INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

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Position Statement on the EU Restriction Proposal on PFAS from IQ Consortium

General Position Statement

This position statement was developed by the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium). The IQ Consortium is a not-for-profit organization composed of pharmaceutical and biotechnology companies that work together to advance science and technology to augment the capability of member companies to identify transformational solutions that benefit patients, regulators, and the broader R&D community.
While IQ appreciates ECHA's dedication to protecting both the environment and public health, it is IQ's position that the current proposal by ECHA to restrict per- and poly-fluorinated alkyl substances (PFAS) needs to be amended so that important and often lifesaving medicinal products may continue to be made available to patients in the EU and the rest of the world. Without these amendments, ECHA's proposed rule will create insurmountable challenges to the ability of pharmaceutical companies to meet the needs of patients in the EU and the rest of the world.

Context

In February 2023, the European Chemicals Agency (ECHA) published a REACH proposal[1] that aims to impose restrictions on a broad group of per and poly-fluorinated substances referred to as PFAS. These substances are often referred to as forever chemicals due to their persistence in the environment. In addition, certain PFAS may bioaccumulate in living tissue, potentially posing risks to human health. These characteristics have prompted several countries such as the US, to propose stringent thresholds for PFAS in drinking water[2]. Moreover, there is an escalating movement across the globe advocating for the disclosure of or limitations on PFAS-containing products, including pharmaceuticals. By ECHA's action noted above, the EU has proposed a broad-based restriction on the manufacture, use, and placing on the market of PFAS and PFAS-containing products and articles.

Potential Impact of the EU Restriction Proposal on the Pharmaceutical Industry

The current ECHA proposed regulation (RO2) [3] includes:

[1] Registry of restriction intentions until outcome - ECHA (europa.eu)

[2] Per- and Polyfluoroalkyl Substances (PFAS) | US EPA

[3] ECHA proposed two Regulatory Options (RO) - Option 2, which includes use-specific derogations and Option 1, which would impose a complete ban.

- Time-unlimited derogation on EU-approved active pharmaceutical ingredients (APIs); and
- Time-limited derogations of 13.5 years for certain medical devices and PCTFE-based packaging.

However, the proposed derogations fail to encompass regulatory starting materials, intermediates, and excipients as well as crucial applications of PFAS-containing articles or materials that are indispensable for pharmaceutical production, thus requiring their phase-out within 18 months after entry into force of the final regulation. If left unchanged, this omission would detrimentally affect all pharmaceutical manufacturing activities within the EU, potentially resulting in a grave and unintended outcome of limiting patient access to essential medicines. Examples of applications that are crucial to the healthcare sector and that are overlooked in the derogations include, but are not limited to:

- Starting materials and intermediates used in the API synthesis[4]
- Non-active ingredients (excipients and intermediates) used in the medicinal product manufacturing
- Process chemicals such as reagents, solvents, catalysts, processing aids, and auxiliaries in the production and quality control (e.g., TFA reagent) [5]
- Packaging materials including elastomers (e.g., PTFE/ETFE coated vial stoppers)
- Industrial manufacturing equipment including spare and replacement parts (e.g., PTFE/ETFE coatings on the stainless-steel piping, PVDF filter membranes)
- Single- or multi-use consumables (e.g., Teflon gaskets)
- Drug delivery devices
- Development of new APIs and medicinal products[5] (for instance hinder the discovery and development of future medicines that would benefit from the unique chemical and biological properties of fluorine in the API structure).

Detailed IQ Position

IQ appreciates ECHA for its dedicated efforts to protect both the environment and public health and its members are firmly committed to assessing and minimizing negative impacts from their operations on the environment and human health. To achieve this, companies have conducted a thorough impact assessment, exploring alternatives, and developing proactive strategies to reduce PFAS use and release.

While companies are taking proactive steps to adapt, many PFAS applications in the pharmaceutical industry were found to be irreplaceable and integral to medicinal product production or too complex to be phased out within the proposed timelines. IQ is especially concerned about the missing uses noted above and the significant impact the proposed rule could have on patient access to medicinal products, as well as on the ability to continue operating in the EU and the associated impact on the local economies in which companies operate. Therefore, IQ recommends that the regulation be revised to provide:

[4] Noted in the ECHA's Webinar Q&A Part 2 3f47fdcc-17c5-4b37-b758-720bb7e462f3 (europa.eu) that all preceding steps necessary to produce the APIs are covered by the same proposed derogation but should be further clarified by ECHA

[5] Noted in the ECHA's Webinar Q&A Part 2 3f47fdcc-17c5-4b37-b758-720bb7e462f3 (europa.eu) that clinical testing would be restricted but the generic R&D exemption under 1 ton/year continues to apply. Further clarification by ECHA is needed.

- **Exemption[6] for the materials technically not feasible to replace by non-PFAS materials** such as API, starting materials, intermediates, excipients, reagents, certain devices, certain packaging materials, and manufacturing equipment used in the API and medicinal product manufacturing. IQ supports ECHA's response in its Webinar Q&A Part 2[7] that all preceding steps required in the API manufacture would be covered by the same API derogation and request that these irreplaceable materials are considered for full exemption. As a highly regulated industry, and as noted below, EMA oversight should be adequate to govern the industry's use of PFAS and PFAS-containing materials.
- **Time-limited derogation with an extended transition period** for those materials that might have feasible candidates for replacement with non-PFAS materials but either not yet available or more time needed, such as certain packaging materials and plant equipment. This would allow sufficient time to identify and make commercially available feasible alternatives and for manufacturing facilities to transition to alternative technologies in a controlled and regulated fashion.

It is essential to note that the production of APIs, medicinal products, and medical devices is strictly regulated under the European Medical Agency (EMA), encompassing rigorous validation procedures and regulatory approvals – a process that often spans over two decades. Requiring the substitution of all PFAS-containing components within eighteen months would be not feasible on the industry and regulatory authorities, going through a time-consuming and costly re-registration, re-qualification and re-validation processes, as well as a complete overhaul of production equipment and manufacturing lines. Simultaneous change to multiple aspects of pharmaceutical production (chemistry, analytical methodology, devices, packaging and equipment) might lead to unanticipated impacts raising the risk of medicines shortage significantly; the multifactorial impact needs to be considered when evaluating the derogation periods.

In summary, IQ supports a measured and thoughtful approach to the regulation of the environment, and human health and safety that relies on good science. Failure to include appropriate exemptions and derogations in this case could significantly challenge the industry's ability to manufacture and supply life-saving and important medicinal products, resulting in the long-term unavailability of these products in Europe and beyond. In IQ's view, the imposed restriction should not negatively impact patients' health, and the desired outcomes can be achieved by providing appropriate exemptions and derogations to all aspects of end-to-end pharmaceutical manufacturing materials and processes from the scope of the regulation. This can be achieved through a considered balance that takes into account the impacts on patients and environment as well as on the industry's ability to operate in an effective and efficient manner.

[6] Note the difference between exemption and time-unlimited derogation. Exemption means fully exempt from the required duties while the latter is partially exempt – exempt from the ban but reporting duty remains.

[7] 3f47fdcc-17c5-4b37-b758-720bb7e462f3 (europa.eu)