Use of Fluoropolymers and Fluoro-Elastomers in Medicinal Product Manufacturing Facilities

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Executive Summary

Medicinal product manufacturing facilities are heavily dependent upon fluoropolymer components present in utilities, piping, equipment (process/utilities), & single use systems. While some alternatives exist, these materials are widely used to maintain safe working environments and enable the production of safe and effective medicines.

Chemical Synthesis Manufacturing

Chemical manufacturing requires materials that are chemical and corrosion resistant. In certain applications, rather than use PTFE lined pipework and process equipment high nickel alloys and glass lined carbon steel pipe work could be used instead. However, flanges on pipework will require PTFE sealing and gasket material. A potential replacement that provides all key functionalities provided by fluoropolymers in particular PTFE will be hard to find. Any alternative with comparable chemical stability, may also be persistent in the environment, resulting in regrettable substitution.

Bioprocessing & Sterile Manufacturing

Manufacturing biologics requires highly controlled environments that fluoropolymers support in various ways. It is very important to thoroughly evaluate risks to product quality, including extractables and leachables, from any change in the equipment used. There are some alternatives in certain aspects of manufacturing already widely in use (i.e. EDPM gaskets, silicone tubing) but depending on the application, they come with other risks (worker safety, product protection) that need careful management. PES is cited in the literature as a potential alternative filter MOC (material of construction) to PVDF, which is used in all low bioburden and sterile manufacturing processes. If re-execution of filtration studies was successful, ISPE member companies surveyed indicated that a complete replacement program could be in the order of 20 years.

Impact of Proposed PFAS Restriction

An alternative that exhibits all the properties of the fluoropolymers used in medicinal product manufacturing facilities is not available at this time. If the proposed PFAS restriction prohibits the supply of these critical raw materials, manufacturing operations at EU facilities will cease when contingency stock levels are depleted. A recent industry survey indicates that the number of active substances associated with manufacturing operations that are dependent on fluoropolymer components in equipment and single-use systems is estimated to be at least 1,794. These active substances are intended to treat conditions such as cancer, cardiovascular disease, diabetes, mental health disorders. Therefore, a time unlimited derogation for the industrial use of fluoropolymers in medicinal product manufacturing facilities is a necessary medicine shortage mitigation measure.

Close partnership across medicinal product supply chain is needed to identify all sources of PFAS, to sufficiently manage emissions from waste streams, and where possible, to develop suitable alternatives that maintain the highly controlled environment required for efficacy and patient safety.

A response to Question 6 of the Annex XV REACH proposal on PFAS is presented in the document that follows.

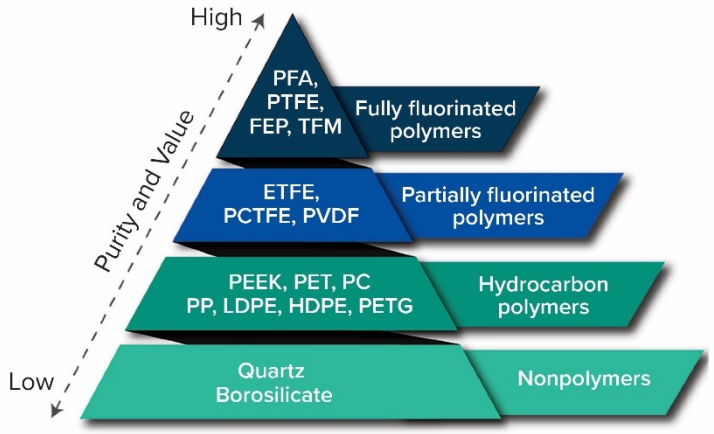
Abbreviations

API	Active Pharmaceutical Ingredient
BAT	Best available technologies
CEWEP	Confederation of European Waste to Energy Plants
CIP	Clean in pace
ECHA	European Chemicals Agency
ECTFE	Ethylenechlorotrifluoroethylene
EEA	European Economic Area
EDPM	Ethylene propylene diene monomer rubber
EFPIA	European Federation of Pharmaceutical Industries Association
EMA	European Medicines Agency
EPDM	Ethylene propylene diene monomer
ETFE	Ethylene Tetrafluoroethylene
EURTIS	European Union for Responsible Treatment of Special Waste
EWC	European waste catalogue
FEP	fluorinated ethylene propylene
FDA	Food & Drugs Administration
FIBC	Flexible intermediate bulk container
FKM	Fluorine Kautschuk Material
GC	Gas chromatography
GMP	Good manufacturing practice
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation
ISPE	International Society for Pharmaceutical Engineers
LPPS	Liquid phase peptide synthesis
MOC	Materials of construction
NMR	Nuclear magnetic resonance
P&ID	Piping and Instrumentation Diagram
PCTFE	polychlorotrifluoroethylene
PCV	Positive Crankcase Ventilation
PE	Polyethylene
PES	Polyethersulfone
PFA	Perfluoroalkoxy alkane
PFAS	Per and polyfluoroalkyl substances
PRV	Pressure relief valve
PTFE	Polytetrafluoroethylene
PVDF	polyvinylidene fluoride
PWEC	Purified water for endotoxin control
QC	Quality control
RP	Reverse Phase Chromatography
SIP	Steam in place
SPPS	Solid phase peptide synthesis
TFM	Modified PTFE
WFI	Water for injection

6(a)- Annual Tonnage and Type of Fluoropolymers / Elastomers

Medicinal product manufacturing facilities are governed by a GMP (good manufacturing practice) certificate, issued by global health authorities. Operation of these facilities are heavily dependent upon fluoropolymer use in utilities, piping, equipment (process/utilities), & single use systems. Fluoropolymer materials are widely used in the pharmaceutical manufacturing industry because of their corrosion resistance and are deemed to be inert by most regulatory agencies and are considered desirable to produce medicinal products, e.g. they are EMA certified.

Examples of Polymers Used in Pharma Manufacturing



Examples of Fluoropolymers:
PFA = perfluoroalkoxy alkane
PTFE = polytetrafluoroethylene
FEP = fluorinated ethylene propylene
TFM = modified PTFE
ETFE = ethylene tetrafluoroethylene
PCTFE = polychlorotrifluoroethylene
PVDF = polyvinylidene fluoride

Non-fluorinated Polymers:
PEEK = polyether ether ketone
PET = polyethylene terephthalate
PC = polycarbonate
PP = polypropylene
LDPE = low-density polyethylene
HDPE = high density polyethylene
PETG = polyethylene terephthalate glycol

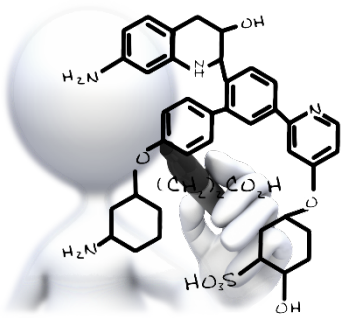
Preparation of a quantitative estimate of all fluoropolymer materials used in plant, equipment and consumables in a typical pharmaceutical manufacturing facility will be a challenge if not impossible because:

- There are kilometres of lined piping (millimetre thickness), valves, check valves and sight glasses in GMP process systems and utility systems.
- Fluoropolymers are also found in the component parts of valves - gasket, joints, sealants, seal rings, pumps, filters and it would be impossible to reliably catalogue each of these very specific applications.
- Fluoropolymers are also found in many single-use items, such as process bags, engineered tubing sets, and process filters.
- The amount of fluoropolymer constituents present in these articles is in most cases regarded as business confidential information by the supplier, and not accessible to the downstream users of such articles.

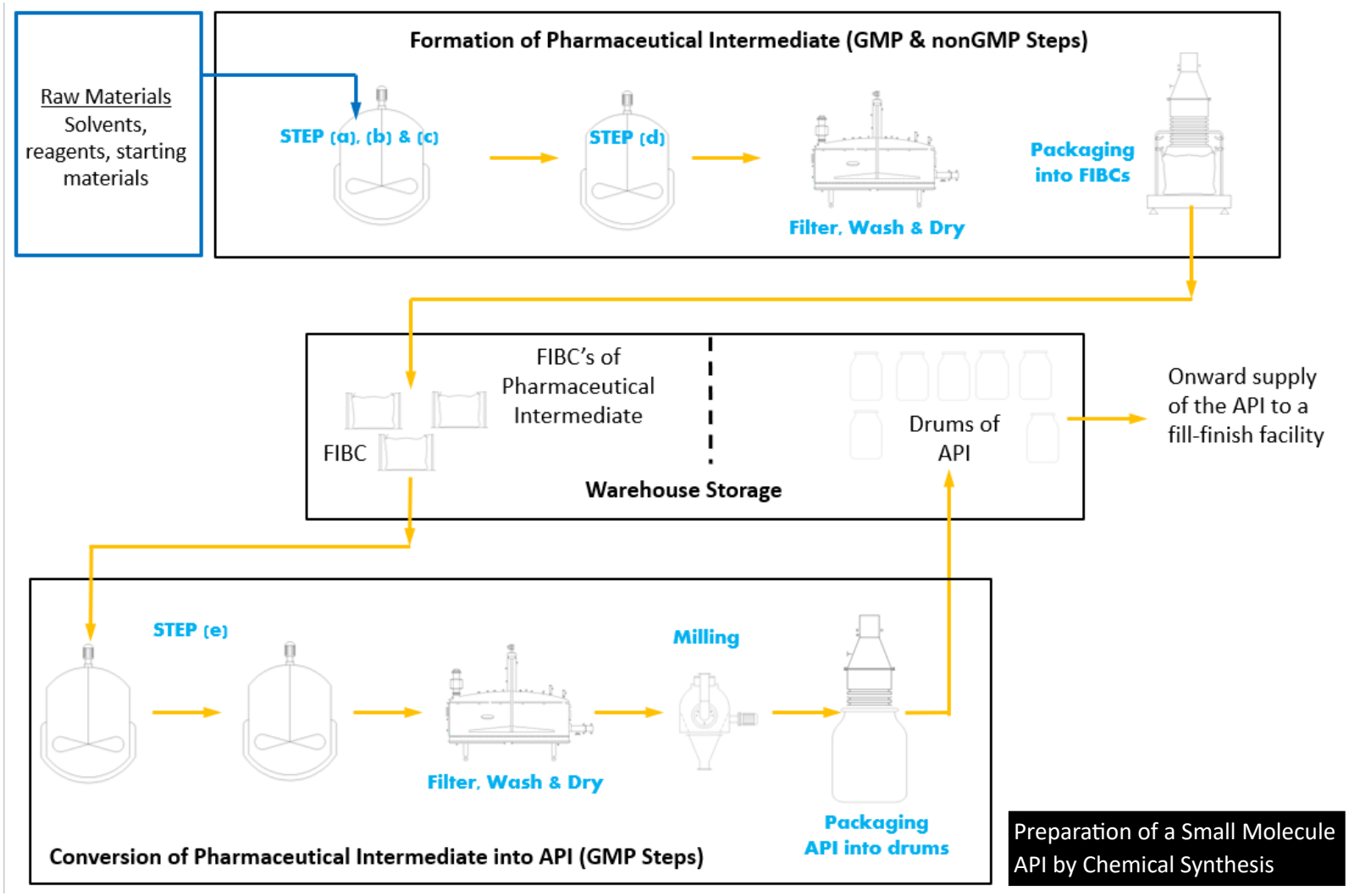
An explanation for the widespread use of fluoropolymer types associated with the manufacturing operations is provided for:

- Small molecule & peptide manufacturing - chemical synthesis of an active substance
- Bioprocessing facility - manufacture of an active substance using biological processes
- Sterile manufacturing - aseptic processing of a parenteral medicinal product
- Tableting process – formulation of a solid dosage form

(i) a Manufacture of a Small Molecule by Chemical Synthesis



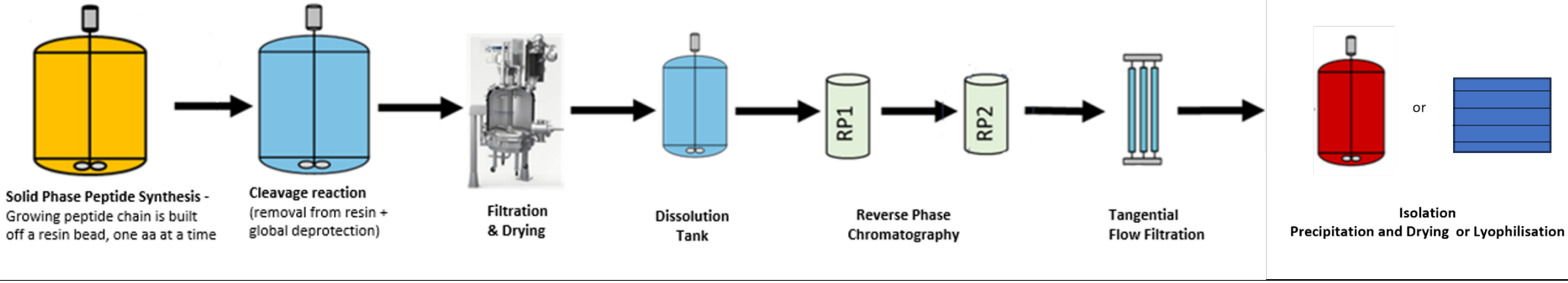
- Small Molecule APIs (active pharmaceutical ingredients) are low molecular weight (≤1000 Daltons) organic compounds
- Molecules are built by a series of chemical reactions (or steps) conducted in a broad set of organic solvents as well as strong acids or bases. Equipment needs to withstand a wide range of operating pressures and temperatures (i.e. from-80 to +180°C)
- QC analysis of raw materials, synthesized intermediates & APIs is a mandatory step to ensure the product meets the required specifications



Preparation of a Small Molecule API by Chemical Synthesis

(i)b Manufacture of a Peptide Therapeutic by Chemical Synthesis (Solid or Liquid Phase Peptide Synthesis; SPPS or LPPS)

- Therapeutic peptides are a unique class of pharmaceutical agents composed of a series of well-ordered amino acids, peptides are usually with molecular weights of 500-5000 daltons.
- Amino acids act as the building blocks in a defined set of unit operations along with coupling agents, organic solvents and deprotection reagents. After the progressive build of peptide on resin or in the solution, the crude peptide is cleaved (only for SPPS) and precipitated.
- Purification is then achieved by chromatography followed by precipitation or lyophilization to produce active pharmaceutical ingredient (drug substance).



GMP & Utility Systems in Chemical Synthesis Plants – Types of Fluoropolymers Used

The following are examples of typical fluoropolymer materials found in the GMP and utility equipment systems of a multi-purpose chemicals synthesis manufacturing plant:

Chemical Synthesis Facilities – type of equipment & consumables containing fluoropolymers	**Fluoropolymer Type**
Mechanical seals on process equipment- vessels, pumps, fans	PTFE
Valve seats on ball Valves, butterfly & gate valves	PTFE/PVDF/PFA
Gaskets on pipework & vessels	PTFE
O-ring seals on vessels & pipework	FEP/PTFE
PTFE lined pipework & hoses	PTFE
Scrubber linings	PVDF/PFA
Flexible tubing chemical synthesis flow reactors	PFA

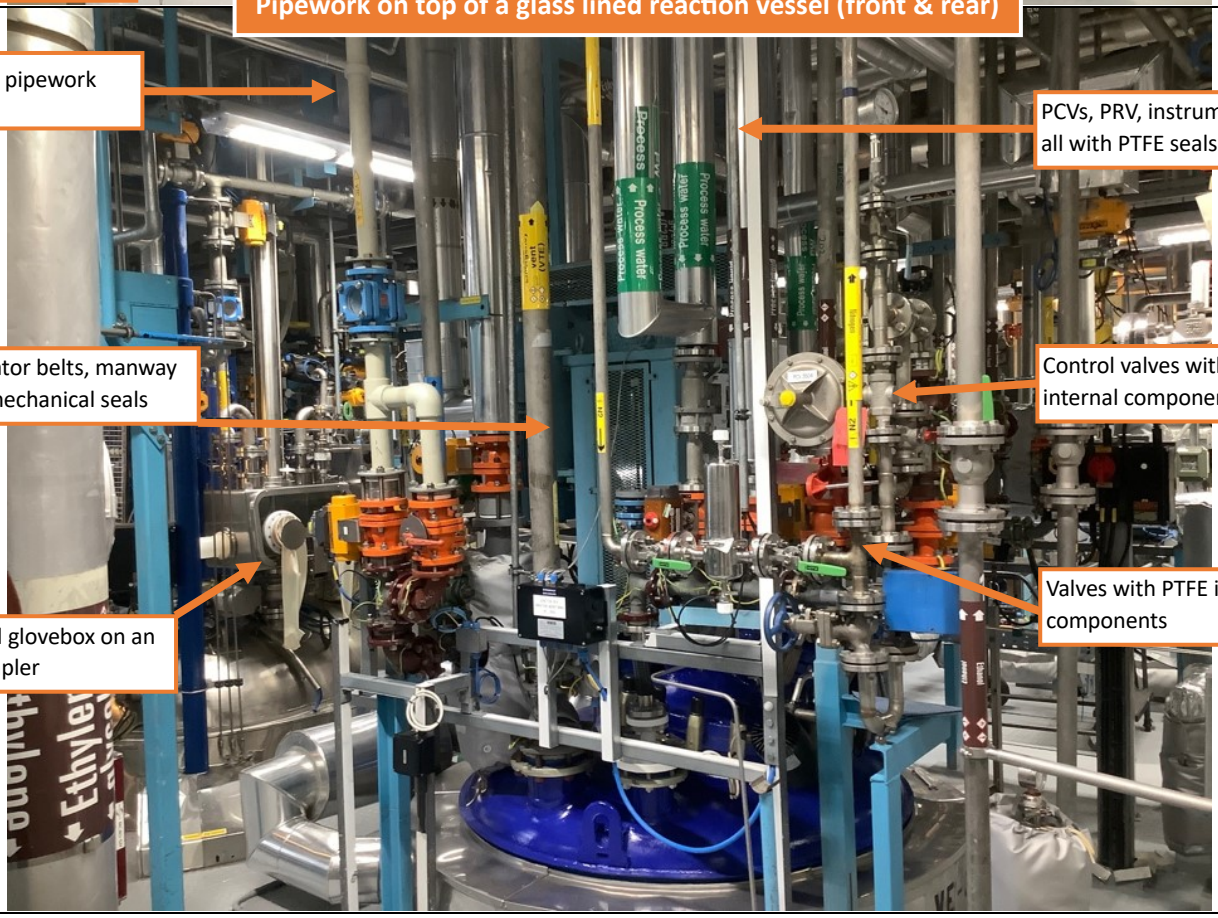
A chemical manufacturing plant is a system of individual parts (reactors, pipework, condensers, receivers, valves, pumps etc). All parts must be compatible with the operating conditions (temperature, pressure, pH) and the materials (solvents, reagents) being handled. Chemical reaction vessels are typically made of Glass-lined (enamelled) Steel, Stainless Steel, or Hastelloy, and can range in size from 10 to 10,000 litres and are usually equipped for heating and cooling via a jacket. Fluoropolymers are used in sealing of (multipurpose) manufacturing equipment including reaction vessels to prevent leakages between equipment (flanges, valves etc.) components. Hence the need for a MOC (Materials of Construction) evaluation when building a new facility, and when introducing a new process into existing equipment. This process safety requirement is intended to minimise the risk of leakage/release of aggressive substances/materials from closed manufacturing systems, thus minimising the risk of injury to employees.

Compared to the other types of pharmaceutical manufacturing facilities (sterile and biological processes), fluoropolymer materials used often have long lifetimes within equipment (or are replaced less infrequently). Structural long-lifetime equipment such as PTFE lined pipework could have an in-service lifespan of up to 20 years. A gasket once fitted could have a lifetime as long as the pipe work it seals, provided it's left undisturbed.

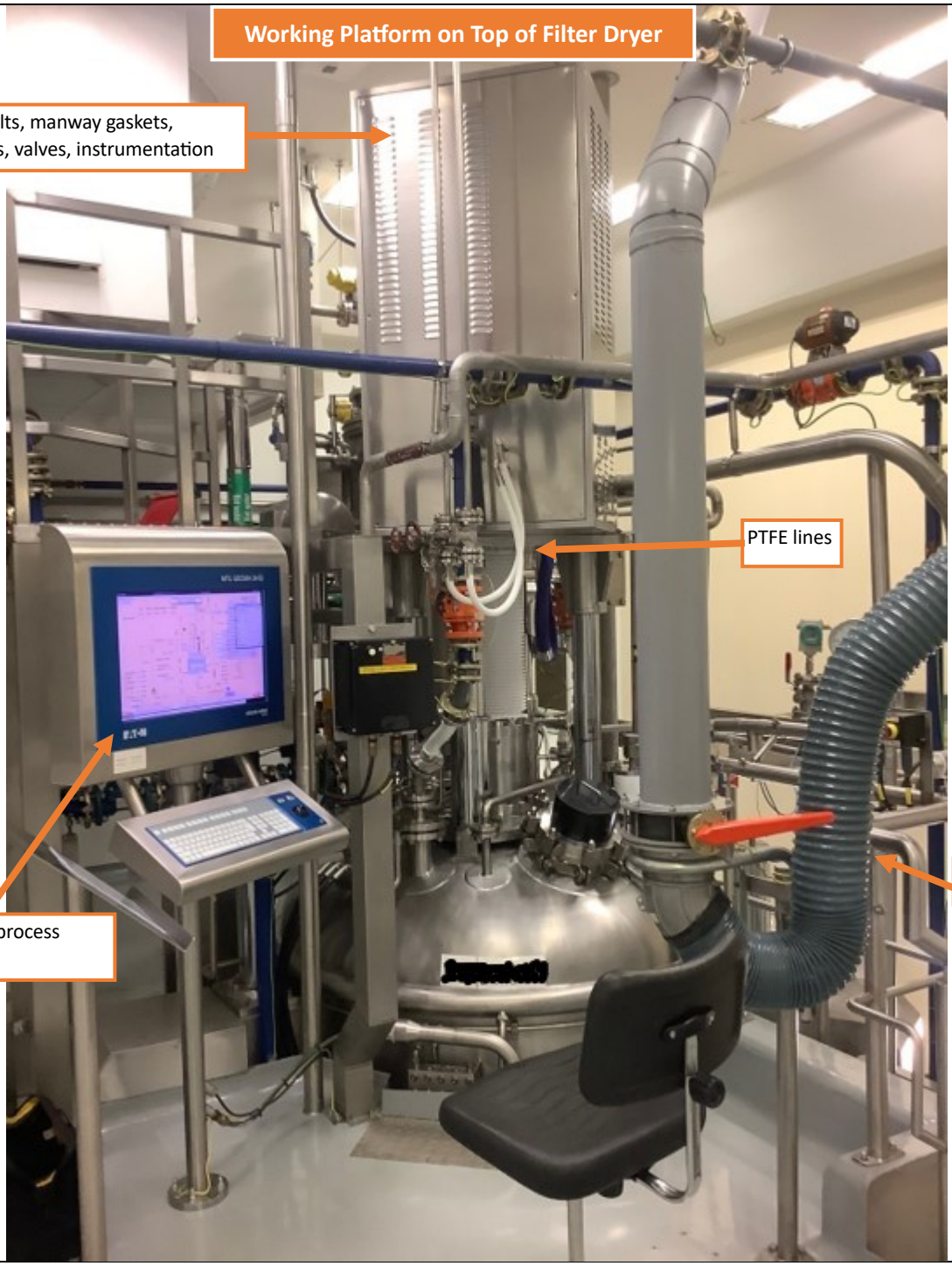
Quality control analysis depends heavily on the presence of fluoropolymers in analytical equipment such as HPLC, GC, NMR instrumentation. The analytical detectors employed are extremely sensitive to impurities. PFAS materials are used in this context e.g. to seal samples, protect tubes because they are inert to other chemicals and do not leach out during their lifetime. Conversely, leaching out of contaminants from alternative equipment parts would lead to false results. Yet, replacing these equipment parts with fluorine-free alternatives would disable a vast number of the aforementioned analytical models and analyses.

Glovebox for Contained Transfer of Solid Materials into Reaction Vessel

Pipework on top of a glass lined reaction vessel (front & rear)



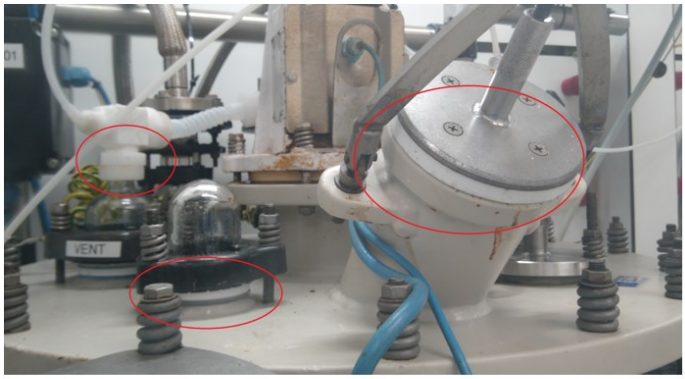
Working Platform on Top of Filter Dryer

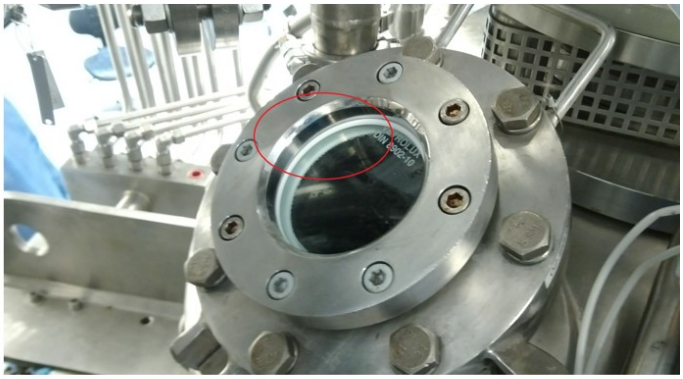


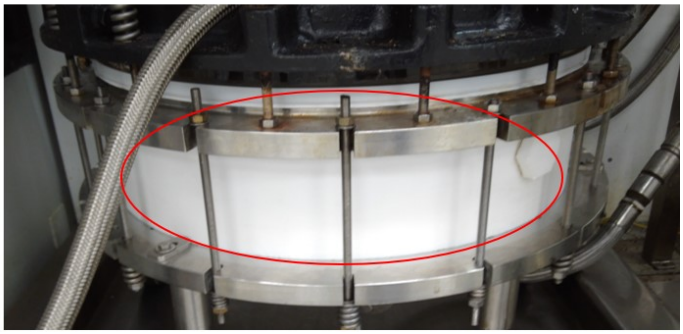

Pack off station PTFE seals and instrumentation, control station, liners

Peptide Synthesis – Reaction Vessel

PTFE, FEP reactors seals, gaskets, fitting







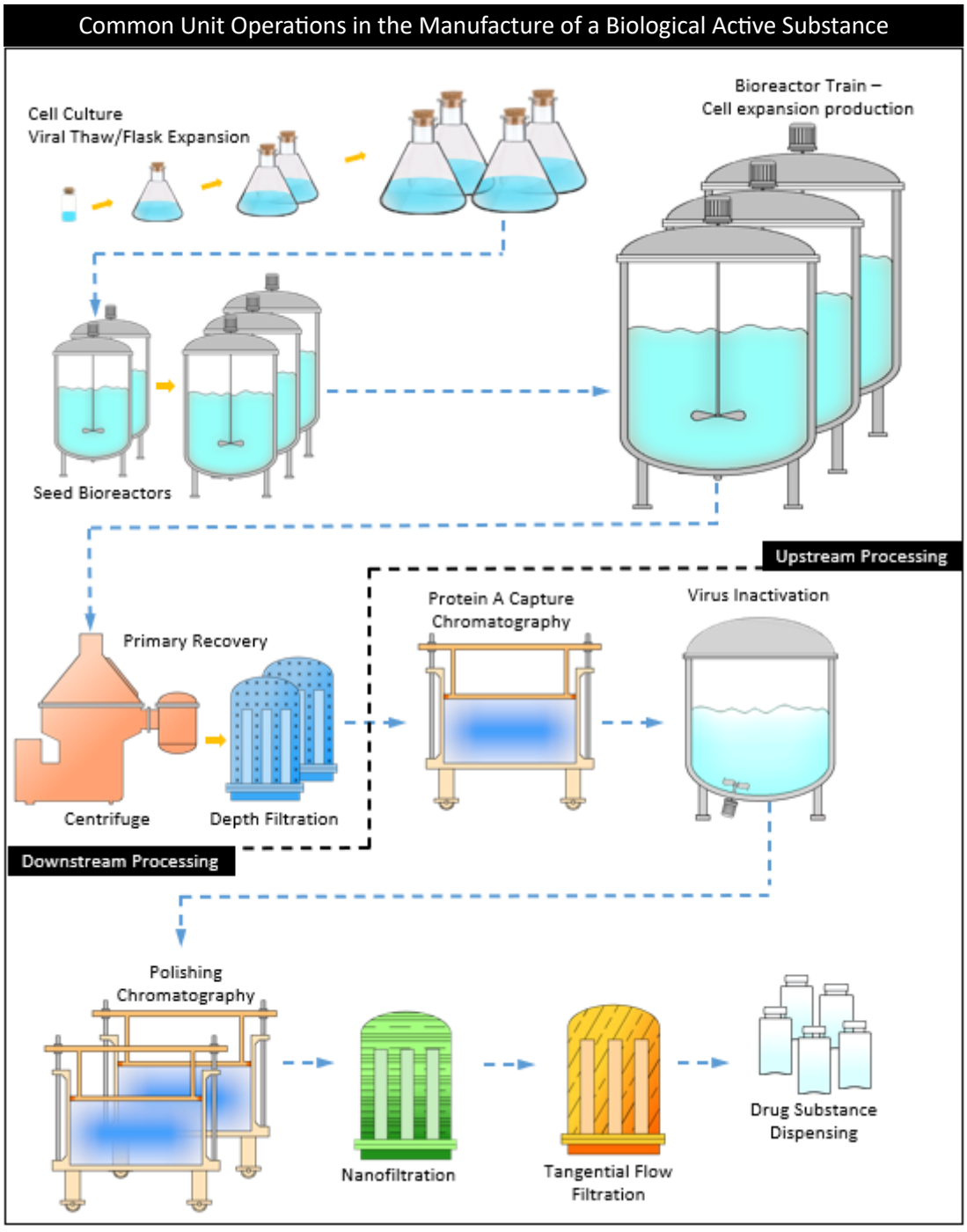
Clean Room Protection Equipment

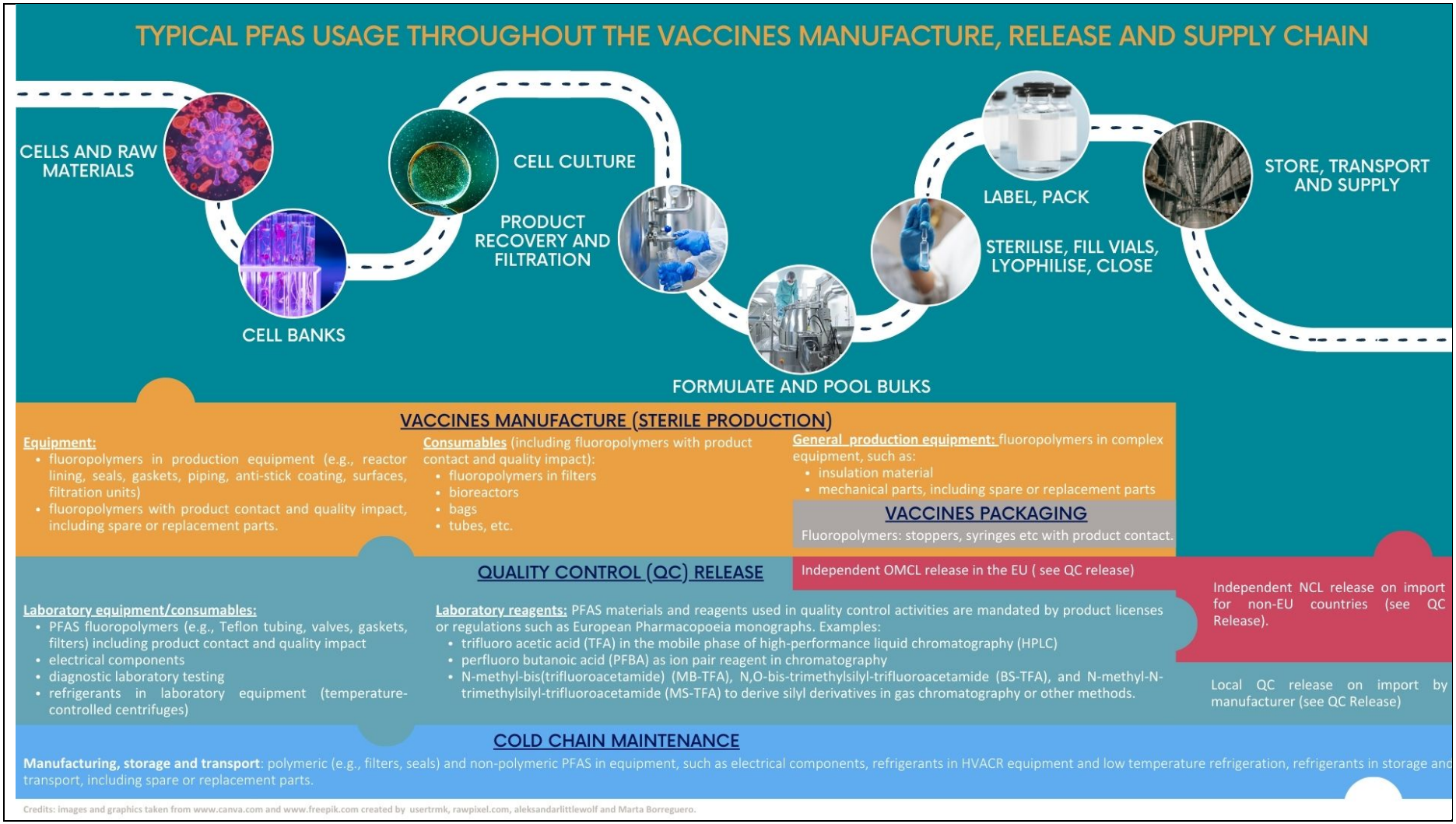
PTFE glovebox/protection screens seals

(ii) Manufacture of an Active Substance by Biological Processes

Biological active substances are produced by complex manufacturing processes using living cells, examples include:

- Monoclonal antibodies, fusion proteins
- Live/attenuated vaccines
- Cell-based Therapies, Gene Therapies
- Blood / Plasma derivatives
- Peptides manufactured using Bacterial/Yeast Fermentation




TYPICAL PFAS USAGE THROUGHOUT THE VACCINES MANUFACTURE, RELEASE AND SUPPLY CHAIN
CELLS AND RAW MATERIALS
CELL BANKS
CELL CULTURE
PRODUCT RECOVERY AND FILTRATION
FORMULATE AND POOL BULKS
STERILISE, FILL VIALS, LYOPHILISE, CLOSE
LABEL, PACK
STORE, TRANSPORT AND SUPPLY
VACCINES MANUFACTURE (STERILE PRODUCTION)
Equipment:
• fluoropolymers in production equipment (e.g., reactor lining, seals, gaskets, piping, anti-stick coating, surfaces, filtration units)
• fluoropolymers with product contact and quality impact, including spare or replacement parts.
Consumables (including fluoropolymers with product contact and quality impact):
• fluoropolymers in filters
• bioreactors
• bags
• tubes, etc.
General production equipment: fluoropolymers in complex equipment, such as:
• insulation material
• mechanical parts, including spare or replacement parts
VACCINES PACKAGING
Fluoropolymers: stoppers, syringes etc with product contact.
QUALITY CONTROL (QC) RELEASE
Laboratory equipment/consumables:
• PFAS fluoropolymers (e.g., Teflon tubing, valves, gaskets, filters) including product contact and quality impact
• electrical components
• diagnostic laboratory testing
• refrigerants in laboratory equipment (temperature-controlled centrifuges)
Laboratory reagents: PFAS materials and reagents used in quality control activities are mandated by product licenses or regulations such as European Pharmacopoeia monographs. Examples:
• trifluoro acetic acid (TFA) in the mobile phase of high-performance liquid chromatography (HPLC)
• perfluoro butanoic acid (PFBA) as ion pair reagent in chromatography
• N-methyl-bis(trifluoroacetamide) (MB-TFA), N,O-bis-trimethylsilyl-trifluoroacetamide (BS-TFA), and N-methyl-N-trimethylsilyl-trifluoroacetamide (MS-TFA) to derive silyl derivatives in gas chromatography or other methods.
Independent OMCL release in the EU (see QC release)
Independent NCL release on import for non-EU countries (see QC Release).
Local QC release on import by manufacturer (see QC Release)
COLD CHAIN MAINTENANCE
Manufacturing, storage and transport: polymeric (e.g., filters, seals) and non-polymeric PFAS in equipment, such as electrical components, refrigerants in HVACR equipment and low temperature refrigeration, refrigerants in storage and transport, including spare or replacement parts.
Credits: images and graphics taken from www.canva.com and www.freepik.com created by usertrmk, rawpixel.com, aleksandarlittlewolf and Marta Borreguero.

Bioprocessing Facilities & Aseptic Processing – Types of Fluoropolymers Used

The following are examples of typical fluoropolymer materials found in the GMP and utility equipment systems of a bioprocessing and aseptic processing facility:

Bioprocessing Facilities & Aseptic Processing – type of equipment & consumables containing fluoropolymers	Fluoropolymer Type
O-rings/gaskets/seals on vessels & pipework	PTFE
Filters	PVDF, PTFE
Pump heads/fittings	PVDF, PTFE
Hoses and tubing	PTFE
Chromatography Column Equipment	PTFE

EU Annex 1 guidance[1] applies to low bioburden and sterile manufacturing techniques used to produce biological active substances which are typically administered to the patient as parenteral medicines. Fluoropolymer components are found in single use consumables, as these materials are deemed to be inert by most regulatory agencies and are considered desirable to produce medicinal products. Extractables and leachable study requirements apply to single use materials which have direct contact with a parenteral product.[2]

To maintain the required equipment cleanliness, strong acids and bases as well as high temperatures and pressures are needed to CIP (clean in place) and SIP (steam in place) production vessels, as well as to produce WFI (water for injection). The areas of facilities that distribute these critical utilities to the main production suites must be closely monitored and maintained with the right equipment to prevent corrosion and ensure a safe working environment. Therefore, PTFE is commonly used in seals, gaskets, hoses, and diaphragm valves due to their resistance to corrosion and mechanical properties.

Other known fluoropolymers used include PVDF, found in components needed for manufacturing such as filters, which supports the product quality. Biologics are sensitive to product quality impact, e.g. adsorption, aggregation, degradation, etc. when using non-fluoropolymer containing filters, which also pose higher risk of leachables which puts patient safety at risk. Fluoropolymers may also be present in single-use systems such as bags and connectors, which are critical to enable future "next generation" continuous bioprocessing, which enable a much smaller production footprint, therefore significantly decreasing the energy and freshwater demands of manufacturing these medicines[3]. Additional data

[1] 20220825_gmp-an1_en_0.pdf (europa.eu)

[2] Regulatory guidelines and regulations for leachables from the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the International Council on Harmonisation (ICH):
21 Code of Federal Regulations (CFR) 211.65(a) specifically states:

> *"Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."*
> Section 6.1.3 of the European Medicines Agency's 2016 Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission states:
> *"When single use equipment is used in evaluation studies, consideration should be given to leachables and extractables. Information should be provided on the nature and amount of potential leachables, and the removal of such impurities. Besides data, this normally includes a risk assessment*.

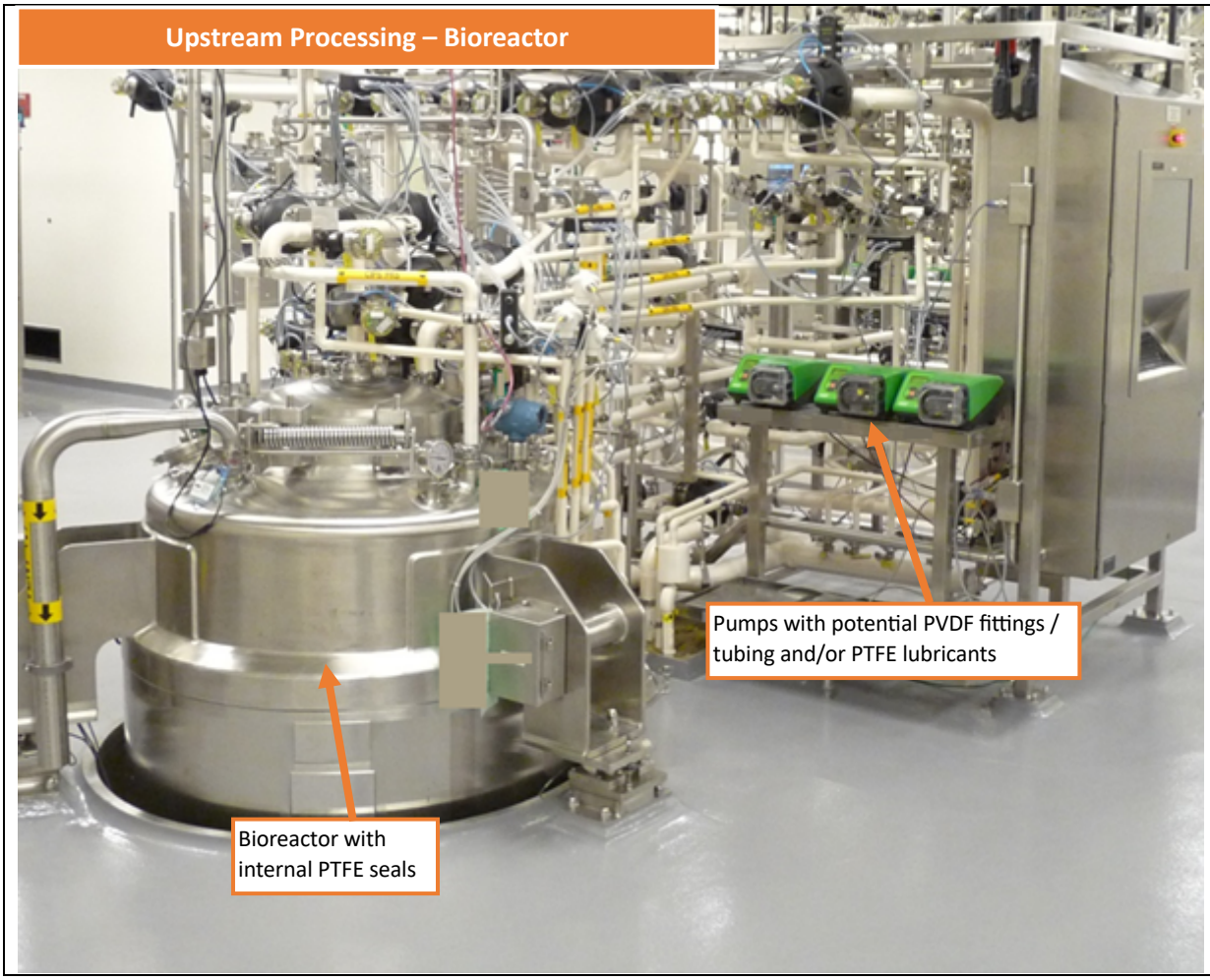
[3] Streamlined life cycle assessment of single use technologies in biopharmaceutical manufacture - New Biotechnology (2022)

gathered indicates that single-use systems manufactured from fluoropolymers are resistant to carbon dioxide ingress during shipping on dry ice[4].

Another advantage of fluoropolymers is that they exhibit very low coefficients of friction. That means that they do not adhere biological materials to process surfaces, have inherent resistance to bioburden and endotoxin, and can be easily cleaned when required. A low coefficient of friction also means that liquids will drain fully from fluoropolymer-based systems because they will roll off container surfaces.

While there are sources of fluoropolymers used throughout a bioprocessing facility, there are alternatives used widely where the mechanical strength and corrosion resistance is not necessary, such as EPDM gaskets and silicone tubing. The following images illustrate typical uses of both fluoropolymers as well as their commonly used alternatives in typical manufacturing settings:

Upstream Processing – Bioreactor

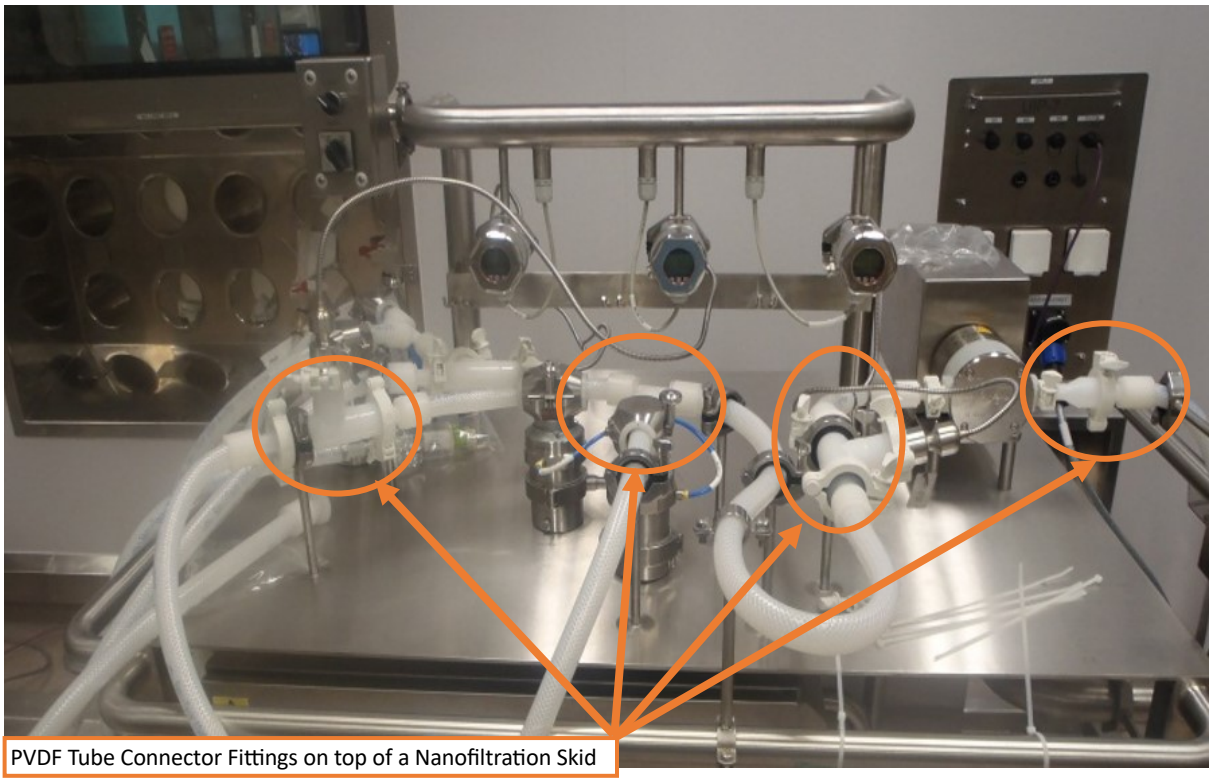


[4] BioProcessing Article, 22 August 2022 Advanced Materials in Bioprocessing

Downstream Processing – Buffer Make Up

- Buffer solutions are made up to adjust pH of the process solution. The buffer solution must be filtered to protect the process solution from microbial contamination – an important step in ensuring the sterility of the medicine product. Equivalent filtration is required for process intermediates prior to hold durations.
- PVDF filter membranes are widely used in filtration units within bioprocessing. Each filter in the industry has specific surface area, pore size and MOC (material of construction). MOC properties are not readily interchangeable. Changing MOC with equivalent surface area and pore size requires re-execution of filtration studies. PVDF filter membranes have higher oxidant resistance and mechanical strength compared to PES (polyethersulfone) filters

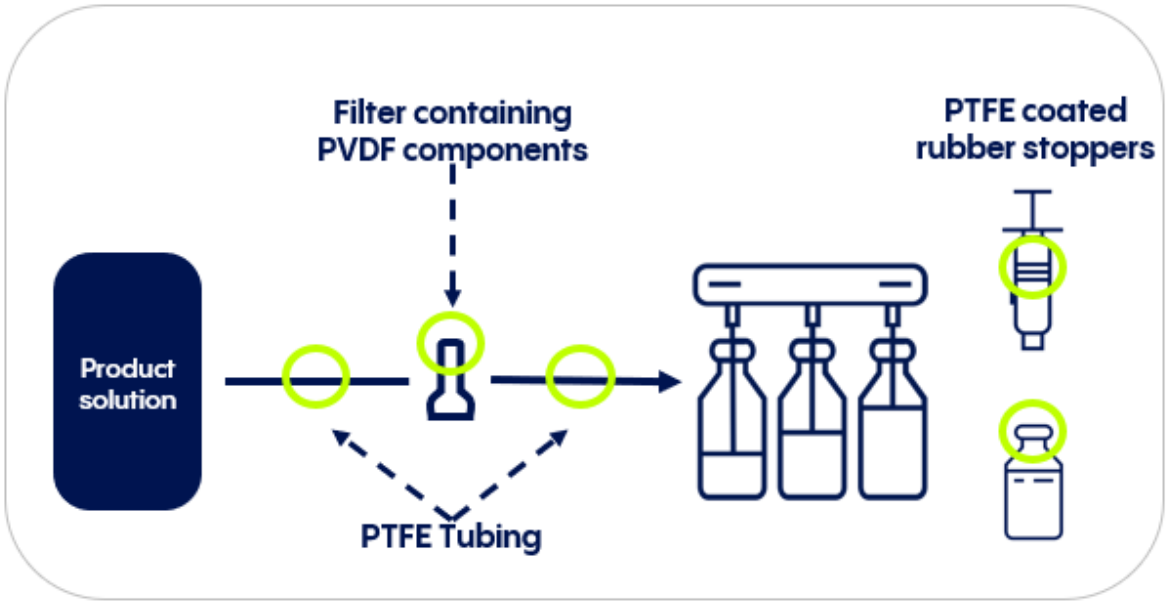
Downstream Processing – Nanofiltration



PVDF Tube Connector Fittings on top of a Nanofiltration Skid

Chromatography columns are critical to purify the Active Pharmaceutical Ingredients. In order to function properly, they must be optimally packed to specified column bed heights using large, fine mesh screens lined with PTFE, which has a low coefficient of friction.

(iii) Formulation – Sterile Dosage Form



Filling process for sterile medicinal products

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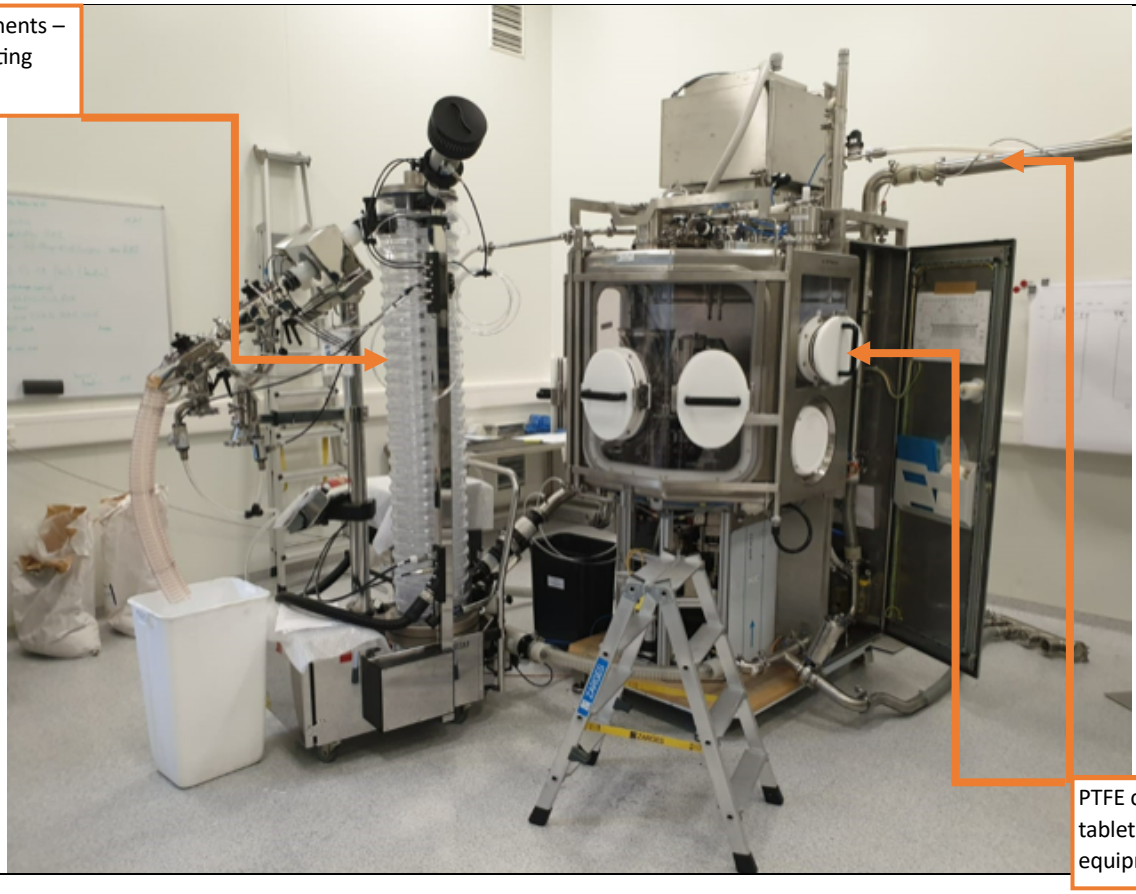
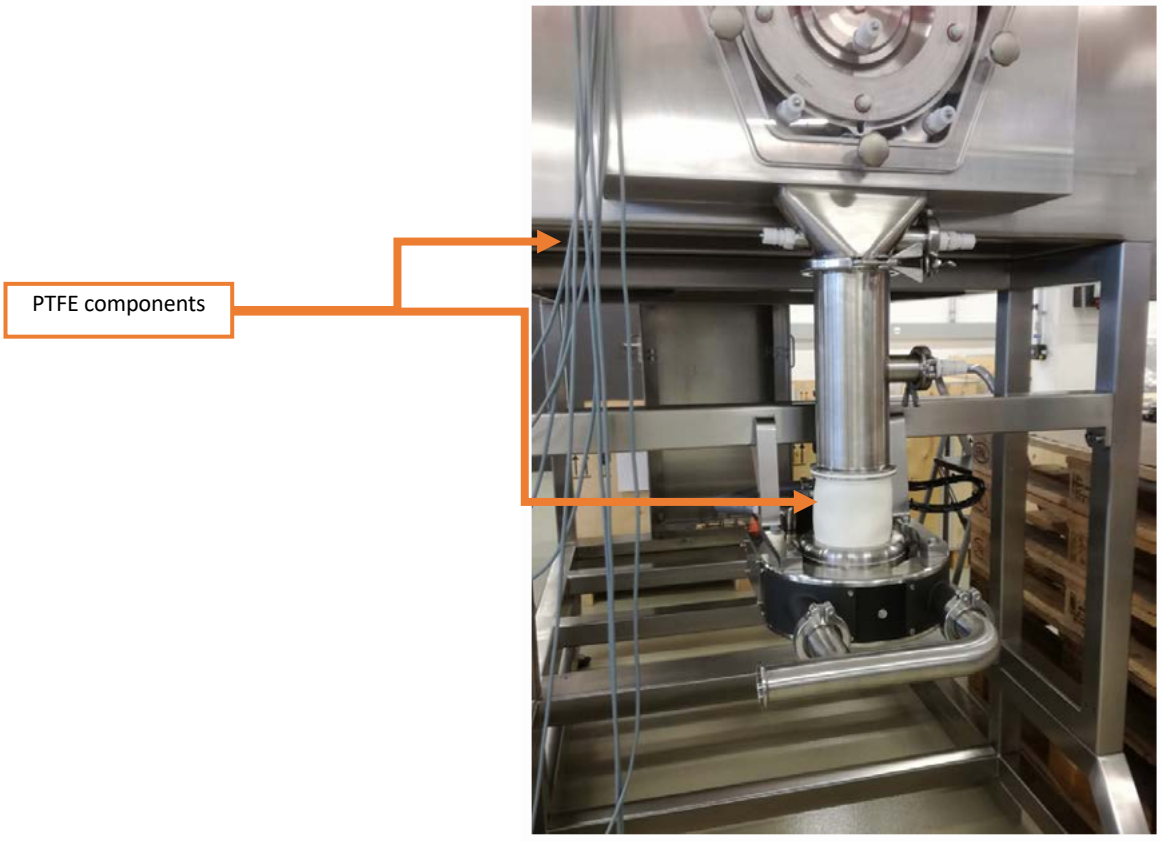
Parenteral Medicines

- Parenteral drug administration refers to medicinal products administered by routes other than the digestive tract, particularly by injection or infusion. Water acts as an excipient in parenteral formulations of a medicinal product and must meet WFI (water for injection) quality standards.
- PTFE coated stoppers were introduced over 20 years ago to avoid cases of pure red cell aplasia associated with leachates from uncoated rubber syringe stoppers

(iv) Tabletting process –formulation of a solid dosage form



SBV valve powder inlet



SBV valve granules outlet

(v) Waste Management

Use of Fluoropolymers in Medicinal Product Manufacturing Facilities occurs in an industrial setting, so worker protection and environmental legislation applies.

Waste streams generated from the operation of medicinal product manufacturing facilities is disposed of as per local legislative requirements as well as locally available disposal treatment. Non-hazardous waste streams will contain non-product contacting articles such as discarded mechanical seals, valves, gaskets, O-rings, cartridges, single use containers, which are likely disposed of either via incineration or licenced landfill facility based on local waste treatment options.

Waste classified as hazardous, will be treated at an industrial incineration facility which must be permitted for the disposal of the particular waste streams as identified by EWC (European Waste Catalogue) code. Experts in the waste sector federations (CEWEP, EURITS) are best placed to provide information on the effectiveness of incineration units operated as per best available technologies (BAT).

Compared to other polymers, recycling of fluoropolymer containing waste is not common practice[5]. Recycling processes must avoid emissions of PFAS break down products or accumulation in the recycled material returned to the supply chain. As PFAS waste treatment technology and analytical methods are evolving, transition to the use of recycled fluoropolymer materials will take time.

[5] Recycling and the end of life assessment of fluoropolymers: recent developments, challenges and future trends - Chemical Society Reviews, (2023)

6(b)- Key Functionalities Provided by Fluoropolymers and Fluoro-Elastomers

Chemical Synthesis Facilities – type of equipment & consumables containing fluoropolymers	Fluoropolymer Type	Key Functionality Provided	Reasons for using fluoropolymer over an alternative material / technology
Mechanical Seals on Process Equipment- Vessels, Pumps, Fans	PTFE	Chemical / Corrosion Resistance Temperature resistance, Mechanical strength	• Performance (incl. lifetime of equipment) • Health, safety & environment • GMP Regulations and standards • Less spare parts management • Fewer options reduce mistakes when replacing parts
Valve Seats on Ball Valves, Butterfly & Gate Valves	PTFE/PVDF/PFA		
Gaskets on pipework & vessels	PTFE		
O-ring seals on vessels & pipework	FEP/PTFE		
PTFE Lined Pipework & Hoses	PTFE		
Scrubber Linings	PVDF/PFA		
Flexible tubing serving chemical synthesis flow reactors	PFA		

Biological active substances are more labile and sensitive to product quality impact, e.g. adsorption, aggregation, degradation, etc. when using non-fluoropolymer containing filters. Additionally, other filter materials have higher leachables which pose a greater risk to patient safety.

Bioprocessing Facilities & Aseptic Processing – type of equipment & consumables containing fluoropolymers	Fluoropolymer Type	Key Functionality Provided	Reasons for using fluoropolymer over an alternative material / technology
O-rings/gaskets/seals on vessels & pipework	PTFE	Temperature resistance, Chemical/Corrosion resistance	• GMP Regulations and standards for patient safety • Performance (incl. lifetime of equipment) • Health, safety & environment
Filters	PVDF, PTFE	Repellence properties	
Pump heads/fittings	PVDF, PTFE	Mechanical strength, Low coefficient of friction	
Hoses and tubing	PTFE	Temperature resistance, Chemical/Corrosion resistance	
Chromatography Column Equipment	PTFE	Mechanical strength, Low coefficient of friction	

6(c)- Number of Companies in the Sector Estimated to be Affected by the Restriction

A survey of ISPE members (see Appendix 1) conducted in August 2023 indicated that at least 157 companies have manufacturing and/or packaging operations in the EU. Due to the short timeframe in which the survey data was collected it is quite possible that pharmaceutical manufacturers have not responded to the survey.

Based on the membership of the trade associations representing actors in the human pharmaceutical sector, there at least 200 companies who depend on the use of fluoropolymers in manufacturing operations and are affected by the proposed Restriction.

6(d)- Information on the Availability, Technical and Economic Feasibility, Hazards and Risks of Alternatives for the Relevant Use

(i) Chemical Synthesis Manufacturing

There are some alternatives to PTFE that are used in lined pipework and process equipment, such as glass or certain metals.

Transitioning to alternate materials like high nickel alloys and glass lined carbon steel pipe requires the use of the inert, stable and very high purity gasket material and flexible expansion bellows on the main connections. In such applications PTFE would be required in the sealing and gasket materials used in pipework connection points. Also taking sealing applications as an example, ceramic seals can also be very inert, but contain fibres that can be released into the medicinal product. Similarly, graphite seals (e.g., gaskets) are not suitable for pharmaceutical processing due to the risk of carbon debris in the final medicinal product. Other materials, such as tantalum or gold can be used in connections between equipment parts but are extremely expensive (many orders of magnitude more expensive than PFAS).

Fundamentally these alternatives, however, are not compatible with a multipurpose manufacturing facility. In general, none of the alternatives provide a broad-spectrum corrosion resistance and their mechanical properties are limited. Chemical compatibility for non-PFAS-made equipment may be very limited, bringing safety and quality issues into a multipurpose manufacturing facility. Ultimately, other alternative materials would limit the use of solvents, chemicals, and process conditions (temperature range, pH values).

(ii) Bioprocessing Manufacturing

Single-use systems were introduced to reduce the environmental footprint of biopharmaceutical manufacturing platforms. In the 1990s the industry started to move away from stainless steel equipment trains to single-use systems[6] that contain some fluoropolymer components to optimize yield and decrease waste from cleaning.

Rigorous cleaning standards are applied to reusable stainless-steel equipment to avoid microbial contamination of produced material. The required equipment cleanliness is provided by CIP (clean in place) and SIP (steam in place) systems which require significant energy and water usage. Lifecycle assessment studies indicate that single use technology exhibits a lower environmental impact due to a reduction facility size, dramatically reducing the energy demand as well as demand for WFI, process water, steam and less requirement for cleaning and sanitization in place[7].

Therefore, fluoropolymers materials used are essential for "next generation" continuous bioprocessing, to enable a much smaller production footprint, therefore significantly decreasing the energy and freshwater demands of manufacturing biomedicines.

6(e) – If Alternatives are not yet Available, Information on the status of R&D Processes for Finding Suitable Alternatives

Research conducted so far indicates that a potential replacement that provides all key functionalities provided by fluoropolymers in particular PTFE will be hard to find.[8]

The C-F chemical bond is one of the most stable bonds in organic chemistry leading to superior chemical resistance against acids, caustics, solvents, oxidizing materials etc. It is possible that any future alternative with the comparable chemical stability and corrosion resistance could be very persistent in the environment, leading to cases of regrettable substitution.

[6] BioProcessing Article, 22 August 2022 Advanced Materials in Bioprocessing

[7] Streamlined life cycle assessment of single use technologies in biopharmaceutical manufacture - New Biotechnology (2022)
Single-use technology and sustainability: quantifying the environmental impact in biologic manufacturing – Cytiva (2020)

[8] University of Warwick, collaboration to find alternatives (Nature: Vol 620 3 August 2023)

6(f)- Cases in which substitution is technically and economically feasible but more time is required to substitute

PVDF filters are used in all aseptic and sterile manufacturing processes. The reason PVDF is used in filters over selected alternatives is better oxidant resistance and mechanical strength. In some publications PES (polyethersulfone) is cited as a potential alternative filter MOC (material of construction) to PVDF. Changing MOC with equivalent surface area and pore size will require re-execution of filtration studies, including extractables and leachable study data. In some applications the equivalent PES filter may not be suitable for the process application or require repeat execution of studies to identify a suitable filter size for the application.

The change management process can require process optimization work, equipment re-qualification and validation, and regulatory approval by all global health authorities. Estimated change over time to successfully replace a filtration unit in a single manufacturing process could take 2 years. As parenteral medicines are marketed internationally each product depending on the filter criticality may require re-registration in each individual target country, and standard times for this are 3-5 years. Many companies will have a significant variety of PVDF filters with some being used in several processes. Depending on the application of the filter, some of the above work will have to be completed for each individual product and each filter type. In total, ISPE member companies surveyed indicated that a complete replacement program may therefore be in the order of 20 years. These timescales consider a single change, however, multiple changes for a company would create production capacity constraints. Thus, putting the supply of medicinal products to patients at risk.

6(g) – If substitution is not technically or economically feasible, information on the potential socio-economic impacts for companies, consumers, and other affected actors.

An alternative that exhibits all the properties of the fluoropolymers used in medicinal product manufacturing facilities is not available. If the proposed PFAS restriction prohibits the supply of these critical raw materials, manufacturing operations at EU facilities will cease when contingency stock levels are depleted.

Transfer of manufacturing operations to non-EEA facilities to ensure continued supply of many medicinal products may not be possible. It is incorrect to assume that there is readily available manufacturing capacity at biotechnology and chemical synthesis production facilities outside of the EEA. Non-EU producers would require sufficient idle production capacity at a drug substance, drug product formulation and packaging facilities to meet the demand created by the unavailability of medicines manufactured in the EEA. It is unlikely that there is surplus idle capacity at non-EU facilities as underutilisation of production capacity is not good business practice.

Should suitable non-EU production capacity become available, time is required to complete the technology transfer of the manufacturing process to a new facility. In the case of the manufacture of a biological active substance, this could take 4 to 8 years:

- Identification of a suitable facility & completion of necessary due diligence 1-2 years
- Carrying out technology transfer process including stability studies 2-3 years
- Completion of global regulatory submissions plus wait time for approval 1-3 years

Commission working document[9] describes vulnerabilities in the global supply chains of medicinal products, including production capacity constraints. The COVID-19 pandemic highlighted vulnerability in global manufacturing capacity for sterile and biological processes. These processes are complex, and therefore must comply with additional quality and regulatory requirements. The length of time required to build new facilities to manufacture biological substances is significant. Recent real-world examples indicate that the amount of time required to design, construct, commission, qualify and obtain regulatory approval for a new biologics manufacturing facility is 5 years.

Annex 2 describes the cross-industry survey undertaken to evaluate the impact to patients if the proposed PFAS Restriction is implemented without a derogation for industrial use of fluoropolymers in pharmaceutical manufacturing. The number of active substances associated with manufacturing operations that are dependent on fluoropolymers used in plant, equipment was consumables was 1794. These active substances are intended to treat conditions such as cancer, cardiovascular disease, diabetes, mental health disorders.

In addition, considering the wide-spread impacts from a changing climate on water and biodiversity, shifting the burden of the global supply of medicines away from one major region of the world would place undue burden elsewhere, including in areas that may face more pressures on nature.

In short, a time unlimited derogation for the industrial use of fluoropolymers and fluoro-elastomers in medicinal product manufacturing facilities is a necessary medicine shortage mitigation measure.

[9] mp_vulnerabilities_global-supply_swd_en.pdf (europa.eu)

Appendix 1

Output from an ISPE Survey on the Impact of a Proposed Ban on Per- and Polyfluoroalkyl Substances (PFASs)

Output from an ISPE Survey on the Impact of a Proposed Ban on Per- and Polyfluoroalkyl Substances (PFASs)

EXECUTIVE SUMMARY

The conclusion from an ISPE survey conducted in August 2023 is that extensive derogation in the form of actions and timescales are required by the pharmaceutical industry and its suppliers resulting from PFAS restriction. Without such derogation there is a very high probability of many drug products required critically by patients becoming unavailable.

Timescales for replacement strategies and actions by companies will be long and uncertain given that substantial studies will be required to support replacement. The majority of responses indicated a range of 3 to 10+ years to complete the technical change. In addition, there is the time taken to obtain regulatory approval, which in many cases will include the need to seek approval in other regions of the world. Evidence suggests this additional regulatory time could be 3 to 5 years. A complete replacement program may therefore be in the order of 20 years total.

For nearly 30% of all impacted cases, technically there is currently no substitution feasible. Such situations may require major redesign of the drug product or its associated process (including drug substance process) or withdrawal from the market.

This technical and regulatory change management process will require substantial resources from marketing authorization holders. In addition, there will be a proportionately high resource needed from regulatory agencies in the EU, and elsewhere to review and approve these changes.

SUMMARY OF RESPONSES FROM ISPE SURVEY

ISPE conducted a survey in August 2023 with the objective of identifying the impact of the European Chemicals Agency (ECHA)'s proposed ban on PFAS on various sectors of the pharmaceutical industry during the production and packaging stages. Responses were received from 130 companies of varying sizes with a very wide spread of activity such as supply of materials and manufacture of drug substance (small molecule and biologics), supply of materials and manufacture and package drug product (sterile and non-sterile), provision of analytical and manufacturing materials and equipment.

The main messages of this survey are:

- 75% of the companies surveyed have factories in Europe. They all are very concerned about the potential impact of a potential PFAS ban or restriction.
- For 30% of the affected entities (chemicals for active ingredient manufacturing or analytics, products, manufacturing processes, equipment, utilities as well as primary packaging materials) there are not technical alternatives, in certain cases not even

after longer development work. For example, no alternatives are available for coated stoppers, which are used in almost all aseptically or sterile manufactured products.

The times mentioned in the survey for the re-registration of all entities concerned do not include the times needed on the part of the registration authorities. For example, internationally marketed products must be re-registered in each individual target country, and standard times for this are 3-5 years, which must be added. A complete replacement program may therefore be in the order of 20 years total. These timescales consider a single change, however, multiple changes for a company may lead to capacity restraints.

SURVEY DEMOGRAPHICS

Responses from 130 small, medium-sized and large pharmaceutical companies as well as suppliers of starting materials, excipients and production aids were received in the survey on PFAS related activities.

Among those were manufacturers of Active Pharmaceutical Ingredients (APIs), non-sterile drug products, sterile products, biotech drug substances, packaging material, equipment, analytical material, production material, excipients and facility construction companies.

60% of all companies supply or import APIs or drug product into the territory of the European Union, 40% of all companies produce material and excipients. 50% of responses are from companies with more than 5000 employees. (see Fig 1)

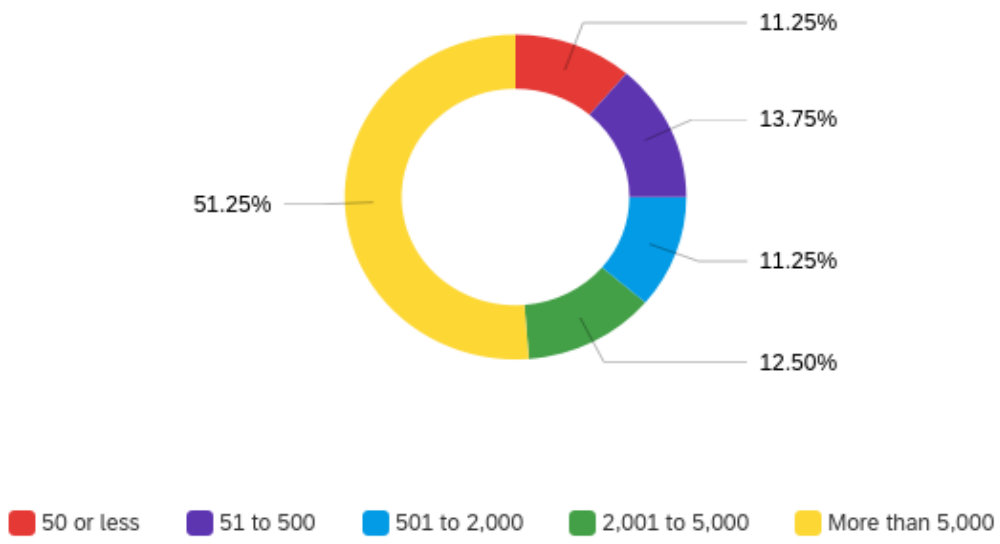


Fig 1. Demographics of ISPE survey on PFAS.

74% of all companies have facilities in the European Union. (see Fig 2), ALL of them are concerned by the impacts of a potential PFAS restriction. (see Fig 4).

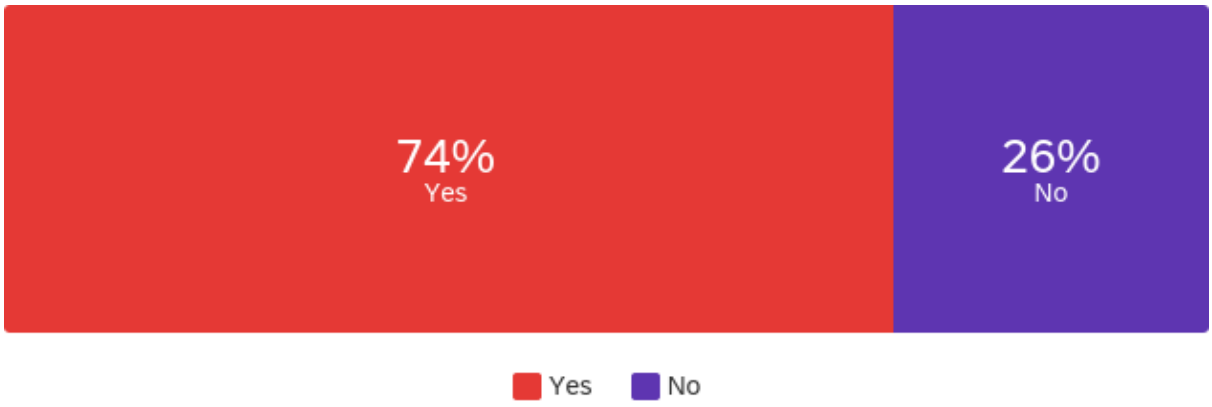


Fig 2. Companies with facilities in the EU.

The activity of these companies is distributed as follows (Fig 3):

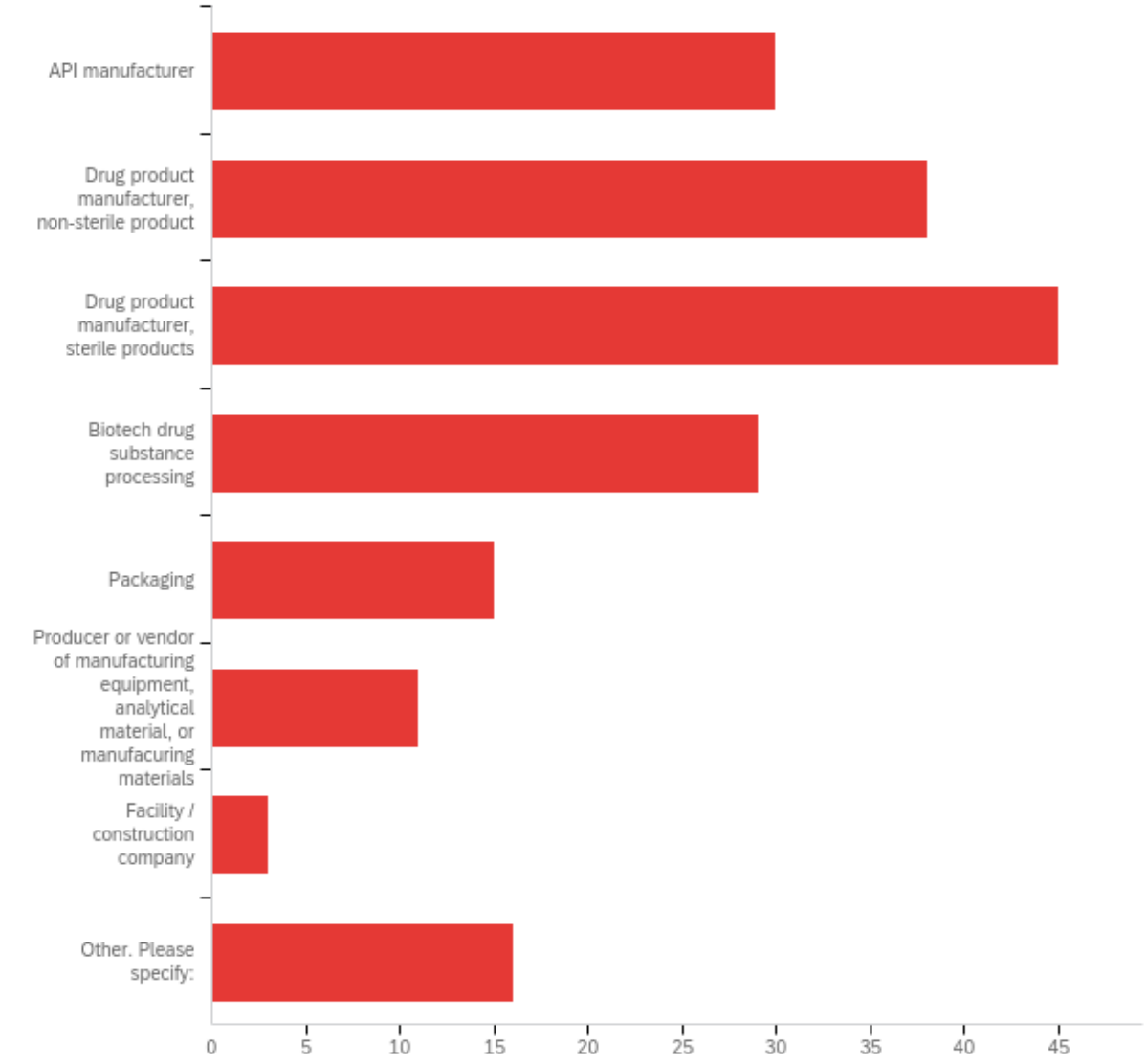


Fig 3. Surveyed companies' activities in the EU.

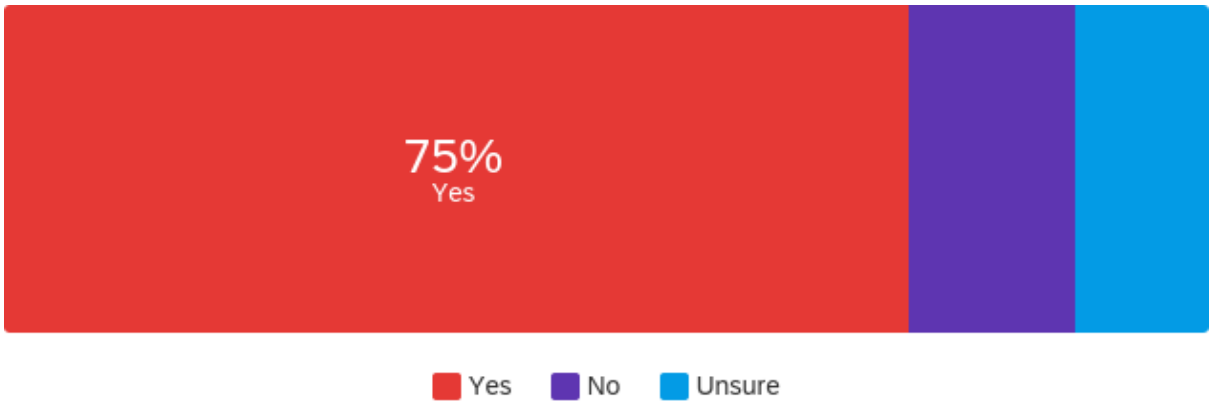


Fig 4. Surveyed companies concerned with the potential PFAS ban.

The highest impact is expected for production material, 30% for container closure system, i.e., vials and stoppers, followed by 29% for packaging materials (bottles and blisters). The second relevant group are fluorinated drug substances 19.5%, followed by fluorinated reagents 13% and fluorinated excipients 8.5%. (Fig 5).

As a pharmaceutical drug is registered with all components included specified packaging material and with the manufacturing process for the API and for the drug product or biological, each change of a component must undergo a regulated change management process with regulatory authorities. This change management process is based on a long list of questions requiring development activities, stability studies and even sometimes new clinical investigations.

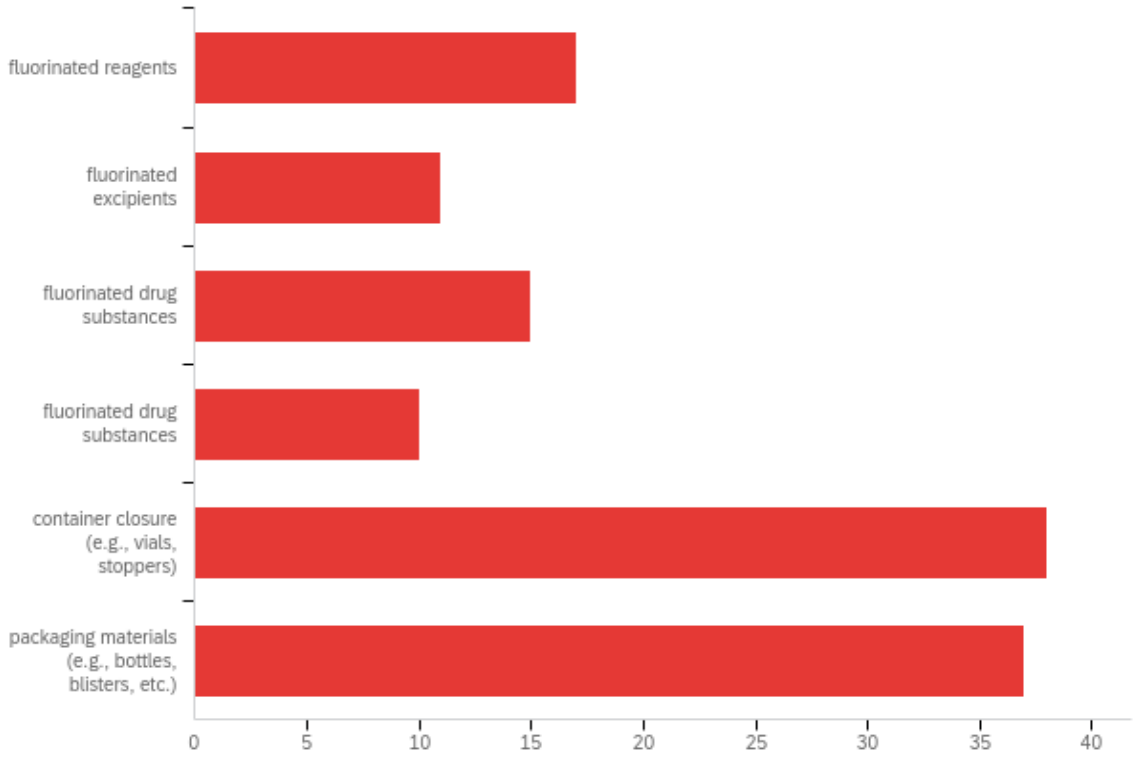


Fig 5: Impact of a potential PFAS ban on substances and packaging materials in direct contact with the product.

In processing equipment there is an equal impact for single use systems (disposable containers, bioreactors, bags, pouches and tubing), equipment gaskets, coated valves and filters. Utility systems, (e.g., manufacturing of sterile water for injection) are all affected (Fig 6).

The concerned processing equipment is essential and affects almost all production steps in a manufacturing process. Substitution requires development activities, tests, optimization, trial runs, qualification, validation – in addition and as a pre-requisite to start a regulated change management with regulatory authorities.

The kind of interaction given between polyfluoropolymers and equipment which has direct contact with the product is material compatibility (leachables and extractables) with potential alternate materials of construction. This requires additional qualification and validation studies and subsequent regulatory approval in the change management process with regulatory authorities.

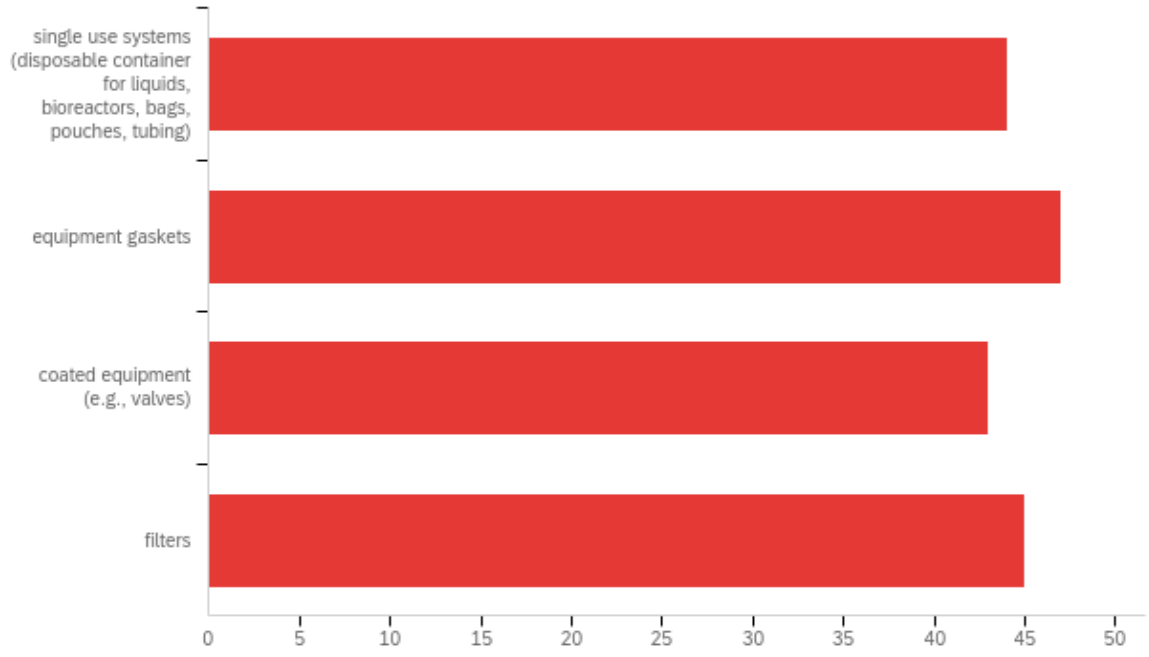


Fig. 6. Impact on a potential PFAS ban on production materials and equipment in contact with the product.

For utilities there is a similar picture. The extent of work is even higher as buildings need to be re-constructed.

CHANGE MANAGEMENT TIME

For 26% of cases, the change over time including all technical preparations with 3-5 years is expected, followed by 15.8 % with 6 to 10 years and for 15% even more than 10 years (Fig 7).

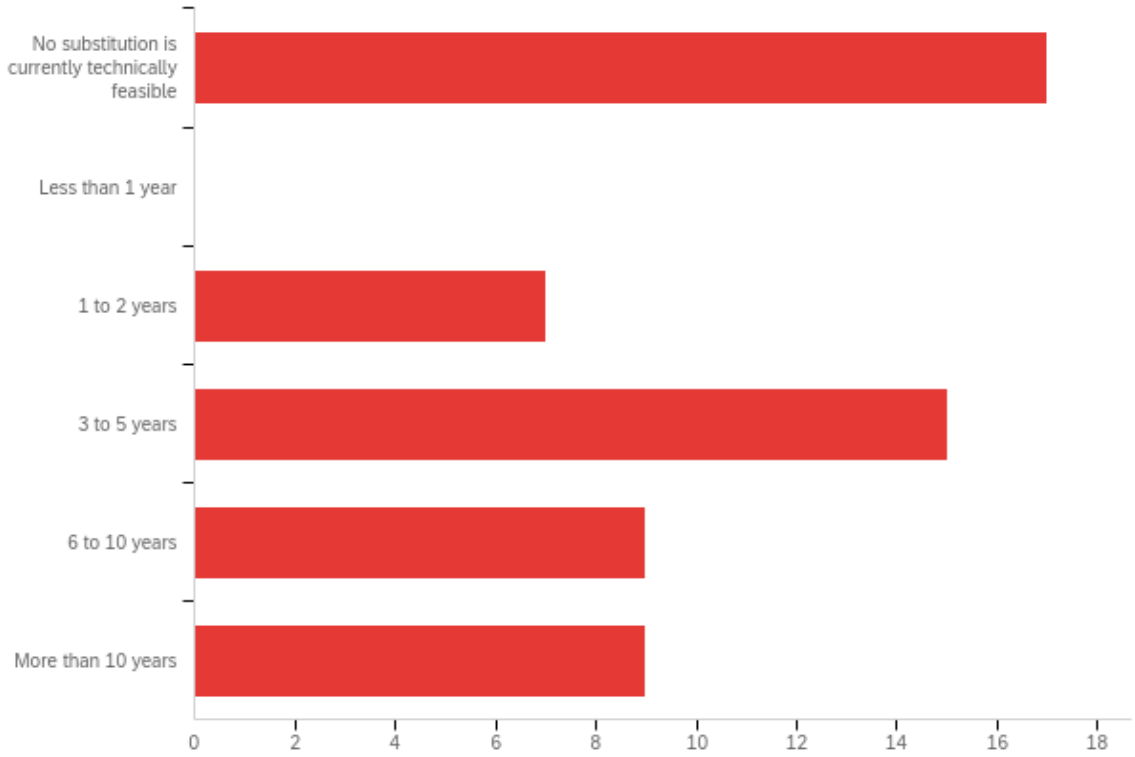


Fig 7. Estimated change over time, where substitution of PFAS components is feasible.

This survey does not include time and capacity constraints for EMA and National Competent Authorities to generate change approvals. A PFAS ban will generate a huge amount of drug product modifications in product components, causing regulatory authorities a bolus of submissions with a short timeline for approval.

Another multiplier is given for internationally registered products as each product is registered in its country of destination and the national competent authority there. Global change over times, just for the registration part, usually takes 3-5 years. This needs to be calculated as an additional time frame.

Highlighting the workload of changes:

Example 1: A regulatory requirement to use product-specific filters àadditional resources required for each product depending on the manufacturing process, there are several filtration steps per product needed. Filter vendors - if they have alternative solutions - must make challenges tests for the filters linked to each product for change management purpose and application changes.

Example 2: PFAS will not concern only APIs, but every product that requires filtering. Nearly 100% of all aseptic and sterile manufactured products require filtering, meaning that all sterile products will be impacted by PFAS restriction. Even with filter alternatives and if filter materials are available, a full validation work will be needed with several runs of Aseptic Process Simulation which will have a huge impact on pharmaceutical operations, including personnel qualification.

ALTERNATIVES

For nearly 30% of all impacted cases, technically there is no substitution feasible.

Example: Coated stoppers have a PFAS based safety barrier in order to protect the product from extractables and leachables from the stopper material. Years of research have not resulted in a safe alternative to the coating material.

There are other examples available.

For alternate substances, excipients, production aids, construction material deeper investigations per product and per process and per factory are needed in order to calculate the resource as needed for a change. For the cases where substitutions are technically not feasible and unavailability of drugs (more severe than temporary drug shortages) is expected, a derogation for these cases is requested in order to ensure patient health and safety.

The highest impact of PFAS restriction for the health world and patients is the likelihood of generating additional drug product unavailability due to product temporary or definitive disruption.