Section III - Non-Confidential Comment

Context

Biotherapeutic filters are process filters used during the manufacturing of bio-therapeutic drug products or samples such as therapeutic replacement of enzymes, antibodies, blood, derivatives of plasma, and biopharmaceuticals. There are two types of these kind of filters: nanofilters and microfilters (together referred as "biotherapeutic filters").

Biotherapeutic filters are made with hydrophilized polyvinylidene fluoride ("PVDF"). They ensure that biopharmaceuticals are safe, ultimately protecting human health and patient safety. Both types of filters do not impose any risk to human health or the environment and as such biotherapeutic filters fall unduly under the prohibitions laid down in the REACH restriction Proposal.

Biopharmaceuticals are vital for medicine and have advantages over synthetic drugs, including targeting specific molecules and causing fewer side effects. They are crucial for treating various diseases, and patients rely on their availability. Regulatory action should not undermine their supply in the EU.

Nanofiltration is an integral part of biopharmaceutical manufacturing, ensuring efficacy and safety as it effectively removes viruses, including those causing blood-borne diseases. Implementing parvovirus-reducing steps improves viral safety. Unlike virus inactivation which leaves residues and virus removal does not target non-enveloped viruses, nanofiltration has no significant disadvantage.

Nanofiltration, usually the last step before a drug substance becomes a drug product, enhances product safety by removing viruses, including small non-enveloped ones. It effectively removes relevant viruses such as HIV, HCV, and HBV. It is a crucial step in ensuring the safety of plasma-derived and recombinant products. Nanofiltration's virus removal capacity is based on size exclusion.

The PVDF filter is particularly used when the level of protein is in high concentration and is therefore, a nice application among the filtering processes in biopharmacy. The safety and efficacy of biopharmaceuticals in humans require drugs of highest purity, right concentration allowing the API to work effectively. Any change in the manufacturing process would require new authorisations and testing which would last years.

Microfiltration is an essential step in the manufacturing process to separate targeted antibodies from the animal cell in the biopharmaceutical manufacturing. PVDF membranes used in microfiltration are not replaceable as all alternatives have a lower transmission of the targeted protein of interest filterability and only PVDF can meet the various performances required for drug product applications.

Regulatory Context

Regulators in Germany point out that there are high requirements for viral shedding filters used in drug manufacturing. For example, the filter manufacturer must validate such filters to ensure virus clearance capacity and, for example, the drug manufacturer must perform virus validation studies as part of the approval process. Extensive regulations and guidelines exist to ensure the viral safety of biological medicinal products such as Directive 2002/98/EC, Directive 2004/23/EC, Guideline on plasma-derived medicinal products, EMA/CHMP/BWP/706271/2010, Guideline ICH topic Q5A (CPMP/ICH/295/95).

Universal REACH PFAS Restriction

On a general basis, it is important to note that the restriction of PFASs must be substance-related and risk-based (Article 68 para. 1 of the REACH Regulation). It is clear that not all PFAS pose an unacceptable risk that would justify a restriction. Especially, the restriction must differentiate between the different groups of PFAS and the risks, and the risks posed by their uses. ECHA, in particular RAC and SEAC members, should consider that

fluoropolymers, such as PVDF, do not pose any risks to the environment and human health and should be generally exempted from the PFAS Restriction or benefit from a time-unlimited derogation.

Risk Analysis

Medical filters, made with substances like PVDF, have excellent properties such as temperature resistance, low permeability, and chemical resistance. They are operated by trained professionals, limiting exposure to workers and patients. No adverse events related to nanofiltration have been recorded, and regulators recognize it as a safe virus removal method.

Fluoropolymers, including PVDF, have heat resistance, biologically stable, and chemically stable. PVDF does not dissolve in water, immobile, insoluble (Water, Octanol, etc.), and too large to migrate to cell membranes and are not bioavailable or bioaccumulate. There are practically no alternatives that can replace the high performance provided by PVDF in in the biopharmaceutical sector.

PVDF, among other fluoropolymers is considered a polymer of low concern by OECD, do not bioaccumulate in living tissues. The fact that nanofiltration enabled by PVDF is used for many years without incident in a highly regulatory environment is a warrant of their safety of human health. Their overall safety is expressed by their use in the medicinal sector, Although not being considered a medicinal product, no biopharmaceutical product would be able to meet regulatory requirements should the use of PVDF in nanofiltration be restricted. After service life filters need to be incinerated due to their contamination with pathogens at special facilities as hazardous waste at high temperatures. Under these extreme conditions the C-F bond breaks down, thus completely destroying any PFAS.

Suggestions

Within that context, we kindly invite ECHA, in particular RAC and SEAC members, to consider the following options:

a) Option 1: biotherapeutic filters should be exempted from the REACH restriction Proposal *a priori* as they should not be covered by the REACH Regulation; or
b) Option 2: biotherapeutic filters should be exempted from the REACH restriction Proposal *a priori* as they are used in a closed system; in alternative,
c) Option 3: biotherapeutic filters should benefit from a time-unlimited derogation as the same rationale of plant protections products, biocides and human and veterinary medicines should apply.

In support of all three options, ECHA, in particular RAC and SEAC members, should consider that fluoropolymers, such as PVDF, do not pose any unacceptable risks to the environment and human health.

We ask ECHA, in particular RAC and SEAC members, to carefully take this information into account and reflect it in their opinions, in accordance with articles 70 and 71(1) REACH as well as the general principles of EU law, such as due process, right of good administration and right of defence.