European Federation of Pharmaceutical Industries and Associations

Pharmaceutical Industry – Identified PFAS Uses



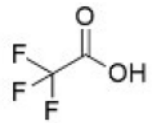



EFPIA [redacted]

Development, Manufacture & Supply of Medicinal Products – PFAS Use

A time unlimited derogation for fluorinated APIs & 13½ year derogation for PCTFE in immediate packaging of medicinal products is proposed – all other parts of the supply chain are in scope of PFAS Restriction, unless derogations are granted

Pharmaceutical Manufacturing -
PFAS containing materials handled in an industrial setting



trifluoroacetic acid

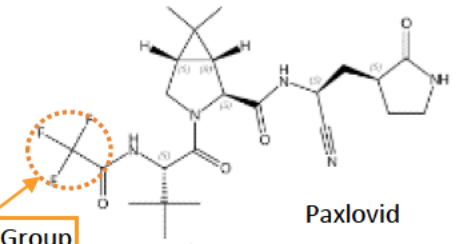
PFAS containing Raw Materials, Starting materials, Intermediates

Fluoropolymer containing plant, equipment, consumables

Substitution challenges - unique substance properties & process validation

Quality Control Analysis
Research & Development

Fluorinated API
(active pharmaceutical ingredient)



Paxlovid

Substitution Impossible (API = molecule)

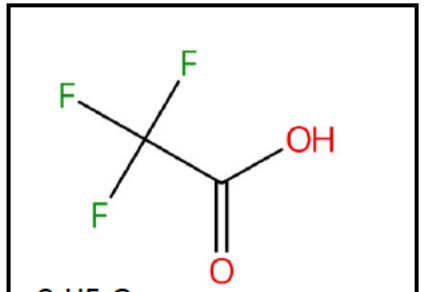
Packaging & Drug Delivery Devices

Challenge: Post Approval changes to Marketing Authorisation of Medicinal Product

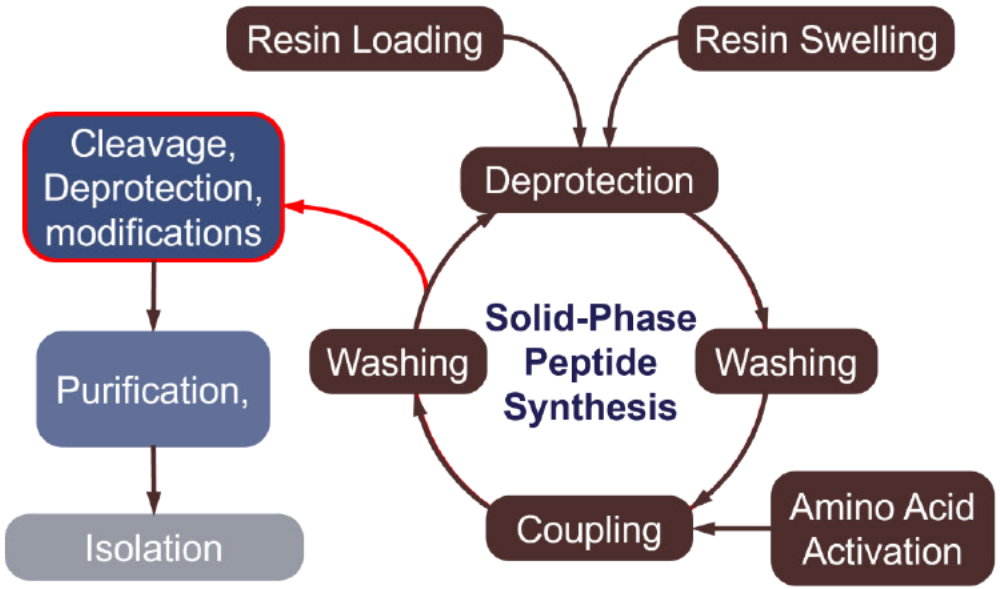
PFAS Chemicals Used in the Synthesis, Purification or Analysis of APIs

EXAMPLE: Use of trifluoroacetic acid in the chemical synthesis of peptide therapeutics

- Therapeutic peptides are a unique class of pharmaceutical agents, intended for a variety of treatments including diabetes, growth deficiency, HIV, osteoporosis etc.
- Amino acids are the building blocks of peptides which are assembled on a resin. TFA is used to cleave the peptide from the resin and for the subsequent global deprotection reaction to remove the protecting groups at the end of synthesis.



$C_2HF_3O_2$
Trifluoroacetic Acid (TFA)



- TFA helps create reaction conditions which inflict minimal damage on the peptide molecule - avoids peptide re-alkylation
- If a technically feasible alternative became available – replacement of TFA would require approval from all relevant global health authorities
- Alternative reagents described in the literature e.g. triflic acid (Trifluoromethanesulfonic acid) is also a PFAS → regrettable substitution

PFAS Chemicals Used in the Synthesis, Purification or Analysis of APIs

EXAMPLE: Use of PFAS in the quality control analysis of medicinal products mandated by Pharmacopoeia Standards

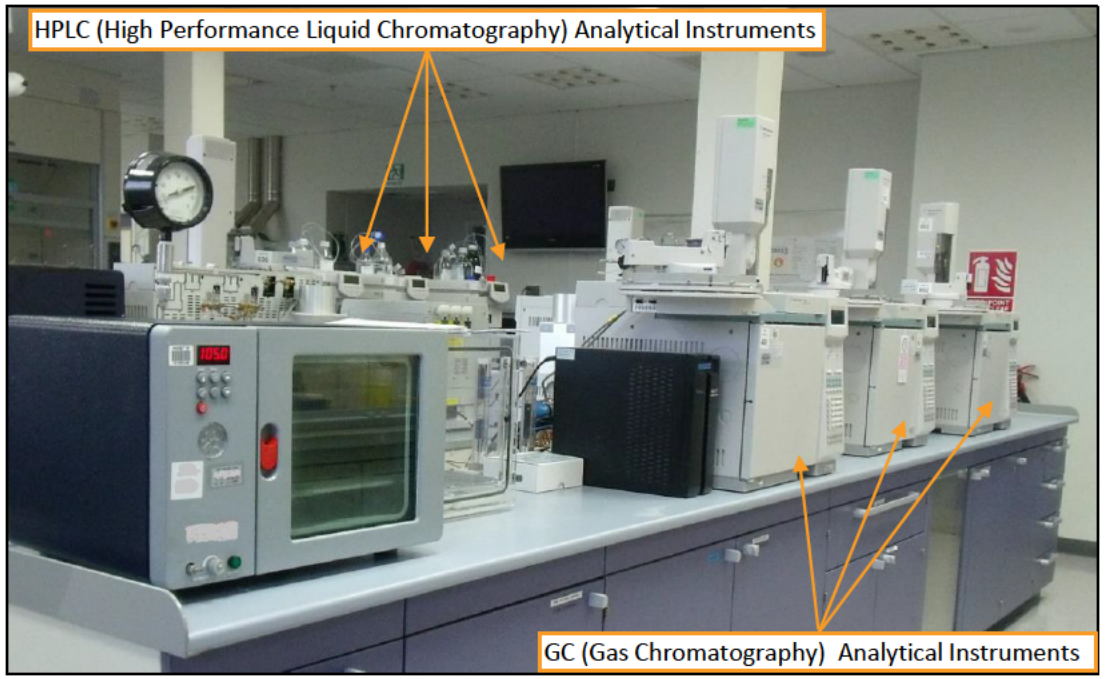
- EDQM produce Pharmacopoeia monographs, which are mandated in the quality control analysis of medicinal products

- PFAS reagents are used in more than 170 pharmacopoeia monographs. Of these, 100 prescribe the use of trifluoroacetic acid in the mobile phase of HPLC analytical methods

- More than 90% of EDQM reference standards (>2500 reference standards), are supplied in glass vials with a PTFE coated stopper or septum. PTFE provides a protective layer to avoid chemical reactions between closure components and contents

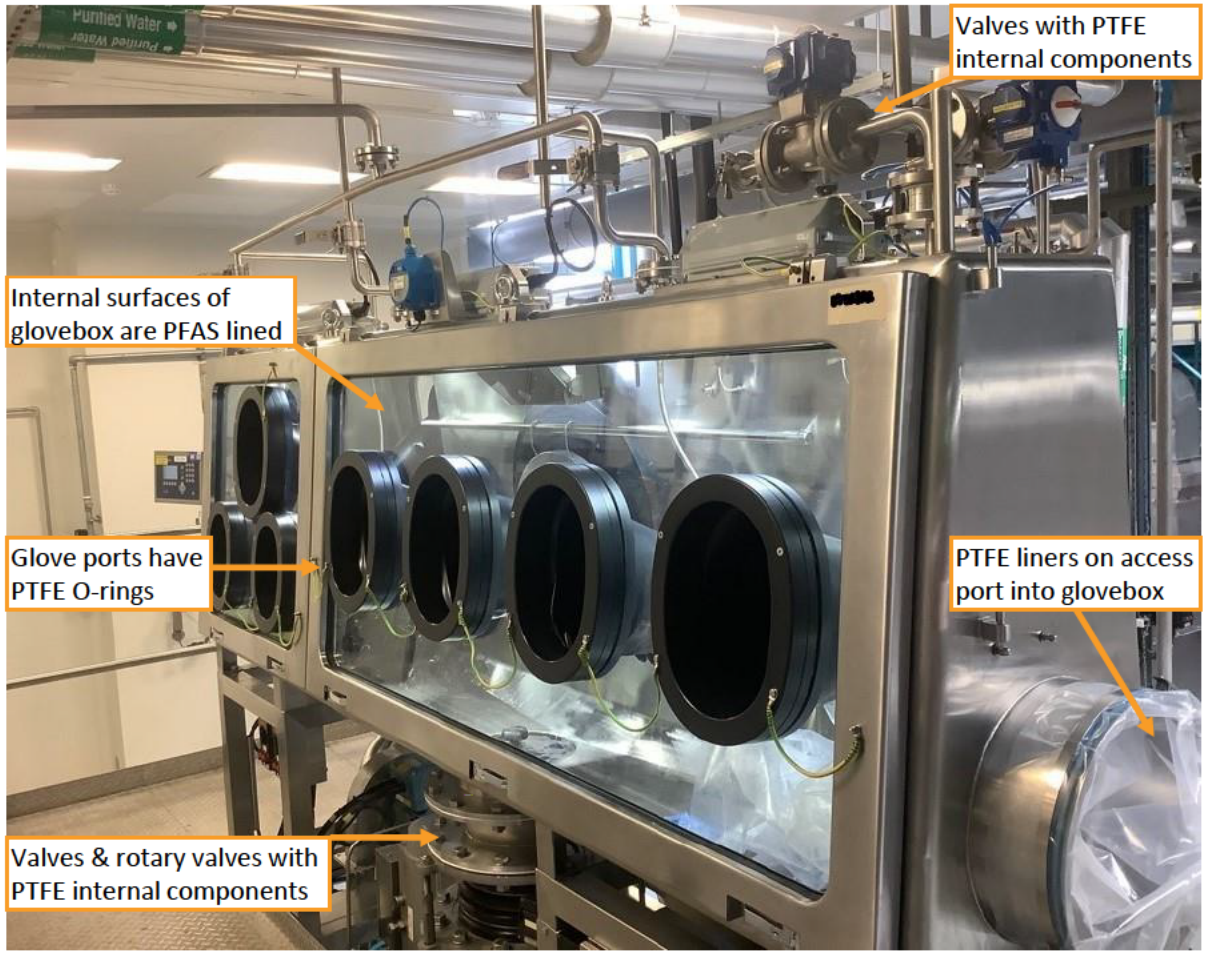
- It is unclear if the Restriction exemption in REACH for research and development applies to QCL (quality control laboratory) analysis

- Supply chain risk in the procurement of PFAS laboratory reagents and articles is a possibility



Use of Fluoropolymers in production equipment such as reactors, pipework, seals, gaskets and single use systems

EXAMPLE - Glovebox for Contained Transfer of Solid Materials into Reaction Vessel in a Small Molecule* Chemical Synthesis Facility



*Small molecule APIs (active pharmaceutical ingredients) are low molecular weight (≤1000 Daltons) organic compounds

Manufacturing facilities are dependent on fluoropolymer use for process safety and product quality reasons

Quantification of fluoropolymer materials used is a challenge:

- Processing and utility systems will contain kilometers of lined piping (millimeter thickness), valves, sight glasses etc.
- Don't have complete overview of PFAS components in complex articles

Single Use Systems - if an alternative became available, regulatory approval by global health authorities is required

Any conditions placed on the production phase of fluoropolymers could result in suppliers exiting the market → supply chain risk is a possibility

There will be an expectation[1] that emissions must be minimised throughout the entire lifecycle of derogated uses

1. Commission document: CARACAL-50, Meeting Presentation (16 November 2023) – *Universal PFAS Restriction, State of Play*

Human Health Medicinal Products Sector Survey – Impact of PFAS Restriction on Patient Access to Medicines & EU Strategic Autonomy

Approximately 1900 active substances impacted by the Restriction because:

- PFAS used in manufacturing and packaging operations at an EU facility and/or
- PFAS constituents present in the intermediate packaging or drug delivery device of a medicinal product placed on the EU market

Only 7% of the active substances contain the PFAS moiety, and therefore fall under the proposed derogation for APIs

Supply chains of 93% of the active substances involve EU manufacturing operations, which depend on fluoropolymers, within plant, equipment and single use systems → if these facilities are sole global supplier in a supply chain, medicine shortages are a possibility

A wide range of therapeutic areas are impacted e.g. cancer treatment, cardiovascular disease, diabetes, mental health conditions, respiratory disorders. Some products are on critical medicines lists:

- >600 medicines on WHO Essential Medicines list
- EU Member State “Critical Medicine” listing e.g. 78% of critical medicines in Norway could be impacted

AESGP efcg EUROPEAN FINE CHEMICALS GROUP efpia medicines for europe better access. better health.

Key Takeaways

The universal PFAS Restriction could have an adverse effect on the supply chains of medicinal products because:

- PFAS materials are used in manufacturing and packaging operations at EU facilities (in synthesis processes, equipment and quality assurance)
- PFAS constituents are present in the packaging or drug delivery devices of medicinal products placed on the EU market

Our ask –

1. Derogations are granted across all parts of supply chains to avoid medicine shortages for patients
2. The Restriction allows sufficient time for further development and standardisation of waste treatment technology and analytical methods
3. Partnerships develop across supply chains to:

- Identify all sources of PFAS & minimise emissions from waste streams
- Develop suitable alternatives that maintain the highly controlled environment required for product efficacy and safety