scienceindustries
Wirtschaftsverband
Chemie Pharma Life Sciences

Nordstrasse 15
Postfach
8021 Zürich
Schweiz

T +41 44 368 17 11
F +41 44 368 17 70
[redacted]@scienceindustries.ch

European Chemicals Agency
P.O. Box 400
F.I.-00121 Helsinki

Finland

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Consultation on a proposed restriction on the manufacture, placing on the market and use of per- and polyfluoroalkyl substances (PFAS)

Dear Sir or Madam

scienceindustries, dem Wirtschaftsverband Chemie Pharma Life Sciences, ist es wichtig, Ihnen hiermit kurz unsere Anliegen zur Positionierung der Schweiz in den internationalen Gremien in Bezug auf diskutierte Ideen zu einem Exportverbot von Pestiziden, die in der Schweiz nicht mehr zugelassen sind, darzulegen.

The purpose of this letter is to comment on the public consultation on a proposed restriction on the manufacture, placing on the market and use of per- and polyfluoroalkyl substances (PFAS).

General remarks

The proposed restriction is of an extremely broad nature PFAS, and is the most complex restriction ever proposed in the EU with significant impact and unintended consequences across various industries. The proposal neither offers a structure of the more than 10’000 substances – which have hugely different intrinsic properties – nor does it differentiate between the risk profiles of the substances but instead proposes a comprehensive ban of the entire substance class. Therefore, while including substances for which a restriction is reasonable, the proposal also contains substances which use is safe and do not pose any environmental hazards. We would like to highlight that while in the communications EU regulators as well as in the recent media coverage, the number of identified PFAS may be around 10'000, theoretically there may be many more. The National Center for Biotechnology Information for example the PFAS PubChem Tree estimates that there are more than 6 million entries matching the OECD PFAS definition. This likely includes a number of Fluoropolymers. Discrete chemicals (i.e. not polymers) that are

traded in significant quantities, are much smaller in number. A study 1from 2021 reports finds less than 300 substances or less than 6%, of the 4730 PFAS substances presented in the 2018 OECD/UNEP Report are commercially relevant globally. Therefore a case by case consideration on the need of further regulatory action on the background of significance of the issue is justified.

The also study suggests that grouping and categorizing PFAS using fundamental classification criteria based on composition and structure can be used to identify appropriate groups of PFAS substances for risk assessment, thereby dispelling assertions that there are too many PFAS chemistries to conduct proper regulatory risk assessments for the commercially relevant substances. The same is asked for by the underlying definition document published by OECD in 2021[2]:

> As PFASs are a chemical class with diverse molecular structures and physical, chemical and biological properties, it is highly recommended that such diversity be properly recognized and communicated in a clear, specific and descriptive manner. The term "PFASs" is a broad, general, non-specific term, which does not inform whether a compound is harmful or not, but only communicates that the compounds under this term share the same trait for having a fully fluorinated methyl or methylene carbon moiety.

It also states:

> The decision to broaden the definition compared to Buck et al. is not connected to decisions on how PFASs should be grouped in regulatory and voluntary actions.

And:

> This report does not make any recommendation on how working scopes should be set up, in terms of which factors to be considered (which depends highly on specific local context), nor on PFAS grouping. However, when a working scope of PFASs is used, this report highly recommends that users clearly provide the context and rationale for selecting their PFAS working scope in order to provide transparency and avoid confusion by others.

This very clearly implies, that due to the diversity of substances that fall under the broad definition, a clearly defined grouping is not only advisable for any user to do so, but as we see it, in particular mandatory for regulators to provide for scientific legitimacy of any subsequent work and thereof resulting regulations.

By adopting a completely generic approach in which – besides producing and placing on the market – any type of use except for a few time-limited exemptions is prohibited goes much further than previous restriction proposals. Despite the level of detail in the current proposal, it reflects only a fraction of the current numerous uses of PFAS, including niche uses. The restriction will impact a huge number of products and value chains as many industries use PFAS in one way or another.
The broad nature and the wide range of uses not yet considered at all poses a major challenge: A complete consideration of all PFAS uses needs to be assessed by the regulator prior to set into force any regulation with such significant, and in some cases severe, consequences on businesses and the general population at large. In particular, we would like to remind the authorities, that:

- **The number of products that rely on PFAS,** either during their production phase and/ or in the final products is largely unknown. Indeed, many Downstream Users (DUs) may place on the market non-PFAS containing products that rely on PFAS in their production process at some point. Many of them may not realise PFAS have been involved.
- **The complexity of the supply chains**. Many supply chains involve multiple players. Whilst information flow is ensured between immediate parties involved in the supply (transmitter and receiver), there is currently no traceability system that ensures that complete information is received by the end user when multiple parties are involved in complex supply chains. This can be further exacerbated where parties are established in different (and some, like in our case, non-EU) jurisdictions. This makes the mapping of the supply chains extremely complicated.

[1] Identification and classification of commercially relevant per-andpoly-fluoroalkyl substances (PFAS)Robert C. Buck, https://setac.onlinelibrary.wiley.com/doi/epdf/10.1002/ieam.4450
[2] Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance, OECD Environment, Health and Safety Publications Series on Risk Management No. 61

Regulatory aspects

The legality of the group-based approach proposed in the restriction proposal raises ques-tions. Article 69 of the REACH Regulation[3] specifies a substance-related approach for re-strictions, which contradicts the proposed group-based approach. It is important to note that this objection remains significant, despite the existence of other restrictions on groups of substances listed in Annex XVII of the REACH Regulation.

Furthermore, the restriction proposal lacks a risk-based approach as it fails to conduct a risk assessment for individual substances or, at the very least, for substance groups with comparable properties. Consequently, the chosen restriction approach does not fulfil the criteria outlined in Article 68(1) of the REACH Regulation, which stipulates that restrictions can be implemented when there are "unacceptable risks." Consequently, imposing re-strictions on substances used in applications that do not present any risks goes beyond the legal framework established by the REACH Regulation.

The primary justification for the restriction proposal is based on the persistence of the substances involved as well as other potential hazard properties such as mobility or bioaccumulation. However, the necessary risk assessment, as mandated by Article 68(1) of the REACH Regulation, which considers both hazard properties and exposures from various uses, has not been conducted. To establish a lawful, appropriate, and proportionate regulation of these substances, a differentiated approach is necessary. This approach should consider the specific properties of each substance and assess whether a PFAS substance or its use poses an unmanageable risk to the environment or human health. It is important to note that if certain applications do not result in environmental exposure, a complete ban may not be justified. It is crucial to allow for the continued safe use of specific PFAS where suitable alternatives are unavailable. Failing to do so would render the restriction proposal disproportionate.

Implications with regard to 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 EU3, 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.

Neither REACH Restrictions in general nor the proposed Text on PFAS do 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 intermediates would remain in scope of the restriction as proposed. Additionally, certain validated

[3] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2008 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), estab-lishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regu-lation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (REACH Regulation) (Consolidated version), OJ 2006 L 396/1.

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.

scienceindustries 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[4].

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.

For additional information and rational we refer to the Position Paper submitted to ECHA by EFPIA and Animal Health Europe by June 2023 in which the considerations on Chemical Rationale, Potential for Substitution, Environmental Considerations and Impact estimates of the Restriction as drafted are being provided for the following aspects of pharmaceuticals:

- Active Pharmaceutical Ingredients (APIs)
- Development products and API under non-EU regulations
- Non-active ingredients (excipients)
- Starting Materials and Chemical Intermediates
- Equipment and Consumables
- Reagents, Solvents, Catalysts, Auxiliaries in Production and Quality Control
- Immediate Packaging Materials and Sterile Barriers for Oral and Injectable Formulations
- Drug Delivery Devices

We would like, however, to endorse the conclusions explicitly in this submission.

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

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

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.

The Royal Society of Chemistry has published a Policy Position on PFAS[5]. 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.

In conclusion we propose the following steps as part of a constructive way forward

For the restriction proposal to be acceptable, we suggest various adaptions which ought to be considered:

- The restriction of PFAS should adhere to a substance-related and risk-based approach, as outlined in Article 68(1) of the REACH Regulation. We strongly oppose the hazard-based approach driven in this restriction dossier. The goal of chemicals legislation should be to protect human health and the environment from proven risks that occur due to emissions of hazardous substances. It is important to note that not all PFAS substances necessarily present an unacceptable risk that would warrant a restriction.
- The restriction should incorporate differentiation among diverse groups of PFAS and consider the risks associated with their specific uses. It is necessary to exclude individual groups of substances, including specific fluoropolymers like PTFE, from the restriction proposal altogether.
- Adequate transition periods are necessary to facilitate the required changes. The proposed general transition period of 18 months is evidently insufficient for the conversion of all applications without exemptions.
- To ensure a legally robust assessment of the impact, it is crucial to establish a clear and well-defined scope for the restriction. In order to effectively analyse the impact across global supply chains, a comprehensive list of substances included in the scope, accompanied by their International Union of Pure and Applied Chemistry Names (IUPAC names) or Chemical Abstract Service Registry Numbers (CAS numbers), is necessary. This will enable a thorough evaluation of all affected uses of PFAS, preventing disruptions in the supply chain and ensuring that essential applications are not unintentionally overlooked or excluded.

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

- Fluoropolymers and fluoroelastomers as “PFAS of low concern” according to the OECD should be exempted from the restriction. Risks in other phases of their lifecycle should be addressed with suitable measures such as industrial emissions threshold, requirements for the disposal of the material or even a waste label.
- It is imperative to conduct a thorough assessment of the economic impacts through-out the entire supply chain, while considering the goals of fostering competitiveness, resilience, and sustainability within Europe.
- Comprehensive exemptions are necessary for socially important applications, particularly those related to safety, as well as key industrial uses such as hoses and seals. These exemptions are crucial to safeguard the uninterrupted operation of numerous industrial facilities and the continued existence of entire value chains and networks within Europe. Specifically, for safety-related applications like paints and coatings involving PFTEs, additional exemptions with longer transition periods are required.
- Some PFAS applications are essential and today with no alternatives to achieve sustainability goals such as climate neutrality, energy efficiency or circular economy. For some applications, even if alternatives exist, they will entail a large step backwards regarding efficiency. One example for this are PTFE valves in building technology which allow for a much more energy efficient flow control of heat, air, or water. In addition, several alternatives listed in the documents do not meet the technical requirements in the respective industrial context. The technical feasibility of alternatives is overestimated in many cases.
- A general transition time of 18 months is by far too short. Several years are usually needed to implement new processes once alternatives are known and proven to be workable. This has to take into account the complex value chains and approval procedures (of official institutions but also of clients).
- Given the technical significance of PFAS, it is crucial to have the option to review, extend, and reapply for exemptions. This is necessary to ensure that the exemptions remain aligned with the evolving understanding of PFAS and their applications. A mechanism should be put in place to prolong exemptions as it cannot be predicted when workable alternatives are available. One example for this is the semiconductor industry that is foreseen for a (much needed) exemption: The technical requirements of the sector are such high in terms of acid resistance, temperature resistance, material stability (in order to avoid impurities), tribological properties etc. that it is highly questionable that an alternative material to PTFE will ever be found.
- Exemptions should be granted to products that have already been introduced to the market for the first time. Without such exemptions, downstream users would be compelled to dispose of their existing stocks of substances, mixtures, and articles. This is due to the fact that, according to the REACH regulation, any process of making products available to third parties is considered as placing them on the market.
- Spare parts, maintenance, refurbishment, and second-hand articles must be exempted from the restriction to not compromise the sustainability goals in circular economy and not producing unnecessary waste. The restriction might make design changes necessary, which will impede the circularity and extended lifetime of products already in use.
- It is questionable that alternatives will be found in all applications (which is the ultimate goal of the restriction proposal) due to physical and chemical reasons.
- It is essential that stakeholders as well as regulators recognise that:
    - Proposed alternatives in some cases turn out to be worse in other aspects. For example, they may show lower lifetime, more abrasion or are less safe.
    - The generic ban of all PFAS would seriously impede other strategic goals of the European environmental policy, such as the European Green Deal, E-mobility and the digital transition of the European economy and society. For the case of Fluoropolymer that means that the following issues need to be thought through properly before regulatory measures are detrimental to other policy goals:

- Fluoropolymers are used in critical applications including smart mobility, clean energy and sustainable industry, semi-conductors and electronics
- Manycriticalapplicationswherefluoropolymersareusedarenoteven-proposedforderogationandwillbebanned18monthsafterentryintoforce.
- e.g.chemicalprocessindustry,pharmaceuticalmanufacturing,aerospace,militar-yanddefense,semiconductormanufacturing,waterandwastewatertreatment
- Periods for time limited derogations are not substantiated by a strong evidence baseandareinmanycasesinadequate.
- Theproposedrestrictioncreatesgeneraluncertaintythatwouldunder-mineinvestmentdecisionsandinnovationincriticalapplicationsthathelpdeliverstrat egicEUambitions(fightagainstclimatechange,EuropeanGreenDeal,theChip-sAct,HydrogenStrategy,andSustainableandSmartMobilityStrategy).
- Fluoropolymerspresentdifferenttoxicologicandeco-toxicologicpro-filesfromPFASthatcanbeconsideredofconcern
- Fluoropolymersdonotposearisktohumanhealthortheenvironmentastheyarenon-toxic,notbioavailable,non-watersoluble,non-mobileanddonotbio-accumulate.

Specific Information Requests

Section 1 Sectors and (sub-)uses: peptide manufacturing

PFAS compounds are a critical and unavoidable part of peptide manufacturing. In the following, our comments will primarily center on the use of PFAS (TFA) for peptide synthesis, as this application is central to our core business. However, it's important to note that proposed PFAS ban outlined in the Annex XV restriction report would also have implications that extend beyond that specific use.
Most peptides produced with Fmoc-based solid-phase peptide synthesis (SPPS) rely on trifluoroacetic acid (TFA) (CAS No. 76-05-1), which per OECD definition is categorized as PFAS. SPPS is a mature technique widely used in research and in production. There are no short to mid-term alternatives available for TFA in peptide manufacturing (further comments in section 6).

Some of our members are leading companies in peptide manufacturing and development, serving more than 56 countries with their peptides. A large share of our sales are generated with peptides that are produced through SPPS, using TFA. This includes some peptide APIs which are on the WHO Model Lists of Essential Medicines (EML).
The application of peptides is manifold, during the past decade they have gained a wide range of applications, thus the peptide market is growing. Amongst other, they are used in the food, cosmetic, biotech, medical technology and most importantly in the chemical and pharmaceutical industry. Therapeutic areas (not exhaustive) range from urology and respiratory, over pain and oncology, to metabolic, cardiovascular, and antimicrobial applications (Source: 1, 2, 3, 4, 5)[6]. A new generation of drugs for diabetes and obesity is currently conquering the market, based on chemically produced complex peptides. Peptide-based applications also show potential in new disease areas such as eye disorders. In addition, chemically manufactured peptides are becoming more widespread as a means of production for generic drugs. There are several socio-economic benefits arising from peptides, they are essential for adequate medical care and their manufacturing is an important part of the European economy. Thus, we appeal for the time unlimited exemption of the peptide manufacturing processes from the PFAS restriction/ ban under EU REACH.

[6] 1: Fisher, E., Pavlenko, K., Vlasov, A. & Ramenskaya, G. (2019), Peptide-based therapeutics for oncology. Pharm. Med. 33, 9–20.
2: Iyengar, S., Ossipov, M. H. & Johnson, K. W. (2017). The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine. Pain 158, 543–559.
3: Ioan, L. A. (2019), Review of glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus in patients with chronic kidney disease and their renal effects. J. Diabetes 11, 938–948.
4: Peterson, S. C. & Barry, A. R. (2018), Effect of glucagon-like peptide-1 receptor agonists on all-cause mortality and cardiovascular outcomes: a meta-analysis. Curr. Diabetes Rev. 14, 273–279.
5: Torres, M. D. T., Sothiselvam, S., Lu, T. K. & de la Fuente-Nunez, C. (2019), Peptide design principles for antimicrobial applications. J. Mol. Biol. 431, 3547–3567.

There are several socio-economic benefits arising from peptides, they are essential for adequate medical care and their manufacturing is an important part of the European economy. Thus, we appeal for the time unlimited exemption of the peptide manufacturing processes from the PFAS restriction/ ban under EU REACH.

Section 2 Emissions in the end-of-life phase

Peptide manufacturing companies use trifluoroacetic acid (TFA) (CAS No. 76-05-1) mainly for the SPPS. Associated with the growing importance of peptides, our TFA consumption has been growing over the past five years and this trend is expecting to continue. Based on the unavailability of alternatives, we assume that this development applies to the entire peptide manufacturing industry. Approximately 95% of TFA volumes consumed has been applied in SPPS, whereas the use of the remaining 5% is related to high pressure liquid chromatography. TFA emissions/ waste solely arise at the manufacture stage of peptides. Neither the use nor the end-of-life stage of peptides results in TFA emissions to the environment.

More than 99% of the TFA waste resulting from the manufacturing of peptides through SPPS is sent directly to incineration. The remaining 1% is at least partially collected in the sewage sludge and incinerated as well (6)[7].

The toxicology of the low to moderate concentrations of TFA currently found in the environment or those predicted in the distant future on organisms is not clear. Currently, there is not sufficient data available to conclusively assess the impact of TFA on the environment (7, 8)[8]. However, TFA has biological properties that differ from the longer chain polyfluoroalkyl substances (PFAS): it does not interact with biological molecules and does not bioaccumulate. It is unlikely to cause adverse effects in terrestrial and aquatic organisms (9)[9]. Also, there is strong evidence that TFA is a naturally occurring substance (10)[10]. Based on the argument above TFA should not be handled as a PFAS and thus its ban is questionable.

Furthermore, according to its REACH registration dossier and Chemical Safety Report, TFA does not meet the Annex XIII REACH standards for a PBT or vPvB substance. It also does not generate comparable degrees of concern under REACH Article 57(f). In this regard, ECHA has already assessed the TFA dossier and concluded that TFA does not require additional regulation.

Section 3 Emissions in the end-of-life phase (waste management options)

See comment section 2.

Section 6 Missing uses – analysis of alternatives and socio-economic analysis

Missing Uses:

1. Production,

2. Purification,

3. Analysis and

4. Development of synthetic peptides using TFA as described in this section.

The peptide manufacturing industry heavily relies on trifluoroacetic acid (TFA). TFA's unique properties make it irreplaceable for synthesizing long and intricate peptides (especially for active pharmaceutical

[7] 6: Stahl T., Gassmann, M., Falk S., Brunn, H. (2018): Concentrations and Distribution Patterns of Perfluoroalkyl Acids in Sewage Sludge and in Biowaste in Hesse, Germany. Journal of Agricultural and Food Chemistry 66,10147–10153.

[8] 7: Norwegian Environment Agency (2017), Study on environmental and health effects of HFO refrigerants, M-917.
8: German Environment Agency (2021), Reducing the input of chemicals into waters: trifluoroacetate (TFA) as a persistent and mobile substance with many sources.

[9] 9: UNEP (2023), EEAP 2022 Assessment Report May 2023E, Environmental Effects of Stratospheric Ozone Depletion, UV Radiation, and Interactions with Climate Change.

[10] 10: EFCTC, Naturally Occurring TFA, https://www.fluorocarbons.org/wp-content/uploads/2020/08/EFCTC-TheEvidenceThatTFAoccursNaturally_A4.pdf

ingredients (APIs)) by solid-phase peptide synthesis (SPPS). A ban on TFA could lead to significant disruptions in the European pharmaceutical industry, potentially causing the outsourcing of peptide production to other continents and endangering the supply of essential medicines to patients. The impact on the peptide manufacturing sector and pharmaceutical companies would result in job losses and economic repercussions. Exempting peptide manufacturing from the PFAS ban is crucial for maintaining global medicine supply and supporting drug innovation in Europe.

A. The annual tonnage and emissions (at sub-sector level) and type of PFAS associated with the relevant use.
   We do not have an estimate for the annual tonnage at the sub-sector level at hand, but we assume that this could reach between 200 – 500 tons of trifluoroacetic acid (TFA) (CAS No. 76-05-1) annually for manufacturing peptides through Fmoc-based solid-phase peptide synthesis (SPPS). Since TFA is used for cleavage, it does not remain in the product and the waste amount equals the total use. Based on current manufacturing processes it is estimated that there might be emission of maximum 1% associated with the described use.

B. The key functionalities provided by PFAS for the relevant use.
   The Fmoc-based solid-phase peptide synthesis (SPPS) uses trifluoroacetic acid (TFA) for liberating the peptide from the resin and removing all acid-labile sidechain protecting groups. This step is ubiquitous in the synthesis of most peptides using SPPS. TFA exhibits a distinctive array of physicochemical properties, serving as both a solvent (enhancing peptide solubility, promoting peptide disaggregation, and facilitating resin swelling) and a reagent (offering optimal acidity to execute efficient cleavage while preventing peptide degradation and unwanted side reactions). These unique attributes make TFA indispensable in this context, with no other reaction mixture capable of replicating its effects.
   Alternative reaction conditions that do not involve TFA possess limited versatility. They are typically suitable only for shorter, less intricate peptides, which demand lower levels of purity and find application primarily in industries such as cosmetics or technical fields, rather than in the production of active pharmaceutical ingredients (APIs). The demand for long peptides is growing globally and can only be met with SPPS using TFA.
   Moreover, TFA plays a pivotal role as a modifier in the purification and analysis of peptides through chromatographic techniques. While there may be instances where TFA can be replaced based on specific peptide characteristics, it is essential to acknowledge that TFA's distinct properties as a modifier are indispensable in certain situations. These properties are critical for achieving the requisite precision in analytical methods and effectively eliminating impurities during chromatographic purification.
   TFA is also used in the purification of peptides through preparative high-performance liquid chromatography (HPLC) and the analytics of peptides through HPLC or UHPLC.

C. The number of companies in the sector estimated to be affected by the restriction.
   It is difficult to express the consequences of the restriction in terms of the number of companies affected. The effect would be extensive, as not solely the peptide manufacturers would be affected but also suppliers and mostly the users/ customers of peptides. Thus, all European peptide manufacturing companies (approx. 4 companies with 1200-3500 employees and 12 manufacturing sites in Europe) would be affected and all their customers from different sectors & countries (mainly pharmaceutical companies), using peptides for manifold applications.

E. Cases in which alternatives are not yet available
   TFA used for cleavage in SPPS:
   - There is no TFA alternative available for producing peptides by SPPS available yet. TFA is used for cleavage in peptide manufacturing. Essentially all peptides that are produced through SPPS cannot be produced without TFA, as there is no alternative substance that can liberate the peptide from the resin meeting the quality requirements needed to achieve the product specification. Our R&D has been looking intensively for alternatives for one decade now, but with limited success. Our membership has invested > 1mCHF for that research and has joined forces with a collaboration partner from the industry. Currently, we are writing a scientific publication to share our experiences and knowledge with the peptide community. We expect to publish it in the near future.

TFA used for the purification of peptides through preparative high-performance liquid chromatography (HPLC):
- There are Peptides that can be purified without TFA. However, TFA is widely used due to its physicochemical properties. For most peptides it will be difficult to find a suitable alternative. Nevertheless, alternatives are routinely tested as standard in process development. Often TFA delivers the best cleaning performance. The alternatives tested have resulted in lower efficiencies, lower yields, and lower purities. Therefore, overall, the continued use of TFA would be less problematic for the environment.

TFA used for the analysis of peptides through HPLC/ UHPLC:
- Generally, the same applies as for the purification of peptides through HPLC (see comment above). Currently, TFA is used per default, but in the scope of the development of methodologies it is tested regularly to see if the substance could be replaced by an alternative. So far, with TFA the best results have been achieved. If possible at all, a TFA based method would have to be replaced by a combination of a number of alternative methods (due to lower performance). It is questionable whether these necessary re-registrations (resulting from new methods) would be accepted by all authorities worldwide.

All in all, TFA is indispensable for the chemical production of peptides. A ban would have a significant impact on European C(D)MOs and the pharmaceutical industry. Because there are currently no alternatives for TFA, peptide production would be moved outside of Europe. Because some of our member companies are exclusive manufacturers of particular peptides, some therapies could not be carried out due to the lack of the active ingredient.

If we were to find alternatives for TFA, we would have to revalidate/requalify all products produced through SPPPS and initiate re-registrations in many countries. This process is time consuming and expensive. These additional costs would make the European Economic Area unattractive for peptide manufacturing and production would most likely be outsourced to other continents.

As a result of a TFA ban in the EU, bottlenecks in the supply of peptic drugs to patients (transfer, revalidation, re-registration...) would be inevitable and Europe would become 100% dependent from other continents regarding the supply of synthetic peptide-based drugs.

F. For cases in which substitution is technically and economically feasible but more time is required to substitute:
TFA used for the purification of peptides through preparative high-performance liquid chromatography (HPLC):
- There are Peptides that can be purified without TFA. However, TFA is widely used due to its physicochemical properties. For most peptides it will be difficult to find a suitable alternative. Nevertheless, alternatives are routinely tested as standard in process development. TFA is only used if it results in clear advantages (such as higher efficiencies, higher yields, higher purities). If the use of TFA was banned, we would no longer be able to produce some peptides in this way, as there is no alternative. For the peptides, which theoretically could be purified with alternatives, compromises in terms of purity and yield would have to be made. There is a high risk that these drawbacks would not be accepted by customers and authorities and that production would be outsourced from Europe.

TFA used for the analysis of peptides through HPLC/ UHPLC:
- Generally, the same applies as for the purification of peptides through HPLC (see comment above). Currently, TFA is used per default, but in the scope of the development of methodologies it is tested regularly to see if the substance could be replaced by an alternative. So far, with TFA the best results have been achieved. If possible at all, a TFA based method would have to be replaced by a combination of a number of alternative methods (due to lower performance). It is questionable whether these necessary re-registrations (resulting from new methods) would be accepted by all authorities worldwide.

Acquiring alternatives, where available, will demand substantial financial and time investments in comprehensive research, development, and validation. Our industry operates within a highly

regulated environment, necessitating stringent quality, safety, and efficacy standards to be maintained. However, there is no assurance that any substitutes will meet the same criteria as our current use of TFA in critical applications. Furthermore, these endeavors might impose a significant strain on the production capacity of alternative materials. Even if raw materials are accessible, the challenge of conducting validation studies to support change control filings remains. These restrictions could expedite the pace of change control processes.
In our rigorously regulated industry, any alterations to registered drug manufacturing and analytical testing procedures, including changes in the use of PFAS materials, necessitate submission and approval by relevant Regulatory Authorities. During this period, the affected drug (to which the peptide produced through SPPS has been processed) cannot be marketed in the associated regions, a process that currently takes 3-6 years. If viable alternatives to TFA are identified, Regulatory Authorities would face a substantial surge in change approval submissions during any derogation periods, inevitably increasing the risk of supply chain disruptions for drugs within these market areas. Furthermore, the costs of re-validation are estimated to reach 5-50mCHF per peptide.

G. For cases in which substitution is not technically or economically feasible
Oligos and PMOs would not be affected by a ban of TFA, small-organic molecules only in a limited number of cases.
If the ban of PFAS (TFA) would be applicable for peptide manufacturing, this would affect the production of peptides through SPPS (i.e., all chemically produced peptides with a length of >10 amino acids, often already > 6 amino acids) globally. A ban would make peptide production in Europe impossible. This would result in shortage of supply of particular products until enough production capacity could be built up outside Europe.
The ban would result in a tremendous loss of EU sales and profits: on the one hand the peptide manufacturing sector would be significantly affected on the other hand the companies that process the peptides (e.g., pharmaceutical companies). Many jobs are linked to these industries. The peptide market is expected to grow a lot over the next 10 years, creating even more workplaces.
Socio-economic impacts:
Some of our peptide APIs are on the WHO Model Lists of Essential Medicines (EML). If the PFAS ban applies to manufacturing of peptides (resp. includes TFA), it would materially impact the supply of these essential medicines to patients worldwide, including tens of thousands of European patients who rely on them.
In general, SPPS produced peptide APIs are important for critical disease areas such as metabolic, cardiovascular, inflammatory diseases as well as cancer and cannot be manufactured TFA free currently anywhere in the world.

Also, for some APIs our company provides very large shares of the global supply. These volumes could not be compensated by any other peptide manufacturing company outside the EU.
If the PFAS ban goes through without exceptions for peptide manufacturing, patient coverage with critical medicines will be impossible in the short run, causing unnecessary patient suffering and increased mortality.
Even companies fleeing the EU regulation to manufacture somewhere else would not be able to fill this gap in time. Establishing a GMP compliant large-scale manufacturing process for these complex molecules takes years. Most likely all SPPS production would migrate to China, India or the US, regulatory zones under less strict control and oversight, giving them a competitive advantage over European companies.
Foreign companies have to use the same TFA-consuming SPPS manufacturing processes, but will likely be less efficient given reduced expertise, experience and process innovation that reduce overall PFAS use, process mass intensity, and carbon footprint by EU manufacturers. Thus, the EU ban will likely end up increasing global TFA usage overall, create a medical coverage gap in European patients (and worldwide), while leading to job losses with innovative European peptide manufacturers.
Conclusion: An exemption of peptide manufacturing from the PFAS ban is needed to uphold the global supply of medicines that were defined as essential by the WHO.
Impact on peptide drug innovation in Europe
Contract manufacturers using SPPS are critical European infrastructure for drug innovation. In collaboration with biotech startups and drug developers, manufacturers work closely together on new API development and process optimization. Drug discovery pipelines are spanning multiple

years, if not decades. There are hundreds of promising peptide drugs currently under development and under investigation in preclinical, phase 1, phase 2 and phase 3 clinical trials with European peptide manufactures (11, 12).[11]

Section 7 Potential derogations marked for reconsideration – Analysis of alternatives and socio-economic analysis

Our member companies are aware that very persistent PFAS may lead to adverse effects for the environment and humans. Therefore, we endorse the aspiration for a thoughtful and precise regulation of PFAS. We want to underscore the significance of adopting a science-based and risk-oriented approach to restrictions (see also section 2 regarding the impact of TFA on the environment and organisms). It is vital to consider the existing scientific data, risk evaluations, and expert insights to guarantee that the restrictions are balanced and directed toward substances presenting substantial risks.
As the manufacturing of peptides relies on TFA, which is categorized as a PFAS, the current restriction proposal would have an extensive negative effect on the peptide manufacturing sector in Europe and its global downstream users. It would lead to a shortage in supply of essential medicines, and ultimately be a threat to human wellbeing.
Thus, we request a time unlimited derogation from the PFAS ban for the development and manufacturing of peptides. We request that PFAS that are essential for developing and manufacturing APIs for medicinal products and peptides for various applications (e.g., medical devices, excipients, cosmetics, etc.) are exempt from the proposed restrictions.
Transitional periods proposed in the Annex XV restriction report do not factor in regulatory timelines in the medicines or medical device sectors. Alternatively, we propose, at the very least, extending the timelines to a realistic extent, accompanied by support measures and initiatives to promote the exploration and adoption of alternatives, facilitating proper implementation. Substantial investments in research and development of alternative technologies and materials are imperative to further evaluate the availability of viable and sustainable substitutes that align with the stringent demands of our industry. We would like to emphasize that regulatory bodies have set very high standards for purity/impurity profiles, and there is no certainty that acceptable alternative techniques for TFA cleavage could be discovered.

On behalf of our member companies as well as their customers. i.e. down stream users, of the chemical and pharmaceutical Industry we would like to add some concerns and opinions we fully share and support for your consideration

Even though trying to compile as much information as possible within the timeframe of the stakeholder consultation and even before, it is difficult for downstream users to know which PFAS is present in which parts. PFAS are for example used as flame retardants in plastics which is mostly a business confidentiality of plastics producers. Actors of the mechanical engineering sector have no chance to know about such ingredients.

Where the presence of PFAS is known, companies often have searched for alternatives due to cost efficiency reasons: The PFAS used for technical reasons are usually expensive materials. Where the presence of PFAS has just recently become known, it was impossible to conduct representative studies on alternatives in the timeframe of the consultation.

Derogations needed

Amongst the foreseen derogations (5.a to 5.t and 6.a to 6.f) the following derogations have been mentioned by companies to be needed:
- 5.g, 5.h, 5.k, 5.n, 5.o, 5.r, 5.s, 5.t, 6.a, 6.b, 6.c, 6.d, 6.e, 6.f

[11] 11: Wang, L., Wang, N., Zhang, W. et al. (2022), Therapeutic peptides: current applications and future directions. Sig Transduct Target Ther 7, 48.
12: Davenport, A.P., Scully, C.C.G., de Graaf, C. et al. (2020), Advances in therapeutic peptides targeting G protein-coupled receptors. Nat Rev Drug Discov 19, 389–413.
Conclusion: The proposed PFAS ban would negatively impact the global peptide drug development pipeline and future peptide medicine supply, which poses economic and public health challenges for the EU. It is also reasonable to expect that European scientific talent and expertise is lost to competitors in US/UK.

In addition, the following potential derogations have shown to be essential:
- 5.v, 5.w, 5.x, 5.bb, 5.cc, 5.ee, 6.g, 6.j, 6.l, 6.n, 6.o.

The derogation for semiconductor manufacturing should be broadly understood:

- 5.ee semiconductor manufacturing process: including e.g. installations, equipment, products, materials, additives, and process chemicals

Additional derogations to be foreseen

According to the information from companies in the European value chains, specific derogations are needed for:

- applications of fluoropolymers in sealings application for the energy sector (equal to the derogation for fluoropolymers in the "petroleum and mining" sector).
- applications of fluoropolymer affecting the proper functioning related to the safety of energy systems and affecting the safety of operators, the environment or infrastructure related to energy systems.
- applications of fluoropolymers under harsh conditions (such as aggressive chemicals, high temperature range, high friction, etc.)
- applications of fluoropolymers for sealing for special applications where no alternative exists.
- applications of fluoropolymers in mechanical engineering such as sealing, bearings, valves, linings, coatings, solid lubricants and others

Scienceindustries believes that a total ban on fluoropolymers is not proportionate and by way of derogation, fluoropolymers and applications containing a fluoropolymer shall not be restricted. The concerns of persistence raised in the restriction proposal can be appropriately managed through the implementation of different regulatory frameworks together with responsible manufacturing and End-of-Life (EoL) risk-management practices. Regulatory frameworks as the Industrial Emissions Directive (IED), theWaste Framework Directive (WFD), and the Occupational Health Safety Directive can address the concerns related to fluoropolymers effectively and in an expeditiously manner compared to the REACH restriction.

Longer derogation times strongly needed

For all the mentioned derogations, finding a technically and economically feasible alternative is only the first step: Adaptations of technical processes, adjustments within the complex value chains and in some specific approval processes are then needed. This takes several years, in addition to the years of research to find an alternative. Therefore, derogation times needed are in most cases at least 13.5 years.

Uses in general commercial and industrial settings:

Chemicals and chemical products are in use in large proportions in non-chemical industry settings. In order to handle chemicals and chemical products safely and to the best use of the individual commercial activity, a wide range of equipment consisting of or containing PFAS is in use. However, the proposal only derogates (for a limited period of time) few PFAS uses in industrial settings. PFAS are typically used in sealants, coatings on valves and piping, gaskets, personal protective equipment/ clothing, refrigerants, membranes, filter materials and membranes, foams, greases/ lubricants, mould release, conveyor belts, O-rings, columns/ internals, diaphragms, processing aids, etc. Without these materials/ pieces of equipment, industrial plants can no longer operate. The required key characteristics of PFAS, including durability, thermal and chemical stability, fire resistance, water and oil repellence, make them indispensable.

Therefore, **a time unlimited derogation on PFAS used in industrial settings is essential.**

Uses in the paints, coatings and printing inks industry

The restriction proposal mentions a wide range of PFAS, with a particular emphasis on fluoropolymers, notably polytetrafluoroethylene (PTFE), which find application in paints and coatings. These substances play a vital role in enhancing various properties of coatings, such as scratch and abrasion resistance, as well as thermal and chemical resistance, which are crucial for specific end uses. They are utilized in anti-friction coatings for industries like automotive, mechanical engineering, and cutting equipment, as well as in non-stick coatings. PFAS-containing coatings are employed to improve the abrasion resistance of aircraft wings. In the domain of powder coatings, PFAS serve as structuring and matting agents, as well as for functional purposes like imparting slip and friction properties or acting as pigments for coloring. Another application of fluoropolymers is as binders (fluoroethylene/vinyl ether (FEVE) polymers), enabling the creation of highly durable outdoor coat-ings.

While certain compounds are used in minimal quantities, they hold significant technical importance, particularly in powder coatings, industrial coatings, automotive applications, and corrosion protection. Coatings with fluoropolymers are crucial for ensuring the functionality and safety of safety-relevant fasteners (such as bolts, nuts, washers, clips, etc.) used in the assembly of chassis and tires. The current state of the art dictates that these coatings are necessary to achieve the required assembly condition, including proper pretensioning and clamping force. This ensures that the connections maintain their functionality and provide the necessary safety measures.
Furthermore, fluoropolymer coatings play a vital role in the proper functioning of seat belt restraint systems, particularly in cars. They prevent the belt from sticking to components in the event of an accident, which can occur due to the high thermal energy involved. This coating guarantees the continued functionality of the seat belt. Additionally, it ensures that the belt buckle can still be operated and opened under load after an accident.

At present, there are no viable alternatives available for these safety-critical applications, and it is unlikely that suitable alternatives can be identified and implemented within the planned transition period. This is because a large number of the substances in scope of the restriction are not classified as hazardous substances under the CLP Regulation.1 Due to the absence of a requirement for raw material manufacturers to disclose information about non-hazardous substances in the supply chain, it is currently extremely difficult for companies in the coatings and printing inks industry to accurately gauge the extent to which individual companies are impacted.

With the information at our disposition, we conclude that the PFAS restriction as currently proposed would have a tremendous negative impact on various value chains within the European Union as well as in Switzerland. Some sectors, uses and many sub-uses have not been taken into account or not been evaluated in necessary detail.
We thank you for your consideration of our concerns and the information submitted and remain at your disposal for any questions.

Kind regards

Dr. Stephan Mumenthaler
Direktor

Dominique Werner
Leiter Chemikalienrecht

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