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

Public consultation

Request for Derogation: Elastomeric components (including syringe plungers) used for container closures in primary packaging and delivery of human and veterinary medicinal products

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I. Summary of Contents

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

With this statement, Gore will provide information to support a time-unlimited derogation for elastomeric components (including syringe plungers) used for container closures in primary packaging and delivery of human and veterinary medicinal products.

The conclusions from our statement are summarized as follows:

- The unique combination of fluoropolymer properties provides critical functionality for elastomeric components (including syringe plungers) used for container closures in primary packaging and delivery of human and veterinary medicinal products.
- This use is described in the restriction proposal in relation to the time-limited derogations in paragraphs 6n and 6j, however it is unclear whether the derogations as written include all relevant uses of this product. Regardless, a 13.5-year derogation is insufficient for this use.
- There are no existing alternative materials that meet the stringent performance requirements and Gore is not aware of potential materials that could meet these requirements in the future.
- Without a time-unlimited derogation for this sub-use in this application, the safety and efficacy of medical devices and the stability of their global supply will be compromised.

II. Derogation Request

Considering the arguments and evidence presented below, Gore respectfully requests to include the following time-unlimited, application-specific derogation in Column 2, paragraph 6 of the proposed restriction:

Elastomeric components (including syringe plungers) used for container closures in primary packaging and delivery of human and veterinary medicinal products

This sub-use is intended for injectable dosage systems that have primary packaging components consisting of elastomeric material combined with fluoropolymer coatings or barrier films[1]. Examples of products that utilize these components include pre-filled syringes and cartridges, pen and jet injectors, lined caps for blow-fill-seal (BFS) plastic containers, and access ports to plastic bags or blow-molded infusion containers.

As described in Section III.b below, this use is listed in several places in the restriction proposal. This specific derogation is proposed for clarity as there is some ambiguity in the scope of products which would be covered under paragraphs 6.n and 6.j in the Restriction Proposal. Alternatively, this use could be included in a derogation that covers **products used for the processing and delivery of human and veterinary medicinal products** based on other inputs to the public consultation.

[1] United State Pharmacopeia ‹382› "Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems"

III. Background

a. Brief Description of the End Use

While the most conventional form of injectable drug delivery involves the classic combination of a vial and a hypodermic needle, more recent innovations have advanced the parenteral administration of Active Pharmaceutical Ingredients (API). Most notably, prefilled syringes have become a very popular method of drug delivery in the past few decades. With a prefilled syringe, the process of administering a drug product can be safer, quicker, and easier for nurses and patients. The prefilled nature of these syringes means nurses or patients are not required to prepare and draw the medicine into the needle, as the correct amount is already present in the barrel ready for quick injection. This creates less room for preparation and dosing errors when compared to vials and enables a more efficient drug delivery process.[2] It also reduces risks of environmental contamination upon transfer from vial to syringe prior to administration.

There are three types of syringe plungers available on the market:

- rubber plunger with no coating or barrier film and a silicone lubricant applied around the circumference
- rubber plunger with a fluoropolymer coating or barrier film at the drug contact surface and a silicone lubricant applied around the circumference
- rubber plunger with a fluoropolymer coating or barrier film on the drug contact surface and around the circumference (no silicone lubricant)

The type of plunger utilized depends on the sensitivity of the medicinal product (including biologics) and the expected duration in the syringe before use. Biologics are a specific category of medicinal substances and include a wide range of products such as vaccines, gene therapy, tissues, and recombinant therapeutic proteins[3]. These biologic products can be more sensitive to storage and packaging conditions than conventional drugs. For example, they can be vulnerable to silicone-induced protein aggregation, particle formation, and drug product precipitation. They can also be vulnerable to leachables from the device components, like syringe plungers, causing safety or efficacy concerns.

An example of this phenomenon is highlighted by an investigation[4] into a substantial increase in the incidence of pure red cell aplasia in chronic kidney disease patients that were treated with Eprex, a biologic medicinal product, in a pre-filled syringe. The study identified leachables from the syringe's uncoated rubber plunger that were shown to increase immunogenicity and concluded that these leachables were the critical factor in the increased incidence. As a result, the uncoated rubber plunger in Eprex pre-filled syringes was replaced with a fluoro-resin coated plunger. Intensive surveillance after this change showed that Eprex no longer causes increased incidence of pure red cell aplasia.

Many syringe plungers used in pre-filled syringes, including silicone-free plungers (plunger stoppers) for pre-filled syringes, utilize a fluoropolymer barrier film that provides a barrier to leachables/extractables, consistent delivery performance over time, and can protect complex and sensitive biologics from silicone, which can induce protein aggregation and particulation[5].

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[2] https://www.pharmaceutical-technology.com/sponsored/prefilled-syringes-benefits-performance-siliconization/
[3] https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers
[4] Kidney International, Vol. 67 (2005), pp. 2346-2353
[5] Further explained below in Section IV a.

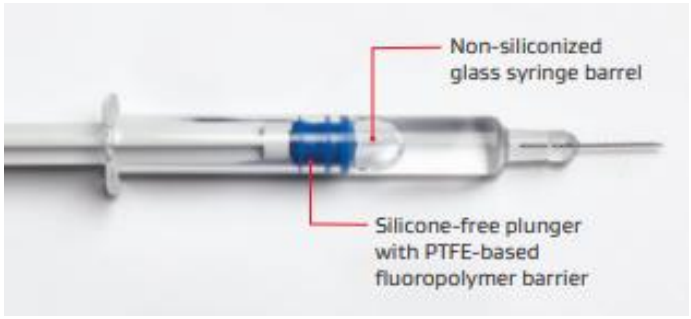

Figure 1. GORE® IMPROJECT® Plunger for Prefilled Syringes

The fluoropolymers used in the barrier film meets the criteria for Polymers of Low Concern (PLCs), under the definition provided by the OECD Expert Group on Polymers. [redacted]

[redacted]

[redacted]

[redacted]

b. References in Restriction Proposal

In Gore's examination of the Restriction Proposal, the following references to plungers were found:

- A.3.10.1.4. Coatings:

*"Coatings are applied in catheters, metal stents, catheter balloons, **plunger stoppers**, needle shields, and membranes. Fluoropolymers are often used as coatings because of their advantageous properties... In some cases, e.g., for **plunger stoppers**, the fluoropolymer coating prevents compounds from leaching into the drug product."*

It is unclear if this sub-use applies to the plunger described in Section III.a because it uses a fluoropolymer barrier film and the definition of a coating is not specified.

- A.3.10.1.7. Packaging:

*"Packaging components like ampoules, single and multi-dose containers, bottles (also in caps and actuators), cartridges; pressurized containers, **syringes** and vials are known to (partly) contain PFAS, especially fluoropolymers. Liquid drug products for injection (e.g., vials, **prefilled syringes**) are packed in closed container systems. These types of packaging are mostly a combination of glass (vial, barrel) and elastomers (**stoppers, plungers**, seals). Because of the extended period of contact between the drug product and packaging, elastomer extractables could leach into the drug product, potentially affecting the product safety. ETFE or PTFE coated elastomeric components are often used to minimize interaction between the drug and the packaging. As this kind of packaging is in direct contact with drug product, they are part of the drug product registration."*

This description of packaging also appears to cover the plunger described in Section III.a since it is considered part of the primary packaging and it is registered with the drug product as a single entity. However, not all of these products are terminally sterilized, as the resulting proposed derogation suggests. For example, most biologic medicinal products cannot be terminally sterilized without risk of adversely affecting the therapeutic safety and efficacy.

In both cases, a 13.5-year derogation is not sufficient to identify an alternative material, develop a product, and gain regulatory approval for use.

c. Regulations

As stated in Section *A.3.10.1.7.* of Annex A of the Restriction Proposal, pre-filled syringes are part of the drug registration. This is described in detail by the European Medical Agency[6], which gives pre-filled syringes as an example of a medicinal product used in combination with a medical device. This means that the medicinal product, pre-filled syringe, and other constituent device components, are approved in combination under EU pharmaceutical legislation (Directive 2001/83/EC or Regulation (EC) No 726/2004) and changes to the syringe, including the syringe plunger, may require requalification of the entire product and reapplication for a Marketing Authorisation. Therefore, putting a derogation restriction on the delivery device or its components essentially puts a restriction on the *medicinal product,* which would contradict the derogations provided for APIs in Column 2, Paragraph 4 of the proposal. It would also restrict or eliminate the availability of many other therapeutics (human and veterinary) that are critical to society over time.

IV. Need and Justification for Derogation

a. Performance Requirements

As noted above, plunger requirements are unique for each drug due to the sensitivity of the drug and the expected duration in the syringe before use. However, the most demanding drugs require the following:

Table 1. Performance Requirements for Plungers used in Syringes for Medicinal Products

Requirement	Description
Low levels of leachables and extractables	For the purposes of this derogation, leachables are defined as compounds that migrate, 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.

[6] Medical devices / European Medicines Agency (europa.edu)

Requirement	Description
	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 high temperatures, such as those used in steam sterilization, and aggressive chemicals, like the reactive gases used in ethylene oxide (ETO), nitrogen dioxide (NO_2), and vapor phase hydrogen peroxide (VHP) sterilization processes.
Low particulation	Protein aggregation and particulate contamination in medicines can affect their efficacy, potency, clinical safety, and immunogenicity. Protein aggregation and particulate contamination are measured by the following standard methods: USP <788> Particulate Matter for Injections [redacted]
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 method: 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. This is an industry requirement that is measured by the following standard method: USP <85> Bacterial Endotoxin Tests
High strength and stability	The material has excellent strength and durability and can withstand exposure to mechanical stresses, particularly during integration into the syringe.
Container closure integrity	The syringe plunger must contain the drug product without leakage, particularly between the glass vial and the plunger.
Low coefficient of friction	Syringe plungers need to slide against bare glass with low force, enabling consistent medicinal deployment.

b. Alternative Assessment

The existing alternative to a fluoropolymer coated plunger is an uncoated rubber plunger with silicone lubricant. Conventional pre-filled syringe systems use silicone to help provide a seal and to act as a lubricant between the barrel and the plunger. However, there can be problems associated with silicone that impact broader drug stability. Estimates indicate that between 10-15% of large molecules may

have decreased drug stability due to potential interaction with silicone.[7] In addition, silicone oil has been shown to cause aggregation and particle formation in therapeutic proteins.

Alternatively, precious metals (e.g., gold, platinum) were cited as a possible future substitution in the Restriction Proposal due to their bio-inertness. The Dossier Submitters state that they have not been able to assess the technical feasibility of precious metals; therefore, evidence is weak that technically and economically feasible alternates are not generally available for the quantities required for use and that the substitution potential is uncertain. The industry has not evaluated these materials as their lack of flexibility would not enable them to be inserted into the syringe tube or maintain container closure integrity. Because they fail to meet these basic functional requirements, precious metals are not a feasible alternative.

c. Supporting Data

Extractables and Leachables

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

An extractables comparison of a fluoropolymer film-coated rubber plunger versus an uncoated (Bare) rubber plunger is shown below. The fluoropolymer-film coated plunger 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.

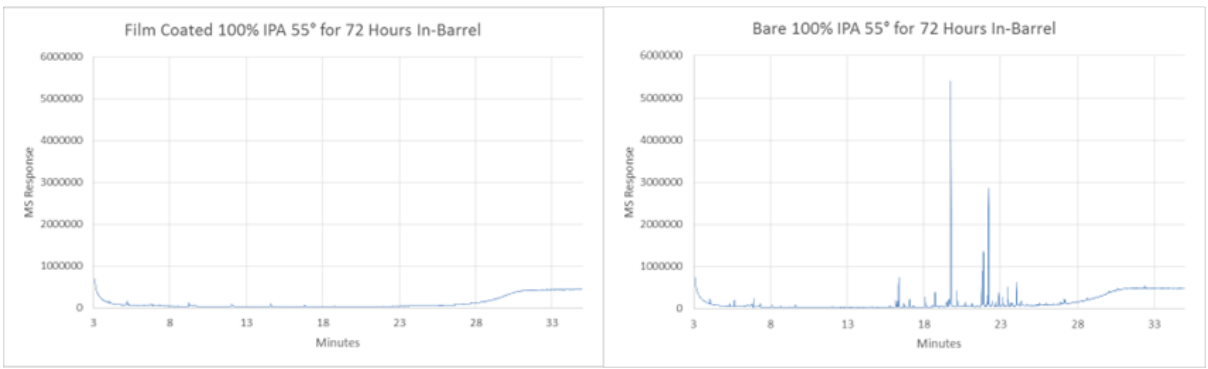

Figure 2: Extractables comparison between plunger with fluoropolymer barrier film and uncoated rubber plunger

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.

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

Low Particulation

Removal of silicone from the pre-filled syringe decreases the particle concentration by an order of magnitude. To demonstrate this, particle levels were measured in syringes with varying drug concentration levels (1 mg/ml and 25 mg/ml) that were agitated to ensure contact with the

[7] Pre-Filled Syringes West Coast 2016." Pharmaceuticals: All, smi-online. co.uk/pharmaceuticals/archive/6-2016/conference/Pre-Filled-SyringesWest-Coast Terumo, SMi Pre-Filled Syringes West Coast, June 2016

fluoropolymer-surfaced plunger in a bare-glass syringe (blue bars) and a traditional siliconized plunger in a siliconized glass syringe (red bars) as measured by micro-flow imaging.

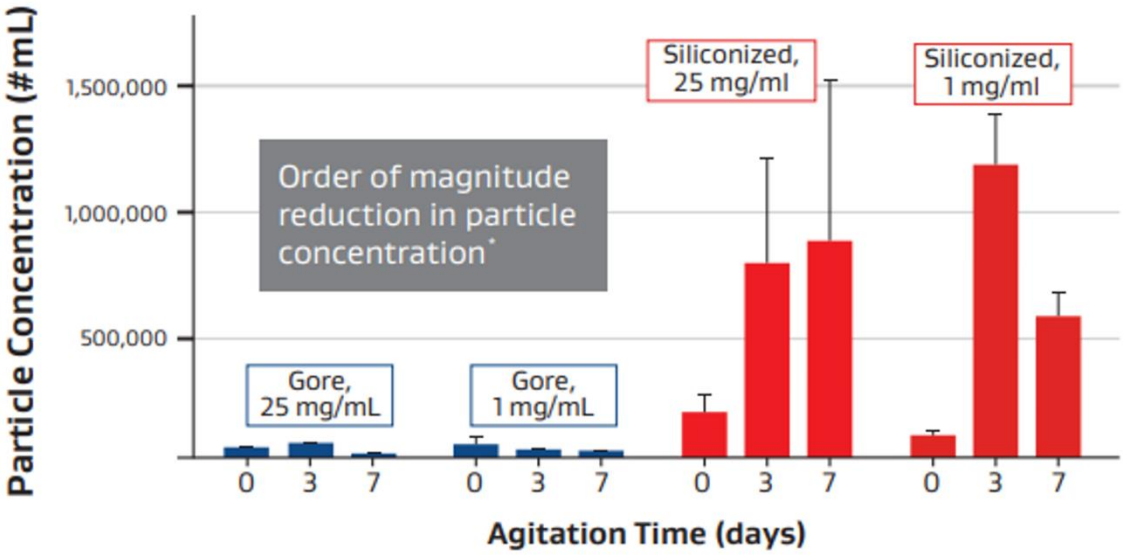

Figure 3. Sub-visible particulate performance[8]

Fluoropolymers enable elimination of silicone, which has been shown to cause aggregation and particle formation in therapeutic proteins.

Low Coefficient of Friction

PTFE has the lowest coefficient of friction of any polymer.[9] This enables PTFE coated plungers to slide easily during use without an additional lubricant.

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

d. Timeline

Without a derogation for this sub-use, the use of fluoropolymer-based syringe plungers 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.

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.[10] While the development of PTFE from the "accidental" discovery to a commercial product took about 10 years,

[8] "Avastin® Filled Syringe": Teska et al., J Pharm Sci. 2016, 105 (7), 2053-2065
[9] Lube-Tech106-PolymerTribology.pdf (lube-media.com)
[10] See https://www.ptonline.com/articles/tracing-the-history-of-polymeric-materials-part-20.

from 1938 to 1948[11], 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 coatings and packaging of medical devices

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**

e. Syringe Plungers are not a Significant Source of Emissions across their Lifecycle

As described in Gore's separate derogation request for fluoropolymers, emissions during processing are negligible thanks to emission control technologies. PTFE and FEP do not erode or off gas, even when exposed to aggressive chemicals or relevant environmental temperatures, which suggests that emissions during service life are negligible.

Additional information on responsible manufacturing, processing, and disposal of fluoropolymers, and products made from fluoropolymers, is also provided in Gore's derogation request for fluoropolymers.

f. Impacts

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

Safety, Effectiveness and Availability of Medical Devices

The use of inferior materials increases the risk of inflammation and immunogenicity response in patients. This is evident in [redacted] the Eprex example shared above. It also removes

[11] https://www.teflon.com/en/news-events/history#:~:text=An%20Accidental%20Discovery&text=Roy%20J.,to%20form%20polytetrafluoroethylene%20(PTFE).

[redacted]

the ability to offer some drugs and vaccines in the most efficient and widely deployable format of a pre-filled syringe.

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.

Disruption to Innovation and Systemic Regulatory Constraints

Assuming manufacturers attempt to use alternative materials in the coating and packaging of medical devices, a restriction on PFAS in this use will cause an unprecedented surge in testing, validation, and regulatory submission simultaneously. In addition to distracting the entire industry in Europe from innovation to develop and produce new medicines, it will place an overwhelming burden on the regulatory process to review and approve changes to prefilled syringes containing fluoropolymer coated plungers.

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[13] . 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.

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