REQUEST FOR EXEMPTION

Our company is specialized in the distribution of intermediates, raw materials and active ingredients for the pharmaceutical industry.
With the present comments we want to support the derogations applying to intermediates, building blocks, and reagents involved in the production of active pharmaceutical ingredients (APIs) and finished drugs.

1. Context of the request

Raw materials and chemical intermediates that qualify as PFASs, according to the definition addressed in the restriction proposal, and applied in pharmaceutical industry are mainly manufactured and processed with the specific purpose of introducing fluorine atoms into API molecules.
In addition, APIs and pharmaceutical products are subject to rigorous registration and market authorization systems under European and Member States regulations, which are aimed at demonstrating their beneficial effects on health, safety of use, and also involve detailed environmental impact assessment. It would therefore be laborious, time-consuming and financially demanding for pharmaceutical industry to research and qualify substitutes, without a clear societal eventual benefit.

A restriction applying to PFASs involved in APIs and human and veterinary drugs production would consequently remove these molecules from the European market, with significant consequences for human and animal patients, as few or none therapeutic equivalent options currently exist.

We deem that raw materials, intermediates and auxiliaries required for the manufacture of APIs and pharmaceuticals products should be exempted from the proposed restriction and subject to a time unlimited derogation, as already proposed for APIs and finished medicinal products themselves.

2. Sectors and (sub-)uses

Many PFAS chemicals are used at various steps of the production process of APIs and finished drugs. In particular, we want to emphasize the importance of a time unlimited derogation for the following chemical substances:

4,4,5,5,5-pentafluoropentan-1-ol [CAS Nr. 148043-73-6; EC Nr. 421-360-9]

This molecule is an important building block for the commercial manufacture of the API Fulvestrant. Fulvestrant is a medication used in hormone therapy for the treatment of advanced and/or metastatic breast cancer in postmenopausal women, who no longer respond to therapy with other antiestrogens. The mode of action is different from that exhibited by other antiestrogenic active ingredients, and the therapy may last for months or years.

Trifluoromethanesulphonic acid [CAS Nr. 1493-13-6; EC Nr. 216-087-5]

Trifluoromethanesulphonic acid is one of the strongest acids known used at industrial scale. Because of its characteristics and properties, as thermal stability and resistance, it is widely used in the manufacture of several pharmaceuticals such as antibiotics, antivirals, glycosides, nucleosides, proteins, and steroids.

3. Emissions in the end-of-life phase

As mentioned, 4,4,5,5,5-pentafluoropentan-1-ol occurs as an intermediate in the production process of Fulvestrant. Accordingly, under the REACH regulation, it is produced, transported, and processed under strictly controlled conditions (SCCs) and any emission in industrial manufacturing environments is well controlled and regulated.
We believe that the reasons for concern that led to the restriction proposal, related to PFASs persistence and the consequences for health and the environment, are thus not relatable to this specific application of 4,4,5,5,5-pentafluoropentan-1-ol, being the substance used in controlled conditions and transformed during the production process.

We are also aware that Fulvestrant still falls under the proposed definition of PFAS, making 4,4,5,5,5-pentafluoropentan-1-ol a PFAS precursor. Nevertheless, it has to be borne in mind that the release of drugs into the environment cannot generally be considered controlled: the excretion of drugs after human and veterinary therapeutic use is the main route of pharmaceuticals emission into the environment and is an inevitable consequence of drug consumption.

In the specific case of Trifluoromethanesulphonic acid, many synthesis products mentioned in paragraph 2 no longer fall under the definition of PFAS: so, this molecule is not always to be considered as a precursor of other PFAS molecules.

Moreover, the pharmaceutical industry is strictly bonded to good manufacturing practices (GMP), which include among their principles maintaining controlled process conditions.

4. Missing uses – Analysis of alternatives and socio-economic analysis

Medicinal products are among the uses marked as *researched in general* in Table A.1 of Annex A of the Annex XV restriction report. Our comment is intended to highlight the importance of extending this sector of use to include not only the final product itself, but also the chemicals necessary for its synthesis.

Most PFAS substances used in APIs and medicinal products development have the specific purpose of introducing fluorine into the molecule. The fluorine atom enhances the pharmacokinetic and physicochemical properties of the drug, such as metabolic stability, membrane permeation, and binding affinity to target proteins. Fluorine presence is then important to achieve proper dose release to the target site of the pharmaceutical product.
Due to the unique properties of fluorine atoms, replacement of fluoro-alkyl groups is not foreseeable and advisable: for example, the substitution of fluorine by other halo-alkyl groups could result in chemicals with serious toxicity for patients.

Because of the long and demanding process involved in the research, development, clinical testing and approval of a new drug, modifying at any stage the synthesis process to substitute a PFAS with another source of fluorine or another catalyst is not technically and economically feasible.

In the specific case of PFAS molecules mentioned in this document, a restriction would result in the exclusion from the EU market of drugs involved in the treatment of several pathologies, especially when considering the wide use of reactions involving Trifluoromethanesulphonic acid. Excluding such pharmaceuticals products would inevitably lead to an increase in the costs of equivalent therapies, where available, and probably also to their shortage with deep consequences for patients and National healthcare systems.

In the specific case of 4,4,5,5,5-pentafluoropentan-1-ol, a ban would lead to the interruption of an essential and potentially lifesaving cancer therapy without known substitutes.

5. Conclusion

The importance of PFAS compounds to European healthcare systems is remarkable and is not limited to the two examples reported in the present document. Many other molecules, that can be considered PFASs according to the definition proposed, are commonly used by the pharmaceutical industry: among others, Trifluoroethanol [CAS Nr. 75-89-8; EC Nr. 200-913-6], 1,1,1,3,3,3-hexafluoropropan-2-ol [CAS Nr. 920-66-1; EC Nr. 213-059-4] and Trimethylsilyl trifluoromethanesulphonate [CAS Nr. 27607-77-8; EC Nr. 248-565-4] are important intermediates in the manufacture of APIs.

The wide use of PFASs makes them essential compounds for the pharmaceutical industry. Therefore, we deem necessary that PFASs qualifying as raw materials, building blocks, intermediates and auxiliaries used at any step of the production process of APIs and finished drugs, and in general involved in specific applications related to the pharmaceutical sector, should be exempted from the restriction proposal and subject to a time-unlimited derogation for the specific sector of use.