Executive Summary

Biotherapeutic filters are used during the manufacture of biopharmaceutical drug products. Biopharmaceuticals are an important class of drugs manufactured or extracted from biological sources of human or animal origin. There are two types of filters used for virus removal and for removal of large particles that can be unintentionally introduced in the manufacturing process. The filters in scope of this study, are manufactured outside of the EU27/EEA and imported for use in the manufacturing of biopharmaceuticals. These filters contain a fully enclosed, engineered filter membrane made from the PFAS[1] material polyvinylidene fluoride (PVDF). The PVDF polymer is inert and meets the OECD criteria to be considered a Polymer of Low Concern. Based on its characteristics it is unlikely to have any intrinsic toxicological hazards. The available information indicates that the only property of concern is persistence.

Biopharmaceuticals

Biopharmaceuticals represent a significant part of the pharmaceutical market and include important therapeutic proteins, which are used to treat a number of prevalent, serious diseases. For example, monoclonal antibodies are used in targeted cancer therapies. Biopharmaceuticals are expected to increase in importance as trends in demographics imply that for example cancer, predominantly a disease of old age, will increase in prevalence. Additionally, with ongoing research and development it is expected that a proportion of the biopharmaceutical products currently at the clinical trials stage will achieve marketing authorisation (licencing/approval), and new types of biopharmaceuticals will be developed. Biopharmaceuticals contribute to meeting the intentions of Europe's Beating Cancer Plan.[2]

Biotherapeutic filters are used for safety and quality assurance of biopharmaceutical manufacturing process

Undesirable viruses may be present in the source materials used to manufacture biopharmaceuticals or may be unintentionally introduced into the process as contaminants. Such viruses can have serious clinical consequences and must be removed from the process. Nanofilters are one technology that is used for virus removal, and as such are integral to the safety and quality assurance of the biopharmaceuticals that are manufactured.

Microfilters are used for clarification/purification to separate the biopharmaceutical product of interest from cell debris and other impurities. As such they are integral to the quality assurance of the biopharmaceuticals that are manufactured. At present these filters are in the market entry/market development stage and are being trialled by some EU drug manufacturers.

PFAS restriction puts the use of Biotherapeutic filters at risk

In January 2023, competent authorities from five European countries [3] submitted a REACH Annex XV restriction proposal to the European Chemicals Agency (ECHA) proposing to restrict or ban the manufacture, use, and placing on the market of all PFAS within the EU, unless a use-specific, time-

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1 Per- and polyfluoroalkyl substance.

2 https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union/cancer-plan-europe_en ; https://www.ipaac.eu/news-detail/en/53-europe-s-beating-cancer-plan-a-new-eu-approach-to-prevention-treatment-and-care/

3 The Netherlands, Germany, Norway, Denmark, and Sweden.

limited derogation of either 5 or 12 years[4] is granted, although no derogation was recommended for this specific use (PVDF for virus removal filtration). This restriction proposal puts the use of biotherapeutic filters at risk.

SEA assesses the impact of a ban on suppliers, manufacturers and patients

Risk & Policy Analysts Ltd (RPA)[5] has been contracted to carry out a socio-economic analysis (SEA) to assesses the expected impact of the proposed restriction and the potential ban of certain types of biotherapeutic filters. The SEA also assesses the expected consequential impact on the ability of EU drug manufacturers that rely on these filters to produce the important biopharmaceuticals that use them (or are expected to use them for biopharmaceuticals currently in development at clinical trials stage), and the consequential impact on the health and wellbeing of current and future patients in the EU. The SEA quantitatively compares a continued use (baseline) scenario against a non-use scenario (NUS). The continued use scenario assumes that biotherapeutic filters containing PVDF can continue to be placed on the EU market and used in the filtration stages of biopharmaceutical manufacturing processes. The Non-use scenario (NUS) assumes a ban on the use of biotherapeutic filters containing PVDF in the EU for use in biopharmaceutical manufacturing.

The SEA comprises an Analysis of Alternatives (AoA), which assesses the technical and economic feasibility, availability, and suitability of potential alternatives to PVDF used in biotherapeutic filters. Alternative substances to PVDF as a membrane used in filtration, and alternative technologies other than filtration have been assessed. The AoA can be considered as a determinant of the extent to which the impacts identified in the non-use scenario will be felt.

Alternatives may provide lower performance

There are two main approaches for ensuring virus levels in biopharmaceutical products are sufficiently low to meet the required industry standards, these are virus removal, and virus inactivation. Virus removal technologies physically separate the virus from the biopharmaceutical product and include filtration methods by size exclusion – this includes both PVDF-based filtration as well as non-PFAS based filtration using materials. Other virus removal methods are chromatography, and precipitation. Virus inactivation technologies reduce virus infectivity by chemical or physical modification and include heat treatment, use of solvents or detergents, acid/alkali treatment, and irradiation. Each of these technologies have advantages and disadvantages and their relative effectiveness and performance depends on the type of virus, the type of cell, and other operating parameters. All these virus removal and virus inactivation technologies are currently used in biopharmaceutical manufacturing processes.

Several metrics are used to assess the performance of virus removal and virus inactivation technologies. The most important metric is viral clearance, which is a measure of the extent to which a virus has been removed from the feed stream during the virus removal stage of biopharmaceutical manufacture. Other parameters are also important, such as protein throughput. Performance metrics must be considered collectively, rather than in isolation, to assess the relative performance of virus removal technologies. Drug manufacturers need to demonstrate adequate virus removal performance in their manufacturing process.

EMA guidance[6] recommends the use of *orthogonal* technologies for virus removal; to use at least two independent virus removal technologies that use different modes of action. Any switch to an alternative type of virus removal must retain this orthogonality requirement. In practice this may

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4 Plus an 18 month transition period beyond the date of entry into force of the restriction.

5 https://rpaltd.co.uk/.

6 https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice

mean that currently used PVDF based virus removal filters would need to be replaced by another virus filtration technology, rather than another virus removal or virus inactivation technology.

Switching to alternatives will take time and be costly to implement

Limited data from customers of certain types of PVDF based biotherapeutic filters (i.e. biopharmaceutical manufacturers) was obtained in the consultation, and these data consequently represent only a small fraction of the nanofiltration market. It has therefore not been possible to prepare a robust estimate of the potential impacts on customers of a ban on the use of respective nanofilters. It is assumed that it would not be possible for biopharmaceutical manufacturers to switch to alternative virus removal technologies while maintaining orthogonality. Some non-PFAS based virus removal filters cannot provide the same performance as PVDF filters in regard to high throughput and high protein concentration preparations. These alternative filters can, however, achieve the same virus removal reduction values. It is expected that many customers would be able to make this switch, however the switching process will require revalidation and the completion of a new viral reduction study to assure acceptable virus removal. Development of a new PFAS-free filtration product is expected to take 10 years, including a viral reduction study, the entire process can take a total of 15 years.

Potential supply interruption for important biopharmaceuticals with impacts on patients

Given the limited data from customers, estimates on the impacts of the NUS on the final users of the biopharmaceuticals is difficult to estimate precisely. Clearly the risk is due to potentially interrupting the manufacturing process for biopharmaceuticals on which many patients suffering from serious diseases relies. Such patients include those undergoing treatments for cancer, immunodeficiency diseases, or cardiovascular diseases. While it is theoretically possible that the NUS would mean that biopharmaceuticals currently manufactured using some types of biotherapeutic filters would no longer be able to be produced, with severe consequences for patients, a more likely scenario would be the requirement for a transition period as drug manufacturers switch their virus removal technology to an alternative and complete the necessary revalidations and viral reduction studies. If this cannot be completed within the proposed 18-month transition period beyond the Entry into Force of the restriction, there is a risk of interruption in the supply of important biopharmaceuticals and as such patients could potentially go without an effective treatment option whilst implementation and recertification are done.