W. L. Gore & Associates' Comments on Dossier Submitters' Draft EU REACH Restriction on PFAS

Public Consultation

Request for Derogation: Products used for the processing and delivery of human and veterinary medicinal products

July 2023

I. Summary of Comments

Gore appreciates the opportunity offered by the public consultation process to provide comments on the Restriction Proposal for Per- and polyfluoroalkyl substances (PFAS).

The conclusions from our statement are summarized as follows:

- The Restriction Proposal has not defined a separate use for products used in the processing and delivery of human and veterinary medicines within the scope of Regulation (EC) 726/2004, Regulation (EU) 2019/6, and Directive 2001/83/EC.
- The unique combination of properties of fluoropolymers provides critical functionality and are ubiquitous in the processing and delivery of human and veterinary medicinal products.
- There are no existing alternative materials that meet the stringent performance requirements of products used for the processing and delivery of human and veterinary medicinal products and Gore is not aware of potential materials that could meet these requirements in the future.
- Without a derogation for fluoropolymers in this application, the safety and efficacy of human and veterinary medicinal products and the stability of their global supply will be compromised.

II. Reference in the Restriction Proposal

In Gore's examination of the Restriction Proposal, the following references to components used to process and deliver human and veterinary medicinal products were found:

- 5e. Textiles for use in filtration and separation media (Annex XV, page 5)
- 6j. Coating applications for medical devices other than Metered Dose Inhalers (Annex XV, page 7)
- 6n. Packaging of terminally sterilized medical devices (Annex XV, page 8)

These references only cover a small portion of the products and materials required to process and deliver human and veterinary medicinal products. Without a derogation for this use sector, the safety and efficacy of these medicines and the stability of their global supply will be compromised.

III. Derogation Request

Gore respectfully recommends adding the following Derogation in Column 2, paragraph 4d, of the proposed restriction:

4. By way of derogation, paragraphs 1 and 2 shall not apply to
   a. active substances in biocidal products within the scope of Regulation (EU) 528/2012
   b. active substances in plant protection products within the scope of Regulation (EC) 1107/2009

c. active substances in human and veterinary medicinal products within the scope of Regulation (EC) No 726/2004, Regulation (EU) 2019/6 and Directive 2001/83/EC
d. **products used for the processing and delivery of human and veterinary medicinal products within the scope of Regulation (EC) 726/2004, Regulation (EU) 2019/6, and Directive 2001/83/EC.**

IV. Brief Description of the End Use

This derogation should apply to all products used for the processing and delivery of human and veterinary medicinal products. This would include, but is not limited to, products used to develop, manufacture, test, store, and deliver these medicinal products. Delivery components would include medicinal products used in combination with a medical device that are regulated under EU pharmaceutical legislation (Directive 2001/83/EC or Regulation (EC) No 726/2004).

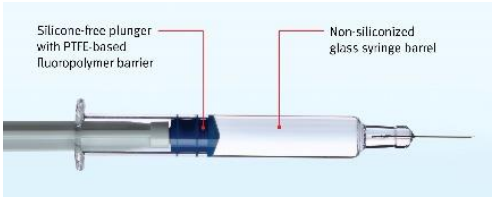
Processes to produce human and veterinary medicinal products are complex, highly specialized, and can vary from one class of medicines to the next. Many medicinal products, especially some of the newest and most advanced technologies related to biopharmaceuticals, are particularly sensitive to produce, which puts stringent demands on the materials with which they come in contact.

1. Product Examples

Fluoropolymer products are ubiquitous in the processing and delivery of human and veterinary medicinal products.

To clearly define the applications that should fall under the proposed derogation, we provide below a detailed description of the product and its reliance on PFAS. The product examples are Gore products, as details of comparable products manufactured by other companies are not publicly available. We believe that these products are representative of products manufactured in and placed on the EU market by other companies.

Table 1. Example Products used in the Processing and Delivery of Medicinal Substances

Product	Illustration	Description
GORE® IMPROJECT® Plunger for Prefilled Syringes		Silicone-free plunger for pre-filled syringes – The fluoropolymer barrier film provides consistent delivery performance over time and protects complex and sensitive biologics from leachables and silicone-induced protein aggregation and particulation.
GORE® LYOGUARD® Freeze-Drying Tray		Single-use, enclosed, freeze-drying trays that keep products such as liquid or lyophilised active pharmaceutical ingredient (API) in the tray during the lyophilisation process. The inert fluoropolymer film allows for a broad range of solvent polarities to be lyophilized while minimising product ejection, reducing operator exposure to APIs, reducing validation costs and eliminating the need for tray cleaning.
GORE® STA-PURE® Flexible Freeze Containers		A fluoropolymer container used for storing and transporting medicinal substances in bulk after freezing at -86 degrees Celsius - greater crack- and impact-resistance during cold chain handling protects the container's integrity hence reduces the risk of losing product during transport, storage, and handling. Its strength, durability, and low leaching properties make the container ideal for high-value biologics bulk substances such as vaccines, monoclonal antibodies, and antibody drug conjugates (ADCs).
GORE® STA-PURE® Pump Tubing		Fluoroelastomer tubing for peristaltic pumps protects against ruptures (even at high pressures), resists aggressive chemicals, enabling low extractables and leachables, and delivers consistent flow rates for days, weeks or even months.

GORE® Microfiltration Media		Fluoropolymer membrane enabled media used for filtration in pharmaceutical, biologics, lab and analytical, and industrial biotechnology applications. Properties include high flow rates and reliable retention of aerosols and particles compared to membranes manufactured from traditional polymers.
GORE® Protein Capture Device with Protein A		Used to purify target molecules from a bioprocessing culture mixture. Designed to improve productivity in affinity purification of antibody-based therapies. Utilises a unique fluoropolymer membrane solution that provides a binding capacity advantage at high flow rates and improves the speed of purification versus traditional affinity chromatography technologies.

The range of products are made of fluoropolymers and other PFASs with the vast majority of the PFAS volume meeting the criteria for Polymers of Low Concern (PLCs), under the definition provided by the OECD Expert Group on Polymers. [redacted]

[redacted]

2. Development, Testing, Approval and Change Requirements

In addition to the technical complexity of manufacturing medicinal products, there are requirements for testing, validation, and change management to ensure the risks to safety and efficacy are minimized. These steps add years and significant expense to developing new medicinal products and their associated manufacturing processes.

When an approved medicinal product experiences a change to the raw materials, packaging, manufacturing process, equipment, or other support system, a revalidation of the product quality is required. Depending on the nature of the change, safety, and efficacy revalidations (i.e., non-clinical and clinical studies) may also be necessary. **For example, changing the nature of the materials that come into direct contact with the drug substances and drug product and may require repeating one or more of the evaluation phases of product development described below which can interrupt the availability of medicinal products and create significant costs that could be otherwise spent on development of new medicines.**

The European Medicines Agency (EMA) is responsible for the scientific evaluation of applications to market medicinal products in the EU and approval is granted by the European Commission. The EMA evaluation includes quality, safety, and efficacy data for the medicinal product.

- Quality –The quality evaluation includes the definition of the drug product, including the container closure system, and describes the specifications, manufacturing processes, and analytical procedures associated with a drug product and its components. In addition, the applicant must fully characterize the components and drug product, including impurities, and demonstrate, through validation, that proper controls are in place to reproducibly manufacture a safe and effective medicinal product. Risks associated with the product and process must also be identified and adequately mitigated.

- Safety – The safety evaluation is a comprehensive synopsis of non-clinical data and an interpretation of its clinical relevance. This includes chemical, biological, pharmacological, and toxicological laboratory testing of the drug product that is produced per the methods and controls stated in the quality data.

- Efficacy – The efficacy evaluation is a critical analysis of the clinical data, which is collected in four phases.[1]
    - Phase 1 – Small scale human trials focused on dosage and safety. (~ 1 year)
    - Phase 2 – Increased scale trial focused on safety and efficacy. (~ 2 years)
    - Phase 3 – Trial in larger populations to generate robust data about safety, efficacy, and the overall benefit-risk relationship of the medicine. The drug product at this stage is typically compared to a placebo and/or to an active comparator. (› 4 years)
    - Phase 4 – Often, post-authorization trials are required. They include thousands of patients globally and can take over 10 years to finalize. They are conducted to get more detailed information on a medicine's efficacy and safety in even larger patient populations.

V. Need and Justification for Derogation

Without a derogation, materials that are critical to the production, storage and delivery of medicinal substances would not be available. This could lead to increased risk to the quality and availability of many medicinal substances and significant costs across the industry and to patients and governments as a result. We propose that a derogation is justified based on the following points:

- The **performance requirements** for processing and delivery of medicinal substances
- The **lack of availability of alternatives** that would provide the required level of performance
- The **time required** for research and development to investigate and evaluate potential alternative materials, and if a feasible alternative is identified, the time required to identify develop, test, and commercialize products and then the medicinal substances made using those products
- The **large and disproportionate socio-economic cost** of restricting the use

1. Performance Requirements

The products listed in Table 1 are representative products from Gore but are only a fraction of the many uses of PFAS in the processing and delivery of medicinal products. There is no single set of performance requirements for this sub-use, as a whole. Instead, the individual requirements vary by product type, the specific medicinal substance, and the processing conditions that lead to unique combinations of specifications. The performance requirements for products relevant to this sub-use typically must meet combinations of the requirements described in the table below.

[1] Marketing authorisation | European Medicines Agency (europa.eu)

Requirement	Description
Low levels of leachables and extractables	For the purposes of this derogation, leachables are defined as compounds that leach, under normal conditions of use, into the drug product formulation from the container closure, resulting from direct contact with the formulation. These leachables contaminate the drug product and may reduce its effectiveness and increase patient risk of adverse effects (e.g., inflammation, immunogenicity responses, systemic toxicity). Leachables in the final product are measured by the pharmaceutical manufacturer. Extractables are defined as compounds that can be removed from the container closure system, packaging material or manufacturing processes under aggressive conditions which include solvent, time, and temperature. Extractables are typically predictive of leachable results. Low levels of extractables are a factor in the selection and qualification of materials used by pharmaceutical and biopharmaceutical manufacturers. Non-fluoropolymer materials are often inadequate for meeting process and product design requirements. Low levels of extractables also greatly simplifies the design and execution of leachable studies for enabling regulatory approvals. The BioPhorum Operations Group (BPOG) and US Pharmacopeia (USP) guidance drives the importance of materials having low levels of extractables and leachables when single use systems are required. Extractables measurement is an industry requirement that is measured by the following standard methods: • BioPhorum best practices guide for extractables testing of single-use components used in biopharmaceutical manufacturing BioPhorum Leachables: Best practices guide for evaluating leachables risk from polymeric single-use systems • USP <665> Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products • USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems • USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
Chemical and thermal resistance	The material needs to be highly resistant to aggressive chemicals, such as strong acids and bases, polar and non-polar solvents, and reactive gases. These properties are essential to pharma processing where (for example) sodium hydroxide is used as part of a standard decontamination process, or (for example) where aggressive solvents are required for critical process steps, like ethanol diethyl pyrocarbonate (DEPC) for mRNA. These properties are also essential to resistance to reactive gases used in sterilization, like ethylene oxide (ETO) or vapor phase hydrogen peroxide (VHP). The material may not degrade in the presence of high temperatures, which are used both in synthesis/manufacturing of small molecule pharmaceuticals as well as to sterilize products used in the processing and delivery of pharmaceuticals and biopharmaceuticals.
Low particulation	Protein aggregation and particulate contamination in medicines can affect their efficacy, potency, clinical safety, and immunogenicity. • USP <788> Particulate Matter for Injections • USP <789> Particulate Matter in Ophthalmic Solutions

Requirement	Description
Bioinert and biocompatible	The material does not initiate a response from the host for this use. This is an industry requirement that is measured by the following standard methods: • USP <87> Biological Reactivity Tests *In Vitro* • USP <88> Biological Reactivity Tests *In Vivo* Class VI • ISO 10993 Biological Evaluation of Medical Devices
Non-pyrogenic	Bacterial endotoxins are fever-causing agents found in the cell wall of certain bacteria, typically introduced through material processing. If introduced into the bloodstream or spinal fluid via a parenteral drug or medical device, fever, septic shock, organ failure, or death can occur. • USP <85> Bacterial Endotoxin Tests
High strength and stability	The material has excellent strength and durability and can withstand exposure to mechanical and thermal stresses in use.
Flexibility and durability at cold temperatures	Proteins can degrade at temperatures above about -86°C, impacting their effectiveness. Therefore, they require processing and storage at very low temperatures. The cold durability market requirements refer to the ability of a container to remain integral throughout the typical lifecycle. Integral means no cracks or holes in the container that would allow the drug substance to leak during the thawing process or contamination to enter the container at any point in the lifecycle. The lifecycle refers to filling the container with bulk drug substance, freezing, handling, shipping, storage, thawing and draining. Freezing and storage are typically done in freezers set at -86°C, where the storage can be anywhere from a couple months to several years. Shipping is typically done globally from one continent to another, and product is kept frozen either by dry ice or in temperature-controlled containers also set down to -86°C.
Low coefficient of friction	Syringe plungers need to slide against bare glass with low force, enabling consistent medicinal deployment.
High binding capacity at high flow rates	The microstructure of the material impacts the binding capacity (or the ability to capture protein) in chromatography devices. Increased binding capacity greatly reducing process time.

2. Alternative Assessment

Gore operates within a segment of the pharmaceutical and biologics market that requires the performance characteristics uniquely enabled by fluoropolymers. Gore has developed products to meet customer's performance specifications that could not be met by other materials. Many of our customers have confirmed that they have investigated alternative materials but have been unable to identify feasible options. Fluoropolymers are generally more expensive than other polymers, so customers have an economic incentive to use other materials, when it is possible to meet their performance requirements. This position is confirmed through the public comments from relevant industry groups in the medical device and pharmaceutical

manufacturing sectors, including those from Bundesverband Medizintechnologie (BVMed e.V), BioPhorum, European Federation of Pharmaceutical Industries and Associations (EFPIA), MedTech Europe, and others.

Based upon Gore's nearly 50 years of expertise and deep knowledge of material science, established polymers cannot meet the vital functions needed to be suitable alternatives to fluoropolymers in the processing and delivery of human and veterinary medicinal products. Gore continually follows external developments of new materials while also pursuing an R&D program to develop novel materials that meet market needs. However, no materials that can replace the need for fluoropolymers in these applications have been identified.

a. Extractables and Leachables

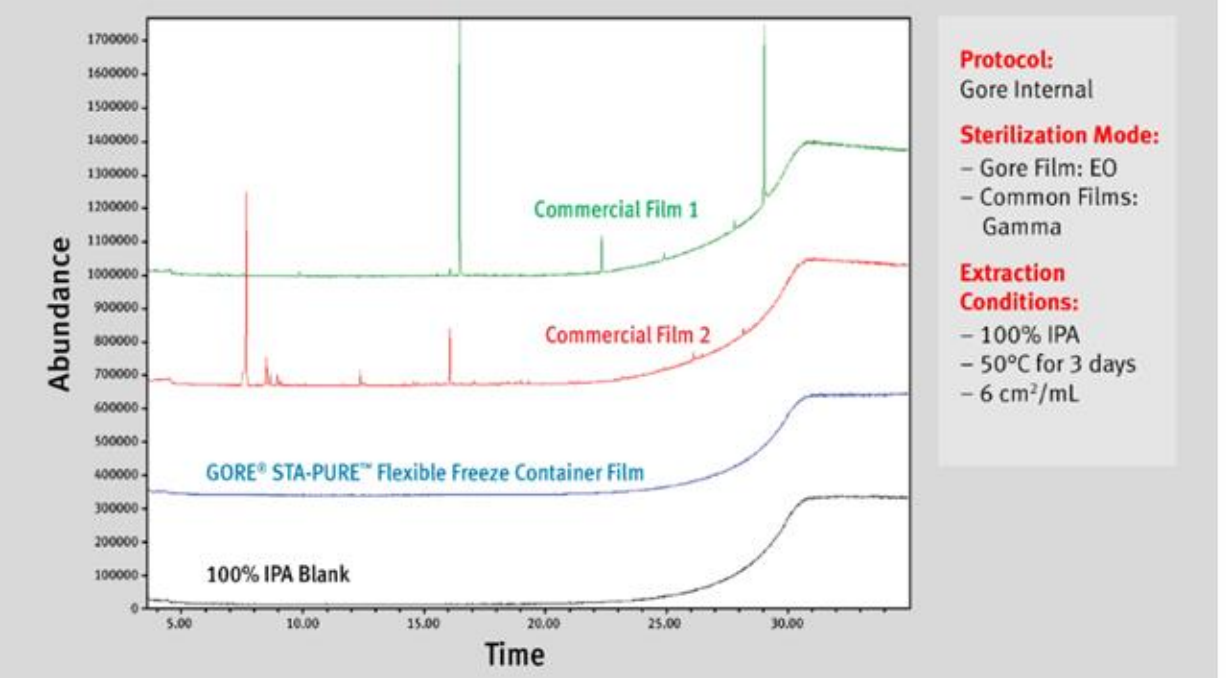
As stated above, extractables are measured under aggressive conditions, and are typically predictive of leachable results.

Unlike alternative materials, fluoropolymers do not require the use of additives (e.g., antioxidants, slip/mold release agents, UV inhibitors, plasticizers) to enhance their chemical, physical, and mechanical properties.

Figure 1, below, shows the stacked extractables comparison[2] of a fluoropolymer film (labeled as GORE® STA-PURE™ Flexible Freeze Container Film) to potential alternative materials: Commercial Film 1 [redacted] and Commercial Film 2 [redacted]. The peaks seen in the Commercial Film 1 and Commercial Film 2 curves are due to impurities that have been extracted from the films. In contrast, the fluoropolymer film curve has the same shape as the control blank, indicating that no impurities were extracted from the material.

[2] Test performed according to the BioPhorum Operations Group Ltd "Best Practice Guide for Evaluating Leachables Risk from Polymeric Single-Use Systems used in Biopharmaceutical Manufacturing," July 2021 (https://www.biophorum.com/download/best-practices-guide-for-evaluating-leachables-risk-from-polymeric-single-use-systems/)

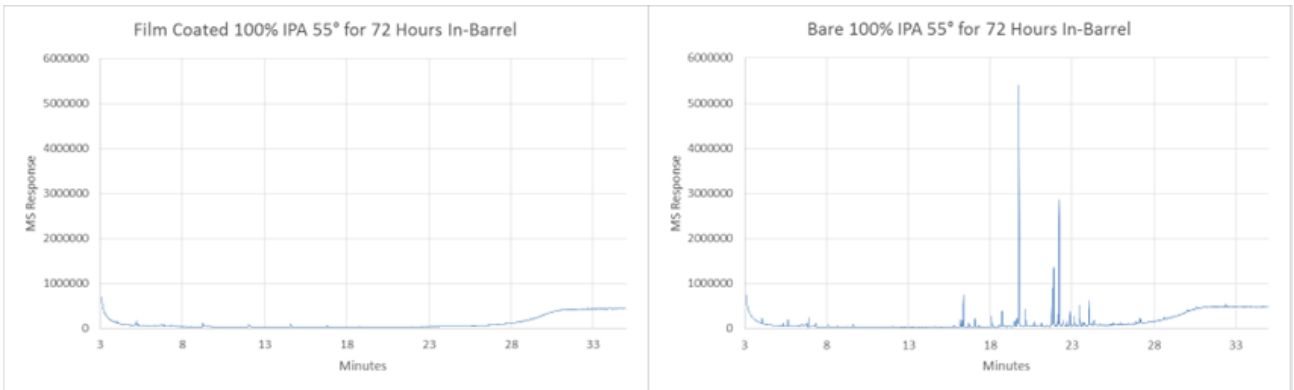
Figure 1: Extractables Comparison between Alternative Solutions and GORE STA-PURE® Flexible Freeze Container Film



Test Details: Following the recommended sterilization protocols for each, a 6cm²/mL sample of Gore film and commonly-used films were tested in 100% IPA at 50°C for 3 days. The impurities were measured using GC/MS.

Another example of low extractables can be seen in the comparison of the GORE® IMPROJECT® Plunger for Prefilled Syringes (rubber plunger with fluoropolymer barrier film) versus an uncoated rubber plunger. Again, the Gore fluoropolymer has no peaks, indicating that no impurities were extracted from the material, while the uncoated plunger shows impurities that have been extracted by the solvent.

Figure 2: Extractables Comparison between Plunger with Fluoropolymer Barrier Film and Uncoated Rubber Plunger



Fluoropolymers are uniquely able to meet the requirements for low extractables and leachables in combination with other typical requirements for this sub-use.

b. Chemical Resistance

Fluoropolymers, like PTFE, FEP and PVDF, are chemically inert and, therefore, have a high degree of resistance to fluids used in the processing and delivery of human and veterinary medicinal products. For example:

- sodium hydroxide is used as part of a standard decontamination process
- aggressive solvents are required for critical process steps, like ethanol diethyl pyrocarbonate (DEPC) for mRNA
- reactive gases, like ethylene oxide (ETO) or vapor phase hydrogen peroxide (VHP) are used in sterilization

This can be seen by analyzing the Labware Chemical Resistance Table[3], which assesses the effects of over 200 chemicals on common plastics used in the industry. The fluoropolymers FEP and PTFE show no damage after 30 days of constant exposure to nearly all chemicals evaluated. Resistance to these chemicals enables fluoropolymers to maintain their structural integrity, which prevents the generation of leachables and particulates and extends the usable life of the products.

Fluoropolymers are uniquely resistant to the broad range of chemicals that are relevant to this sub-use.

c. Flexibility and durability at cold temperatures

As indicated in Section V.1, materials for certain medicinal product processing and storage must remain flexible and durable at very low temperatures.

[redacted]

Fluoropolymers are the only material that remains flexible and strong at the necessary process temperatures and meets other process requirements related to extractables and biocompatibility, among others.

3. Timeline

As the Dossier Submitters did not broadly discuss the use of PFAS and the lack of potential alternatives in the processing and storage of medicinal products, the use of PFAS-based components in those applications is proposed to be banned 18 months after EiF. We have demonstrated that no alternative is currently available. This section underlines the timeframe needed in the uncertain case that a new material would be discovered or invented for this application.

[3] https://tools.thermofisher.com/content/sfs/brochures/D20480.pdf

Due to the unique material properties described in the Alternatives Assessment, Gore, and other key actors in the supply chain, do not believe that alternative materials can be developed to replace fluoropolymers in these applications. This first step involves discovery, for which a specific timeline cannot be predicted.

Examples from the past, show that the time span to develop new materials can vary significantly. For example, the development of acrylic polymer took several decades. The process from the first synthesis of acrylic acid to the introduction of the commercial polymer, was an 85-year journey.[4] While the development of PTFE from the "accidental" discovery to a commercial product took about 10 years, from 1938 to 1948[5], and then decades more to mature that technology into the materials used today. Development advances over this time have had to occur in polymerization, finishing, lubrication and blending, pelletization, extrusion, etc. In absence of such an initial unexpected discovery, we can only speculate that developing a new polymer until commercial availability will take **more than 25 years**.

Timelines to develop and validate alternative materials in the highly regulated medicinal product industry can be significantly longer than in other industries. To estimate the time required to bring an unknown alternative to market, Gore has divided the effort into three phases:

Table 3: Steps for developing an alternative to fluoromaterials in processing and storage of medicinal products

Phases	What activities does this step entail?	Time required for step
Time for Gore to develop alternative	For this application, Gore has shown that invention or breakthrough processing technology is required to develop an alternative. The likelihood of this is low and the timeline is long and unpredictable.	**Unknown** Estimate >20 years
Time for Gore to Validate and Commercialize	Internal evaluations of material performance and process validations following ISO13485 and ISO15378 quality system requirements. Supply chain establishment.	~3 years
Time for Customer to Validate and Commercialize	This estimate includes performance validations, process integration validations, clinical studies, and regulatory submissions	> 5 years
Total		**Unknown** **>25** years

[4] See https://www.ptonline.com/articles/tracing-the-history-of-polymeric-materials-part-20.
[5] https://www.teflon.com/en/news-events/history#:~:text=An%20Accidental%20Discovery&text=Roy%20J.,to%20form%20polytetrafluoroethylene%20(PTFE).

4. Socio-economic Impacts

Without a derogation, there will be multiple types of impacts in the EU impacting both quality of healthcare and costs.

By restricting the use of fluoropolymers in these applications, businesses with products used in the processing and delivery of human and veterinary medicinal products must either (i) use materials that are not capable of performing their required functions, or (ii) move processing outside of Europe, where fluoropolymers may be used. Since the current European share of global pharmaceutical revenue is 23.4% and the estimated Research and Development spending is 41.5 bn Euro (2021, statista.com), both options would require enormous time and cost investments. In addition, this would result in compromised safety and efficacy, instability of global supply, and a hiatus on new drug development, as resources focus on revalidating existing medicinal products.

a. Safety, Effectiveness and Availability of Medical Devices

Some examples of product related consequences associated with the restriction of the Gore products discussed in this document include:

- GORE® IMPROJECT® Plunger for Prefilled Syringes – Increased risk of inflammation and immunogenicity response in patients [redacted] and the inability to offer some drugs and vaccines, in the most efficient and widely deployable format of a pre-filled syringe.
- GORE® LYOGUARD® Freeze-Drying Tray – Increased risk of cross-contamination leading to drug product loss.
- GORE® STA-PURE® Flexible Freeze – Increased risk of drug product loss due to bag breakage or contamination during transport, storage, and handling.
- GORE® STA-PURE® Pump Tubing – Increased risk of tubing failure, leading to contamination and drug product loss during processing.
- GORE® Microfiltration Media – Increased risk of drug contamination which limits vaccine/drug supply or increased harm to patient.
- GORE® Protein Capture Device with Protein A – Loss of productivity (6 – 10x), causing increased drug development time, increased processing time, increased manufacturing footprint and consumables, and increased risk of contamination during storage.

b. Financial Impact

A restriction on a critical component in a range of medical devices will also have financial implications to individuals, industry, and governments. Across a range of uses, costs may increase due to:

- Increased costs and reduced yield on expensive medical product production due to components or quality control failures.

- Increased patient care costs due to limited availability of necessary medicinal products.
- Increased cost to industry for development, testing and validation of alternate solutions which are demonstrated not to meet all the performance requirements.
- Costs to industry, and eventually to patients and governments, related to relocating manufacturing outside the EU where PFAS-based components remain available.

c. Disruption to Innovation and Systemic Regulatory Constraints

Assuming manufacturers attempt to use alternative materials in the processing of medicinal substances, a restriction on PFAS in this use will cause an unprecedented surge in testing, validation, and regulatory submissions simultaneously. The unprecedented surge in activity will distract the entire industry in Europe from innovation to develop and produce new medicines. A subsequent concern would be the resulting increased magnitude of burden on the regulatory process to review and approve changes to the manufacturing of the vast majority of medicinal products.

An instructive example is the recent implementation of EU MDR 2017/745. This regulation replaced the previous EU Medical Device Directive (MDD 93/42/EEC) with sweeping changes to the clinical, quality, and technical requirements for medical devices; the vast majority of the previous directive was re-written for the MDR, and placed significant burdens on the Manufacturer, Notified Bodies, and other supply chain actors to verify and ensure safety and efficacy. This led to the need to have all products certified by notified bodies. Initially a transition period of 7 years was intended. The long transition period for EU MDR 2017/745 was developed considering the medical device industry complexities, however it was insufficient. Due to the significant risk of medical device shortages, the transition period was recently extended by 3-4 years[6]. This medical device shortage risk stems from limited notified body capacity to certify these devices under the regulation.

A change due to a PFAS restriction will likely be more complicated since it has the potential to impact the medicinal product itself, drive the need to redo prior testing and validation work, and introduce additional uncertainty due to components that are not expected to have sufficient performance.

[6] Extension time depends on risk classification of affected medical devices. Regulation (EU) 2023/607 amended the MDR on 20 March 2023.

VI. Additional Information

1. Use Assessment

Additional Information can be found in the Use Assessment that was provided in March 2022 (Annex I). Gore has learned that because this assessment received by the Dossier Submitters after the end of the Call for Evidence in September 2021, it may not have been reviewed.

Some topics covered in the Use Assessment that are not covered here include:

- Volumes of PFAS Used (Section 3.2)
- Emissions (Section 3.3)
- Market Information (Section 5)
- Consequence of no exemption (Section 7)
- Justification for a derogation (Section 8)

Please note that the Use Assessment covers all products in our life science business. Therefore, it also contains information on other Gore products which fall under other applications/sub-uses.

2. Gore's Derogation Request on Fluoropolymers

Additional information on biocompatibility, responsible manufacturing, processing, and disposal of fluoropolymers are provided in Gore's separate derogation request for fluoropolymers.

[redacted]