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Subject: 2023 ECHA Annex XV Restriction Report Proposal

To whom it may concern:

These comments are submitted on behalf of the ASME Bioprocessing Equipment (BPE) Standards Committee regarding [1] *ECHA Annex XV Restriction Report Proposal* drafted for REACH by Danish, German, Swedish and the Netherlands Agencies. We take the opportunity to respond to the per- and polyfluoroalkyl substances (PFAS) REACH restriction public consultation period to share our initial views on how the proposed restrictions (The Proposal[i]) could impact the Bioprocessing Equipment Industry.

The following comments represent the majority opinions of the American Society of Mechanical Engineers (ASME) Bioprocessing Equipment Standards Committee members, rather than those of ASME. This Committee is responsible for the administration of the ASME Bioprocessing Equipment (BPE) standard. This standard is developed under procedures accredited by the American National Standards Institute (ANSI) as meeting the criteria for American National Standards. This standard is reviewed and updated on a regular basis with input from the Committee, industry, the public, and regulators using the consensus voting process. The ASME BPE Standards Committee has a diverse membership, comprised of members from engineering, government, and manufacturers from the United States and internationally.

Founded in 1880, ASME[ii] is a global standards organization that publishes consensus standards to help guide users in product manufacturing, current best practices, technology selection, and compliance with codes and regulations. Since its publication as a standard in 1997, the ASME BPE Standard (the Standard) has grown to become the world standard for equipment used in the production of biologics. The Standard represents the combined consensus efforts of hundreds of biopharmaceutical stakeholders representing the entire supply chain from material manufacturers, component, assembly and equipment manufacturers to the drug manufacturers themselves (equipment owner/users).

Proposal Impact Summary

In summary, without the availability of fluoropolymers and fluoroelastomers used in bioprocessing equipment, pharmaceutical manufacturers may not have the ability to produce life-saving drugs, including those already exempted under the Proposal. To date, the vast majority of biopharmaceutical manufacturing processes depend on components and equipment that utilize these materials due to their unique properties. Their properties are qualified to ensure a high-quality drug. As a result, the Proposal as written would severely impact the purity and efficacy of the drug, and also the cost of developing, manufacturing, and distributing biologics worldwide. At this time, there are no foreseeable equivalent alternatives for many applications and drug products.

Proposal Impact Evaluation

Both fluoropolymers and fluoroelastomers are mentioned as options to manufacturers in the Standard for use in the equipment intended for drug, vaccine, and other related manufacturing processes (see Appendix 1 of this document). In many material selection applications, the Standard presents options and then the equipment owners/users qualify their selections for use, often following long periods of testing, including human studies (e.g., COVID-19 vaccines). This testing and qualification of materials is frequently required by many regulatory bodies around the world, including the EMA and the US FDA. Although the current *ECHA Annex XV Restriction Report Proposal* under public comment suggests exemptions or time unlimited derogations for PFAS containing Medicinal Products (MPs), their API's and necessary packaging and dispensing (*see 2.2.3. Active substances in Plant Protection Products (PPP), Biocidal Products (BP) and Medicinal Products (MP*)), the Bioprocessing Equipment used in their manufacture is not specifically mentioned. Based on opinions shared by ECHA speakers during an April 5 webinar[iii] the equipment used in the production of PFAS containing drugs may also be derogated from the scope of the Proposal although spare parts for the equipment are not. It is important that all equipment, components and spare parts used in the production and delivery of all MPs (including non-PFAS MPs and their equipment) be specifically and clearly derogated or exempted as many different PFAS containing materials are specifically and intentionally utilized in their production. Without this processing equipment with its selected materials being included as a general category, 18 months after the Proposal comes into force, the MPs, APIs, packaging and dispensing of all biologics would be impacted, severely disrupting the bioprocessing industry.

Material selections are made based on the conditions of the process, such as cleaning and sterilization techniques (sometimes multiple conditions in the same location at different stages of the process), material chemical compatibility with solutions, biocompatibility and extractable testing, and mechanical performance – to name a few. Significant safeguards are necessary to validate a process such as a toxicological review of leachables and ongoing monitoring of the drug product and bulk drug substance in order to meet stringent product specifications and to ensure that impurities remain within worldwide recommended and regulated acceptable limits (e.g ICH Q3C, Q3D).[iv] Some Bioprocessing Equipment is designed to make more than one MP,

especially in contract manufacturing, introducing a wide variety of exposure conditions and required performance. Fluoropolymers and fluoroelastomers may be chosen specifically because of their compatibility with the drug products and wide range of performance.

Once these material selection decisions are made, and a bioprocessing product's regulatory filing is finalized, it is critical in many cases that not even a small change to the manufacturing process takes place. Unevaluated changes create the potential for negative impacts to the final pharmaceutical product (affecting the product's qualified identity, strength, quality, purity, or potency), which can lead to injury or even death of patients taking the MP.

Within the Standard, specific areas of mention for the use of fluoropolymers and fluoroelastomers (such as PTFE[v], FEP, PFA, ETFE, PVDF, VF2/HFP, FKMs and FFKMs)[vi] are pipes, tubes, fittings, seals, gaskets, vessels, sterile filters, and more. Understanding the considerations mentioned already, the universal ban of PFAS (encompassing the sub-category of fluoropolymers and fluoroelastomers) could be devastating to drug manufacturers in the sense that alternate materials used in the process must undergo proper evaluation, not just within the process itself, but on the effects to the end product. This concern is critical to the safety of patients, and multiplied by the thousands of drug products potentially affected by the Proposal.

Companies that utilize the Standard and choose fluoropolymers and fluoroelastomers have already considered or even tested other options and found fluoropolymers and fluoroelastomers to be the optimal choice to this point. Notwithstanding the cost to re-evaluate new manufacturing processes, a drug may have to be retested on the public to do proper diligence. If an alternative was possible (we are not sure that would be possible in all cases), it could take several years to safely qualify the change, and every change of material selection would need to be qualified independently based on unique process conditions. Examples of risk that necessitate these change evaluations would be: not knowing what happens to a prospective replacement rubber when repeatedly subjected to steam cleaning; unexpected extractables coming from an alternate piping or tubing product that could change the efficacy of a drug; unexpected equipment breakdown in the process leading to production stoppage of major seasonal vaccines; and particles created by chemical exposure over time that could contaminate the whole manufacturing process. The time represented by this required requalification equates to the potential delay of many drug and vaccine makers being able to supply currently approved life-saving products to the public at large.

Proposal Recommended Action

The ASME BPE Standards Committee position is to recommend that the Proposal grant the Bioprocessing Equipment systems and components (including spare parts) used to manufacture all MPs (including their intermediates and the raw ingredients) the same exemptions and time-unlimited derogations as PFAS drugs (MPs), since the MP and its process are both qualified and tested together. This will help minimize disruption to the patient, the drug supply, and the biopharmaceutical industry.

We ask that you take these considerations specific to the Bioprocessing Equipment Industry into account before rendering any final decisions that all fluoropolymers and fluoroelastomers receive any kind of restriction from your committee.

The ASME BPE Standards Committee appreciates the opportunity to comment on the 2023 ECHA Annex XV Restriction Report Proposal.

Thank you for your consideration of these comments.

Very truly yours,

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[i] *ECHA Annex XV Restriction Report Proposal* drafted for REACH by Danish, German, Swedish and the Netherlands Agencies - https://echa.europa.eu/documents/10162/f605d4b5-7c17-7414-8823-b49b9fd43aea, - Prepublication 07.02.2023.
[ii] ASME – American Society of Mechanical Engineers, Two Park Avenue, New York, NY 10016-5990, www.asme.org.
[iii] *ECHA UPFAS Infosession, April 5, 2023*, Mercedes Marquez-Camacho, Restriction Process Coordinator. European Chemicals Agency, Moderator.
[iv] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), *Route de Pré-Bois, 20. P.O Box 1894. 1215 Geneva. Switzerland.* E-mail: admin@ich.org, https://ich.org/.
[v] And Modified PTFE
[vi] ASTM D833 – *Standard Terminology Relating to* Plastics, ASTM D1600 - *Standard Terminology for Abbreviated Terms Relating to Plastics*, ASTM D1418 - *Standard Practice for Rubber and Rubber Latices—Nomenclature*

Appendix 1: ASME BPE 2022 edition, Current Standard References to PFAS

ASME BPE Standard, 2022 edition, References to PFAS, fluoropolymers, and fluoroelastomers			
Keyword	**Comment**	**# of Instances**	**Found on pgs**
"fluor-"	Instances related to fluoropolymers and fluoroelastomers; excludes reference to inorganic chemicals, fluorescence, elemental fluorine.	21	13,16,17, 42,358, 359
PTFE	All instances	29	17,42,126, 132,245,247, 324,358,359, 396
FEP	All instances	1	42
PFA	Only instances related to the polymeric PFA.	4	16,42,48
ETFE	All instances.	1	48
PVDF	All instances.	4	17,42,48
FKM	All instances, including FFKM.	8	42,245,358, 359,374