EFPIA response to a study claiming non-PFAS alternatives exist for active pharmaceutical ingredients (APIs)
(July 2026)

Executive Summary

- **EFPIA fully supports ambitious action to reduce pharmaceutical emissions and protect the environment. The pharmaceutical sector supports proportionate, evidence-based regulation**
- **The study does not demonstrate that fluorinated medicines have readily available replacements.** It identifies medicines used for similar therapeutic purposes but does not assess whether they are clinically interchangeable, equally effective or even approved for the same patients. Treatment decisions remain complex clinical judgements made on an individual patient basis.
- **Fluorination is often fundamental to the performance of medicines.** It is deliberately used to improve potency, selectivity, metabolic stability, duration of action and safety. In many cases, removing fluorine fundamentally changes the medicine and would require the discovery, development and approval of an entirely new product.
- **Chemical structure alone is not a measure of environmental impact.** The document highlights that environmental risk should be assessed using substance-specific data and real-world emissions rather than broad structural classifications. It also notes that claims regarding environmental advantages of non-fluorinated alternatives are not supported by comparative evidence.
- **Patients must remain at the centre of decision-making.** Fluorinated medicines are used to treat many serious diseases—including cancer, HIV, diabetes, cardiovascular disease, neurological disorders and mental health conditions—and many are included on the WHO Essential Medicines List.

A study conducted by the German Environment Agency (UBA) and the University of Freiburg[1] suggests that many fluorinated active pharmaceutical ingredients (API) framed as PFAS could be replaced by non-fluorinated alternatives. They claim that for the 111 APIs in scope, alternatives would be readily available. To identify these alternatives, API were grouped by therapeutic use (ATC code level 3 or 4[2]), with the result that for the same area some API structures fulfil the PFAS definition as adapted in 2021, while others do not. Numerous media [3,4,5] have attracted significant attention to this study.

This concept of alternatives should be interpreted with caution. Identifying a substance in the same ATC category does not establish clinical substitutability. The ATC classification system was developed for drug utilisation statistics and research and is not intended to determine therapeutic equivalence or guide substitution decisions. Clinical interchangeability requires robust evidence demonstrating comparable efficacy, safety and benefit-risk in the relevant patient population. The study itself acknowledges that it did not assess whether the identified potential alternatives could be used as therapeutic substitutes, and that such decisions remain with prescribing physicians. This is critical:

[1] https://doi.org/10.1016/j.scp.2026.102416
[2] In the Anatomical Therapeutic Chemical (ATC) classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels.
[3] Chemikalien - PFAS in vielen Medikamenten ersetzbar | tagesschau.de: https://www.tagesschau.de/investigativ/ndr-wdr/pfas-chemikalien-medikamente-100.html
[4] https://www.umweltbundesamt.de/presse/pressemitteilungen/pfas-in-arzneimitteln-sind-oft-ersetzbar
[5] https://www.faz.net/aktuell/wissen/medizin-ernaehrung/pfas-sogenannte-ewigkeitschemikalien-sind-als-medikamente-nicht-notwendig-200948348.html

medicines cannot be exchanged on the basis of therapeutic use alone, but require a patient-specific assessment of efficacy, safety, contraindications, interactions, route of administration and overall benefit-risk. From a regulatory perspective, a different medication can only be considered a potential alternative when both are approved in the same region. We do not see that this significant limitation was considered in the study. In media reports this concept of grouping by therapeutic use is depicted as readily available alternatives, which is a misrepresentation we find neither correct nor helpful.

The study is motivated by valid environmental concerns when pharmaceuticals or their breakdown products are emitted to the environment. However, the presentation of these effects is strongly biased, as only fluorinated API are discussed. The study recognises that fluorination can materially influence pharmacological and pharmacokinetic properties, including target binding, metabolic stability, half-life, lipophilicity and blood-brain barrier penetration. These properties are central to the clinical performance of a medicine, but also to the environmental impact. Fluorination increases stability in the environment, but also in the human body, so less API is required for a longer effect, which results in lower emissions. The study, however, fails to demonstrate a lower environmental impact of the proposed potential alternatives, although substance specific data is available for API. As these substances were individually assessed during development and market authorisation, we do not see how a broad structural categorisation of fluorinated versus non-fluorinated API adds value.

The patient benefit by access to fluorinated API is significant. Industry survey[6] evidence identified 1,922 active substances in scope of the OECD 2021 PFAS definition, covering all 14 main ATC therapeutic groups and 192 pharmacological/therapeutic groups. Impacted areas include diabetes, chronic respiratory disease, cardiovascular disease, cancer and mental health disorders, and 674 impacted references appear on the WHO Essential Medicines List.

EFPIA supports proportionate, science-based measures to reduce environmental emissions and advance sustainability. However, regulatory decisions must avoid oversimplified assumptions that “alternative” means “replaceable”, or that environmental impact can simply be linked to structural features. Any transition must be based on robust evidence, clinical assessment, regulatory feasibility and safeguards for patient access.

[6] https://www.efpia.eu/media/b1rcqvlt/annex-2-patient-impact-survey_human-health-associations.pdf

Citation 1: ***"This analysis shows that alternatives are either already available or will be in the near future for all APIs identified as PFAS for human use."***

We are concerned by over-simplification in the outlook of the analysis and inaccurate wording of media reports, where potential alternatives become replacements (Ersatz). These conclusions appear neither correct nor consistent. As any medication has an individual profile in terms of efficacy, adverse effects, contraindications, incompatibilities or synergies with other medications or diseases, any existing alternative cannot be considered a replacement. Calling potential alternatives "already available" without any reference to market availability or even approval in the same region is contradictory to the conclusion of the outlook, where they are called "potential alternatives", and "the study did not address the question of whether these alternatives could be used as therapeutic alternatives". This is utterly confusing, as API were grouped by same therapeutic category (ATC classification, ATC code level 5). However, this does not mean they are clinically interchangeable, let alone a replacement. If a medicine, such as a cancer treatment, does not have the desired effect, an alternative option can be of vital importance. Interindividual variability in treatment response further limits interchangeability within a substance class. Patient-specific factors, including age, organ function, comorbidities, concurrent medication, and genetic variability, can significantly influence efficacy and safety profiles across patients. Switching between compounds within a given class may therefore introduce variability in treatment response. This is of particular concern for medicinal products used in the management of conditions that require highly consistent and precisely controlled drug exposure to maintain disease stability. Therapeutic substitution is a complex medical decision that is not just based on an indication. If the study claims that the question of therapeutic alternatives was not addressed, it contradicts the bold claims made in both the highlights / abstract and in media reports. These risks are particularly relevant for chronic diseases requiring long-term disease control, including oncology, multiple sclerosis, epilepsy, psychiatric disorders, cardiovascular disease, autoimmune diseases, transplantation and haematological conditions, where maintaining treatment stability is often critical.

Citation 2: ***"The overarching goal should be to reduce the use of PFAS"***
In our view, the overarching goal should be the protection of the environment, in this case by reducing the emissions of persistent chemicals to an absolute minimum. A broad structural definition such as "PFAS" can be helpful to prioritise potentially concerning groups in a universe of chemicals, but hardly adds value in a regulated area where individual substance data are readily available. The study suggests, without substantiated evidence, that non-fluorinated APIs are environmentally preferable based solely on chemical structure, as defined by the OECD. This assumption does not adequately consider ecotoxicological profiles or intrinsic substance properties and does not provide robust data to support such conclusions. Chemical structure alone is insufficient to assess environmental risk. A science-based, risk-informed approach needs to prioritise factors such as production volumes and intrinsic hazard properties to ensure appropriate environmental risk assessment. The final conclusion of the analysis agrees to these shortcomings. The media reports even consider the absence of PFAS environmentally friendly (umweltfreundlich), which is a claim not supported by evidence.

While report and study may contribute to the discussion on environmental risk of fluorinated pharmaceutical ingredients, they both fail to mention or assess their benefits, or the complementary risks and benefits of non-fluorinated API. The industry is aware of environmental concerns raised by medication or breakdown products and actively works on mitigation and solutions.

Citation 3, in the context of the restriction on PFAS proposed to ECHA in 2023: ***"Polyfluorinated pharmaceuticals were excluded a priori" and "APIs need to be reassessed for their persistence and environmental hazards just like any other chemicals"***

The most concerning part of the study is linked to the understanding of the regulatory landscape. The introduction starts with a reference to the pending universal PFAS restriction by the chemicals agency ECHA and states a common misconception that “medicinal products … were excluded a priori”, citing the original Annex XV report. This is inaccurate. The proposal is structured as a general restriction on PFAS, with specific derogations where justified. Medicinal uses are therefore not categorically excluded from the proposal; rather, the Annex XV dossier proposes time-unlimited derogations for PFAS used as active substances in human and veterinary medicinal products. We understand that the unprecedented concept of “ban by omission” is confusing even to the scientific community, and find these incorrect assumptions actually underline our call for a clear and applicable regulatory landscape. The lack of research into existing regulations by the study authors becomes evident when they call for API assessment of “environmental hazards just like any other chemicals” in the abstract. Unlike chemicals, API can only be placed on the market after detailed testing, assessment and market authorisation. Emission footprints are substance specific with data and risk mitigation being available and apply to fluorinated and non-fluorinated substances alike. The industry supports proportionate, scientific approaches based on substance properties and footprints, but rejects overly simplified approaches based on structural features and broad grouping approaches. Moreover, regulatory development has to fit into the pre-existing structure that applies to chemicals and pharmaceuticals respectively, be effective in advancing sustainability and proportionate in its application.

Health and environmental data of each individual substance are part of the pharmaceutical regulatory framework which is mostly separated from and incompatible with REACH, is internationally recognized and continually developed. Innovation and the search for improved medicines are central to pharmaceutical research, and the industry is committed to strengthened environmental goals.

Citation 4 on *TFA Formation: 84% of PFAS API could be TFA precursors*

While the paper states that 84% of PFAS-APIs are potential TFA precursors based on the presence of -CF3 groups, it also makes clear that this reflects only a theoretical structural potential, not demonstrated environmental formation. Available evidence shows that TFA formation from pharmaceuticals is limited to specific molecular structures, in addition TFA formation has been observed primarily under artificial, strongly oxidative laboratory conditions, which are not representative of wastewater treatment or environmental processes. The paper crucially acknowledges that a large fraction of environmental TFA originates from fluorinated gases (F-gases), highlighting the dominance of non-pharmaceutical sources. Environmental monitoring and modelling corroborate this, showing no clear link between pharmaceutical use and TFA levels. The structures provided in the Annex demonstrate that fluorinated APIs themselves exhibit substantial diversity in structure, that potentially influence their reactivity and environmental fate. Treating PFAS-APIs as a single uniform group based only on structural considerations risks disproportionate regulation. A scientifically robust approach must consider both TFA formation likelihood and real environmental exposure, not theoretical hazard or structural classification alone."

Citation 5, in the context of environmental effects of pharmaceuticals and their transformation products: *“responsibility must be extended to the entire life cycle” (eco-pharmacovigilance)*

EFPIA supports environmental stewardship throughout the medicine lifecycle. However, responsibility must remain proportionate to the degree of practical control and applicable regulatory frameworks. Manufacturers already operate under one of the world's most comprehensive regulatory systems. New active substances undergo extensive environmental, toxicological, pharmaceutical quality and clinical evaluation before authorisation. Once medicines leave the manufacturing site, manufacturers no longer control prescribing decisions, patient adherence, excretion, wastewater treatment or disposal. Consequently, downstream environmental emissions cannot be managed solely through

manufacturer responsibility. Environmental protection should therefore focus on measures capable of reducing emissions in practice, including improved wastewater treatment, appropriate disposal systems, sustainable manufacturing and continued pharmaceutical innovation.

Fluorination itself cannot be viewed solely as an environmental liability. Medicinal chemists deliberately introduce fluorinated motifs to optimise target binding, selectivity, metabolic stability, permeability and safety. Many recent and expected breakthrough medicines rely upon these design principles, particularly in oncology, infectious diseases and central nervous system disorders. In turn, responsible stewardship should not be limited to a sub-group of products, and any prioritisation can be based on scientific environmental impact assessments.

Conclusion

The study correctly identifies medicines within similar therapeutic categories, but this should not be interpreted as evidence that fluorinated medicines can simply be replaced. Therapeutic substitution is a complex clinical decision requiring consideration of efficacy, safety, patient characteristics, formulation, treatment sequencing and regulatory approval. Fluorination is frequently integral to the therapeutic performance of a medicine, and replacing fluorinated chemistry often requires the discovery, development and approval of an entirely new medicinal product.

Additional evidence underlines why the conclusion that non-PFAS "replacements" are readily available is overly simplistic. Fluorinated motifs such as $–CF_3$ and $–CF_2–$ are not incidental features in many medicines; they are deliberately used in medicinal chemistry to optimise target engagement, selectivity, permeability, metabolic stability and systemic exposure. Survey evidence from medicinal chemists indicates that avoiding these motifs is technically and scientifically challenging, particularly in therapeutic areas such as oncology and central nervous system disorders, where molecular optimisation requirements are especially demanding.[7] Medicinal chemists do not introduce fluorinated groups arbitrarily. Fluorination is routinely used to optimise target binding, potency, selectivity, membrane permeability, metabolic stability, half-life and tissue distribution. In many cases these properties cannot be reproduced simply by removing or replacing fluorinated motifs, and doing so fundamentally changes the pharmacological characteristics of the molecule. As a result, replacing fluorinated chemistry frequently requires the discovery and development of an entirely new medicinal product rather than modification of an existing one.

The study also overlooks the broader role that fluorinated chemistry has played in pharmaceutical innovation. Numerous medicines across oncology, infectious diseases, cardiovascular disease, neurology and metabolic disorders owe key therapeutic properties to fluorinated motifs that were intentionally introduced during optimisation. Their success reflects decades of medicinal chemistry research rather than the availability of interchangeable non-fluorinated alternatives.

The patient relevance is also significant. Recent medicines containing $–CF_3$ or $–CF_2–$ motifs include therapies for neuropathic pain, HIV, SARS-CoV-2, migraine, lymphoma, acute myeloid leukaemia, Friedreich's ataxia, cystic fibrosis and breast cancer. Several medicines falling within the OECD PFAS definition are also included on the WHO Essential Medicines List, across areas such as infectious disease, oncology, CNS disorders, respiratory disease and anaesthesia.

It is also important to distinguish between the presence of PFAS motifs in the final active substance and the broader role of PFAS chemistry in pharmaceutical manufacturing.[8] PFAS may be "visible" in the final API, "contributing" as upstream starting materials needed to install a fluorinated motif, or

[7] https://chemrxiv.org/doi/full/10.26434/chemrxiv.15002892/v1
[8] https://chemrxiv.org/doi/full/10.26434/chemrxiv.15003710/v1

“invisible” as reagents, catalysts, solvents or protecting/deprotecting agents that do not remain in the final medicine. Replacing such materials in already approved manufacturing processes is not a simple substitution exercise; it can require process redevelopment, impurity control reassessment, GMP validation and regulatory approval across multiple jurisdictions.

Therefore, EFPIA supports proportionate, science-based measures to reduce environmental emissions and advance sustainability, but conclusions must not depict potential “alternatives” as clinically interchangeable “replacements”. Any transition must be based on robust evidence, clinical assessment, regulatory feasibility and safeguards for patient access.

Illustrative examples of why fluorination matters

Fluorination is not an incidental chemical feature. In medicinal chemistry it is deliberately introduced to improve potency, selectivity, metabolic stability, tissue penetration and overall clinical performance. The examples below illustrate why replacing fluorinated active substances is not simply a matter of selecting another medicine in the same therapeutic class. For example, all prostate cancer therapies contain PFAS, no medicinal alternatives available.

Medicine	Therapeutic area	Role of fluorination	Comment
Fulvestrant	Breast cancer	Introduction of a **CF_2CF_3** group transformed a promising research compound into a successful medicine by substantially improving biological activity.	Demonstrates that fluorination can be fundamental to the success of a medicine rather than an interchangeable chemical modification.
Celecoxib	Inflammatory disease	The **trifluoromethyl (CF_3)** group provides the precise size and electronic properties required to achieve selective COX-2 inhibition.	Fluorination can determine the selectivity of a medicine and reduce unwanted effects by enabling highly specific target binding.
Fluoxetine (Prozac)	Depression	The **CF_3** group markedly increases affinity for the serotonin transporter, producing the pharmacological profile required for antidepressant activity.	Fluorination can fundamentally influence the mechanism of action and therapeutic effectiveness of a medicine.
Efavirenz	HIV infection	Fluorination substantially increases antiviral potency while protecting the molecule from metabolic degradation.	Demonstrates the combined benefits of improved efficacy and longer duration of action.
Sitagliptin	Type 2 diabetes	Fluorinated groups anchor the molecule within the enzyme binding pocket, providing sustained inhibition and prolonged glucose control.	Fluorination contributes directly to therapeutic performance and duration of action.

These examples illustrate that fluorination is intentionally incorporated into medicinal chemistry to achieve specific therapeutic objectives, including improved target selectivity, potency, metabolic stability, tissue penetration and duration of action. The presence of another medicine within the same Anatomical Therapeutic Chemical (ATC) category does not demonstrate that it can deliver equivalent

clinical outcomes or replace a fluorinated medicine. For many products, fluorination is integral to the medicine's pharmacological profile, and replacing it would require the discovery, development, clinical evaluation and regulatory approval of an entirely new medicinal product.