

EFPIA (Representing European Pharmaceutical industry) and AnimalhealthEurope (representing Animal Health Industry) position on use and risk of “per- and polyfluorinated alkyl substances” (PFAS)¹ in Europe, in the light of an emerging Restriction under REACH.

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Context

The EU is planning a REACH restriction for a broad group of fluorinated substances, the so called per- and polyfluorinated alkyl substances (PFAS). The addressed risk is based on the high persistence of the compounds, resulting in potential accumulation in the environment and food chains. Restrictions - under Title VIII of REACH² - do not include a general exemption for medicinal products. Therefore, the manufacture of Active Pharmaceutical Ingredients (API) using polyfluorinated building blocks or raw materials, and the placing on the market of these APIs and medicine containing them are potentially in scope of the PFAS restriction that is under consideration. Furthermore, PFAS materials used in validated production processes, for the production of medical devices or for packaging are also in scope.

Position

EFPIA and AnimalhealthEurope contribute by generating data and knowledge about PFAS and their uses, to support a responsible and adequate use of essential materials. The term PFAS is used in this position paper for any compound that is affected by any PFAS regulation. We are aware that the recently adapted OECD PFAS definition³ differs significantly from the one used by the US EPA⁴. We encourage a unique global definition of identical technical terms, and in the meantime use “PFAS” in the widest possible sense.

Our member companies are committed to make a positive impact on the lives of human and animal patients, and to adhere to environmental regulations and other agreements. Sustainability strategies consider both social, economic and ecologic aspects of our operations.

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 PFAS criteria are currently used by EFPIA and AnimalhealthEurope members. These substances can be categorised in the following groups:

(1) Active Pharmaceutical Ingredients (APIs)

a. Overview

More than 300 fluorinated compounds have been launched as drugs over the last few decades and over 500 more are in late-stage clinical trials,⁵ and today about 30% of all APIs contain fluorine.⁶ This indicates the importance of fluorine in pharmaceutical compounds, both for existing drugs as well as for an increasing number of hopeful future candidates. Of the launched and (pre)registered drugs, about 100 contain polyfluorinated alkyl (-CF₂- or -CF₃) substituents. Several of these are on the World

¹ <https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas>

² https://ec.europa.eu/growth/sectors/chemicals/reach/restrictions_en

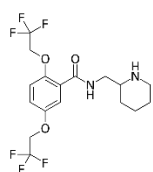
³ <https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/terminology-per-and-polyfluoroalkyl-substances.pdf>

⁴ <https://www.epa.gov/chemical-research/research-and-polyfluoroalkyl-substances-pfas>

⁵ Clarivate Integrity; <https://clarivate.com/>

⁶ <https://www.solvay.com/en/chemical-categories/fluorine-chemicals/organic-fluorinated-compounds>

Health Organization's List of Essential Medicines⁷ covering treatments across a large variety of diseases. Examples are efavirenz (AIDS), mefloquine (malaria), fluoxetine (depression), and gemcitabine (cancer). From the top 200 small molecule drugs according to sales in 2018⁸, 25 contain polyfluorinated alkyl (-CF₂- or -CF₃) substituents, again across therapeutic indications. Examples are sitagliptin (diabetes), enzalutamide (prostate cancer), teriflunamide (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 parasite infestations potentially at the origin of zoonotic disease in humans have been identified. All of these match the OECD PFAS criteria. However, these molecules containing one or two aliphatic -CF₂- or -CF₃ groups are not polyfluorinated or perfluorinated in the real 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 APIs that are under discussion:



Flecainide⁹ has the highest API volume in the Report Summary provided with the 2nd Stakeholder Consultation¹⁰ save for Pantoprazole, which is no longer covered by the revised OECD PFAS definition. It is a typical API molecule to meet the PFAS criteria, as it has only a few perfluorated alkyl groups in a fairly large molecule. Consequently, these molecules are not persistent in the human body (half-life for flecainide was 12 to 27 hours in patients; NDA 18-830)¹¹, and some of them, as in the case of flecainide, neither in the environment¹², but fluorinated metabolites or breakdown products may have an environmental impact.

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 drug, 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 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 a drug molecule, it will impact key properties required to make a drug 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 drug such as permeability, binding affinity to the target and drug efflux, and can reduce undesired side effects, thereby increasing the therapeutic index.

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 -CF₂- or -CF₃ such as carboxylic esters, amides, nitro, or cyano, but they

⁷ <https://www.who.int/medicines/publications/essentialmedicines/en/>

⁸ <https://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster>

⁹ <https://en.wikipedia.org/wiki/Flecainide>

¹⁰ [https://www.reach-clp-biozid-](https://www.reach-clp-biozid-helpdesk.de/SharedDocs/Downloads/DE/REACH/Verfahren/Beschr%C3%A4nkung/Consultation-PFAS.pdf?__blob=publicationFile&v=3)

[helpdesk.de/SharedDocs/Downloads/DE/REACH/Verfahren/Beschr%C3%A4nkung/Consultation-PFAS.pdf?__blob=publicationFile&v=3](https://www.reach-clp-biozid-helpdesk.de/SharedDocs/Downloads/DE/REACH/Verfahren/Beschr%C3%A4nkung/Consultation-PFAS.pdf?__blob=publicationFile&v=3)

¹¹ https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/018830Orig1s000rev.pdf

¹² Posselt et al., 2020

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 coexist with non-fluorinated drugs 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, complications with other prescribed medication or individual response. 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, 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 authorization application. For veterinary medicinal products a similar obligation has been in place since the mid-nineties (Directive 92/18/EEC); currently this is regulated by Directive 2001/82/EC, which will be replaced by Regulation 2019/6 as of January 2022. Also, a broader concern of the environmental impact of pharmaceuticals is already in focus of the Strategic Approach to Pharmaceuticals in the Environment,¹³ which also considers the potential of persistent metabolites. In our view, further improvement of environmental compatibility should happen by development of these regulations. Applicability of a REACH Restriction to some pharmaceuticals would introduce high complexity and addresses only the API meeting the PFAS definition, regardless of environmental impact.

(2) Starting Materials and Chemical Intermediates

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 wastewater. Intermediates are assigned to appropriate containment bands based on available health hazard data and pharmacology screening¹⁴. To evaluate the effectiveness of controls in place, exposure monitoring data is collected for APIs and compared to health based occupational exposure limits (OELs) derived

¹³ https://ec.europa.eu/health/human-use/environment-medicines_en

¹⁴ 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

by company toxicologists. Procedures used to establish in-house OELs for pharmaceuticals have been described in the literature¹⁵.

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 intermediates would be a strong incentive to move production abroad. This conflicts with recent EU strategies to reduce dependency on supply chains located mainly outside of the EU.

(3) Auxiliaries and Production Materials

Auxiliaries and production materials are a broad range of products required to achieve the desired quality 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 for chemical reactors, vials and in devices such as membrane filters.

(4) Synthetic and Analytical Reagents

Reagents are 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 synthesis¹⁶, and TFA in vaccine production. Perfluorinated reagents are effective in the development of new chemical manufacturing processes as both activating reagents and catalysts (e.g. triflic anhydride and nonaflate). TFA is also an essential reagent in numerous QC analytical procedures such as HPLC. Unlike synthesis, research and analytics are exempted under REACH, but broad restrictions may have impact on substance availability.

The synthesis of API in Europe depends on the availability of both auxiliaries and reagents on the market, as 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. It is the responsibility of the Pharmaceutical Industry to ensure that drug products are manufactured to the highest standards. 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-EU 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

¹⁵ 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

¹⁶ 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 65-80 Guy, 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.

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.

(5) Primary Packaging Materials

Tablets use 'Blister' packaging to preserve and protect them from external factors and facilitate use. PCTFE (Polychlorotrifluoroethylene) is among the materials used for 'thermoform' types of blisters. 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. PCTFE is currently not listed under the OECD definition of PFAS. However, if ECHA broaden the definition of PFAS to "substances containing at least one -CF₂- or -CF₃ group", then PCTFE would be impacted. Alternatives such as PVC are available but adding a layer of PCTFE gives technical advantages for those medicines that require a higher level of protection.

The Pharmaceutical Industry encourage the collection and incineration of Waste blisters (containing medicinal products) across the EU. These are generally collected via Pharmacies and other health settings¹⁷.

Liquid drug products for injection are packaged in container closure systems (vials, prefilled syringes, or cartridges) that are made of an assembly of primary packaging components (PPC). These PPCs are commonly made of glass (vial, barrel) and elastomers (stoppers, plungers, seals). PPC's are designed to stay in contact with the drug product for an extended period (shelf life) without affecting its chemical, visual, and microbial attributes. A typical drug product / PPC interaction is linked to elastomer extractables that can leach into the drug product thus potentially affecting the drug product efficacy and patient safety (toxicity).

ETFE or PTFE film coated elastomeric components provide an effective barrier against organic and inorganic extractables and minimize interaction between the drug and the PPC. Furthermore, ETFE or PTFE film reduces absorption and adsorption of the drug product. Elastomeric PPC's also require a lubrication to prevent stickiness during storage and processing. We could use a typical silicone lubricant, but the silicone can be a source of particles in the drug product. The ETFE or PTFE film provides a particle free lubrication and prevents or reduces the use of silicone.

All of these PFAS materials are in direct contact with the drug product. As such, they are part of the drug product qualification and registration. As far as our industry is aware, there are no feasible alternatives though we continue to engage with our Supply network to identify any alternatives available in the required volume.

Any replacement of a primary packaging material of medicine 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:

¹⁷ <http://www.pharmanet.com.br/pdf/blister.pdf>

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

(6) Medical Devices

A medical device can be a fairly simple part or a highly complex machine. Potential PFAS parts may be seals, lubricants, filters or surface treatment. As in other machinery, supply chain communication may be complex, as the presence of PFAS in assembled units can go unnoticed. Medical Devices are regulated under Regulation (EU) No 2017/745¹⁸, and the applicability of a chemicals-oriented REACH Restriction in addition to existing regulations may conflict with existing approvals.

On contact with pharmaceuticals and marketing authorization, the points made about primary packaging apply here as well. In the continuum of packed medicine to medical devices, so-called combination products do also exist. As an example, metered dose inhalers (MDI) are used for the treatment of respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD). Hydrofluorocarbons act as safe propellants to aerosolize the active pharmaceutical ingredients (API) and ensure the delivery of the medicine to the lungs. 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 and adheres to the canister walls, which impacts the dosage. The API will also be more susceptible to chemical degradation by contact, also increasing the dosage variability. The coating of the canister has been tested to guarantee the quality of the medicinal drug product, the efficacy of therapy and patient safety. Changes of the canister coating would require reformulation, stability studies and regulatory approval by health authorities.

Conclusion

The Human and Animal Pharmaceutical sectors manufacture a variety of APIs that contain at least one aliphatic -CF₂ or -CF₃ group which would make them fall under the current broad scope of the PFAS group. At the same time, perfluoro containing building blocks and raw materials are used to introduce the fluorine into the API 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. Any change in the molecule has profound effects and voids approvals and marketing authorizations.

API, pharmaceutical products and medical devices undergo rigorous registration and market authorization schemes, proving their beneficial health effects, safety of use and entailing a detailed assessment of environmental impact. It would therefore add significant burden, with no clear benefit, if all existing and new pharmaceuticals would need to apply for individual derogations under the Essential Use scheme.

Raw materials, intermediates and auxiliaries required for manufacture of pharmaceuticals and medical devices should also be exempt, as these are not products that go on the market. Any emission in industrial manufacturing environments is well controlled and regulated. Complex regulatory frameworks to justify individual Essential Uses will therefore not reduce PFAS emissions, even if substitution occurs, but rather incentivize relocation of manufacturing to non-EU countries.

¹⁸ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745>

The Royal Society of Chemistry has published a Policy Position on PFAS¹⁹. 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.

Regulatory concerns arise when multiple, potentially conflicting regulations apply to the same group of substances. Pharmaceuticals are exempt from both Registration and Authorisation under REACH, but not from Restrictions. Any further progress in mitigating the environmental impact of pharmaceuticals should be initiated by developing the applicable sectorial regulations, to avoid conflicts, simplify the application and expand the scope to all pharmaceuticals rather than just the fraction meeting a certain chemical definition.

To allow for the continued research and manufacturing of innovative medicines, pharmaceuticals should generally be derogated from the PFAS restriction that is under consideration. Reducing patients’ access to medicines would be an unintended consequence of this restriction and must therefore be considered as part of this position.

Proposal

EFPIA and AnimalhealthEurope members propose that authorized products such as API, finished pharmaceuticals including approved packaging and medical devices be exempted from the proposed PFAS restriction. As described above, this proposal is based on 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 hazard²⁰. The chemical substances approved under pharmaceutical regulations (API) should be exempted generally rather than individually, such as under an Essential Use derogation, to reflect the API exemption in REACH Authorization procedures and avoid regulatory conflicts.

In addition, the raw materials, intermediates and auxiliaries required for manufacture of these pharmaceuticals and medical devices should also be exempted, on the basis that any emission in industrial manufacturing environments is well controlled and regulated. Manufacturing should remain in EU countries to reduce dependency on supply chains located mainly outside of the EU.

¹⁹ <https://www.rsc.org/globalassets/22-new-perspectives/sustainability/a-chemicals-strategy-for-a-sustainable-chemicals-revolution/pfas-policy-position-dec-2021.pdf>

²⁰ <https://www.sciencedirect.com/science/article/pii/S0160412019309493>