Subject: Possible Restriction of PFAS – impact on critical medicines supply

Sep 3rd, 2024

Dear Sir and Madam,

Today, we are approaching you on behalf of Medicines for Europe, the European organisation representing the off-patent pharmaceutical industry.

On 13 January 2023, the competent authorities from Germany, the Netherlands, Denmark, Sweden and Norway submitted a restriction dossier[1] for PFAS (per- and polyfluoroalkyl substances)[2] falling in the scope of the OECD definition[3], under the REACH Regulation (Regulation (EC) No 1907/2006[4]). The proposed restriction is intended to ban the manufacturing, placing on the market, and use of at least 10,000 known PFAS as such or in mixtures and articles above certain concentration limits.

Acknowledging the concerns about PFAS, the generic pharmaceutical industry is working to reduce the use of PFAS in the manufacturing, packaging, and delivery processes of medicines and in processes that may release PFAS into the environment. The ban of more than 10,000 PFAS substances would, however, irreversibly affect the healthcare industry and undermine manufacturing in Europe. This could lead to supply shortages, and a discontinuation of life-saving technologies, medicines and services across the EU where viable alternatives have not yet been developed or approved from a regulatory perspective.

Therefore, any decision to restrict the use of PFAS in medicinal products should only be made after a careful analysis of whether, how, and in what time periods, PFAS can be replaced in these products without putting their availability and thereby patient safety at risk. It should also be assessed whether the specific use has the potential to release a significant amount of PFAS into the environment.

In view of the large number and variety of pharmaceuticals concerned and the complexity of their manufacturing and regulatory approval processes, such a thorough analysis requires sufficient time.

As the industry is collaborating with authorities to identify and implement the most effective solutions, finding proper alternatives to PFAS is a complex journey requiring extensive research and thorough studies, over several years. Therefore, and to ensure the continued manufacturing of life-saving medicines, there must be a general derogation period from the proposed PFAS restriction for the manufacturing of pharmaceutical products, long enough to switch to adequate alternatives regarding patient safety. **Our**

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[1] Annex XV Proposal submitted by Germany, the Netherlands, Denmark, Sweden and Norway

[2] Per- and polyfluoroalkyl substances (PFAS) are a large group of manufactured substances that do not occur naturally in the environment and are extremely resistant to degradation

[3] OECD, Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance, 9 July 2021

[4] Regulation (EC) No 1907/2006 of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

appeal considers the balance between healthcare needs and environmental concerns.

For a further outline we have compiled two examples regarding pharmaceuticals which underline our concerns:

1) According to a Dutch case study[5], **a potential ban on PFAS could affect** medicinal products that constitute **64% of all medicines used in the Netherlands**. These include some of the most important drugs currently in use. It would also jeopardize the production of all pharmaceutical substances in Europe and would be in conflict with the EU's strategy of reducing dependency on nations outside of the EU in the event of shortages or pandemics.

2) In addition, there is a case study on a sterile cancer medicine, used in hospitals for slowing or stopping the growth of a cancer, which needs to be administrated by injection or infusion. It is therefore accompanied by a primary packaging, consisting of a pharmaceutical-grade glass vial and a fluoropolymer-coated rubber stopper, similar to polytetrafluorethylene (PTFE-like). The stopper protects the medicine and ensures its compatibility and stability. The tested alternatives, e.g. simple non-coated stoppers, do not provide the same functions as the coated rubber stopper, and suffer from higher extractability and leachability of the compounds, leading to negative consequences on the quality of the products and patient safety. Because of the importance of the primary packaging, several years would be required to find the most suitable alternative (including testing, product stability studies, compatibility studies, extractable and leachable studies), before asking the EMA or the national competent authorities to approve the variations brought to the marketing authorisation.

For more detailed information, please find enclosed our position paper on the restriction proposal. We also submitted our position to the Public Consultation led by the European Chemicals Agency (ECHA) on the restriction proposal last year.

Yours sincerely,

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[5] Joint study by AESGP, EFCG, EFPIA, Medicines for Europe and Vaccines Europe, Human Health Medicinal Products Sector Survey - Impact of Proposed PFAS Restriction on Patient Access to Medicines & EU Strategic Autonomy

Case study 1 – medical device – metered dose inhaler

Describing the medicine and the indication

The selected medicine is a respiratory product that contains an active ingredient that causes relaxation of airway smooth muscle. It is used for symptomatic treatment of asthma, including short-term relief in case of asthma attacks, and for prevention of exercise or allergen-induced bronchospasm both in children and adults. The active ingredient is delivered using a pressurized metered-dose inhaler (MDI). (1)

MDIs are pocket-size hand-held drug delivery devices utilizing the energy of compressed propellant(s) for aerosol generation. They have the drug in solution or suspension in the propellant(s), or a mixture of propellant(s) and co-solvent(s). MDIs deliver small metered drug doses either directly, or via add-on devices to the patients. (2)

Where per- and polyfluoroalkyl substances (PFAS) are used and why they are needed

Propellants, or propellent mixtures, represent the bulk of the MDIs' formulation. It provides the force to create the aerosol cloud that delivers the medication to the lungs and acts as the medium in which the active ingredient is suspended or dissolved. Furthermore, inactive ingredients known as excipients may be included in the formulation to enhance overall product efficacy. These excipients include volatile and non-volatile co-solvents that dissolve the drug, surfactants that stabilize suspensions, bulking agents that increase the product's volume, and lubricants that ensure the smooth operation of the valve. (2)

Any medical propellant must be non-toxic. This is to be demonstrated by non-clinical safety assessments that include acute toxicity, repeat dose toxicity, genetic toxicity, carcinogenicity, safety pharmacology (such as cardiovascular functional assessments), and reproductive and developmental toxicity. For the device, biocompatibility testing is required. Furthermore, the formulation of the inhaler (which includes the active ingredient, propellant and other co-formulants) has to ensure uniformity of the delivered dose, suitable aerodynamic particle size distribution and plume characterization; extractable and leachable testing has to be also conducted. (3)

Following the international agreement in 1987 (Montreal Protocol on Substances that Deplete the Ozone Layer), the pharmaceutical industry has formed two consortia to find a suitable replacement for the "first generation" propellants belonging to the group of chlorofluorocarbon (CFC) compounds. Two candidates -- HFC-134a and HFC-227ea – were tested and approved for use in MDIs in 1994 and 1995. (2) Both of these, representing the "second generation" of medical propellants, are currently used in the majority of MDIs. It is important to note that both of them are PFAS, therefore in the scope of the ongoing review of the restriction proposal under REACH Regulation (Registration, Evaluation, Authorisation and Restriction of Chemicals). (4). At the same time, these two propellants are already subject to policies and regulations (the 2023 revision of the F-gases Regulation EU No 517/2014 and the Kigali Amendment to the Montreal Protocol) aimed at phasing them out over the next several years in light of their carbon footprint and impacts on the climate.

Lastly, the drug-delivery device itself may also contain fluoropolymers. The drug formulation is contained under pressure in an aluminium container with or without an inner coating. The coating may serve as a protective barrier, preventing the drug from breaking down due to contact with the canister wall, reducing drug sticking or particle accumulation on the canister walls, and ensuring the canister material's resilience against corrosion in acidic formulations. These unwanted occurrences ultimately lead to diminished

stability and/or inconsistent dose delivery. Fluoropolymers, such as polytetrafluoroethylene (PTFE; brand name Teflon) or polyfluoroalkoxyalkylene (PFA) are used for this coating. (2)

What are the options for alternatives and the timelines and requirements for implementing them

In light of the abovementioned policies aiming to reduce the emissions of, among others, the current propellants (HFC-134a and HFC-227ea) the pharmaceutical industry is searching for suitable alternatives. The two potential "third generation" propellants (HFO-1234ze – PFAS - and HFC-152a – non-PFAS) are currently being tested and are not available for patient use. As described above, MDIs are complex devices and the new medical propellants must meet a specific range of technical performance characteristics as well as favourable non-clinical safety characteristics a new propellant cannot simply be "dropped in". Furthermore, the global regulatory health authorities are still in the process of determining the specific clinical study requirements for switching from the "second generation" to "third generation" propellants in MDIs. Notably, the European Medicines Agency (EMA) has released its draft guidance on the expectations it has for companies transitioning to new propellants. Overall, the generation of a robust evidence package and the subsequent regulatory approval of MDI using alternative propellants may take between 6 and 10 years. (3)

It must be noted, that dry powder inhalers (DPI) represent an already existing technical alternative to MDIs. DPIs, as the name suggests, contain a powdered formulation of the medicine that is drawn in by the force of the patient's breath and does not require propellent to function. Therefore, they do not share the same impact on the climate. DPIs have their own set of advantages, including their breath-actuated mechanism, demanding less coordination from the user compared to MDIs. However, this advantage also represents a limitation as DPIs require sufficient inspiratory flow to de-aggregate the powder, which cannot be always achieved by asthmatic patients, particularly younger children and frail older people. (5) It is crucial to asthma care to select the right inhaler for the individual patient. When choosing the most appropriate inhaler, the preferred medication, available devices, patient skills, environmental impact and cost should be taken into consideration. (6)

Disposal of the PFAS chemicals and materials

As the PFAS material is part of the primary packaging of the medicine, it is the patient's responsibility to dispose of it safely. Many EU Member States have medicines disposal programs, where patients can return unused medicines and their packaging via community pharmacies. Patient education about this is also supported by the MedsDisposal Campaign (7), which was developed as a collaborative project between healthcare professionals and the pharmaceutical industry. In the case of MDIs, the take-back programs are going even further and community pharmacists are instructing the patients to return the empty MDIs to the pharmacy. In all cases, the waste collected through these schemes is disposed of and incinerated by firms specializing in handling dangerous waste.

Conclusion and impact

As described, MDIs are highly complex medical devices and changes to any of its parts are not a trivial matter. It is important to consider that the comprehensive research and development activities outlined above will require the assessment of a diverse range of individual pMDIs, encompassing different dosages and strengths. The IPAC/IPAC-RS survey demonstrates that multiple companies manufacture numerous pMDIs in the European Union (at least 349 million units, and as many as 250 unique pMDI types). This reformulation effort will involve significant financial commitments, reaching billions of euros. (3)

Furthermore, switching patients to new medicines (such as DPI) must be handled carefully and driven by clinical factors. For a patient with stable asthma or COPD, introducing a new device may lead to potential destabilization of the disease, which can cause patient harm and unnecessary emergency room visits. At the same time, switching inhaler may not be an option for many patients. For example, DPIs are not appropriate for younger children, and the need for a particular medication may restrict device choice. Of course, considering the environmental impact when selecting an inhaler at treatment initiation or when stepping up or down treatment is reasonable as long as the patient's needs, preferences, ability to use the inhaler and response to treatment are considered. (8)

Given the ongoing efforts to phase down the currently used propellants ("second generation"; HFC-134a and HFC-227ea) and substitute them with the new generation of propellants ("third generation"; HFO-1234ze and HFC-152a), it is important to ensure that this transition will be done rationally. The "second generation" propellants need to be given a sufficiently long transition period to prevent any immediate negative impact on the patients and the security of supply, such as shortages of both MDIs (due to the supply disruption of the propellant) and DPIs (due to increased demand as a consequence of MDIs shortage). The "third generation" is an important solution to deliver lower climate burden respiratory care in future. As such, the propellant in the scope of the PFAS restriction proposal (HFO-1234ze) should be permanently derogated, as it is important to preserve the choice from multiple suitable propellants.

It must be noted that this case study is mainly focused on the use of fluorinated gases as propellants in inhalers. The selected medicine, as well as DPIs, would be also impacted by the PFAS restriction, due to the use of PFAS materials in the manufacturing process itself, such as in tubing, collecting vessels, some filters as well as machinery. More details about this issue can be found in *Case Study 2 – manufacturing of biologic medicines* and *Case Study 5 – manufacturing of final dosage forms.* It can be expected that without a sufficient derogation of medicines manufacturing from the PFAS restriction, the medicines supply chain will become even more vulnerable, leading to a decrease in medicines availability to the patients and a higher occurrence of medicine shortages.

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Case study 2 – manufacturing of biologic medicines

Describing the medicine and the indication

The medicine selected for this case study is biological medicine. It works in the same way as the natural hormone by stimulating the bone marrow to produce red blood cells. It is used for the treatment of anaemia (low red blood cell count) in patients with chronic renal failure or cancer patients.

The medicine is a sterile liquid, administered to the patient either subcutaneously or intravenously. (1) The primary packaging consists of a pre-filled syringe.

Where per- and polyfluoroalkyl substances (PFAS) are used and why is it needed

Biologic medicines are typically administered to patients parenterally. The manufacturing requires low bioburden (low number of microorganisms on a surface or within a liquid) and sterile manufacturing techniques specific requirements for such medicines following the EU Guidelines for Good Manufacturing Practice (GMP) for Human and Veterinary Use Annex 1. (2) Furthermore, the manufacture of biological medicinal products requires tailored considerations arising from the nature of the products and the processes employed. The distinct steps of production, quality control, and administration demand particular precautionary measures as described in Annex 2 of the above-mentioned guidelines. (3)

To achieve the required level of equipment cleanliness, potent acids, bases, elevated temperatures, and pressures are crucial for “clean-in-place” and “steam-in-place” procedures of the production vessels as well as in the production of “water for injections” (water of extra high quality without significant contamination). To safeguard the integrity of facilities that distribute critical utilities to the main production site, rigorous monitoring and maintenance are essential. Polytetrafluoroethylene (PTFE; brand name Teflon) is widely employed in seals, gaskets, hoses, and diaphragm valves due to its resistance to corrosion and favourable mechanical properties, ensuring a safe working environment. (4)

PTFE and other fluoropolymers are also used in single-use systems like bags and connectors, which are essential for enabling “next-generation” continuous bioprocessing. This method significantly reduces the manufacturing environmental footprint, minimizing energy and freshwater utilization. (4)

To guarantee the sterility and safety of the finished product, various liquids used in the manufacturing process undergo filtration at multiple points. These filters often include polyvinylidene fluoride (PVDF), another fluoropolymer. Biologics are susceptible to product quality issues like adsorption, aggregation, and degradation when non-fluoropolymer-containing filters are used, elevating the risk of leachables that endanger patient safety. (4)

Finally, perfluoroalkoxyalken (PFA) is employed for production flasks. This material was chosen due to its extensive range of beneficial properties, including compatibility with a wide temperature range, compatibility with various cleaning and sterilization processes (autoclaving, depyrogenation, or gamma irradiation), a low leachable and extractable profile, exceptional chemical resistance, and a smooth interior surface.

In general, a notable benefit of fluoropolymers is their remarkably low coefficients of friction. This feature translates into a non-adhesion property, preventing biological materials from sticking to processing surfaces. By this characteristic, fluoropolymers inherently resist bioburden and endotoxins, making them

readily cleanable when required. Moreover, the low coefficient of friction facilitates complete liquid drainage from fluoropolymer-based systems, as liquids effortlessly roll off container surfaces. (4)

What are the options for alternative timelines and requirements, such as revalidation of the processes, for implementing them

While there is no single replacement for PTFE in pharmaceutical manufacturing, some alternative sealing materials exist, including ceramic seals, which exhibit exceptional inertness but may release fibres into the medicinal product, and graphite seals, which are not suitable for pharmaceutical applications due to the risk of carbon debris in the finished product. Additionally, materials like tantalum or gold can be used for connections between equipment components, but their high cost (many orders of magnitude higher than PTFE) makes them impractical for widespread adoption. (4)

PVDF filter membranes have become ubiquitous in filtration units within bioprocessing due to extensive testing and established reliability. Each filter within the industry has unique properties, including surface area, pore size, and "Material of Construction" (MOC). These MOC properties are not readily interchangeable, making it necessary to re-conduct filtration studies when changing MOCs while maintaining equivalent surface area and pore size. PVDF filters stand out for their superior oxidant resistance and mechanical strength compared to PES (polyether sulfone) filters, which are sometimes considered PVDF filter substitutes. (4)

In any case, alternative materials must be discussed with the machine manufacturers and various on-site departments, to ensure compliance with Good Manufacturing Practice (5) such as process validation, site engineering, packaging, quality compliance and assurance, technical compliance as well as compliance with rules for equipment for potentially explosive atmospheres (ATEX)(6). Furthermore, the change management process will require process optimization work, equipment re-qualification and validation, and regulatory approval by all global health authorities.

For example, the estimated change over time to successfully replace a filtration unit in a single manufacturing process could take 2 years. Each product depending on that filter may require re-registration in each target country where it is registered, which takes between an additional 3 and 5 years. These timescales consider a single change, however, multiple changes within a company would create production capacity constraints. (4)

Disposal of the PFAS chemicals and materials

The waste management adheres to the rules as laid down by both European (e.g. Directive 2008/98/EC on waste) and local rules in the country of manufacturing. Based on Teva's internal operating procedures, all of the waste produced by the plant producing the medicine in this case study is separated waste into approximately 75 different types of waste streams with four overarching categories. Two of these categories, which contain manufacturing and laboratory waste are transported to waste-to-energy plants. These plants have multi-stage exhaust gas cleaning systems and undergo voluntary environmental monitoring, which can be used to prove that the plant has no measurable negative impact on the environment.

Conclusion and impact

In case no alternatives will be identified or an insufficient derogation period to find and implement suitable alternative solutions will not be provided, it is expected that the European production of the affected

biologic medicines will cease or relocate to non-EEA countries. (7) However, the transfer of manufacturing operations to non-EEA facilities to ensure the continued supply of many medicinal products may not be possible. It is incorrect to assume that there is readily available and suitable manufacturing capacity outside of the EEA. During this relocation period, the global supply capacity would be significantly diminished. (4)

It must be noted that this case study specifically focused on the use of fluoropolymers in the biological medicines manufacturing process. This case study can be further expanded by the impact described in *Case Study 3 – the use of fluorinated raw materials*. The selected medicine would be also impacted by the PFAS restriction, due to the use of PFAS materials in the primary packaging – the pre-filled syringe contains a fluoropolymer-coated rubber plunger. More details about this issue can be found in *Case Study 4 – fluoropolymers in primary packaging.* In general, it is expected that without a sufficient derogation of medicines manufacturing from the PFAS restriction, the medicines supply chain will become even more vulnerable, leading to a decrease in medicines availability to patients and a higher occurrence of medicine shortages.

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Case study 3 – Use of raw fluorinated material in the medicine synthesis

Describing the medicine and the indication

The active substance is a long-acting modified glycoprotein produced by biotechnology in bacteria called Escherichia coli. It is used in adults and children aged 2 years and older as an adjuvant therapy for the management of side effects of cytotoxic chemotherapy. The medicine is a sterile liquid, administered to the patient subcutaneously in the hospital environment. The primary packaging consists of either a pre-filled syringe or a vial. (1)

Where PFAS material is used and why is it needed

Trifluoroacetic acid (TFA) raw material is used in critical process steps

Recombinant DNA technology is a powerful method that allows to preparation of large quantities of therapeutically important peptide and protein products. After genetic engineering and fermentation technology produce the initial protein product, it has to undergo thorough purification and processing before being formulated into its final dosage form. The purification process needs to efficiently separate the desired protein product from the complex fermentation matrix. Moreover, the purification process must be capable of reducing the levels of highly similar but not desired byproducts. For manufacturing at scale, reversed-phase high-performance liquid chromatography (RP-HPLC) has been the industrial standard for many years. (2)

The protein solution is applied to an RP-HPLC column and fractions are eluted using a mobile phase composed of acetonitrile which is acidified by the addition of a very small amount of TFA (in the range of 0.05-0.1%) gradient in water. Since its introduction almost 40 years ago, TFA has become the staple mobile phase additive in RP-HPLC of peptides and proteins throughout all branches of the industry. TFA is used to fine-tune the elution parameters and acts as the protein structure stabilization agent. TFA is used in preference to other acids because of its volatility and UV transparency. (3)

The resulting purity of the main component in this process step ensures the required purity, quality and consistent content for further manufacturing process steps.

TFA is used in Quality Control release/stability testing for both Drug Substance and Drug Product

To assure the desired product quality, as part of a comprehensive quality control package multiple RP-HPLC-based methods are used on a routine basis (for release and stability testing). TFA properties and use rationale, presented above apply to the analytical scale as well.

What are the options for alternatives (if any) and timelines and requirements, such as revalidation of the processes, (and costs if you know them) for implementing them

Exchange to alternative raw materials would require process re-development, re-validation and re-submission. (4,5) The implementation of this scenario would result in a new development of the production technology. Components of the development are 1) process development, 2) process implementation at production scale and validation, 3) impurities clearance study, 4) product extended characterization, 5) stability studies, 6) evaluation of the impact on patient safety and efficacy, 7) variation submission for Regulatory Authorities and approval. For any alternative to the currently registered TFA used in the approved medicinal product, various guidelines have to be considered.

The timeline below is based on Teva's internal estimates and applies only in case equivalently performing substitute material is possible and available. There are three major phases of the implementation process:

- New technology needs to be developed on a laboratory scale – estimated 3 years
- In case of success, new technology needs to be implemented at production scale and validation. Then impurities profiling studies and product stability studies need to be performed – estimated 3 years.
- Preparation and filing of a major variation (Type II) (6) for regulatory submission and approval in EU and global markets – estimated 3 years for all markets.

In the best-case scenario, new process development and introduction would take about 9 years and also would require significant financial investments (Teva's internal estimate is several million dollars). Also, this best-case scenario would be applicable only on condition, that approval from the regulatory authorities would be granted.

At the same time, a re-development, re-validation and re-submission of analytical methods would be required and may impact currently approved specifications (7).

- Re-development of at least 4 analytical methods will be required in case of a TFA non-use scenario. Estimated method development and method validation financial investment would reach hundreds of thousands of dollars. Estimated timelines for methods development and validation - 2 years.
- Preparation and filing of a major variation (Type II) (6) for regulatory submission and approval in EU and global markets – estimated 3 years for all markets.

Disposal of the PFAS chemicals and materials

All of the waste management adheres to the rules as laid down by both European (e.g. Directive 2008/98/EC on waste (8)) as well as the local rules in the country of manufacturing.

The waste from the manufacturing-scale and analytical chromatography is collected into a closed waste collection system and given to a specialized waste disposal company, that incinerates all of the waste. The waste disposal company also takes care of the single-use systems (e.g. bags) used in the process which had contact with TFA-containing substances.

Reusable materials that came into contact with TFA, such as mobile tanks or the glassware used in laboratory and manufacturing are washed and the wastewater is drained into an equilibration tank. Here the wastewater is treated for neutral pH and temperature before being released into the communal wastewater system.

Conclusion and impact

Due to the nature of the product-related impurities and their similarity to the desired molecule, it is possible that a process employing an alternative material might not be able to generate the currently approved impurity profile, which would result in a different impurity profile. This could subsequently lead to discontinuation of the product or the need to conduct new clinical studies. Moreover, the final medicine is an originator product, which means there will be no biosimilars available in the foreseeable future. If the product is discontinued, there is no direct replacement for it.

It must be noted that this case study specifically focused on the use of fluoropolymers in the medicines manufacturing process. The selected medicine would be also impacted by the PFAS restriction, due to the use of PFAS materials in the primary packaging – the pre-filled syringe contains a fluoropolymer-coated

rubber plunger and the vial contains a fluoropolymer-coated rubber stopper. More details about this issue can be found in *Case Study 4 – fluoropolymers in primary packaging.* In general, it is expected that without a sufficient derogation of medicines manufacturing from the PFAS restriction, the medicines supply chain will become even more vulnerable, leading to a decrease in medicines availability to patients and a higher occurrence of medicine shortages.

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Case study 4 – fluoropolymers in medicines packaging

Describing the medicine and the indication

The selected medicine is an oncology product that contains an active ingredient which slows or stops the growth of cancer cells. It is used to treat a type of cancer of the white blood cells called B-cell chronic lymphocytic leukaemia (B-CLL). (1)

The selected medicine is a sterile solution, administered to the patient in hospital settings intravenously as an injection or most often as an infusion. (2) The primary packaging consists of a pharmaceutical-grade glass vial and a fluoropolymer-coated rubber stopper.

Where per- and polyfluoroalkyl substances (PFAS) are used and why are they needed

As mentioned above the primary packaging contains a stopper made of special rubber, coated in fluoropolymer similar to polytetrafluorethylene (PTFE-like). Generally, the PTFE-like coated stoppers are inert and help protect the product ensuring good stability and compatibility of the product. Moreover, the coating prevents the leaching of unwanted compounds into the medicine, whose presence may have negative consequences for the patients. (3). At the same time, the coating provides additional comfort to the point of non-stickiness during steam sterilization and drying.

What are the options for alternatives and the timelines and requirements for implementing them

At the moment, there are no like-for-like alternatives to the coated rubber stoppers. (3) Some existing alternative materials could be considered for use in the pharmaceutical industry - either non-coated or siliconized rubber stoppers. However, neither of the alternatives offers the same characteristics as coated stoppers and additionally suffers from specific issues.

Simple non-coated stoppers are in most cases not suitable for use in pharmaceuticals. The reason is that non-coated stoppers suffer from higher extractability of the compounds from the stopper material in the presence of a solvent and high leachability of the compounds from the stopper material in the presence of the medicine compared to the coated stopper. The presence of these compounds may have negative consequences on the quality of the product and patient safety. (3)

Siliconisation of non-coated stoppers is done to counteract their natural slight stickiness, which leads to an increase in the complexity of the medicine filling lines. The siliconization process prevents the rubber closures from sticking together and simplifies the processing. However, it also comes with its downsides. The silicon oils used in the siliconization can leave residues on the surface of the stopper and create droplets in the liquid that can be both visible and invisible to the naked eye. (5)

All the materials in medicine’s primary packaging are carefully selected based on the medicine's characteristics in line with current pharmaceutical scientific standards laid down in guidelines issued by global and regional Regulatory Authorities. Any changes to the primary medicines packaging have to be accompanied by rigorous testing, including product stability study, compatibility studies, container closer integrity, extractable and leachable studies, etc. before any change can be made. (6) This has to be done per product and the changes in the primary packaging stated in the dossier have to be submitted as a variation to the marketing authorisation for each market. (7) Based on Teva’s internal estimations, on average, it may take around 40 months from the identification of the alternative to the distribution of the first batch with changed stopper to patients.

Disposal of the PFAS materials

As the PFAS material is part of the primary packaging of the medicine, it is the patient's responsibility to dispose of it safely. Many EU Member States have medicines disposal programs, where patients can return unused medicines and their packaging via community pharmacies. Patient education about this is also supported by the MedsDisposal Campaign (8), which was developed as a collaborative project between healthcare professionals and the pharmaceutical industry. In all cases, the waste collected through these schemes is disposed of and incerinated by firms specializing in handling dangerous waste.

Conclusion and impact

The packaging of sterile medicines is highly specific and challenging due to the requirements of the products to ensure that the medicine is free of any possible contamination and thus safe for administration to the patient. (9)

Due to the complexity of changing the primary packaging of a drug product, it can take several years to switch from PTFE-coated stoppers to an alternative material if available. This is because all of the necessary testing, including product stability studies, compatibility studies, and extractable and leachable studies, must be completed before the change can be made. (6)

It must be noted that this case study specifically focused on the use of fluoropolymers in medicine primary packaging. The selected medicine would be also impacted by the PFAS restriction, due to the use of PFAS materials in the manufacturing process itself, such as in tubings, collecting vessels, some filters as well as the machinery. More details about this issue can be found in *Case Study 2 – manufacturing of biologic medicines* and *Case Study 5 – manufacturing of final dosage forms.* It is expected that without a sufficient derogation of medicines manufacturing from the PFAS restriction, the medicines supply chain will become even more vulnerable, leading to a decrease in medicines availability to the patients and a higher occurrence of medicine shortages.

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Case study 5 – manufacturing of final dosage forms

Describing the medicine and the indication

This medicine is an antibiotic used for the treatment of a range of adult and paediatric infections, including those of upper and lower respiratory tract (e.g. pneumonia, bronchitis, sinusitis), skin and soft tissue infections, and some sexually transmitted diseases (STDs). (1) It is available on prescription in various dosage forms such as film-coated tablets, hard capsules, powder for oral suspension, as well as for intravenous administration. (2)

Where per- and polyfluoroalkyl substances (PFAS) are used and why are they needed

Each dosage form requires a specific manufacturing process with a variety of steps and machinery involved. The operation of pharmaceutical manufacturing facilities is governed by EU Guidelines for Good Manufacturing Practice (GMP) for Human and Veterinary Use (3) Fluoropolymers are indispensable in various components, including tubing, piping, process and utility equipment, and single-use systems, contributing significantly to the smooth running of these facilities. Fluoropolymer materials have become ubiquitous in pharmaceutical manufacturing, owing to their exceptional water repellency, which translates into superior corrosion resistance. They also possess non-stick and friction-reducing properties. Further, their inertness is widely recognized by regulatory bodies, making them highly sought-after for the production of medicinal products. (4)

In the case of the powder for oral suspension dosage form (which is reconstituted into syrup by a pharmacist), a fluoropolymer called polytetrafluoroethylene (PTFE; brand name Teflon) is used in the primary packaging filling, specifically in three places. First is the mechanical seal rings on the shafts for dosing augers and piping connections, where durability and non-reactivity are the desirable properties. Second, is the dosing nozzles and dosing centring nozzles, which play a role in dosing the powdered product into the primary packaging. Here the non-stickiness and resistance to static electricity prevent a build-up of the dry powder in the nozzles while safeguarding the properties of the powder.

For machines in the production of oral solid dosage forms (such as tablets), PTFE is used in different steps of the manufacturing of seals and gaskets. During mixing on the mechanical shafts on dosing augers and piping connections and the automatic valves, due to the materials' durability and non-reactivity. In a granulation machine, a PTFE ring is used on the chopper knife (which prepares the dry material into the desired particle size) due to its self-lubricating and low friction properties – the chopper knife moves from hundreds to thousands of rotations per minute. In milling machines (which are further adjusting the particle size) PTFE is used as a seal for one of the parts. The non-stickiness of PTFE is used during the compression of the powder into the tablet in the compression machine’s roller seal. Lastly, the purified water necessary for the compounding PTFE is used as the material for the valve membranes.

Lastly, in the sterile production of the powder for solution for infusions, PTFE is used as valves, membranes and gaskets on the compounding vessel.

For all products in the manufacturing facility, PTFE is used in valve membranes for all clean utility piping, notably water for injections (extremely pure water), clean steam (sterile steam used for sterilizing or cleaning items in the production) and purified water.

What are the options for alternatives and the timelines and requirements for implementing them

There is no universal alternative to the use of PTFE in pharmaceutical manufacturing. Some sealing materials could be seen as alternatives to the use of PTFE, such as ceramic seals (very inert, but contain fibres that can be released into the medicinal product), or graphite seals (not suitable for pharmaceutical manufacturing due to the risk of carbon debris in the final medicinal product). Other materials, such as tantalum or gold can be used in connections between equipment parts but are extremely expensive (many orders of magnitude more expensive than PFAS). (4)

In any case, alternative materials must be discussed with the machine manufacturers and various on-site departments, to ensure compliance with Good Manufacturing Practice (3) such as process validation, site engineering, packaging, quality compliance and assurance, technical compliance as well as compliance with rules for equipment for potentially explosive atmospheres (ATEX)(5). Significant investments will have to be made to make the changes to the machines. However, the exact timelines and costs can only be evaluated after initial feedback from the machine supplier. According to Teva's internal estimations, it is expected that changes to the manufacturing processes would range from 24 to 60 months per PFAS material use case in the best-case scenarios.

Disposal of the PFAS chemicals and materials

All of the waste produced by the plant is separated waste into different types of waste streams. In general, if PFAS-containing materials are in contact with hazardous substances those materials are disposed of according to the procedure for hazardous materials, which is incineration in specialized facilities. If PFAS-containing materials are not in contact with hazardous materials those are disposed of conventionally according to the national law.

Conclusion and impact

In case no alternatives will be identified or a sufficient derogation period to find and implement suitable alternative solutions will not be provided, it is expected that the European production of the affected medicines will cease or relocate to non-EEA countries. However, the transfer of manufacturing operations to non-EEA facilities to ensure the continued supply of many medicinal products may not be possible. It is incorrect to assume that there is readily available and suitable manufacturing capacity outside of the EEA. (4) Furthermore, the required investments into transitioning to non-PFAS materials will lead to an increased cost of manufacturing which might render the manufacturing of some medicines, especially low-priced ones, unsustainable.

It must be noted that this case study specifically focused on the use of fluoropolymers in the manufacturing of the final dosage forms of the selected medicine. Medicines in general may also be impacted by the PFAS restriction, due to the use of PFAS materials in the primary packaging or the drug delivery device. It is expected that without a sufficient derogation of medicines manufacturing from the PFAS restriction, the medicines supply chain will become even more vulnerable, leading to a decrease in medicines availability to the patients and a higher occurrence of medicine shortages.

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