Bio-Process Systems Alliance
Advancing Single-Use Worldwide

TO: **European Chemicals Agency (ECHA) Consultation Members**

FR: **Bio-Process Systems Alliance (BPSA)**

RE: **2023 ECHA Annex VI Restriction Report Proposal Impact on (Bio)Pharmaceutical Processing Equipment**

DT: **SEPTEMBER 8, 2023**

Dear ECHA Committee Members,

We fully support efforts to minimize and mitigate the presence of substances which pose a threat to human health and the environment. However, restrictions to commonly used materials such as fluoropolymers pose a risk to the EU's ability to supply itself with lifesaving therapies, both due to material shortages as well as regulatory approval backlogs from having to revalidate the manufacturing processes of the biologicals due to material/tool changes in their manufacturing processes. The proposed broad restriction of PFAS covering fluoropolymers would have unintended consequences on the global manufacturing of life science and biopharmaceutical products ultimately impacting availability of existing medicinal therapies (e.g., COVID vaccines), development of new medicinal therapies, and cost to patients. Recent assessments of the dependence of biopharmaceutical manufacturing processes on materials impacted by the PFAS ban proposal range from 94% to virtually all biologics medicinal therapies [1] [2] [3].

We propose a new sector for the pharmaceutical and biopharmaceutical industry, including single-use bioprocessing consumables, QC analysis and the supply chain critical to the manufacture of these goods, with an unlimited derogation, similar to that for medicinal products. We also propose separate categorization and perhaps subcategorization of fluoropolymers within the broad scope ECHA PFAS definition, to differentiate compounds of high toxicity concern (e.g. PFOA, PFOS) from those identified by multiple, credible authorities as polymers of low concern [4] [5].

About the Bio-Process Systems Alliance (BPSA)

The Bio-Process Systems Alliance (BPSA) was formed in 2005 as an industry-led international industry association dedicated to encouraging and accelerating the adoption of single-use manufacturing technologies used in the production of biopharmaceuticals and vaccines. BPSA is an affiliate of the Society of Chemical Manufacturers and Affiliates (SOCMA). BPSA's Mission is to facilitate, globally, the development and manufacturing of biopharmaceuticals through the implementation of robust, safe, and

sustainable Single-Use Technologies. BPSA presently represents approximately 70 member companies spanning the global single-use bioprocessing industry.

Recognition of the Pharmaceutical and Biopharmaceutical Processing as a Missing Use Sector

Materials falling under the broad ECHA PFAS definition (e.g., PVDF, PTFE, FKM, PFA, FEP, ETFE) are used extensively throughout biopharmaceutical processing, including APIs (active pharmaceutical ingredients), single-use bioprocessing consumables (e.g., single-use systems), QC analytics consumables, and the equipment used to produce these materials. A review of United States Pharmacopeia (USP) **drug monographs and standards** finds 100 references to "fluoro", 78 to "PVDF", and 68 to "PTFE". Similar searches have identified **68** such **references** in the ASME Biopharmaceutical Process Equipment BPE **standard** [6]. Additional information on the specific types of applications where PFAS are used is included further below under "Missing Uses" and "Applications". We request the pharmaceutical and biopharmaceutical processing, including their supporting supply chain, be regarded as a sector, and permitted the same exemption or unlimited derogation as medicinal products.

Impact on Sourcing, Testing, Validation of Alternatives

Materials used in the bioprocess industry can range from use in non-critical to highly critical applications, with the later requiring extensive testing to assess and validate how the material impacts the drug manufacturing process and critical quality attributes of the drug product. Given the large variety of conditions used for pharmaceutical conditions (e.g., process fluids, process volume, contact time, duration, sterilization condition, etc), validation studies that meet regulatory expectations and patient safety requirements can **take years for materials that are well-chosen and well-suited for their intended use**. In this regard, materials are often subjected to highly controlled, limited sourcing strategies. Changes to such materials, where alternatives are available and suitable to the drug manufacturing process can require similar timelines and costs [6].

Fluoropolymers, due to their unique chemical inertness and thermal stability, often exhibit minimal impact to the drug manufacturing process. **Alternatives**, where available and suitable, **need to be more carefully evaluated** as they likely **pose a higher risk** of **impacting** the **drug product quality** or drug manufacturing process.

Resources focused on identifying and validating alternatives, where available and suitable, for many different pieces of single-use process equipment for each of many pharmaceutical manufacturing processes will pose an enormous challenge on pharmaceutical manufacturers and their supply chains. More critically regarding timelines, the market capacity for performing such revalidations, where possible, is limited and would not be able to sustain the level of testing for the vast number of impacted materials and medicinal products even in a 15 year or longer span [6]. This resource diversion will unequivocally impact the manufacturing of existing therapies and development of new medicinal products, including vaccines, with the **ultimate impact of cost and drug shortage risks being passed directly to patients**.

Regulatory Approvals

Due to the risks to patient safety, bioprocess is a highly regulated industry, with strict requirements and regulatory approvals, both for medicines newly launched into the market, as well as for changes to existing pharmaceutical manufacturing processes. As medicinal products manufactured in Europe are

often manufactured for Europe as well as rest of world, such changes may require approval of not just the European Medicines Agency (EMA), but other health authorities globally before the manufacturing process can be made. The process of **global regulatory approvals** for **each medicinal product** can easily **take** between **3 to 6 years** by the pharmaceutical manufacturer, for cases where suitable alternative materials and the supporting data are available.

Categorization of Fluoropolymer vs PFAS

The broad scope PFAS definition groups well-documented hazardous, small molecular weight chemistries (e.g., PFOA, PFOS) in the same group as 10,000+ potential compounds of highly varying properties, including fluoropolymers. This **one size fits all grouping**, includes fluoropolymers used in bioprocessing, which meet stringent safety testing requirements for use in pharmaceutical processing, including **biological reactivity testing** (USP <87>, USP <88>, ISO 10993) as well as **toxicological safety assessments** of the extractables and leachables compounds that may migrate from these materials. Moreover, such fluoropolymers including PVDF and PTFE, are successfully used as implants for vascular grafts and stents, facial augmentation, trachea reconstruction, pacemaker leads, glaucoma drainage membranes, intestinal sleeves, hernia repair meshes, and intracochlear hydrophones. Additionally, as polymers of low concern are those deemed to have insignificant environmental and human health impacts, polymers which meet these established criteria should have reduced regulatory requirements [7].

Subgrouping and classification strategies for PFAS have been published in peer reviewed literature [8] [5], and industry reports [9]. Additionally, it is noted that some fluoropolymer formulations used commercially today within the bioprocess industry (e.g., PVDF) are already manufactured without the use of PFAS processing aids, thereby mitigating risk during polymer manufacturing. Clearly there are differences in the vast number of materials falling into the singular PFAS grouping, with greatly differing safety profiles, tonnage used in the industry, contribution to environmental concerns, control strategies and socioeconomic value. Hence, we request separate categorization, and perhaps sub-categorization of fluoropolymers to assess their specific material risks, potential environmental impact, lifecycle management strategies, unique functionality and applications, and extensive socioeconomic impact.

In an analogy from Solzhenitsyn, “If only it were all so simple! If only there were evil people somewhere insidiously committing evil deeds, and it were necessary only to separate them from the rest of us and destroy them. But the line dividing good and evil cuts through the heart of every human being. And who is willing to destroy a piece of his own heart?” This analogy exemplifies how the seemingly simple, one size fits all approach can be greatly misguided, while yielding enormous socioeconomic consequences.

Improved Environmental Stewardship & Waste Management

The BPSA maintains a core commitment to sustainability and safety with industry leading guidance publications that advocate proper management and sustainable strategies for waste streams [10] [11] [12]. Separate categorization of fluoropolymers used in bioprocess applications and their supply chain will enable continued industry progress to managed sustainability goals while ensuring continued availability and development of life saving therapies.

Missing Uses Associated with Bioprocess Applications

The applications bulleted further below are critical to business continuity in the biopharmaceutical processing sector. In almost all cases, the suitability or any alternative materials depends on the material

interactions with the pharmaceutical fluid and manufacturing process conditions (temperature, time, flow). This is a central regulatory requirement for pharmaceutical equipment as stated in the European good manufacturing practice (GMP) guidelines.

> *"Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard."* [16]

This requirement for validation of pharmaceutical manufacturing processes is often a lengthy, costly process specific to each component, material, and manufacturing drug process. In some cases, (i) alternatives such as PES filters, may be available and suitable as an alternative for PVDF filters with the understanding there will be performance trade-offs and a potential impact to the drug product quality that requires additional assessment, and in some cases update of regulatory filings for each medicinal product and acceptance by multiple regulatory entities worldwide (as process that can easily take 3 to 6 years for each case and filing). In other cases, (ii) the alternative (e.g., PES membranes) may not be suitable and able to be validated as the performance characteristics of biotech components often depend strongly on the nature of the chemistry of each pharmaceutical fluid, reagent, and process conditions. For example, squalene emulsions, frequently used as ingredients for manufacture of vaccines, can result in performance challenges for PES sterilizing-grade filters to achieve the validated state of absolute microbial retention.

- **Fluoropolymer-based liquid filtration membranes and devices.** Sterile filtration, virus filtration, particulate/bioburden filtration ensure purity, cleanliness and safety of the biopharmaceutical or the fluids used to prepare and formulate the pharmaceutical.
- **Fluoropolymer-based gas filtration membranes and devices.** Sterile (i.e., bacteria removing) vent filters on single-use systems, IV sets, bioreactors, etc.
- **Fluoropolymer gaskets and seals**. Ubiquitous through bioprocessing.
- **Fluoropolymer single-use components.** Fittings (e.g., tube to tube connectors), bags, tubing clamps, pump parts, valves, mixer parts, tubing, etc.
- **Fluoropolymers used as auxiliaries on sites to manufacture single-use products or chemicals vital to the bioprocessing industry**. Chemically inert, non-stick, temperature resistant materials used in thermal and sonic welding, pump valves, tubing, material coatings, equipment gaskets, seals, production of bioreactors and storage bags, etc. It is believed there are an abundance of materials in the supply chain and manufacturing operations that require further time to properly understand.
- **Fluoropolymer membranes and consumables used for laboratory analysis and quality control testing supporting pharmaceutical development and manufacturing.**
- **Fluoropolymer bags, bottles, and vials for biopharmaceuticals.** Bags with relatively inert chemical reactivity properties that are highly suited for freezing and low temperature storage of biopharmaceuticals and cell therapies. The mechanical compliance properties of perfluoropolymer bags minimize risk of breakage and loss of high value biopharmaceuticals and cell therapies, each of which could be > € 0.5-10 M per batch.
- **Fluoropolymer bags for cell culture/cell therapy applications.** Bags are used for cell culture production processes in cell therapy applications, as well as freezing and storage. Key attributes include purity, gas exchange, water barrier, clarity, chemical and biological inertness, as well as

low temperature performance critical to storage in liquid nitrogen (-196°C). This is key for safety of drug products which in the case of personalized medicine/cell therapy are considered rare and nearly impossible to replace.

- **Hydrophobic and/or Oleophobic Filtration Membranes in Pharmaceutical Processing.** In these cases, small molecular weight chemistries are associated with filtration membranes that allow the flow of gas but prevent passage of microorganisms. The hydrophobic/oleophobic chemistries are critical to the surface tension characteristics of the membrane, non-binding properties, and ability to mitigate pore blockage of small-scale membranes by moisture. Many membranes previously used PFOA or PFOS-based chemistries and were redeveloped using other chemistries, that are now in scope of the current ECHA PFAS definition. Such hydrophobic/oleophobic membranes are well suited to venting applications in pharmaceutical processing requiring moisture repellence and the maintenance of a sterile barrier. As alternatives will need to be developed, tested, and validated by the supplier, and then by the pharmaceutical manufacturer, this process will take extensive time (12+ years). The maximum derogation is requested for these materials.

Case Study Example of Timeline for Risk Evaluation of Sterilizing Grade PVDF Filter for Liquids

PVDF sterilizing-grade filters are used to ensure sterility of the pharmaceutical fluid at multiple stages or entry points for fluids into the pharmaceutical manufacturing process. Due to their relatively inert, low binding, low fouling characteristics they are frequently recommended for complex pharmaceutical formulations and well suited for late stages of the pharmaceutical manufacturing process. Potential alternative types of sterilizing grade filters include PES and nylon filters, each with specific material and performance characteristics that can impact the quality of the drug and viability of the manufacturing process. For example, PES filters may offer higher volumetric flow properties for simple fluids, such as buffers, but pose challenges for many complex drug formulations to achieve a validated state of absolute microbial retention, which is the essential requirement of such filters. Similarly, nylon filters, pose challenges with binding or adsorption of the pharmaceutical or formulation stabilizers, and nylon is less tolerant of sterilization by ionising radiation, which has become essential to single-use bioprocessing and rapid scale out of high value drug manufacturing such as experienced with COVID vaccines. In cases where a suitable alternative may exist, validating the alternative is essential to demonstrate that (i) the sterility of the drug manufacturing process is maintained with the specific drug formulation and manufacturing process conditions (sterilization conditions, time, temperature, volume throughput, etc), (ii) chemicals do not migrate from the filter that impact the quality of the drug product or patient safety, and (iii) the filter does not react with or absorb essential components of the formulation. As indicated in the applications summary table further below, it is estimated that no more 50% of use cases could be validated with an alternative, and that the validation resource cost will be very high thereby competing for budget, lab testing capacity, and subject matter expert resources for each use case. When alternatives and resources are available this part of the process can take between 1 to 3 years.

Moreover, fundamental changes in the base material of a validated sterilizing grade filter are deemed major changes by most global regulatory authorities, and thereby warrant strong supporting data and pre-approval by global health authorities, often in multiple global jurisdictions, before the alternative can be implemented. The regulatory preparation and approval steps, depending on the application and number of regulatory approvers, can take an additional 3 to 6 years per use case. Any expectation that

the pharmaceutical bioprocessing industry has the lab testing resources, budget, subject matter experts, and regulatory reviewers necessary to safely execute these changes over a 13-year period for all cases where filter alternatives are available, is implausible.

PFAS Types Common to Bioprocessing

Fluoropolymers (PTFE, PVDF, FKM, PFA) as well as PFAS-treated oleophobic membranes are the most common PFAS types understood used in the single-use bioprocess industry.

For PTFE, the high cost of these materials generally warrants these only for applications involving high temperature compatibility (i.e., steam sterilization, high temperature gases), caustic stability (oxidative gasses) and chemical compatibility where few to no other alternative materials exist. Hence these represent a small volume segment of the biotech materials, but one in which there are few to no alternatives to meet the aggressive chemical and process compatibility requirements.

For PVDF, this material is used in a wider capacity throughout bioprocessing including membranes, fittings, tubing, mixers, clamps, and so forth. For applications involving PVDF, there are in a moderate to large number of cases, alternatives (~50%). However, this varies depending on the application type and specific pharmaceutical manufacturing process. Moreover, given that many PVDF manufacturers have moved away from PFAS-based polymeric processing aides, the environmental and toxicologic safety risk associated with categorization of PVDF as a PFAS material is negligible.

Application Summary Table

The table below highlights initial assessments of biopharmaceutical applications and likelihood that existing alternatives could replace the current application. The table does not represent an in depth through analysis and is not intended to represent a conservative worst-case analysis. It is intended to provide some assessment and industry perspective within the relative short consultation period. Please note that where alternatives may be available, there is often a high economic trade-off, risk of product loss, or incurrent revalidation time and cost.

Application	PFAS Material	Potential Alternatives	Feasibility/Likelihood of Replacement*	Replacement cost/Process development/ Revalidation	Typical Replacement where available Timeline (yrs.)**	Patient Safety /Drug Quality Impact Risk	Market Fraction / Impact
Liquid Filtration – Sterile	PVDF	PES membranes, Nylon Membranes	<50%	Very High	9+ **per case**	High	Very High
	PTFE	""	<10%	Very High	9+ **per case**	High	Low
Liquid Filtration - particulate	PVDF	PES, Nylon	75%	Moderate	5+ **per case**	Moderate	High
	PTFE	PES, Nylon	30%	Moderate/High	5+ **per case**	Moderate	Low
Liquid Filtration - Virus	PVDF	PES	80%	Very, Very High	8+ **per case**	Moderate	Moderate
Gas filtration	PVDF	TBD	<10%	Moderate	4+ **per case**	Moderate	Very, Very High
	PTFE	TBD, PE	<10%	High	7+ **per case**	Moderate	Moderate
Gaskets & Seals	PVDF	TBD	50%	Moderate	TBD	High	Moderate
	PTFE	TBD	<20%	Moderate	TBD	High	Moderate
Components, Fittings, Tubing, Mixers, etc	PVDF, FEP, PTFE	PES, PP, Silicone, TPE	90%	High	3+ **per case**	Moderate	High
Pharmaceutical cryostorage Bags	PTFE, FEP, Custom Fluoropolymer	ULDPE bags, EVA	<50%	High	TBD	High	Growing
Cell culture cryostorage bags for cell therapy applications	FEP	EVA or EVA blends	75% (with significant trade-offs)	Very High	10+ **per case**	High	Growing
Non-Fluid Contact Materials (tubing clamps)	PVDF	Nylon, PP	High	Low	<1	Low	Moderate
Oleophobic/hydrophobic vent membranes	PFAS-coated PES	(Must redevelop)	>90% with redevelopment	High	11+ **per case**	High	High

*Table 1. Non-exhaustive overview of common bioprocess materials, including likelihood of identifying alternatives for each drug manufacturing use, estimated replacement resource cost and timelines when suitable alternatives are available, the risk to drug product quality and patients, and overall prevalence of use in the bioprocess market. For additional applications, please see text. *Feasibility/Likelihood of Replacement represents best estimates of the number of drug manufacturing use cases where a suitable alternative may exist and replaced with an alternative. **Typical Replacement Timeline represents the estimated time per drug application use case, when testing and qualification resources are available.*

Volume of PFAS Materials Placed on Market by Single-Use Bioprocess Sector

The volume of plastics imposed by the single-use bioprocess industry on the market has been estimates as less than 0.01% of the plastics market [12].

For PVDF, it is difficult to openly share the volumes we purchase. However, general assessments of the sector volume based on the major users of this materials employing standard market size estimate approaches estimate the single use sector volume on the order of no more than 0.5% of global PVDF production (global PVDF market: 67 metric kilotons) [17].

For PTFE, it is difficult to openly share the volumes we purchase. However, general assessments of the sector volume based on the major users of this material estimate the single use sector volume on the order of no more than 0.1% of global PTFE production (global PTFE market: 200,000 metric kilotons) [18].

Support for Related Bioprocess Industry Positions.

BPSA members are also engaged in parallel industry sector groups related to biopharmaceutical processing and supports the positions below, which help to create a more holistic view of the impact of the broad sweeping PFAS definition and ban on the biopharmaceutical processing industry.

- European Federation of Pharmaceutical Industries (EFPIA) and Associations and Animal Health Europe [3]
- BioPhorum response to the Annex XV proposal for universal PFAS restrictions [13]
- European Sealing Association [14]
- American Chemistry Council [15]
- American Society of Mechanical Engineers – Biopharmaceutical Process Equipment [19]

Socioeconomic Impact

Implementation of the 07FEB2023 ECHA proposals as is, will have an enormous and devastating impact on the bioprocess industry, its supply chain, and the availability of life impacting patient therapies. This includes vaccines, such as COVID therapies. As noted, it is estimated that virtually all medicinal therapies are impacted, and the resource cost to identify or develop alternatives, confirm, and validate potential alternatives in the multitude of locations within each unique biomanufacturing process, file and obtain global regulatory approvals where needed, will greatly exceed 13 years. In addition, many alternatives where available on the market may yield considerably poorer performance or significant additional manufacturing and economic risk to the drug manufacturing process. Ultimately these costs, including increased risk of drug shortages, and lack of development of new therapies will be passed to patients. Additional socioeconomic risks could conceivably include offshoring of impacted pharmaceutical manufacturing process and dependence on other geopolitical regions for the availability of impacted medicines.

Request for Exemption or Maximum Derogation Period

Given the enormous impact of the proposed restrictions on the bioprocessing industry, their supply chain, and the availability of patient therapies, we strongly request (i) recognition of Bioprocessing and its supply chain as industry sector under “missing Uses”, (ii) separate categorization of fluoropolymers used in bioprocessing, and (iii) an exemption or time-unlimited derogation for this sector.

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