ESMO feedback on scientific and technical information on the manufacture, placing on the market and use of per- and polyfluoroalkyl substances (PFAS)

The European Society for Medical Oncology (ESMO) is the leading professional organisation for medical oncology, with more than 30,000 members from over 160 countries. ESMO is committed to preventing new cancer cases, improving the quality of cancer care and promoting equal access to optimal treatments for all cancer patients.

Given the current scourge - an estimated 2.7m new cases and 1.3m deaths in the EU in 2020[1] - of cancer and the increasing threat - lives lost to cancer in the EU are set to increase by more than 24% by 2035[2], making it the leading cause of death in the EU - that it poses to Europe's patients, their families and friends, timely, regular access to innovative cancer medicines has never been more important to our patients.

ESMO notes the draft proposal's aims to prevent PFAS accumulation in the environment and food chain and welcomes its efforts to improve human health. However, it is pivotal that such action is based on a comprehensive and consistent review of the available evidence as there are growing concerns about the possible impact of the draft proposal on the production, availability and manufacturing of cancer medicines.

For example, the proposed Annex XV definition of PFAS includes a variety of active pharmaceutical ingredients (APIs) – e.g. gemcitabine hydrochloride, a type of chemotherapy drug used as a treatment for different types of cancer, including pancreatic, lung, bladder and breast cancer – that are vital for the manufacture of various anti-cancer medicines.

Accordingly, ESMO welcomes the proposal for unlimited derogations to permit the continued use of PFAS as active substances in medicinal products. Nevertheless, with regard to the proposed time-limited derogations, we do not believe that the views of the manufacturers or healthcare professionals have been given sufficient consideration in their drafting as the implementation of the time-limited derogations could cause supply-chain disruptions and, ultimately, impact upon the timely provision of cancer medicines to patients.

To take just one example, due to the unique properties of fluorine, - used in medicines to treat brain tumors, lung cancer, hepatocellular carcinoma, prostate lesions, and bladder cancer -a direct replacement is not available. Whilst there are other electrons - withdrawing groups similar to -CF2- or -CF3 such as carboxylic esters, amides, nitro, or cyano; they differ in stability, permeability, and toxicity. Replacement of fluoroalkyl by other halo-alkyl groups such as chloro-alkyl will lead to reactive agents with serious toxicity issues. A restriction applying to the use of APIs containing perfluoro alkyl groups would consequently remove these molecules from the European market, with severe consequences for patients as relatively few therapeutic options exist. As such, rather than seeking to restrict the use of these APIS, we believe that it would be more effective to seek to improve the surveillance and control of such allegedly toxic compounds.

Even if PFAS APIs such as fluoxetine or sitagliptin coexist with nonfluorinated medicinal products in the same therapeutic class, it is incorrect to assume that these APIs are interchangeable. Due to their

pharmacology and side effect profiles, a medical professional will select between them based on the unique circumstances - e.g. health status, potential for interaction with other prescribed medications or individual response – of their patients. Limiting the options in a therapeutic class because some have fluorinated groups would have a profound impact on our members' ability to treat patients with safe and efficacious medicines.

The draft proposal includes two Restriction Options (RO). In RO1, the manufacture, import and placing on the market of these APIs or medicinal products containing them would no longer be possible under the European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), although this would be in clear conflict with existing and valid market authorisations under the sectorial medicinal products legislation. In RO2, APIs with EU approval would benefit from a time-unlimited derogation accompanied by reporting requirements, adding an obligation under REACH to the complex pharmaceutical regulatory framework.

ESMO would support the latter RO; however, under this scenario the manufacture, and their subsequent use in cancer medicines, of APIs in Europe could still be at risk because of the impact of the current proposed ban on the use of PFAS in manufacturing equipment, as well as the ban of PFAS in intermediary steps for the manufacturing of derogated APIs. Furthermore, substances falling under the PFAS definition might be used as solvents, catalysts, intermediates in the synthesis of not only APIs falling under the PFAS definition but also those which do not fall under the PFAS definition. While final APIs are included within the proposed time unlimited derogation, process chemicals and raw materials used in their manufacturing are currently not derogated and would ultimately be banned 18 months after entry into force, thereby rendering the API derogation as null and void. Accordingly, their manufacturing within the European Economic Area (EEA) would be impossible with API importation from outside the EEA being required instead, thereby further complicating the manufacture of cancer medicines and, ultimately, delaying their use by our members in the treatment of their patients.

The human and veterinary pharmaceutical sectors manufacture a variety of APIs that contain at least one aliphatic -CF2- or -CF3 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 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.

ESMO considers that the raw and starting materials, intermediates, auxiliaries, equipment, and consumables required for the 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, consequently making the use of such products by medical oncologists impossible.

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. A time-unlimited, notwithstanding any future research demonstrating the carcinogenic nature of such substances, derogation of PFAS chemicals is recommended to covering the following uses:

- EU approved APIs manufactured for the EEA market
- APIs manufactured for export without EU registration
- APIs under development, prior to registration (PPORD) including non-EU regulated products
- Non-active ingredients (excipients)
- Starting materials and chemical intermediates
- Process Chemicals (reagents, solvents, catalysts, auxiliaries in production and quality control)
- Industrial Manufacturing Equipment including spare and replacement parts
- Single or multi-use Consumables
- Immediate packaging materials
- Drug delivery devices
- Medical devices (as per EU Medical Devices Regulation 2017)

Without additional derogations, there is a serious risk that the pharmaceutical industry will no longer be able to manufacture any APIs (whether classified as PFAS or non-PFAS APIs) or associated medicinal products in the EEA and, consequently, may move such the production out of the EEA. As such, we fear that the universal PFAS restriction proposal could hinder the manufacture of medicinal products in the EU and dramatically reduce patients' access to medicines.

Noting ESMO's mission - *to improve the quality of prevention, diagnosis, treatment, supportive and palliative care… whilst promoting equal access to optimal cancer care for all cancer patients* – we believe that the aforementioned approach is necessary to secure an uninterrupted supply of innovative cancer medicines to our patients and help us deliver the goals of the Europe's Beating Cancer Plan (EBCP) by tackling the entire disease pathway, from prevention through to the treatment and care of cancer patients.

Given the rapid pace of emerging research in this area and the importance of ensuring that EU policy is genuinely evidence based, ESMO looks forward to playing a constructive role in ensuring that the correct balance is struck between advancing human health through environmental improvements and ensuring that anti-cancer drugs can be produced in the requisite manner to allow our members to treat their patients in a timely and efficacious manner.

1. European Cancer Information System (ECIS)

2 Cancer Tomorrow (iarc.fr)