Fluoropolymers used in the manufacturing equipment of Active Pharmaceutical Ingredients (API)

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Introduction

Fluoropolymers are widely used in industrial equipment and consumables. Owing to their exceptional chemical resistance (e.g. against acids, bases and many other organic and inorganic substances and solvents), high thermal stability, and low friction properties, they have found application in a wide range of equipment, including reaction vessels, piping, gaskets, seals, and filter membranes. Their unique characteristics contribute to minimize contamination risks, optimizing process efficiency, enhancing asset life cycle times and maintaining the quality, consistency, and reliability of the entire manufacturing process involved in active substances production. In this document, we provide two examples of production of active pharmaceutical ingredients to discuss and visualize where fluoropolymers are used and why they are needed. Additionally, an example of medicinal product production (formulation and filling) is provided. Of course, every plant is different but these examples of uses of fluoropolymers in production equipment are not specific to production of APIs but in the same way can be and are used in all chemical production facilities.

General requirements for plants and equipment

To meet environmental regulations, materials are used that meet the legal requirements. The Technical Instructions on Air Quality Control, Germany (Technische Anleitung zur Reinhaltung der Luft) and the German Federal Water Act (Wasserhaushaltsgesetz) are examples of these requirements in Germany. High standards for manufacturing of medicinal products and medical devices are given via e.g. EU regulation 2020/561, Directive 2001/83/EC. The manufacturing equipment must not influence the purity of the medicinal product/ medical device, which means that migration from production equipment into the product (API) needs to be avoided. Therefore, materials used must also meet the requirements of food contact material (EU regulation 1935/2004, Commission Regulation (EC) No 2023/2006) and FDA regulations (e.g. FDA 21 CFR-Part 177.1550 for PTFE and FEP and US Food and Drug Administration (FDA) 21 CFR-Part 117.2600 for fluor-elastomers) for the manufacturing of medicinal products.

In order to meet the specified requirements, all equipment and equipment components, including gaskets, must be resistant to the acids, bases, and solvents to be used in order to avoid product (API) contamination and environmental emissions.

Contrast Media as Example

The production in process engineering systems takes place using stirred-tank reactors, heat exchangers, mixers, centrifuges, dryers, and filling stations.

Various acids and solvents are required to produce the iodinated contrast medium Ultravist, for example: thionyl chloride, ethylene chloride, sulfuric acid, hydrochloric acid and methoxyacetic acid chloride. The production in process engineering systems takes place using stirred-tank reactors, heat exchangers, mixers, centrifuges, dryers, and filling stations.
The following table (Table 1 Chemical Resistance of Typical Plant Materialsuses the example of seal materials to show that fluorine-free materials have no or insufficient chemical resistance.

Table 1 Chemical Resistance of Typical Plant Materials

Solvent/Acid	Chemical resistance of equipment materials at 20 °C [1,2,3])							
	Non-PFAS			PFAS				
	NBR	EPDM	VMQ (Silikon)	FKM (Viton®)	FFKM (Kalrez®)	PTFE	FEP	PFA
Thionyl chloride								
Ethylene chloride								
Sulfuric acid <=51%								
Hydrochloric acid <=36%								
Methoxyacetic acid chloride								

[1]) Literature sources: Dechema material table; BAM List 2021 (Bundesamt für Materialprüfung; Requirements for tanks for the transport of dangerous goods); Corrosion Data II; DuPont Brochure; SIS handbook 149, Knowledge gained during long production history

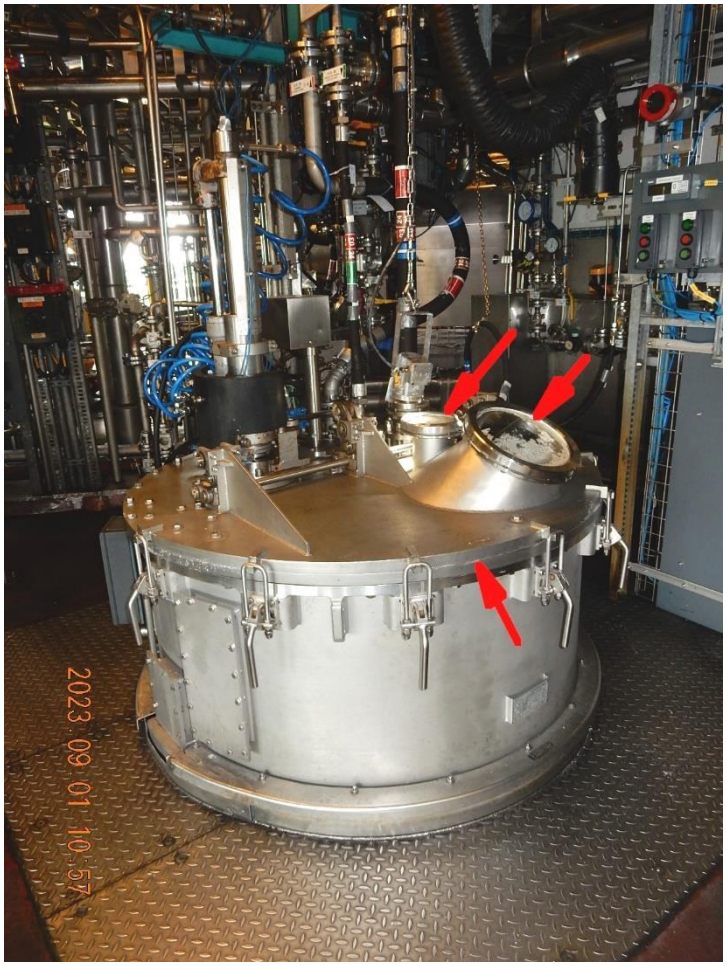
[2]) Rating: resistant partially resistant non-resistant unknown

[3]) Overview of typical available materials: NBR: nitrile butadiene rubber; EPDM: ethylene propylene diene monomer rubber; VMQ: vinyl methyl silicone; FKM: fluorine kautschuk material; FFKM: fluorinated fluorine kautschuk material; PTFE: polytetrafluoroethylene; FEP: fluorinated ethylene propylene; PFA: Perfluoroalkoxy alkanes

For the production of contrast media, a large amount of equipment and parts are required, in which fluoropolymers and fluor-elastomers are integrated. Examples include piping, hoses, pumps, safety valves, dryers, stirred-tank reactors, gaskets, etc. The fluoropolymers serve as corrosion protection, gaskets and/or construction materials.

The below example of a centrifuge used in the production of Ultravist shows the use of gaskets that are in direct contact with the contrast media. The centrifuge is used for solid/liquid separation of a suspension (red arrows = position of fluoropolymers).

Centrifuge



PTFE Gasket on viewing porthole

PTFE Gasket in product space

Summary

Considering the required resistance of the materials and their use in the equipment, we are not aware of possible alternatives to substitute the fluoropolymers and fluor-elastomers. The high quality demands placed on pharmaceuticals like X-ray contrast media, including their purity, and compliance with environmental regulations are currently only be met by using these materials.

Hormones as an Example

In this chapter the hormone Levonorgestrel is chosen as example. Levonorgestrel and its respective intermediates require, amongst others, the following solvents in the synthesis process: tetrahydrofuran, methanol, acetylene, and acetone.
Table 2 shows the chemical resistance of standard PFAS and non-PFAS materials against the above-mentioned solvents.

Table 2 Chemical Resistance of Typical Plant Materials

Solvent	Chemical resistance of equipment materials at 20 °C [1,2,3])							
	Non-PFAS			PFAS				
	NBR	EPDM	VMQ (Silikon)	FKM (Viton®)	FFKM (Kalrez®)	PTFE	FEP	PFA
Tetrahydrofuran								
Methanol								
Acetylene								
Acetone								

1) Literature sources: Dechema material table; BAM List 2021 (Bundesamt für Materialprüfung; Requirements for tanks for the transport of dangerous goods); Corrosion Data II; DuPont Brochure; SIS handbook 149; Knowledge gained during long production history

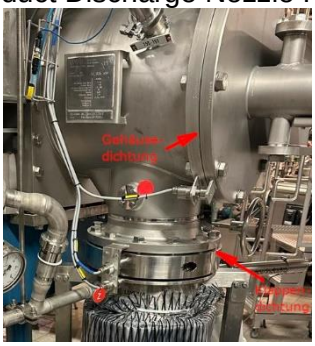
2) Conclusion: resistant partially resistant non-resistant unknown

3) Overview of typical available materials: NBR: nitrile butadiene rubber; EPDM: ethylene propylene diene monomer rubber; VMQ: vinyl methyl silicone; FKM: fluorine kautschuk material; FFKM: fluorinated fluorine kautschuk material; PTFE: polytetrafluoroethylene; FEP: fluorinated ethylene propylene; PFA: Perfluoroalkoxy alkanes

Examples for production equipment where fluoropolymers and fluor-elastomers are used in manufacturing of levonorgestrel are stirred-tank reactors, piping, pumps, hoses, and gaskets. Below a pressure filter and a pump are shown, both of which are used in the levonorgestrel manufacturing process.

Pressure filter

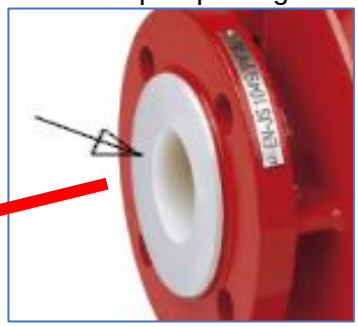
Product Discharge Nozzle FEP



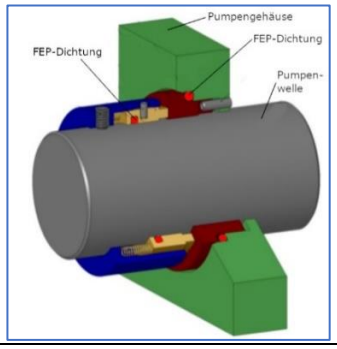
Housing Gasket Silicone lined with FEP

Pump with PFA lining

PFA pump lining



Detailed figure of shaft seal which contains FEP



Conclusion

No direct replacement alternative of fluoropolymers and fluor-elastomers, which enable manufacturing under high environmental (tightness of plant) and quality standards (GMP), is available for the levonorgestrel manufacturing as far as we can judge as downstream users. With a restriction of fluoropolymers and fluor-elastomers used in industrial production equipment, no manufacturing of levonorgestrel in the EEA would be possible as soon as spare parts or consumables are needed.

Formulation and filling of drug product

PFAS materials are not only used in small molecule API manufacturing equipment but also in formulation and filling of the final drug product.

Below some examples are displayed for membrane valves. These membrane valves are used in hot water/steam systems. The membrane valves contain a soft EPDM layer lined with heat resistant PTFE. The PTFE liner enables temperatures of 150°C which are needed for sterilization processes. The PTFE containing membrane valves are marked with pink arrows in the figures below, which shows how often these valve types are used in formulation and filling of drug products.

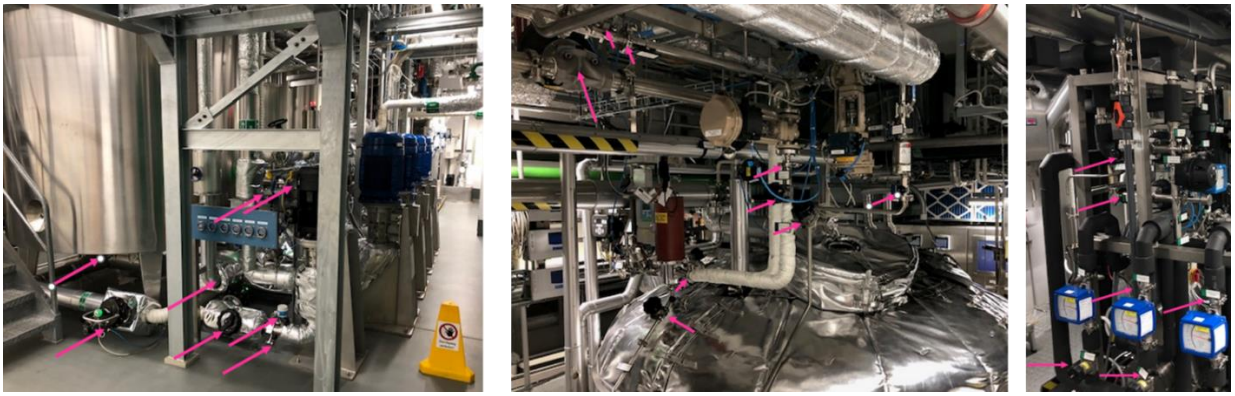


Figure 1 Clean Media – Generation and distribution, pink arrows mark membrane valves.

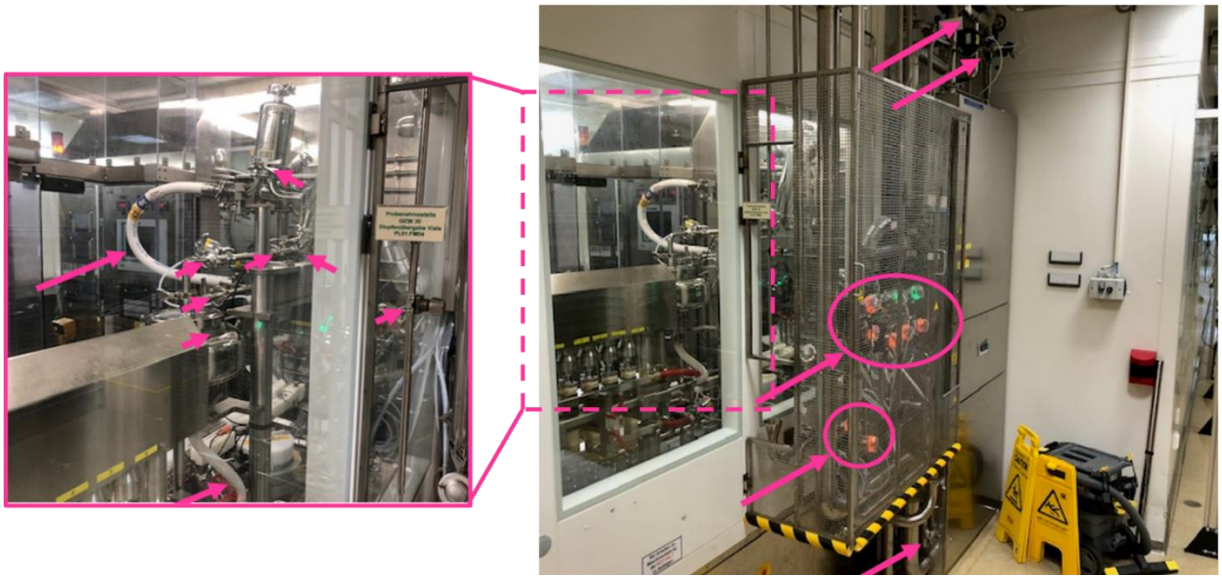


Figure 2 Filling line, pink arrows mark membrane valves.

Figure 3 Formulation area, pink arrows mark membrane valves.

Conclusion

The PFAS materials are used in this example mainly due to their heat resistant property. We as downstream users are not aware of alternative membrane valves which allow temperatures up to 150 °C. With a restriction of fluoropolymers used in industrial production equipment, no formulation and filling of drug products in the EEA would be possible as soon as spare parts or consumables are needed.

Importance of ability to produce API

For patients

Contrast media and their production in EU

Iodinated contrast media (ICM) are used to enhance X-ray based imaging procedures such as Computed Tomography (CT) or Cardiac Catheterization procedures. While for CT typically 30-40% of all procedures are contrast-enhanced, for cardiology or emergency department procedures contrast media are mandatory.

ICM are used in millions of imaging procedures every year, as those are an essential part of modern medicine, guiding the diagnosis and treatment in cancer indications, cardiovascular, neurological diseases, among many others.

Radiology and Cath Lab departments are highly organized modern healthcare facilities which are very sensitive to any type of disruption (e.g. shortages of ICM).

ICM are generic and have been on the market since the 1980s. Bayer is one of four original manufacturers – the oligopulistic market is characterized by fierce price pressure and very tight supply logistics. A recent COVID disruption at a key fill-and-finish site in China led to an ICM supply crisis in the US market, which could not be buffered by the other suppliers as ICM production is a relatively complex and costly process, needing a high level of long-term expertise.

Bayer Bergkamen traditionally produces the Bayer key ICM products to meet the global market demands (previously exclusively, now still producing the majority). The ICM products themselves do not contain fluorine and are therefore no PFAS APIs.

Bayer's ICM is used in about 20 million patient applications every year.

In case of any disruptions in the manufacturing process (e.g. non functioning equipment due to non availability of sealants) this will have an impact on imaging procedures for patients globally.

Levonorgestrel and its production in EU

Levonorgestrel was synthesized in the early 1960s and was introduced for medical use in combination with ethinylestradiol in 1970. This combination became a key component of combination birth control pills, contributing to the effectiveness of oral contraceptives.

Levonorgestrel is considered an essential medication and is listed on the World Health Organization's List of Essential Medicines. This recognition underscores its importance in global healthcare[i].

Levonorgestrel is a widely used progestin in various contraceptive formulations, including combined oral contraceptive pills, subcutaneous implants, and intrauterine devices (IUDs). It is also used for emergency contraception approved by the World Health Organization (WHO) and the FDA for preventing pregnancy when taken within 72 hours of unprotected sexual intercourse or when there is a presumed contraceptive failure[ii][iii].

Long-acting reversible contraceptives, which include the implant and both hormonal and non-hormonal intrauterine devices (IUDs), are highly effective and acceptable options requiring minimal routine follow-up or prescription renewal. Intrauterine contraception is used by around 160 million women worldwide, accounting for about 14% of all contraceptive users[iv].

The levonorgestrel-releasing intrauterine device is one of the most effective forms of long-acting reversible contraception (LARC). LARC has many advantages for women in terms of convenience and ease of continuation. The levonorgestrel-releasing intrauterine device is

equally effective in women of all ages (when using the pill, patch or vaginal ring, younger women have significantly higher contraceptive failure rates than older women). Other potential advantages of the levonorgestrel-releasing intrauterine device include its role in treating menorrhagia and dysmenorrhoea.

The World Health Organization (WHO) recommends that every individual is ensured the opportunity to make informed choices about their use of contraception without discrimination for a range of methods, including emergency, short-acting, long-acting and permanent methods. LARC should be among the available contraceptive choices for all women, including young and nulliparous women. The levonorgestrel-releasing intrauterine device is available and is a popular choice in the United States of America and European countries. Its use is increasing in Africa, Asia, and Latin America. Efforts aimed at facilitating broader access to the levonorgestrel-releasing intrauterine device in low and middle-income countries have increased since 2020. Notably, there are plans to add the method to product catalogues, to increase procurement of the method and to ensure that commodity funding does not prevent wider access to contraception[v].

[i] WHO Model Lists of Essential Medicines

[ii] Safety of levonorgestrel-alone emergency contraceptive pills (who.int)

[iii] Plan B One-Step (1.5 mg levonorgestrel) Information | FDA

[iv] K Gemzell-Danielsson et al. Thirty years of Mirena: A story of innovation and change in women's healthcare

Acta Obstet Gynecol Scand, 100: 614-618. https://doi.org/10.1111/aogs.14110

[v] 9789240021730-eng.pdf (who.int)

For the site

About the Bergkamen, NRW, Germany supply center site

The Bergkamen Supply Center is Bayer AG's largest location for the production of active pharmaceutical ingredients. Around 1,800 employees including trainees produce steroid hormones, contrast agents and active ingredients for innovative therapeutics in the highest purity.

This is done through an optimal combination of microbiological fermentation steps and chemical reactions, for which the site is known worldwide, particularly in the field of hormone synthesis.

The Bergkamen Supply Center also includes another area in Berlin-Charlottenburg. There, some of the active ingredients produced in Bergkamen are finely ground and prepared for further processing - be it as a tablet or as a solution. The focus of the work of the Supply Center Bergkamen is the production of active pharmaceutical ingredients in the required quality, quantity and time for the benefit of patients all over the world.

The Bergkamen site is the legacy Schering production site opened in the 1950ies and since then a key production site for the traditional product area contrast media and hormone-based contraception.

The products produced in Bergkamen (and in case of contrast media filled and finished at the Berlin Charlottenburg site) serve markets, patients and users globally.

For the described products Bergkamen is the key global production site.