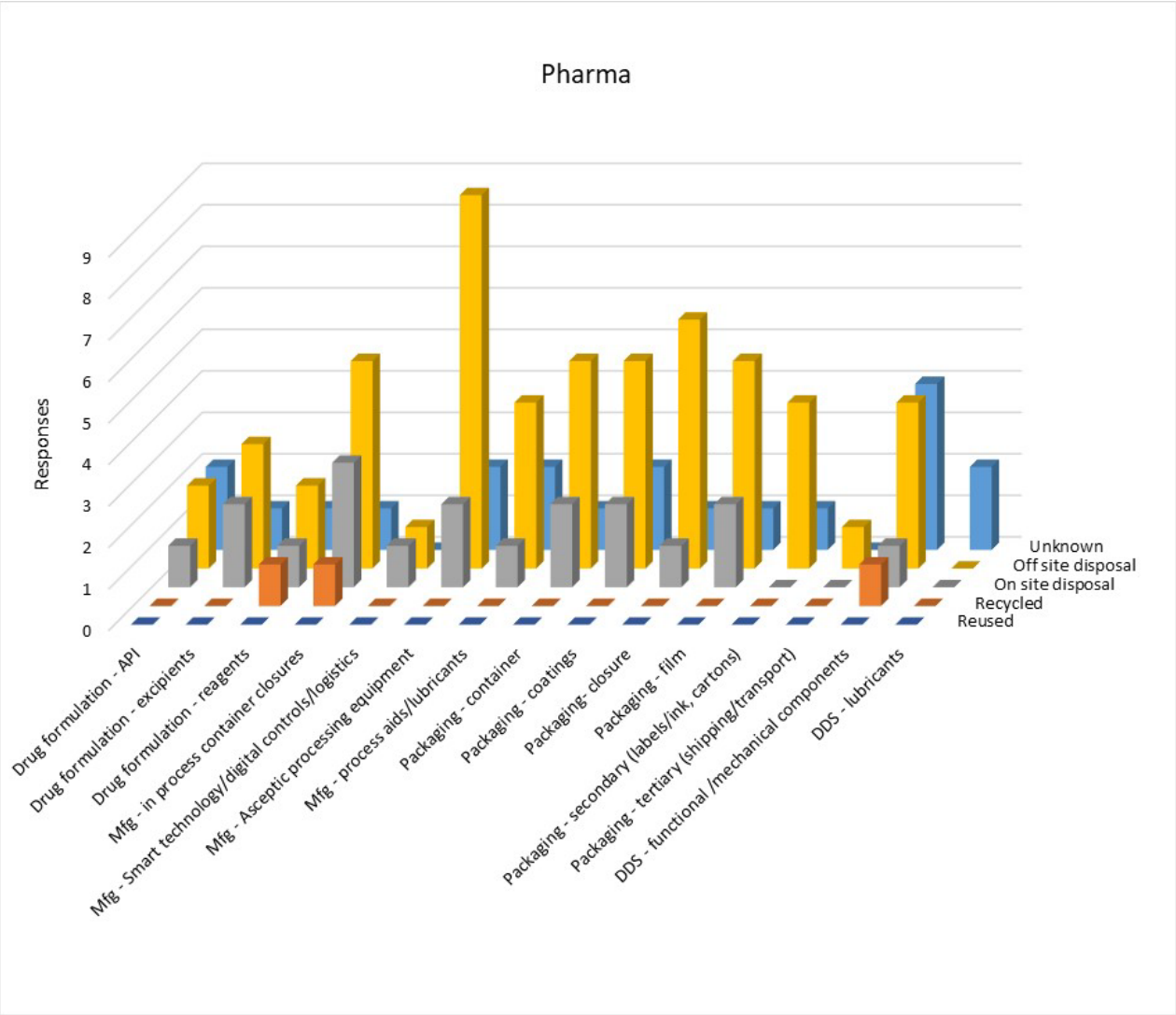

Figure 10 End of Life treatment of materials containing PFAS at Pharmaceutical Manufacturers

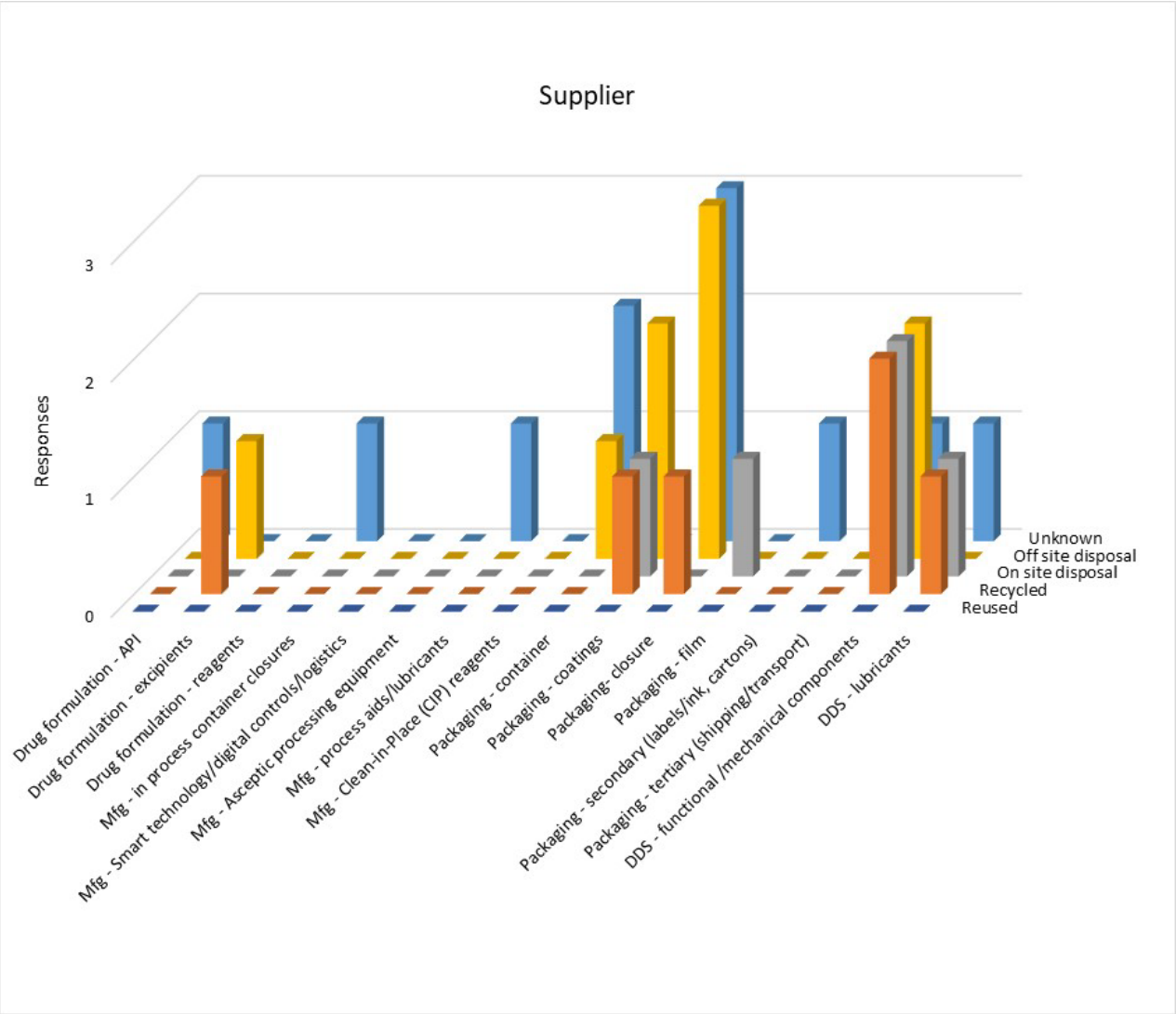

Figure 11 End of Life treatment of materials containing PFAS at Suppliers

Risks to the environment and human health are a significant concern in the pharmaceutical industry, as are practical approaches for risk management to protect patients. Net-Zero Standards adopted by many pharmaceutical manufacturers expect that companies invest above and beyond, but not instead of deep emission cuts in line with science [11]. Environmental priority continues to evolve, as evidenced in the 2023 SBTi Report. A total of 131 pharmaceutical and biotechnology companies set targets to reduce emissions consistent with the Paris Agreement goals [12]. Typically, pharmaceutical waste is incinerated based on current practice to eliminate the inherent risk of medicinal products in the environment.

Literature has shown potential for recycling of materials from used patient medicines as evidenced by examples in the UK: recovery of un-used propellants from patient returned inhalers, (the Take-AIR 12-month pilot scheme in the UK accepted all inhalers and the recovered pressurized metered-dose inhalers (pMDIs) were dismantled and component parts recycled where possible; the remaining propellant gas was extracted for reuse in refrigeration and air conditioning industries. Other inhaler types were incinerated in an 'energy-from-waste' facility and recycling of empty medicine blister packs from medicines is also possible [13, 14, 15].

Feasibility studies for innovative waste management technologies for upstream suppliers and downstream users are ongoing. There is still a lot of information to be gathered to support PFAS policy decisions to ensure the society would not be negatively impacted by banning all PFAS.

Request #2 Summary- Emissions in the end-of-life phase – manufacture, use, end-of-life

Manufacturers have requirements and controlled processes for disposal. Baseline emissions and waste in the Annex XV restriction report are highly uncertain. Also, there is no, or insufficient data on bioaccumulation for the majority of PFASs. Safe concentration limits are highly uncertain. Due to the risk of environmental contamination, most of the pharmaceutical waste is diverted from landfills and incinerated. New recycling technologies and design principles are emerging and signal a reduction of environmental PFAS in the near future.

Request #3 Emissions in the end-of-life phase – incineration effectiveness

Topic not addressed in this paper

Request #4 Impacts on the recycling industry

Topic not addressed in this paper

Request #5 Proposed derogations – Tonnage and emissions

Several PFAS or PFAS containing articles with long-term and short-term, exposures and use conditions are used throughout development, manufacture, packaging and delivery of medicinal products. There are currently no rules or regulations in place to monitor the PFAS proposed to be banned, which may number as many as 10,000. Emissions data is not also readily available and proxy data is not substantiated. The Annex XV restriction report emphasizes the high uncertainty for baseline emissions data and environmental waste [1]. Tracking emissions with respect to PFAS (substances/precursors, gases, and polymers) across the pharmaceutical lifecycle for each medicinal product and all PFAS is not readily achievable due to the complexity of the supply chain. More time is needed to identify all PFAS sources, types and uses to enable a comprehensive estimate of tonnage and emissions.

Request #6 Missing uses – Analysis of alternatives and socio-economic analysis

Defining PFAS: Grouping, Properties and Hazard Assessment

The restriction of PFAS must be substance-related and risk-based (Article 68 para. 1 of the REACH Regulation [16]). The restriction must differentiate between the different groups of PFAS and risks posed by their uses. Although various definitions for PFAS exist, there is no consensus; PFAS scope for this proposal is aligned with the OECD definition. This is a very broad application to define PFAS as, “any substance that contains at least one fully fluorinated methyl (CF3-) or methylene (-CF2-) carbon atom (without any H/Cl/Br/I attached to it” [1]. This scope would include a minimum of 10,000 PFAS that are grouped as per and polyfluoroalkyl substances, which can be categorized into 2 primary categories; polymers and non-polymers. These 2 categories are further simplified into 5 classes of PFAS:

- Perfluoroalkyl substances
- Polyfluoroalkyl substances
- Polymeric perfluoropolyether

- Side chain fluorinated polymers
- Fluoropolymers

The non-polymer category includes perfluoroalkyl substances and polyfluoroalkyl substances, while the polymer category includes fluoropolymers, perfluoropolyethers, and side-chain fluorinated polymers. It is important to note that polymers generally have very different physical, chemical, and biological properties than do non-polymer chemical substances of low molecular weight. There are notable differences between the 5 classes of PFAS. For example, perfluorooctanoic acid (PFOA), a process aid, in the non-polymer perfluoroalkyl substances class, is mobile, and persistent and has been phased out. Subsequent to the phase-out, perfluoroalkyl substances with <8 carbons were substituted and consequently are now in the environment. Side-chain fluorinated polymer class compounds such as 8:2 fluorotelomer alcohol may degrade to form PFOA and therefore are subject to regulatory management. Finally, polymeric perfluoropolyethers represent a class of PFAS exemplified by oxygen linkages in the polymer backbone. The primary concern for PFAS and/or their degradation products is the potential for very high persistence in the environment and associated properties of long-range transport, mobility, accumulation in plants, bioaccumulation, ecotoxicity, endocrine activity and effects on human health [1].

The proposed grouping approach to assess over 10,000 compounds for their effect on human health does not correlate to the presence of PFAS in the environment from industrial uses. An independent expert panel investigated PFAS grouping for human health assessments and concluded that persistence is generally not deemed scientifically valid way to group “all PFAS” for the purposes of assessing human health risk [17]. Certain chemical-physical properties were considered potential predictors of hazards and exposure for grouping PFAS when specific information was lacking, but not sufficient alone for informing exposure or potential hazards or toxicological effects and dose response for risk assessment. The most critical data gaps identified were (1) exposure, (2) dose-response, and (3) mode of action studies. It was also noted that there are critical gaps in understanding PFAS chemistries, mixture composition toxicity and handling overall uncertainties. Overgeneralized statements should be avoided and different strategies would be needed to support various risk management options such as restrictions in manufacture and use. The expert panel agreed that a broad definition, such as the OECD 2021 PFAS definition, may be a useful starting place, but that the definition needs to be refined for specific risk assessment goals. The OECD report also states this: “individual users may define their own PFAS working scope for a specific activity according to their specific needs by combining this general definition of PFASs with additional considerations” [18].

One possibility for subgrouping according to health hazard is to consider the OECD criteria for polymers of low concern (PLC) [19]. Fluoropolymers are inert, not mobile and can meet the criteria. The OECD definition of a polymer has been widely adopted and incorporated in the regulation of many governments. However, this harmonization has not been reached for the criteria used to identify PLC. It was also noted that except in the EU system, all other jurisdictions integrate the concept of polymers of low concern into their regulation. In March 2007, the OECD Task Force on New Chemicals Notification and Assessment organized an Expert Group Meeting on polymers in Tokyo, Japan. The recognition and acceptance of the PLC concept then constituted the basis for the discussions during the meeting. To reinforce this position, a definition of a PLC was agreed upon. The proposed definition of a PLC emerged as the following: **“Polymers of low concern are those deemed to**

***have insignificant environmental and human health impacts*. Therefore, these polymers should have reduced regulatory requirements."[19]**

The criteria for PLC may include polymer composition, molecular weight and molecular weight distribution, weight % oligomer, electrical charge, reactive functional groups, functional group equivalent weight, low molecular weight leachables (including residual monomers), particle size, water solubility and octanol/water partition coefficient, polymer stability (e.g., hydrolytic stability, thermal stability, photostability, oxidative stability), abiotic stability and biotic stability. Examples of PLC are listed in Table 1.

Table 1 OECD Polymers of low concern

Fluoroplastics	Fluoro elastomers
PTFE	FKM
ETFE	FFKM
PFA	FEPM
FEP	FVQM
PVDF	
ECTFE	

PFAS in the Pharmaceutical Supply Chain

As evident from the PQRI survey, major uses of PFAS in the pharmaceutical supply include drug formulation, manufacturing processes, packaging, and delivery. Specific examples include API, excipients, propellants, manufacturing equipment, aseptic processing equipment, reagents, cleaning agents, processing aids, flow agents, laboratory equipment, medicinal packaging, delivery system components, lubricants, electronics, storage and transport. Without all of these, medicinal products could not be made or tested. Any change to replace them (if it were possible to do so) could involve a complete redesign/rebuild of equipment and auxiliary materials. PFAS uses and sub-uses across the pharmaceutical supply chain are listed, but not limited to, those shown in Table 2.

Table 2 PFAS Uses and Sub-uses in Pharmaceutical Sector and Potential for Derogations

Uses	Sub-uses*	Derogation/ Recommended Derogation
Drug Formulation	Excipients, Propellants, Solvents, Reagents	Annex XV Report: API: time-unlimited derogation Recommended Derogation: reconsideration of scope for time-unlimited derogations for co-formulants, chemical intermediates, excipients and other PFAS used in the pharmaceutical supply chain. Clarity and alignment with EMA.
Facilities	Air Filtration, Refrigerants, HVACR, Equipment, PPE, Seals, Pipes, Tubing, Water Purification, Gases	Annex XV Report: 6.5 or 13. 5 years after EiF Recommended Derogation: reconsideration of time-unlimited derogation for those PFAS used in the

Uses	Sub-uses*	Derogation/ Recommended Derogation
		pharmaceutical supply chain and availability of upstream supplier inventory.
Equipment: Manufacturing, Lyophilization and Aseptic Processing	Pipes, Valves, Gaskets, Seals, O-Rings, Filters, Tubing, Seals, Valves, Separation Media, Ion Exchange Membranes, Filters, Sensors, Liners, Distillation Systems, Capping/Sealing Systems, Reaction Vessels/Bags, Stirrers, Tubes, Storage Containers, Coatings, Needles, Conveyor Belts, Vacuum Pumps, Water Purification Equipment, PPE, Cleaning Agents, Process Aids, Lubricants, Coatings, Engineering Fluids, Refrigerants, Compressors, Hydraulic Fluids, Coolants	Annex XV Report: 6.5 or 13.5 years after EiF Potential derogation (silicone, PTFE, heparin) Recommended Derogation: reconsideration of time-unlimited derogation for those PFAS used in the pharmaceutical supply chain and availability for upstream supplier inventory.
Laboratory Equipment	Refrigerants, Filters, Membranes, Connectors, Seals Labware, Analytical Reference Materials, PPE, Coated Test Equipment, Tubing, Monitors/Sensors	Annex XV Report: 13. 5 years after EiF with unlimited derogation for PFAS analytical reference materials Recommended Derogation: reconsideration of time-unlimited derogation for PFAS used in sample handling material and instrument operation.
Medicinal Packaging Containment and Delivery	Primary and Intermediate Vial, Stoppers, Seals, Syringes Barrels, Needles, Tip Caps, Coatings, Polymer Articles, Drug Delivery Systems, Device Components Including (Tubing, Pumps, Batteries), Lubricants, Post Processing/Washing/Sterilization Equipment, Secondary Packaging, Labels, Inks, Adhesives, Solvents, Cleaning Agents, Tertiary Packaging, Outer Wraps, Polymer, Metal, Paper, And Cardboard Products	Annex XV Report: 6.5 or 13.5 years after EiF Recommended Derogation: reconsideration of time-unlimited derogation for those PFAS used in the pharmaceutical supply chain and availability for upstream supplier inventory. Alignment with EMA approval requirements.
Electronics	Electronics, Semiconductors, Smart Devices, Computers, Temperature Monitors, Electronic Documentation, Data Storage Systems, Analytical Data Capture, HVAC/Environmental Monitoring, Stability Chambers, Security Systems, Controlled Access, Payments, Ordering, Shipping, Electronic Safety	Annex XV Report: Semiconductor mfg 13.5 yr after EiF Recommended Derogation: Reconsideration of time-unlimited derogation for those PFAS used in the pharmaceutical supply chain and availability for upstream supplier inventory.
Storage and Transport	On Site Refrigeration/Freezing for Manufacture/Distribution Warehousing and In Transit, Controlled Temperature and Pressure	Annex XV Report: 6.5 years after EiF Recommended Derogation: reconsideration of time-unlimited derogation for those PFAS used in the pharmaceutical supply chain and availability for upstream supplier inventory.

Uses	Sub-uses*	Derogation/ Recommended Derogation
*Uses and sub-uses include data from PQRI survey, other category and ECHA consult reviews		

As shown in Figure 12 and Figure 13, several types of PFAS are used in various types of drug products at each point in manufacturing, storage and delivery. If pharmaceutical manufacturers are unable to assure high purity raw materials and qualified manufacturing and containment materials, products will not meet label claims. Sequential steps are necessary over the pharmaceutical lifecycle from the point of discovery to approval and change management.

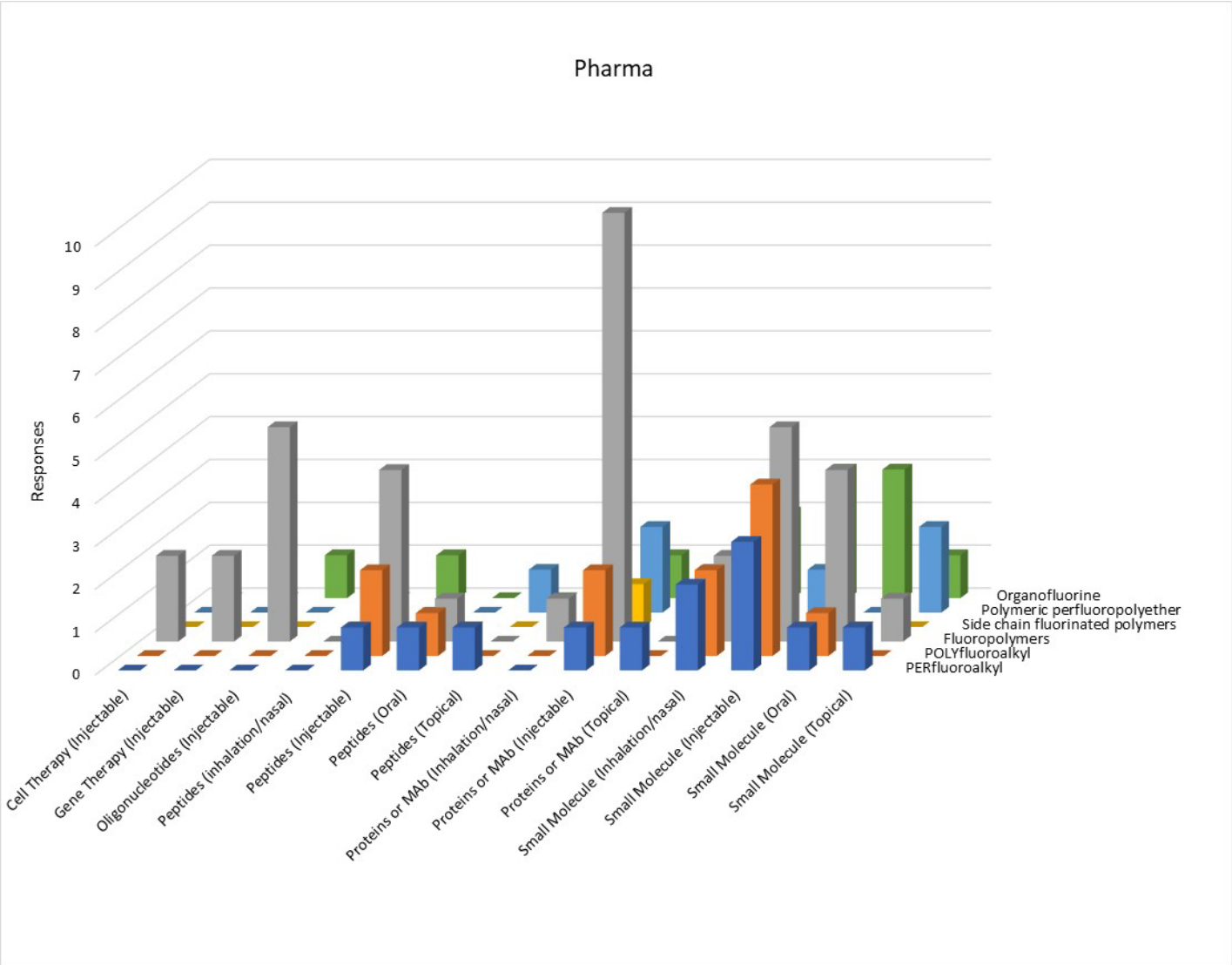

Figure 12 PFAS types used in pharmaceutical products - molecules and routes of administration.

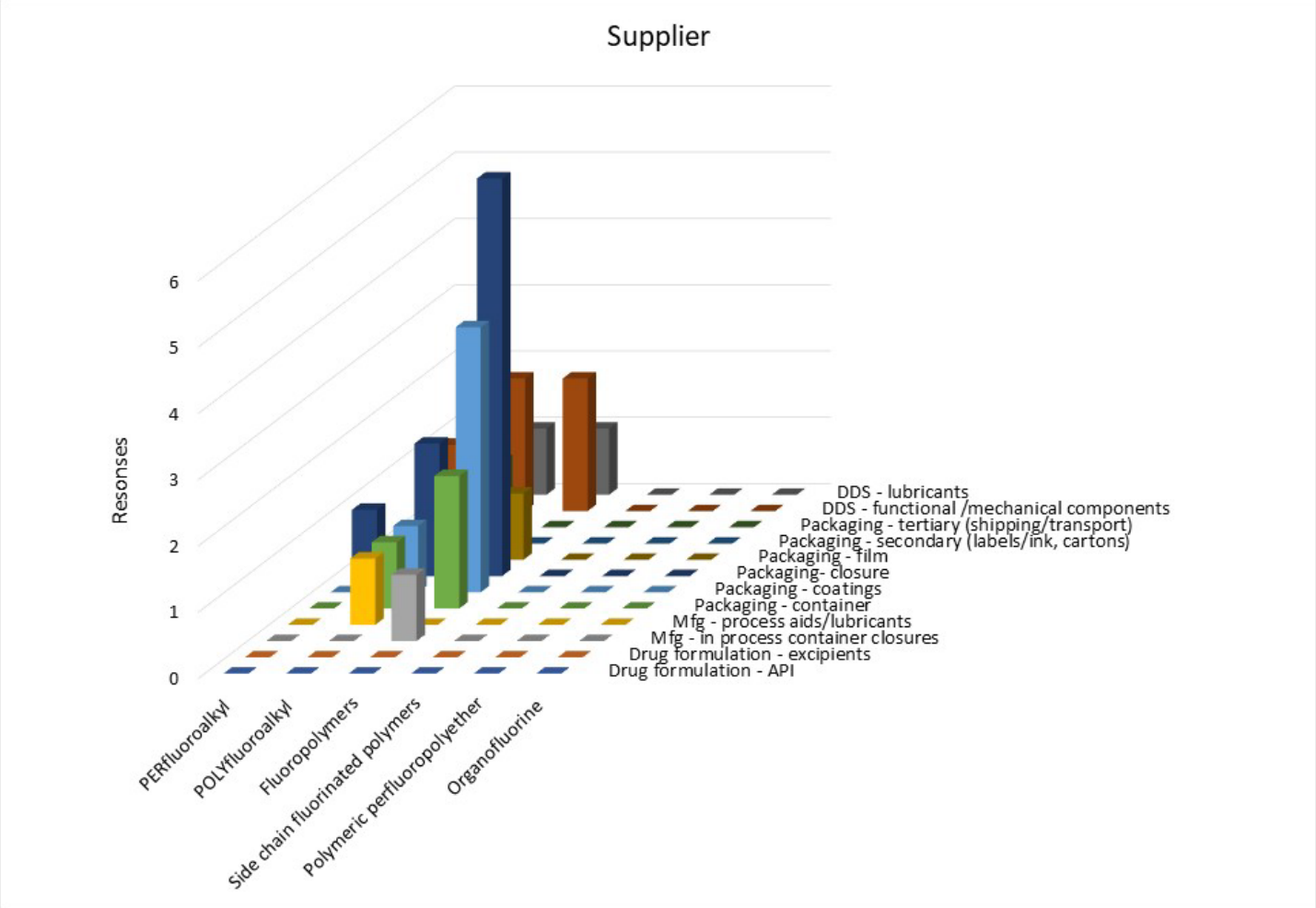

Figure 13 PFAS types used in materials provided by suppliers to the Pharmaceutical Sector

There may be some ancillary substances that are not recognized as containing PFAS that are also used in pharmaceutical applications. For example, cleaning agents can contain PFAS and some suppliers have already given notification for withdrawal of their products. Some substitution may be possible, but it takes time to identify an appropriate replacement, validate the process or qualify the material and implement the change. If a substitute is available, the process of the change itself can be time consuming and may require data generation and submission/approval of the change.

The actual material may not contain PFAS, but a precursor or a process may include one or more PFAS. If these materials are banned in the EU, there may be an impact on the global supply as companies previously supplying to a global market may not have sufficient market share to sustain the manufacturing supply chain. If costs were to increase, this could also have an impact on continued supply as medicine prices in the EU are negotiated and pharmaceutical companies may not be able to absorb cost increases incurred as a consequence of any PFAS restriction, which may lead to withdrawal of medicines and companies ceasing to supply markets.

Rationale for Pharmaceutical Sector PFAS Usage and Sub-uses

In each section below a rationale is provided for PFAS use and sub-uses.

Drug Formulation

The Pharmaceutical Sector manufactures a variety of APIs that contain at least one aliphatic $-CF_2-$ or $-CF_3$ group and fall under the current very broad scope of the PFAS group. Perfluoro-containing building blocks and raw materials are used to introduce the fluorine into the API and to manufacture specific groups of medicines (e.g., peptide synthesis). Fluorine, because of its small size and strong electron withdrawing properties, is widely used in the human and animal health pharmaceutical industries to improve medicinal products based on:

- molecule potency and permeability,
- pKa modulation and lipophilicity,
- reduced rate of clearance,
- control of structural conformation.

The intentional use of fluorine in the design of pharmaceuticals has been proven to be safe for human and animal patients as assessed via extensive nonclinical, human, and environmental testing as currently required by governing bodies for market authorization. The environmental impact of pharmaceuticals is not limited to perfluoro alkyl groups and includes metabolites. In accordance with medicinal products directive [Article 8(3) in Ref. 20], the potential environmental impact of medicinal products is assessed. Since 2006, environmental fate and effects data with an API and an environmental risk assessment of that API are already required at the time of submission of a marketing authorization application [21].

Due to the unique properties and function of fluorine, the use of alternatives has serious negative impact on both safety and desired effect of the drug molecule. The pharmaceutical intermediates used in the synthesis of the API if registered as intermediates according to REACH, will be handled under strictly controlled conditions in closed systems. Intermediates are assigned to appropriate containment band on the basis of available health hazard data and pharmacology screening. To evaluate the effectiveness of controls that are in place, exposure monitoring data is collected for APIs and compared to health based OELs derived by company toxicologists. Procedures used to establish in-house OELs for pharmaceuticals have been described in the literature [22, 23, 24, 25, 26, 27].

The proposed restriction indicates a derogation that only applies to API in human and veterinary medicinal products within the scope of Regulation for pharmacovigilance [28] authorization of veterinary medicinal products [29] and medicinal products for human use Directive [20]. In addition to APIs, the precedence of the use derogation for medicinal products has already been established in the recently proposed Annex XV restriction report on intentionally added microparticles [30]. The use-specific restriction in the microparticle proposal applies to human and medicinal products inclusive of all drug components.

PFAS substances can be present in the API precursors, and other components of the formulated drug product such as excipients, colorants, coating, adjuvants, etc. PFAS substances are also found in manufacturing and processing equipment and reagents, including equipment gaskets, protective coatings, filters, tubing, and lubricants. In many cases, there are no known substitutes for these items as they have unique properties, such as for corrosion prevention and contamination control. If the ban becomes effective it could cause disruption to the entire pharmaceutical supply chain.

Excipients enable the dose required (often as low as a few micrograms) to be delivered to the patient in a stable and reproducible dosage form. Excipient properties are essential for the formulations they are included

and approved within medicinal products. Propellants are one example as they must be safe, compatible with the container closure used, not react with the active ingredients, and deliver the required dose consistently to the patient. Each propellant has different physical properties (e.g., density) that enable appropriate selection to generate a stable product for use by the patient. More information on medicinal propellants is found in the IPAC/IPAC-RS submissions to ECHA [31, 32, 33, 34].

Drug Formulations Alternative Potential

More than 300 fluorinated compounds have been launched as drugs over the last decades and over 500 more are in late-stage clinical trials [35], which indicates the importance of fluorine in pharmaceutical compounds. Due to the unique properties of fluorine in API, alternatives are not available in most cases. There are other electron withdrawing groups similar to -CF2- or -CF3 such as carboxylic esters, amides, nitro, or cyano, but these carry various liabilities related to stability, permeability, and toxicity. Replacement of fluoro-alkyl by other halo-alkyl groups such as chloro-alkyl will lead to reactive agents with serious toxicity issues. To improve oxidative metabolism of C-H bonds, instead of replacing it with a C-F bond, replacement with deuterium has been another strategy. However, this typically only results in modest improvements compared to the use of fluorine [36, 37]. The extensive application of fluorine in drug research is related to the unique properties of this element. Fluorine is both small and has the highest electronegativity of all elements. To evolve a molecule into a potent and safe drug, many parameters need to be optimized in parallel. The introduction of fluorine is often an essential part of achieving an optimally balanced profile. The size of a fluorine atom is comparable to a hydrogen atom, but the stability of a C-F bond is higher than for a C-H bond and fluorine will change the lipophilicity and electron density of the molecule. The replacement of a hydrogen by fluorine will impact key properties required to make a drug efficacious and safe and lead to reduced clearance, and enhanced permeability. Due to fluorine's electronegativity, the molecule pKa will be decreased and subsequently impact key parameters for permeability and drug efflux, that can reduce undesired side effects, thereby increasing the therapeutic index.

Medicinal products cannot be formulated without excipients, although these are inactive ingredients they possess critical functions, e.g., stabilization of active, distribution and absorption of the medicine. Excipients are necessary for medicine to function as intended and verified throughout the clinical development phases by studies that take years to complete before EMA approvals. Major drug formulation changes could require cost-prohibitive non-clinical and clinical studies to support safety and efficacy. A similar approach to that taken in the Annex XV report for intentionally added microparticles [30] is justified for the proposed PFAS restriction proposal to avoid significant market disruption and drug shortages. Appropriate alternatives for medicinal product excipients may not be readily available at the time of implementation of the restriction and in most cases, do not exist.

Furthermore, there will be indirect consequences if a PFAS ban progresses for other industrial chemicals which are either used as excipients or are used to manufacture excipients, and which may not have derogations. In many cases the amount of an excipient used in pharmaceutical applications is only a small percentage of the main volume of these chemicals produced by a manufacturer and may not be able to be sustained for pharmaceutical use if the materials are no longer available for use in other industries. There may not be any suitable alternatives for these excipients since they are already difficult to source. The lack of availability of these industrial chemicals could contribute to the lack of availability of medicines that could be considered to be life-saving or life-sustaining

Facilities

Pharmaceutical facilities/site systems must be designed for purpose according to GMP requirements, and with respect to local building codes and environmental laws. Facilities and maintenance practices rely on related sector uses/sub-uses e.g., construction materials, manufacturing materials, utilities, and supply (air, water, gases environmental controls). The facility requirements to install and qualify highly complex manufacturing and laboratory testing equipment must be met for safe and efficient operations. Examples of facilities requirements include clean rooms, biohazard rooms, ventilation, secured storage and access and other related functions for manufacturing and testing medicinal products. Medicinal product shortages can arise due to general capacity restraints already realized from the COVID-19 pandemic response. Other considerations include updating aging facilities, or upgrades to accommodate new technologies. Various PFAS are used throughout pharmaceutical manufacturing facilities to enable production of safe and effective medicines. It is not feasible to identify, verify, substitute, and eliminate all PFAS uses in a short period of time without experiencing some unintended consequences due to multiple changes in a highly controlled and complex facility.

Manufacturing Equipment: Lyophilization, Aseptic Processing

The manufacturing and process equipment to produce medicinal products is designed specifically for each product to meet label claims, avoid cross contamination or external contamination. The same molecule moieties can treat multiple indications, and the API can vary in amount and formulation, including excipients, dosage forms, routes of administration, and delivery systems. The manufacturing equipment, operations, and other materials used to contain, store, transport and administer medicinal products must also be qualified under pharmaceutical GMPs. Multiple PFAS are used throughout production processes to ensure safety, enhance efficiency, reduce friction, wear, degradation, and energy consumption. Fluoropolymers, coatings, lubricants, and processing aids are used for multiple purposes in precision manufacturing with equipment and filling operations. If these materials were not available, unintended consequences could include malfunction of equipment, increased maintenance and costs, increased downtime, and low inventories. The time needed to maintain sufficient inventory would be exacerbated by substitution of multiple non PFAS alternatives (assuming they exist). It is possible equipment may need to be redesigned around alternative materials, including auxiliary materials to ensure new materials would not negatively impact the medicinal product and to be able to withstand the lyophilization, sterilization, filling, or other processes. A lack of materials for the manufacturing and processing equipment could therefore lead to a lack of medicinal products. Additionally, advanced manufacturing processes utilize microprocessors, sensor, computer vision and other semiconductor-enabled electronic systems to ensure reliable, speedy, and effective drug product manufacture and delivery of life-saving drugs to patients.

Laboratory Equipment

Laboratory equipment is necessary for the Pharmaceutical Sector to characterize medicinal products during development and release them per label claims. Testing incorporates a multitude of different methods, equipment and auxiliary materials depending on the attributes to be measured for each medicinal product. Release testing of final product is required but is relatively simple compared to R&D evaluations on chemical constituents and impurities of APIs, reagents, intermediates, excipients, and formulated drug products. The chemical, physical, functional, and mechanical characteristics of auxiliary materials must also be evaluated for use and introduces other types of test equipment, all of which use various PFAS. Additionally, advanced analytical instruments, automation and controllers utilize microprocessors, sensors, and other semiconductor-enabled

electronic systems. The implementation of multiple advanced analytical technologies to meet performance and operational requirements for sophisticated measurements involves many PFAS materials for sample handling and equipment operation. This is a much broader range of PFAS materials associated with testing than the PFAS reference materials exempted in the Annex XV restriction report (see Ref. 1, proposed Restriction Option 2).

Medicinal Packaging, Containment, and Delivery

Packaging for use in the Pharmaceutical Sector is approved together with the medicinal product. The primary packaging comes into direct contact with the medicinal product and must be shown to be compatible with filling operations and contact materials and verified to be stable over the shelf life. The primary packaging involves a container-closure system and can also be part of an administration/delivery system with specific mechanical and functional requirements. Product contact materials compatibility must be validated for use with the chemical, functional, and physiochemical properties of the medicinal product. The primary packaging system must also protect the medicine to maintain quality attributes and sterility for each medicinal product and protect contents from microbial ingress or leaching of chemicals from materials for each intended use. Certain products can be extremely sensitive to light, moisture, and air. In the case of biological products, there is a risk of adsorption onto contact materials and the potential to impact drug formulation ingredient structural conformation, which can result in patient adverse effects. Packaging materials are composed of glass, plastic, paper, metal, and elastomers which can be enhanced with fluoropolymers e.g., to reduce adsorption and also create a barrier to chemical migration. Another key attribute of fluoropolymers is low surface energy to minimize adherence of particles onto surfaces during manufacturing to avoid risk of contamination of medicinal products. Fluoropolymers and other PFAS containing materials are used in secondary packaging for components and tertiary packaging for storage and shipping. Pharmaceutical packaging is essential to assure drug product quality, efficacy, and patient safety. Each material must be validated for intended use with each drug product for approval as well as requalified based on changes post-approval. Various PFAS are used in non-product packaging components and to facilitate manufacturing processes. Alternatives for every type of PFAS used in packaging have yet to be identified, qualified, and approved for specific use. Substituting all PFAS with non-PFAS packaging components will not be feasible until alternatives are available and systematically qualified for approval by EMA. Examples of timelines are in Figure 1. There is a need for unlimited derogation to contain, protect and deliver medicinal products. Environmental emissions information has been included for pharmaceutical packaging in the Food Contact Materials and Packaging Sector in Annex A Manufacture and Use and Annex B Information Hazard Assessment [1], however, the Pharmaceutical Sector has unique uses and requirements beyond food and feed applications. EMA evaluation and approval of both medicinal products and any subsequent post-approval changes play a critical role throughout product lifecycle management.

Electronics

The electronics and semiconductor industries are critical to all aspects of discovery, development, manufacturing, deployment and lifecycle management for pharmaceuticals. R&D automation, high throughput screening, analytical instrumentation and data systems, manufacturing systems, supply chain security and integrity controls, drug delivery systems, submissions, micro-electromechanical (MEM) systems, such as sensor chips and smart devices – everything utilizes computers/ microprocessors and related electronics. Any impact of the PFAS ban on the supply of electronics (as PFAS materials are essential to the process of manufacture of semiconductors) would broadly impact many other areas of pharmaceutical production. Current industry trajectory and regulatory expectations are driving toward digital transformation, “lights-out” automation and manufacturing and AI/ML solutions to ensure digital data quality and integrity and greatly improve speed and

effectiveness of delivery of innovative and life-saving medicines for key therapeutic indications to critical patient populations. Therefore, much information has been digitized to expedite decision making and reduce the use of paper and printing (resulting in reduction of energy, pollution, shipping and storage that was associated with paper usage). Submissions to regulatory authorities are also electronic to facilitate improved processing of the submission and make the handling of the vast amounts of data and information contained within a single Marketing Authorisation more manageable. The entire supply chain, manufacture, development, submission and monitoring are all impacted by electronics and a retrograde move to paper would be a significant impact and potentially stop many processes and impede or halt significant progress that has been made in health care. Even patient information can be accessed electronically.

Storage and Transport

Shipping and storage throughout the supply chain at cold, refrigerated, or deep freeze conditions are required for many medicinal products to enable the full shelf life of the product to be achieved. Failure to store a product under appropriate conditions can result in the product potentially being unacceptable and destroyed or assigned a much shorter shelf life (depending on the product requirements), which will impact product availability. Fluoropolymers are critical to containers used for ultracold storage, which must have flexibility and maintain integrity for shipping and freeze/thaw cycles required for biopharmaceutical bulk drug substances such as vaccines, monoclonal antibodies, and antibody drug conjugates. Storage and transport operations include sophisticated means of ensuring supply chain security and integrity utilizing smart data solutions (e.g., blockchain) and other semiconductor-enabled electronic systems. If it is not possible to safely transport intermediate or finished medicinal products, due to extreme temperature fluctuations, pharmaceutical companies and patients would experience a major loss and health risks. The Pharmaceutical Sector relies on the Transport sector as well as specialty pharmaceutical packaging to supply medicines to patients.

Rationale for Missing Uses

The Pharmaceutical Sector has distinct applications and quality standards for compliance to ensure safe and effective medicines. It can be shown (see Figure 9) that PFAS use in the Pharmaceutical Sector are similar to PFAS uses that have been identified for other sectors already identified in the Annex XV restriction report. Although the requirements for these similar uses may serve as a baseline, they do not meet the needs of the Pharmaceutical Sector. (e.g., regulatory requirements for EMA approvals, lack of equivalent alternatives, and time involved for post-approval changes). Examples of these uses and rationales for classifying them as missing uses are provided in Table 3.

Table 3 Rationale for missing uses in Pharmaceutical Sector

Relevant Sector	Related Use	Pharma Sub-use	Inadequacy to address Pharma Sub-use
TULAC	Professional Apparel	PPE, Sterile Gowning	Particulates and sterile processing stringent requirements
Food Packaging	Food, Feed and Pharmaceutical Packaging (Annex A and B) Industrial Food Production	Packaging: Plastic, Elastomers, Metals, Paper, Paper Board	Pharmaceutical Packaging regulated under EMA stringent requirements for medicinal products.

Relevant Sector	Related Use	Pharma Sub-use	Inadequacy to address Pharma Sub-use
Metal Plating	Chrome Plating, Metal Manufacture	Surface Corrosion Coating Delivery Systems Component Fabrication	Coatings for containers, delivery systems, manufacturing, and storage systems. Specific requirements under pharmaceutical GMPs and EMA
Consumer Mixtures	Cleaning Agents, Waxes	Manufacturing Lines, Clean Room, Fill Finish Operations, Storage	Specific requirements under pharmaceutical GMPs
Fluorinated Gases	Refrigeration, Air Conditioning, Heat Pumps, Solvents, Propellants	MDI Propellants Deep Freeze Storage (-180C to -100C)	Critical application for inhalation medicines and cell and gene therapies
Medical Device	MDI Coating and Propellant	Chronic Respiratory Disease Treatments	Device considerations, not medicinal product considerations, which are different
Transport	Sealing Applications, Electrical Engineering, Information Technology, Hydraulic Fluids, Coatings, HVCAR	Raw Materials, Chemical Intermediates, Finished Products Shipments	Maintain temperatures and pressures for product quality, which may have tighter tolerances
Electronics and Semiconductors	Coating, Solvents, Cleaning Agents, Wires, Cables, Electronic Components, Heat Transfer Fluids	Facilities, Manufacturing Technologies and Operations, Alarms, Stability Chambers, Delivery Systems, Communications, Tracking Systems Production Records, Inventories, Finance	Specific applications for pharmaceuticals critical to monitoring operations, safety requirements, product quality, corrective/preventative actions pharmacovigilance, data integrity
Energy Sector	Lithium-ion Batteries	Manufacturing, Delivery System Dosing	Critical to monitoring manufacturing and safe patient administration
Lubricants	Low Viscosity, Film Lubrication, Release Agents, Greases	Manufacturing, Processing, Laboratory Equipment	Specific pharmaceutical GMPs for manufacturing operations, packaging, and shipping
Petroleum and Mining	Antifoaming Agents, Water and Gas Tracers, Lining of Piping, Seals, Sensors.	Facilities, Manufacturing, Monitoring	Requirements for specific pharmaceutical use

PFAS Used to Produce and Deliver Medicinal Products Alternative Potential

Fluorinated polymers were found to have the highest number of responses in the PQRI survey. These materials comprise a wide range of thermoplastic and elastomeric components ranging from semi-crystalline to totally amorphous with numerous applications in the Pharmaceutical Sector. Fluoropolymers have a unique

set of properties that are unmatched and are described in Table 4. There are other polymers that have some of these properties but lack the complete set of attributes required to meet the needs of the pharmaceutical supply chain. These properties are all necessary within one product.

There is no alternative material available that combines all these properties. Based on review of Annex XV restriction report Appendix E.2 Hazard Assessment [1], it was observed that the type of PFAS and usages were limited, and hazard information was listed as insufficient. There is no material possessing all these properties that has been identified or commercially available to evaluate.

Another type of PFAS that is unlikely to have alternatives readily available are propellants used in pharmaceutical delivery systems. Metered dose inhalers (MDIs) for oral inhalation use fluorinated propellants (e.g., HFA-134a and HFA-227) that fall under the broad Annex XV definition of PFAS. These propellants are small, low molecular weight, volatile, two and three carbon fluorinated hydrocarbons. They are non-toxic, non-flammable, and of low chemical reactivity with the complex milieu of metal, plastic, and elastomer materials the MDI formulation contacts. Their low reactivity better assures uniform emitted dosing and product stability over time. Further, their phase behavior at ambient temperatures makes it such that a balance between pressurized liquid / gas phase in the canister persists providing working pressures low enough to be safe and high enough to initiate forming the very small particles / droplets necessary for successful inhalation therapy (e.g., 1-5 micron sized) throughout the life of the MDI. The two-phase gas/liquid mix in the MDI canister allows the liquid to vaporize during the use-life to maintain the necessary equilibrium working pressure. There are no other known substances that possess all these properties; and the loss of these propellants for MDI use could initiate a public health crisis for patients with respiratory diseases such as asthma and COPD (chronic obstructive pulmonary disease). As shown in Figure 14 and Figure 15 there is minimal chance that alternatives are currently available for PFAS used throughout the Pharmaceutical Sector.

Table 4 Unique properties of fluoropolymers

Specific Material Properties	Functionality
Temperature Stability	Tolerance of high temperatures for manufacturing and processing; low temperatures for cryogenic applications
Mechanical Strength	Toughness and resilient under stress and stress strain
Compressive Strength	Withstand pressure and load without deformation or cracking
Dielectric Strength	Reduced interfacial tension and liquid and gas flow
Low Surface Energy	Non-stick, non-adsorptive, hydrophobic, and resistant to hydrolysis
Low Friction	Lubricious to impart slide properties, and increase fluid flow rates
Low Abrasion	Withstand wear and particle risks during manufacture and usage
Low Stiffness	Resist fatigue and flexible for fluid processing equipment
Hydrophobic and/or Oleophobic	Non-wetting and low chemical absorption
Low permeation	Low gas/vapor absorption and chemical transport
Inert	Chemically nonreactive
Barrier	Resist migration of chemicals and moisture. Prevents chemical interaction of product with underlying material and inhibits corrosion
Durable	Resistance to aging and oxidative stress, with a long service life
Range of Melt Temperatures	Moldability for use in production of articles
Ultra Clean	Smooth surface, low static charge

Material Stability	Resist chemical, biological, and environmental degradation. Does not chemically react with or contribute leachables into products during use or storage.

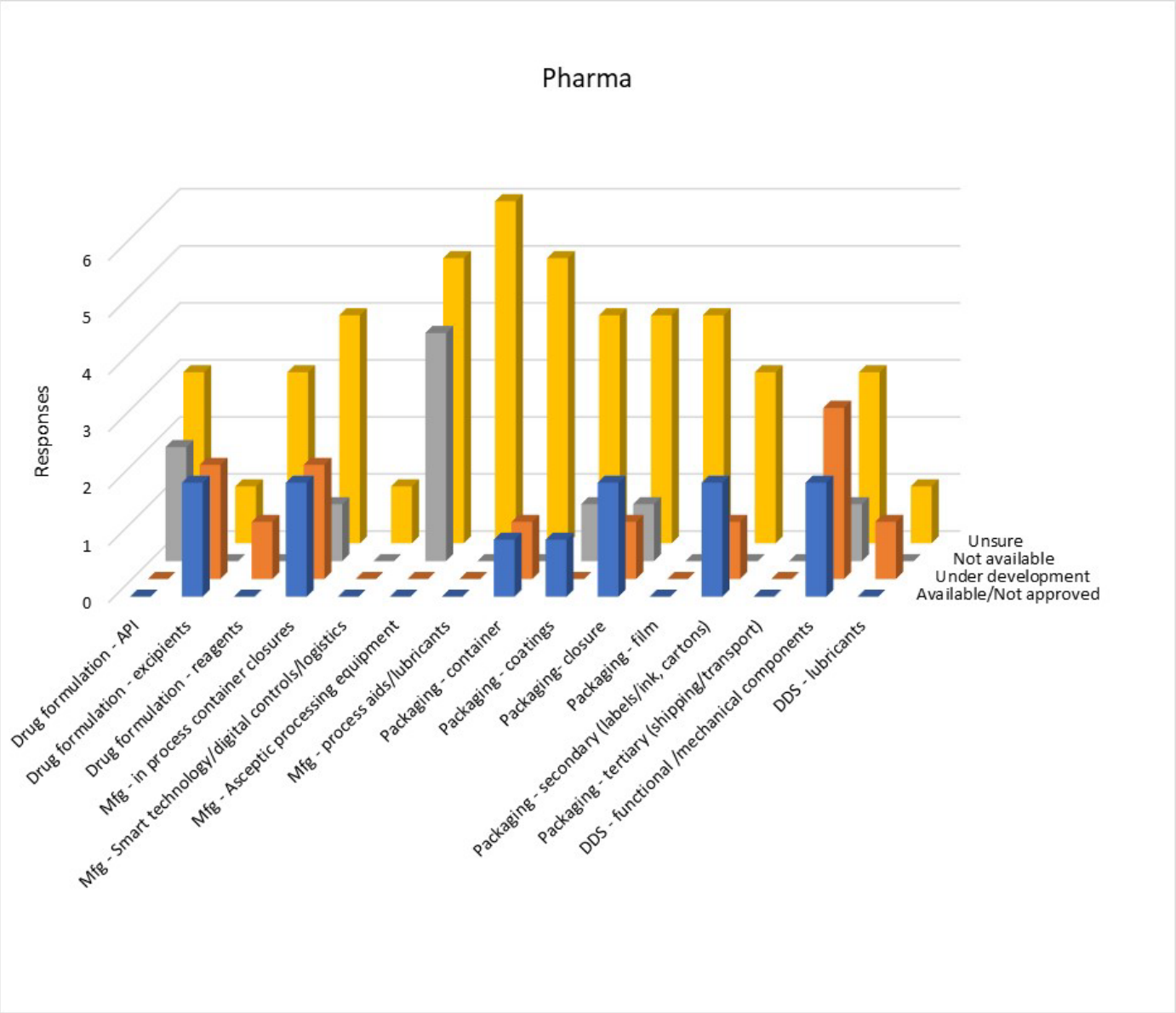

Figure 14 Availability of PFAS alternatives to Pharmaceutical Manufacturers

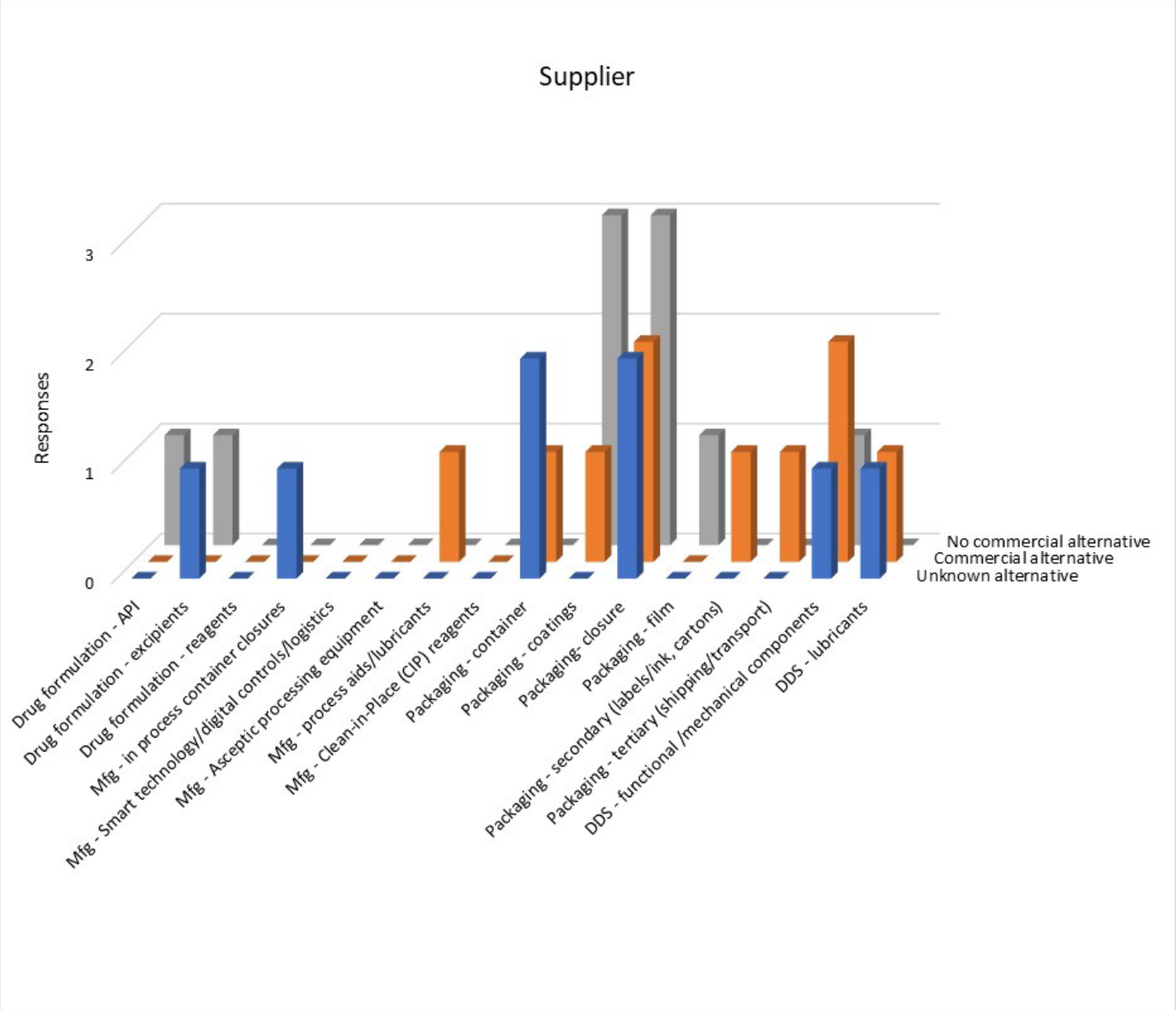

Figure 15 Availability of PFAS alternatives to Suppliers to the Pharmaceutical Sector

It is unlikely that all the potential PFAS changes may be integrated seamlessly in one amendment (all done at once) – multiple changes are likely to be sequential as all the input change aspects may not be available at the same time (as each will take different timelines depending on the change required and the complexity). Also, the impact of each change on the product/process needs to be understood and if there is a product/process where several aspects are changed, locating the cause/reason for an unexpected result is essential to enable this to be resolved. It may be possible to explore several changes in parallel, but attempting to change too many variables without understanding the impact of each could cause a program to fail.

Should materials become unavailable, there will be a need to prioritize the changing of products; as in the pharmaceutical industry and supply chain, each item is unique, and it is not possible to transfer the change from one product to another without undertaking studies on each specific product/item. The interactions with different products and formulations are not the same – the solution for one will not necessarily transfer to

another (it is not a 'drop in' replacement). Each needs to go through a rigorous change process to confirm whether the replacement is viable. Additionally, the resources required to update the items cannot be underestimated. The existing medicines and devices have been developed and approved over decades – effecting a change on many at the same time (due to PFAS restrictions) will overwhelm available capacity for development – expertise is required to develop and change materials and products. Taking the example from the IPAC/IPAC-RS submission to ECHA, the attachment 'IPAC Timeline Regulatory Milestone' indicates 6 years just to affect the transition to a new propellant for a single pressurized metered dose inhaler (pMDI) [32]. Even though there is a derogation permitted for the coated canisters utilized within pMDIs, there is not necessarily a replacement available – the coating provides several benefits to the system; reducing the likelihood for adhesion of the formulation with the canister; protecting the container from being affected by the formulation; protecting the formulation from degradation. These properties are conferred by the materials (which are fluoropolymers) which enable them to fulfill all the requirements.

There will be some areas where alternatives are possible, and some of these may already be under development. For example, the use of non-fluorinated polymerization agents in fluoropolymers has been cited as an alternative for materials used in the Pharmaceutical Sector [38]. However, in most cases, it is not currently possible to match the properties and quality requirements for intended use to be suitable with every drug product. Alternatives must be proven safe and effective for patients, qualified for use in materials and/or validated for use in processes to support regulatory approval. This can result in a long timeframe before alternatives can be incorporated into medicinal products that are approved for patient use. While several patents on PFAS alternatives exist, it is not clear if there are sufficient inventories or commercialized products available.

The interdependencies and complexity of the supply chain of the pharmaceutical supply should not be underestimated. There are numerous instances of PFAS usage at every level of the pharmaceutical lifecycle; any change will trigger a change control and may require EMA approval. There is potential for multiple PFAS materials to change at the same time and decommission the production of critical medicines and create an overwhelming regulatory burden leading to consequences for patients requiring treatments. Taking a closer look at the pharmaceutical supply chain (see Figure 16) clearly indicates that elimination of one PFAS compound used upstream could completely eliminate the availability of a medicinal product. The survey revealed that there may be PFAS compounds several levels upstream in the supply chain. The lack of starting materials could bring about an inability to innovate the development of new medicines to treat and even cure diseases. Consideration should be given to the benefit of developing new medicinal products to treat disease versus the risk of allowing starting materials, some of which may be low environmental risk and needed at low volumes, to continue to be manufactured.

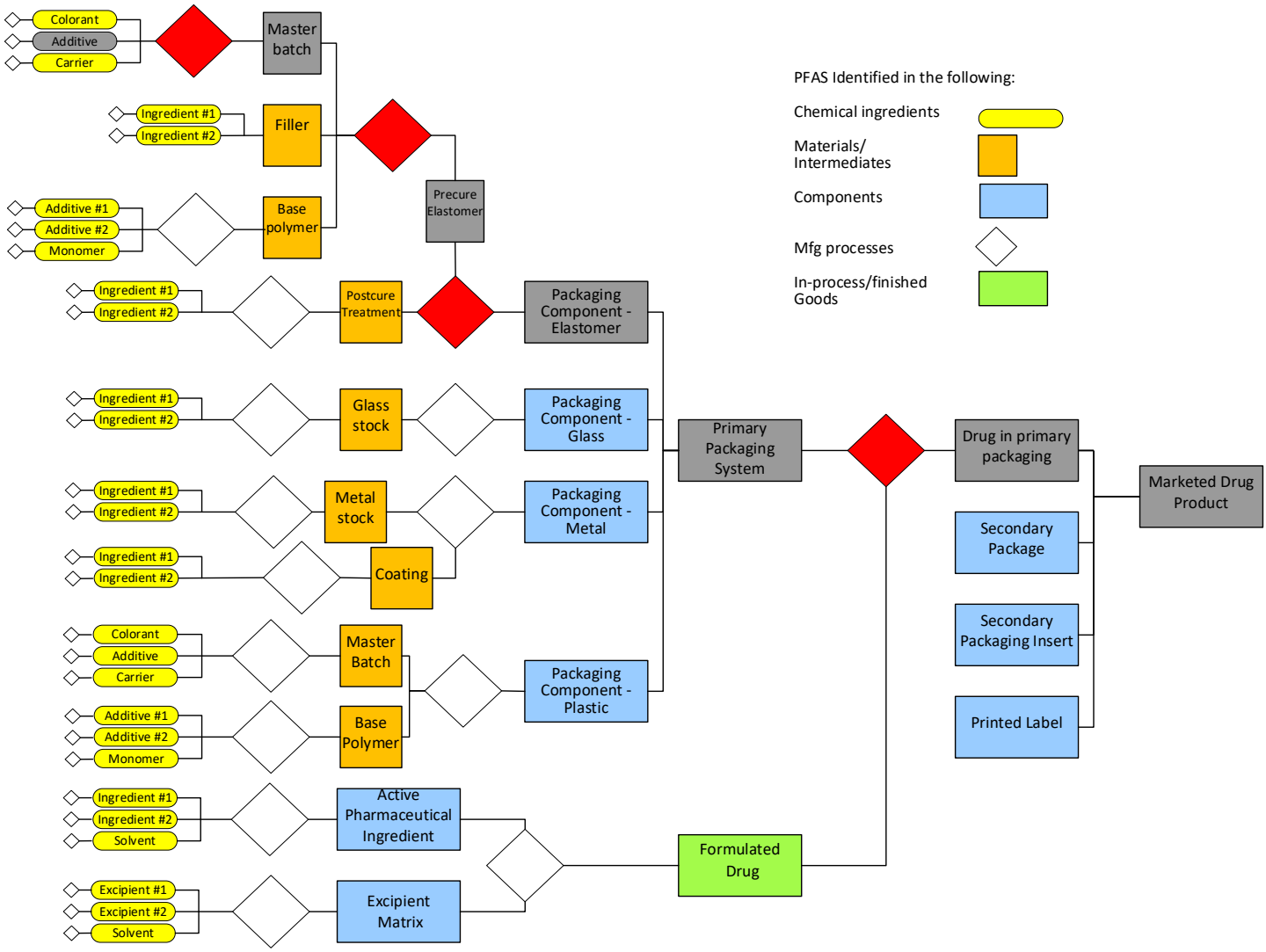

Figure 16 Pharmaceutical supply chain for medicinal product in a packaged container closure (Note: grey boxes indicate items unavailable; red diamonds indicate processes impacted)

Request #6 Summary Missing Uses Alternatives and substitution considerations

The PFAS uses in the Pharmaceutical Sector are prevalent and not captured in the Annex XV restriction report Table 2 [1]. Distinguishing factors for pharmaceutical usage include strict requirements for treatment of disease and chronic illnesses, proven materials, and manufacturing processes for each medicinal product, conducting early to late phase clinical studies and meeting EMA requirements for approval and post-approval changes. The consequences for not considering the impact of a PFAS ban on the pharmaceutical supply chain could lead to shortages of medicinal products to treat diseases. PFAS alternatives either currently do not exist commercially or it is unknown whether there are substitutes with the required properties that are safe to use and safe for the environment.

Request #7 Potential derogations marked for reconsideration-Analysis of alternatives and socio-economic analysis.

Evidence for underlying assessment of PFAS in the Pharmaceutical Sector is absent. The pharmaceutical supply chain encompasses a broad range of PFAS usages with significant reliance on other sectors to ensure patient

accessibility to life-saving medicines (Illustrated in Figure 9). The derogations outlined in the Annex XV restriction report ([1] restriction option #2, paragraphs 1,2,5,6 and 7) have not been considered in the context of the Pharmaceutical Sector. The potential derogations marked for reconsideration after report consultation are relevant to the Pharmaceutical Sector as well. The feasibility and practicality of proposed limits and test methods for medicinal products have not been considered.

There are gaps in understanding PFAS identity and usage across the pharmaceutical supply chain, totality of emissions, or fate in the environment. The time limited derogations of 6.5 years and 13.5 years (1.5 years transition plus 5 years or 12 years) after EiF is not practical for replacement (if an alternative exists) within the Pharmaceutical Sector.

Pharmaceutical manufacturers have already received notifications of materials containing PFAS, and the number of responses varied depending on the type of material (see Figure 17). When queried about the time it would take to substitute an alternative both pharmaceutical manufacturers and suppliers indicated that several years would be required to identify alternatives, incorporate them into the design, build up inventory and commercialize the product.

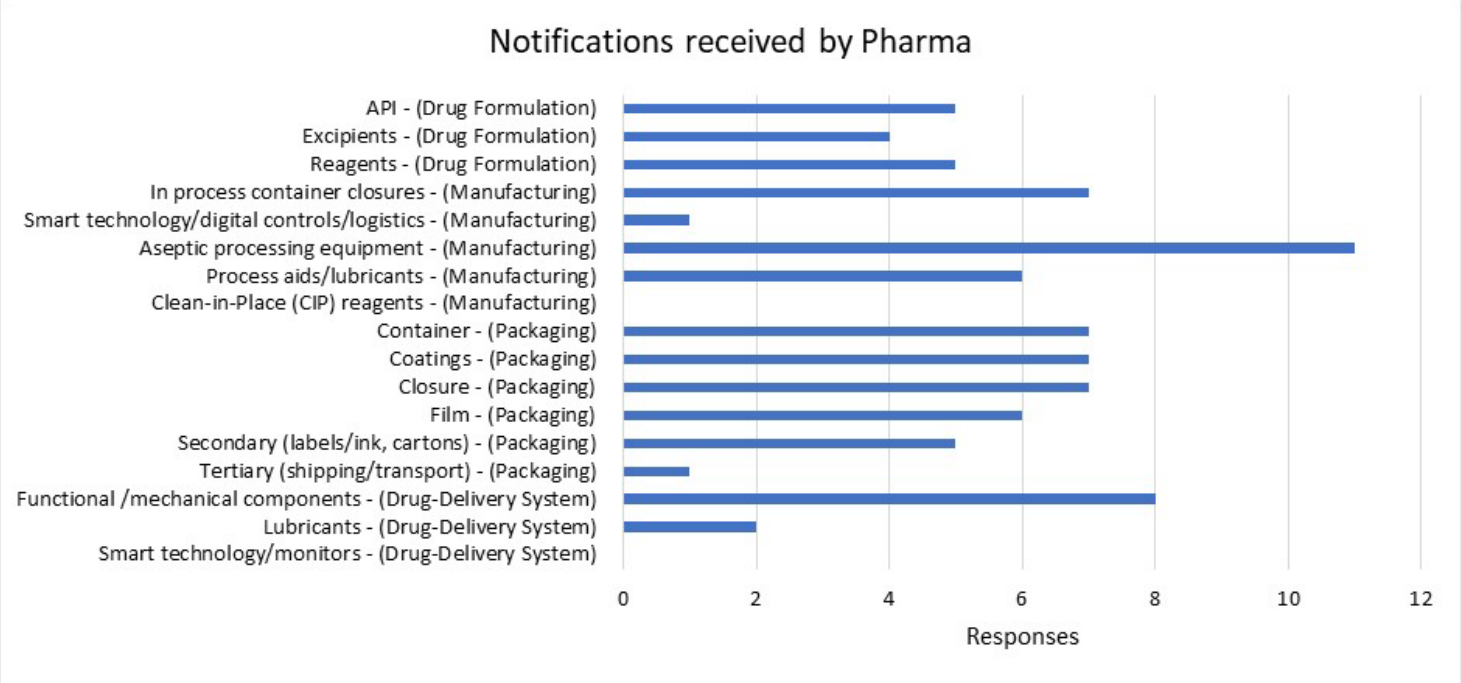

Figure 17 Supplier notifications received by Pharmaceutical Manufacturers

To implement a PFAS alternative that involves at least one supplier, the supplier will need to develop the material/component for the intended purpose first, assuming an alternative exists. The supplier would need to identify the alternative and incorporate it into the design, verify it for use and build-up commercial inventory. The pharma implementation can start at the point the solution is available to them; in some cases, the supplier may commercialize and start to build inventory in parallel with the medicinal product development. Alternatively, the commercially available alternative may be evaluated by the pharmaceutical manufacturer and, if found acceptable, it could be verified and used to build up commercial supply of a medicinal product.

From the PQRI survey it was found that at least 1-3 years, and more often 5-10 years, would be required to incorporate an alternative into the design, build inventory and commercialize the supplied material or medicinal product. Based on pharmaceutical manufacturer and supplier responses, the cumulative effect of these times to implement a PFAS alternative was estimated to be a combined total of 20- 60 years as shown in Figure 18. The length of time for implementation is longer than the timeline reflected in Figure 1 for a new product because it is assumed that materials are already available. Therefore, the timelines to generate products using alternatives (if one is available with the required properties) are much longer than the cumulative 6.5 or 13.5 years that the time-limited derogations would allow. Exemptions for PFAS used in the Pharmaceutical Sector and its supply chain are requested with unlimited derogation due to the socioeconomic need for medicines (both existing and future).

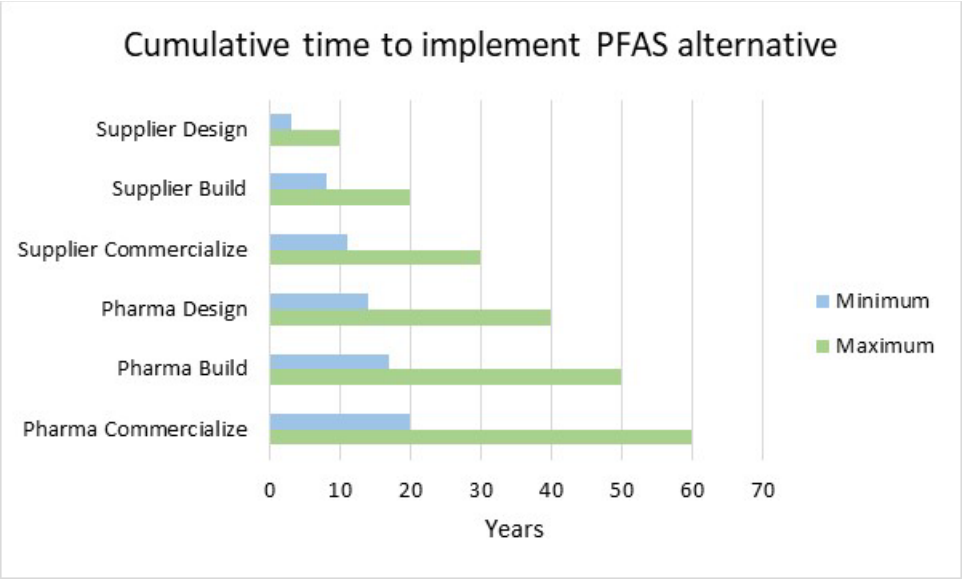

Figure 18 Time to implement PFAS alternative.

Request #7 Summary – Potential derogations marked for reconsideration current derogations not feasible.

A current derogation for the Pharmaceutical Sector does not exist but there are derogations afforded to pharmaceutical upstream and downstream suppliers. It is essential to have PFAS available for the pharmaceutical synthesis, formulation, manufacturing, packaging, storage, shipment, and delivery of medicine to patients. The opportunities for EiF at 6.5 years and 13.5 years are not adequate to identify and address all the PFAS used throughout the pharmaceutical supply chain. This timeframe is not sufficient for the identification and implementation of alternatives for most PFAS uses. Replacement of PFAS used, either directly or indirectly, for the production of all medicines in development is not pragmatic due to unique applications. A complete replacement requirement would also shut down the production of marketed products. The numbers of affected medicines and patients are staggering (see Figure 20). The proposed PFAS targets, methods and limits for the environment do not directly correlate to the Pharmaceutical Sector usage, production, waste, or emissions. Time is necessary to understand the usage in this sector and the societal effects, including the impact on the environment and innovation of new technologies to combat PFAS pollution.

Request #8 Other identified uses – Analysis of alternatives and socio-economic analysis

Although the proposed restriction options RO1 and RO2 are deemed proportionate to the risk, this assessment was done without consideration of the unintended consequences to the Pharmaceutical Sector. As it currently stands, there are no cures for chronic diseases such as respiratory and diabetes among others that could result in death in Europe. As demonstrated from the survey results in Figure 5 through Figure 7, the entire supply chain for all drug types is dependent at some level on various PFAS. The proposed restriction is focused on new products being placed on the EU market and this will directly affect the medicinal products currently in development, which are many. As indicated by the survey results in Figure 19, more than half of the total number of products represented in the survey are in development. This is consistent with data obtained separately from PharmaCircle [39] that shows (see Figure 20) that, for most product types, there are many more products in development than the number of marketed products. According to PharmaCircle the top six indications that are currently targeted for pharmaceutical development programs include cancer, infections, neurological disorders of the central nervous system, inflammation/immune conditions, endocrine/metabolic diseases, and cardiovascular disease (see Figure 21). Some of these indications were also identified as leading causes of death in Europe by the recent OECD report [40].

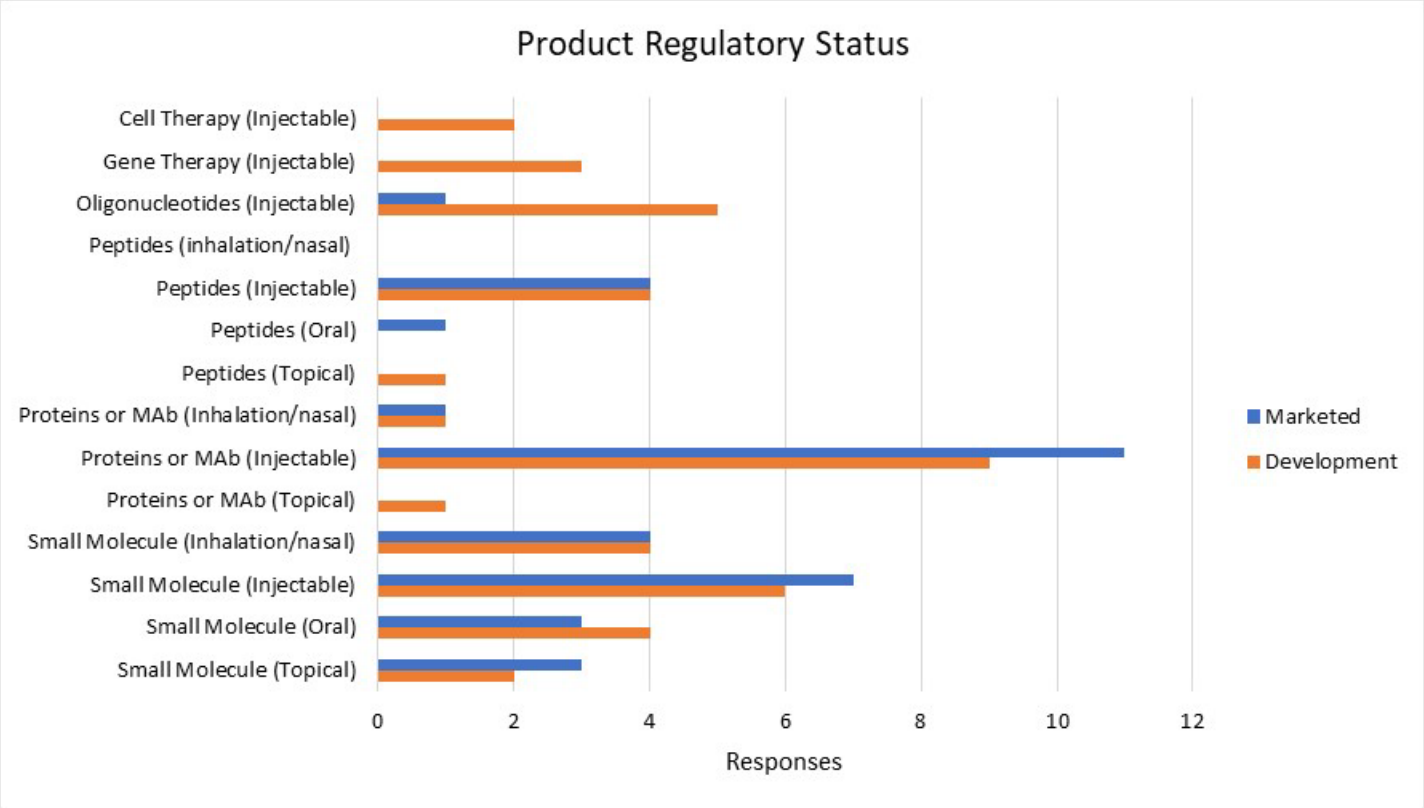

Figure 19 PQRI Survey responses indicating regulatory status of product types

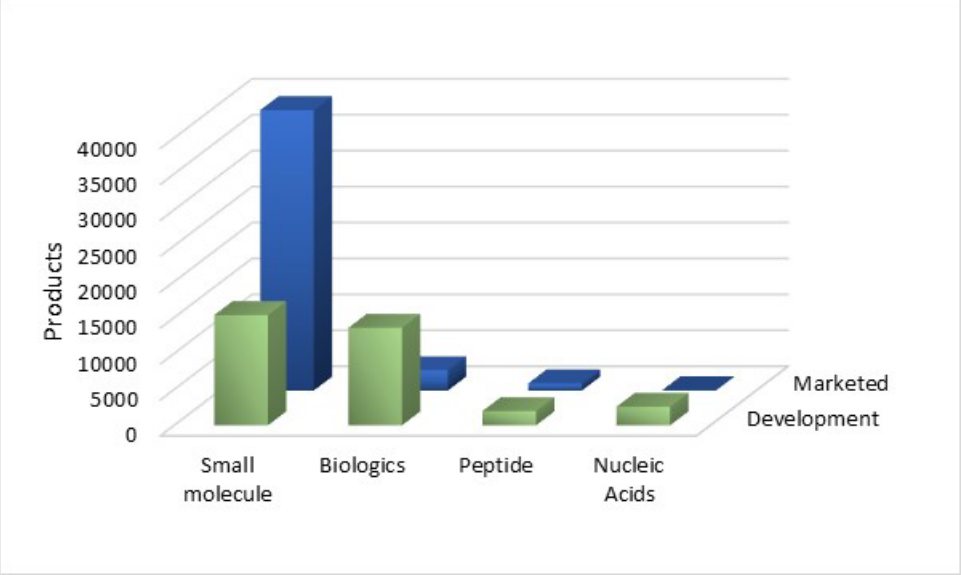

Figure 20 PharmaCircle information on regulatory status by product type

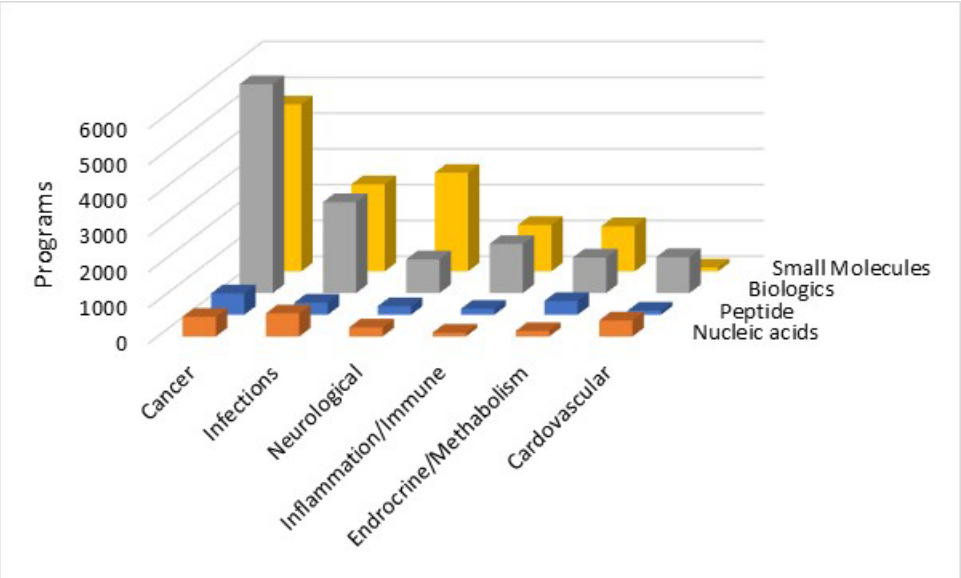

Figure 21 PharmaCircle Top Six Indications by Molecule in Development

The PQRI survey further queried actions respondents might take if the PFAS used in their products were to be banned in the EU. From the supplier perspective (see Figure 22) it is quite likely that there would be discontinuation, or at least modification, of their products that support drug formulation, manufacturing, packaging, and delivery. The level of uncertainty regarding what action might be taken was lower for the supplier than the pharmaceutical manufacturers. From the pharmaceutical manufacturer's perspective (see Figure 23), across all product types, there were several responses indicating discontinuation, modification, and uncertainty. With regard to PFAS use in pharmaceutical manufacturing materials or components (see Figure 24), across all product types, there were fewer responses that indicated the discontinuation of the product, except for small molecules. In addition to a fair amount of uncertainty, there were indications that the manufacturing process might be changed or moved outside Europe. That same level of uncertainty was reflected regarding action that might be taken if a PFAS ban were enacted that impacted storage facilities, equipment, or processes. The primary responses indicated that the products would be discontinued, or the

storage facility would be modified (see Figure 25). From the supplier and pharmaceutical manufacturer responses, it was clear that there is a realistic possibility that several products would be discontinued in the EU market.

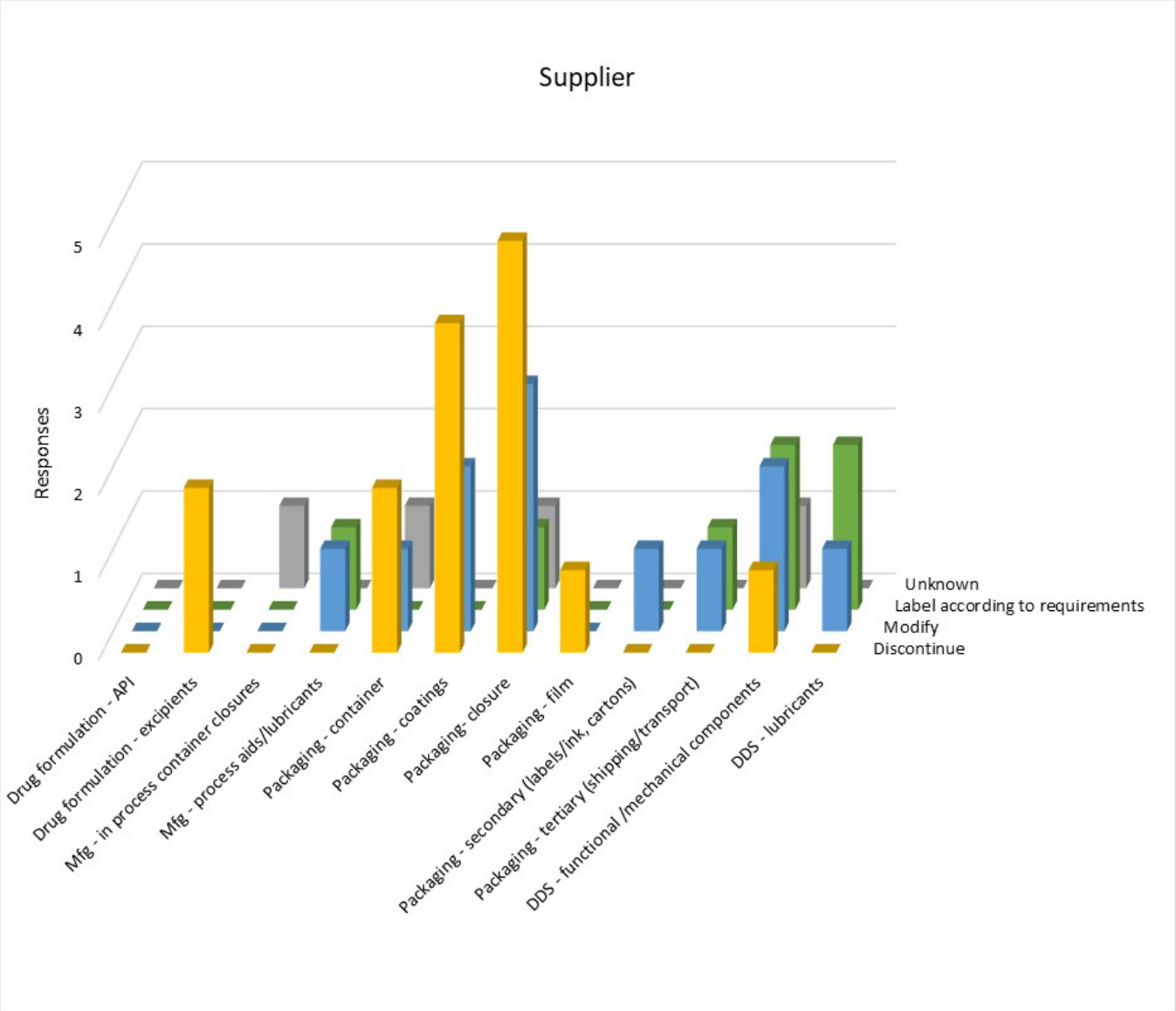

Figure 22 Action to be taken on Supplies to Pharmaceutical Sector in case of PFAS ban.

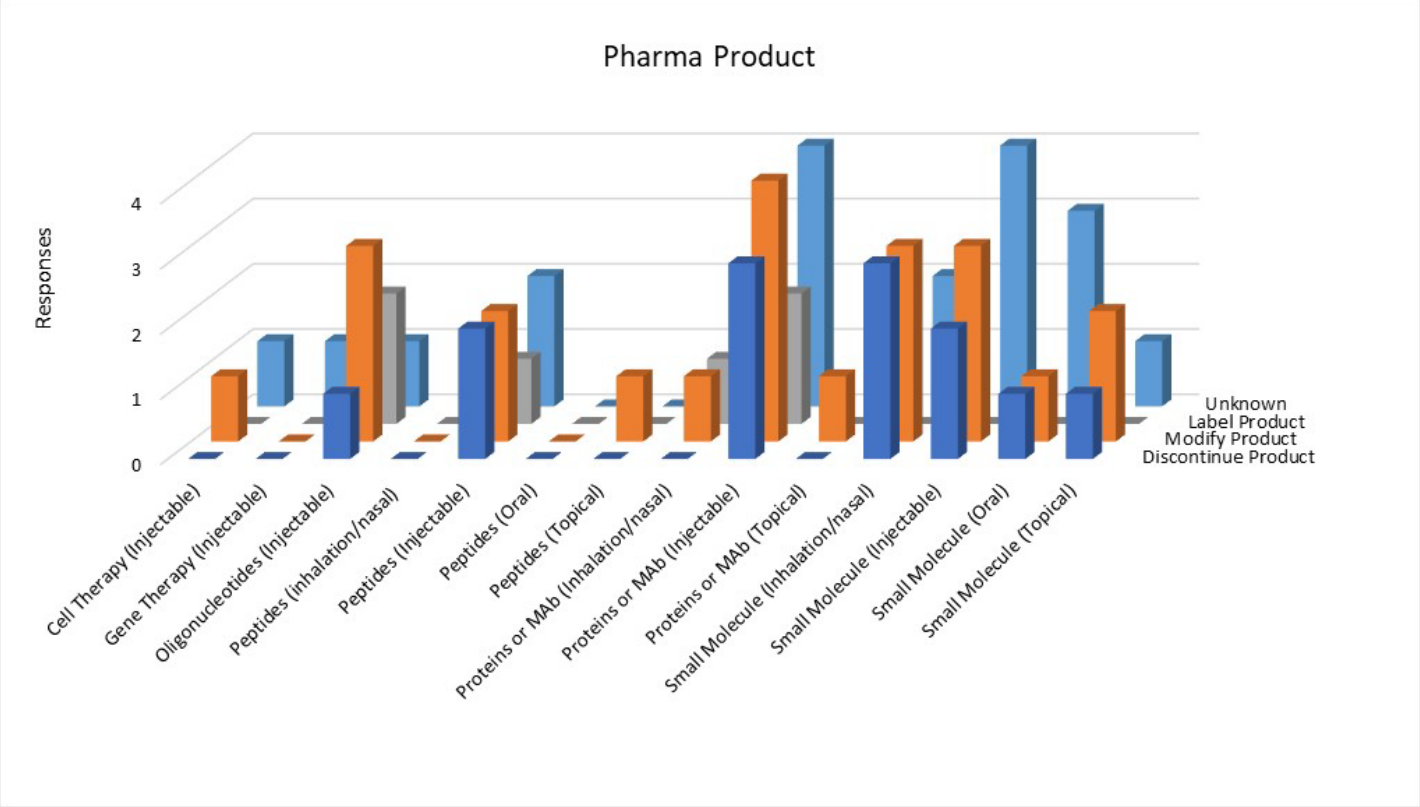

Figure 23 Action to be taken on Medicinal Products in case of PFAS ban

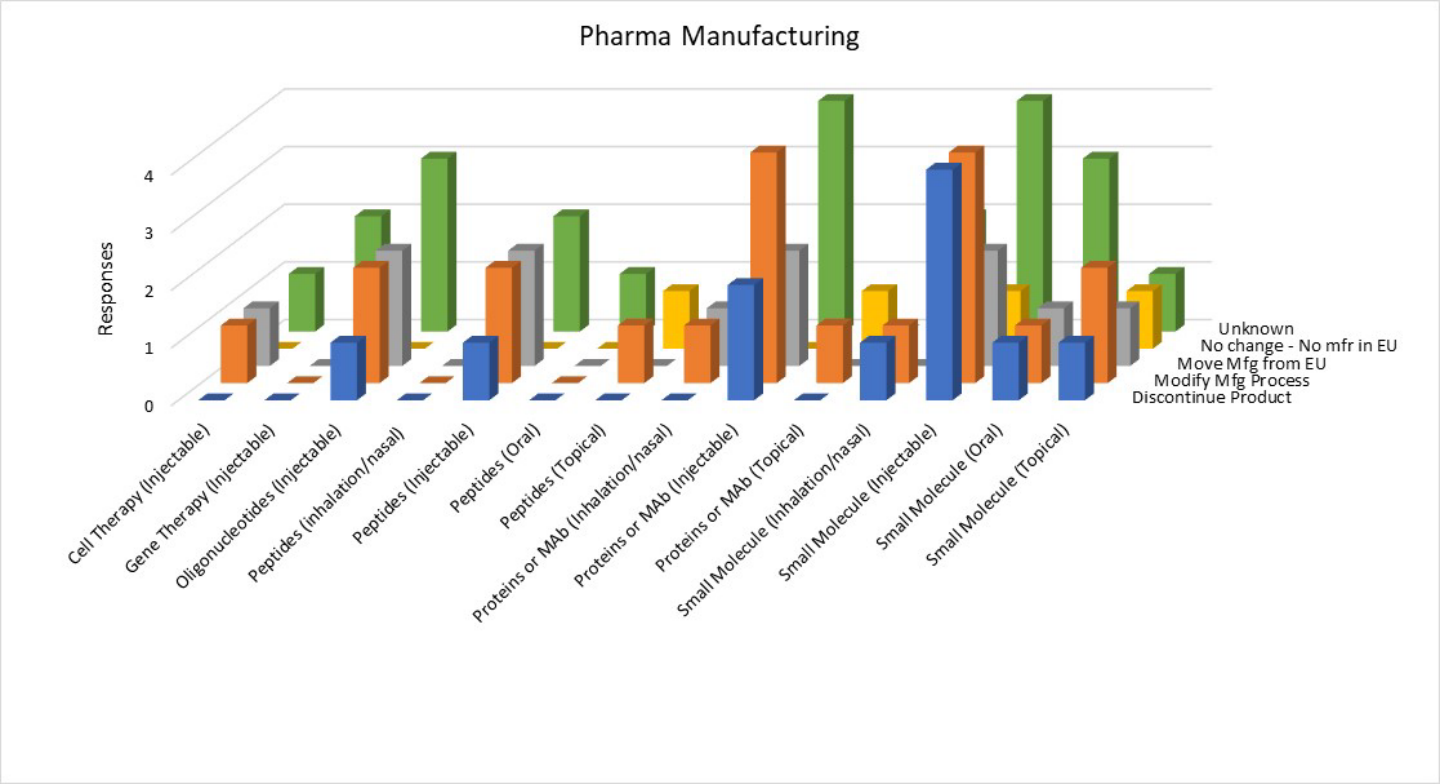

Figure 24 Action to be taken on Medicinal Product Manufacturing in case of PFAS ban.

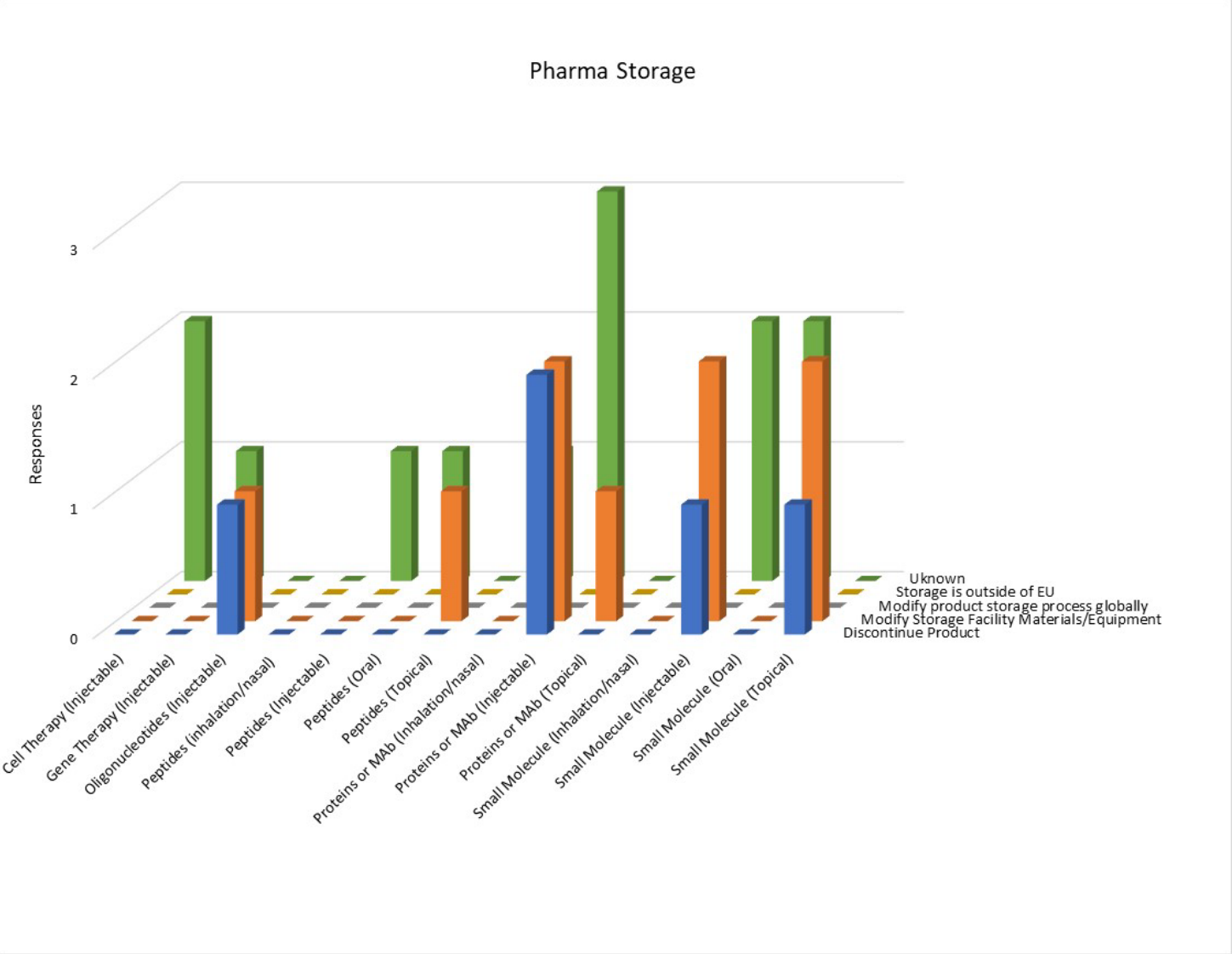

Figure 25 Action to be taken on Medicinal Product Storage in case of PFAS ban.

The disruption of the medicinal products supply highlighted in the PQRI survey suggests that products will be discontinued/withdrawn from the EU market and that products may be modified. There are scenarios possible where the product will be withdrawn and not replaced. Products may also be discontinued at the point of the ban before replacement products are developed, as the timelines for developing new products (see Figure 1) are longer than the timelines for the proposed ban/withdrawal of PFAS materials from the market (18 months to 13.5 years). In fact, when queried on the topic of implementation time for a PFAS-free alternative, pharmaceutical manufacturers' primary response across the majority of products was "unsure," emphasizing this uncertainty (see Figure 26).

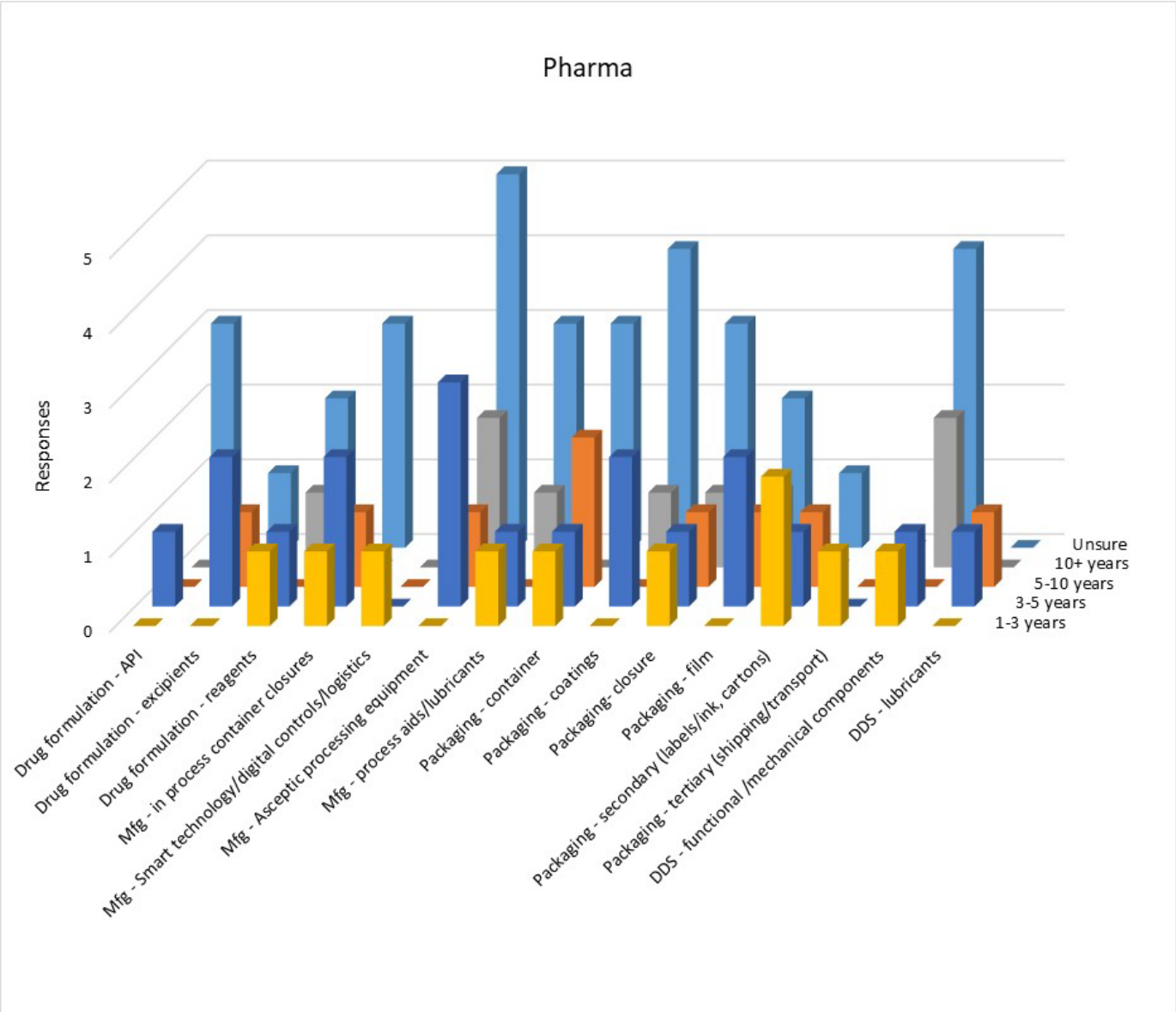

Figure 26 Time to implement PFAS-free Medicinal Product

To better understand the impact of a PFAS ban on patients suffering from life-threatening diseases the results from the PQRI survey were plotted alongside the PharmaCircle and OECD information. As shown in Figure 27, most of the life-threatening diseases were represented in the PQRI survey. The relative levels of responses from the PQRI survey are generally consistent with the relative numbers of programs identified in the PharmaCircle data for each disease area. Therefore, since the proposed restriction on PFAS has been demonstrated to impact all the drug product types used to treat these life-threatening diseases, it is possible that lifesaving medicines that are currently in development or placed on the market would not be able to be manufactured if the proposed restriction were to come into force. If the medicinal products are not available patients may suffer adverse effects from disease progression and even death.

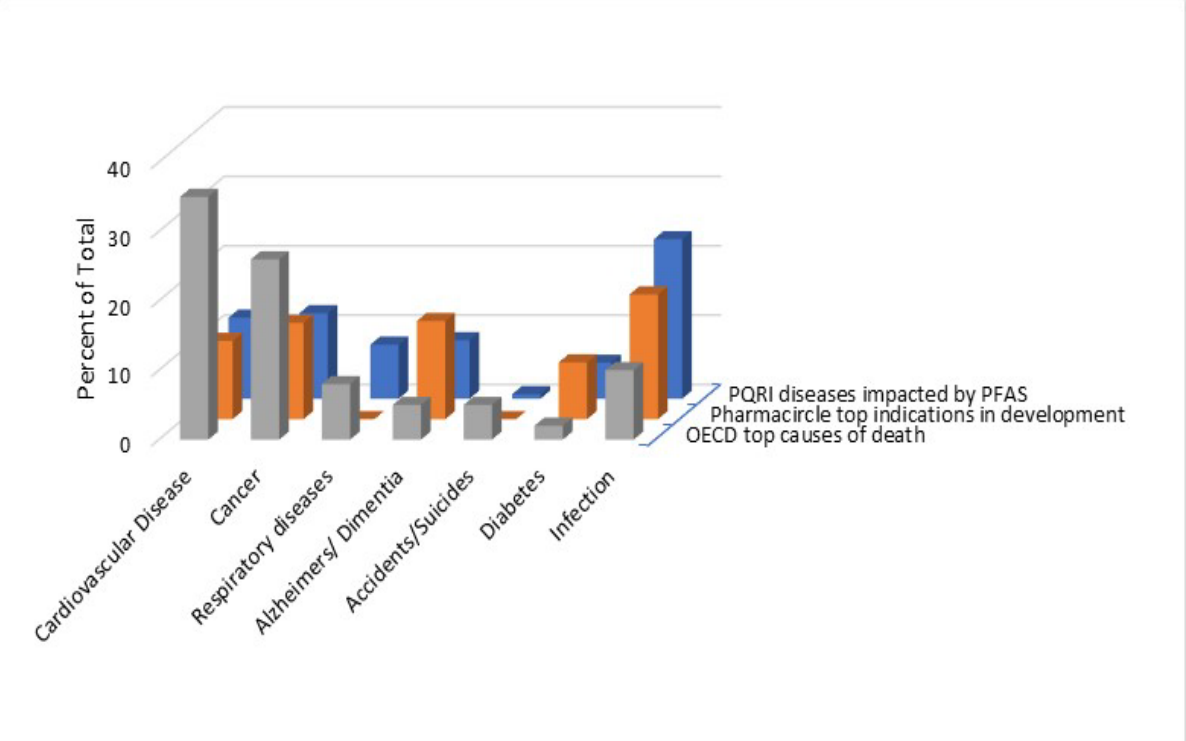

Figure 27 Impact of proposed PFAS restriction on treatment of life-threatening diseases

Request #8 Summary – Other identified uses Societal Cost of Ban for Pharma

The practical application of the results of the PQRI survey has shown that a restriction of PFAS in the Pharmaceutical Sector will likely result in the discontinuation of marketed life-saving medicinal products and the lack of ability to manufacture new life-saving medicinal products that are currently in development in Europe. In a similar way, the impact of the proposed PFAS restriction may result in a lack of maintenance medicinal products that are used to treat prevalent chronic diseases such as respiratory and diabetes (6% and 7% of the EU population respectively, [40]). Considering just these two diseases alone and the current population [41], over 96 million patients could be affected in the European Union.

Request #9 – Degradation potential of specific PFAS sub-groups

Topic not addressed in this paper.

Request #10 – Analytical methods

Topic not addressed in this paper.

Closing Remarks: Bringing back points to consider and patient impact.

The core concern for PFAS in the environment is their potential to have persistent, mobile, and toxic (PMT) properties. We acknowledge that this is part of a larger initiative that was implemented in 2020. The European Commission Chemicals Strategy for Sustainability (CSS) is intended to increase innovation for safe and sustainable chemicals while protecting the environment and human health [42]. This strategy incorporates the establishment of the chemical environmental footprint to enable the identification of hazardous substances in the environment and the risk of exposure to biota and humans. This includes the phase-out of chemicals (e.g., PFAS) unless their usage is essential. Pharmaceutical companies share the CSS's goals and are committed to the health and well-being of patients [11]. PQRI has taken this opportunity to provide qualitative data with

supplemental literature references to ECHA to explain the essential usage of PFAS across the pharmaceutical supply chain, the potential for alternatives and risks to the supply of critical medicines in the EU.

Historically, there have been other initiatives to ban specific types of fluorinated molecules based on scientific data. Since the 1950s, PFOS and PFOA have been widely used and subsequently found in the environment based on thorough investigations. In early 2000, the production of PFOS was phased out and at the end of 2015, PFOA was eliminated. Since the signing of the Montreal Protocol in 1987, the Pharmaceutical Sector has worked to reduce or eliminate certain types of fluorinated molecules used as propellants in MDIs for the sake of the environment [1]. Recently, other long chain PFAS and related substances have been restricted under REACH. Shorter chain PFAS have been substituted for the long chain PFAS over time and now these have also been detected in the environment.

The entire group of 10,000 PFAS chemicals, as defined by ECHA, are suspected (but not proven) PMT and proposed to be banned. This definition of PFAS presents an unprecedented challenge for the methodical identification of sources and PMT characterization for thousands of unique medicines in the EU. Although the PFAS ban is aimed at new entities, each marketed product will need some degree of requalification and approval for any and all changes that might result. In terms of patient safety and efficacy, a broad PFAS grouping structure is not appropriate for risk management and will inevitably add to medicinal product shortages.

The complexity and interdependency of the pharmaceutical supply chain is substantial. The essential properties and multiple applications of PFAS are currently irreplaceable. There are several obstacles to overcome across the pharmaceutical supply chain to achieve timely replacement of PFAS, including identification of targets and all sources to be assessed in order to create a reliable footprint for usage and emissions. This will allow companies to build a PFAS action plan to make science- and risk-based decisions. Taking a systematic approach will avoid disruption of the pharmaceutical supply chain and ensure the accessibility of safe and effective medicines in the EU. We can conclude we share a common goal of protecting the environment and human health. Our aim is to provide sufficient information on risks to the production of medicines and the essential usage of PFAS in the Pharmaceutical Sector. On behalf of PQRI, we request consideration of the pharmaceutical supply chain to inform restriction decisions based on the following considerations:

1. Include a Pharmaceutical Sector and their PFAS missing uses/sub-uses in addition to the other 14 sectors identified in the Annex XV restriction report.
2. Group PFAS to enable safety risk assessments as appropriate for the environment (emissions, biota, workers, and consumers) and include safety risk assessments that are suitable for patient populations.
3. Invest time to understand types of PFAS, emissions, and environmental contributions from the Pharmaceutical Sector to enable justifications for derogations.
4. Reconsider time-unlimited derogation for those PFAS used in the pharmaceutical supply chain and availability of continued PFAS supply from upstream and downstream supplier inventories.

Respectfully Submitted,

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Chair, Board of Directors, PQRI

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