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THE VOICE OF THE ANIMAL MEDICINES INDUSTRY

Position of the European Human Pharmaceutical and Animal Health Industry on the use of "per- and polyfluorinated alkyl substances" (PFAS)[1] in Europe, in the light of a proposed Restriction under REACH as published[2]

June 2023

Context

On March 22nd, 2023, the European Chemical Agency, ECHA opened a consultation on a draft REACH restriction for a broad group of fluorinated substances, the so called per- and polyfluorinated alkyl substances (PFAS), which also covers mixtures and articles containing PFAS. The high persistence of many PFASs results in potential accumulation in the environment and food chains. This REACH Restriction aims to ban the manufacture, use and placing on the market of at least 10,000 PFAS, and is the most complex restriction ever proposed in the EU with significant impact and unintended consequences across various industries, including the pharmaceutical sector.

The Human and Veterinary Pharmaceutical sectors manufacture a variety of medicines using materials that meet the broad definition of PFAS. In addition to the many active ingredients (API) captured within the definition used by the European Union in its proposed restriction, building blocks and the raw materials used within chemical synthesis of PFAS and non-PFAS medicines and reagents would also fall within the scope.

The restriction text proposes derogations in paragraphs 4, 5 and 6. Some of these are applicable to certain industry sectors, such as 6.f. (petroleum and mining industry). The (bio)pharmaceutical and animal health industries have not been identified as sectors in the draft restriction. This is problematic in the light of fair competition rules as promoted by the EU[3], and because the sectors are not defined in the regulation. Substances and products can be derogated when they have a clearly defined legal status, such as in paragraph 4, where active ingredients for regulated products are listed. We welcome this important derogation to avoid negative impacts on human and animal health, as any change to the molecular structure of an active pharmaceutical ingredient or composition of the medicinal product voids regulatory approval and marketing authorisation. Human and Veterinary medicine manufacturing and development is a highly regulated environment where all parts of a process including environmental impact are assessed. The application of Title VIII of REACH[4] and the consequences for marketing authorisations increase the risk of supply disruption, ultimately affecting the provision of medicines to patients.

REACH Restrictions do not include a general exemption for medicinal products and related manufacturing. Though paragraph 4 c of the draft restriction proposal includes a derogation for the Active Pharmaceutical Ingredients (API) in human and veterinary medicinal products, the Annex XV dossier as published would have an immense impact on both the human and animal healthcare in Europe. API that are manufactured using fluorinated building blocks as starting materials or

[1] https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas
[2] https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/72301/term
[3] https://european-union.europa.eu/priorities-and-actions/actions-topic/competition_en
[4] https://ec.europa.eu/growth/sectors/chemicals/reach/restrictions_en

intermediates would remain in scope of the restriction as proposed. Additionally, certain validated synthetic routes for APIs which are not PFAS themselves depend on either PFAS process chemicals, like solvents, catalysts or intermediates. Furthermore, PFAS materials used for immediate packaging or in medical devices, medicinal product containers maintaining sterility and delivery devices could be banned, although they are integral parts of medicinal products and their market authorisations. Finally, all known production depends on fluoropolymers in production equipment. Ultimately, the entire portfolio of medicinal products placed on the EEA market (or exported) and produced within EEA is expected to be impacted by the PFAS restriction.

Position

EFPIA and AnimalhealthEurope welcome the proposed time-unlimited derogations for API in the draft restriction, recognizing the essential role of fluorinated compounds in medicinal products.

We strongly support that authorised products such as API but also finished medicinal products be derogated from the scope of the proposed PFAS Restriction. This is justified by the societal necessity of medicines, the limited ability for substitution with non-PFAS chemicals, the fact that APIs are already subjected to environmental risk assessment, and the low risk that these materials have for impact on the environment due to both limited volume and minimal hazard[5].

Supply chain and development of derogated products should also be taken into account. The raw materials, intermediates, and auxiliaries required for manufacture of these medicinal products should be derogated, on the basis that any emission in industrial manufacturing environments is well controlled and regulated, and manufacturing should continue to take place in EU countries. The same applies for reagents required for diagnostic and quality control procedures if their use is mandated for quality reasons or by regulations or license agreements. The derogation for API as currently drafted would not allow continued manufacturing of many API in the EEA, which conflicts with recent EU strategies to reduce dependency on supply chains located mainly outside of the EEA. For these reasons, we would support that all the manufacturing steps essential to the production of medicinal products should similarly benefit from a time-unlimited derogation from the PFAS restriction.

Fluoropolymers are not volatile or bioavailable. As the only common property is persistence, their emission should be restricted rather than the use of the substances. If emission control is in place and covers the waste stage, a ban is neither justified nor proportionate, regardless of transition periods. This would be the case for industrial use under management plans as outlined by paragraph 8 of the restriction proposal.

PFAS Uses: Rationale and Impact

EFPIA and AnimalhealthEurope have been collecting scientific and technical data and additional knowledge of PFAS and their application in our industry sector, to support responsible and sustainable use of these materials. Our member companies are committed to making a positive impact on the lives of human and animal patients, and to adhere to environmental regulations and other agreements. Our sustainability strategies consider both socio-economic and ecologic aspects of our operations. Even though we are committed to phasing out problematic substances wherever possible, the replacement

[5] https://www.sciencedirect.com/science/article/pii/S0160412019309493

of PFAS is limited by availability, technical applicability, and environmental trade-offs of alternatives. It can be expected that any time-unlimited derogation will be revoked if suitable alternatives become available. Should substitution attempts fail, all time-limited derogations pose a threat to the supply chain, unless reviewed and optionally extended before the deadline.

The definition used in the draft Restriction is based on the recently adapted OECD PFAS definition[6] and imposes the same restriction on individual compounds with a wide range of properties. This PFAS definition differs significantly from the working definition used by the US EPA[7]. We encourage adoption of a unique global definition which incorporates identical technical terms.

To identify this position, the drug development and commercial portfolio of medicinal products and starting materials used in manufacture has been investigated, and several substances meeting the proposed PFAS definition are currently used by EFPIA and AnimalhealthEurope members. These substances can be categorised in the following groups e.g.:

1. APIs;
2. Development products and API including global programs, ie non-EU regulated products;
3. Non-active ingredients (excipients);
4. Starting materials and chemical intermediates;
5. Equipment and consumables;
6. Reagents, solvents, catalysts, auxiliaries in production and Quality Control;
7. Immediate packaging materials and sterile barriers; and
8. Drug delivery devices.

In this document, we provide information on chemical rationale, emissions, potential for substitution and impact of the restriction for each of the uses in focus.

(1) Active Pharmaceutical Ingredients (APIs)

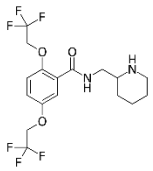
a. Overview

More than 300 fluorinated compounds have been launched as medicinal products over the last few decades and over 500 more are in late-stage clinical trials.[8] Today about 30% of all APIs contain fluorine.[9] This indicates the importance of fluorine in pharmaceutical compounds, both for existing medicinal products as well as for an increasing number of hopeful future candidates.

Of the launched and (pre)registered medicinal products, about 100 contain at least one perfluorinated methyl (-CF_2- or -CF_3) substituent. Several of these are on the World Health Organization's Model List of Essential Medicines[10] covering treatments across a large variety of diseases. Examples are efavirenz (AIDS), mefloquine (malaria), fluoxetine (depression), and gemcitabine (cancer).

[6] https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/terminology-per-and-polyfluoroalkyl-substances.pdf
[7] https://www.epa.gov/chemical-research/research-and-polyfluoroalkyl-substances-pfas
[8] Clarivate Integrity; https://clarivate.com/
[9] https://www.solvay.com/en/chemical-categories/fluorine-chemicals/organic-fluorinated-compounds
[10] https://www.who.int/medicines/publications/essentialmedicines/en/

From the top 200 small molecule medicinal products according to sales in 2018[11], 25 contain perfluorinated methyl (-CF_2- or -CF_3) substituents, again across therapeutic indications. Examples are sitagliptin (diabetes), enzalutamide (prostate cancer), teriflunomide (multiple sclerosis), fulvestrant (breast cancer), and celecoxib (inflammation). In the veterinary field, a number of fluorinated compounds for the treatment of life-threatening infections and (potentially zoonotic) parasite infestations have been identified with 16 of those qualifying as PFAS under the OECD definition and, as such, falling under the proposed PFAS restriction. All inhalation anaesthetics used in complex surgery also qualify. However, these molecules, containing one or two aliphatic -CF_2- or -CF_3 groups, are not polyfluorinated or perfluorinated in the technical sense and do not meet the criteria of concern raised by the competent authorities planning to prepare a restriction on PFAS. This is illustrated by the highest volume PFAS API that are under discussion:



Flecainide[12] has the highest API volume in the Report Summary provided with the 2nd Stakeholder Consultation[13] save for pantoprazole, which is no longer covered by the revised OECD PFAS definition. It is a typical API molecule meeting the PFAS criteria, which has only trifluoro methyl groups as part of a large molecular structure. Consequently, these molecules are not persistent in the human body (half-life for flecainide was 12 to 27 hours in patients; NDA 18-830)[14], and some of them, as in the case of flecainide, neither in the environment[15]. The concern raised by the initiators of the restriction are not the "PFAS API" themselves, but the formation of persistent breakdown products (arrowhead concept). This breakdown product is most likely trifluoro acetic acid (TFA)[16] in the case of trifluoro methyl groups in a molecule.

b. Chemical Rationale

The extensive application of fluorine in drug research is related to the unique properties of this element. Fluorine is small and has the highest electronegativity of all elements. To evolve a molecule into a potent and safe medicinal product, many parameters need to be optimized in parallel. The introduction of fluorine is often an essential part of achieving an optimally balanced profile. The size of a fluorine atom is comparable to a hydrogen atom, but the stability of a C-F bond is greater than that of a C-H bond. In addition, introduction of fluorine will change the lipophilicity and electron density of the molecule. Therefore, while replacement of a hydrogen by fluorine may not significantly change the size of an active ingredient, it will impact key properties required to make a medicinal product efficacious and safe. It will not only affect potency but can also lead to reduced clearance in the human or animal body, and enhanced permeability. Due to fluorine's electronegativity, introduction of fluorine will attract electrons, making a molecule more acidic or less basic (decreasing its pKa). This will subsequently impact key parameters required for a successful medicinal product such as permeability, binding affinity to the target and medicinal product efflux, and can reduce undesired side effects, thereby increasing the therapeutic index.

[11] Clarivate Integrity; https://clarivate.com/
[12] https://en.wikipedia.org/wiki/Flecainide
[13] https://www.reach-clp-biozid-helpdesk.de/SharedDocs/Downloads/DE/REACH/Verfahren/Beschr%C3%A4nkung/Consultation-PFAS.pdf
[14] https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/018830Orig1s000rev.pdf
[15] Posselt et al., 2020
[16] https://pubmed.ncbi.nlm.nih.gov/27351319

c. Potential for Substitution

Due to the unique properties of fluorine, a direct replacement is not available. There are other electron withdrawing groups similar to $-CF_2-$ or $-CF_3$ such as carboxylic esters, amides, nitro, or cyano, but they differ in stability, permeability, and toxicity. Replacement of fluoro-alkyl by other halo-alkyl groups such as chloro-alkyl will lead to reactive agents with serious toxicity issues. A restriction applying to the use of API containing perfluoro alkyl groups would consequently remove these molecules from the European market, with severe consequences for human and animal patients, certainly where few therapeutic options exist. But even if PFAS APIs such as fluoxetine or sitagliptin coexists with non-fluorinated medicinal products in the same therapeutic class, it is incorrect to assume that these APIs are interchangeable. Due to their pharmacology and side effect profiles, a medical professional will select between them based on the unique circumstances of the patient such as health status, potential for interaction with other prescribed medications or individual response. The same is true in veterinary medicine, where in addition species- or even breed-specific sensitivities may prohibit the use of specific medicines within a therapeutic class. Limiting the options in a therapeutic class because some have fluorinated groups would have a profound impact on the ability to treat patients with the most safe and efficacious medicine.

d. Environmental Considerations

Most APIs manufactured in the EU are subject to company generated, risk-based discharge limits applied to protect aquatic species downstream of the manufacturing facility. In accordance with Article 8(3) of Directive 2001/83/EC for human medicines, the potential environmental impact of medicinal products is also assessed. Since 2006, for human medicinal products, environmental fate and effects data for an API and an environmental risk assessment of that API are already required at the time of submission of a marketing authorisation application. For veterinary medicinal products similar obligation has been in place since the mid-nineties (Directive 92/18/EEC), which is under Regulation (EU) 2019/6 as of January 2022.

Also, a broader concern of the environmental impact of pharmaceuticals is already the focus of the Strategic Approach to Pharmaceuticals in the Environment[17] which also considers the potential of persistent metabolites. Furthermore, on the 26 April 2023, the Commission adopted the pharmaceutical package to revise the present legislation which includes strengthening the environmental risk assessment. In our view, further improvement of environmental compatibility should happen through development of these regulations. Applicability of a REACH Restriction to some pharmaceuticals would introduce high complexity and address only the API meeting the PFAS definition, regardless of their environmental impact compared to non-PFAS API.

e. Impact of the Restriction as drafted

In Restriction Option 1, the manufacture, import and placing on the market of these API or medicinal products containing them would no longer be possible under REACH, although this would be in clear conflict with existing and valid market authorisations under the sectorial medicinal products legislation.

In Restriction Option 2 (preferred option), API with EU approval would benefit from a time-unlimited derogation accompanied by reporting obligations, adding an obligation under REACH to the complex

[17] https://ec.europa.eu/health/human-use/environment-medicines_en

pharmaceutical regulatory framework. Nevertheless, under this scenario, the manufacture of APIs in Europe would still be at risk because of the impact of the current proposed ban on the use of PFAS in (all) manufacturing equipment, as well as the ban of PFAS in intermediary steps for the manufacturing of (derogated) APIs. Furthermore, substances falling under the PFAS definition might be used as e.g. solvents, catalysts, intermediates in the synthesis of not only APIs falling under the PFAS definition but also those which do not fall under the PFAS definition. While final APIs are proposed to be derogated, process chemicals and raw materials used in their manufacturing are currently not derogated and would ultimately be banned 18 months after entry into force, thereby rendering the API derogation as null and void. No manufacturing within the EEA would be possible, instead only API importation from outside EEA.

(2) Development products and API under non-EU regulations

a. Overview

Promising candidates are developed to become API in a process which takes about ten to fifteen years. The last phase of development of human pharmaceuticals is the clinical phase III, which can be considered the first phase of treatment of clinical study participants; on the veterinary side use in the target animals is studied even earlier in the development process. To establish parameters like dosage and efficacy, certain amounts of API are needed to administer the API to patients as part of the clinical trials, and the produced volume of API can exceed the 1-ton threshold (also applicable for intermediates needed in manufacturing the API). Above 1 ton per year, the R&D exemption from registration under REACH no longer applies, and a PPORD notification must be submitted. As no derogation for PPORD is included in the restriction as drafted, the ban fully applies to these candidates for active ingredients.

Exported API: the manufacturing infrastructure required for either small molecule API or biological products is usually not dedicated to certain products. Pharmaceutical companies operate on a global scale, and the manufacturing of API is not only for the local market but can also be intended for export. As the derogation is based on EU regulation, it is not applicable to non-EU API. This is damaging to the EU as a location for the industry, which currently has a large footprint in manufacturing, employment and research.[18]

b. Chemical Rationale, Potential for Substitution, Environmental Considerations

These apply as stated above in the API section.

c. Impact of the Restriction as drafted

As the use for PPORD is not derogated under the current proposal, and development products are not yet authorized as API under the medicinal products legislation, both the manufacture and application (clinical trial) of PFAS API in EEA would be no longer possible in both Restriction Options. If the restriction becomes effective during clinical trials, studies cannot be continued. As the restriction may come into effect as soon as 2027, developments of PFAS API are already moving out of the EEA. API manufactured for export only may not have EU registration for various reasons, including regional

[18] the-pharmaceutical-industry-in-figures-2022.pdf (efpia.eu)

prevalence of the diseases they treat. These products will no longer be able to be manufactured once the restriction becomes effective.

(3) Non-active ingredients (excipients)

a. Overview

Pharmaceutical products contain ingredients other than the active, to support application, stability and/or release of the API. These are called excipients. The only excipients identified as PFAS are F-Gas propellants, used in Metered Dose Inhalers (MDI), which act as safe propellants to aerosolise the API and ensure the delivery of the medicine to the lungs. However, PFAS chemicals are used as processing aids in excipient manufacture. Residues or cross-contamination in manufacturing plants can lead to trace contamination with PFAS material. The low proposed cut-off limit of 25 ppb for individual PFAS can lead to certain excipients falling into the scope of the restriction.

b. Chemical Rationale, Potential for Substitution, Environmental Considerations

Trace contamination may be avoidable, but their environmental impact is low because of the insignificant overall substance volume. MDI propellants are used because of their non-toxic and non-flammable properties. Their environmental impact is mitigated and regulated through the F-Gas Regulation (EC) No. 517/2014.

c. Impact of the Restriction as drafted

No derogation is foreseen for non-active pharmaceutical ingredients. Substances falling in scope of the restriction would no longer be available for manufacture, which has corresponding impact on the supply chain and the availability of medicinal products.

(4) Starting Materials and Chemical Intermediates

a. Overview

To introduce fluorine into the API molecules, starting materials and chemical intermediates that qualify as PFAS according to the broad PFAS working definition are used and/or manufactured. Whilst the concern with PFAS chemicals is persistence in the environment, controls are put in place to protect workers in manufacturing settings and to minimize emission to the environment. The materials and intermediates used in the synthesis of API are controlled and monitored, e.g. in air and waste water and the waste streams contained in case these are not fully consumed in the synthesis process. Intermediates are assigned to appropriate containment bands based on available health hazard data and pharmacology screening[19]. To evaluate the effectiveness of controls in place, exposure monitoring data is collected for APIs and intermediates and compared to health based occupational exposure limits (OELs) derived by company toxicologists. Procedures used to establish in-house OELs for

[19] Araya S. et al (2015) Mutagenicity assessment strategy for pharmaceutical intermediates to aid limit setting for occupational exposure, Regulatory Toxicology and Pharmacology, 73 (2015) 515-520; Fiori J. & Meyerhoff R. (2002) Extending the threshold of regulation concept: de minimis limits for carcinogens and mutagens, Regulatory Toxicology and Pharmacology, Volume 35, Issue 2, April 2002; Maler M. (2011) Setting occupational exposure limits for unstudied pharmaceutical intermediates using an in vitro parallelogram approach, Toxicology Mechanisms and Methods, 2011 21(2):76-85

pharmaceuticals have been described in the literature[20]. When necessary, waste streams are incinerated.

Given the risk management measures put in place to minimize worker exposure and emissions to the environment in production, the use of PFAS in the chemical synthesis of APIs should be exempt from any restriction. Restrictions on use of intermediates would be a strong incentive to move API production out of the EEA. This conflicts with recent EU strategies to reduce dependency on supply chains located mainly outside of the EEA.

b. Chemical Rationale, Potential for Substitution

PFAS starting materials and chemical intermediates are necessary to introduce the PFAS moiety, such as a fluorinated methyl group, in a PFAS API. Substitution is not possible as alternative intermediates would be a PFAS as well. Additionally, PFAS intermediates might be unavoidable to manufacture non-PFAS APIs (e.g. to introduce fluorine in a non-fully fluorinated carbon center).

c. Environmental Considerations

Starting materials and chemical intermediates are used only in industrial settings and are handled under controlled conditions, where exposure to workers and the environment is lowered to the minimum technically feasible level. Waste is handled under industrial waste management rules.

d. Impact of the Restriction as drafted

The current proposal bans the use of PFAS starting materials and chemical intermediates 18 months after entry into force. Any intermediary step requiring the production or use of PFAS starting materials and chemical intermediates would need to be done outside the EEA, meaning that the synthesis of PFAS API would require to be moved outside the EEA.

(5) Equipment and Consumables

a. Overview

Auxiliaries and production materials are a broad range of products required to achieve the desired product quality and production safety during manufacture of both devices and chemicals, and which are not part of the final product. In production, polyfluorinated polymers such as polytetrafluoroethylene (PTFE) are often used as seals or lining for chemical reactors, piping, gaskets, pumps, vials and in devices such as membrane filters. They are equivalent to the food contact materials used in processing by the food and feed industry, but have to meet the rigorous standards required for pharmaceutical product. Fluoropolymers integral to manufacturing equipment are especially

[20] Agius R. (1989) Occupational exposure limits for therapeutic substances – Annals of Occupational Hygiene - Volume 33, Issue 4, 1989, Pages 555–562; Association of the British Pharmaceutical Industry (1995) Guidance on setting in-house occupational exposure limits for airborne therapeutic substances and their intermediates - ABPI Publication October 1995; Dolan D. et al. (2005) Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations - Regulatory Toxicology Pharmacology - 2005 Oct;43(1):1-9; Naumann B. & Weideman P. (1995) Scientific basis for uncertainty factors used to establish occupational exposure limits for pharmaceutical ingredients – Human and Ecological Risk Assessment - Volume 1, 1995 - Issue 5; Sargent E. & Kirk D. (1988) Establishing Airborne Exposure Control Limits in the Pharmaceutical Industry American Industrial Hygiene Journal - Volume 49, 1988 - Issue 6

important in single-use systems and other sterile manufacturing equipment used for the manufacture of biological therapies and vaccines.

b. Chemical Rationale

Key chemical characteristics of fluoropolymer components used in pharmaceutical production environment are inertness, chemical and thermal resistance, including a suitable barrier towards other compounds used. Mechanical durability is relevant to prevent abrasion and contamination with particles, as well as maintaining the function under stress or pressure. Smooth hard surfaces with non-stick properties are required to facilitate cleaning and disinfection, while a certain elasticity is needed to work as seals.

c. Potential for Substitution

Fluoropolymers are about one order of magnitude more expensive than other plastics, which incentivises substitution and prevents over-use. The substitution potential is low, as high stability towards chemicals, heat, abrasion and time correlates with persistence. Therefore, even in cases where non-fluorinated alternatives can be found, these are most likely persistent, too. As the use of the materials has environmental benefits and only the waste stage is problematic, the emissions should be restricted rather than the substances itself. Proper inventory and waste management pre-empt the need for substitution.

d. Environmental Considerations

As these materials do not become part of any product, the waste stage is the only emission source. This can be fully managed by appropriate waste handling, minimizing any environmental risks. Thermoplastic fluoropolymers can be recycled, when the somewhat inferior properties of the recyclate are acceptable, or even re-converted to their monomers to achieve circularity.[21] Additionally, literature data is available which already shows complete mineralisation of e.g., PTFE in municipal waste incineration plants.[22] On the other hand, the durability and reliability of these materials in seals and barriers are important to minimize emissions from production plants and prevent incidents such as spills or uncontrolled release. In many cases, the superior properties of fluoropolymers increase the lifetime of the product or allow for longer maintenance intervals, which contributes to waste reduction.

e. Impact of the Restriction as drafted

As there is neither reporting nor labelling obligation for PFAS materials in place, the industry as a downstream user needs to conduct complex investigation across the supply chain to identify the components impacted by the PFAS restriction to have a complete overview. The current proposal bans the use of PFAS in sealants, gaskets, as internal lining in manufacturing equipment like valves and piping, o-rings, as filter materials and membranes and many other applications in pharmaceutical production processes where substitution has to be assessed individually. Without these components and equipment containing fluoropolymers, EU manufacturing plants cannot operate. Manufacturing Processes are qualified and validated processes covered by sectorial legislations and global marketing

[21] https://multimedia.3m.com/mws/media/973095O/publication-in-magazine-kunststoffe-international-closing-the-recycling-loop.pdf
[22] https://reader.elsevier.com/reader/sd/pii/S0045653519306435

authorisations. These are severely impacted by the restriction. The regulatory oversight over equipment and the validation for operation is necessary to assure a consistently manufactured product; one that had been proven to be safe and effective during clinical development. The manufacturing equipment must demonstrate that it will not introduce an unacceptable impurity into the product authorized for market. Concerns exist around the timeframe for identification, testing and validating alternatives for components that need to be replaced, in the rare case that alternatives are feasible and available. A ban of these substances or even a time-limited derogation will create a serious competitive disadvantage for the EU in global manufacturing. In practice, such a ban would impact all human and veterinary medicinal products including biopharmaceuticals and vaccines,and would seriously affect medicines availability even in the longer term.

(6) Reagents, Solvents, Catalysts, Auxiliaries in Production and Quality Control

a. Overview

The manufacture of medicinal products in Europe depends on the availability of multiple auxiliaries and reagents on the market. Manufacturing of both API and finished product (the medicine) are strictly regulated under pharmaceutical legislation and are subject to assessment, validation, and inspection prior to regulatory approval. This rigid registration and validation framework of API manufacture limits the potential for substitution, and analytical methods used for QC are mostly binding. If essential materials are no longer available in the EU for regulatory reasons, the only option is to relocate manufacturing to non-EEA territory. This could be avoided by either exempting pharmaceutical manufacture processes, or by out scoping materials that are not released to the environment at any life cycle stage in significant amounts. The environmental risk of chemicals in industrial production is mitigated, as emissions and disposal are regulated and monitored. Controls are employed on all manufacturing processes that use fluorinated reagents so that emissions to air and water remain well within license parameter emission limit values, therefore minimizing impact on the environment. Emission limits employed by the regulator are those set out in the relevant Best Available Techniques (BAT) reference documents associated with the Industrial Emissions Directive (Directive 2010/75/EU) and controlled and reported in accordance with regulations. Since widespread dispersive use of PFAS chemicals does not occur in pharmaceutical manufacturing settings, this application should be exempt from any proposed restriction.

b. Chemical Rationale

Examples for reagents required in manufacturing, R&D and for analytical purposes in Quality Control (QC) laboratories: e.g. trifluoro acetic acid (TFA), hexafluoro isopropanol and trifluoro ethanol are indispensable in peptide synthesis[23], and TFA in vaccine production. Perfluorinated reagents are effective in the development of new chemical manufacturing processes as both activating reagents, solvents, ligands and catalysts (e.g. triflic anhydride and nonaflate, homogeneous catalysts like Crabtree-Pfaltz-type catalyst or other precious metal catalysts that feature CF_3-substituted ligands). TFA is also an essential reagent in numerous QC analytical procedures such as HPLC and GC. Other uses

[23] Jad Y. et al (2019) Green Transformation of Solid-Phase Peptide Synthesis ACS Sustainable Chem. Eng. 2019, 7, 3671-3683; Pedersen S. W. et al (2013) Synthesis of Peptides Using Tert-Butyloxycarbonyl (Boc) as the α-Amino Protection group Peptide Synthesis and Applications 2013 pp 65-80Guy, C. A., & Fields, G. B. (1997). Trifluoroacetic Acid Cleavage and Deprotection of Resin-Bound Peptides Following Synthesis by Fmoc Chemistry. In Methods in Enzymology, Vol 289 (pp. 67-83). Academic Press.

of PFAS in analytical chemistry are e.g. PFBA as ion pair reagent in chromatography; MBTFA, BSTFA, and MSTFA to derive silyl derivatives in gas chromatography. Unlike synthesis, research and analysis are exempted under REACH, but broad restrictions may have an impact on substance availability.

c. Potential for Substitution

Alternatives to the use of PFAS reagents are not one to one replacements. Alternatives may require the complete redesign of the synthesis process of an API to remove the need to use a certain reagent or solvent. For each case where a PFAS reagent is used, the manufacturer would need to conduct a specific analysis of alternative including all required testing and studies as per sectorial legislations. In most instances, no alternative process nor alternative chemical are known at this date. Furthermore, analytical methods including the reagents can be stipulated by regulations, standards (e.g. pharmacopoeia) or licensing agreements. For biological products, changes to the use of auxiliary materials such as sterile single use systems would require development of unique materials and extensive testing to establish compatibility with biological materials and to control sterility.

d. Environmental Considerations

These materials do not become part of any product. The waste stage is the only emission source. This is managed by appropriate waste handling under local regulations by the manufacturer, minimizing any environmental risks.

e. Impact of the Restriction as drafted

For API already on the market and close to their patent expiration, the cost of substitution and validation might not sufficiently justify the benefits, leading to mitigation measures such as relocating the manufacture of such API outside EU, or ceasing the manufacture of the API altogether.

For an API in development, because of the lengthy substitution timeline, the R&D and PPORD activities are currently already being moved out of the EEA to mitigate the risk of a ban interfering with clinical trials. For biological therapy and vaccines manufacture, new manufacturing auxiliaries and facilities would need to be developed and integrated into supply chains, assuring no impact on the quality or safety of biological products. Given that the change process, including the regulatory requirements to demonstrate over extended time that there is no impact on the complex biological products this may take decades to implement in each case.

(7) Immediate Packaging Materials and Sterile Barriers for Oral and Injectable formulations

a. Overview

Solid oral dose formulations generally use 'Blister' packaging to facilitate use and to preserve and protect contents from external factors. Fluoropolymers such as PCTFE (Polychlorotrifluoroethylene) are used in ‘thermoform’ types of blisters.

Injectable formulations are packaged in container closure systems (vials, prefilled syringes, or cartridges) that are made of an assembly of immediate packaging components (IPC). These IPCs are commonly made of glass (vial, barrel) and elastomers (stoppers, plungers, seals). IPCs are designed to

stay in contact with the medicinal product for an extended period (shelf life) without affecting its chemical, visual, and microbial attributes.

b. Chemical Rationale

The unique features of PCTFE (high barrier to moisture, transparent, thermoformable, chemically very stable and inert, non-sticking, non-aging and sterilizable) make PCTFE the ideal solution for products that require a high level of protection. Alternatives such as PVdC are available but adding a layer of PCTFE gives technical advantages for sensitive medicines. Additionally, PVC is also in focus of REACH restrictions or the new Packaging and Packaging Waste Regulation, which may effectively eliminate PVdC as a packaging option.

In terms of Injectable formulations, ETFE or PTFE film coated elastomeric components provide an effective barrier against organic and inorganic leachables and minimize interactions between the liquid formulation and the packaging. Furthermore, ETFE or PTFE film reduces absorption and adsorption of active ingredient. Elastomeric IPCs also require a lubrication to prevent stickiness during storage and processing and to ensure usability of the product. Therefore, silicone lubricants are typically used, however they can be a source of particles in the injectable. The ETFE or PTFE film confers a low-particle lubrication while preventing or reducing the use of silicone oil.

c. Potential for Substitution

All of these PFAS materials are in direct contact with the medicinal product. As such, they are part of the medicinal product qualification and registration. As far as our industry is aware, there are no *feasible* alternatives for all immediate packaging types though we continue to engage with our Supply network to identify any alternatives available in the required volume. Alternatives such as PVdC is available for blisters however, PVdC is facing additional regulatory pressures in EU (possibly a restriction) so blisters manufactured using just PVdC may also be banned in the medium term. Additionally, the Packaging and Packaging Waste Regulation (as proposed) will require 'recyclability at scale' and therefore PVdC blisters will also be impacted by that requirement.

Any replacement of an immediate packaging material of medicinal products in the market triggers a full requalification with the relevant Health Regulators. This process would take at least five years depending upon which global market the products are sold into and would entail the following activities:

- Compatibility / Stability study – shelf-life qualification
- Extractables / Leachable assessment
- Functionality qualification
- Processability qualification
- Re-submission to health authorities

d. Environmental Considerations

The Pharma Industry encourages the collection and incineration of waste blisters (containing medicinal products) across the EU. These are generally collected via Pharmacies and other health settings[24].

e. Impact of the Restriction as drafted

Although a time limited derogation for immediate packaging (PCTFE containing blister) is proposed (paragraph 6 l), other immediate packaging types (eg sachets, sealing pads in caps, vial stoppers, syringe plungers etc) or other fluoropolymers are not considered for derogation in the PFAS restriction proposal. There is no distinction between existing market authorisations versus newly introduced packaging, and the abovementioned regulatory timelines are not taken into account in the substitution timeline. This has huge impact on the manufacture of (most) injectables, but also other dosage types. Unless an alternative can be identified and implemented within the proposed timelines (18 months after EIF for elastomers), manufacturing of impacted liquid formulations will be moved out of the EU; there would also be a severe impact to patients as we would be unable to market these liquid formulations in EU. The REACH ban on using fluoropolymers in elastomers, conflicts with existing pharmaceutical market authorisations, which use these types of immediate packaging.

(8) Drug Delivery Devices

a. Overview

Drug delivery devices can be co-packed products such as a syringe with medicinal product in the same package, a pre-filled syringe, a single use injector pen or reusable devices for medicinal product application. Potential PFAS parts may be seals, silicones, lubricants, filters, barriers [25]; therefore the applicability of a chemicals-oriented REACH Restriction in addition to existing regulations, may conflict with existing medical and/or drug delivery combination device approvals.

b. Chemical Rationale

PFAS, generally PTFE and related fluoropolymers, are used in drug delivery device components which have large areas of contact and require tight tolerance with other components. PTFE allows for tight tolerances of plastic components while allowing easy hand operation by most of the user population. PTFE can also be used for dosing purposes. The fluoropolymers provide lubricity and durability. The durability of PTFE allows for devices to be single dosed or used multiple times during their lifetime (up to 5yrs).
Another example would be metered dose inhalers (MDI) that are used for the treatment of respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD). Fluoropolymers are used as coatings of the MDI canister and they are needed to preserve the quality of the medicinal product. Without the fluorinated coating, the API in the formulation would be exposed to and adhere to the canister walls, which impacts the dosage. The API will also be more susceptible to chemical degradation by wall contact, also increasing the dosage variability.

c. Potential for Substitution

The chosen materials have been tested to maintain product quality throughout the shelf life. This safeguards the efficacy of the therapy and patient safety. Changes of medicinal product contact

[24] http://www.pharmanet.com.br/pdf/blister.pdf
[25] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745

materials would require reformulation, stability studies and regulatory approval by health authorities. Furthermore, environmental trade-offs such as higher carbon footprint in manufacture or transport, impact on recyclability or shortened shelf life must be carefully evaluated.

d. Environmental Considerations

Coatings and thin films are mineralized when incinerated. This was shown for PTFE in municipal waste incineration plants.[26] An environmental risk persists if product is not properly disposed of.

e. Impact of the Restriction as drafted

When developing a new device, there are several International Standards for Medical Device Development that must be considered as part of the device design and development process (US – 21 CFR (Code of Federal Regulations) Part 820; EU – MDR (Medical Device Regulation) 2017/45 Annex I; ISO 13485).

Device design development and commercialization occurs through several phases before it is launched. Total development time for a new device can vary and on average takes approx. 5 – 7 years (for a drug delivery device). Unless an alternative can be identified and implemented within the proposed timelines (18 months after EIF), manufacturing of impacted Devices will be moved out of the EU; there would also be a severe impact to patients as we would be unable to market these devices in EU or add spare PFAS parts to larger medical devices to enable continue use (thereby creating more waste). The REACH ban on using fluoropolymers in devices conflicts with existing regulatory approvals for these under EU MDR.

Conclusion

The Human and Veterinary Pharmaceutical sectors manufacture a variety of APIs that contain at least one aliphatic $-CF_{2-}$ or $-CF_3$ group, qualifying them as PFAS in the current broad PFAS definition. At the same time, perfluoro-containing building blocks and raw materials are used to introduce the fluorine into the API (both PFAS and non PFAS APIs) and to manufacture specific groups of medicines (e.g., peptide synthesis), respectively. As the pharmaceutical effect is directly linked to the molecular structure, an API molecule cannot be substituted by another substance as this is fundamentally why they are active. Any change in the molecule has profound effects, including lower efficacy, making it a different API, and voiding regulatory approvals and marketing authorisations.

API, medicinal products and medical devices undergo rigorous registration and market authorisation schemes, proving their beneficial health effects and safety of use; they also undergo an Environmental Risk Assessment (ERA). To avoid regulatory conflicts, additional requirements should be raised by the sectorial legislation and not via the REACH Regulation.

Raw and starting materials, intermediates, auxiliaries, equipment, and consumables required for manufacture of pharmaceuticals and medical devices should also be exempt, as these are handled under controlled conditions and without them, manufacturing of medicinal products and devices is impossible. Any emission of industrial manufacturing into environments is negligible and controlled and regulated via other existing EU legislation. Any risk posed by emissions of these substances can be further mitigated through waste management or circularity regulations.

[26] Waste incineration of Polytetrafluoroethylene (PTFE) to evaluate potential formation of per- and Poly-Fluorinated Alkyl Substances (PFAS) in flue gas - ScienceDirect

The Royal Society of Chemistry has published a Policy Position on PFAS[27]. Given the large structural diversity of PFAS in the current definition, they propose a risk-based approach in which risk management measures are aligned to the existing evidence on hazard and risk for subgroups of PFAS. When the proposed scheme is applied to medicinal products or manufacturing materials, they end up "green listed" for the reasons outlined in this position.

To allow for the continued research, development and manufacturing of innovative medicines, pharmaceuticals should generally be derogated from a universal PFAS restriction, including all steps which are necessary for manufacturing medicinal products including biopharmaceuticals and vaccines in the EEA. The currently discussed universal PFAS restriction proposal would reduce patients' access to medicines and would hinder manufacture of medicinal products in EEA.

Finally, as of the nature of PFAS being stable respectively or efficacious as treatment, every replacement may raise the same environmental concerns.

Glossary

API	Active pharmaceutical ingredient
BAT	Best Available Techniques
BSTFA	N,O-Bis(trimethylsilyl)trifluoroacetamide
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EIF	Entry into force
ERA	Environmental Risk Assessment
ETFE	Ethylene tetrafluoroethylene
HPLC	High pressure liquid Chromatography
IPC	Immediate packaging components
MDI	Metered Dose Inhalers
MBTFA	N-Methyl-bis(trifluoroacetamide)
MSTFA	N-Methyl-N-trimethylsilyl-trifluoracetamid
OELs	Occupational exposure limits
OECD	Organisation for Economic Co-operation and Development
PCTFE	Polychlorotrifluoroethylene
PFAS	Per- and polyfluoroalkyl substances
PFBA	Perfluorobutanoic acid
PPC	Primary packaging compounds
PTFE	Polytetrafluoroethylene
pKa.	-log of the acid dissociation constant
PPORD	Product and process orientated research and development
PVC	Polyvinyl chloride
PVdC.	Polyvinylidene dichloride
QC	Quality Control
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
TFA	Trifluoro acetic acid

[27] https://www.rsc.org/globalassets/22-new-perspectives/sustainability/a-chemicals-strategy-for-a-sustainable-chemicals-revolution/pfas-policy-position-dec-2021.pdf