LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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

About the Swedish Medical Products Agency

The Swedish Medical Products Agency (Swedish MPA) is the national authority responsible for regulation and surveillance of the development, manufacturing and sale of pharmaceuticals and other medicinal products. The Agency's task is to ensure that both the individual patient and healthcare professionals have access to safe and effective medicinal products and that these are used in a rational and cost-effective manner.

Summary

Swedish MPA is generally in favour of a restriction of PFAS and considers that a regulation with the objective to minimize emissions of PFAS is needed to reduce negative effects of this group of substances on people's health and the environment.

However, the proposal raises some major questions regarding its application to the medicinal products and medical devices sectors which could affect the availability of these products with serious consequences on public and animal health. Swedish MPA therefore wishes to express the following concerns.

Sweden, like other European countries, has a challenging situation with medicinal shortages. Work is carried out both to prevent shortages and to mitigate the consequences of shortages. This is done together with other stakeholders in Sweden. The Pharmaceutical trade associations has raised concerns about the proposal affecting the entire pharmaceutical industry. Swedish MPA considers that their concerns should be taken seriously and sees an increased risk that the consequences of this proposal may further affect access to medicines.

In addition, the member states of the EU are actively working to increase the production of pharmaceuticals in Europe. This wide restriction of PFAS could increase the incentive to move production outside the EU and make the ongoing transition more difficult.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, Sweden
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0) 18 17 46 00 Fax: +46 (0) 18 54 85 66
Internet: http://www.lakemedelsverket.se, E-mail: mailto:[redacted]@lakemedelsverket.se

Discussion

Regarding the justification of a broad restriction of PFAS

Swedish MPA acknowledges the benefits of a general restriction of PFAS as a group *and not as individual substances* (most notably effectively reducing exposure and the risk for regrettable substitution). It is clear that many PFAS and their arrowhead end products are persistent and some PFAS chemicals (e.g. PFOS and PFOAs) are also considered to pose a risks to humans and/or and the environment. This underscores the urgency to minimize exposure to these substances. However, the class as defined by OECD consists of substances with very different physico-chemical properties which most likely differ in their potential for bioaccumulation, toxicity and potency. With exposure, bioaccumulation and toxicity data largely missing for many PFAS chemicals it is not considered justified to extrapolate hazards associated with certain PFAS to the whole class based only on the commonality of persistence. Considering the impact of the proposal, a general ban is not supported. Instead, a risk-based approach where substances considered vital to society are prioritized for risk assessment and management would be preferable. Here, the concept presented by the Royal society of chemistry is noted and worth considering.

Medicinal Products

Even though the active pharmaceutical substances (APIs) in human and veterinary medicinal products, including the manufacturing of said APIs, are derogated in the proposed restriction there are several aspects that need to be addressed to enable continuous access to medicinal products on the European market as well as continued research, development and production of active substances and medical products within Europe.

Human and veterinary products are strictly regulated by sector-specific legislations and expert bodies/authorities as detailed in Article 8(3) of Directive 2001/83/EC and Regulation (EU) 2019/6) respectively. This includes extensive evaluations of the quality, safety, and benefit both pre- and post-approval. In addition, the environmental impact of medicinal products is assessed at the time of marketing authorization in the EU. Of note, the environmental risk assessment is also expected to be further strengthen through the ongoing revision of the legislation for human medicines.

PFAS use in medicinal products and impact of the restriction proposal

Active pharmaceutical ingredients (APIs)
There are several APIs in approved human and veterinary products that contains aliphatic $-CF_3$ or $-CH_2-$ groups that will fall under the proposed restriction of PFAS. The use of fluorine in active substances is primarily due to its size, approximately the size of a hydrogen atom, the stability of the C-F bond and the high electronegativity. Due to these properties, an introduction of a fluorine instead of a hydrogen in a molecule will not significantly affect the size or the three-dimensional structure of the active substance but may change properties such as potency, lipophilicity, permeability, and clearance, properties that are important for the efficacy, safety, and stability of the active substance. Alternative structures, if the C-F containing groups are exchanged or removed, may not share the activity and/or safety of the

original compound. Hence, the derogation for active substances in human and veterinary medicinal products within the scope of Regulation (EC) No 726/2004, Regulation (EU) 2019/6 and Directive 2001/83/EC is regarded as necessary to enable access to medical products on the European market and supported.

Research and development of APIs
Before a substance is approved and defined as an API there are many years of research and development. New active substances, intermediates, starting materials, reagents, catalysts, auxiliaries, and solvents defined as PFAS are used during research and development. The equipment used in chemical synthesis need to be inert and often possess chemical and thermal resistance due to the harsh conditions and reactive chemicals used and often contain PFAS. The proposed derogation of APIs, including the manufacturing, do not include research and development. This might lead to a relocation of the research and development to countries outside of Europe and could affect availability of new medicines in the EU/world-wide.

Intermediates and starting materials
Substances used as intermediates or starting materials defined as PFAS are often used in the manufacturing of APIs and a replacement of these starting material or intermediates is not possible. The synthesis of the corresponding active substances, the production and supply chains of such APIs will have to be relocated outside of Europe if intermediates and starting materials defined as PFAS are not derogated. This is concerning as the lack of API production in the EU will increase the risk for supply problems and medicine shortages in the EU which seriously could affect public and animal health. This would also be counterproductive to ongoing work by EU member states to increase production of pharmaceuticals in Europe. In addition, relocation of production to countries with less restrictive legislations would lead to increased PFAS emissions in other parts of the world which is negative from a global perspective. Hence, a derogation of the manufacturing of APIs is supported. Lifting restrictions on small PFAS groups such as the -CF_3 may also be considered.

Reagents, catalysts, auxiliaries, and solvents
Reagents, catalysts, auxiliaries, and solvents that falls under the PFAS definition proposed in the restriction are needed throughout the development and production of a medicinal product, e.g., during research and development, manufacturing, and quality control. Reagents defined as PFAS are used as activating agents, solvents, ligands, and catalysts in synthesis and e.g., trifluoroacetic acid is used in many analytical procedures such as HPLC and prescribed in many test methods in the European Pharmacopoeia (see comments raised regarding the use of PFAS in the European Pharmacopoeia below).

Since intermediates and starting materials, reagents, catalysts, auxiliaries, and solvents defined as PFAS might be used in all synthetic steps of the API residues might be present in low amounts in the API. Alternatives for replacements in all these steps will not be available, evaluated and regulatory approved within the proposed time-frame of 18 months. As stated above the proposal will likely lead to relocation of research, development and production outside of Europe with consequences for availability of medicines in Europe. Furthermore, the proposed low concentration limits will require development of advanced analytical

methods to verify that any PFAS impurities from intermediates, reagents, catalysts auxiliaries, solvents, or cross contamination does not exceed these limits. These analytical methods need to be validated and approved.

Equipment for manufacturing and quality control
During the production of medicinal products, APIs, intermediates, and starting materials the manufacturing equipment need to be inert and often possess chemical and thermal resistance due to the harsh conditions and reactive chemicals used in many production steps. Hence, PFAS are often used in e.g. chemical reactors, gaskets, pipes, membranes and pumps. A restriction of equipment containing PFAS will affect the production and quality control of medicinal products, APIs, intermediates, and starting materials. To identify suitable (and safe) alternatives, if available, and to qualify and validate the new manufacturing processes as required by the sectorial legislations is a complex and time-consuming procedure. As above, it is foreseen that if derogation of equipment for manufacturing and analysis of medicinal products is not included in the proposal this might lead to a relocation of the production to countries outside of Europe and could affect availability of medicines in the EU/world-wide.

Excipients
Excipients are pharmaceutical substances other than the active pharmaceutical ingredients used in medicinal product.

Propellants used in metered dose inhalers (MDI) are excipients that may fall under the proposed regulation. Even though there are alternative propellants available today, several approved medicinal products contain propellants defined as PFAS. A replacement of the propellant constitutes a major change to the finished product formulation with a potential impact also on the construction of the inhaler. A replacement requires a new regulatory approval of the medicinal product and there are several studies that need to be performed, including long term stability studies and new safety and stability studies (nonclinical and clinical) to confirm that the safety and efficacy of the product is not altered. Hence, a restriction of the use of propellants defined as PFAS might affect the access to medicinal products on the European market. Note that propellant gases in MDI are listed as PFAS in medical devices in the restriction report and the appendices. This is not entirely correct, as MDIs are placed on the market as medicinal products (integral drug-device combinations). Hence, restrictions on propellant gases will mainly affect manufacturers of medicinal products and need to be handled within the regulatory framework on medicinal products.

Primary packaging for medical products
PFAS is used in the primary packaging in many medical products e.g., in blisters containing PCTFE (polychlorotrifluoroethylene) and as coating of rubber stoppers used for infusion flasks and vials.

The packaging of a medicinal product is vital for functionality and safety and a medicinal product is approved with its primary packaging to assure that the quality is maintained during the approved shelf life. It is also verified that any impurities from the packaging material is toxicologically qualified or below set limits. Changes in primary packaging requires new investigations (e.g. long-term stability studies and risk assessments if impurities (leachables)

are idenfied) to support regulatory approval. To take into account the time needed for finding suitable alternatives, performing necessary evaluations and the regulatory processes of the new packaging material, a 12-year derogation is proposed, unless the risk can be mitigated by waste management, to avoid supply issues. Importantly, derogations should not be limited to PCTFE-based packaging but including all relevant polyfluorinated polymers used.

Medical devices for drug delivery:
Some medicinal products are developed and approved for use co-packed with specific drug delivery devices (e.g. pre-filled injection pens and metered dose inhalers). Many of these drug delivery devices contains PFAS as essential parts, for example seals, silicones, lubricants, filters etc that provide durability, preserve quality of the medicinal product and minimize dosing variability. Making changes or developing a new device will have to take into account both medical device regulations as well as pharmaceutical legislations and requires regulatory approval, a process which takes at least 12 years provided suitable alternatives are identified.

To conclude

In the proposal for a restriction of PFAS, active pharmaceutical ingredients (APIs), including the manufacturing of APIs, in human and veterinarian medicinal products are exempt from the ban. This is fully supported, but not considered sufficient to ensure that development and availability of medicinal products in EU is not affected. Importantly, PFAS substances are also critical in the research and development of new APIs and the packaging of most pharmaceuticals. Finding suitable alternatives (if feasible) and to replace PFAS not covered by the derogation will be challenging. In addition, PFAS may also be present in trace amounts as an impurity in the active substance/final product. The very low limits proposed for PFAS will lead to a requirement for development, validation and regulatory approval of sensitive analytical method for many medicinal products. It is also reasonable to assume that restrictions enforced by the EU/Ph. Eur., if not shared by other major pharmacopoeias such as the USP and JP, may lead to additional risks for the availability of medicines in Europe.

Given the scale of use these tasks will require major efforts, time and resources. This will increase costs for the industries and the society, but more concerning increase the risk for medicine shortages and delayed access to new treatments.

Swedish MPA proposes

- The derogation for active substances in human and veterinary medicinal products within the scope of Regulation (EC) No 726/2004, Regulation (EU) 2019/6 and Directive 2001/83/EC is regarded as necessary to enable access to medicinal products on the European market and supported. However, to enable continuous research, development and production of medicinal products, APIs, intermediates and starting materials within EU all steps of the production of medicinal products need to also to be derogated for unlimited time including the use of intermediates, starting materials, reagents, catalysts, auxiliaries, solvents and equipment defined as PFAS in

the proposed regulation. The derogation is proposed to be combined with incentives to stimulate the development of PFAS-free alternatives.

- A derogation for research and development of active pharmaceutical substances is proposed.
- For propellants in Metered Dose Inhalers (MDIs) and medical devices for drug delivery a 12-year or longer derogation from the proposed regulation is proposed.
- For primary packaging and drug delivery devices co-packed with the medicinal product derogation based on a risk-based approach is proposed which could take into account hazard and level of exposure. If risk cannot be managed by waste management a 12-year derogation is proposed.

Finally, Swedish MPA considers it important to combine the proposal for restriction of PFAS with incentives and appropriate funding to stimulate the development of PFAS alternatives in all sectors, including the pharmaceutical area.

European Pharmacopoeia

Background and legal framework

The European Pharmacopoeia is a single reference work for the quality control of medicines in the signatory states of the Convention on its elaboration.

The official standards published within provide a legal and scientific basis for quality control during the development, production and marketing processes.

All producers of medicines and/or substances for pharmaceutical use must therefore apply these quality standards in order to market their products in the signatory states of the Convention.

Several legal texts make the European Pharmacopoeia mandatory. These are as follows:

- The Convention developed by the Council of Europe on the Elaboration of a European Pharmacopoeia and a Protocol adopted in 1994 and amending the Convention to prepare for the accession of the European Union,
- European Union Directive 2001/83/EC as amended, on medicines for human use and Regulation (EU) 2019/6 on veterinary medicinal products.

Comments

The use of different PFAS as reagents is prescribed in many test methods in the European Pharmacopoeia. To develop new methods and ensure they are suitable for publication as standards in the European Pharmacopoeia is time consuming and follows set procedures.

PFAS materials are also part of analytical equipment which are regulated by the European pharmacopoeia.

To conclude

The replacement of PFAS prescribed in the European Pharmacopoeia in test methods and analytical equipment cannot be accomplished within18 months.

Swedish MPA proposes

- That the European Pharmacopoeia is given a 12-year derogation, the same as proposed for diagnostic laboratory testing and that the derogation could be extended if necessary after 12 years alternatively an exemption from the restriction of use is given.

Analytical methods for Quality control of API and drug products

A restriction of PFAS would have a huge impact on the laboratory quality control/surveillance of medicinal products as reagents prescribed in the analytical methods e.g., trifluoroacetic acid (TFA), and analytical equipment contain chemicals and/or materials defined as PFAS. Analytical methods for quality control are approved by regulatory authorities, public standards and mandatory (see comments raised regarding the use of PFAS in the European Pharmacopoeia above).

Replacement of PFAS in analytical methods and equipment requires development of suitable and safe alternatives. This is time consuming, and both the pharmaceutical industry and manufacturers of analytical instrumentation need enough time to find environmentally friendly alternatives.

To conclude

The replacement of PFAS in analytical methods and equipment cannot be accomplished within18 months.

Swedish MPA proposes

- A 12-year derogation, the same as proposed for diagnostic laboratory testing, is seen as necessary to replace PFAS in analytical test methods and equipment. It is also foreseen there may be a need to expand the derogation after 12 years or to be granted an exemption from the restriction of use.

Medical Devices

Medical devices (MDs) and In vitro-diagnostic medical devices (IVDs) are in a regulatory transitional period that will continue for several years to come. Two EU regulations, 2017/745 (MDR) and 2017/746 (IVDR), are replacing a legislation based on directives 90/385/EEC (AIMDD), 93/42/EEC (MDD) and 98/79/EC (IVDD). This transition has already faced major challenges in the implementation of MDR and IVDR and the transition period has been extended until the end of 2027 and 2028 respectively. There are still concerns that even the extended transitional provisions will not be sufficient for all concerned parties (mainly manufacturers and notified bodies but also competent authorities and the EU Commission) to get all aspects in place. Therefore, an increased burden of replacing vital substances and materials in the devices will contribute negatively to an already strained situation. Therefore,

Swedish MPA is concerned that the proposed transitional period in the proposal on restrictions on PFAS will not be long enough and will introduce a risk of shortages of MDs and IVDs vital to the healthcare providers.

In many applications, there is no clear “drop-in replacement” for materials and substances that will be encompassed by the restrictions of PFAS. While some possible replacements are identified and listed in Appendix E2, there will still be lengthy processes of research and development to find alternative materials and substances to develop prototypes that can go on to further evaluation.

When viable prototypes have been developed, the process to ensure that they meet all the requirements on safety and performance (e.g., biocompatibility, durability) for the MDs and IVDs will also be a lengthy process. Manufacturers shall generate a large body of data with different characteristics to be able to develop the necessary technical documentation (technical file) for the updated devices that subsequently shall be assessed by the notified bodies. The required data include technical data, physico-chemical data, pre-clinical data, and clinical data that support the maintained (or improved) safety and performance of the updated devices. All things considered; this will be a process that will take several years to complete. Therefore, even without the added complexity of the transition to MDR and IVDR the proposed timeframe for the restrictions on PFAS is not generous enough.

Swedish MPA is of the opinion that the restrictions on PFAS need to take the usage scenarios into consideration. For example, a small coronary stent covered in PTFE does in itself only contain a small amount of PTFE. Such stents are only used when absolutely vital and imperative, and in a very controlled hospital environment. It is not reasonable to treat such devices in the same manner as other products, and even MDs and IVDs, that contain far larger amounts of PFAS (say, PTFE) used directly by consumers in an uncontrolled manner. Consumer products, including MDs and IVDs, are generally sold and used in larger volumes than MDs and IVDs for specialised health care. Therefore, Swedish MPA advocates restrictions with a larger consideration of the usage scenario to enable vital MDs and IVDs to remain on the market until viable alternatives have been developed. Furthermore, the disposal of PFAS-containing devices used in the controlled environment of hospital and other healthcare facilities could be regulated and controlled to prohibit the dispersal and distribution of PFAS into the environment.

Swedish MPA is of the opinion that the restrictions on PFAS need to take the physico-chemical properties of molecules and materials into consideration. The potential dispersal and distribution of small molecular species and/or particles (e.g., gases and aerosols) are markedly different from large polymers and “bulk materials”. While Swedish MPA acknowledges that any molecule that contains a fully fluorinated methyl or methylene group is of environmental concern, the Agency does advocate that the inherent potential for dispersal and distribution of different species need to be considered.

Similar to medicinal products, restricting the use of PFAS may also affect the manufacturing, testing, verification, and calibration of MDs and IVDs within EU/EEA, as PFAS may be required during these processes. The inability to perform these processes will cause shortages of such MDs and IVDs in health care. These processes are also generally

performed in an environment where the risk of dispersal and the disposal of PFAS may be controlled to a large extent. Therefore, the use of PFAS in manufacturing, testing, verification, and calibration of MDs and IVDs requires additional consideration.

To conclude

There are several challenges facing the manufacturers that may result in a shortage of MDs and IVDs crucial to the functioning of European health care if the proposal on restrictions of PFAS is implemented in the near future. Even in the best of circumstances, it is a very lengthy process to implement significant changes in MDs and IVDs. In this particular case, there are additional main challenges with the ongoing regulatory transition to the EU regulations (MDR and IVDR) and the lack of clearly identified substitutions for PFAS that risk to substantially prolong the processes. Furthermore, Swedish MPA does not think it is proportionate with broad, almost all-encompassing, restrictions where MDs and IVDs are treated as any other product category despite their importance to the health care.

Swedish MPA proposes

- That the transitional provisions for the restrictions on PFAS in MDs and IVDs are carefully reconsidered to prevent shortages of MDs and IVDs. The Agency does believe that a longer transitional period than the proposed is needed. In some corner cases, it may not be feasible to substitute PFAS entirely.
- That it may be considered to introduce restrictions and/or guidelines to enable controlled disposal and waste management of MDs and IVDs to mitigate the risk of dispersal of PFAS into the environment. The Agency does believe that this is a feasible route as many MDs and IVDs are used and handled in limited volumes within a controlled health care environment.

Cosmetics

Swedish MPA would like to take the opportunity to emphasize that some PFAS are today used in sunscreen products. This is because of their specific properties e.g., making the product more waterproofed. Sunscreens are very important for the public health since they are used as a complement in the protection from UV-radiation and subsequently important for skin cancer prevention. A possible PFAS restriction should allow for a realistic and an adequate transitional period for reformulation.

Swedish MPA proposes

- That the transitional provisions for the restrictions on PFAS in cosmetic sunscreens are in line with what the industry considers as realistic.

This opinion has been decided by Director General Björn Eriksson after presentation by Investigator Katharina Högdin.