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Additional Information on Missing Uses with regard to the ANNEX XV Restriction Report on Per- and polyfluoroalkyl substances (PFASs) as published by ECHA on March 22nd, 2023

Content

Use Sector

Merck Healthcare KGaA is one of the three business sectors of Merck KGaA. All three of our business sectors – Electronics, Life Science and Healthcare have submitted substantial comments to the PFAS restriction proposal. Merck Healthcare KGaA manufactures medicinal products, API and medical devices for human patients. We are member of the European Federation of Pharmaceutical Industries and Associations (EFPIA), and part of the Pharmaceutical and Biopharmaceutical Industry (not regarded in tables 8 and 9 of the Annex XV report).

Information on Uses Covered in the Annex XV Report

EU Approved Active Pharmaceutical Ingredients

EU API under Directive 2001/83/EC, Sitagliptin, meeting the PFAS definition, are foreseen to be derogated under Restriction Option 2. This is therefore not a missing use, but additional data is provided as Restriction Option 1 is still mentioned to be proportionate in the report. Banning EU API under REACH limits patients to access essential medicine. Conflicts with pharmaceutical law are generated, as these products are under explicit registrations and market authorizations.

F-Gases

We use F-Gases in applications, mainly for heating, ventilation, air conditioning or cooling (HVACR). Many refrigerants in industrial cooling, production or storage environments fall both under both the F-Gas and the PFAS definition. We are a downstream user of these products and have limited stakes in the nature of the refrigerants in use. We noted, however, certain conflicts if both regulations are applicable in parallel. As the Annex XV report focuses on structure rather than substance properties, it bans options that are preferrable from a sustainability perspective (lower GWP), which jeopardizes the goal set by both regulations. As the F-Gas regulation plans a phase-out of the problematic substances in a framework that is known to work, the benefit of an additional regulation is also not evident. A double regulation should be avoided.

Information on Uses Not Covered in the Annex XV Report (Missing Uses)

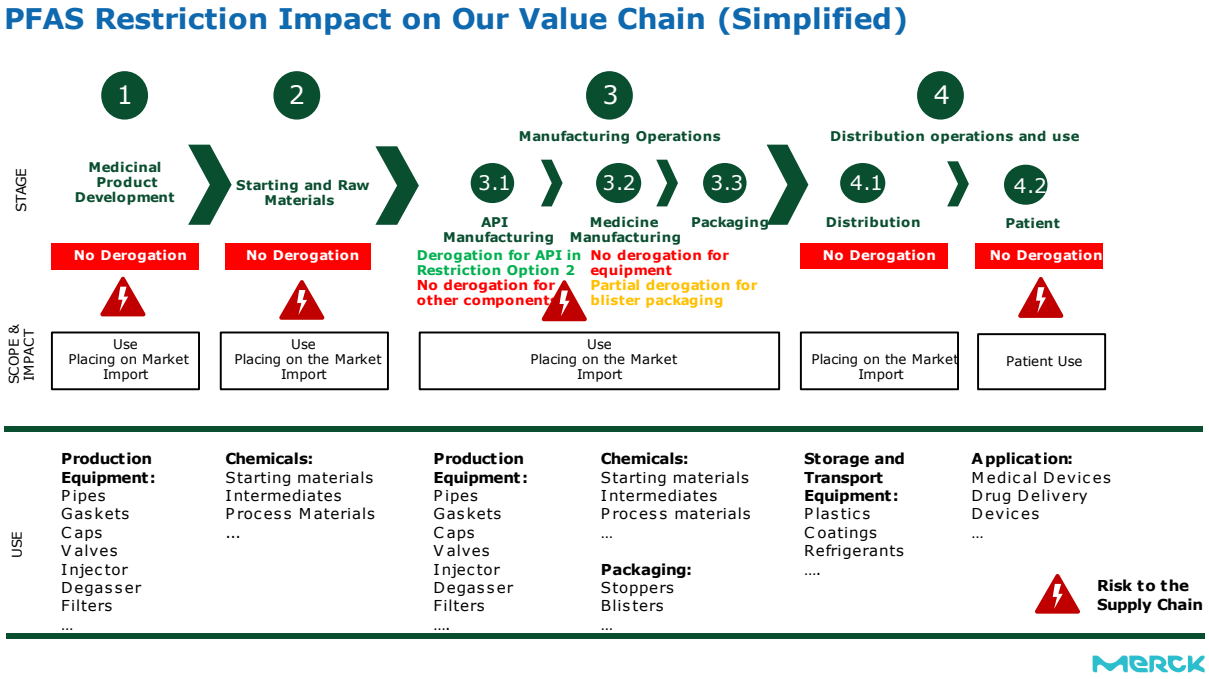
Medicinal Products

A medicinal product, also called pharmaceutical or drug (U.S. terminology), is a general term to describe the item that patients get for therapeutic

indications. They include a multitude of application forms, such as tablets or injectables, and may be subject to subscription by a doctor or freely accessible for patients. They are compounds of one or more active ingredients (API), other supplementary ingredients (excipients), an immediate packaging, overpacks and patient information. They can only be placed on the market if a market authorization has been granted, and high standards are met in the full supply chain including manufacturing, labeling and pharmacovigilance.

The Annex XV report does **not** derogate or mention medicinal products. This is in stark contrast with the impression many stakeholders seem to have, as the deceiving message that pharmaceuticals are derogated or even exempt is regularly re-iterated by NGOs,[1] consultants,[2] the press,[3] legal experts[4] and even authorities such as the German BAuA.[5] This apparent misconception is probably based on the proposed time-unlimited derogation for active ingredients. While the API is an essential component, lacking derogations for other parts of the medicinal product as laid out in this document, or the medicinal product itself, moves them in scope of the restriction.

[1] The top 12 PFAS producers in the world and the staggering societal costs of PFAS pollution (chemsec.org)
[2] 3E Webinar Watch: New PFAS Regulations Around The Globe - https://promos.3eco.com/od-webinar-pfas-around-the-globe/
[3] Newsletter from [redacted]@politico.eu, Tue, 7 Feb 2023
[4] https://www.steptoe.com/en/news-publications/pfas-leaked-draft-echa-opinion-signals-risk-for-biocides-plant-protection-products-and-other-sectors.html
[5] https://www.reach-clp-biozid-helpdesk.de/SharedDocs/Downloads/DE/REACH/Verfahren/Beschr%C3%A4nkung/FAQ-PFAS.pdf



Fluoropolymers in Industrial Use

Fluoropolymers are plastic materials with the highest performance when resistance to chemicals, radiation, abrasion or heat is relevant. These properties make them indispensable to all high-tech, high-performance or high purity industries. They provide smooth hard surfaces which are easily disinfected and a long service life. As non-hazardous polymers they are not subject to registration or labeling under REACH and CLP, respectively. For lack of other communication, reporting or disclosure requirements, the full extend of both uses and nature of fluoropolymer materials remains unknown. This applies e.g. to non-stick surfaces in pharmaceutical manufacturing equipment. Excellent examples with detailed substantiation for fluoropolymer use in production and laboratories were submitted by Merck Electronics to this public consultation.[6]

As the materials are selected because of their properties, rather than their chemical structure, they can in theory be substituted with non-fluorinated materials of equal performance. As the performance characteristics are long-term resistance against chemicals, irradiation, heat, abrasion and mechanical stress, we expect any potential substitute to be highly persistent too.

The Annex XV report foresees derogations for certain fluoropolymer materials, applications, product properties, industrial sectors or combinations thereof. As our sector is not included, we consider this a missing use, and want to raise the concern that the production of our drugs could not happen

[6] Attachments to submissions #4448 and #4450 in Document 18 as published

due to lack of materials and consumables with direct impact on our patient supply.

The materials do not become part of products, which means they are still under control of the manufacturer at the end of their service life. "Industrial Use" is well established under REACH and allows for application of proper management methods.

Waste management can reduce emissions of fluoropolymers or breakdown products to any desired level. If we identify a possibility to replace PFAS materials in a responsible and sustainable way, we will search for and use the best substitutions. With established recycling or circularity patterns, the materials can significantly contribute to improving sustainability (high purity, easy cleaning, long service life).

Starting Materials, Reagents, Intermediates, Solvents, Auxiliaries

For the manufacture of API meeting the PFAS definition, starting materials and chemical intermediates also fall into this category. This is unavoidable, as the PFAS moiety has to be introduced into the molecule. The ambiguity in the restriction proposal, whether a time-unlimited derogation for API also implies their upstream ability to manufacture them, should be avoided by clear wording in the restriction text.

Reagents and solvents are required in analytical procedures, such as stipulated by pharmacopoeias or QC requirements. One example is trifluoro acetic acid (TFA) in high performance liquid chromatography (HPLC). It is our understanding that those materials fall under the scientific research and development (SR&D) exemption under REACH, but concerns persist as to the future availability of these materials on the European market.

Reagents and solvents in production deserve special attention. Unlike starting materials or intermediates, their structure does not become part of the final molecule. The materials are selected for optimum performance in the manufacturing process based on their properties and could theoretically be substituted for non-PFAS materials. We assessed all our manufacturing processes in the EEA and found that we do not use any PFAS chemicals in production processes. This reflects our past and ongoing efforts to increase sustainability in all our processes, including the wastewater scores. There are, however, some important points to consider:

- Significant changes in production processes take a long time, as under GMP re-validation and/ or re-qualification is required
- As shown by the example of octyl phenol ethoxylate (Triton X), which is under a REACH Authorization scheme, production can largely depend

on a single chemical. In the Covid-19 pandemic, both tests[7] and vaccines[8] rely on Triton as essential component.

For these reasons, an appropriate derogation which takes in consideration the registration process timelines are necessary. This would give any upstream supplier sufficient time to adapt their processes, thus avoiding a supply chain disruption. In addition, the regulation should include a clause that allows to temporarily lift any ban in the case of global pandemics or other medical emergencies, when their use is proportionate.

In pharmaceutical research and analytical laboratories reagents, solvents, catalysts, intermediates, test items or reference substances are used in laboratory environments. As they are used under the SR&D exemption in Article 3(23) of REACH.[9] It was noted, however, that under 5. t in the Annex XV report, an apparently time-unlimited derogation was granted for calibration and reference materials. This causes confusion, as validated analytical procedures cannot be conducted without them. If this derogation is extending the scope, it should indeed be added to the SR&D exemption rather than individual restrictions.

Active Pharmaceutical Ingredients in Development Products

The discovery of new molecules with therapeutic effect is a lengthy and complex process.[10] After the toxicological properties of a candidate substance have been established in pre-clinical trials, the compound undergoes three clinical trial phases to establish patient safety, galenic, dosage and efficacy. These studies involve significant patient numbers and manufacture of medicine. The SR&D exemption under REACH is no longer applicable if the annual manufacturing volume for the active ingredient exceeds one ton,[11] and a PPORD notification must be submitted. As there is no derogation foreseen for any substances under PPORD in the Annex XV report, and the API derogation under Directive 2001/83/EC is not yet applicable prior to approval, this gap means that both manufacture and application (clinical testing) cannot happen in the EU. This has impact on both the clinical community as well as patients, particularly those with unmet medical needs.

In case clinical trials has been started in Phase 2 already where the finished drug product would be classified as PFAS according to the restriction proposal, the impact of the draft proposal would force us to move the clinical trials outside the EU, and subsequently the manufacturing of the drug product. This leads not only to a significant time delay in the development of

[7] Stellungnahme zum SARS-CoV2-Antigenschnelltest von Roche Diagnostics (sein-ev.de)
[8] The hidden allergen: Triton X-100, a derivative of polyethylene glycol (jaci-inpractice.org)
[9] Guidance on Scientific Research and Development (SR&D): v2.1 (europa.eu)
[10] https://en.wikipedia.org/wiki/Drug_development

the drug, additional costs and loss of innovative strength within the European Union. Furthermore, the loss of clinical trials in the EU would slow down innovation, impacts patients with unmet medical needs, reduces the competitiveness of the pharmaceutical industry and in the end put the goal of more resilience of the European Union into jeopardy.

In medicinal chemistry, the trifluoro methyl moiety is an important building block as an electron-withdrawing non-toxic substituent, that also protects the molecule against metabolic de-activation through enzymes (particularly cytochrome P450). Not using the structure would severely hamper the development of new treatment options. In a later stage of development, the environmental risk assessment (ERA) determines to what degree the final molecule is problematic in the environment. This depends on many substance properties such as biodegradability, aquatic toxicity and distribution in compartments (water, air, sediment, living tissue), and cannot be determined by a structure alone. The application of the OECD 2021 definition would ban a chemical structure rather than a substance group of given properties, which we consider impact for the supply chain of drugs within the EU and for the human health by restricting patient's access to new and existing medicine.

Immediate Packaging of Injectable Medicinal Products

Injectable medicinal products are usually packed in a vial with a rubber stopper. The stopper allows for the penetration with a syringe needle, so the injectable can be transferred without the risk of contamination. The vial seal must maintain sterility and / or protect the product from moisture, air, particles and any compounds leaching from the rubber to the product. For optimum performance, many manufacturers offer a product line with fluoropolymer coated elastomers. These products have a thin spray-coating or lamination of ETFE or undisclosed PFAS elastomers that provide optimum protection and avoid selective adherence of API to the rubber, which may lead to dose variation.

The fluoropolymer coating maintains product quality and patient safety throughout the shelf life. As stability is a key factor in granting market authorizations, any change in the immediate packaging would require stability studies and changes in packaging technology. Even in the unlikely event that uncoated materials perform equally well in the studies, the time until the restriction becomes effective is insufficient to re-acquire the market authorization. Without market authorization, the product of course becomes unavailable to patients in the European Union.

Products which easily adsorb to surfaces leads to depletion of the available quantity and can deteriorate its quality. In order to avoid such surface interactions of active ingredients, so-called surface acting agents ("surfactants") are used in biologics formulations. Container closures like plunger stoppers, made from synthetic rubber, have hydrophobic surfaces and therefore readily adsorb protein active ingredients. PFAS polymers are used as coatings or laminations on such rubber components to efficiently prevent adsorption of the active ingredient. No alternative is known so far which could replace PFAS compounds as container closure coatings.

Another example are biologic products delivered to patients in a freeze-dried (lyophilized) state, as these packaging materials are unrivalled in maintaining sterility of the content.[11] In addition to the sterile barrier, it also maintains product quality.

If the Annex XV report is implemented as written, REACH would restrict the placing on the market of products that are under specific pharmaceutical market authorizations. These conflicts cannot be resolved and should be avoided by a clear scope of the restriction. Any products under strict regulatory schemes should be exempt from the scope of the restriction, rather than derogated, to avoid double regulation, legal pitfalls and complexity. This applies to API, medicinal products, and medical devices under EU MDR and EU IVDR including the full supply chain, i.e. starting materials, necessary equipment and packaging.

Medical Devices

Modern approaches to facilitate drug delivery are pre-filled syringes already containing the injectable product, or injection pens for home use of the patient. They differ from injectables packaging as described above as medical device requirements (e.g. under EU MDR) have to be met in addition to the medicinal product approvals (marketing authorization). Technically they are comparable, in the way that elastomer parts with contact to the medicinal product are often fluoropolymer coated. In the example of a pre-filled syringe, the plunger has drug product contact throughout the shelf life, and our line of argumentation laid out in the packaging section applies likewise.

Conclusion

The draft restriction proposal does not take into account the very specific challenges and constraints of the pharmaceutical industry. Apart from the huge gaps in the analysis of the supply chain of medicinal products, timelines for development and licensing are not considered. The development,

[11] See for example Why FluroTec® Barrier Film for Lyophilization Stoppers - West (westpharma.com)

production and supply of pharmaceuticals in the European Union are not guaranteed with the conditions of the draft restriction proposal and will put the priority of European resilience into danger.