

Budapest, 22 September 2023
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European Chemicals Agency
Telakkakatu 6, P.O. Box 400,
FI-00121 Helsinki

Subject: Comment on REACH restriction proposal of per- and polyfluoroalkyl substances

Dear Madam/Sir,

Please, allow me to draw your attention to our pharmaceutical industry association's comment on the REACH restriction proposal regarding per- and polyfluoroalkyl substances on which we have been working together with association member companies, followed by our addendum on protective groups containing fluorine.

Thank you in advance for your consideration.

Yours faithfully,

Ms Erika BURAI
REACH contact person
Egis Pharmaceuticals PLC

Enclosed:

- 1) The Hungarian Pharmaceutical Manufacturers' Association's position statement
- 2) Annex on pharmaceutical industry uses not identified in the restriction proposal
- 3) Addendum on protective groups containing fluorine

MAGYOSZ'S DETAILED POSITION STATEMENT

ON THE EUROPEAN USE OF "PER- AND POLYFLUOROALKYL SUBSTANCES" (PFAS),¹ CONSIDERING THE RESTRICTION PROPOSAL SET FORTH IN THE REACH² REGULATION

BACKGROUND AND BASELINE CONSIDERATIONS

Founded in 1990 to represent the Hungarian pharmaceutical industry, the Hungarian Pharmaceutical Manufacturers' Association (MAGYOSZ) has been operating in strategic partnership with the Ministry of Foreign Affairs and Trade, and thus indirectly with the Government of Hungary, since 2020.

The pharmaceutical industry is not only the oldest industry, but it also has extraordinary potential, acting as a flagship of the national and foreign economy, and is one of the most innovative processing industry branches in Hungary. According to financial reports submitted by the pharmaceutical manufacturer members of the Hungarian Pharmaceutical Manufacturers' Association, the companies' 2022 revenue exceeded HUF 1,500 billion, with export accounting for 81% of this sum. Furthermore, this traditional industry is a powerhouse of novelties with an expenditure on research and development (R&D) activities and on investments amounting to almost HUF 100 billion and more than HUF 90 billion annually, respectively, while employing almost 15,000 people and providing a living for 50,000 people indirectly.

However, the crisis caused by the coronavirus pandemic pointed out that a domestic and regional history of pharmaceutical manufacturing is a significant advantage for Hungary and the European Union, and thus production is on a stable footing. Domestic pharmaceutical manufacturers are of vital importance not only from an economical aspect, but for patient supply as well: currently, every other patient is cured in primary care using products from Hungarian manufacturers.

The pharmaceutical industry is a highly regulated industry, which has demonstrated excellent results in Europe in terms of compliance with quality, healthcare, safety and environmental regulations.

Founded in order to promote the safe use of chemical substances, the European Chemicals Agency (ECHA) published on 07 February 2023 the dossier specified in Annex XV of Regulation (EC) No 1907/2006 (REACH), proposing the restriction of a broad category of fluorinated substances called per- and polyfluoroalkyl substances (PFASs) as well as mixtures and articles containing such substances. Basically, they consider that the risk lies in the high persistence of PFASs which might result in their possible accumulation in the environment and food chains. The REACH restriction proposal affects at least 10,000 PFASs, covering the ban of their manufacturing, use and placing on the market. This is the largest restriction ever proposed in the European Union (EU), which has a significant impact on different industries, including the pharmaceutical industry.

The proposal contains two different restriction options: a full ban (1) and a ban with derogations (2). As far as MAGYOSZ has been informed, the latter one is preferred by ECHA as it includes some derogations.

In the REACH Regulation, neither Title I on general provisions nor Title VIII on restrictions³ specifies an exemption for pharmaceuticals or for the use in pharmaceuticals.

Although section 4.c of the restriction proposal⁴ provides a derogation to active substances in human and veterinary medicinal products, if approved, it would still exert a significant impact on the European healthcare industry, as the manufacturing of active pharmaceutical ingredient (API) using polyfluorinated constituents (intermediate products as per the REACH, intermediates) and starting materials, as well as the medicinal products containing the API would still fall under the scope of the restriction.

To ensure secure medicines supply, we would like to request the legislators for consideration of inclusion of pharmaceutical uses that are currently missing from the identified uses, derogations and

¹ <https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas>

² <https://echa.europa.eu/restrictions-under-consideration/-/substance-rev/72301/term>

³ https://single-market-economy.ec.europa.eu/sectors/chemicals/reach/restrictions_en

⁴ <https://echa.europa.eu/documents/10162/f605d4b5-7c17-7414-8823-b49b9fd43aea>



exemptions set in the restriction proposal. By pharmaceutical uses, we mean the manufacturing of active pharmaceutical ingredients and medicinal products in their finished state, including all substances used in all preceding and proceeding steps (reagents, intermediates, packaging material), all manufacturing technologies and systems (including analytical and research & development activities necessary for manufacturing) and the devices used.

GENERAL REMARKS

The PFASs defined in the Regulation **do not have** such hazardous properties that **are common to all substances belonging to this group**. Some fluoropolymers are approved even for contact with food. The concern is the persistence⁵ of either the substance itself or its decomposition products, however, the restriction proposal does not provide derogation for all PFASs that are clearly proved to be degradable. Therefore, one cannot claim that persistence would be a common property of the substance group to be regulated.

Transition period: the deadlines for substitution (either 5 or 12 years) are aligned to technical substitutions. Pharmaceutical regulatory deadlines are not considered, for example, mandatory stability testing or resubmission of the marketing authorisation of regulated products.

REMARKS FROM THE PHARMACEUTICAL INDUSTRY'S PERSPECTIVE

The Hungarian pharmaceutical industry is committed to complying with the regulations protecting human health and the environmental. The relevant health and environmental protection and socio-economical aspects are considered in the development of our sustainability strategies and during our operations. The pharmaceutical industry pays special attention to chemicals, including PFASs, to be manufactured, used, stored, transported and quality controlled in a closed system, so that risks are kept at the lowest level possible. We are committed to the responsible and sustainable use of PFASs and we are open to reporting in a reasonable manner to serve this purpose.

However, adoption of the restriction proposal might hinder the feasibility of the objectives set forth in the European pharmaceutical reform (Pharmaceutical Strategy for Europe⁶) intended to ensure a safe supply of medicines in Europe. This strategy aims for the following objectives among others: (1) providing access to affordable medicinal products to patients; (2) supporting the pharmaceutical industry's competitiveness, innovation and sustainability in the EU, as well as the development of high-quality, safe, effective and more environmentally friendly medicines (covering the entire lifecycle of medicinal products, in line with the objectives set forth in the European Green Deal); (3) managing drug shortages, improving preparations for and responding to crisis, as well as improving diversified and safe supply chains; (4) ensuring that the EU has a high impact on the global pharmaceutical industry by promoting high-level quality, effectiveness and safety regulations.

We are worried that the current wording of the PFAS restriction **will have a serious impact on the development and manufacturing of medicines EU-wide**, especially due to the extended definition of what a "PFAS" is and the extremely broad range of use of these substances. The reasons are as follows:

- Despite that **active pharmaceutical ingredients which qualify as PFAS** are exempted from the restriction, such APIs still cannot be manufactured within the European Union as the intermediates necessary for the manufacturing could neither be produced nor purchased from other sources due to their PFAS molecular parts.
- Those **active pharmaceutical ingredients that themselves do not qualify as PFAS** might be highly dependent on their PFAS processing chemicals (for example, solvents, catalysts, intermediates) or depend on fluoropolymers in their manufacturing equipment (for example, highly resistant coatings, sealings). This means for derogated substances, where their European development and manufacturing are still not covered by derogation, that the processes of production and procurement from other sources will likely be forced to leave Europe.

⁵ Persistence: the property of a substance to remain chemically unchanged in an environmental compartment (<https://echa-term.echa.europa.eu/>)

⁶ https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en



- **There is no alternative to active pharmaceutical ingredients.** The use of fluorine in the API molecule is an indispensable part of the development of effective and safe candidates. Essentially, any modification to the API molecule would require the development of a completely new candidate. Drug development process generally takes 12 years. If the restriction proposal is accepted as it is, PFAS active pharmaceutical ingredient candidates from the last 12 years cannot proceed from research to the subsequent phase, potentially causing a 12-year gap in development for many candidate APIs. There are no alternatives for APIs, developmental products, **starting materials and intermediates**, as they impact at molecular level due to the unique properties of fluorine-containing unique molecular structures.

According to the above reasons, if intermediates and the affected processing chemicals, thus the manufacturing of active pharmaceutical ingredients, are forced outside of Europe, a possible disruption of the supply chains can lead to a shortage of APIs and medicinal products, rendering European pharmaceutical manufacturers, thus indirectly the healthcare institutions and the general population, to a position of economic dependence.

In addition to medicinal products and active pharmaceutical ingredients, the restriction would also put other areas of the healthcare industry at risk. PFASs present in **medical devices** directly or in their sterile packaging would also fall under the scope of the restriction, which would be of concern for those patients in need who need these drug storage, dispensing and drug deliver devices. If adopted, the PFAS restriction will likely have a negative impact on the entire range of medicinal products manufactured and placed on the market in the EEA, or, in specific cases, exported.

The manufacturing and placing on the market of APIs, medicinal products and medical devices are subject to separate regulations and authorisation procedures specific for this sector. Products which already have such authorisation have not been considered separately in the restriction proposal, therefore a general restriction of these products leads to regulatory contradictions.

If **restriction option 1** is applied, **all chemical, pharmaceutical and biotechnological manufacturing would have to leave the EEA** as manufacturing and development might be highly dependent on fluoropolymers. From a manufacturing safety aspect, it can also be claimed that there is no alternative substance due to the beneficial physicochemical properties provided by fluorinated structural elements. **Non-substitutability would have a serious impact on the manufacturing of APIs and medicinal products, and thus the supply of medicines.** The proposed restriction would cover already approved active pharmaceutical ingredients, packaging of medicinal products authorised for marketing, their administration devices as well as the equipment and production lines necessary for manufacturing. The same applies to restriction option 2, albeit to a smaller extent.

Currently, Europe's share of global pharmaceutical industry income amounts to 23.4%, while research and development expenditures make up an estimated sum of 41.5 billion Euros (2021, statista.com). EPPA (www.eppa.com) has carried out a socio-economic impact analysis in cooperation with the European Federation of Pharmaceutical Industries and Associations (EFPIA) member companies, which will be submitted by EFPIA to ECHA during the open consultation period, supporting the consequences that the proposed restriction will foreseeably have on the pharmaceutical industry and the supply of medicinal products.

Number and use of PFASs identified by 5 MAGYOSZ member companies* so far:

Number of PFASs identified at 5 MAGYOSZ member companies	Number of affected finished products (active pharmaceutical ingredients)	Active substance	USES			
			Commercial manufacturing: raw material, intermediate, solvent, reagent	Packaging material	R&D use	Identified alternative is available
126	53	12	103	2	37	Appropriate alternative could not be specified in any of the cases so far

*The survey is incomplete as, for example, the assessment of packaging materials has not been carried out so far at most member companies, therefore the number of identified uses is **expected to rise significantly** in the upcoming months.



The table does not include PFAS-containing equipment and technological devices available at all companies (filter-dryers, vacuum evaporator, containers, mixer devices, fermenters, separators, evaporators, decanters), the integrated flatseals, O-rings, shaft seals, compensators, folds, container coatings, tubes, pumps, bearings, cogwheels, sealing cords, self-adhesive sealings, maintenance accessories, as well as parts of tableting machines and injection lines. Laboratory analytical equipment and tools, which are of vital importance in production runs for quality control, are also part of the list.

Without the above, no production is feasible in the absence of suitable and approved alternatives.

REMARKS CONCERNING THE USE AND EMISSION OF PFASs BY THE PHARMACEUTICAL INDUSTRY

In the case of **fluoropolymer-containing equipment for industrial use**, PFASs remain integral parts of the equipment even at the end of their lifecycle (they are not emitted). Therefore, the waste phase is the only source of emission which can be controlled by appropriate waste treatment. Restricting the use of chemicals might become devoid of reason if the objective of the restriction is feasible using other measures. Restriction of future use of PFASs in equipment would pose challenges to the pharmaceutical industry by hindering or preventing subsequent procurement of spare or replacement parts. This **might lead to an unjustified shortening of the equipment's usability and lifecycle**, which is not reasonable, moreover, should be avoided from waste management and sustainability perspectives. Due to the size of the equipment used in the pharmaceutical industry, their scrapping would generate an extremely high volume of waste, including the preliminary entry of PFASs in the waste stream.

As for the **packaging** of medicinal products and medical devices, emission depends on the national waste management provisions. In Hungary, waste disposal incinerators are available which use best available technology to clean gas fumes under strict authority emission control. A characteristic use of PFASs for packaging is a thin fluoropolymer foil (generally PCTFE or ETFE) laminated with other plastics or elastomers, thus facilitating incineration. As published, PFASs might become mineralized during incineration⁷.

In some cases, there are **alternatives to fluoropolymers in manufacturing, packaging and in devices**. However, required properties include resistance to heat, light, chemicals, the passing of time as well as wear and tear, which is automatically associated with persistence. This means that most likely, the alternatives are also persistent substances. During manufacturing and packaging, the use of fluoropolymers is closely related to other aspects of sustainability (recyclability, long service life, durability, production or transportation resources/emission, energetical considerations, etc.). These environmental management compromises are not considered if the regulation is based only on the chemical characteristics of the substance.

The **benefits** of fluoropolymers in manufacturing, packaging and devices include the following: heat and chemical stability; smooth, hard surfaces which are easy to clean and disinfect; excellent barrier properties which protect the product from air, humidity, contamination, substances potentially dissolved from the packaging, as well as particles. This ensures product safety and quality over their entire shelf life, which are aspects of special importance in the pharmaceutical industry as human lives might be at stake.

In the case of PFAS **active pharmaceutical ingredients**, emission from the use by patients is assessed as part of the marketing authorisation procedure, within the scope of an environmental risk assessment. Pharmaceutical industry initiatives such as PIE (Pharmaceuticals in the Environment), IMI (Innovative Medicines Initiative) and PREMIER (Prioritisation and risk evaluation of medicines in the environment) have been launched to enhance the environmentally friendly properties of active pharmaceutical ingredients. Additionally, disposal systems are created and developed for unused PFAS active pharmaceutical ingredients.

⁷ <https://www.sciencedirect.com/science/article/pii/S0045653519306435>



PROPOSAL

In line with the EFPIA position paper, MAGYOSZ **kindly requests the consideration of final or indefinite-period derogations** covering the following items:

- **PFAS active pharmaceutical ingredients and the intermediates generated and used during their synthesis, including transported isolated intermediates and manufacturing reagents, as well as excipients (for example, solvents and catalysts) used during the manufacturing process**, adding these to the particulars described in restriction option 2 so that these products may still be manufactured and placed on the EEA market. Remark: A ban would limit patients' access to safe and approved medicines in Europe, including life-saving and anti-cancer medicinal products. The Model List of Essential Medicines⁸ published regularly by the World Health Organization (WHO) lists several active pharmaceutical ingredients which are identified as PFASs. If the restriction proposal were adopted as currently is, manufacturing of these APIs would be forced outside of the EEA, potentially resulting in a shortage of medicines and dependency on third countries.
- Extending the above-referred exemption to non-EU, i.e., not registered as per Directive 2001/83/EU, active pharmaceutical ingredients and developmental products (product and process orientated research and development [PPORD] according to REACH) as well. A ban imposed at any time would force manufacturing and research & development out of the EEA. Disruption of the supply chain would have a serious impact on patient care. Negative consequences could also be expected from economic and innovation aspects if the EEA would not be suitable to carry out clinical research on new API candidates.
- Fluoropolymers for industrial use, according to the management plans specified in Section 8 of restriction option 2. No data is available concerning the presence of fluoropolymers in more complex products and devices, as there are no information, labelling, registration or publishing requirements within the supply chain. Restricting the exemption to industry sectors (foods and feeds in Section 6.a of the restriction proposal, or petroleum industry and mining in Section 6.f) triggers issues with definitions and justification. In the industry, emission can be regulated and is limited to the waste phase only.
- Packaging materials of medicinal products and devices according to the particulars specified in Section 6.l of restriction option 2, however the scope of the derogation should be extended not only to the PCTFE substance but to all fluoropolymers approved by drug regulatory agencies, without time limitation. Besides technical feasibility, any substitution also requires regulatory measures to be considered in the roadmap in order to prevent any disturbances affecting the availability of medicines, and which are unlikely to be resolved in 13.5 years. The deadline specified for the replacement depends on the technology and cannot be defined in a uniform manner, furthermore all changes are followed by a validation period.
- Regarding the individual use of PFASs identified in the pharmaceutical industry supply chain. These include starting materials, reagents, solvents, catalysts as well as single-use or repeat-use devices necessary for drug manufacturing and any related processes, including quality control or diagnostic testing.
- Each and every already approved medicinal product in order to prevent regulatory contradictions. This includes medicines or medicinal products with a valid marketing authorisation obtained according to Directive 2001/83/EU, as well as medical devices as per Regulation (EU) 2017/745 (MDR).

⁸ <https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02>



ANNEX I – PHARMACEUTICAL INDUSTRY USES NOT IDENTIFIED IN THE RESTRICTION PROPOSAL

This is a list of identified methods of use in our industry, including those which are completely or partly covered by the derogations specified in restriction option 2. For your convenience, all uses are listed where the proposed exemptions are indicated if relevant.

The pharmaceutical industry has identified the following methods of use for PFASs:

Active pharmaceutical ingredients

- EU active pharmaceutical ingredients qualifying as PFAS by definition, in line with the derogation included in restriction option 2 (**NOT** a missing use [Section 4.c of the restriction proposal]) and further processed goods containing them (medicinal products).
- Active pharmaceutical ingredients qualifying as PFAS which are intended for exporting and are not approved according to Regulation (EC) No 726/2004 or Directive 2001/83/EC, as well as further processed goods containing them (medicinal products).
- Manufacturing and use (e.g., for clinical tests) of PFAS API developmental products within the scope of product and process orientated research and development (PPORD), as well as further processed goods (medicines, active pharmaceutical ingredients).

Other ingredients (excipients)

- Presence of such excipients in medicinal products that contain PFAS impurities up to the approved concentration. A certain level of impurities is inevitable even for the highest quality medicines. 100% purity is extremely rare. In our opinion, excipients used in medicinal products seldom can comply with the concentration limits specified in Section 2 of restriction proposal 2, whereas other (and also strict) pharmaceutical regulations allow a higher proportion of impurities.
- Propellant gases of dosing inhalers – use is **NOT** missing as it is included in Table 2 of the REACH Annex XV restriction report but the derogation is required.

Fluoropolymers for industrial use: equipment and disposables

- Chemical industrial, pharmaceutical industrial, biotechnological, sterile manufacturing: fluoropolymers in manufacturing equipment including spare and replacement parts (reactor lining, sealings, tube lines, non-adhesive coatings, surfaces, filtration units, etc.) where fluoropolymers come in contact with the product and can affect its quality.
- Chemical industry, pharmaceutical industry, biotechnology sectors: PFSA disposables and single-use goods (filters, sachets, tubes, etc.) where fluoropolymers come into contact with the product and can affect its quality.
- Manufacturing: fluoropolymers not contacting the product in complex equipment, including insulation material, mechanical parts, spare and replacement parts.
- Analytical laboratory equipment, for example teflon tubes, valves, sealings, filters, etc.

Raw and starting materials, chemical intermediates, reagents, solvents, excipients used in production, including storage, transportation and quality control

- Chemical and biotechnological manufacturing of PFAS and non-PFAS active pharmaceutical ingredients: PFAS reagents, catalysts and ligands or solvents which do not become integral part of the API molecule, for example homogenous catalysts, i.e., the Crabtree/Pfaltz-type catalysts or other noble metal catalysts containing CF₃ substituted ligands, trifluoro-acetic acid, hexafluoro-isopropanole, anhydrous trifluoro-methane-sulphonic acid, trifluorotoluene, etc.
- Chemical production of PFAS active pharmaceutical ingredients: PFAS raw and starting materials, as well as intermediates as building blocks of the API molecule.
- Chemical production of excipients: PFASs used as processing excipient for the manufacturing of functional excipients.



- PFAS substances and reagents used during quality control activities set out in product authorisations and specifications, e.g., European Pharmacopoeia monographs. These include, for example, trifluoroacetic acid (TFA) in the mobile phase of high-performance liquid chromatography (HPLC); perfluorobutanoic acid (PFBA) as ion-pairing reagent in chromatography; N-methyl-bis(trifluoroacetamide) (MB-TFA), N,O-bis(trimethylsilyl)trifluoroacetamide (BS-TFA) and N-methyl-N(trimethylsilyl)trifluoroacetamide (MS-TFA) for the production of silyl derivatives in gas chromatography or other methods.
- Storage, manufacturing and transportation: non-polymer PFASs in equipment, for example in electric parts, refrigerants in HVACR equipment and low-temperature refrigerators, refrigerants in storage and transportation, including spare and replacement parts.
- Quality control and research & development: non-fluoropolymer PFASs in equipment, for example in electric parts, in diagnostic laboratory tests, in refrigerants of laboratory equipment and temperature-regulated centrifuges.

Packaging of medicines or medicinal products: immediate packaging and closing foils

- Immediate packaging of medicines and APIs, like containers or closures coming into contact with the product, using approved fluoropolymer substances or coatings like PCTFE, ETFE or PTFE. Applies for blisters, sachets, tubes, other metal or plastic containers, vial stoppers or other coated elastomers – according to Section 6.l of restriction option 2, this is **NOT** a missing use, **IF** the legislators consider medicines as ‘medicinal preparations’ too. For medicinal preparations, the terminology needs to be clarified. Currently, the draft wording is limited to PCTFE-based packaging, which is insufficient in the pharmaceutical industry to ensure that their products are always packaged in compliance with drug safety and quality requirements.
- Packaging containing fluoropolymer foil that protect medicines or medical devices from air, humidity and other contaminants or maintain their sterility and stability, in accordance with Sections 6.m and n of the restriction proposal, but not limiting the wording to certain products or materials – this is **NOT** a missing use as it is included in Table 2 of the relevant REACH Annex CV report, although a general derogation is missing.

Drug dispensing (delivery) devices

- Fluoropolymer substances used for the operation and in components of devices applied in one integrated medicinal product as regulated by the pharmaceutical Directive 2001/83/EC; device components are covered by Annex I of Regulation (EU) 2017/745 (MDR) on general safety and performance requirements, according to Article 117 of the MDR. Accordingly, it is accepted that (1) the device component conforms with the MDR (has a CE marking); or (2) conformance with the MDR Annex I is assessed and certified by a notified body if no CE marking is available; or (3) meets the previous requirements set forth in previous regulations (e.g., pre-filled syringes, pre-filled autoinjector pens, on-body delivery systems). It is **NOT** a missing use **IF** the device component is coated (Section 6.d of the restriction proposal concerning the coating of dosing inhalers and Section 6.j on the application of the coating of medical devices other than dosing inhalers) but use is missing in case of other applications (parts, membranes, etc.).
- Fluoropolymer substances applied for the operation and in components of MDR-compliant (CE marked) medical devices used in conjunction with specified medicines which may be packaged separately or with medicines (for example, refillable pens or empty syringes which can be packaged together with injectable medicinal vials). It is **NOT** a missing use **IF** the device component is coated (Section 6.d of the restriction proposal concerning the coating of dosing inhalers and Section 6.j on the application of the coating of medical devices other than dosing inhalers) but use is missing in case of other applications (parts, membranes, etc.).
- Fluoropolymer substances as long as their use is justified for the operation of drug dispensing devices and their components during the development of MDR-compliant medical devices.



EGIS' ADDENDUM ON PROTECTIVE GROUPS CONTAINING FLUORINE

During multi-step chemical syntheses, we often face with the problem of chemoselectivity, in which several similar functional groups of the molecule can react simultaneously during a reaction. This is particularly harmful, since during our processes we want to achieve as much selectivity as possible in the steps (aiming for clear chemical transformation) and as much production as possible. At the same time, we try to use as simple and as less cleaning processes as possible. Overall, we therefore try to maximise the atom-efficiency of our processes and, in parallel, minimise the generation of waste and pollutants. To solve this problem, the "protective group concept" was created for the chemical transformation of multifunctional compounds in general, the principle of which can be summarised with the following elementary steps:

- Some of the functional groups of a molecule with similar reactivity are transformed by a selective chemical reaction in such a way that their reactivity changes temporarily, or more precisely, they become inactive in a certain chemical process. This step is called "functional group masking", and the reactant with which this is achieved is called 'protective group'.
- The desired chemical transformation is carried out on the compound with the partially blocked, "masked" functionality.
- In the process closing step, the protective group is selectively removed, thus the initial molecular functionality is restored.

The main purpose of protective groups is to significantly improve the selectivity of the subsequent reactions that follow. An important consequence of the above is that, although these protective groups do not appear in the final molecules, but they generate unavoidable temporary intermediates on the synthetic routes.

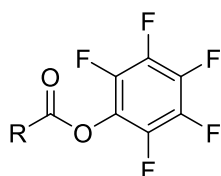
For the practical feasibility of the concept above, enormous research and innovation resources have been invested worldwide, and today, the daily application of this knowledge is essential in organic chemical synthetic work. Moreover, the research of more selective protective groups has never stopped but is continuously going. Selectivity and reversibility are key issues in protective groups' chemistry. This can be ensured by fine-tuning at molecular level only, where the use of benefits of unique properties of the high electronegativity fluorine atom is unavoidable and irreplaceable.

You can find several important protective groups below which would fall under the scope of the proposed restriction. Obviously, this list is far from complete and further items can be added any time.

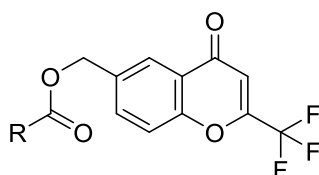
[Reference: P.G.M. Wuts & T.W. Greene: Green's protective groups in organic synthesis; 4th edition, Wiley-Interscience, 2007]

Carboxyl group protection

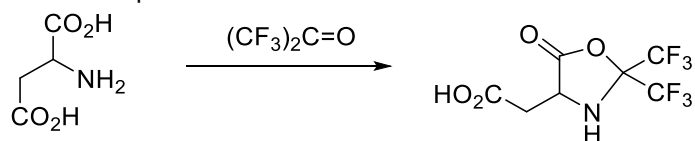
a) Pfp



b) Tcrom Ester

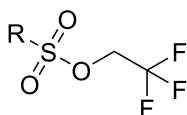


c) Aminoacid protection



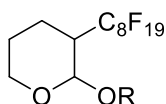
Sulfonic acid protection

a)

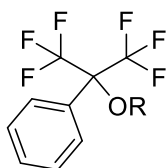


OH protection

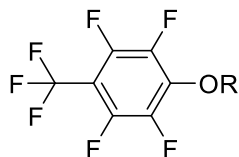
a)



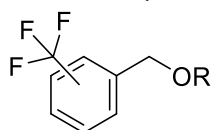
b)



c)

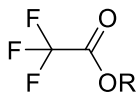


d) in 2-, and 4-positions

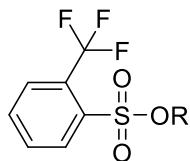


Various „fluorous-alkyl silyl ethers“

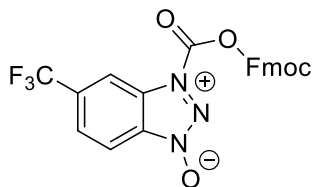
e)



f)



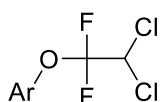
- g) Reagents, necessary for incorporation of protective groups
e.g.:



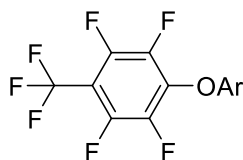
for Fmoc formation

Phenolic OH protection

a)

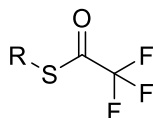


b)



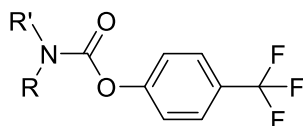
Thiol protection

a)

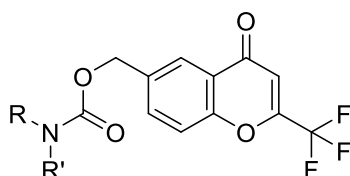


Amino group protection

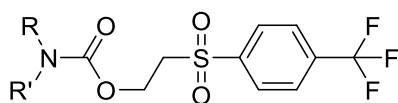
a)



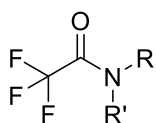
b) Tcroc-NRR'



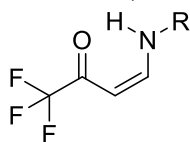
c) Tsc-NR₂



d) TFA

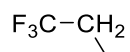


e) Tfav-NR₂ (Aminoacid protection)



Phosphate group protection

a)



b)

