ECHA: PFAS Restrictions under Consideration
Comments on Annex XV Report

Our company requests an exemption for the manufacture of components made from certain PFAS materials (PTFE, ETFE, PFEP, PFA, PVDF) that are regularly used in the production of medical isotopes or radiopharmaceuticals. In view of the specific requirements in the medical radioisotope and radiopharmaceutical production, including the acceptance of materials by EU and US FDA regulatory bodies, the use of components from these materials cannot be substituted in the foreseeable future. Restrictions on their use would inevitably lead to a halt of production and supply of radioisotopes and radiopharmaceuticals, with the according destructive consequences on the industry, health care systems, and patients.

Our company is a mid-sized German company with more than 500 employees, engaged in the development, production and distribution of radioisotopes for medical use (e.g. Lu 177, Ac 225), as well as of radiopharmaceuticals. The Radioisotopes are generally used by radiooncological centers and by the industry for the synthesis of radiopharmaceuticals being administered to patients with severe diseases, i.e. advanced cancers. Our company is the leading Lu 177 n.c.a manufacturer worldwide, and currently heavily investing in a new facility to cope with strongly increasing ww demands for this radioisotope (in fact, there is a current global shortage situation for Lu 177 n.c.a).

Our company is using appr. 100 components from established PFAS compounds, i.e. PTFE, ETFE, FEP (PFEP), PFA and PVDF, in its manufacturing processes for the radioisotopes; for the reasons described in the following, the used components from these materials cannot be skipped or replaced by other, made from non PFAS containing materials within the foreseeable future. Restrictions on the use of components made from the mentioned PFAS materials will make the manufacture of our products impossible, with dramatic impact on our company, their industrial or medical customers, the Healthcare system, and patients. Our company therefore requests that no restrictons are posed on the use of the mentioned materials, if the use is for the manufacture of components employed in the medical isotope or radiopharmaceutical manufacture.

Components from PTFE, ETFE, FEP (PFEP), PFA, PVDF (valves, tubes, capillaries, nuts, ferrules, locks, adapters, seals, locks, PTFE coated stoppers, PVDF filter membranes, incl. sterile filters) are widely used in radioisotope/ radiopharmaceutical manufacture: the favourable properties of components made from these materials are well established, they include high strength, toughness and self-lubrication in a large temperature range (up to 260 °C), good flexibility, extreme resistance against most chemicals and solvents also at higher temperatures, absence of leachables and extractables, physiological inertness and regulatory acceptance of the use in the manufacture of pharmaceuticals according to EU and US FDA guidelines.

In the manufacture of radioisotopes, especially the extreme resistance against concentrated acids (HCl, HNO3) and solvents is important, and the mechanical stability also under these conditions. Depending on the amount in our Lu 177 manufacture, e.g., the Lu 177 is formed in small amounts through the irradiation of Yb 176 with thermal neutrons; the dissolution of Yb 176 requires the prolonged heating with conc. HNO3 at high temperatures (up to 100 °C). Where increased resistance against (alpha, beta, gamma) radiation is required, e.g. where radioisotope containing solutions, including concentrated acid solutions at elevated temperatures, are in direct contact with valves,

seals, tubes etc., components made from PFAS materials with particularly high resistance against (alpha, beta, gamma) radiation are selected, e.g. ETFE. The advantageous properties of the material and its mechanical stability also in aggressive environment (e.g. chemical stress plus radioactivity) is of utmost importance to allow a controlled, safe manufacturing process. Due to the irradiation, most of the manufacturing steps are carried out in shielded hot cells, which do not allow a direct intervention by the operator in case of broken seals or capillaries or other damages related to the mentioned components. In such case, not only the batch is lost, but the manufacture in the respective line has to pause for days or weeks, until a reasonably safe decontamination is possible.

Components from PVDF in the process are mainly filters with PVDF membrane, incl. sterile filters; their use combines stabile filtration results with high resistance against chemically aggressive and radioactive solutions. Employment of such PVDF filters in the process for pre - and sterile filtrations is inevitable (radioisotope products and radiopharmaceuticals generally need to be labelled as sterile solutions), their use is long established in the pharmaceutical manufacture, and well accepted by the pharmaceutical regulatory and supervisory authorities.

Any potential replacement of mentioned PFAS components in the process would not only require comprehensive process and process validation studies, but also studies on potential degradation in the specific process environment, on leachables and extractables, likely followed by according toxicological studies, inevitably ww variation procedures for the pharmaceutical regulatory files, and finally the inclusion in the according EU and US listings of materials accepted for pharmaceutical manufacture. The outcome of such materials studies is open, the estimated time demand until a product specific and general regulatory clearance in any case > 15 years. The consequences for industry, health care systems, and especially for patients would be disastrous, if the restriction will not contain exemptions for the manufacture of components made from certain PFAS materials (PTFE, ETFE, PFEP, PFA, PVDF) that are regularly used in the production of medical isotopes or radiopharmaceuticals. Thus, it is highly recommended to reconsider the current restriction proposal.