BioPhorum Response to the Annex XV report on the proposal for universal restrictions (Part II)

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Opening Statement:

The Biopharmaceutical (BioPharma) industry, represented here by BioPhorum, acknowledge the concerns raised regarding the potential adverse effects of various Per- and polyfluoroalkyl substances (PFAS) materials on human health and the environment, and fully support efforts to minimise and mitigate the presence of these, and other potential substances of concern in our manufacturing processes and products. Our industry sector shares a responsibility to work with all relevant stakeholders to manage the transition away from materials of concern while maintaining our ability to ensure the safety and wellbeing of patients and the communities in which we operate. Any efforts to restrict usage and production of materials of concern by our industry must be pragmatically considered; the risk of drug shortages and therefore failure to supply medicines to patients must be evaluated against the risk the materials pose to the environment and that very same population.

BioPhorum are a global biopharmaceutical manufacturing industry collaboration comprising all major manufacturers and their key suppliers (over 150+ companies, representing > 98% of all biopharmaceuticals manufactured worldwide); the 30 members of BioPhorum who participated in this collaboration included, but was not limited to:

AGC Biologics, Bayer, Cobetter, Janssen, Lonza, NewAge Industries Inc., Pfizer, Qosina, Roche, Sartorius Stedim Biotech GmbH, Takeda, UCB, Watson Marlow Fluid Technology Solutions.

While the Annex XV report includes consideration of the use of various PFAS in medical devices and some limited pharmaceutical applications, the BioPharma industry has not been specifically considered as a sector in the framework of the current proposal (refer to Table A.1 from the Annex XV report) and needs to be appropriately evaluated due to the considerable impact the proposal will have on our ability to supply safe and effective therapies to patients suffering from life threatening/debilitating illnesses.

Table A.1. Overview of PFAS applications and the level at which they were researched.

PFAS applications			
PFAS manufacture	Textile, upholstery, leather, apparel and carpets (TULAC)	Food contact materials and packaging	Metal plating and manufacture of metal products
Consumer mixtures	Cosmetics	Ski wax	Applications of fluorinated gases
Medical devices	Transport	Electronics and semiconductors	Energy sector
Construction products	Lubricants	Petroleum and mining	Waste stage PFAS applications
Laboratory equipment & filtration	Plant protection products and biocides	Chemical industry	Firefighting foam
Medicinal products	Plastics (other than packaging) and rubber/elastomer production (including flame retardants)	Pyrotechnics	Personal care products other than cosmetics
Fracking (currently hardly applicable in EEA)	Immersion cooling (currently hardly applicable in EEA)	Defence industry	Printing inks
Cement industry	Professional cleaning and polishing	Other niche applications	Uses (yet) unknown

- Green uses are researched in detail
- Blue uses are researched in general
- Orange uses not researched in detail
- Purple use: Separate restriction proposal

Biopharmaceuticals (or biologics), a subsector of the pharmaceutical industry, include biological therapies such as monoclonal antibodies, cell and gene therapies, mRNA and vaccines which treat a wide range of disease indications including immunology, neurology, infectious diseases, diabetes, oncology, cardiovascular conditions, and others. Advancements in biomedical science hold vast potential for growth of the Biopharma market and the ability of these drugs to treat chronic diseases that were earlier untreatable is increasing its demand enormously with newer therapies under development increasingly being in the biopharmaceutical category.

Today, 50% of the top 100 drugs sold globally are biopharmaceuticals, with predications that this will increase to 55% of all innovative drug sales by 2027 [1], and the industry generates global annual revenues of USD 163 billion. A significant proportion of that revenue is generated in Europe (**USD 48.19 billion** in 2022[2]) with the European Biopharmaceuticals market estimated to be growing at a CAGR of 8.89% to reach USD 73.78 billion by 2027.

100% of the biopharmaceutical products currently being developed or already licensed for sale in the EU utilise PFAS somewhere in their development, manufacture, testing, storage of intermediates or in their drug delivery systems. If the ban is enforced, all those drugs would be removed from the market until PFAS alternatives could be developed, sourced, validated, and approved for use thus preventing access to life saving therapies.

While the proposed restriction is intended for enforcement in the EU which will directly affect companies who manufacture and sell their products in that region, it will also have significant and wide-reaching impact on the export of drugs manufactured in the EU and supplied to the rest of the world, on global industries supplying materials to drug manufacturing facilities in Europe and to companies who import and sell their products into the European market. It would also limit the ability to develop new drug therapies since PFAS materials are also utilized directly and indirectly in drug discovery & preclinical development. For medicines which are still under patent or are orphan drugs there are no alternative drugs available for use if their production is prevented due to PFAS restrictions.

Significant investment has been made in Europe to build and resource state of the art drug manufacturing facilities; an inability to manufacture product due to unavailability of PFAS materials would result in movement out of the region with potential closure of the facilities and resultant impact on the people, workforces (according to a European Commission report in 2019 the biopharma industry employs 2.4 million people [3] however this does not take in to account all suppliers and their suppliers across the supply chain) and revenues currently generated in the region with irreversible damage to the economy. The restriction on importing or placing on the market of both direct and indirect materials will impact the entire global supply chain and has the potential to shut down BioPharma manufacturing in Europe and the supply of critical drugs to patients within a very short timeframe. In time, this could lead to organizations outsourcing/relocating their manufacturing activities to locations without PFAS restrictions and impede plans for future investment in the EU with significant detrimental socioeconomic impact.

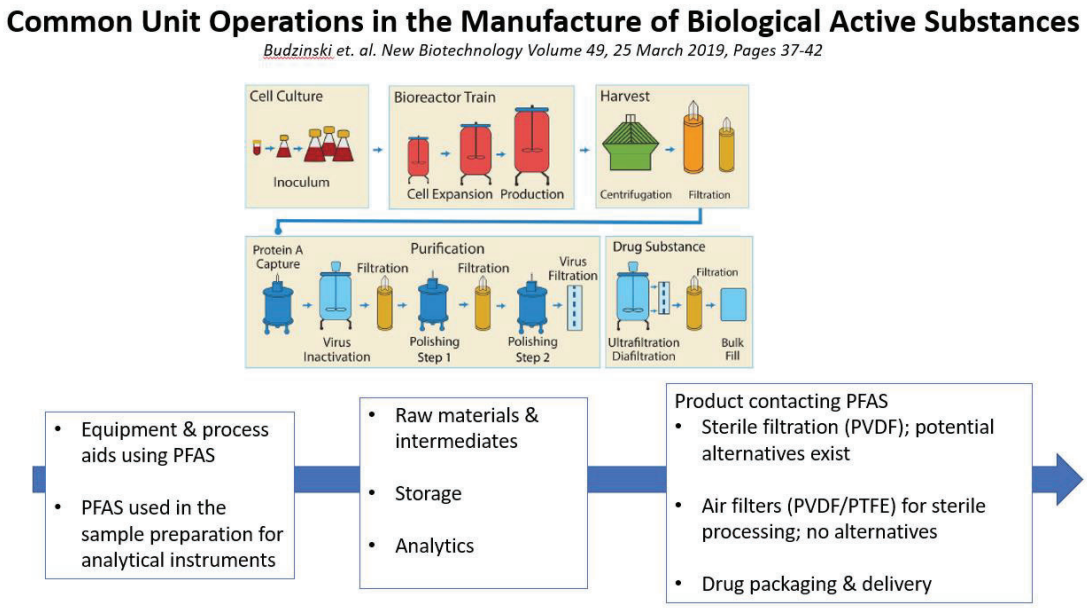
While this specific response is focussed on the BioPharma sector, BioPhorum and its member companies recognise that the scope of PFAS use and resulting impact of the proposed restrictions on other industries is far wider across the Pharmaceutical and Healthcare industries and beyond.

The biopharma industry is required by GMP legislation to use materials that are not reactive or additive to our product streams. Specific PFAS materials (PVDF, PTFE, FKM, FPM, FEP, etc.) have been chosen as they present negligible reactive properties and are particularly low in terms of adding anything to medicinal products either at drug substance or drug product manufacturing processes. It should be noted that the BioPharma Industry acts as downstream

users of PFAS materials and does not own the technical solution outside of end-application qualification.

Within the BioPharma sector there are multiple sub-uses and applications of PFAS materials (mainly fluoropolymers) across the value chain, the majority of which are not included in the restriction report, and which are therefore assumed to be subject to an immediate ban under the current proposal.

These sub uses can be further categorized as:
a) **direct** fluoropolymer materials used in BioPharma processing with critical quality attributes (i.e. with direct impact on drug product quality).
b) **other indirect PFAS** materials used in BioPharma manufacturing processes (including manufacturing precursors/starting materials, intermediates, product testing and engineering & support system components).



This collaboration of suppliers and end users of PFAS materials operating within the BioPharma industry and represented here by BioPhorum, are requesting full exemption (or time unlimited derogations) for:

- fluoropolymer materials used in industry that are required for delivery of safe medicines.
- other low risk, non-polymer PFAS materials used in BioPharma.
- indirect materials used in supply chain, manufacturing, and quality control processes.

A non-exhaustive list of PFAS applications across the BioPharma industry with indication of possible alternatives and an analysis of the complexity and anticipated cost of substitution is included in Appendix 1.

Note: Appendix 1 was prepared in collaboration with BioProcess Solutions Alliance (BPSA).

Further details of PFAS applications in the BioPharma industry are detailed in our response below. It should be noted here that if the BioPharma industry *is* granted an exemption from the restrictions and is permitted to utilise fluoropolymers/PFAS materials where no alternatives exist, there still remains a very serious concern that restrictions or removal of PFAS materials

from the wider market will reduce or remove the availability of PFAS materials for BioPharma applications, resulting in a significant risk of disruption to the supply of critical medicines.

When evaluating the impact of the proposed ban on the BioPharma industry 4 core categories of change are important to consider:

1. Where no suitable alternative is available
2. Where alternatives are available but are not suitable/fit for purpose in every application
3. Where alternatives are available and fit for purpose but there is no stable, reliable supply chain
4. Where alternatives are available and fit for purpose, but regulatory approvals will be delayed due to overload of the regulatory bodies who must evaluate and approve (or reject) every submitted change

Below is our collaboration's response to the request from ECHA for more information on Missing uses – Analysis of alternatives and socio-economic analysis (Q6):

a. *The annual tonnage and emissions (at sub-sector level) and type of PFAS associated with the relevant use.*

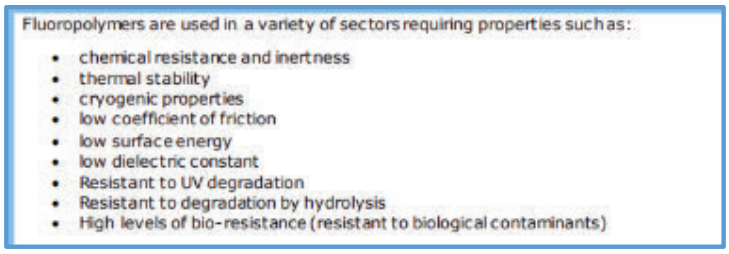
With a multi-tier, complex supply chain that is nearly impossible to evaluate and quantify, any number we could suggest would be an estimate.

PFAS usage by the biopharma industry and subsequently their suppliers make a miniscule contribution to the total annual usage and emissions from other industries (around 45 million tonnes of PFAS is supplied to the EU market annually with a global figure likely to be at least 3 times this), the impact of a ban on our industry is disproportionate to the risk and would be very detrimental to the patient population as well as the European BioPharma manufacturers and suppliers.

Sector-based estimates, shared by the BioProcess Systems Alliance (BPSA), indicate that the single-use biotech/biopharma industry accounts for approximately 0.1% of PTFE production and 0.5% of PVDF production.

b. *The key functionalities provided by PFAS for the relevant use.*

PFAS materials have been selected for use in the BioPharma industry for their core properties, some of which are listed in Annex A of the restriction report (refer to the below table copied from the report): inertness, chemical resistance, oleo- and hydro-phobicity, cleanliness, lack of chemical interaction with drug products, lubricant, and heat resistance/cryogenic properties etc.


Fluoropolymers are used in a variety of sectors requiring properties such as:

- chemical resistance and inertness
- thermal stability
- cryogenic properties
- low coefficient of friction
- low surface energy
- low dielectric constant
- Resistant to UV degradation
- Resistant to degradation by hydrolysis
- High levels of bio-resistance (resistant to biological contaminants)

All these unique properties of PFAS provide key functionality in assuring integrity of drug product quality in the multiple applications they are used in across the end-to-end manufacture and supply of drugs. This includes ensuring quality of production

processes, assurance of sterility and stability throughout product shelf life, axenicity and safe delivery/dosage to the patient.

c. The number of companies in the sector estimated to be affected by the restriction.

100% of the approximately 830 BioPharma manufacturers in Europe, their global suppliers (and in turn their intermediate material suppliers) including 3rd party testing and validation service providers would be impacted across the complex and multi-tiered supply chain. This supply chain has yet to fully recover from the pandemic shortages.

Additionally, where alternatives to PFAS are available, any changes to drugs manufactured in Europe which are filed and distributed in Europe and/or in regions beyond must be submitted for approval to the European Medicines Agency and other global regulatory authorities; this is required to maintain license to operate and market authorisation. The volume of changes requiring review and approval resulting from the proposed restrictions will out-pace capacity of the authorities and put the supply of critical therapies at risk with drug stock-out situations becoming a reality.

The exact number of companies impacted is extremely difficult to quantify due to the complexity of the supply chain however there are at least 830 BioPharma companies with facilities in Europe alone. Every biologic drug currently licensed for sale in Europe and those in development but not yet licensed will be manufactured and packaged using PFAS materials somewhere in the process and will be impacted by these restrictions.

If drug manufacturing is moved out of the region to other geographies which do permit the use of PFAS, availability of these drugs may be impacted; an example of this is the current challenge in accessing some antibiotics in certain member states of the EU due to sourcing outside of the region. Movement to other less well-regulated regions where raw material quality is lower and regulatory compliance is less regulated may also impact drug quality resulting in a risk to patients. Any such external manufacturing locations will still require significant time to secure the appropriate licensing (as indicated for the case where alternatives exist).

d. The availability, technical and economic feasibility, hazards, and risks of alternates for the relevant use, including information on the extent (in terms of market shares) to which alternative-based products are already offered on the EU market and whether any shortages in the supply of relevant alternatives are expected.

The proposed timeline for consultation and implementation of the restrictions, if the proposal is accepted, has not permitted the biopharma industry sufficient time to fully identify, qualify and implement suitable non-PFAS alternatives for all applications. In this highly regulated industry sufficient time is required to perform several activities when making changes to the manufacturing process of drugs currently licensed for sale:

1. Research & development of potential alternatives with functional equivalence by the suppliers.
2. Perform development work to demonstrate “equivalence” of the products (characterization) to demonstrate **suitability** and **safety** of the materials in the specific biopharmaceutical processes. Note: a functionally equivalent product is not necessarily suitable in all end user applications.
3. **Validate** the biopharmaceutical product manufacturing process. One critical application of PFAS is in the filtration of drug intermediates to ensure sterility of

final drug product using e.g., fluoropolymer (Polyvinylidene fluoride, PVDF) filter membranes. Factors such as different drug adsorption to different membrane materials can significantly affect yield and quality, and therefore availability of and cost to manufacture drugs. Exposure to solvents, surfactants and chemical mixtures throughout the drug manufacturing, packaging, and storage process (which will be specific to each drug) will have variable impact on the stability and durability of the materials and may result in leaching of substances during the manufacturing processes which pose a risk to patient safety if not fully tested and validated. Significant effort has been made during drug development to demonstrate that all materials currently used are safe and non-toxic for patients, switching to new non-PFAS materials would require significant time and cost investment to ensure no new risks are introduced. Currently, there are few (if any) alternatives to PFAS that encapsulate the required chemical and physical properties to fully emulate the performance of the components currently in use.

4. Generate stability data for the drug substance/product for its required shelf-life – this is a critical rate limiting step and will vary from product to product.
5. Update product licences for review and approval by regulatory authorities in every country that the product is marketed in (likely 3-6 years after time taken to complete steps 1-4). This is also a critical, rate limiting step-

   Regulatory authorities are likely to be overwhelmed by applications for license updates therefore the time required to complete this step is currently unknown and entirely unpredictable; every drug manufacturer globally is likely to be submitting additional license updates (1:1 submission for every biologic drug currently licensed for sale in the EU market). This will be applicable to licenses held for drug substance and drug product, without an exemption or at least an appropriate derogation this restriction will cause drug shortages in countries where the alternative material has not yet been approved.

   Note: This does not account for drugs currently being developed and not yet licensed. Therefore, availability of new drugs will also be critically impacted by the proposed restrictions. Nor does it reflect the severe disruptions placed on supply chains that would be observed during any future pandemic situation; the BioPharma supply chain is still recovering from the impact of Covid and has not yet established pre-Covid stability.

Even if the industry were granted the current maximum derogation of 12 years (plus 18-month transition) there is no guarantee that alternatives could be sourced, tested, and approved in that timeframe; if PFAS materials are removed from the supply chain while alternatives (where they are available) are being sourced there is a significant risk of interruption to the supply of critical drugs.

Mapping of PFAS use applications across the biopharma value chain (both direct and indirect uses) and indication of known, available alternatives is described in Appendix 1. Note: this information was prepared in collaboration with Bio-Process Solutions Alliance (BPSA).

We must also be cognisant of another dimension to finding alternatives to PFAS, they have been chosen in drug manufacturing processes because of their unique properties provided by their chemical composition and there is a risk of regrettable substitution i.e., replacing PFAS components with alternative materials which have properties that may impact the quality of the drug.

e. *For cases in which **alternatives are not yet available**, information on the status of R&D processes for finding suitable alternatives, including the extent of R&D initiatives in terms of time and/or financial investments, the likelihood of successful completion, the time expected to be required for substitution (including any relevant certification or regulatory approvals) and the major challenges encountered with alternatives which were considered but subsequently discarded.*

The sourcing of and switching to non-PFAS alternatives needs to be considered from four critical perspectives- the design and manufacture of novel chemistries, adoption into plastic resin and intermediate articles, incorporation into Bioproduction equipment and processes including qualification and validation of the alternative material in its specific application (including safety evaluation to protect the ultimate user, the patient) and finally the regulatory review and approvals.

For suppliers to develop non-PFAS alternatives (if alternatives can be identified and developed), it will take up to or possibly more than 20 years of Research & Development followed by 2-3 years of validations to get to commercial availability for use in biopharmaceutical processes. However this is just the start of the substitution journey for biopharmaceutical end users who must then complete their own evaluation and validation in every application plus submit any changes under regulatory filings and await approval before implementation post-approval of the impacted licenses (refer to point d).

Drug product packaging such as PFAS lined closures for glass vials/syringes and vial stoppers (drug delivery systems) are likely the most difficult materials to change due to the lack of suitable alternatives in this application. The manufacturers of certain primary drug product packaging systems have failed to identify any viable alternatives. Fluoropolymers (such as ETFE) laminates on rubber closures provides the best protection to sensitive drugs and no suitable alternatives have been identified or become commercially available over the last 20 years.

Vent and gas filtration in equipment requiring in-place steaming/sterilization is performed using PVDF/PTFE based filters for which no robust alternatives were developed over the last 20 years either. The fluoropolymer membranes exhibit unique characteristics providing resistance to the chemical and thermal environment that other membranes could not so far sustainably provide. No PFAS free alternatives for membranes used in venting and gas-filtration applications are available today. Restrictions in the availability of PFAS based air- and vent filters would result in an inability to manufacture biopharmaceutical drug products.

Alternatives with the necessary specific properties that PFAS fulfil in drug packaging applications (such as high purity solvent resistance), are not currently available.

f. *For cases in which substitution is technically and economically feasible but more time is required to substitute:*

The biggest risk is the time required to a) develop alternatives, b) test alternatives and then c) obtain regulatory approval to switch to new materials in every single country where each product is marketed (refer to point d above). This process will take several years (easily beyond 20 years) for each change and each product under consideration. Without a sufficiently long derogation for the industry and the health authorities to adapt (beyond 20 years), this legislation could cause drug shortages in countries where the new material has not yet been approved.

For drug manufacturing processes which utilise PFAS at multiple stages and in multiple applications across the end-to-end value chain (essentially all drug manufacturing processes) there are two possible scenarios:

1. Best Case: every component part or ingredient which contains PFAS has an alternative which can be "dragged and dropped" into the process and where comparability studies show that the substitution does not impact product quality and Regulatory Authorities have no additional barriers to change.

2. Worst Case: any or all identified alternatives fail the comparability studies and cannot be substituted thus requiring continued use of the current PFAS material- if PFAS is removed from the market under the current proposal the ability to manufacture that drug would be at significant risk.
   There is no regulatory alignment with the change and every asset needs to be approved (essentially the process detailed above would be multiplied by the number of drugs and countries impacted).

   In both cases the exercise in completing the required studies will require significant investment in resource, materials and time and would be required for every drug manufactured by each company in both development efforts and in commercial production. If critical resources are diverted to address the multiple changes resulting from a ban this will compete for vital and limited R&D resources, thus delaying introduction of new life saving technology and therapeutics.

   A specific example of substitution requiring more time is for viral filters used in recombinant therapeutic protein purification processes, where demonstration of viral retention must be executed today for each process/product synthesised in mammalian/insect cell lines and be conducted in facilities that are accredited for virus manipulation. The availability of such facilities is low and conducting an industry wide change of viral filtration technology will result in a huge bottleneck and delay of the availability of support data to submit to regulatory authorities.

   The supply and qualification of the fluoropolymer materials currently used in the biopharma industry has been evolving over the last 30 years to fully support their safe and effective use in drug manufacture, it is not inconceivable that finding and transitioning to alternatives (if they can be found and safely and sustainably produced) could take another 30 years.

i. The type and magnitude of costs (at company level and, if available, at sector level) associated with substitution (e.g., costs for new equipment or changes in operating costs).

For pharma/biotech manufacturers, the biggest impact is the time, cost and (human) resources required to a) test alternatives and then b) obtain regulatory approval to switch to new materials in every single country where each product is marketed. This process can take several years for each change and product under consideration.

When determining the cost of substituting PFAS materials with alternatives there are multiple factors to consider: the time and resource for research and development, qualification and validation of their use in existing manufacturing processes (studies which may ultimately fail and require sourcing and testing of another alternative), the capacity of 3rd party test labs to evaluate extractables and leachables of the alternatives and which could quickly become a bottleneck at industry level, the resource required within health authorities to review and approve changes (again this is not a guaranteed process and may result in

rejection of changes). This applies to all impacted drugs and registrations around the globe which would result in additional burden on resources at suppliers, biomanufacturer and regulatory authorities to complete all required activities. In the proposal there is no derogation for the Biopharma industry, and we would be subject to an immediate ban.

A key consideration is also the capacity of the suppliers to support increased demand for the alternative materials, there are currently still some supply issues with existing materials following a rapid increase in demand during Covid, is the supply chain in place and robust enough to support new demand for new materials?

The cost of completing all the above noted points is anticipated to be vastly disproportionate to the impact of the small quantity of stable fluoropolymers sent for incineration (consumable parts) or retained as components of long-life instrumentation. It is difficult to estimate due to the complex, multi-tier supply chain and the requirement for regulatory scrutiny of changes within our highly regulated industry.

ii. The time required for completing the substitution process (including any relevant certification or regulatory approvals).

In the best-case scenario where an alternative is known, it is functionally equivalent and commercially available, requiring only process validation by the drug manufacturer and assessment and approval by regulatory authorities – estimated 5-8 years.

In the worst-case scenario-a full cycle of material identification and functionality assessment at the supplier, process validation in specific processes and assessment and approval by regulatory authorities- will take an estimated 20+ years. A non-exhaustive summary of key steps and timelines for finding and approving alternatives is described in the table below.

Anticipated steps for substitution if alternatives are available.

Step	Activity	Estimated Timeline
Develop a new, suitable disposable	Selection of small scale for small scale studies	Min 6 months
Establish new disposable in GMP environment	Change request, inventory system update, review of certificates & documents, ordering, initial E&L assessment. Development of release testing method	1-2 months 2-6 months
Ordering of GMP/full scale	Procurement, supplier lead time	3-12 months
Release of disposable	Certificate/document check Release testing	Up to 3 months
Supplier/Manufacturer Qualification	Staged concept, Audit	6 months
Validation (late phase/commercial)	Validation in several batches (compat bility, functionality…), process validation (if required), comparability exercise for resulting DS/DP (release testing, stability studies…), Leachable studies	6-12 months + stability (multiple years)
Regulatory filing of changes / Amendments/Approvals	Update of TRDs, submission to relevant Health Authorities, approval by Health Authorities	Multiple Years

iii. Information on possible differences in functionality and the consequences for downstream users and consumers (e.g., estimations of expected early replacement needs or expected additional energy consumption).

In many cases, alternative materials may be available however the alternatives may be suitable/applicable for some applications but not others.

Consequences of substitution of PFAS components are increased extractable risk for the patient and may include reduced stability of biopharmaceuticals and other unforeseen consequences.

Reduction in microbial/bacterial contamination of drugs is a critical step in assuring product and therefore patient safety, and biologic drugs are typically sterilized by filtration using membranes commonly constructed from the fluoropolymer PVDF. The membrane material is highly durable, and the drug does not adsorb to the surface; alternative non-PFAS materials are constructed from cellulose acetate (CA), Nylon and polyether sulphone (PES), which constitute different limitations e.g. PES is also highly durable but shows higher adsorption for certain drugs and constituents such as excipients and surfactants in the drug formulation which could impact stability of the medicine. Switching to alternatives could result in lower product yield thereby increasing production costs and reducing availability of the drug on the market.

iv. Information on the benefits for alternative providers.

On the basis that our industry has not identified suitable alternatives in most of the applications no further comment is appropriate.

g. For cases in which substitution is not technically or economically feasible, information on what the socio-economic impacts would be for companies, consumers, and other affected actors. If available, please provide the annual value of EU sales and profits of the relevant sector, and employment numbers for the sector.

The European Biopharmaceuticals Market is projected at USD 48.19 billion in 2022 and estimated to be growing at a CAGR of 8.89%, to reach USD 73.78 billion by 2027 [3].

As detailed in the response above there are many applications of PFAS across the Biopharma industry where no technically suitable alternatives exist; if alternatives do exist there is a risk that the time required to qualify and approve those alternatives would exceed any maximum derogation period currently proposed by ECHA.

Removal of the impacted drugs from the market (either to allow for qualification and approval where alternatives exist or complete removal when no alternatives with comparable performance attributes are available) would result in significant economic impact to the global manufacturers of these drugs and their suppliers resulting in facility closure, loss of employment and reduced revenue in Europe. Those organizations with alternate manufacturing provisions outside the EU would likely move manufacturing to that region with detrimental impact on future investment within the EU and potentially delaying the supply of therapies (including those in development) due to lack of capacity in the alternative facilities.

It is also important to note that the non-EEA production capacity would not be able to cope with the current EEA demand. There is negligible readily available production capacity at biotechnology manufacturing facilities outside of EU-27. If global capacity is not available, shortages in life saving and life prolonging medicines would become a realistic possibility.

Indeed, the most critical impact would be to the patients who would have no access to current and developing lifesaving and life prolonging therapies resulting in needless suffering and potential mortality.

References:

1. europeanpharmaceuticalreview.com)
2. Marketdataforecast.com
3. European Commission Priority sector report: Biopharmaceuticals ec.europe.eu
4. Budzinski et al., New Biotechnology, Vol 48, 25Mar2019, 37-42.

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Appendix 1

PFAs Applications in BioPharma (non-exhaustive list)

Application	PFAS Type	Potential Alternatives	Feasibility of Replacement	Cost to replace	Patient safety/drug quality impact risk	Comments
Sterile Liquid filtration membranes	PVDF	(PES Nylon Cellulose) *	50%	Very high	High	*No alternative technology immediately available that would maintain product quality in all applications. This is a high-risk application area (particularly virus clearance filters): close proximity to patient, particularly of primary filling applications, dictates regulatory scrutiny and would require additional validation and regulatory approvals across multiple jurisdictions to support global supply chains of pharmaceuticals/API, diagnostics, and other controlled sectors. Cost of validation would be significant, capacity of 3rd party validation services would be a potential bottleneck; concern that current production volumes of PES are not adequate to meet demand and won't be available within the proposed derogation period. Alternatives have very high adsorption so overall yield may decrease and have cost implications (e.g. increased vaccine costs due to lower yield). Applications in Buffer/sterile filtration may be easier to switch.
	PTFE	PES Nylon	<10%	Very high	High	
Liquid filtration- virus clearance	PVDF	PES	80%	Extremely high	Moderate	

Application	PFAS Type	Potential Alternatives	Feasibility of Replacement	Cost to replace	Patient safety/drug quality impact risk	Comments
Films/plastics as primary contact material in manufacture and containment of drug intermediates (drug substance). • Containers/films/bottles • Single use processing bags • Single Use bioreactors • Probes/inserts	PVDF PTFE bottles FEP bags/bottles	†	TBD	TBD	TBD	This is a high-risk application area: close proximity to patient dictates regulatory scrutiny and requirement for extensive requalification, validation, and risk assessment. Changes must be submitted, reviewed, and approved by Regulatory Authorities.
Biopharma drug cryostorage bags and Cell culture cryostorage bags	PTFE FEP Custom fluoropolymer	ULDPE, EVA or EVA blends	<30%*	High	High	*For cell culture cryostorage bags feasibility of replacement is 75% with significant trade offs
Films/plastics (Primary contact material) for final drug product sterile packaging: • cap or stopper coatings/liners • Vial stoppers • Syringe stoppers • Seal linings	ETFE (cap or stopper coatings/liners) PTFE (coating for vial and syringe stoppers and seal linings)	no alternatives for drug product requiring barrier coating	0	N/A	High	This is a high-risk application area as the materials provide protection of the drugs throughout their shelf life. As of today, no alternative has been identified and would require development by the suppliers of containment solutions with subsequent testing, qualification at product level and submission for review and approved by Regulatory Authorities. They would also be subject to potentially lengthy stability studies. Removal of fluoropolymer barriers would also introduce a risk of occurrence of leachables and/or drug adsorption to the non-PFAS alternative.

Application	PFAS Type	Potential Alternatives	Feasibility of Replacement	Cost to replace	Patient safety/drug quality impact risk	Comments
Films/plastics (Primary contact material) for final drug product non-sterile packaging- blister packs	PCTFE	Suggested alternatives have been proposed but they do not confer sufficient protection	<5%	High	High	Blister packs confer protection to the Active Pharmaceutical ingredient in final drug products. Feasibility of alternatives has not been demonstrated and the currently proposed 13.5-year time limited derogation will be insufficient to allow current blister packed products to remain on market. Manufacturers may not have capacity to qualify alternatives (if feasible) and this situation would place additional burden on regulatory authorities to approve
Intermediate, raw material or ancillary material used in manufacture, purification and testing of protein-based drugs	TFA (tri-fluoroacetic acid) or PFAS related compounds	No alternatives	0	N/A	High	This is a specific case not applicable to all biologic drugs however, where PFAS materials are used, any restrictions or removal of the PFAS material would result in an inability to manufacture the drug.
Vent and/or Gas Filtration (of bioreactors/carboys)- filter membranes	PVDF	No alternatives	<5%	Moderate	Moderate	This is a high-risk application area. There are no PFAS free alternatives for membranes used in Steam in Place filters. No PFAS free alternatives for membranes used in venting- and gas-filtration applications are available today. Restrictions in the availability of PFAS based air and vent filters would result in an inability to manufacture bio-pharmaceutical drug products.
	PTFE	No alternatives	<5%	N/A	Moderate	

Application	PFAS Type	Potential Alternatives	Feasibility of Replacement	Cost to replace	Patient safety/drug quality impact risk	Comments
Tubing & tube fittings (manufacturing engineering systems and transfer of drug material intermediates and final product, lab testing applications) incl gaskets & O-rings	PVDF (tubing)	No alternatives	<5%	N/A	High	Used in bioproduction and technical applications such as chromatography, trace metal analysis, pollution sampling, highly reactive catalyst procedures, metallurgical corrosion testing, pharmaceutical work, dissolutions, and hot acid etchings where chemical compatibility and concerns over leaching is essential. Critical in fluid handling within analytical instrumentation, including nearly all equipment identified in Annex E4 of the restriction proposal used in the identification and quantification of PFAS. None of the alternatives match the inert properties of the PFAS materials
	PVDF (Fittings)	polycarbonate polypropylene polysulfone	<5%	Moderate	High	
	PTFE	No PFAS free alternatives	<5%	N/A	High	
	FKM (tubing/O-rings / gaskets)					
	FEP					
	PFA					
	PTFA					
Hardware systems (lined pipes, TFF cassette seals/components/solvent exchange systems/lined valves/gaskets). Pumps & components (diaphragm)	PVDF PTFE FKM	No alternatives	<5%	N/A	High	None of the alternatives match the inert properties of the PFAS materials
Ultra-low temperature refrigerant (low boiling temp gases <-60ºC) for freezing drug intermediates or final product.	Multiple PFAS	CO_2: however energy consumption by alternatives is increased by 50%	100% but with energy pay-offs	High	N/A	PFAS materials were selected in this application to replace previously banned CFC materials. Alternatives may require substantial retrofitting or replacement of equipment (with subsequent qualification of the equipment to work with alternatives). To function as effectively as PFAS materials alternatives would require increased energy consumption.

Application	PFAS Type	Potential Alternatives	Feasibility of Replacement	Cost to replace	Patient safety/drug quality impact risk	Comments
Films/plastics (1º contact material) in laboratory reagents and standards	PTFE	No known universal alternative (use case specific)	<5%	TBD	TBD	Critical to non scientific research and development laboratory activities in pharmaceutical and API manufacture, life science and applied applications. Essential for preventing container leakage due to incompatibility- creating unwarranted hazards for chemical storage and shipping for many essential smaller (laboratory) scale reagents. Essential for high purity solvents and standards where minute quantities of leachable organics interfere with critical analysis (including High Performance Liquid Chromatography applications for detection of PFAS).
Laboratory Apparatus (funnels, flasks/containers, stirring bars etc)	FEP PTFE	Glass for some applications (compatibility dependant) but increased safety risks due to breakage.	<5%	TBD	TBD	Risk to non scientific research and development laboratory activities in pharmaceutical and API manufacture, life science and applied applications.

Applications not specific to BioPharma and which will also impact other industries.

Application	PFAS Type	Potential Alternatives	Feasibility of Replacement	Cost to replace	Patient safety/drug quality impact risk	Comments
Heat and/or chemical resistant, nonreactive coatings/insulation/lubricants used e.g. as components of electronics and stainless-steel vessels/skids.	Additive of PFAS origin	†	†	†	†	Impact to biopharma: not used directly in drug manufacture but are used in electronic components in system controllers/skids, PLCs s (Programmable Logic Controller) and stainless-steel equipment e.g. vessels and skids.

† Further assessment required; alternatives may be application specific; substitution with a particular non-PFAS material may not be suitable for all applications