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WHITE PAPER

Proposed ban on PFAS compounds and its impact on the use of PVDF membrane filters in sterile filtration in Biopharmaceutical Manufacturing Processes

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"PFAS" stands for per-and polyfluoroalkyl substances. These are synthetically made chemicals that emerged in the 1940s and have been used in multiple industrial and consumer products. These consist of the strongest C-F bonds and have different intermolecular and intramolecular physicochemical interactions, that provide these with unique properties that can be applied for their use in multiple applications in food contact materials, medical devices, electronics, biopharmaceuticals etc. In Biopharmaceuticals, fluoropolymers such as PVDF and PTFE membranes are used for sterile filtration of air and liquids. PFAS persists in the environment as these does not break down easily and can build up in humans, animals and the environment over time. Considering this, the European Chemicals Agency "ECHA", has proposed a ban on the use of PFAS compounds. This white paper discusses the key concerns raised by BPOG against the proposed ban and its implication on the pharma/ biopharma sector and the existing potential alternatives of current PVDF membranes for sterilizing filtration applications.

Keywords: Biophorum, European Chemicals Agency (ECHA), fluoropolymers, per-and polyfluoroalkyl substances (PFAS), polyvinylidene fluoride (PVDF)

Introduction to PFAS

The acronym "PFAS" stands for per-and polyfluoroalkyl substances, a class of synthetically made chemicals. The definition of PFAS continues to evolve and Organization for Economic Co-operation and Development (OECD) in 2021 revised the PFAS definition as fluorinated substances that contain at least one fully fluorinated alkyl moiety, either methyl ($–CF_3$) or methylene carbon atom ($–CF_2–$) (1).

PFAS consist of either fully fluorinated (per) or partly fluorinated (poly) carbon chains attached with different functional groups (2). Based on fluorinated carbon chain length, PFAS can be distinguished as short and long-chain PFAS which also influences the behavior of the substance in the environment and its ecotoxicity & bioaccumulation.

The properties of fluorine and its bond with carbon (C-F) in the PFAS largely influence the unique chemical structure and physiochemical interactions inside the PFAS molecule, such as larger vanderwaal radius, low intermolecular and intramolecular interactions, low polarizability, which accounts for higher chemical and physical stability such as rigidity, higher volatility, surface wettability, oleophilic and hydrophobic character (3).

Polytetrafluoroethylene (PTFE) was the first PFAS compound synthesized as a fluoropolymer in the U.S. The credit for the accidental discovery of PTFE was given to Roy J. Plunkett in 1938 who was employed by DuPont de Nemours, Inc. that later patented the discovery of PTFE under the company Kinetic Chemicals in 1941 (4).
Since 1940s, PFAS have been incorporated into multiple industrial and consumer products such as PTFE-based non-stick coatings, protective coatings, stain and water-resistant products as these possess excellent grease and water-repellent properties. Other commonly used PFAS compounds are PTFE, ETFE, PVDF, FKM, FEP, PFA.

Ban on PFAS

Over the years, PFAS have been linked with human health effects as these are detected as environmental pollutants. Backed by numerous research studies, these have been proven to pose a threat to humans and the environment as they are persistent and resist degradation. "C-F" bonds in PFAS are among the strongest bonds in organic chemistry and some PFAS persist in the environment longer than any other synthetic

substance. This signifies that humans and other species will be exposed to much greater concentrations of PFAS, indicating that even if we fully eradicate the use and production of PFAS immediately, these will continue to be present in the environment and humans for many generations. Owing to this, these are also known as "Forever Chemicals".

Some PFAS have been found to accumulate in plants, groundwater, and animals, posing health risks and toxic effects. These are released in the environment directly from industrial facilities and indirectly during the use of consumer products, from food contact material.

Germany, Denmark, the Netherlands, Sweden and Norway have proposed a restriction proposal to ban PFAS under Article 68 of the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) to curb unacceptable risks to human health or the environment. This proposal focuses on the entire group of PFAS substances in order to avoid one PFAS being replaced by another (5). European Chemicals Agency (ECHA) is implementing a series of restrictions on the manufacture and use of PFAS.

PVDF And Biopharmaceuticals

The biopharmaceutical manufacturing process involves sterilizing filtration of air and liquids such as media, growth regulators, process intermediates, buffers, drug substances and drug products. PVDF, a highly non-reactive, high-performance thermoplastic fluoropolymer, made by polymerization of vinylidene difluoride is widely used for manufacturing of sterilizing grade membrane filters.

PVDF membrane filtration devices offer many attributes making these suitable for the wide range of sterilizing filtration applications. Hydrophobic PVDF membrane filters are used for air filtration and venting applications, and hydrophilic PVDF membrane filters, due to there low protein binding character, are suitable for filtration of therapeutic proteins and mABs.

Also, PVDF membrane filters are compatible with gamma irradiation, a key requirement for gamma sterilized single use systems, which are increasingly being used in biopharmaceutical processes. However, PVDF being a fluoropolymer, is also one of the PFAS substances that comes under the Family tree of PFAS substances produced by the OECD which are banned by ECHA as shown in figure. 1 (6).

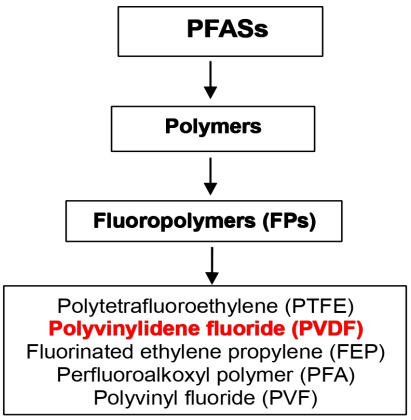

Figure 1.

Biophorum, a global biopharmaceutical manufacturing industry collaboration comprising all major manufacturers and their key suppliers (over 150+ companies, representing > 98% of all biopharmaceuticals manufactured worldwide) in their response to the ban proposed by ECHA have stated "PFAS compounds (mainly fluoropolymers PTFE, PVDF, FKM, FEP, PFA) are used extensively across multiple industries including biopharma due to their unique functional properties and low reactivity. It is considered by the BioPhorum collaboration that unless ECHA provide the biopharmaceutical manufacturing industry, which is highly regulated, with appropriate exemptions or derogations to find, test and validate alternatives and execute a transition out of these materials (where alternatives are available), there will be a real threat to the global availability of critical vaccines and biotherapeutics".

While acknowledging the concerns raised regarding potential adverse effects of PFAS on human health and the environment, it highlights the impact on biopharma manufacturing and supply of critical, lifesaving vaccines and

medicines. The development and production of these involve complex processes requiring adherence to stringent quality standards, regulatory compliance, and extensive testing. Any significant changes in these practices can have far reaching consequences for patients, innovation, and the ability of the industry supply chains to respond e.g., to future global pandemic threats.

It further states that the proposed change would require appropriate exemptions or derogations to find, test and validate alternatives, for transitioning out of PFAS materials (7).

Alternative to PVDF membrane filters

Polyethersulfone (PES) membrane filters are a credible alternative to hydrophilic PVDF membrane filters. These filters are widely used in the biopharmaceutical processes for a multitude of critical applications ranging from sterile filtration of media, buffers, process intermediates, drug substances and drug products. PES membranes offer lower protein binding, higher throughputs and wider pH compatibility (1-14 pH range) when compared to PVDF membrane filters. However, replacing hydrophilic PVDF membrane filters, is a daunting task, as any changes to registered drug manufacturing and analytical testing processes must be submitted to, and approved by, the relevant Regulatory Authorities during which the drug cannot be sold in the associated markets. Such regulatory compliances to change requirements shall require but not limited to filter validation with the drug product in question, and a comparative toxicological assessment of the filter extractable profile. This process can currently take 3-5 years, as it also means that the regulatory authorities will be facing a significant increase in change approval submissions (7).

On the other hand, hydrophobic PVDF membrane is used for air and gas filtration, which are non-product contact processes. Although replacing hydrophobic sterilizing filters for these non-product contact applications can have relatively faster regulatory approvals, there is no available alternative.

mdi has developed a new hydrophobic membrane which does not have any of the PFAS compounds. The membrane offers comparable hydrophobicity and is gamma stable, making it suitable for single use systems requiring sterilizing filtration of air/gases.

Conclusion

Considering ECHA's proposed ban on PFAS substances, PVDF (a PFAS polymer) membrane filters, which are used widely in disposable single-use systems for critical biopharmaceutical processes, need to be replaced. However, given the various challenges with regard to replacing these with existing alternatives and also finding new ones, a structured approach is needed to develop and implement a program, that facilitates and helps accelerate the required change.

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