Victoria Mwanza

Who is commenting? *(choose the best fit)*
Representative of a product manufacturer(s)

If you are commenting as a representative, what is the name of the entity you are commenting on behalf of?
BioPhorum

If you represent a product manufacturer or industry group, what industry(ies) do you represent?
The global biopharmaceutical manufacturing industry (including biologics, monoclonal antibodies, cell and gene therapies, vaccines, mRNA platforms) and supporting suppliers.

If you represent a product manufacturer, what types of components, products, or product categories do you manufacture that you will be requesting a CUU determination for?
BioPhorum may seek CUU determinations for all PFAS-containing products used in biopharma, including:
• Production (Manufacturing Process Equipment & Components): Sterile filtration membranes (PVDF, PTFE), Vent/gas filters, Tubing, gaskets, O-rings, connectors (PVDF, PTFE, FKM, FEP), Hardware systems (lined pipes, TFF cassettes, pumps)
• Testing (R&D, QC, Analytical Use): Laboratory materials essential for R&D (PTFE, FEP apparatus)
• Storage (Cryogenic & Controlled-Temperature Materials): Cryostorage bags (PTFE, FEP) and, Ultra-low temperature refrigerants used for drug storage (multiple PFAS).
• Delivery (Drug-Contact & Final Product Components): Primary drug-contact films, stoppers, vial/syringe coatings (ETFE/PTFE) and On-body delivery devices/systems (OBDDs/OBDSs) These uses constitute essential components in drug manufacturing, packaging and delivery.

Do you have any recommended changes or other considerations that you think the MPCA should take into account when defining the term "essential for health, safety, or the functioning of society"? *(Please review the proposed definitions in the rule concept document prior to answering)*
BioPhorum strongly recommends explicit recognition of biopharmaceutical manufacturing as essential because:
• 100% of biologic drugs rely on PFAS at some stage of production, testing, storage, or delivery.
• PFAS removal would immediately halt manufacture of medicines treating cancer, immunological disease, diabetes, infectious disease, neurological disorders, and rare diseases.
• These drugs directly protect life, prevent mortality, and treat chronic illness, meeting all MPCA criteria for essentiality.

Do you have any recommended changes or other considerations that you think the MPCA should take into account when defining the term "alternative"? *(Please review the proposed definitions in the rule concept document prior to answering)*
BioPhorum urges MPCA to emphasize that:
• Functional equivalence is not sufficient; biopharma requires materials that do not interact chemically with the drug stream.
• Many proposed alternatives result in drug adsorption, yield loss, leachables, or safety failures, making them unsuitable.
• Alternatives must also be compatible with GMP requirements, validated for patient safety, and globally regulatory-approved.

Do you have any recommended changes or other considerations that you think the MPCA should take into account when defining the term "reasonably available"? (*Please review the proposed definitions in the rule concept document prior to answering*)
“Reasonably available” must factor in:
• 20+ years R&D timelines for alternatives to be developed and validated. Given the need to identify and develop technically
suitable PFAS-free materials, then establish robust, resilient global supply chains capable of producing these materials at commercial scale, the timelines for implementing alternatives are expected to exceed 20 years. While initiatives such as the European Innovative Health Initiative (IHI) have launched five-year programs to identify potential replacement materials, these efforts focus primarily on material discovery and do not address the substantial further work required to industrialize those materials, expand manufacturing capacity, or qualify suppliers under the stringent regulatory and quality systems required in the life-sciences sector. Even once alternative materials are identified, suppliers and sub-suppliers must develop capability to manufacture them consistently and at the necessary volumes, and then undergo
extensive qualification and certification processes. There is potential new suppliers will not initially meet the regulatory, GMP, or ISO-based standards required for Tier 1 supply, meaning additional time is needed for capability building, facility upgrades, and regulatory compliance. Only once these supply chains are robust, stable, and globally scalable can downstream validation activities begin.
The regulatory burden then adds a further sequential and interdependent layer: Tier 1 suppliers must submit updated raw-material and component-level submissions across numerous international markets. Drug manufacturers and biomanufacturers must then submit their own product-level changes to demonstrate safe and effective use of these newly qualified materials within their specific manufacturing processes. Regulatory authorities must therefore evaluate a very large number of linked filings, where product-level approvals depend on prior acceptance of the supplier's data. This multi-market, multi-stage regulatory review structure compounds the overall timeline.
Taken together, material discovery, supplier capability development, supply-chain industrialization, component- and product-level validation, and the high volume of interdependent regulatory approvals across global jurisdictions the end-to-end implementation of fully validated PFAS-free alternatives represents a multi-decade effort extending well beyond 20 years.
• Biopharma’s strict requirement that materials not chemically interact with medicines.
• Global regulatory approval timelines of 8–20 years per product, even when alternatives exist. To appreciate the regulatory scale involved in transitioning PFAS-containing

components to fully validated alternatives, it is important to consider the volume of products currently overseen by the U.S. Food and Drug Administration (FDA). According to the FDA's At a Glance report 2020 (1), the agency has over 20,000 prescription drug products approved for marketing in the United States. In addition, the FDA oversees more than 6,500 distinct categories of medical devices, covering everything from simple Class I consumables to complex Class III implantable systems and diagnostic technologies. These figures demonstrate the breadth of products for which manufacturers would need to file amendments if PFAS-containing materials were altered or replaced. For each affected drug or device, Tier 1 suppliers must submit revised component-level data, and manufacturers must subsequently submit product-level updates for regulatory review. In a regulatory environment already responsible
for tens of thousands of active product approvals, this scale of sequential, interlinked submissions further underscores why
transitioning to PFAS-free alternatives will demand multi-decade timelines, even before considering the added challenges of material identification, supply-chain readiness, and global market synchronization. Note the numbers cited were as of 2020, in the last six years we would have expected many more to be authorized
• Severe supply chain risks, many alternatives are not produced at scale.
Severe supply-chain risks persist because many potential PFAS alternatives are not produced on a commercial scale, and in several cases have not yet been industrialized at all. Even when early-stage materials are identified, such as those expected to emerge from initiatives like the IHI five-year program, these efforts focus only on discovery and do not address the far
more extensive work required to build robust, high-volume global supply chains. To be viable for regulated life-science applications, suppliers and sub-suppliers must demonstrate consistent manufacturing capability, secure adequate plant capacity, and meet stringent GMP, ISO, and sector-specific certification requirements. Potential many prospective vendors would not initially meet the quality or regulatory thresholds required for Tier 1 supply, meaning significant investment, facility upgrades, training, and qualification cycles would be necessary before any alternative material could be adopted. Until these supply chains are established, diversified, and proven reliable, PFAS-free materials cannot be considered reasonably available for critical biomanufacturing and tier 1 supply applications. PFAS alternatives are therefore not reasonably available for critical applications.

When considering the proposed definition of "product category", how broadly should the agency group product categories? *(Examples: "vehicles" versus "sedans, SUV's, vans, trucks, RV's" or "printers" versus "receipt printers, thermal printers, label printers, residential printers, commercial printers, etc.")*

BioPhorum recommends narrow, specific product categories, because:
• Each bioprocessing component has unique performance, safety and regulatory requirements.
• Grouping categories broadly (e.g. "filters") obscures the fact that virus-removal filtration, sterile-filtration, and gas-filtration have entirely different PFAS requirements.
Over-broad categorization risks misclassification and patient harm.
Alternatively, While many biopharma stakeholders support narrow categories due to technology specificity, others highlighted the need for broader categories, particularly for systems used in FDA-regulated production, so that no critical use falls outside the scope of CUU

determinations.

Should each request for a CUU determination be limited to a single product category, or should applicants be allowed to submit a request for a CUU determination for multiple product categories?
This should be multicategory, biopharma processes rely on integrated systems where multiple PFAS-containing components work together.
• A single biologic manufacturing process may rely on 50–200 PFAS-containing components from different categories.
A “one category at a time” approach would be impractical and not reflective of real manufacturing use.
It would be suggested grouping CUU requests for products used collectively in FDA-regulated manufacturing, noting that changes to one component typically require revalidation of the full system. This would reduce regulatory burden and prevent inconsistent outcomes

What safety or other standards require the use of PFAS in a product? *(Please include the specific citation)*
PFAS are required to meet numerous regulatory and safety standards, including:
• GMP regulations (21 CFR 211.65) requiring non-reactive, non-additive materials in equipment. PFAS are uniquely compliant.
• Sterility assurance standards for filtration, where no PFAS-free membranes can withstand sterilization or maintain performance.
• Drug packaging standards requiring chemical inertness and barrier protection, met only by PTFE/ETFE coatings.
Without PFAS, medicines cannot meet safety requirements.
Stakeholder input emphasized that PFAS-based polymers uniquely meet Good Manufacturing Practices (21 CFR 211.65) requiring non-reactive and non-additive materials. They also noted that PFAS-free films or membranes currently cannot meet required sterility assurance and chemical compatibility standards.

The agency is seeking feedback on the potential that the initial positive CUU determination duration for existing products will expire eight years from the date of issuance regardless of product category. This is intended to stagger renewal deadlines and ease the administrative burden of processing renewals.

- Do you have any concerns about unintended consequences with this proposal?
- Do you have any alternative recommendations to stagger renewal deadlines?

An 8-year duration is incompatible with:
• Could be 20+ year pharmaceutical validation cycles based on the information supplied in Question 7.
• Stability studies that can last 5–10 years per product. Depending on the material or product, stability studies may need to span 5–10 years to support the full shelf-life, particularly for Tier 1 raw materials and single-use components, recognizing that some drug products require shorter (e.g., 3-year) studies, while biologics or components with longer shelf-life expectations require extended stability programs.
• Global regulatory approval timelines that may exceed the CUU renewal horizon.
BioPhorum recommends permanent exemption for CUU for biopharma PFAS due to thermal destruction at end-of-life and essentiality.

Some suppliers indicated that, due to the volume of specialised components and the administrative effort involved, they may be forced to halt shipments to Minnesota rather than risk non-compliance if renewal cycles are too short or burdensome.

The MPCA has developed a preliminary list of potentially eligible data categories that may be considered for trade secret requests. *(Please review the rule concept document for the list of potentially eligible data)*

- Do you have any concerns about unintended consequences with this proposal?
- Do you have any alternative recommendations for data that should or should not be eligible for trade secret requests?

Biopharma supports expanding trade secret protection because:
• Supply chains are n-tiered and highly proprietary; component-level PFAS identification is often impossible.
• Disclosure requirements would violate supplier IP and jeopardize safety-critical supply.
• Many PFAS-containing components (e.g., multilayer films, membranes) are protected formulations.

What are the potential ongoing costs to society if the commissioner issues a positive currently unavoidable use determination for the continued use of PFAS within a product or product category? *(For example: environmental, human health, or remediation costs)*
If CUU is granted for biopharma:
• The societal cost associated with PFAS used in biomanufacturing is regarded as low, since these materials are typically incinerated at end-of-life and therefore do not persist in the environment. This is particularly true for drug-substance and drug-product manufacturing processes; however, some drug-delivery devices or primary packaging may not always be thermally destroyed, and these exceptions should be acknowledged.
• Conversely, denial of CUU risks:
o Drug shortages
o Halted clinical pipelines
o Loss of access to critical therapies
o Global manufacturing relocation
o Increased mortality

For manufacturers: Administrative cost of requesting a CUU determination (Part 1 of 2). *Please provide your best estimates or rough orders of magnitude (for example "approx. 200 hours"). Precise accounting data is not necessary to answer this question.*

If your company currently possesses information regarding intentionally added PFAS (to the CAS number level) for all components in your product lines, please estimate the number of technical staff hours that were required to establish this baseline.
Other (please specify)
See attachment for full comment.

For manufacturers: Administrative cost of requesting a CUU determination (Part 2 of 2). *Please provide your best estimates or rough orders of magnitude (for example "approx. 200 hours"). Precise accounting data is not necessary to answer this question.*

If your company does not possess information regarding intentionally added PFAS (to the CAS number level) for all components in your product lines, please estimate the number of technical staff hours needed to obtain this data from your Tier 2 or 3 suppliers for a single product line.
Other (please specify)
See attachment for full comment.

For manufacturers: Expenditure considerations when seeking non-PFAS alternatives (Part 1 of 2). *Please provide your best estimates or rough orders of magnitude (for example "primary cost is CapEx"). Precise accounting data is not necessary to answer this question.*

If you have identified a technically viable non-PFAS alternative for one of your products that contains intentionally added PFAS, does implementing this alternative require Capital Expenditure (such as purchasing new molds, retooling machinery) or primarily Operational Expenditure (such as purchasing more expensive raw materials)?

- Please estimate the ratio of Capital Expenditure to Operational Expenditure (or indicate which category is the dominant cost driver).

Where alternatives exist (rare), implementing them requires:
• For new/novel PFAS replacements the suppliers will need to recover the development and commercialization costs which will feed into the price when brought to market.
• New equipment, tooling, and validation, significant CapEx.
• Higher-cost materials, substantial OpEx.
• Additional regulatory filings and process redesign.
Most substitution scenarios require both, with CapEx as the primary driver.

For manufacturers: Expenditure considerations when seeking non-PFAS alternatives (Part 2 of 2).

If you have not identified a technically viable non-PFAS alternative for one of your products that contains intentionally added PFAS, have you conducted a Research & Development (R&D) feasibility study?

- If so, what was the cost of that study?

BioPhorum members report that:
• Feasibility studies for PFAS replacements require multi-year programs.
• Costs can reach millions of dollars, depending on the application.
• Many studies fail because no viable alternatives exist.

For manufacturers: Research and development safety validation cycles.

What is the typical duration of the R&D and safety validation cycle for a reformulated product in your sector (from concept to market entry)?

Does this cycle align with the 5-year renewal period typically associated with regulatory exemptions?

- If not, please explain the specific technical barriers that would require a longer validation period.

Typical end-to-end timelines:
• 5–8 years: minimal substitution (where alternative is already known)
• 20+ years: full replacement requiring new materials, testing,
validation, and regulatory approvals. Achieving full PFAS replacement across biopharmaceutical and medical-device applications is a multi-decade undertaking, well beyond 20 years, because it requires the discovery of entirely new materials, the development and industrialization of robust global supply chains, extensive multi-year stability and performance validation, and sequential regulatory approvals across thousands of affected products. As outlined in the detailed questions above, many alternative materials are not yet identified or produced at commercial scale; suppliers will need years of capability building and certification; manufacturers must revalidate processes and update filings; and regulators face a substantial volume of interdependent submissions from both Tier 1 suppliers and product manufacturers. Taken together, these interconnected scientific, industrial and regulatory barriers reinforce that PFAS-free materials cannot be substituted quickly and that full replacement timelines necessarily extend over multiple decades.
• This does not align with the proposed five-year renewal cycle.

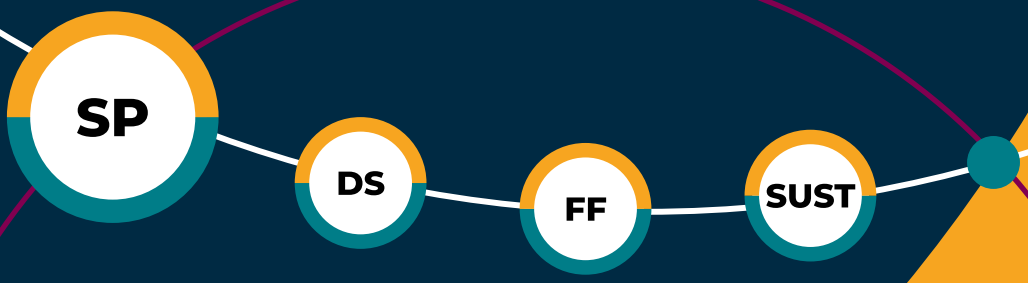
Please provide any additional information or documentation needed to support your answers to any of the questions posed.
Note - This comment has been uploaded by the MPCA on behalf of the commenter. Commenters located outside of the United States are unable to access the comment portal website due to network security. Accommodations were made to accept these comments in an alternative format and upload them on behalf of the commenters.

Do you have any additional questions or comments regarding the PFAS in products: Currently unavoidable use rule? *(Please note that we may be unable to respond to specific questions regarding rule content in this phase of the rulemaking process)*
BioPhorum emphasizes:
• The biopharma sector is unique in that PFAS use directly supports patient safety and survival.
• No PFAS-free substitutes exist for most pharmaceutical applications.
• A CUU framework must recognize the global public health impact of PFAS restrictions.

BioPhorum

PFAS RESPONSE TEAM

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



CONNECT
COLLABORATE
ACCELERATE™

About BioPhorum

BioPhorum's mission is to create environments where the global biopharmaceutical and device industry can collaborate and accelerate its rate of progress, for the benefit of all.

Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum's membership now comprises top leaders and subject matter experts from global biopharmaceutical manufacturers and suppliers, working in both long-established and new Phorums. They articulate the industry's technology roadmap, define the supply partner practices of the future, and develop and adopt best practices in drug substance, fill finish, process development and manufacturing IT.

In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

Opening statement

The biopharmaceutical (biopharma) industry, represented here by BioPhorum, acknowledges 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 minimize 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 well-being 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 is 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 were 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 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 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 and 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

Researched in detail | Researched in general | Not researched in detail | Separate restriction proposal

Biopharmaceuticals (or biologics), a subsector of the pharmaceutical industry, include biological therapies such as monoclonal antibodies, cell and gene therapies, messenger ribonucleic acid (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 $163 billion. A significant proportion of that revenue is generated in Europe (**$48.19 billion** in 2022[2]) with the European biopharmaceuticals market estimated to be growing at a compound annual growth rate (CAGR) of 8.89% to reach $73.78 billion by 2027.

One hundred per cent of the biopharmaceutical products currently being developed or already licensed for sale in the EU utilize 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 lifesaving 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 and pre-clinical 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 into 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 socio-economic impact.

While this specific response is focused on the biopharma sector, BioPhorum and its member companies recognize 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 good manufacturing practice (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 (DS) or drug product (DP) 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.

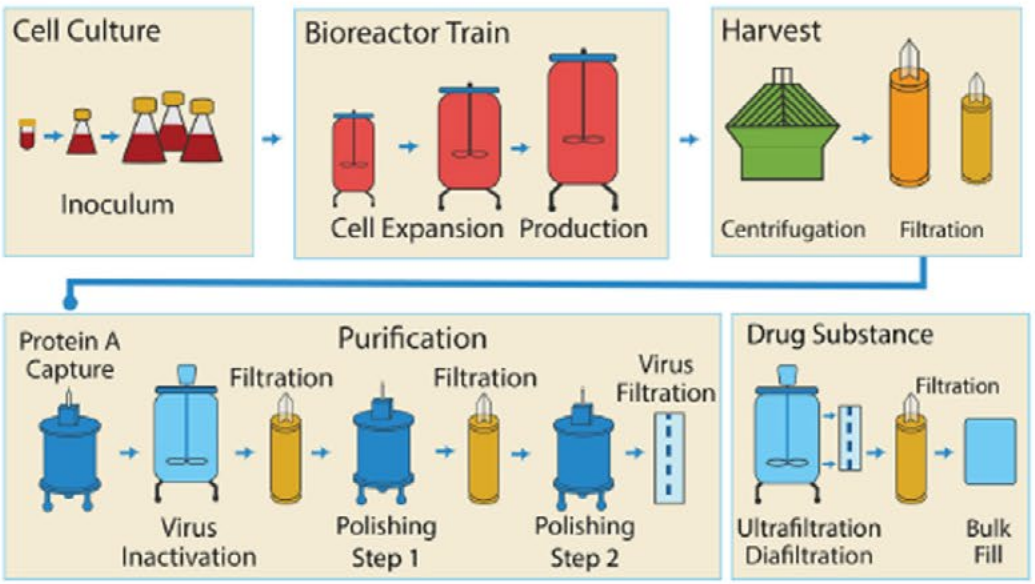
Responses

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 and support system components).

Figure 1: Common unit operations in the manufacture of biological active substances



Budzinski et al. *New Biotechnology* Volume 49, 25 March 2019, pages 37-42[4]

- Equipment and process aids using PFAS
- PFAS used in the sample preparation for analytical instruments

Raw materials and intermediates

- Storage
- Analytics

Product contacting PFAS

- Sterile filtration (PVDF); potential alternatives exist
- Air filters (PVDF/PTFE) for sterile processing; no alternatives
- Drug packaging and delivery

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 the 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 utilize 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 four 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 European Union Chemicals Agency (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 makes 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 three 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 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 DP 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.

One hundred per cent of the approximately 830 biopharma manufacturers in Europe, their global suppliers (and in turn their intermediate material suppliers), including third 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 authorization. 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 and 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 DP 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 DS and DP, 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 the 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 R&D 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).

DP 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 DP packaging systems have failed to identify any viable alternatives. Fluoropolymers (such as ETFE) laminates on rubber closures provide 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 DPs.

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 utilize 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 lifesaving 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 synthesized 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/biopharmaceutical 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 R&D, 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 third 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.

Table 2: Overview of PFAS applications and the level at which they were researched

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 and documents, ordering, initial extractables and leachables 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 (compatibility, 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 $48.19 billion in 2022 and estimated to be growing at a CAGR of 8.89%, to reach $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 lifesaving 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.

Appendix

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 third party validation services would be a potential bottleneck; concern that current production volumes of PES are not adequate to meet demand and will not 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	
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	PTFE	Suggested alternatives have been proposed but they do not confer sufficient protection	<5%	High	High	Blister packs confer protection to the API in final DPs. 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 biopharmaceutical drug products.
	PTFE	No alternatives	<5%	N/A	Moderate	
Tubing and tube fittings (manufacturing engineering systems and transfer of drug material intermediates and final product, lab testing applications) incl. gaskets and 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 are 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 and 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 <-60°C) 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 (1° 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 dependent) 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.
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 (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

References

1 **europeanpharmaceuticalreview.com**

2 **marketdataforecast.com**

3 European Commission Priority sector report: **Biopharmaceuticals ec.europe.eu**

4 Budzinski et al., *New Biotechnology*, Vol 49, 25 March 2019, 37-42.

https://doi.org/10.46220/2023SP005