PFAS PUBLIC CONSULTATION: INITIAL BRIEF PCTFE IN MEDICAL PACKAGING

Brussels, 10 August 2023

***EuPC** is the leading EU-level Trade Association, based in Brussels, representing European Plastics Converters. EuPC now totals about 51 European Plastics Converting national and European industry associations, it represents close to 50,000 companies, producing over 50 million tonnes of plastic products every year. The European plastics industry makes a significant contribution to the welfare in Europe by enabling innovation, creating quality of life to citizens and facilitating resource efficiency and climate protection. More than 1.6 million people are working in about 50,000 companies (mainly small and medium-sized companies in the converting sector) to create a turnover in excess of 280 billion € per year*

Introduction

Following our initial submission, EuPC intends to comment on specific applications. Since those are very diverse, each will be covered in a separate submission. This brief is the initial brief for **PCTFE used in medical packaging**. We intend to further complete this submission by the end of the consultation period.

This submission is built upon a survey conducted in collaboration with Honeywell, the supplier of PCTFE film from outside the EU, as well as key market leaders responsible for producing multilayer packaging utilizing this film within the EU. This survey is anticipated to encompass approximately 90% of the total usage of PCTFE in medical packaging, ensuring a robust representation of industry insights and practices.

Use of PCTFE in medical packaging

PCTFE (Fluoropolymer PolyChloroTriFluoroEthylene, EC number: 618-336-7, CAS number: 9002-83-9) is a long-chain polymer used in pharmaceutical blister packaging for Oral Solid Dosage Form (more precise than 'Medical Devices') and to package and make MEDICAL DEVICES such as parenteral containers and to manufacture MOLECULAR DIAGNOSTIC KITS. The report summaries listed above in this questionnaire did not yet include the use of PCTFE in packaging for medicinal preparations, medical devices and molecular diagnostics. In these applications, PCTFE film is used for several decades as a reliable high-performance moisture barrier. It enables to prevent contamination and loss of product integrity and efficacy of medicinal preparations. PCTFE film is laminated to PVC and other materials to become part of a laminated thermoformable film which is used to shield critically sensitive pharmaceutical substances, medical devices and diagnostic kits. The packaging materials used for these products are strictly regulated in the incumbent regulatory ecosystem (EMA, Pharmacopeia standards, etc.). PCTFE-based films are a critical primary packaging and their composition is an integral part of the submission package in order to obtain approval for market authorisation of the medicinal

product. From a regulatory perspective, it is of equal importance as the excipients[1] of the medicinal product [2].

Critical use for pharmaceutical packaging includes blister-packaging of moisture-sensitive substances. Examples of moisture-sensitive are contraceptive drugs, acyclovir, erythromycin, antibiotics, ciprofloxacin, HIV-antiretroviral drugs, cancer-chemotherapeutic drugs and some of the corticosteroid substances which are used to treat COVID-patients. Without sufficient protection moisture-sensitive pharmaceutical compounds will be affected by hydrolysis, they can degrade, the crystalline order can be disturbed and intermolecular interactions can affect the integrity of the product. The inherent overall risk of exposure to moisture is the loss of therapeutic effectiveness of the drug, thereby jeopardizing the reliability of the pharmacokinetic response, potentially leading to illness and loss of life. The use of high-performance barrier film is critical to keep pharmaceutical drugs safe from ambient moisture, especially during transportation and storage and in unstable climate conditions.

No hazardous properties justifying a restriction

PCTFE whilst it is very persistent by design does not display any hazardous property/property of concern referred to by the dossier submitter i.e., bioaccumulation, mobility, long-range transport potential (LRTP), accumulation in plants, ecotoxicity, endocrine activity/endocrine disruption, effects on human health and concerns triggered by a combination of these properties.

PCTFE fluoropolymers are manufactured both from non-PFAS raw materials and the non-PFAS monomer Chlorotrifluoroethylene (CTFE), and polymerized without the involvement of other PFAS substances (processing aids, surfactants, additives, or agents).

PCTFE adheres to the OECD definition of a polymer of low concern[3]. It demonstrates characteristics of being insoluble in both water and fat (see Honeywell submission Nº 4083). Moreover, no reactive functional groups or functional groups of functional weight have been identified. Oligomers content is negligible as well as monomer content (one has to note that the starting monomer is not a PFAS).

PCTFE should be excluded from the scope of the restriction

Based on the above, PCTFE should in our view excluded from the scope of this restriction. We however provide additional information showing both its negligible emission and the disproportionate socio-economic impact that would be linked to its substitution. In the event it is determined that PCTFE shall not be excluded from the scope of the restriction, then our analysis

[1] Excipient: Constituent of a medicine other than the active substance, added in the formulation for a specific purpose.

[2] Directive 2001/83/EC on the Community code relating to medicinal products for human use; and Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

[3] Korzeniowski, S. H. et al. A critical review of the application of polymer of low concern regulatory criteria to fluoropolymers II: Fluoroplastics and fluoroelastomers. 2022. *https://setac.onlinelibrary.wiley.com/doi/full/10.1002/ieam.4646*

suggests that the industry would need a minimum of a 12-year transition period to discover suitable alternatives.

Note: the following sections numbers correspond to the sections numbers from ECHA's Comments for Annex XV restriction report for Per- and polyfluoroalkyl substances (PFAS).

1. Sector and sub-use

This comment is related to the following use: PCTFE-based packaging for medicinal preparations, medical devices and molecular diagnostics.

2. Emissions during the end of life

According to a recent study conducted by Conversio on behalf of ProK[4], it has been found that the disposal of medical and pharmaceutical waste predominantly involves incineration, accounting for approximately 90% of the total waste generated. On the other hand, landfill disposal constitutes only 7% of the overall waste generated in this sector – see p. 39, ratio recalculated excluding metal. Additionally, there are some recycling efforts, 3%, particularly in the form of mixed plastics recycling sourced from household waste.

It is essential to highlight that, according to WHO guidelines (Table 2: Methods of disposal of uncontaminated packaging, pp. 140, Guidelines on packaging for pharmaceutical products, WHO Technical Report Series, No. 902, 2002. source: *https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs902-annex9.pdf?sfvrsn=82b4c57d_2*), incineration is highly recommended for the disposal of uncontaminated medical packaging.

Emissions in the landfill would be negligible given PCTFE is not soluble in water (5mg/L) or oily media (1-octanol). It is based on non-PFAS monomers (CTFE), has negligible impurity and its manufacturing does not involve the use of any PFAS substances (processing aids, surfactants, additives, or agents).

For behaviour in incineration, see the next section.

[4] Fluoropolymer Waste in Europe 2020 – End-of-life (EOL) Analysis of Fluoropolymer Applications, Products and Associated Waste Streams." Final Report Made on Behalf of pro-K, Conversio. July 2022.

URL: *https://www.ft.dk/samling/20222/almdel/euu/spm/49/svar/1951975/2698345.pdf*

3. Emissions from incineration

Incineration above 850 °C does not release PFAS-related materials [5] [6] [7], nor detectable levels of Trifluoroacetic acid (TFA) (Bakker, J., et al. (2021) ibidem). Those temperatures can only be found in municipal waste incinerators, as they are mandatory according to the Industrial Emissions Directive 2010/75/EU (Article 50), which prescribes that waste incineration plants must be designed to ensure that flue gases reach a temperature of at least 850 °C for at least 2 seconds in order to ensure the proper breakdown of toxic organic substances).

5. Proposed derogation tonnage and emissions

In July 2023, a comprehensive survey was conducted, specifically targeting the primary converters of medical packaging. The companies interviewed collectively account for approximately 90% of the EU's PCTFE-based film production. Based on the insights gathered from this survey and supplementary information, we can reasonably estimate that the volume of PCTFE utilized in medical packaging across the EU amounts between 1000-2000 tonnes/year – an average of 1,500 tonnes/year. This results in between 4,000 to 8,000 tonnes/year of multilayer film placed on the market – an average of 6,000 tonnes/year; the balance being other polymer layers such as PVC, PE, PA, EVOH, and PET; which are materials without PFAS content.

5.1. Emissions during manufacturing of PCTFE (Aclar®) film

The PCTFE film utilized in this context is imported into the EU as it is not manufactured within the region. Notably, Honeywell, conducted film extrusion at a temperature of 250°C, revealing no signs of degradation in PCTFE. Indeed thermal degradation is expected at temperatures above 350°C. This confirms the film's robustness and suitability for its intended application in medicinal packaging, providing assurance of its high-performance characteristics.

5.2. Converting of PCTFE film into multilayer film and related emissions

PCTFE film serves as a high-performance barrier layer, and it is efficiently laminated with other polymer layers such as PVC, PE, PET, and EVOH for medicinal packaging, particularly blister packs. The

[5] Aleksandrov, K. Waste Incineration of Polytetrafluoroethylene (PTFE) to Evaluate Potential Formation of Per- and Poly-Fluorinated Alkyl Substances (PFAS) in Flue Gas. 2019, 226, 898-906.

DOI: *https://doi.org/10.1016/j.chemosphere.2019.03.191*

[6] Taylor, P. H. Investigation of Waste Incineration of Fluorotelomer-Based Polymers as a Potential Source of PFOA in the Environment. Chemosphere 2014, 110, 17-22.

DOI: *https://doi.org/10.1016/j.chemosphere.2014.02.037*

[7] Bakker, J., et al. Per- and Polyfluorinated Substances in Waste Incinerator Flue Gases. Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Report 2021-0143.

DOI: *https://doi.org/10.21945/RIVM-2021-0143*

lamination process takes place within the temperature range of 15 to 80°C, ensuring that the PCTFE film remains stable without experiencing any degradation.

As PCTFE enters the converters' facilities in the form of a film, the possibility of solid losses, including microplastic pellets, is estimated to be negligible. Moreover, converters have proactively committed to the Operation Clean Sweep (OCS) pledge, aiming for zero pellet and microplastic losses within their facilities. Additionally, any internal waste generated during the conversion process is effectively recuperated and directed towards recycling.

Considering these efforts, emissions at this stage are estimated to be minimal and, consequently, pose no significant environmental concerns.

5.3. Blister manufacturing

Medicinal blister packs are produced in-house by the pharmaceutical company using a thermoforming process on supplied multilayer films. The thermoforming of PVC, at temperatures ranging between 110 and 170 °C – depending on the polymer combination; i.e., PVC, PE, PET, PA, EVOH –, allows the creation of the blisters. It is important to note that, even at these temperatures, no degradation of PCTFE has been identified, ensuring the integrity and performance of the packaging material throughout the process.

7. Derogation for reconsideration: information on socio-economic impact and analysis of alternatives

7.1. Analysis of Alternatives

7.1.1. PCTFE

For several decades, PCTFE film is the barrier material of choice used in blister packaging due to its outstanding properties: biochemical inert, transparency, and high moisture barrier. It is stable and has an enhanced shelf life. It may withstand varying environmental conditions (wet, cold, heat) ensuring the stability of medicines and drugs. The film is very flexible and enables also deep cavities to receive the pills. It also results in less material to be used than alternatives.

7.1.2. survey description and methodology

An analysis of alternatives is conducted based on the results of the data gathered from the EU's PCTFE film provider and the downstream converters who produce PCTFE-based medicinal packaging films. We conducted an analysis of alternatives with suppliers of multilayer films for blister packaging – more than 90% of downstream users of PCTFE for medicinal packaging.

Methodology: companies had to allocate a score from 0 (property not fulfilled) to 5 (property fully fulfilled). Individual interviews with converters were then conducted.

Table 1 summarizes the performance comparison of alternative films regarding key properties between PCTFE-based solutions and other medicinal packaging that could be used as alternatives.

7.1.4. Discussion of technical properties of alternatives compared to PCTFE

- PVDC offers remarkable process stability, rendering it comparable to PCTFE. Its mechanical properties are medium, similar to PCTFE under ambient conditions, but it can exhibit brittleness at temperatures below 10°C. While PVDC provides good moisture protection, it falls slightly short of PCTFE in this aspect, resulting in a medium shelf life. This reduction in shelf life could potentially lead to increased film wastage or impact drug validity. On a positive note, PVDC showcases high transparency, akin to PCTFE.
  However, it is important to note that PVDC is not fully compatible with current operational process conditions used for PCTFE-based films; this would necessitate investments for the implementation of the alternative, such as installing new production coating lines and/or adopting different processing methods and equipment for the thermoforming form/fill/seal medical packaging operation.
- Aluminium (Cold Foil Forming, CFF) has high process stability, but it falls short in terms of compatibility with the operational process conditions of PCTFE. The mechanical properties of Aluminium-based films are medium – against PCTFE, needing a much larger blister layout. Its moisture/oxygen protection is very high, offering a high shelf life, comparable to PCTFE. In terms of bio-chemically inertness and chemical resistance, it scores lower than PCTFE due to its vulnerability at acid/basic pH exposure. Moreover, it is not transparent – for a discussion of the negative on patient compliance to treatment see section 7.2. It is typically layered with PVC, and increases all pack sizes 2X; this is because the cavity needs to be of enough size to allow the forming of aluminium. Additionally, the processing speed may be reduced by a factor of 2X against PCTFE film thermoforming, thus adding to the cost and complexity.
  When Coil Foil Forming (CFF) technique is used, aluminium is usually layered with PVC, and the thermoforming speed may be reduced by a factor of 2.
  CFF compatibility with operational process conditions is low. It would need major reinvesting for a technology that was superseded decades ago by PCTFE film solutions.
- Cyclic Olefin Copolymer (COC) has high process stability. Its compatibility with operational process conditions is medium, as well as its mechanical properties. However, its moisture/oxygen protection is low. On the positive side, COC exhibits high transparency, but increases material thickness 3X, and material usage doubles compared to PCTFE.

7.1.5. Availability of alternative materials

There is an indication that alternative materials such as PVDC are in short supply compromising those as a substitution option for industry. This alternative is the one that might be implemented with fewer process modifications than others.

7.1.6. Cost of substitution

PVDC: Cost of substitution to PVDC would be limited both in capital investment, 100,000-1,000,000 €/company, for the packaging lines and an additional cost for film producers to lay out PVDC coating

lines which typically would sum up for the sector to 4 x 6,000,000 €; and raw material cost; i.e., overall cost under 5,000,000 €.

However, it does not display the required properties enabling enough flexibility for the pharmaceutical industry; i.e., brittleness under 10°C – according to industrial converters.

CFF: This is not a really plausible alternative due to low thermoforming speed potentially decreasing the throughput by a factor of 2X. In case investment would be considered, one should consider an investment of 5 million € per line (one line is assumed to package two drugs); i.e., a capital investment of 2,5 million € per drug.

Requalification cost

The cost of requalification by pharma companies is important. We estimate a cost of about 500,000 € per drug and per dosage tested – including testing, registration cost, and tooling –, this means that if a formulation is offered in multiple dosages, each of them requires a requalification application. Typically the testing takes 24 months in non-accelerated stability tests.

Table 2. Substitution cost

	PVDC (see supply uncertainty)	**Aluminium (CFF)**
Number of drugs	625	625
Investment in multilayer film manufacturers	4 x 10,000,000 € = 40 million €	6,000,000 € x 4 = 24 million € (high-end lamination line)
Investment in pharma companies (thermoforming)	625 x 50,000 € = 31.25 million €	625 x 2.5 million € = 1,562.5 million €
Requalification cost	625 x 50,000 € = 312.5 million €	625 x 500,000 € = 312.5 million €
Total	**383.75 million €**	**1,899 million €**

7.1.6. Time needed for substitution/potential socio-economic effects

In case PCTFE use in medical packaging would not be derogated, one has to consider the time necessary for substitution.

Depending on the availability of the alternative, changes to film manufacturing equipment could take 1 to 3 years. Adaptation to cold forming would also take at least 3 years. Requalification of packaging

takes a minimum of 2 to 3 years. The main issue is the capability to test all drugs (625 packaged in PCTFE, Aclar®) in combination with the new packaging. The process would have to be repeated by every pharma company for every film supplier. The needed cumulated time to requalify currently packaged drugs would take 10 to 15 years at the minimum.

7.2. Socio-economic impact

Based on our interviews, it is unlikely that, in case PCTFE would be banned, activities would stop at the film converters level. The overall turnover for such applications is estimated at 120-150 million €/year.

We have indicated substitution costs ranging between 317-1,875 million € across the supply chain, including pharma companies.

The main risks are however for patients and would create additional societal costs.

To begin in case of a derogation period shorter than the intended 12 years and given the high requalification cost by the pharma industry it is likely that some drugs especially "generic drugs" or drugs with low volumes of patients (orphan diseases) would cease to be offered in Europe at least temporarily.

In case one would go back to aluminium packaging, this would not only lead to increased cost (twice as much material used) but could also decrease patient compliance when taking treatment. Indeed, there is evidence indicating that non-transparency and the increased size of aluminium packaging lead to difficulties with patient compliance [8], an increase in incorrect medication dosage and an overall increase in healthcare costs. PCTFE-laminated blister films enable higher therapeutic compliance – especially for the ageing population, in part because a visible inspection of blister packaging containing tablets/capsules is possible. PCFTE is the only known barrier material that retains its color and transparency in specific applications where moist sensitivity is critical. In an era of active and healthy ageing, clear blister packaging of pharmaceutical oral solid dosage reduces the risk of 'overlooking' or 'forgetting'/'wrong dosing', this is supported by independent studies [8] [9] [10] [11]. This is important since up to one-third of the patient may be made more compliant by the development of adequate compliance strategies, packaging design being one of the contributors to the behavioral/ educational strategies put in place.

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[8] Stockwell, M.; Schulz, R. M. Patient Compliance—an Overview. Journal of Clinical Pharmacy and Therapeutics 1992, 17, 283-295. DOI: *https://doi.org/10.1111/j.1365-2710.1992.tb01306.x.*

[9] Hummler, H.; Sarwinska, D.; Weitschies, W.; Gollasch, M.; Page, S. Parameters to Consider for Successful Medication Use in Older Adults - An AGePOP Review. Eur. J. Pharm. Sci. 2023, 187, 106453. DOI: *https://doi.org/10.1016/j.ejps.2023.106453*

[10] The USA And A Shift From Bottles To Blisters: What the Rest of the World Already Knows. Available online: www.pharmaworks.com. *https://files.pharmaworks.com/assets/Whitepapers/Pharmaworks_White-Paper_A-Shift-from-Bottle-to-Blister_RevA_20220630_2022-07-01-174649_cuao.pdf* (Accessed on 03 August 2023).

[11] Izzah, Z.; Zijp, T.R.; Åberg, C.; Touw, D.J.; van Boven, J.F.M. Electronic Smart Blister Packages to Monitor and Support Medication Adherence: A Usability Study. Patient Prefer. Adherence 2022, 16, 2543-2558. DOI: *https://doi.org/10.2147/PPA.S374685*

The very high clarity without impact on optical properties of PCTFE may not be guaranteed for the same shelf life or as enabler patient compliance (retaining of colour) with alternative plastics solutions. For storage and shelf life, it is of vital importance that medicines, in the form of pills, are not exposed to environmental moisture. Products with compromised stability have reduced therapeutic effects. Furthermore, toxic degradants formed due to the degradation of the drug(s) and/or excipient(s) can seriously affect patient or consumer safety [12].

7.3. Proportionality

We have demonstrated above that PCTFE, a polymer of low concern, is unlikely to lead to the release of hazardous PFAS compounds, whilst the substitution cost is prohibitive, 300-1,900 million €, not to talk about the potential impact of withdrawn drugs or decrease in patient compliance.

8. Conclusion/Summary

Based on the above, PCTFE should in our view excluded from the scope of this restriction. We, however, provide additional information showing both its negligible emission and the disproportionate socio-economic impact that would be linked to its substitution. Additionally, the transition to alternative substances necessitates an adjustment period in terms of industrial practices and requalification procedures to meet the regulatory standards applicable to medicinal and medical devices applications. For this, certain time lapses exist that, if not provided with a minimum transition period of 12 years, will compromise the supply of some medicinal/medical devices which are essential for society and human wellbeing.

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[12] N. Veronica, P. Wan Sia Heng, C. V. Liew. Relative Humidity Cycling: Implications on the Stability of Moisture-Sensitive Drugs in Solid Pharmaceutical Products. Molecular Pharmaceutics 2023, 20 (2), 1072-1085. DOI: *https://doi.org/10.1021/acs.molpharmaceut.2c00812*

Table 1. Comparison of alternatives against PCTFE-based medicinal packaging barriers

	PCTFE	**PVDC**	**Aluminium** (CFF [1])	**COC** [2]
Process Stability	VERY HIGH	VERY HIGH	HIGH	HIGH
Compatibility with current operational process conditions	VERY HIGH	HIGH	LOW	MEDIUM
Mechanical Properties	HIGH	MEDIUM	MEDIUM	MEDIUM
Moisture/Oxygen Protection	VERY HIGH	MEDIUM	VERY HIGH	LOW
Shelf Life	VERY HIGH	MEDIUM	VERY HIGH	MEDIUM
Bio-chemically Inert	VERY HIGH	MEDIUM	HIGH	LOW
Chemical Resistance	VERY HIGH	MEDIUM	MEDIUM	LOW
Transparency	HIGH	HIGH	VERY LOW	HIGH
Color Stability	VERY HIGH	LOW (yellowing under heat and light)	VERY HIGH	VERY HIGH
Other	-	-	CFF typically uses PVC. The packaging layout needs to be increased 2X due to mechanical restrictions. Blister processing speed is 50% lower.	Increases material thickness 3X and material usage doubles.

[1] CFF: Cold Forming Foil. [2] COC: Cyclic Olefin Copolymer.