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BUILDING COMPROMISES · FOSTERING BREAKTHROUGHS

CONFIDENTIAL

FOR THE ITALIAN REACH COMPETENT AUTHORITY

PFAS Restriction under REACH:

Why PVDF for use in Biotherapeutic Filters Must Be Derogated

[redacted]

13 July 2023

Agenda

1. **Introduction** [redacted] of PVDF in product portfolio
2. **Annex XV:** Our Concerns
3. **Annex XV:** What Impact on PVDF?
4. **Way Forward**

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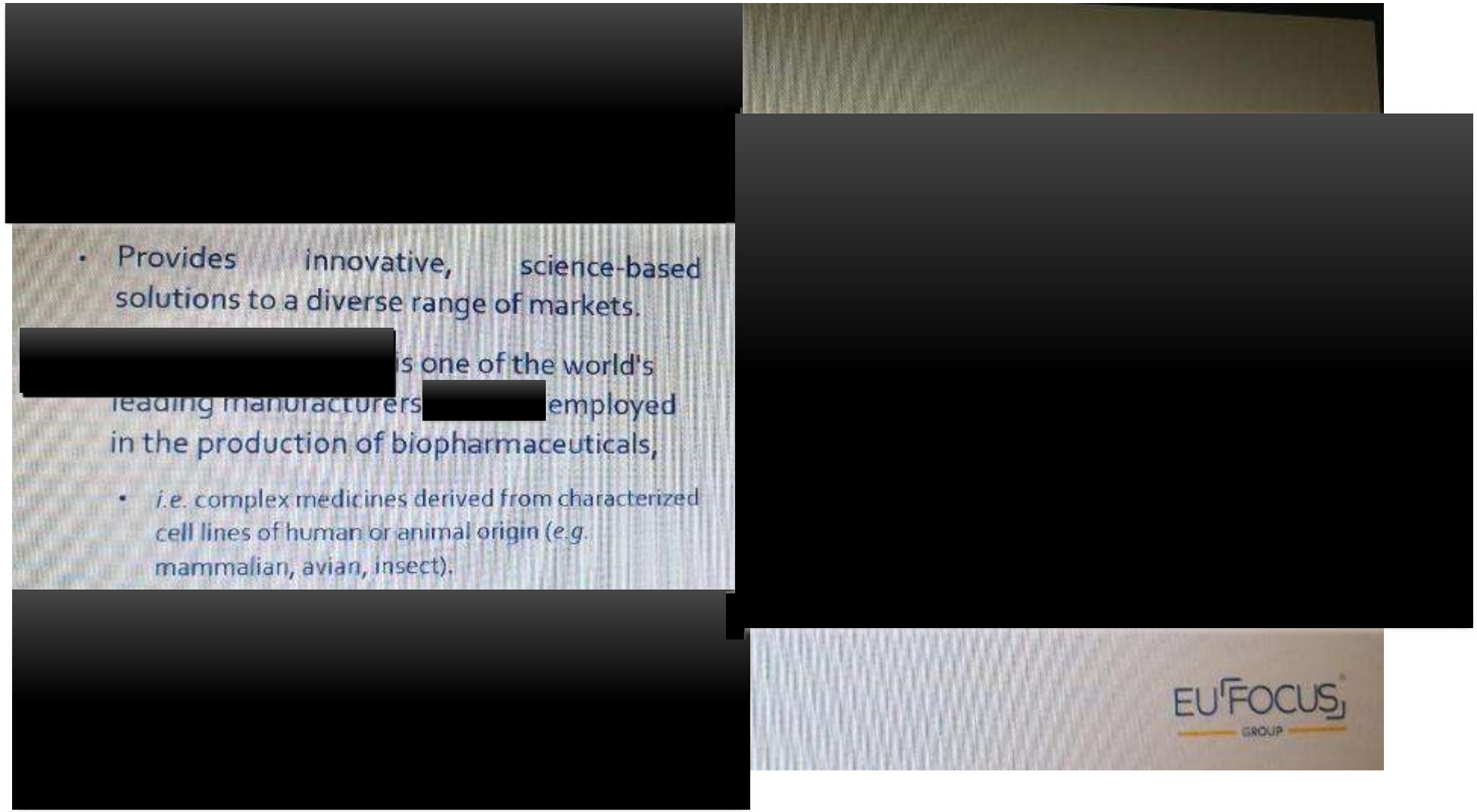
• Provides innovative, science-based solutions to a diverse range of markets.
s one of the world's
leading manufacturers employed
in the production of biopharmaceuticals,
• i.e. complex medicines derived from characterized cell lines of human or animal origin (e.g. mammalian, avian, insect).
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Substances and Articles of Concern

PVDF

[redacted] (hydrophilized polyvinylidene fluoride ("PVDF") hollow fibers)	[redacted] (polyvinylidene fluoride ("PVDF") hollow fibers
• a new generation **of virus filter** made with, designed to achieve **robust retention of parvoviruses** and other small viruses under a broad range of operating conditions.	• a new generation of **cell clarification filter** for **purification of protein solution**.

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About Biopharmaceuticals

- Biopharmaceuticals are produced in living cells or extracted from human plasma, unlike synthetic drugs which are the result of chemical processes.
- Since its introduction in 1982, biopharmaceutical drugs have revolutionized the treatment of a broad spectrum of diseases and are increasingly used in nearly all branches of medicine.
- In recent years, the biopharmaceuticals market has developed much faster than the market for all drugs
- They are crucial for treating various pathologies such as cancer, and patients rely on their availability.

Advantages over synthetic drugs

they target only specific molecules, rarely causing the side effects associated with conventional small-molecule drugs.

Thus, they are vital for patients in volatile conditions.

Biopharmaceuticals are vital for medicine and have advantages over synthetic drugs, including targeting specific molecules and causing fewer side effects.

They exhibit high specificity and activity.

some patients react poorly to synthetic drugs, thus they are dependent on the broad availability of biopharmaceuticals

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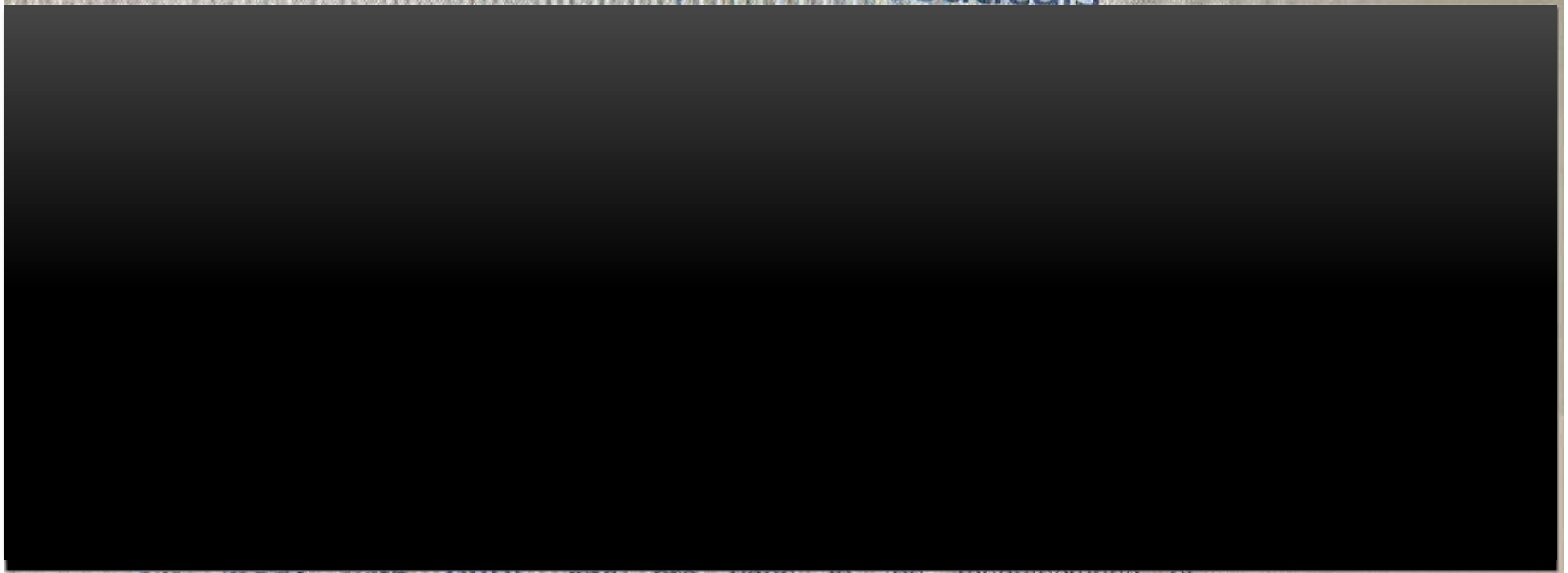
Manufacturing of Biopharmaceuticals



are made with PVDF and are used in the manufacturing of biopharmaceutical drugs, ensuring that biopharmaceuticals are safe, ultimately protecting human health and patient safety.

- Required step by various Directives and Guidelines

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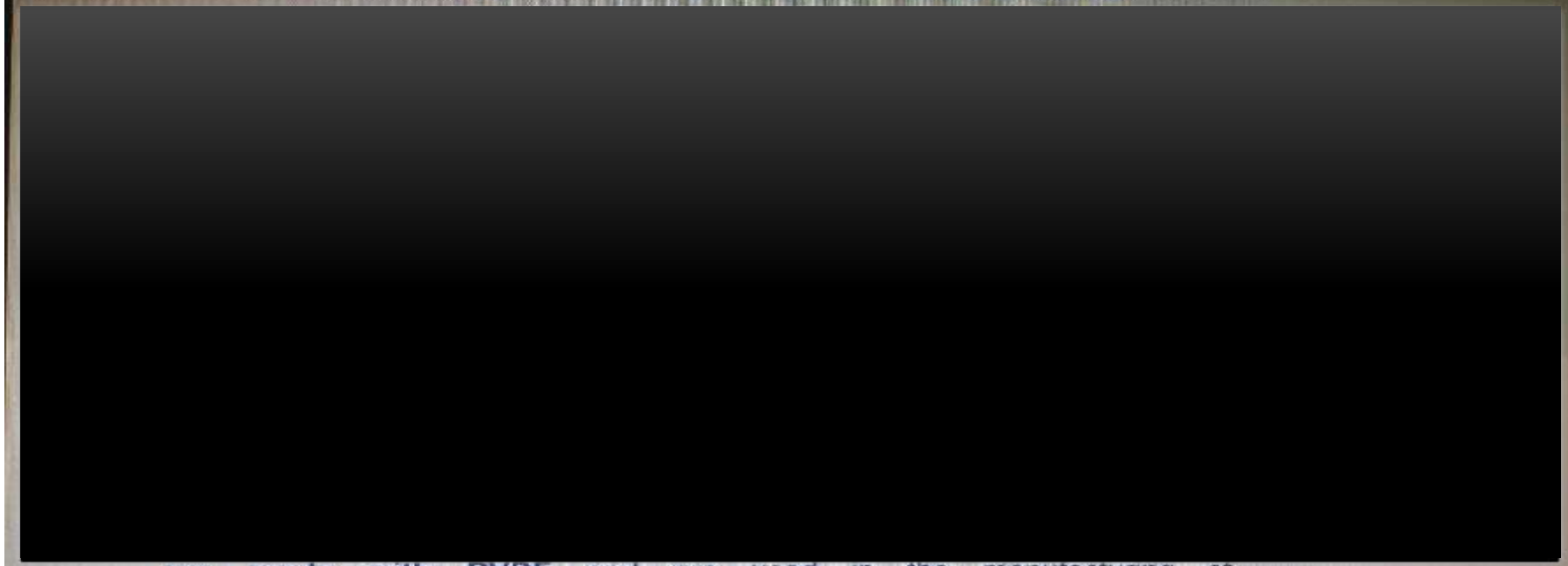
Manufacturing of Biopharmaceuticals



are made with PVDF and are used in the manufacturing of biopharmaceutical drugs, ensuring that biopharmaceuticals are safe, ultimately protecting human health and patient safety.

- Required step by various Directives and Guidelines

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Nanofiltration & Microfiltration

Nanofiltration

- a well-established method allowing the removal of viruses
- based on size-exclusion that entails filtering of protein solutions through membranes with pores of nanometric sizes that have the capability to effectively retain a wide range of viruses.
- The use of this filter during nanofiltration is a necessary step in the production of biopharmaceuticals to effectively remove viruses from the end-products, *i.e.* human medicines.

Microfiltration

- designed to have a higher filterability of antibodies.
- a well-established method that allows the separation of the antibodies (proteins) from the animal cells.
- The use of this filter during microfiltration occurs upstream in the filtration of impurities, before the virus removal stage.
- Necessary step in the production of biopharmaceuticals aimed to separate the animal cells from the antibodies.

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Why nanofiltration in the first place?

1. Inherent risks

- Biological products, made from human or mammalian cells possess an inherent risk of being contaminated by viruses that can be pathogenic to humans.

2. Societal Implications in case of a viral contamination

- significant burden from financial, regulatory and time aspects
- implies that production at the facility where it occurred is stopped until the causes are eliminated.
- may lead to product shortages for patient treatments

3. Product Requirement

- In addition, the safety and efficacy of biopharmaceuticals in humans require drugs of highest purity, right concentration allowing the API to work effectively

Examples of removed viruses

(HIV, HAV, and B19V), and model viruses covering a wide range of physicochemical properties and sizes .

parvoviruses (B19V, BPV, CPV, MVM, PPV;),

picornaviruses (HAV, BEV, EMCV, PEV, HPV-1, TMEV;

caliciviruses (FCV;),

papovaviruses (SV_{40};),

flaviviruses (BVDV, WNV),

togaviruses (SINV, SFV),

reovirus 3 (Reo_3;),

retroviruses (HIV;),

rhabdoviruses (VSV), and herpesviruses (PRV, HSV, IBRV)

Coronaviruses (SARS-CoV-1, SARS-CoV-2)

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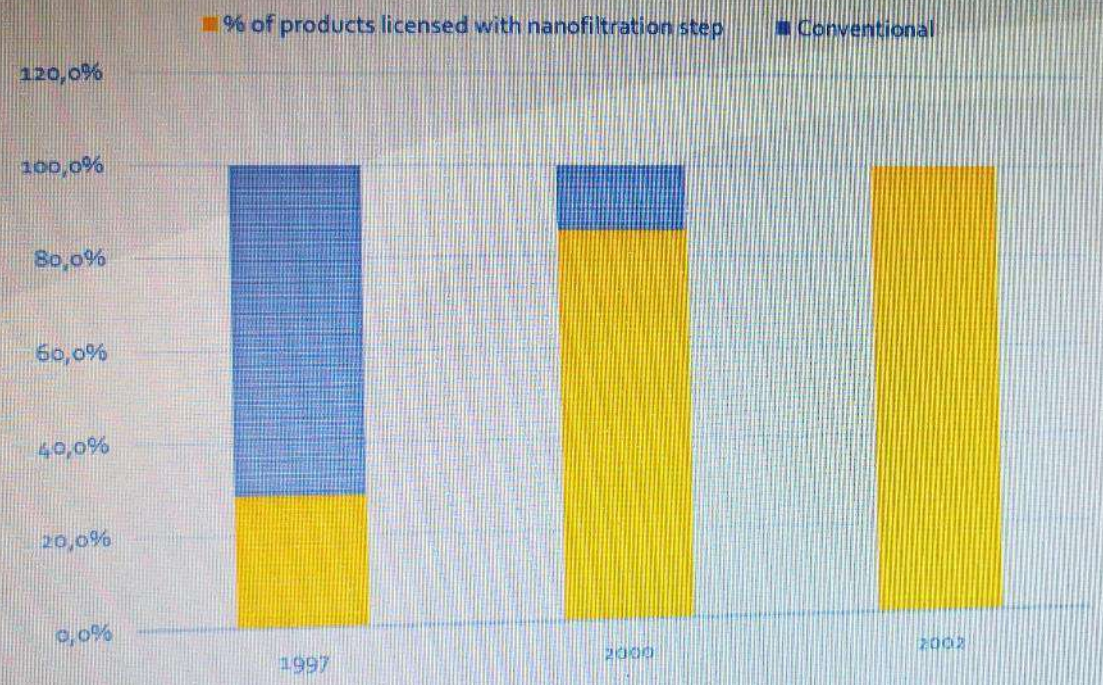
Nanofiltration is an integral part of the manufacturing process of biopharmaceuticals



In recent years nanofiltration has increasingly become dominant in the field of human plasma derived products. 1997 two out of seven products licensed contained a nanofiltration step, this rate increased to 6 out of 7 in 2000 and 100% in 2002 and 2003

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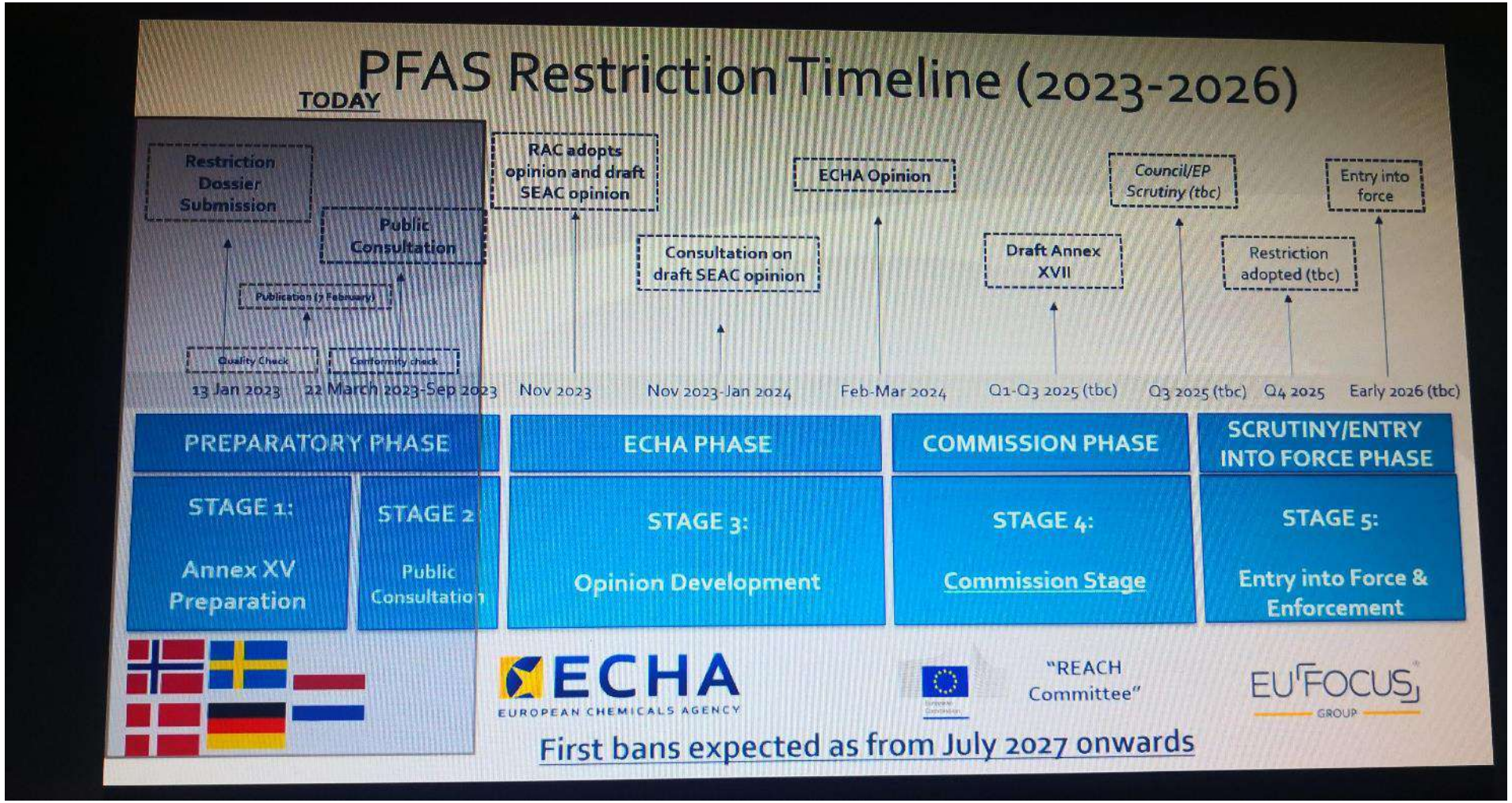
Source: Innouye, M., & Burnouf, T. (2020). The Role of Nanofiltration in the Pathogen Safety of Biologicals: An Update. Bentham Science Publishers. doi:10.2174/1573413715666190328223130


PFAS Restriction Timeline (2023-2026)
TODAY
Restriction Dossier Submission
Public Consultation
Publication (7 February)
Quality Check
Conformity check
13 Jan 2023
22 March 2023-Sep 2023
RAC adopts opinion and draft SEAC opinion
Nov 2023
Consultation on draft SEAC opinion
Nov 2023-Jan 2024
ECHA Opinion
Feb-Mar 2024
Draft Annex XVII
Q1-Q3 2025 (tbc)
Council/EP Scrutiny (tbc)
Q3 2025 (tbc)
Restriction adopted (tbc)
Q4 2025
Entry into force
Early 2026 (tbc)
PREPARATORY PHASE
ECHA PHASE
COMMISSION PHASE
SCRUTINY/ENTRY INTO FORCE PHASE
STAGE 1: Annex XV Preparation
STAGE 2: Public Consultation
STAGE 3: Opinion Development
STAGE 4: Commission Stage
STAGE 5: Entry into Force & Enforcement
ECHA
EUROPEAN CHEMICALS AGENCY
"REACH Committee"
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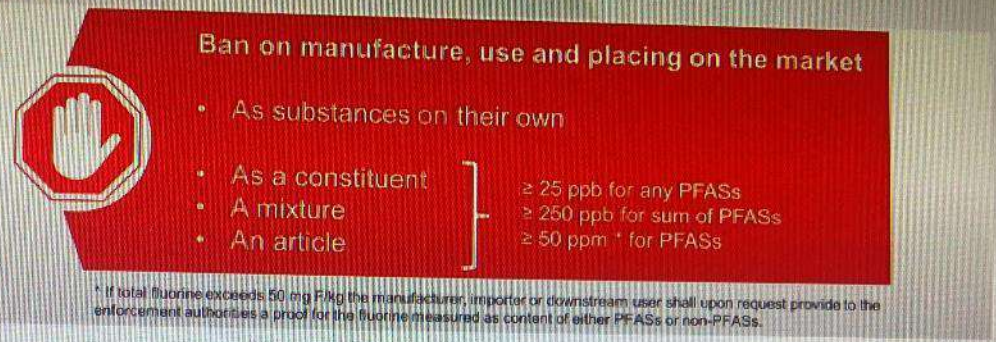
First bans expected as from July 2027 onwards

Approach of the Five Countries: "BAN, BAN, BAN"



"Universal Ban"

- Annex XVII restriction to apply to all PFAS (fulfilling OECD definition),
- 18 months of 'transition period' after Entry into Force (EiF).

Derogations

- pesticidal active substances
- biocidal active substance
- human and veterinary medicinal products

Time-limited derogations = "delayed ban"

- applied either 6.5 or 13.5 years later from EiF
- tentative derogations proposed in square brackets [...] where data is not enough

Time-limited derogations = "delayed ban"

- Dominating "anti-PFAS" narrative is based on old technologies based PFOS, PFOA
- PFOS, PFOA are banned since more than 10 years in Europe!

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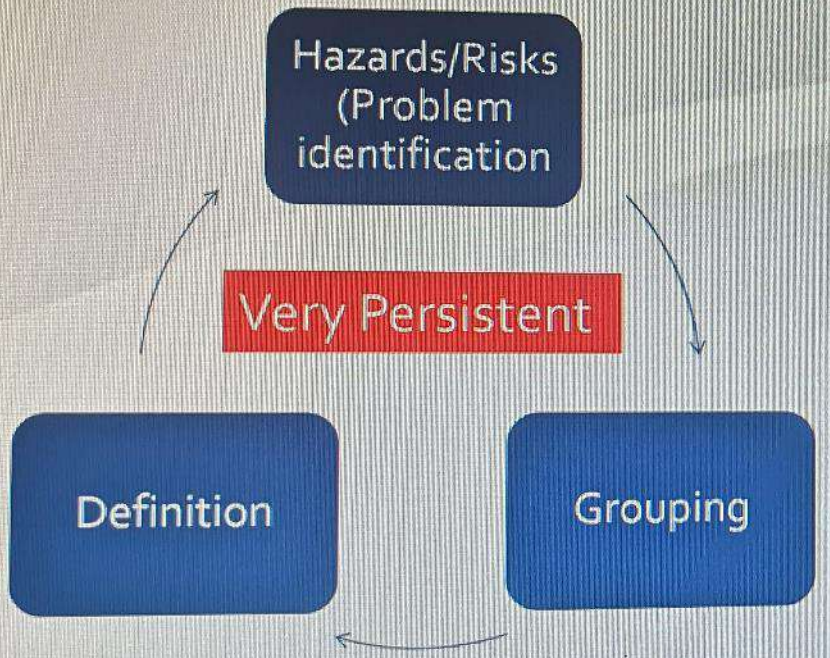
Main Concern of the Five Countries: PERSISTENCY



L.C.D.: carbon-fluorine bond particularly strong and highly persistent *"All PFASs are considered to be very persistent, either on the basis of their own very persistent properties or the very persistent properties of their terminal degradation product (arrowhead)" (p.22)*

"P-Sufficient approach"

"Additional hazardous properties depend on the specific structure of a PFAS":

- ~~Long-range transport potential ("LRTP")~~
- ~~Mobility~~
- ~~Accumulation in plants~~
- ~~Bioaccumulation~~
- ~~Ecotoxicity~~
- ~~Endocrine Activity/Endocrine Disruption~~
- ~~Effects on Human Health~~

Referenced "additional hazardous properties" are not applicable to fluoropolymers

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REACH PFAS Annex XV – Our Concerns

THE PROPOSAL BY 5 COUNTRIES IS FLAWED

- ***No derogations, only bans (+18 months after EiF) or "delayed bans" (+6.5 or +13.5 years after EiF)***
- Persistency – main criterion for ban ("P-sufficient approach"):
  - No hazard assessment
  - No information on use resulting in emissions
  - Nor risk assessment
  - Insufficient analysis of alternatives
  - No causal link between alleged presence of PFAS and actual fluoropolymers usage
- Wrong premises (e.g. non-fluorinated polymerization aids are 'better' for the environment)
- Alternative RMOs not considered

OVERALL: no demonstration of unacceptable risk & no recognition that fluoropolymers can be produced responsibly

DIRECT IMPACT ON PVDF

1. **All PFAS as per definition,** unless explicitly derogated, will be banned as from July 2027
2. **Most substances will be** completely banned after a transition period (if at all)
3. While the report includes consideration of the use of PFAS in medical device and some limited pharmaceutical applications, the **biopharma sector is a missing** use category and needs to be appropriately considered
4. **PVDF in medical biotherapeutic filters are** in scope of restriction proposal.
5. **Fluorinated Polymerization aids** are banned for the production of PVDF
6. **Transported isolated intermediates** used under strictly controlled conditions are banned (contrary to REACH).

OVERALL: indirect ban on high-tech economic sectors, including green technologies, relying on fluoropolymers.

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Fluoropolymers

- very persistent (vP)
- Not toxic (T)
- No bioaccumulation (B/vB)
- Not mobile (M or vM)
- Stable in environment
- Biologically inert

Fluoropolymers are:

- Distinct subclass of PFAS
- Thermal decomposition in waste to energy plants

Example of Fluoropolymers: PVDF, PTFE, PFA

Proposal: The durability of Fluoropolymers provides applications the essential longevity and needed performance and should be exempted from any potential restrictions.

**According to the OECD criteria*

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Preliminary assessment – May be subject to change

Risk Assessment: Biotherapeutic filters

NO Hazards

- very persistent (vP)
- Not toxic (T)
- No bioaccumulation (B/vB)
- Not mobile (M or vM)
- Stable in environment
- Biologically inert
- Polymer of Low Concern (OECD*)

NO Exposure

Manufacturing

- Not manufactured in the EU
- Concerns regarding manufacturing can be addressed at site (at Source)

Use

- operated by trained professionals, with no exposure to workers or patients as the PVDF membrane is encapsulated in the filter.
- No adverse events related to nanofiltration have been recorded, and regulators recognize and mandate it as a safe virus removal method.

End of life

- Filter are considered as **hazardous waste** under the Waste Framework Directive.
- filters **need to be incinerated** due to their contamination with pathogens at special facilities as hazardous waste at high temperatures
- Under these extreme conditions, the C-F bond breaks down, thus completely **destroying any PFAS (confirmed by several studies) → next slide**

NO Risks

Fluoropolymers, such as PVDF, do not pose any risks to the environment and human health and should be generally exempted from the PFAS Restriction

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Alternatives

- There are three primary types of nanofiltration, **each designed for their unique use case and environment**, as such they cannot be interchanged.
- PVDF enables nanofiltration, which is the **only process** in the nanofiltration targeting effectively smaller viruses
- There are practically **no alternatives that can replace the high performance** provided by PVDF in in the biopharmaceutical sector **and** Protein concentration plays a crucial role in determining the right filter. (Image)
- alternatives have a lower transmission of the targeted protein of interest while only PVDF can meet the various performances required for drug product applications
- **PES and polysulfone** require an asymmetric pore structure, **causing the clogging** of the membrane interior progresses during filtration

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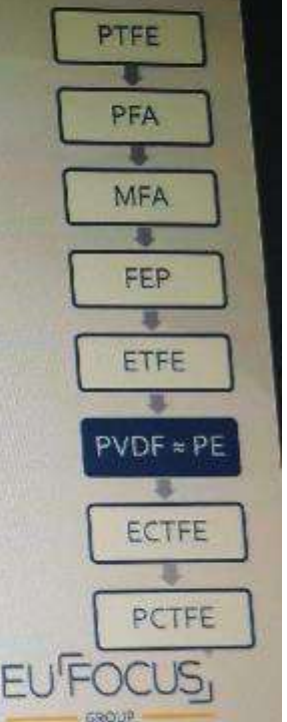
End of Life – Mandated Incineration

- Under EU and national legislations, filters **need to be incinerated** due to their contamination with pathogens at special facilities as hazardous waste at high temperatures.
- For hazardous waste, the minimum temperature of the combustion gases must be **1100 °C**
- Polytetrafluoroethylene (PTFE or [redacted] is the most stable fluorine containing polymer and it can be concluded that complete thermal decomposition is achieved at a temperature of **about 800 °C**.
- Other fluorine-containing polymers thermally decompose completely at a temperature of 850 °C.
  → thermal resistance chart to the right
- A perfect, complete combustion of PFASs results, in theory, in the emission of water, CO_2, HF and, depending on the functional groups in the PFAS, sulphur dioxide, phosphorus oxide and nitrogen dioxide
- Additional cleaning steps for the flue gas are required/mandated to remove potential remaining pollutants

Source: Dutch National Institute for Public Health and the Environment, RIVM report 2021-0143

Order of thermal resistance (high to low):



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Way Forward

Preferred RMO

- The restriction of PFASs must be substance-related and risk-based (Article 68 para. 1 of the REACH Regulation).
- It is clear that not all PFAS pose an unacceptable risk that would justify a restriction. Especially, the restriction must differentiate between the different groups of PFAS and the risks, and the risks posed by their uses.
- Fluoropolymers, such as PVDF, do not pose any risks to the environment and human health and should be generally exempted from the PFAS Restriction or benefit from a time-unlimited derogation.

Alternative RMOs

Option 1:

[redacted] ould be exempted *a priori* from the Proposal as they **should not be covered by** the REACH Regulation; or,

Option 2:

[redacted] should be exempted *a priori* from the Proposal as they are used in a **closed system**; in alternative,

[redacted] roducts should benefit from a time-unlimited derogation in relation to the Proposal **as the same rationale of plant protections products, biocides and human and veterinary medicines** should apply.

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ELECTRICAL SYSTEMS, WIRES, CABLES, AND SEMICONDUCTORS

- Semiconductor chips
- Lambda/O2 sensor conduit & grommet
- Electric mirror lubrication
- DC motor bearing lubrication
- Oxygen/NOx Sensor
- Heated seat wire
- Diesel pump wire
- ABS transmission brake sensor wire

[redacted]

- High tension ignition cable
- Battery terminal wire
- Convoluted wire harness conduit
- Cable tie wraps
- Xenon/bi-xenon headlight wire
- Throttle body injection wire
- ABS sensor cables
- Printed Circuit Boards

TRANSMISSION & TRANSAXLES

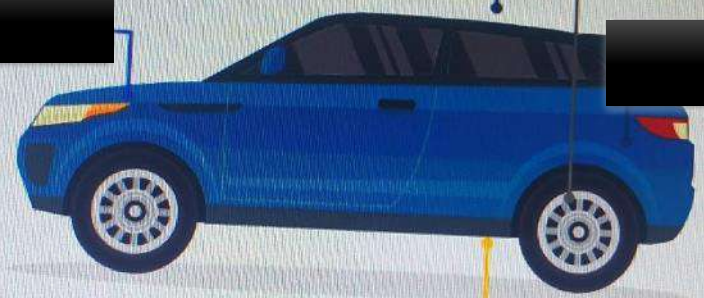
[redacted]

- Internal shift seal ring/clutch piston ring
- Clutch pilot and release bearings
- Clutch bearing lip seals
- Dual mass flywheel replacement
- Auto ORC de-coupler for alternators
- Driveshaft: CV joint lubrication

ENGINE & POWERTRAIN

[redacted]

- Head cylinder & oil pan gasket
- Transmission & crankshaft seals
- Valve stem seals
- Bearing lubrication
- Flexible O-ring & piston skirt coating
- Front engine accessory drive Throttle body bearings & lubrication
- ETC lubrication
- Actuator assembly, valve belt tensioner
- Air intake manifold gaskets
- Turbocharger hoses
- EV binder for battery and seals



[redacted]

FUEL SYSTEMS

- Fuel line: feed return, vapor
- Fuel line quick connector seals
- Interconnect hoses
- Filler neck hose
- Fuel rail crossover
- FIORs
- Fuel sender seal
- Connector o-rings
- Diaphragm pressure regulator
- Anti-expulsion tank valve
- Pressure injection bushing
- EV battery cooling

CHASSIS

- ABS interconnected hose
- Hydraulic break lines
- Impulse hose at wheel
- Brake pad clips, shim and wear indicator
- Insulating foams and sound dampening
- Shock struts/absorber piston seals
- Dry Lubricant bearing door hinges
- Axle seals
- Adhesives
- NVH busing – lubrication
- Steering ball bushing incl. lubrication
- Steering ball joint insert and shaft steering splines
- Steering assist pump piston rings
- Cabin comfort and heating

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