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

Disclaimer: This document was prepared in good faith by represented associations for the purposes of preparing the public consultation response to the PFAS Restriction proposed under Title VIII of the REACH Regulation. The timeframe of the survey undertaken to gather the evidence was very short and companies therefore prioritised the compounds for which they would provide information with the intent to provide as much substantiated information as possible during the ECHA consultation period. The information received does not cover the full EU portfolio of the human pharmaceutical industry.

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1. Executive Summary

The European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Fine Chemicals Group (EFCG), the Association of the European Self-Care Industry (AESGP), Medicines for Europe (MfE) and Vaccines Europe represent the major associations of the European human pharmaceutical supply chain.

The restriction proposal plans to restrict the manufacture, marketing and use of per- and polyfluoroalkylated substances and will be the widest ever put in place, as it could concern up to 10,000 substances and would have an irredeemable impact on many industrial sectors, including the essential health products and technologies sector. The procedure currently underway could lead to a ban on all PFASs by 2027, with very limited derogations.

It is our interpretation that the most important socio-economic impact to evaluate, is non-availability of medicinal products on patients. The associations therefore gathered evidence across their membership to justify derogations, to prevent medicine shortages, and to inform ECHA and the Commission of the potential impact of the PFAS Restriction on medicinal product supply chain.

Such a restriction will have an in-depth impact on the EU's Strategic Autonomy targets and competitiveness, as well as on the accessibility and availability of medicinal products for European citizens. The expected consequences of the ban will jeopardise all production of pharmaceutical substances in Europe and will work against the efforts of most European Member States to relocate critical pharmaceutical production chains on EU territory. Furthermore, it will definitely curb the initiative of European Member States to promote a "Critical Medicines Act" to reduce Europe's health dependence on non-European countries.

To allow for the continued research, development and manufacturing of medicines including biopharmaceuticals and vaccines, the products in scope of specific regulations should generally be derogated from a universal PFAS restriction, including all steps which are necessary for their manufacturing, packaging and delivery devices, in the EEA.

Highlights on evidence gathered:

- The 40 companies participating in the survey identified 1922 active substances, which will be impacted by the proposed Restriction. At least 93% of APIs and or medicinal products are produced in a manufacturing facility which depends upon fluoropolymer use in piping, equipment (process/utilities), & consumables for process safety and regulatory reasons;
- Only 7% (139 out of 1922) of APIs contain the PFAS moiety, and therefore fall under the proposed derogation for APIs
- 9.5 % (169 out of 1794) APIs were reported to be undergoing R&D, at an EU manufacturing facility, and would have to be produced at a non-EU facility
- Only 86 APIs out of 1,922 (4.4%) are manufactured completely outside of the EU showing the importance of pharmaceutical manufacturing in the EU;
- The number of critical medicines impacted if EU manufacturing operations ceased, results in 61% - 78% when comparing with EU member state critical medicines lists.
- 674 references are on the WHO essential medicines list.

2. Glossary of Terms

Raw Material	"A raw material is a substance or mixture of substances that is used in the production process of a drug substance, but which is not incorporated as a significant structural fragment into the structure of the drug substance (e.g. process solvent, catalyst, reagent)". => Pharmaceutical manufacturers are typically the downstream user of raw materials
Starting Material	API starting material is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. API Starting Materials normally have defined chemical properties and structure. ICH Guideline Q7A => Meets the definition of Intermediate as defined in REACH Article 3(15)
Pharmaceutical Intermediate	A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. [ICH Guideline Q7A] => Meets the definition of Intermediate as defined in REACH Article 3(15)
Active pharmaceutical ingredient	An active substance or API (Active pharmaceutical ingredient) is intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. [ICH Guideline Q7A "Good Manufacturing Practice Guide for Active Pharmaceutical ingredients"] => As per Article 2(5)(a) of REACH – Active substances used in the manufacture medicinal products are exempt from Authorisation and Registration
Medicinal Product	Medicinal product as defined in Directive 2001/83/EC - Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.
Excipient	A constituent of a medicine other than the active substance (https://www.ema.europa.eu/en/glossary/excipient) => As per Article 2(5)(a) of REACH – excipients used in the manufacture medicinal products are exempt from Authorisation and Registration
Bulk product	Any product which has completed all processing stages up to, but not including, final packaging [EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines]
Finished medicinal product	A medicinal product which has undergone all stages of production, including packaging in its final container [EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines]
Drug Delivery Device	Drug delivery device (non-integral): any device intended to administer medicinal products, tissues or cells of human or animal origin, or their derivatives, or biological substances. A non-integral drug delivery device is governed by Regulation 2017/745 and is CE marked. (Regulation 2017/745 (EU MDR – definition 9)) Drug delivery device as part of single integral product: if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC. A single integral drug delivery device is not CE marked and is subject to a Notified Body Opinion on the conformity to Annex I General Safety and Performance Requirements. (EMA guideline on quality documentation for medicinal products when used with a medical device)

On-site or transported intermediate	As per Article 3(15), an intermediate is a substance that is manufactured for and consumed in or used for chemical processing in order to be transformed into another substance (hereinafter referred to as "synthesis"). If the manufacture and subsequent synthesis of an intermediate into another substance takes place on the same site, this is an on-site intermediate. If an intermediate is transported between or supplied to other sites, for synthesis into another substance, this is a transported intermediate. => Article 2(8)(b) of REACH - intermediates, as defined in Article 3(15), are exempt from Authorisation. Article 68(1) of REACH - restrictions in general do not apply to on-site intermediates

3. Introduction

The Associations acknowledge the bona fide human health and environmental risk associated with some of the fluorine-containing compounds that fall within scope of the proposed PFAS Restriction. The proposed PFAS restriction is a deliverable of the chemical strategy for sustainability[1], the objectives of which are strongly supported by our sector. However, the PFAS Restriction as proposed has the potential to conflict with the pharmaceutical strategy for Europe[2], which aims to support competitiveness, innovation, and sustainability of the EU's pharmaceutical industry. It is our interpretation that the proposed universal ban on PFAS will accelerate the erosion of innovation in EU, discourage medicine manufacturing, jeopardize jobs and growth as well as negatively impacting patients' access to medicines.

More than 10,000 PFAS chemicals could fall within the scope of the PFAS Restriction, which makes it the most complex ever proposed in the EU. For example SEAC guidance (SEAC-52 of 15 September 2021[3]) on the preparation of the potential impact of a proposed restriction on consumers, notes an exception for medicinal products, where patients stand to lose the corresponding health benefit. It is our interpretation that the most important socio-economic impact to evaluate, is non-availability of medicinal products on patients.

As part of the preparation of a submission to the ECHA consultation on the proposal for an EEA ban on all PFAS, the European based human pharmaceutical trade associations carried out a survey across their memberships to outline how the proposed PFAS Restriction could impact patient access to medicines and hinder the utilisation of pharmaceutical manufacturing capacity in the EU. The objective of this work was to gather evidence to justify derogations, to prevent medicine shortages, and to inform ECHA and the Commission of the potential impact of the PFAS Restriction on medicinal product supply chains.

4. Survey Methodology

This report presents the findings of a comprehensive industry-wide inter-association survey of pharmaceutical manufacturers in Europe. A survey questionnaire was open to members of the aforementioned trade associations over a 6-week period in July and August 2023.
To aim of this survey was to identify:

- Which pharmaceutical substances are currently relying on the use of PFAS chemicals in their manufacturing processes, composition, and packaging?
- What would the impact of the restriction be on these products and the patients who rely on them?

Given the short timeframe of the ECHA consultation, a full assessment of companies' portfolios was not feasible for all respondents. Member companies with larger product

[1] https://environment.ec.europa.eu/strategy/chemicals-strategy_en
[2] https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en
[3] https://echa.europa.eu/documents/10162/0/afa_seac_surplus-loss_seac-52_en.pdf/5e24c796-d6fa-d8cc-882c-df887c6cf6be?t=1633422139138

portfolios were instructed to prioritise the active substances included in the survey. Therefore, the received findings represent an "at minimum" estimation of PFAS use in pharmaceuticals and should be seen as a starting point in the further exploration of the overall impact of the ban on the industry and patients. The scope of the survey covered:

- APIs in manufacturing and packaging operations at a facility in the EEA and / or
- Medicinal products with PFAS constituents present in the intermediate packaging or drug delivery device of a medicinal product placed on the market in the EEA.

Respondents were asked to provide ATC code[4] data and number of global marketing authorisations for each active substance in company product portfolios. By obtaining the number of impacted active substances associated with each ATC code, it was possible to identify the disease states that are affected most and summarise epidemiology information from publicly available sources. Using ATC data, it is possible to conduct a search of critical medicines lists e.g. WHO Essential Medicines List, EU Member State's critical medicines lists. In addition, respondents were asked to indicate if an active substance is on the WHO Essential Medicines list.

In addition to EU medicinal products legislation, raw materials and other chemicals used in pharmaceutical production facilities are regulated by REACH. Therefore, respondents were asked to indicate if an active substance:

- Is produced in a manufacturing facility which depends upon fluoropolymer use in piping, equipment (process/utilities), and consumables and / or
- Containing a CF_2 / CF_3 functional group which is specified in the marketing authorisation of medicinal product.

In this survey, a specified substance refers to a raw material, solvent, catalyst, reagent, starting material[5], intermediate, active pharmaceutical ingredient, excipient listed in the CTD (common technical document). The CTD is submitted as part of a marketing authorisation application and includes a description of the manufacturing process, in which specified substances are identified. As already indicated the proposed restriction (RO2) as written only proposes a derogation for active pharmaceutical ingredients with EU marketing authorisation containing a CF_2 / CF_3 functional group.

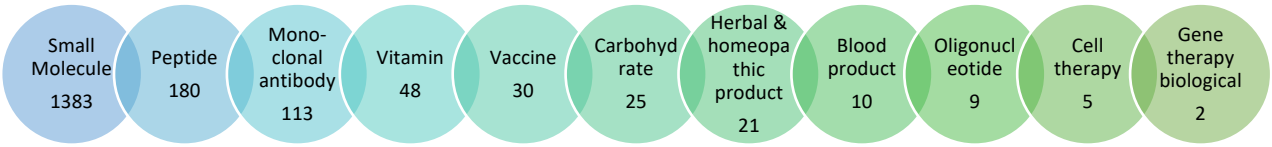
The PFAS restriction, as phrased in the proposal, will generate a significant number of changes to the marketing authorisations of medicinal products. This survey does not evaluate the time and capacity constraints for EMA, national or global health authorities. It is foreseen that these regulatory agencies would be faced with a significant volume of submissions for variations to marketing authorisations.

[4] The ATC (Anatomical Therapeutic Chemical) code is an internationally accepted classification system for medicines which is maintained by WHO. An ATC code is a unique identifier assigned to a medicine according to the organ or system it works and how it works.

[5] API starting material is defined in ICH Guideline Q7A - a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. Starting material meets the definition of an Intermediate as defined in REACH.

5. Survey Findings

Data was received across 40 companies representing a range of prescription-only medicines (POMs) and over-the-counter (OTC) products, 80 % and 20 % respectively. This accounted for 47 677 global marketing authorisations across 12 product categories

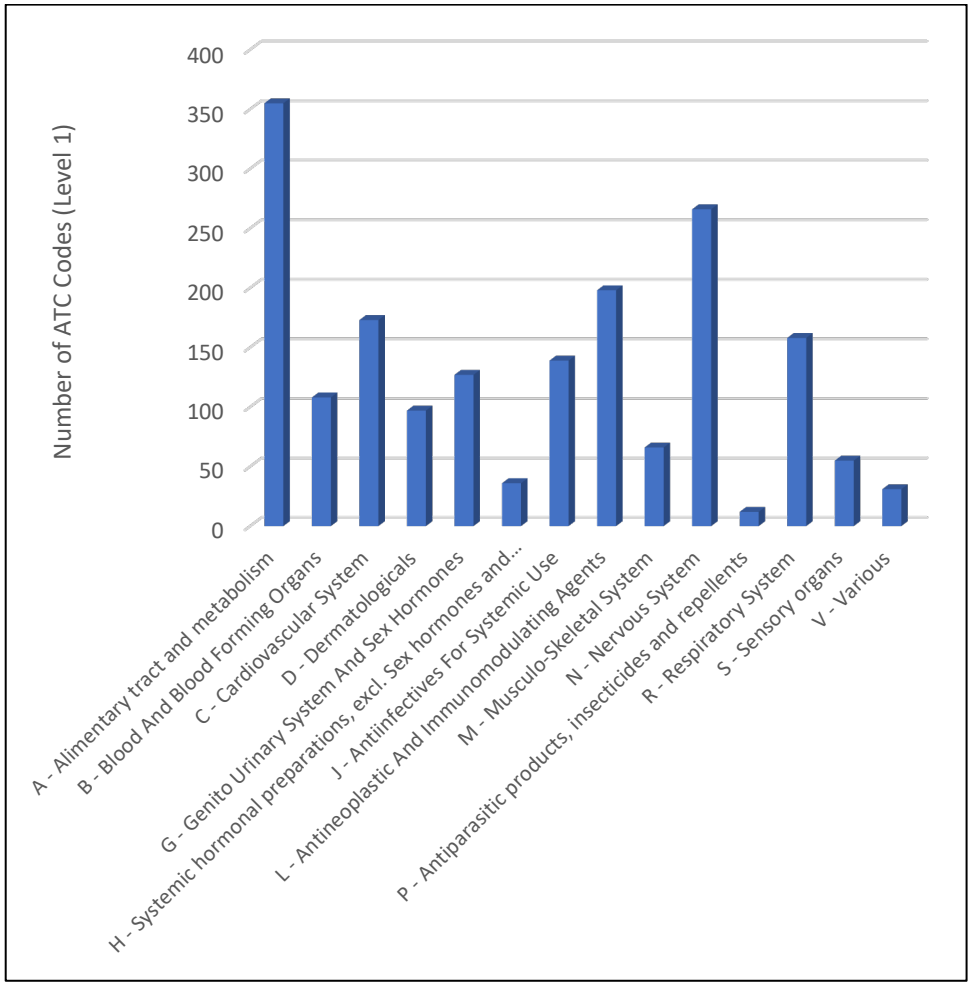


Evidence received for this report covers the types of therapeutic areas which will be impacted, including the impact across existing market authorisations in the EU and globally. The report further focuses on PFAS use scenarios across research & development; use in the plant, equipment & single use systems within manufacturing facilities; raw, starting materials and intermediates of both fluorinated and non-fluorinated APIs; APIs and excipients with PFAS moiety; and packaging and drug delivery devices. We provide further information on the expected patient Impact considering medicines impacted from the WHO essential medicines list and critical medicines list of various EEA member states.

5.1 ATC Code Analysis & Types of Therapeutic Areas Impacted

This survey represents a wide range of the pharmaceutical industry. This is evident as all 14 main anatomical/pharmacological groups (1st level ATC codes) are represented in this survey. The chart below shows the distribution of these groups.

Figure 1: Distribution of the 14 main anatomical/pharmacological groups (1st level ATC codes) are represented in this survey



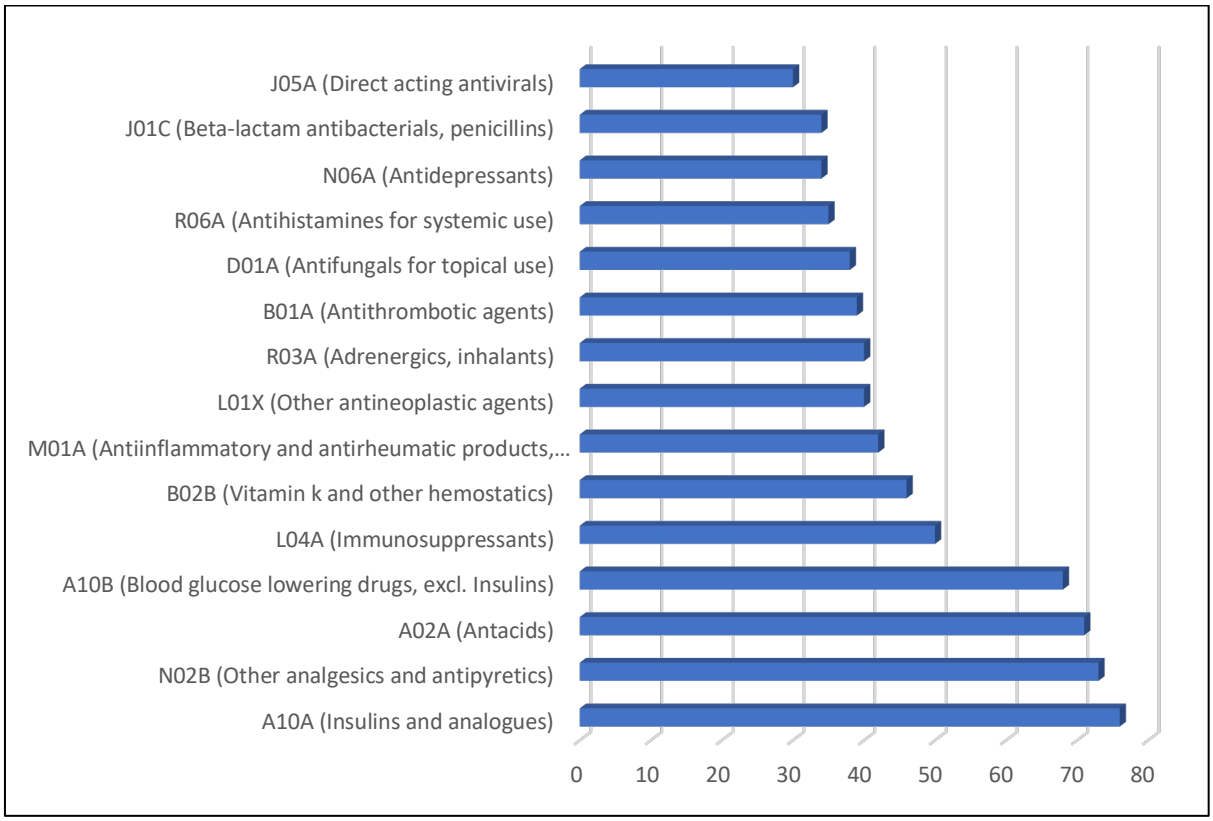
Out of these, 674 references are on the WHO essential medicines list[6] of which 499 prescription-only medicines (POM) and 171 over-the-counter (OTC) medicines.

The companies participating in this survey have provided information on how the proposed restriction on PFAS will affect the supply and availability of medicines. The level of detail provided allows us to differentiate between the impacts on different pharmacological/ therapeutic groups (3rd level ATC code).

In this survey, 192 pharmacological/therapeutic groups (3rd level ATC code) are represented. The 15 most commonly reported are presented in the table below. It is evident that these represent both important and diverse pharmacological/therapeutic areas.

[6] 2023 WHO model list of essential medicines (23rd list): https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02

Figure 2: The 15 most reported ATC codes (level 3)

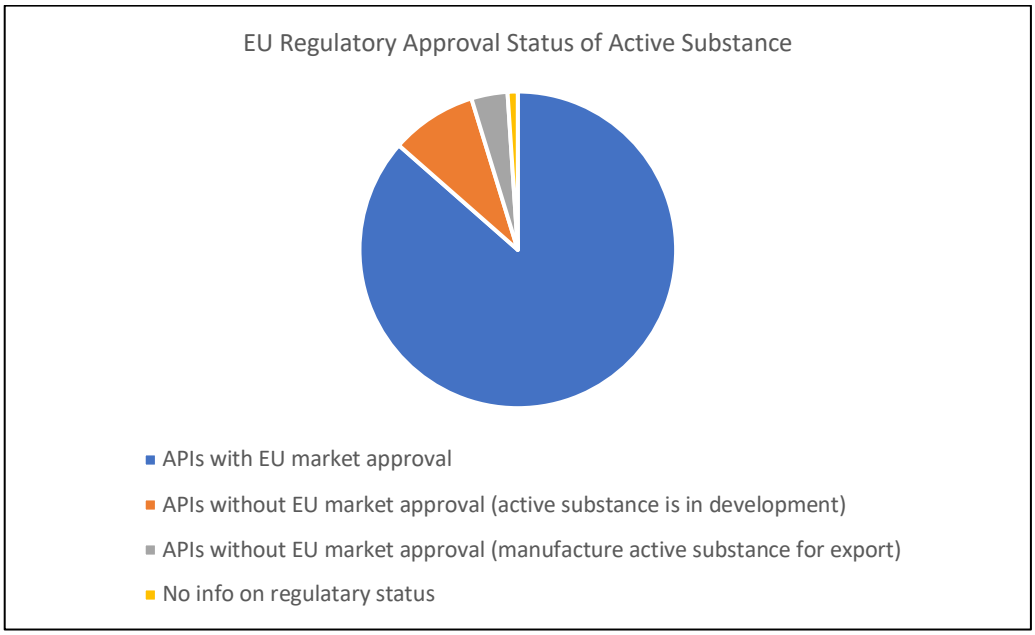


An overview of the distribution of pharmacological/therapeutic areas (3rd level ATC codes) is provided in Appendix 1.

5.2 Medicinal Product Regulatory Approvals – Global & European Impact

In restriction proposal option 2 (RO2)[7], APIs with EU marketing authorisation are proposed a time-unlimited derogation from the full ban. It is important to note, that not all API production in EU have marketing authorisation. As can be seen from Figure 3, 13 % of APIs manufactured in EU will not be derogated by proposed RO2 4c, as they are still under development or are only manufactured for export. Further, the regulatory status of 1% of the APIs in the survey was not provided.

Figure 3 EU Regulatory Approval Status of Active Substance



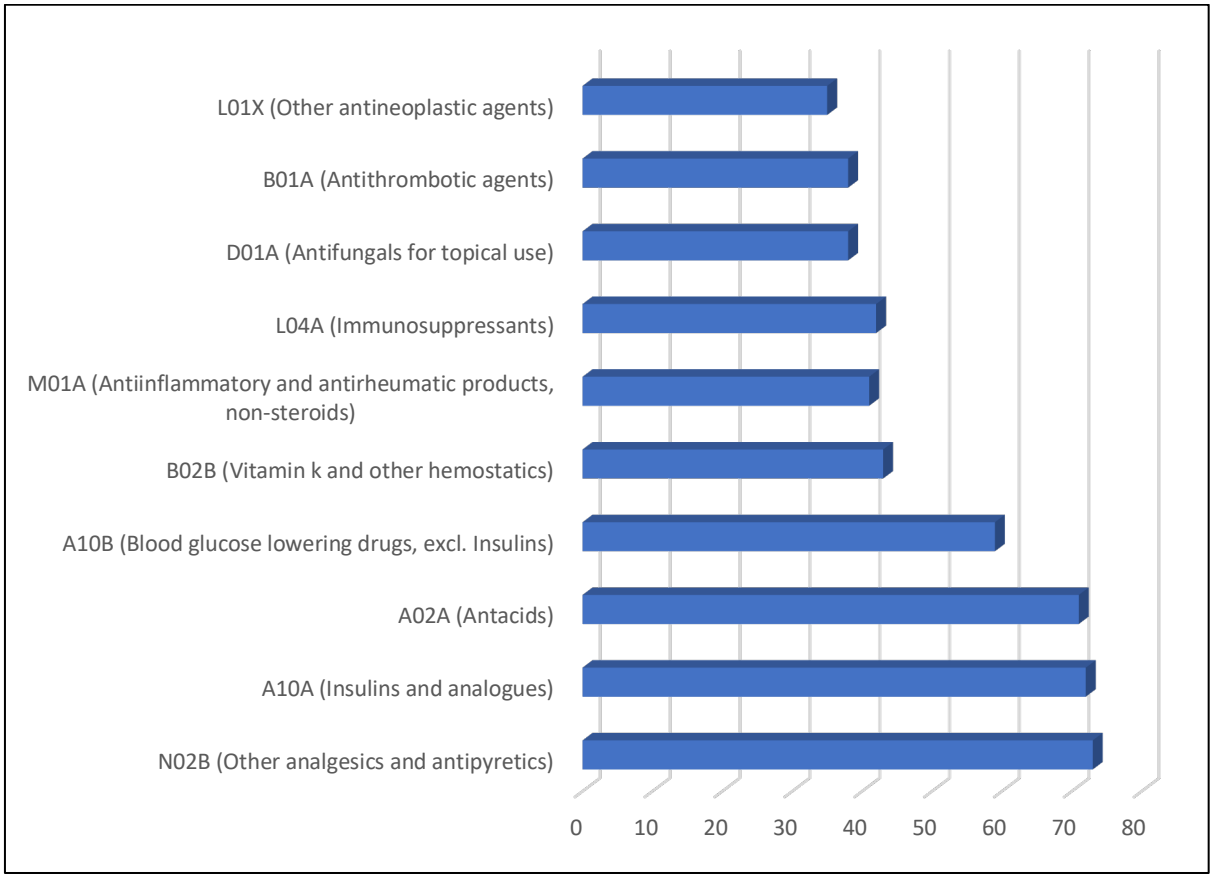
In total 1696 ATC codes were reported for the 1662 APIs with EU market approval[8].

[7]Restriction proposal option 2 of the Annex XV restriction proposal (https://echa.europa.eu/documents/10162/1c480180-ece9-1bdd-1eb8-0f3f8e7c0c49) for PFAS proposes a ban with use-specific derogations and indicates a time unlimited derogation for active substances

[8] More than one ATC code can be reported for each API

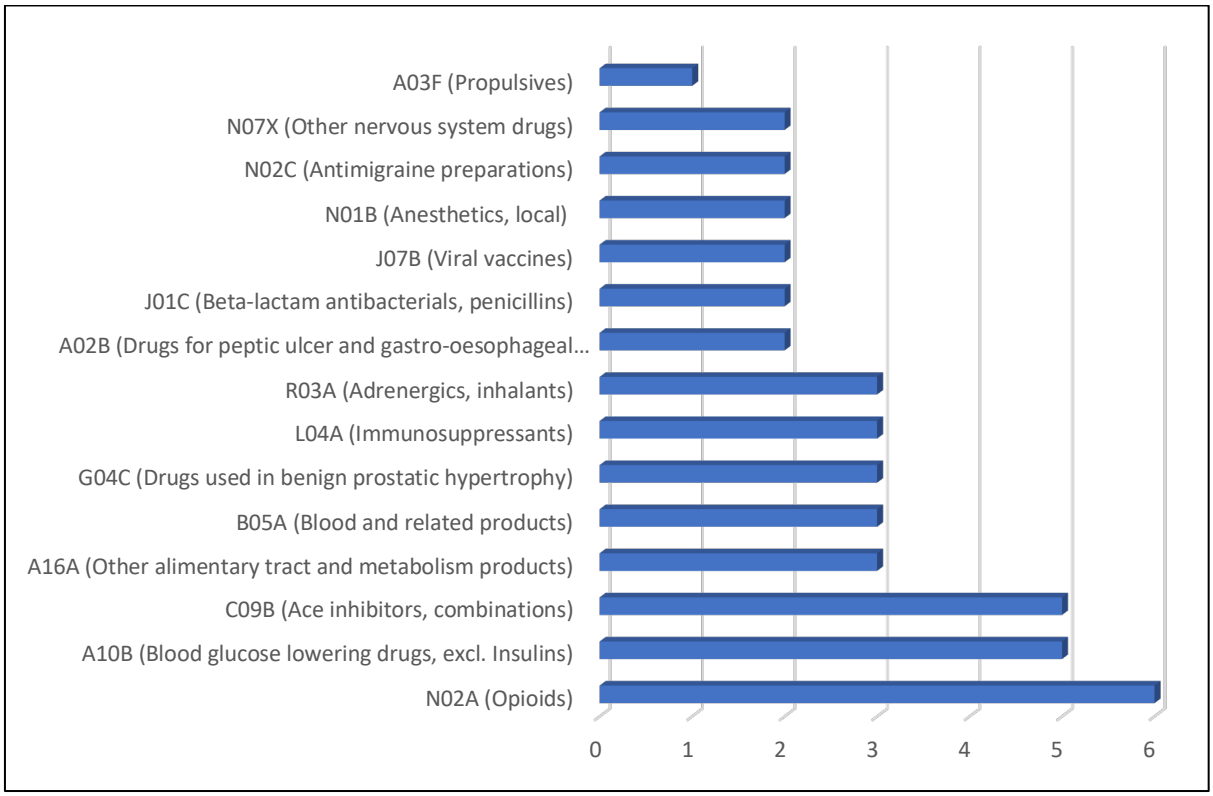
Figure 4 lists the top 10 most reported pharmacological/therapeutic areas (3rd level ATC codes) with EU market approval in this survey. The full list of Level 3 ATC codes for APIs with EU market approval in this survey with number of times the ATC code is reported can be found in Appendix 1.

Figure 4 – Top 10 Therapeutic Areas Associated with Active Substances Approved in the EU



Of the 1922 APIs reported in this survey, 71 (3.7%) were reported to be manufactured in EU only for export. Figure 5 shows the 10 most reported ATC codes without EU market approval in this survey. Table ZYX: The full list of 3rd level ATC codes for APIs for export with number of times the ATC code is reported can be found in Appendix 1.

Figure 5 Top 15 Therapeutic Areas Associated with Active Substances not Approved in the EU (export)



In the survey, 169 APIs were reported to be under late-stage development. Out of these, 15 (8.8%) reported the relevant ATC code. Hence, details on therapeutic area in this section is regarded insufficient to report. Information on the 3 rd. level ATC codes for APIs in development can be located in Appendix 1.

5.3 PFAS Use Scenarios

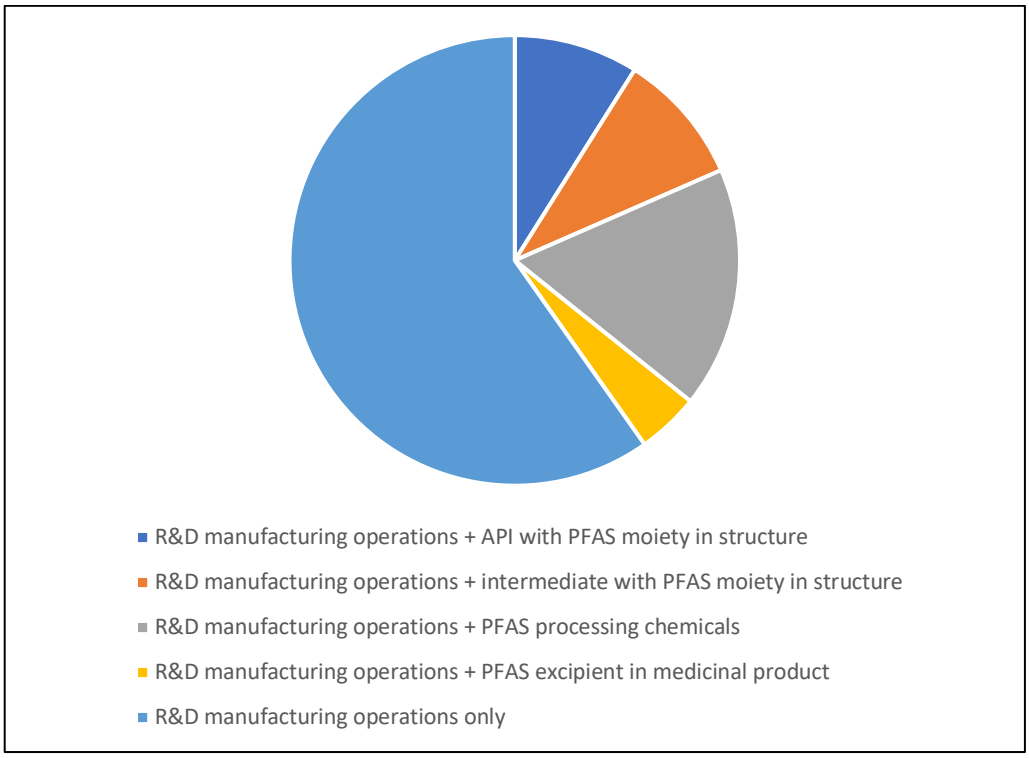
5.3.1 Research & Development – PPORD Justification

New APIs under development in the EU are not included in the proposed time-unlimited derogation. The generic exemption for scientific research and development is capped at 1000kg. When a new medicinal product is in late-stage clinical trials[9], the size of manufacturing campaigns (and its intermediate steps in production) can exceed 1000kg per year. The produced material may be used to supply clinical trials, or the product launch campaign post a successful regulatory approval.

The PFAS Restriction must include a derogation for PPORD (Product, process-oriented research, and development) to facilitate both development of API manufacturing processes and clinical trial supply campaigns. If not, the development of medicinal products in the EU would be severely impacted by the restriction proposal.

In the survey, 169 APIs were reported to be under development, at an EU manufacturing facility. These facilities depend on fluoropolymer materials in plant, equipment, and single use systems. Figure 6 provides an indication of how the development of these APIs could be impacted, i.e. manufacturing operations only or manufacturing operations and use of a specified substance containing a PFAS moiety occurs.

Figure 6 – Impact of PFAS Restriction on R&D Manufacturing Operations (169 Active Substances)



[9] Late-stage clinical trials refers to the third and last stage in the clinical development of a new medicinal product.

Of these APIs under development 49 (29%) indicated that at least one specified substance containing a $-CF_2-$ or $-CF_3$ group was used in the manufacture of the API. This final development of these APIs will not be possible in EU if the restriction proposal is accepted in its current wording.
Only 15 (8.8%) of the APIs under late-stage development had ATC code reported. Hence, details on therapeutic area in this section is regarded insufficient to report.

16 APIs are under development (9%) with at least one $-CF_2$ or $-CF_3$ group. These will not be covered by the proposed derogation as an EU marketing authorisation has not yet been obtained. Hence, the final development of these APIs will not be possible in the EU.

17 APIs under development (10%) reported using staring material and/or intermediates with at least one $-CF_2$ or $-CF_3$ group. These will not be covered by the proposed derogation as an EU marketing authorisation has not yet been obtained. Hence, the final development of APIs will not be possible in EU with these starting materials with the consequence that either the final development will take place outside of the EU or a substantial delay will occur in the development and placing on the market of the medicinal product if another starting material has to be identified, tested and approved.

21 APIs under development (12%) reported using process chemicals with at least one CF_2 or CF_3 group. These will not be covered by the proposed derogation as currently there are no derogation for process chemicals used for pharmaceutical manufacture. Hence, the final development of APIs will not be possible in EU with this manufacture process. It should be noted that changes to the manufacture process in late-stage development could result in new clinical trials and registrations with authorities.

Eight APIs under development (5%) reported using non-active ingredients (excipients) which contained at least one CF_2 or CF_3 group in the final pharmaceutical product. These will not be covered by the proposed derogation as currently there are no derogation for non-active ingredients (excipients) in medicinal products. Hence, the final development of the medicinal product will not be possible in EU. It should be noted that changes to the non-active ingredients in late-stage development would likely require additional clinical trials.

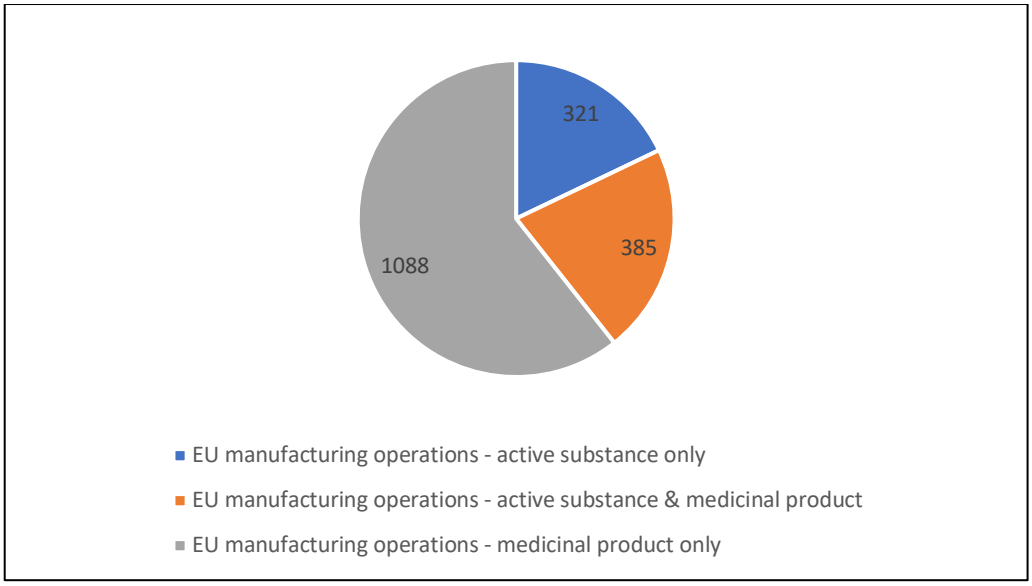
In short, the proposed PFAS Restriction has the potential to severely hinder or stop research and development of new medicinal products containing both fluorinated and non-fluorinated APIs.

5.3.2 Fluoropolymers used in the plant, equipment & single use systems within Manufacturing Facilities

Medicinal product manufacturing facilities are governed by a GMP (good manufacturing practice) certificate, issued by global health authorities. Operation of these facilities are heavily dependent upon fluoropolymer use in utilities, piping, equipment (process/utilities), and single use systems. Fluoropolymer materials are widely used in the pharmaceutical manufacturing industry because of their corrosion resistance and are deemed to be inert by most regulatory agencies and are considered desirable to produce medicinal products, e.g. they are EMA certified.

Commission working document[10] describes the complexity and geographical diversification of medicinal product supply chains. Active substances may or may not be manufactured at a facility in the EU. In some supply chains formulation of the medicinal product may take place in a non-EU facility but final packaging operations occur at an EU facility. Supply chains of 1794 out of 1922 (93%)[11] active substances included in the survey involve manufacturing operations at an EU facility. Respondents were asked to indicate what type of manufacturing operations take place at an EU facility as this will influence fluoropolymer usage. Figure 7 provides a breakdown of EU manufacturing operations.

Figure 7 EU manufacturing operations - active substance and / or medicinal product



The type of manufacturing operation will influence the fluoropolymer used. Chemical synthesis of an active substance will depend on the use PFA, PTFE, PVDF and ETFE lined

[10] mp_vulnerabilities_global-supply_swd_en.pdf (europa.eu)

[11] Supply chains of 86 APIs do not involve EU manufacturing operation but fall within scope of the survey because a PFAS component is present in the packaging or drug delivery device. For 42 survey records information on location of manufacturing operations was not provided

components, to provide corrosion protection against aggressive process solutions. In parenteral[12] manufacturing facilities, product filling lines depend on single use sterilisation filters containing PVDF components and PTFE tubing, to ensure sterility of the medicine.

Respondents were asked to indicate mitigation options, if a ban of PFAS containing manufacturing equipment and consumables were to be introduced. Only for 23 APIs (1.2%), available alternative, non-PFAS options were selected as a mitigation measure. In the majority of cases (66.3%) the field about mitigation was left blank or 'don't know' was selected as response. This indicates that there are currently no non-PFAS alternatives readily available or yet been identified that would not constitute a regrettable substitution both from a regulatory and from a performance viewpoint. Also, this concurs with a more in-depth analysis of the types of fluoropolymer materials used in pharmaceutical manufacturing facilities conducted by ISPE (International society of pharmaceutical engineers)[13].

A further consequence of the proposed restriction could be a severe decrease of the production of APIs in the EU. For about 183 (9.2%) APIs it was stated that the production would be moved outside of EEA if suitable manufacturing capacity is available and for about 318 (16.5%) APIs EEA manufacturing operations will eventually cease.

The survey indicates that supply chains of 93% active substances involve EU manufacturing operations, which depend on fluoropolymers, within plant, equipment and single use systems. Compared to the wider chemicals industry, the pharmaceutical sector could be regarded as a niche user of fluoropolymer materials. If the proposed PFAS restriction prohibits the supply of these critical raw materials, manufacturing operations at EU facilities will cease when contingency stock levels are depleted. Therefore, a derogation for fluoropolymers in the plant, equipment and single use systems within manufacturing facilities is needed to keep manufacturing of medicinal products in EEA.

[12] Parenteral drug administration refers to medicinal products administered by routes other than the digestive tract, particularly by injection or infusion. For patient safety, sterile manufacturing operations are required to produce parenteral medicines.

[13] See Annex 3 – Industrial Use of Fluoropolymers in Pharma Manufacturing

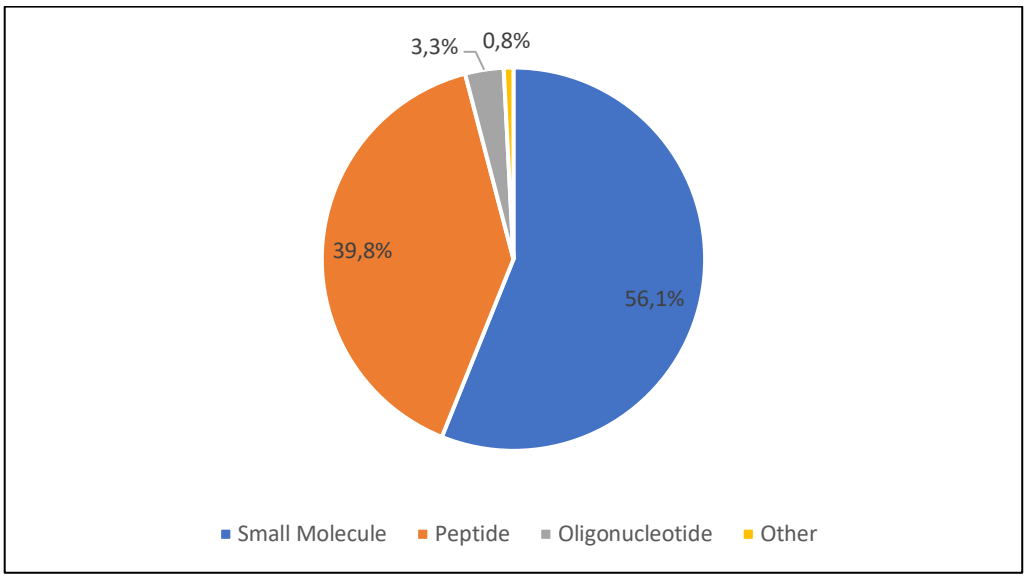
5.3.3 PFAS Process Chemicals used in the Manufacture of Fluorinated & non-fluorinated APIs

The chemical identity of raw materials, starting materials and intermediates are specified in the marketing authorisation of the medicinal product.

An in-depth analysis of the findings of the survey indicates that PFAS are used additionally as raw materials in 119 records (6.2% of total records). Respondents were asked to provide a CAS number of any raw material or starting materials that fulfil the PFAS criteria. A list of the CAS numbers provided by survey respondents is provided in Appendix 1. This list is regarded as a non-exhaustive list and should not be used as the basis for any substance specific derogation for processing chemicals used in the manufacture of pharmaceuticals.

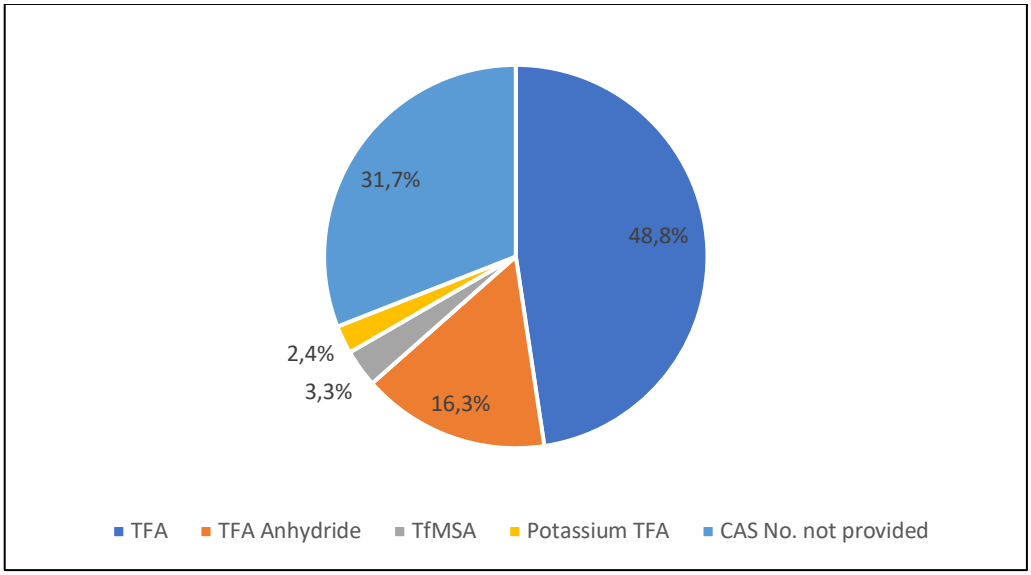
20 different PFAS compounds were reported to be used in the manufacture of small molecules, peptides and oligonucleotides. Trifluoroacetic acid (TFA) is the most commonly used chemical accounting for 50.4% (60 instances of use), followed by Trifluoracetic anhydride 16.8% (20 instances of use) and Trifluoromethanesulfonic Anhydride (TfMSA) 3.4% (4 instance of use). The most commonly used PFAS raw material, TFA, is employed in the manufacture of peptides 41.2% (49 instance of use), small molecules 7.6% (9 instances of use), and oligonucleotides 1.2% (2 instance of use).

Figure 8 – Usage of PFAS Process Chemicals by Product Type



It is not unexpected that the only product type identified are small molecules, peptides and oligonucleotides, as these are produced by chemical synthesis manufacturing methods.

Figure 9 – Most Frequently Identified PFAS Processing Chemicals



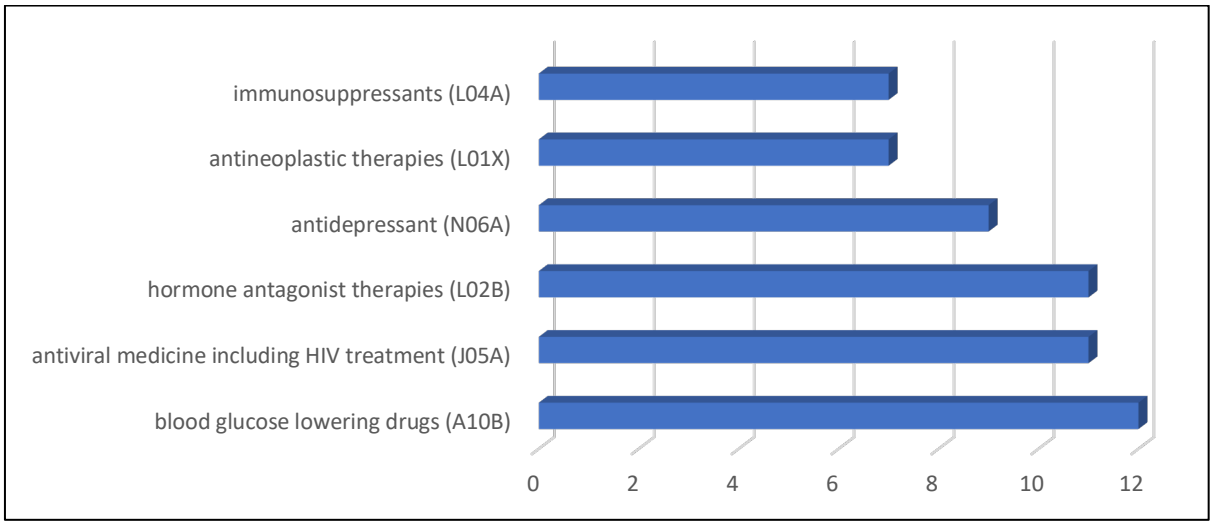
As mentioned above, this listing of PFAS used as raw materials in Appendix 2 should not be used as the basis for any substance specific derogation, as it is not considered to be complete. Some survey respondents were not able to cover entire product portfolios in the short timeframe available to conduct the survey. Even with this limited data it is apparent what damage could be caused to the European API manufacturing industry if there will be a lack of, or partial derogation.

5.3.4 APIs with PFAS moiety

The restriction dossier mentions APIs, but only those corresponding to the definition of PFAS: "active substances in medicinal products often only contain one or more CF_3-group(s) in an otherwise complex non-fluorinated molecular structure. In many cases the CF_3-groups are attached to aromatic rings". Based on the survey 139 APIs with PFAS moity have been reported by the companies (7.2% of total records), 133 of which are small molecules and 5 are peptides-modality APIs.

A total of 44 different ATC (Anatomical Therapeutic Chemical) codes associated with these types of APIs. The top 6 ATC codes are related with blood glucose lowering drugs, excluding insulins (A10B), antiviral medicine including HIV treatment (J05A), hormone antagonist therapies (L02B), antidepressant (N06A), antineoplastic therapies (L01X) and immunosuppressants (L04A).

Figure 10 – Top 6 Recorded ATC codes (level 3) for APIs with PFAS moiety



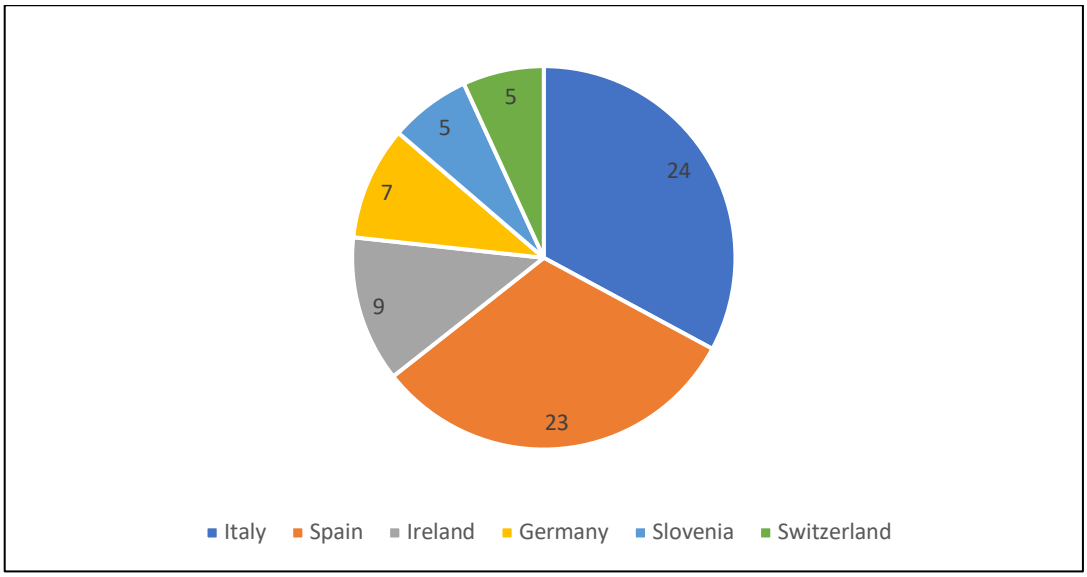
Starting materials and intermediates are required to build a final fluorinated API structure. For the 139 APIs with PFAS moity identified in the survey, respondents indicated that 63 PFAS starting materials and/or intermediates would also be impacted. It is common business practice for starting materials and pharmaceutical intermediates to be imported into an EU based manufacturing facilities for the synthesis of small molecule APIs. Any derogation for APIs must also include the fluorinated starting materials and intermediates that are required to efficiently build a final API structure.

These materials would be regarded as transported intermediates from a REACH perspective and should also be included in the derogation for APIs.

The identified locations from the survey of these API manufacturing facilities are Italy, Spain, Ireland, Germany, Slovenia and Switzerland. It is important to note that not all survey respondents indicated locations of manufacturing facilities. A lack of derogation or restricted

derogation for PFAS raw materials, starting materials and intermediates which are part of the process manufacturing of APIswith PFAS moity will start an “exodus” or partial movement of manufacturing API facilities to non-EU locations.

Figure 11 – Member State Locations of Chemical Synthesis Facilities that Produce PFAS APIs



5.3.5 Excipients with PFAS moiety

PFAS are used as excipients in 23 (1.2% of total records) provided records in the survey. 1,1,1,2-Tetrafluoroethane was the most commonly used PFAS chemical based on the information provided and is employed as an excipient accounting for 43.5% (10 instances of use), and other PFAS substances (with no CAS supplied) was used in 56.5% of cases (13 instances of use).

Figure 12– CAS Number information Provided on Excipients with PFAS moiety

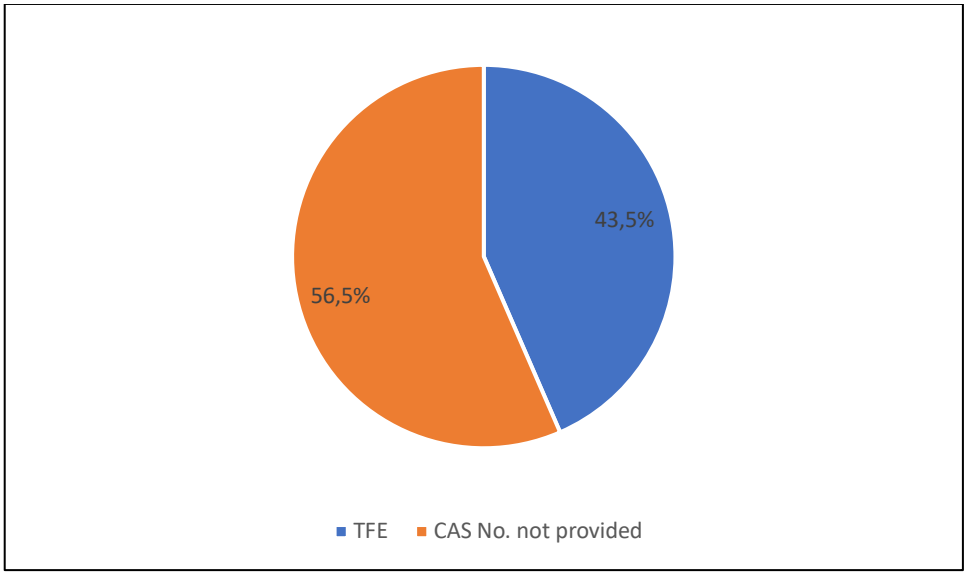
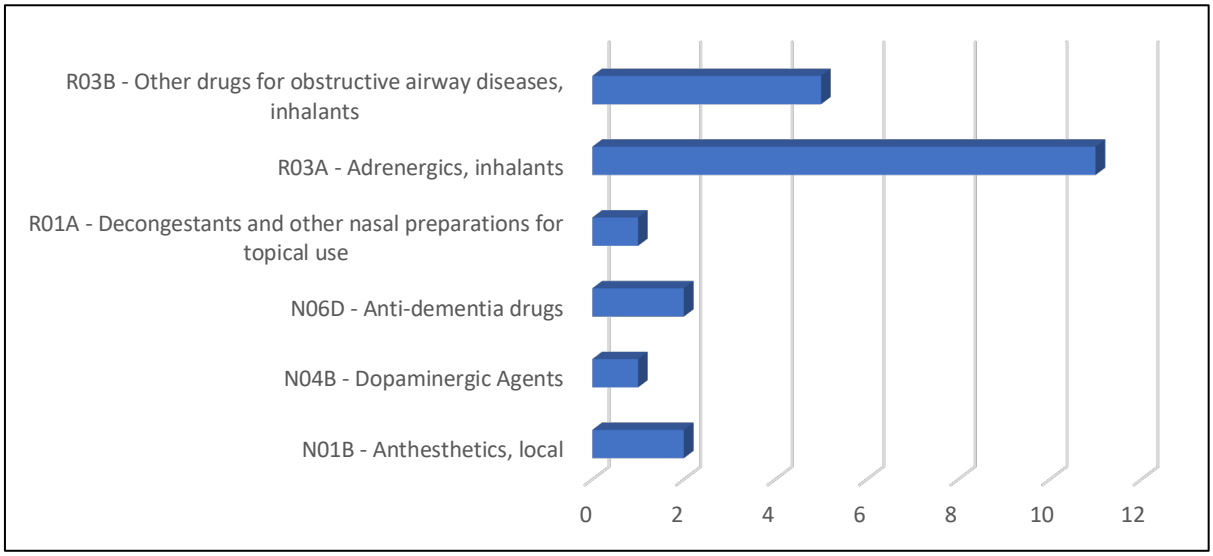


Figure 13- Recorded ATC codes (level 3) for Excipients with PFAS moiety



All cases of PFAS use for excipients are related with the manufacture of small molecule based medicinal products and will affect at least 38 medicinal product manufacturing facilities which reported use of PFAS excipients during production of drug product. 86% identified are located in EU (Italy, France, Germany, Poland and Spain). Assuming potential lack of derogation or partial derogation in the near future, transition to new non-PFAS excipient will most likely not be completed across products and geographies. The consequence will be a shortage or a withdrawal of medicinal products from markets.

5.3.6 Packaging containing PFAS constituents or components

Primary packaging is an integral part of a drug product. Depending on the product it can have a role in protecting the product from adverse environmental conditions, ensuring sterility, enhancing stability, allowing compliance with child safety regulations (child resistant packaging) and enabling usability (for example with the geriatric population). All primary packaging materials and drug delivery devices form part of the valid marketing authorisation and so any restriction will impact the supply of medicines in Europe and beyond.

Fluoropolymers are used in the packaging of medicinal products include Laminated films for blister packs and PFAS coated elastomers in vials, cartridges and syringes.

Looking at the data contained within the survey there are several conclusions that can be made:

- There are 276 products utilising polymeric PFAS in their packaging and listed as having a Marketing Authorisation in Europe.
- The impacted products are distributed between all 14 of the main ATC (1st level ATC codes) groups as listed in the graph in Figure 1.

In other geographies there are 16 314 products with Marketing Authorisations that would be impacted in the same 14 ATC code groups but with different rankings (see graphs in Figure 14, Figure 15).

There are also 9 products (5,3%) undergoing clinical studies or regulatory approval in the EU. There is currently no technically viable alternative for packaging. Packaging is part of registered medicines, therefore the regulatory environment requires toxicological evaluations, extractive and leachable studies and product stability to ensure the continued quality of the product. In addition, child resistance and patient usability studies may be required. All this takes over 10 years. This data will form part of a regulatory assessment and approval processes taking between 6 months to 2 years.

There is a need to evaluate these potential substitutions to avoid immediate drug shortages and an appropriate derogation timing must be allowed to allow the full program of activities to be completed and regulatory approval to be gained if a technical solution can be developed.

Figure 14: Total Number of EU Marketing Authorizations for each ATC (1st level ATC codes) group

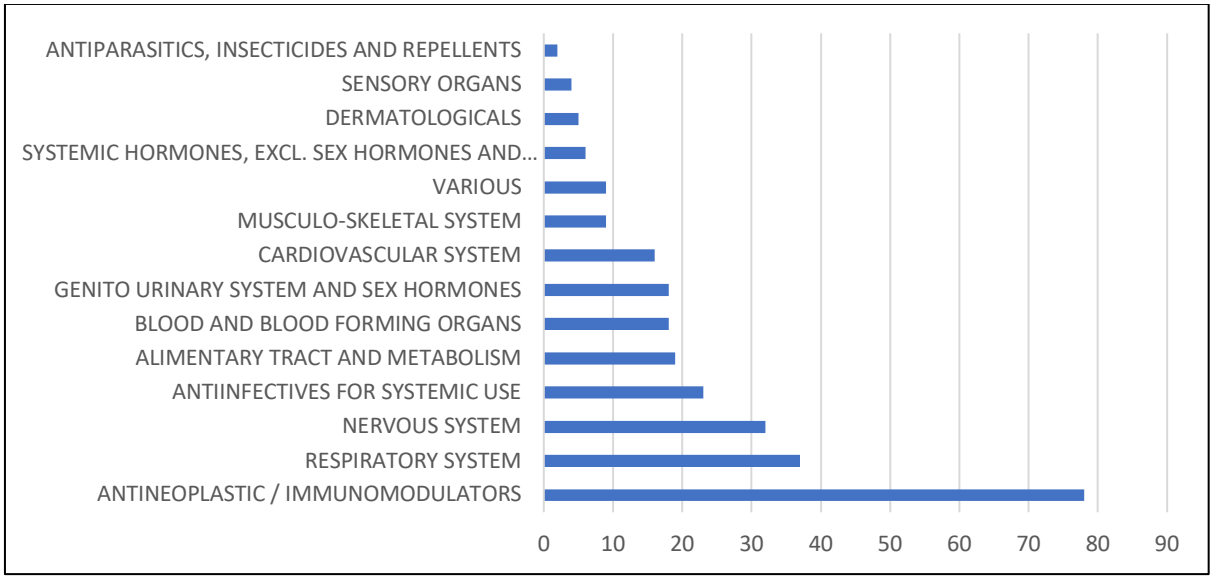
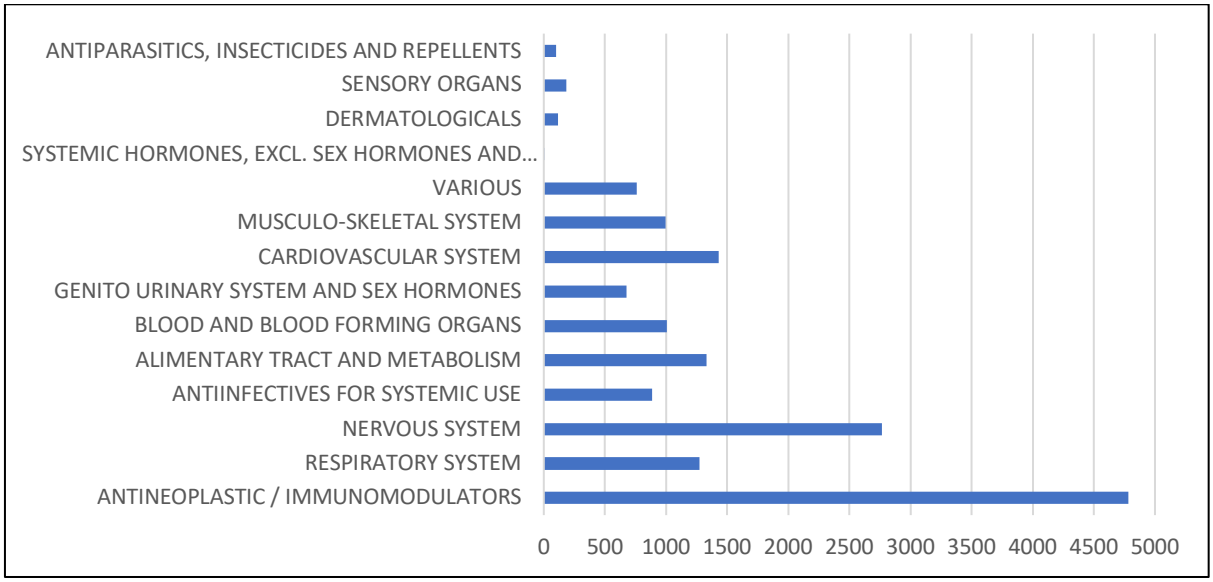


Figure 15: Total Number of non-EU Marketing Authorizations for each ATC (1st level ATC codes) group



5.3.7 PFAS constituents or components present in drug delivery devices

All drug delivery devices form part of the valid marketing authorisation and so any restriction will impact the supply of medicines in Europe and beyond. There are many examples of drug delivery device using PFAS which include prefilled syringes, prefilled pens, autoinjectors and transdermal patches.

Looking at the data contained within the survey to which an ATC code has been allocated there are several observations that can be made:

- For the 98 products listed as having a Marketing Authorisation in Europe there are products in 12 of the main 14 WHO ATC (Anatomical Therapeutic Chemical) code groups:

- Alimentary Tract and Metabolism
- Antineoplastic / Immunomodulators
- Respiratory System
- Nervous System
- Blood and blood forming organs
- Various
- Musculo Skeletal System
- Anti-infective for systemic use
- Systemic hormones excluding sex hormones and insulins
- Cardiovascular system
- Dermatologicals
- Sensory organs

In other geographies there are 5192 Marketing Authorisations that would be impacted in the same 12 ATC code groups but with different rankings (see graphs in Figure 16 and 17).
There are also 6 products undergoing clinical studies or regulatory approval in 3 ATC groups in the EU:

- Respiratory system
- Sensory organs
- Nervous system

For respiratory medicinal products (e.g. metered dose inhalers, MDI) these also use PFAS. Currently the REACH proposal specifically calls out that 'Given the sufficiently strong evidence pointing to the existence of technically and economically feasible alternatives …, no derogation is proposed'. If this is not revised, it will be very difficult to continue to manufacture MDIs in Europe.

If a technically feasible alternative is identified, then, as these products are registered medicines, the regulatory environment will, depending on the product, demand; toxicological evaluations, extractive and leachable studies and product stability (including end of shelf-life functionality). To ensure the continued quality of the product. In addition, child resistance and patient usability studies may be required.

Once this data is obtained, and if it is acceptable, then there are regulatory assessment and approval processes that need to be undertaken. Depending on the market these processes can be between 6m months to 2 years before the marketing authorisations are modified for the changed packaging material and the product can legally be supplied. In general, it is anticipated that it may take at least 10 – 20 years to find, test and implement replacements avoiding regrettable substitutions.

There is a need to evaluate these potential substitutions and, to avoid immediate drug shortages, a time unlimited derogation must be allowed to allow the full program of activities to be completed and regulatory approval to be gained if a technical solution can be developed.

Figure 16: Total Number of EU Approved Devices for each ATC (1st level ATC codes) group

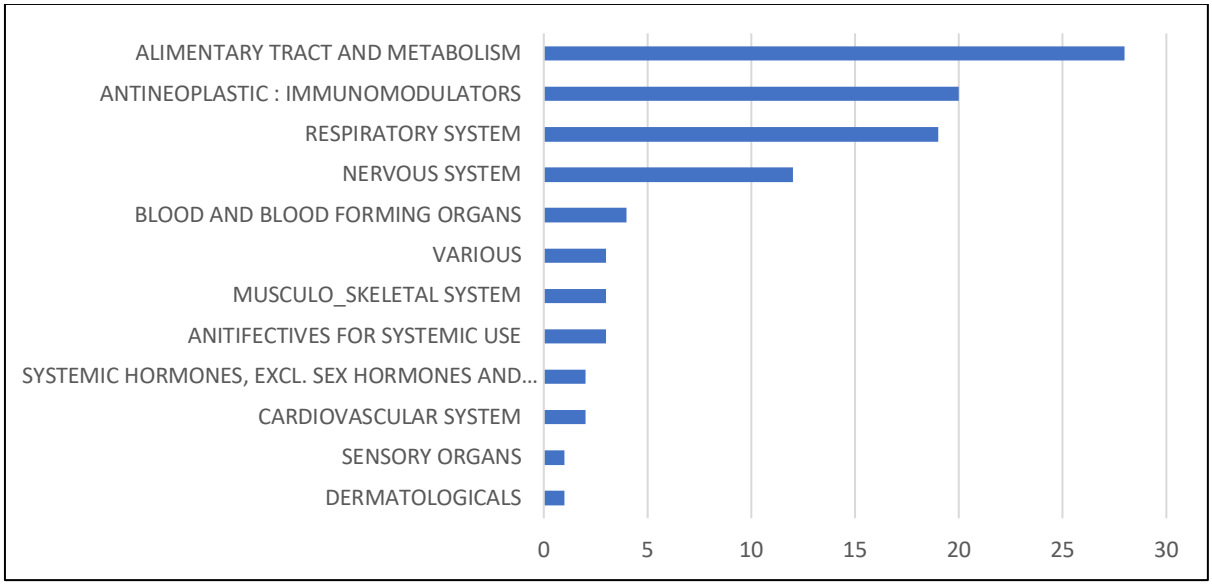
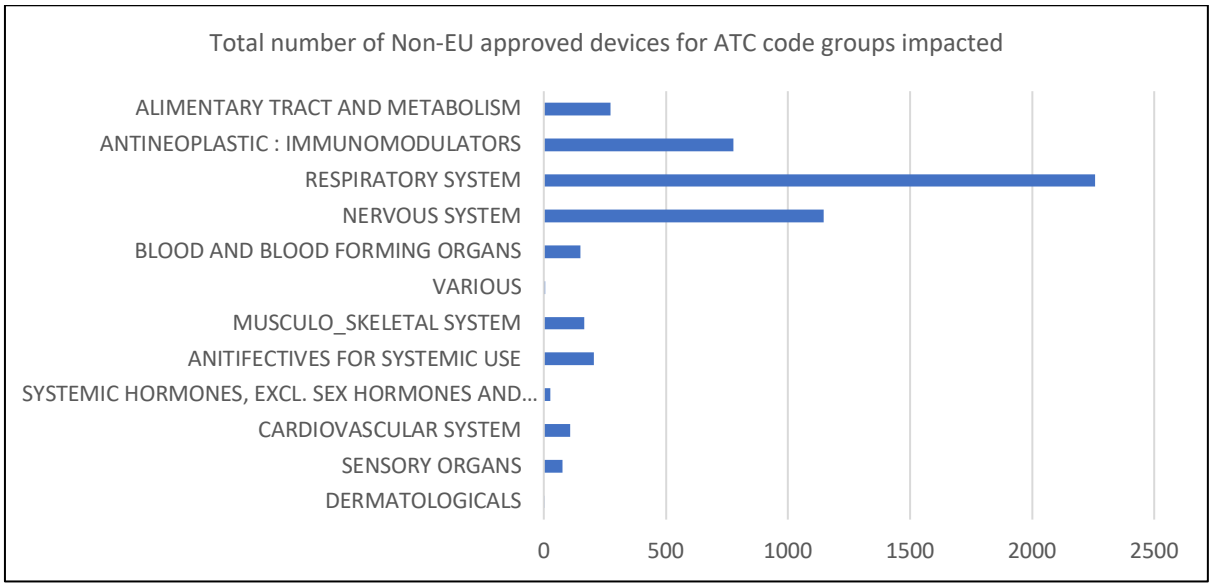


Figure 17: Total Number of non-EU Approved Devices for each ATC (1st level ATC codes) group



5.4 Patient Impact

5.4.1 Prevalence of Disease State & Patient Number Estimates

EU based manufacturing facilities are global suppliers of medicines. As indicated in Figure 1 the impacted medicinal products are from important and diverse pharmacological/ therapeutic areas. From this list, the following five non-communicable diseases, were selected for further analysis:

	Total Count (*No of active substances*)
Cardiovascular disease C03A (Low ceiling diuretics, Thiazides); C08C (Selective Calcium Channel Blockers); C09A (ACE Inhibitors); C07A (Beta Blocking Agents); C10A (Lipid modifying agents)	85
Chronic respiratory disease R03A (Adrenergic Inhalants); R03B (other drugs for obstructive airway diseases, inhalants); R06A (Antihistamines for systemic use)	87
Cancer L01A (Alkylating agents); L01B (Anti-metabolites); L01C (Plant Alkaloids and other natural products); L01E (Protein Kinase Inhibitors); L01F (Monoclonal antibodies and antibody drug conjugates)	58
Diabetes A10A (Insulins and Analogues): A10B (Blood glucose lowering drugs, excluding Insulins)	144
Mental health disorders N06A (Antidepressants)	34

Patient numbers associated with these disease states are increasing. To give an indication of the global patient numbers, a literature search was conducted, particularly looking at WHO data. There are several observations that can be made:

- **Asthma & COPD**: Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, causing 3.23 million deaths in 2019. Asthma affected an estimated 262 million people in 2019 and caused 455,000 deaths.[14] Asthma affected an estimated 262 million people in 2019 and caused 455 000 deaths[15].

- **Mental health**: In 2019 1 in every 8 people, or 970 million people around the world were living with a mental disorder.[16]

- **Cardiovascular diseases** (CVDs) are the leading cause of death globally, taking an estimated 17.9 million lives each year.[17] Currently there are more than 6 million new cases

[14] https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
[15] Asthma (who.int)
[16] Mental disorders (who.int)
[17] Cardiovascular diseases (who.int)

of CVD in the EU and more than 11 million in Europe as a whole, every year. With almost 49 million people living with the disease in the EU in 2019[18]. In a recent World Health Statistics report, the number of adults aged 30–79 years with raised blood pressure (hypertension) is estimated to have almost doubled to 1.28 billion between 1990 and 2019, mainly due to population growth and ageing. There was little change in the overall rate of hypertension globally, although the burden has shifted from high-income to low- and middle-income countries.[19]

- **Cancer**: Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. There are an estimate 18.1 million cancer deaths around the world in 2020[20]. Results of an epidemiology study on the incidence of early onset cancers in adults under 50 years was published in the BMJ. It indicates that cancers historically perceived to be more common in older age groups are now being diagnosed in younger adults, including colorectal breast, oesophageal, gastric, and pancreatic cancers, amongst others[21].

- **Diabetes**: The IDF Diabetes Atlas (2021)[22] reports that 10.5% of the adult population (20-79 years) has diabetes, this is around [23] . Diabetes is a chronic (long-lasting) health condition which has a significant impact on the health and well-being of individuals, families and societies.

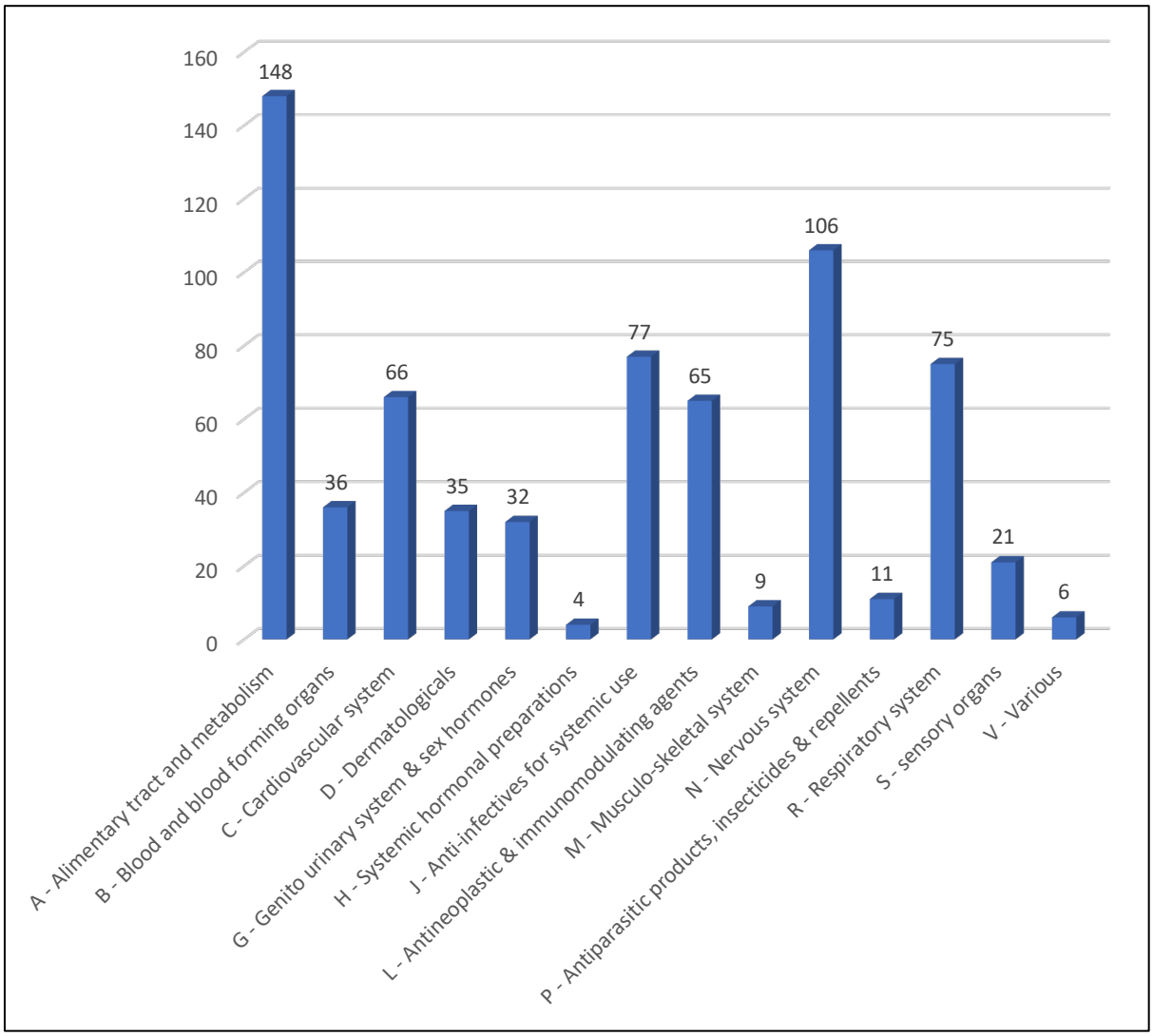
[18] Fact sheets for Press (escardio.org)
[19] https://iris.who.int/bitstream/handle/10665/356584/9789240051140-eng.pdf?sequence=1
[20] https://www.wcrf.org/cancer-trends/worldwide-cancer-data/
[21] Hamilton AC, Coleman HG. Shifting tides: the rising tide of early onset cancers demands attention. *BMJ Oncology* (2023)
[22] https://idf.org/about-diabetes/diabetes-facts-figures/
[23] https://www.who.int/health-topics/diabetes#tab=tab_1

5.4.2 WHO Essential Medicines List

A WHO Expert Committee on the Selection and Use of Essential Medicines is responsible for the development and the revision of Essential Medicines List (EML) every 2 years. This list is often used as a reference point for countries to define products which are essential to the functioning of healthcare systems.

Respondents indicated if the active substance appears on the current WHO Essential Medicines List. **35%** or 674 of the 1922 active substances were found on the WHO list. A strong indication that the proposed PFAS restriction will have a significant impact on the availability of these products to patients all around the world. Figure 18 shows the distribution of pharmacological/therapeutic groups that could be impacted. This is the breakdown by ATC code family, the total is > 691 because some medicines had multiple ATC codes, both in the same family or in different families.

Figure 18 - Impacted Medicines on the WHO Essential Medicines List in each ATC (1st level ATC codes) group

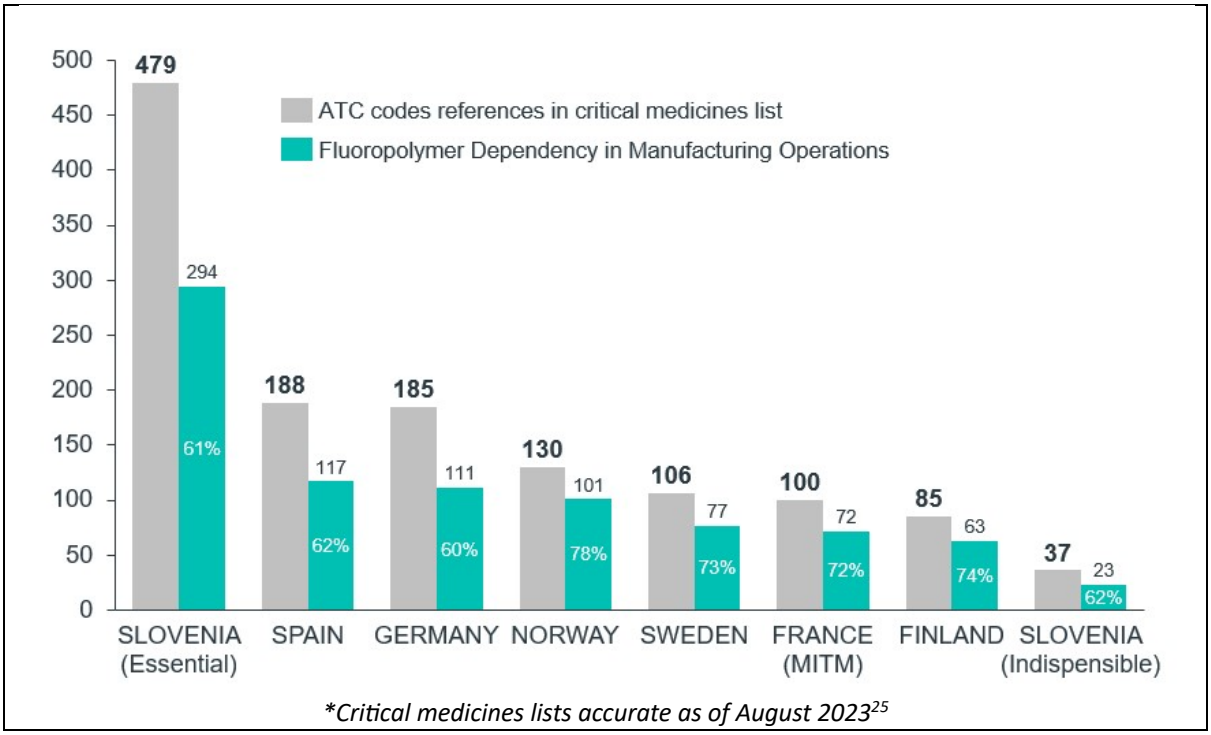


5.4.3 Critical Medicines List – EU Member States

Critical medicines are a subgroup of essential medicines which certain EU member States have set up to ensure there should never be supply problems in the health system[24]. They are, for example, those that are considered by the EU (EEA) Member State to be most critical, due to their importance for the resilience of health care systems, public health and patient care at all times or due to the vulnerability of the supply chain. They are often selected with due regard to the therapeutic indication of the medicine and / or the availability of adequate alternatives.

For the 1794 active substances, with associated manufacturing operations at an EU facility, ATC data was cross checked against national critical medicines lists in Finland, France, Germany, Norway, Slovenia, Spain, and Sweden. Figure 19 illustrates the potential impact on critical medicines lists if these facilities are unable to manufacture active substance and / or the medicinal product.

*Figure 19: Impact on European Critical Medicines Lists if Derogation is not Granted for –Use of Fluoropolymers Manufacturing Operations**



Critical medicines lists accurate as of August 2023[25]

[24] In May 2023, 21 Member States endorsed a Non-Paper on 'Improving the security of medicines supply in Europe' that provides for three points of action to address severe medicines shortages:

(i) Installing a voluntary solidarity mechanism within the Executive Steering Group on Shortages of Medicines caused by Major Events (MSSG) to, as a last resort, temporarily alleviate acute shortages in Member States;

(ii) Establishing a European list of critical medicines whose supply, production and value chains must be monitored;

(iii) Exploring a Critical Medicines Act to reduce dependencies for critical medicines and ingredients, particularly for products where there are only a few supplying manufacturers or countries

[25] Slovenia (Essential) list is characteristic of an essential medicines list; however, it is intrinsically linked to a second list, Slovenia's (Indispensable) list, which is more typical of a critical medicines list and therefore both are included in this analysis. France MITM - Medicines of Major Therapeutic Interest

The number of critical medicines impacted if EU manufacturing operations ceased, results in overlaps with 61% (Slovenia) - 78% (Norway) of the ATC codes identified in the survey with the European member state critical medicines lists.

When considering how to strengthen supply chains, both the environmental impact as well as the potential impact of environmental legislation on supply should also be considered.

5.4.4 Netherlands Case Study

When estimating the impact of the proposed ban on patients, it is important to look at the implications in relation to the availability of products on the market in case no derogation for PFAS used in the manufacturing process or as the substance in all medicinal products is secured. In this case study we attempt to do so using the example of the Netherlands. The data from the Dutch Healthcare Institute over the last three years provides insights into the potential impact of this ban on specific medicine categories. Extrapolating these findings to the EU level, we can anticipate similar consequences for patients across the European Union.

Our analysis indicates a large therapeutic dependence on the products which, under the proposed ban, could face unavailability. ATC data from the industry survey was cross checked against the Dutch Healthcare Institute prescription information. 691 products that hold marketing authorisation in the country would be impacted. This accounts for 64% of all medicines contained in the Dutch Healthcare Institute public database on the use of medicines in the country.

Many of the medicines manufactured using PFAS are used in treating life-threatening conditions, including cancer and cardiovascular diseases. In the absence of derogations to the ban, patients would face delays or be forced to switch to less effective treatments, compromising patient outcomes and safety. In many cases, they would completely lose access to treatments. In particular patients with rare diseases or unique conditions may be disproportionally affected by the ban, as alternative treatments may not be available or affordable.

In total for all associated ATC codes, there are more than 40 million users per year in the Netherlands. [26] In terms of product characteristics, substances which will be affected by the ban are found across various ATC groups. Table 1 and Table 2 present an overview of the top 20 and bottom 20 affected substances in terms of the number of users per year in the country. As indicated in the table, the ban will affect both widely used products (e.g., proton pump inhibitors, laxatives, beta blockers and wide-spectrum antibiotics), as well as less frequently used medicines including medications for rare diseases. For 205 of the identified substances, only up to 5 products are authorised, making them particularly vulnerable to supply disruption caused by changes in the composition of the market. For 76 of the identified substances, the product impacted by the PFAS ban is the only available medicine on the market in the country. For these products, the impact would be critical to patient access. A full overview of all affected products and the respective patient population in 2022 is available in the Appendix 3 to this report.

[26] Note: here individual users for every product are counted. One patient can receive numerous products; therefore the number is higher than the total country population.

Table 1 Top 20 substances impacted by the PFAS ban by the number of patients in the Netherlands in 2022

Substance name	ATC code	Number of patients	Substance name	ATC code	Number of patients
Proton pump inhibitors	A02BC	2.219.000	Dihydropyridine derivatives	C08CA	1.010.000
HMG CoA reductase inhibitors	C10AA	1.991.000	Vitamin D and analogues	A11CC	1.003.000
Osmotically acting laxatives	A06AD	1.421.000	Selective beta-2-adrenoreceptor agonists	R03AC	902.850
Contact laxatives	A06AB	1.421.000	Other antihistamines for systemic use	R06AX	858.660
Beta blocking agents, selective	C07AB	1.331.000	Acetic acid derivatives and related substances	M01AB	858.520
Platelet aggregation inhibitors excl. heparin	B01AC	1.195.000	Other ophthalmologicals	S01XA	767.650
Propionic acid derivatives	M01AE	1.116.000	Angiotensin II receptor blockers (ARBs), plain	C09CA	743.690
ACE inhibitors, plain	C09AA	1.081.000	Imidazole and triazole derivatives	D01AC	689.160
Penicillins with extended spectrum	J01CA	1.032.000	Biguanides	A10BA	672.420
Other emollients and protectives	D02AX	1.021.000	Combinations of penicillins, incl. beta-lactamase inhibitors	J01CR	648.350

Table 2 Bottom 20 substances impacted by the PFAS ban by the number of patients in the Netherlands in 2022

Substance name	ATC code	Number of patients	Substance name	ATC code	Number of patients
Enzymes	A16AB	1	Calcitonin preparations	H05BA	34
Antidotes	V03AB	1	Ascorbic acid (vitamin C), plain	A11GA	39
Phosphonic acid derivatives	J05AD	2	Methanolquinolines	P01BC	68
Enzymes	B01AD	4	Ergot alkaloids	G02AB	70
Estrogens, combinations with other drugs	G03CC	5	Estren derivatives	A14AB	74
Folic acid analogues	L01BA	8	Antibiotics	J02AA	77
Anti-gonadotropin-releasing hormones	H01CC	9	Pyrazolones	N02BB	156
Other plain vitamin preparations	A11HA	11	Other muscle relaxants, peripherally acting agents	M03AX	170
Blood substitutes and plasma protein fractions	B05AA	12	Drugs for treatment of hypoglycemia	V03AH	189
Biguanides and amidines	D08AC	14	Drugs used in hereditary angioedema	B06AC	217

Case study methodology and limitations

For this case study two data sources were consulted, namely the data provided by the pharmaceutical manufacturers as a part of the inter-association survey on the PFAS use in the pharmaceutical value chain, and the publicly available data[27] on national medicine use by the Dutch Healthcare Institute.

The respondents of the inter-association industry survey were asked to identify ATC codes for products where PFAS (fluoropolymer) are used either in the industrial manufacturing process (in Europe) or as substances (API and other materials) in the products, product packaging and/or delivery devices. The underlying goal was to identify how many products would be affected by the PFAS ban, or more specifically by the manufacturing and regulatory restrictions that accompany the ban.

The product ATC codes were extracted from the inter-association industry survey responses and linked to the medicines use data available in the Dutch database for the same ATC codes (at the same level), thus connecting the ATC code with the number of users in the country.

[27] https://www.gipdatabank.nl/

Connecting the two datasets allows us to estimate which patient categories may be impacted by the restriction and support evidence-based policymaking.
For both datasets, 4th-level ATC codes were analysed. Whilst the 4th level ATC code does not allow identifying the actual product, it provides a granular classification of medicines compared to higher levels, allowing us to gain insights into specific medicine classes and subcategories.

The here-presented analysis also has several methodological limitations which need to be acknowledged:

- The responses received through the inter-association industry survey do not present a complete overview of all products which may be affected by the PFAS ban but should be seen as the "minimum list of affected products".
- Not all the ATC codes received through the inter-association industry survey were available in the Dutch database. This may be due to certain products not being in use in the country.

The results of the analysis provide a glimpse into the potential impact of the ban on the availability of medicines in the Netherlands. Whilst this case study can serve as an indication of the impact in other European countries, the findings should be carefully extrapolated taking into account the specifics of each Member State in relation to medicines use, prescription practices and other health system-related considerations.

6. Summary Conclusions

The 40 companies participating in the survey identified 1922 active substances, which could be impacted by the proposed Restriction because:

- APIs in manufacturing and packaging operations at a facility in the EEA and / or
- Medicinal products with PFAS constituents present in the intermediate packaging or drug delivery device of a medicinal product placed on the market in the EEA.

Key Survey findings:

- In the survey, 169 APIs were reported to be undergoing process development, at an EU manufacturing facility. A PPORD derogation is necessary to support the research and development of new medicinal products containing both fluorinated and non-fluorinated APIs. In this way material manufactured in EU facilities can be used to supply clinical trials been conducted to meet unmet medical needs.
- Supply chains of 93% of active substances involve EU manufacturing operations, which depend on fluoropolymers, within plant, equipment and single use systems. If the proposed PFAS restriction prohibits the supply of these critical raw materials, manufacturing operations at EU facilities will cease when contingency stock levels are depleted.
- There is a specified substance with a PFAS moiety in the medicinal product marketing authorisation filed for 18% of the active substances with EU manufacturing operations. These include raw materials, starting materials, intermediates, APIs and excipients. Only 139 APIs with PFAS moiety have been reported by the companies and would therefore fall under the proposed derogation for APIs.
- There is currently no technically viable alternative for packaging. Packaging and drug delivery devices are part of registered medicines, therefore the regulatory environment requires toxicological evaluations, extractive and leachable studies and product stability to ensure the continued quality of the product. In addition, child resistance and patient usability studies may be required. All this takes over 10 years. This data will form part of a regulatory assessment and approval processes taking between 6 months to 2 years.
- The survey identifies at least 47,677 global marketing authorisations that could be impacted If the proposed restriction is implemented, a significant number of critical medicines will no longer be available impacting patients access to medicines. The WHO Essential Medicines List (EML) is a reference point for countries to define products which are essential to the functioning of healthcare systems. 674 medicines from the WHO list, distributed across a variety of pharmacological/therapeutic groups that could be impacted. Furthermore, a heavy impact was identified across the European Member State's "Critical Medicines lists" developed to counter shortages and to reduce Europe's health dependence on non-European countries. For example, 78% of the critical medicines list in Norway could be impacted by the proposed Restriction.

Evidence suggests that for the continued research, development and marketing of medicines (biopharmaceuticals and vaccines), including all steps which are necessary for their manufacturing, packaging and delivery devices of medicines in the EEA, they should generally be derogated from a universal PFAS restriction. Furthermore, currently for all PFAS use scenarios associated with the development, manufacture, and supply of medicinal products there are no suitable alternatives. This further strengthens the need for a derogation that encompasses all parts of the supply chain as this is a necessary medicine shortage mitigation measure.

Appendix 1

Overview of distribution of ATC codes (level 3)

A: Alimentary tract and metabolism	
A01A	5
A02A	71
A02B	23
A03A	9
A03F	5
A04A	3
A05A	1
A05B	1
A06A	14
A07A	1
A07D	3
A07E	3
A08A	3
A09A	3
A10A	76
A10B	68
A11A	7
A11C	1
A11D	3
A11E	17
A11G	13
A11H	5
A11J	2
A12A	1
A12B	1
A14A	3
A16A	13
SUM	*355*
B: Blood And Blood Forming Organs	
B01A	39
B02A	3
B02B	46
B03A	4
B03X	4
B05A	5
B05B	1
B05X	4
B06A	2
SUM	*108*
C: Cardiovascular System	
C01B	3
C01C	2
C01D	3
C01E	4
C02A	2
C02B	1
C02C	1
C02K	7
C02L	1
C03A	13
C03B	3
C03C	5
C03D	2
C07F	5
C08C	11
C08D	3
C08E	1
C08G	2
C09A	18
C09B	8
C09C	8
C09D	7
C03E	2
C04A	1
C05A	7
C05B	1
C05C	6
C07A	20
C07B	2
C10A	23
C10B	1
SUM	*173*
D: Dermatologicals	
D01A	38
D01B	2
D02A	1
D03A	10
D04A	3
D05A	5
D06A	5
D06B	2
D07A	3
D07B	1
D07C	7
D08A	9
D09A	1
D10A	2
D10B	1
D11A	7
SUM	*97*
G: Genito Urinary System And Sex Hormones	
G01A	20
G02A	3
G02B	1
G02C	2
G03A	12
G03B	11
G03C	18
G03D	11
G03E	4
G03F	14
G03G	9
G03H	3
G03X	1
G04B	9
G04C	9
SUM	*127*
H: Systemic hormonal preparations, excl. sex hormones and insulins	
H01A	15
H01B	2
H01C	10
H03A	2
H03B	2
H04A	1
H05A	1
H05B	3
SUM	*36*
Antiinfectives For Systemic Use	
J01A	1
J01C	34
J01D	21
J01E	1
J01F	2
J01G	3
J01M	1
J01R	1
J01X	3
J02A	8
J04A	2
J04B	3
J05A	30
J06B	5
J07A	2
J07B	18
J07C	4
SUM	*139*
Antineoplastic And Immunomodulating Agents	
L01A	2
L01B	10
L01C	6
L01D	12
L01E	23
L01F	17
L01X	40
L02A	5
L02B	24
L03A	9
L04A	50
SUM	*198*
M: Musculo-Skeletal System	
M01A	42
M01B	1
M02A	8
M03A	2
M03B	3
M04A	4
M05B	5
M09A	1
SUM	*66*
N: Nervous Syste	
N01A	3
N01B	7
N02A	21
N02B	73
N02C	17
N03A	18
N04B	14
N05A	20
N05B	5
N05C	6
N06A	34
N06B	14
N06C	6
N06D	13
N07B	8
N07C	3
N07X	4
SUM	*266*
P: Antiparasitic products, insecticides and repellents	
P01B	6
P01C	2
P02B	2
P02C	1
P02D	1
SUM	*12*
R: Respiratory System	
R01A	13
R01B	20
R02A	6
R03A	40
R03B	12
R03C	1
R03D	11
R05C	6
R05D	2
R05X	0
R06A	35
R07A	3
RO3B	9
SUM	*158*
S: Sensory organs	
S01A	*9*
S01B	*7*
S01C	*5*
S01E	*13*
S01G	*5*
S01L	*4*
S01X	*6*
S02A	*2*
S02C	*2*
S03A	*2*
SUM	*55*
V: Various	
V03A	*18*
V04C	*2*
V08A	*2*
V08C	*3*
V09A	*2*
V09I	*2*
V10X	*2*
SUM	*31*
Blanks	**125**
TOTAL	**1944**

Table Level 3 ATC codes for all APIs with EU market approval in this survey (number of times the ATC code is reported)

N02B (73)	A02B (20)	C03A (13)	M02A (8)	S01G (5)	M03B (3)	A07D (3)	G02C (2)	C02B (1)	J01A (1)
A10A (72)	L02B (19)	G03A (13)	G04B (8)	J06B (5)	J01G (3)	J01X (3)	S02A (2)	D09A (1)	A07A (1)
A02A (71)	C09A (18)	A11G (13)	N07B (8)	D05A (5)	D07A (3)	A08A (3)	C03D (2)	H04A (1)	C07B (1)
A10B (59)	N05A (18)	R03B (12)	C09D (7)	N05B (5)	J04B (3)	J01F (2)	D01B (2)	D07B (1)	A05A (1)
B02B (43)	C10A (17)	L01F (12)	C09C (7)	N05C (5)	G02A (3)	C01C (2)	A11J (2)	P02C (1)	B05B (1)
M01A (41)	V03A (18)	L01D (12)	S01B (7)	A11H (5)	H05B (3)	S01L (2)	R05D (2)	A12B (1)	A11C (1)
L04A (42)	G03C (17)	C08C (11)	D06A (7)	N01B (5)	C01D (3)	B06A (2)	M03A (2)	G02B (1)	J01E (1)
D01A (38)	L01E (17)	R03D (11)	C02K (7)	A01A (5)	J07C (3)	V09I (2)	N01A (4)	P02D (1)	C08E (1)
B01A (38)	A11E (17)	G03D (11)	C05A (7)	C03C (5)	C01B (3)	V10X (2)	C03E (2)	P01C (1)	R03C (1)
L01X (35)	N03A (16)	N06D (10)	A11A (7)	M04A (4)	D10A (3)	S02C (2)	D06B (2)	D02A (1)	J01R (1)
R06A (35)	J07B (16)	A16A (10)	C05C (6)	B03X (4)	C08D (3)	P02B (2)	H03B (2)	A12A (1)	C02L (1)
N06A (34)	N02C (15)	G03B (10)	S01X (6)	M05B (4)	B02A (3)	S03A (2)	H03A (2)	M01B (1)	
J01C (29)	N02A (15)	D03A (10)	D11A (6)	P01B (4)	G03H (3)	A04A (2)	C02A (2)	A13 (1)	
J05A (28)	G03F (15)	H01C (9)	G04C (6)	J02A (4)	V08C (3)	J07A (2)	R07A (2)	R05X (1)	
R03A (27)	H01A (14)	G03G (9)	D07C (6)	B03A (4)	A14A (3)	N07X (2)	H01B (2)	NOTA (1)	
C09B (27)	N06B (14)	L03A (9)	R05C (6)	C07F (4)	A11D (3)	N07C (2)	V04C (2)	V09A (1)	
J01D (21)	A06A (14)	S01A (9)	R02A (6)	G03E (4)	A03 (3)	A09A (2)	C08G (2)	H05A (1)	
C07A (20)	R01A (13)	L01B (9)	L02A (5)	A03F (4)	D04A (3)	B05A (2)	J04A (2)	C02C (1)	
R01B (20)	N04B (13)	D08A (9)	L01C (5)	B05X (4)	A07E (3)	RO3B (2)	M09A (1)	C05B (1)	
G01A (20)	S01E (13)	A03A (9)	S01C (5)	C01E (4)	C03B (3)	V08A (2)	D10B (1)	C04A (1)	

Table Level 3 ATC codes for APIs for export (number of times the ATC code is reported)

N02A (6)	J07B (2)	C09C (1)	L01A (1)					
A10B (5)	N01B (2)	C10B (1)	M01A (1)					
C09B (5)	N02C (2)	C10A (1)	N03A (1)					
A16A (3)	N07X (2)	G03B (1)	N05C (1)					
B05A (3)	A03F (1)	G03X (1)	N06C (1)					
G04C (3)	A04A (1)	G04B (1)	N07C (1)					
L04A (3)	A09A (1)	H01C (1)	P01B (1)					
R03A (3)	A10A (1)	J05A (1)	P01C (1)					
A02B (2)	B01A (1)	J07C (1)	V09A (1)					
J01C (2)	C07B (1)	L01X (1)						

Table Level 3 ATC codes for APIs for development (number of times the ATC code is reported)

A10B (3)	B02B (2)	A10A (2)	L04A (2)	H01A (1)	A05B (1)	N06D (1)	D11A (1)
L01E (1)	R03A (1)						

Appendix 2

PFAS Process Chemicals Identified by the Survey*

CAS No.	Chemical Name
11550-02-00	MPS-EDA•TFA, trifluoroacetic acid salt of N-(2-aminoethyl)-3-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)propanamide
121788-73-6	(R,R)-N,N'-Bis(trifluoromethanesulfonyl)-1,2-diphenylethylenediamine
14533-84-7	Pentafluorophenyl trifluoroacetate
1493-13-6	Trifluoromethanesulfonic acid
27607-77-8	Trimethylsilyl Trifluoromethanesulfonate
2923-16-2	Potassium Trifluoroacetate
2923-18-4	Sodium Trifluoroacetate
2923-28-6	Silver trifluoromethanesulfonate
32247-96-4	3,5-Bis(trifluoromethyl)benzyl Bromide
33454-82-9	Lithium Trifluoromethanesulfonate
351-35-9	3-(Trifluoromethyl)phenylacetic Acid
358-23-6	Trifluoromethanesulfonic Anhydride
375-72-4	Perfluoro-1-butanesulfonyl Fluoride
407-25-0	Trifluoroacetic Anhydride
6226-25-1	2,2,2-Trifluoroethyl Trifluoromethanesulfonate
75-89-8	2,2,2-Trifluoroethanol
753-90-2	2,2,2-Trifluoroethylamine
75706-12-6	Leflunomide
76-05-1	Trifluoroacetic Acid
79271-56-0	Triethylsilyl Trifluoromethanesulfonate
811-97-2	1,1,1,2-Tetrafluoroethane
886536-37-4	4-(2,2,2-Trifluoroethoxy)benzeneboronic acid
98-08-0	α,α,α-Trifluorotoluene
98-17-9	3-Trifluoromethylphenol

*This list is not an exhaustive list and should not be used as the basis for any substance specific derogation for processing chemicals used in the manufacture of medicinal products

Appendix 3

ATC code (level 4)	Substance name	2018	2019	2020	2021	2022
A02BC	Proton pump inhibitors	2.139.000	2.214.000	2.233.000	2.218.000	2.219.000
C10AA	HMG CoA reductase inhibitors	1.966.000	1.971.000	1.929.000	1.947.000	1.991.000
A06AD	Osmotically acting laxatives	1.307.000	1.319.000	1.290.000	1.374.000	1.421.000
A06AB	Contact laxatives	1.307.000	1.319.000	1.290.000	1.374.000	1.421.000
C07AB	Beta blocking agents, selective	1.355.000	1.351.000	1.335.000	1.325.000	1.331.000
B01AC	Platelet aggregation inhibitors excl. heparin	1.206.000	1.206.000	1.191.000	1.189.000	1.195.000
M01AE	Propionic acid derivatives	1.110.000	1.188.000	1.074.000	1.089.000	1.116.000
C09AA	ACE inhibitors, plain	1.037.000	1.066.000	1.059.000	1.072.000	1.081.000
J01CA	Penicillins with extended spectrum	1.121.000	1.070.000	805.110	805.020	1.032.000
D02AX	Other emollients and protectives	916.670	930.160	914.150	972.430	1.021.000
C08CA	Dihydropyridine derivatives	856.950	904.410	926.280	972.890	1.010.000
A11CC	Vitamin D and analogues	1.110.000	961.800	930.860	983.040	1.003.000
R03AC	Selective beta-2-adrenoreceptor agonists	939.420	949.510	874.420	841.490	902.850
R06AX	Other antihistamines for systemic use	823.600	839.480	840.630	869.610	858.660
M01AB	Acetic acid derivatives and related substances	1.154.000	993.470	860.060	842.520	858.520
S01XA	Other ophthalmologicals	679.660	716.820	698.030	735.840	767.650
C09CA	Angiotensin II receptor blockers (ARBs), plain	699.720	742.640	707.770	721.990	743.690
D01AC	Imidazole and triazole derivatives	773.010	744.910	681.780	639.740	689.160
A10BA	Biguanides	651.630	658.230	659.650	666.830	672.420
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	658.870	653.340	560.540	556.960	648.350
D06AX	Other antibiotics for topical use	652.870	639.360	556.710	550.600	623.570
R03AK	Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	588.440	585.540	577.590	566.830	602.680
R05DA	Opium alkaloids and derivatives	653.090	621.670	393.220	388.350	590.620
N06AB	Selective serotonin reuptake inhibitors	548.670	556.670	558.540	565.850	584.780
D07AC	Corticosteroids, potent (group III)	573.380	588.720	541.450	570.280	576.540
C03AA	Thiazides, plain	656.450	671.190	608.730	606.600	574.620
H03AA	Thyroid hormones	501.000	511.820	516.850	520.080	531.040
N02AA	Natural opium alkaloids	509.470	481.740	459.670	489.610	520.840
B01AF	Direct factor Xa inhibitors	211.710	277.440	330.380	391.890	454.500
N02AX	Other opioids	428.300	425.650	419.330	430.830	448.960
R06AE	Piperazine derivatives	446.420	437.330	433.640	441.940	425.800
J01AA	Tetracyclines	593.730	539.920	378.600	310.730	406.100
C03CA	Sulfonamides, plain	371.480	366.440	358.080	355.890	353.770
J01CF	Beta-lactamase resistant penicillins	323.480	318.180	309.770	308.690	344.030
G04CA	Alpha-adrenoreceptor antagonists	301.360	308.890	309.390	319.910	332.610

ATC code (level 4)	Substance name	2018	2019	2020	2021	2022
R03BA	Glucocorticoids	374.300	366.170	342.400	320.330	327.930
B03AA	Iron bivalent, oral preparations	280.110	285.860	276.030	300.580	326.670
A10BB	Sulfonylureas	304.010	308.320	311.110	320.220	325.010
N06AA	Non-selective monoamine reuptake inhibitors	285.160	292.510	287.920	293.870	305.260
J01MA	Fluoroquinolones	337.230	311.400	282.640	276.410	294.530
A03FA	Propulsives	307.960	296.520	281.930	290.190	291.880
N06AX	Other antidepressants	291.300	291.500	285.740	285.070	288.530
N05BA	Benzodiazepine derivatives	302.100	300.110	297.360	291.090	287.640
N03AX	Other antiepileptics	256.650	266.550	267.620	273.150	286.150
G03AA	Progestogens and estrogens, fixed combinations	345.200	349.310	326.850	290.340	285.590
N06BA	Centrally acting sympathomimetics	225.960	227.480	231.360	239.200	264.910
C01DA	Organic nitrates	263.240	249.190	247.910	250.310	252.620
N05AH	Diazepines, oxazepines, thiazepines and oxepines	182.840	194.350	205.570	213.290	217.990
C10AX	Other lipid modifying agents	139.240	161.240	177.270	195.460	216.800
M04AA	Preparations inhibiting uric acid production	201.730	205.800	206.400	208.210	213.330
N02CC	Selective serotonin (5HT1) agonists	202.390	205.470	201.120	203.810	209.910
C03DA	Aldosterone antagonists	161.200	167.460	171.630	190.370	205.380
N01BB	Amides	180.570	188.380	174.860	189.700	197.540
A10AE	Insulins and analogues for injection, long-acting	192.270	193.900	194.060	195.140	194.930
B01AA	Vitamin K antagonists	315.830	278.860	244.760	212.520	185.210
C07AA	Beta blocking agents, non-selective	204.400	204.160	185.630	182.910	184.160
M01AH	Coxibs	183.170	178.190	162.660	166.550	178.510
J01XX	Other antibacterials	186.710	167.460	193.180	179.190	177.930
A10AB	Insulins and analogues for injection, fast-acting	169.810	169.370	169.310	170.990	169.650
C09DA	Angiotensin II receptor blockers (ARBs) and diuretics	250.750	215.160	190.170	179.030	168.790
B01AB	Heparin group	177.120	171.110	147.590	156.190	161.240
J02AC	Triazole and tetrazole derivatives	173.070	165.230	146.070	140.940	158.330
R03AL	Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids	97.497	114.000	116.010	127.970	143.580
G01AF	Imidazole derivatives	216.970	210.870	197.050	187.200	143.140
G03CA	Natural and semisynthetic estrogens, plain	119.500	123.070	120.580	129.440	142.180
N02AJ	Opioids in combination with non-opioid analgesics	157.600	151.490	141.000	136.290	134.400
L04AX	Other immunosuppressants	124.410	128.370	128.030	129.740	132.300
A04AA	Serotonin (5HT3) antagonists	75.994	83.088	76.093	102.910	126.550

ATC code (level 4)	Substance name	2018	2019	2020	2021	2022
A10BK	Sodium-glucose co-transporter 2 (SGLT2) inhibitors	15.443	16.887	19.946	39.715	113.180
D10AF	Antiinfectives for treatment of acne	132.590	128.160	116.450	119.180	112.790
N02AB	Phenylpiperidine derivatives	104.760	102.620	104.630	106.300	105.920
J01CE	Beta-lactamase sensitive penicillins	47.138	82.872	56.059	55.052	95.960
J01FF	Lincosamides	81.890	85.407	83.251	84.639	94.358
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives	85.614	94.446	84.354	84.019	93.450
J05AB	Nucleosides and nucleotides excl. reverse transcriptase inhibitors	88.392	90.127	86.115	86.970	91.513
C09BA	ACE inhibitors and diuretics	123.700	116.500	103.090	95.601	88.528
D01BA	Antifungals for systemic use	83.702	81.263	69.607	76.321	85.268
A10BJ	Glucagon-like peptide-1 (GLP-1) analogues	15.895	26.253	39.515	54.928	82.581
L01BC	Pyrimidine analogues	55.332	64.350	69.385	76.981	82.169
D11AH	Agents for dermatitis, excluding corticosteroids	62.456	64.804	67.216	74.767	82.134
D05AX	Other antipsoriatics for topical use	73.148	77.343	75.386	77.216	80.503
N05AX	Other antipsychotics	75.118	77.192	77.493	77.564	78.803
C08DA	Phenylalkylamine derivatives	66.060	67.812	67.866	69.692	71.505
N05CF	Benzodiazepine related drugs	62.228	61.717	62.392	62.267	69.206
D01AE	Other antifungals for topical use	62.544	63.086	61.806	66.702	68.196
G03DC	Estren derivatives	72.390	67.273	44.061	51.448	66.395
C01CA	Adrenergic and dopaminergic agents	52.519	53.416	52.645	50.766	65.926
R06AA	Aminoalkyl ethers	85.324	80.426	70.128	69.753	65.105
A07AA	Antibiotics	72.567	68.657	63.934	62.347	64.906
C03BA	Sulfonamides, plain	71.385	74.466	69.471	66.956	63.375
N05AD	Butyrophenone derivatives	71.896	66.958	68.091	64.763	61.553
B01AE	Direct thrombin inhibitors	60.460	63.342	61.656	60.964	60.175
N07CA	Antivertigo preparations	78.154	72.551	66.533	62.043	58.638
G04CB	Testosterone-5-alpha reductase inhibitors	56.416	56.990	57.224	57.628	58.240
S02AA	Antiinfectives	54.612	55.260	57.031	50.183	54.373
C09DX	Angiotensin II receptor blockers (ARBs), other combinations	17.243	21.851	27.364	39.375	52.900
M01AC	Oxicams	76.269	71.097	54.154	53.459	52.362
N04BC	Dopamine agonists	50.164	50.314	49.644	50.247	50.360
A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	38.148	44.219	46.885	48.884	47.838
R03DC	Leukotriene receptor antagonists	48.485	48.742	47.414	46.260	46.076
C08DB	Benzothiazepine derivatives	44.030	44.151	44.613	44.243	44.475
P01BA	Aminoquinolines	47.050	46.826	46.593	43.774	43.789
G03DA	Pregnen (4) derivatives	33.244	31.890	31.914	37.143	42.517
C01BC	Antiarrhythmics, class Ic	43.768	43.224	41.820	41.721	42.156

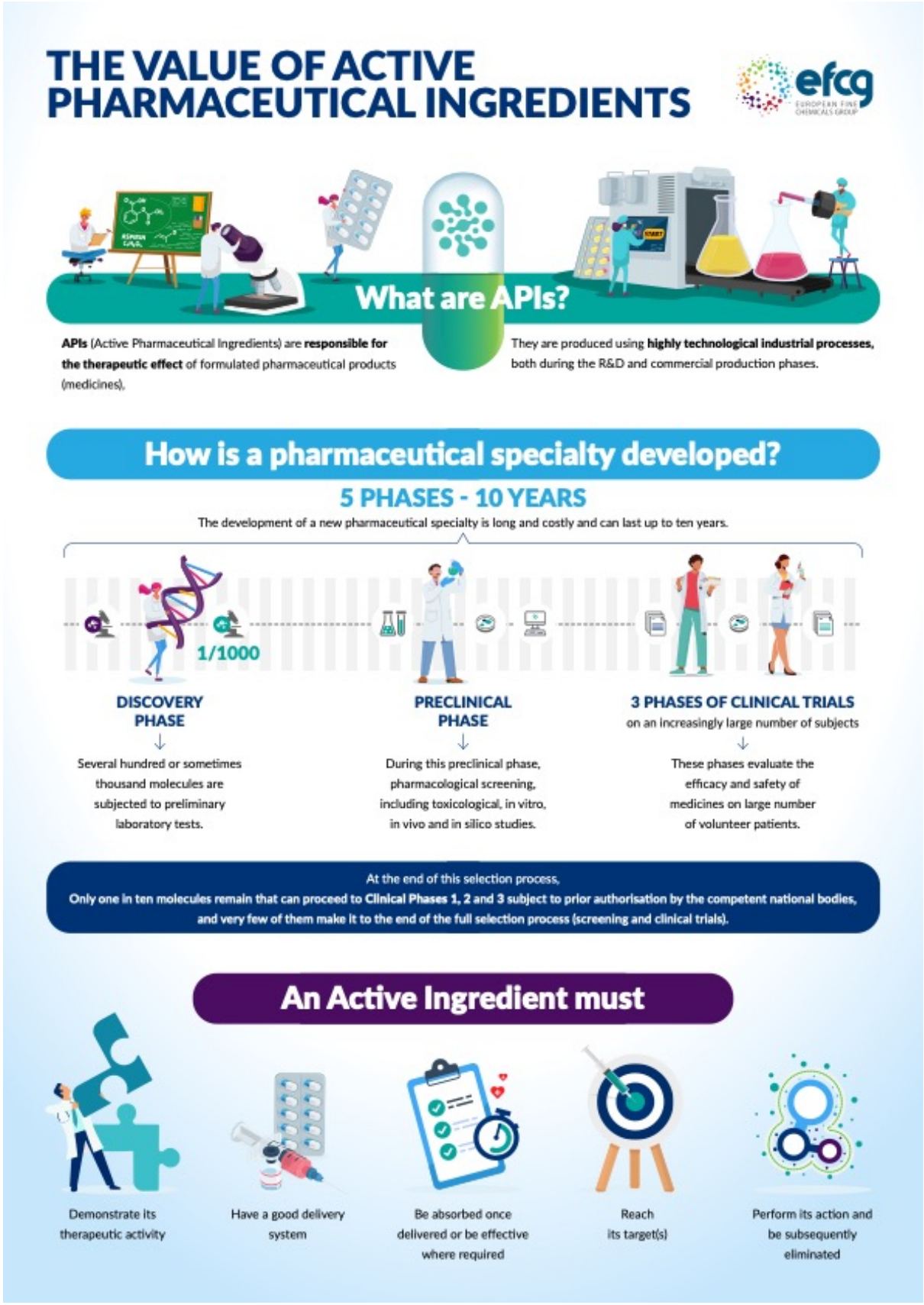
ATC code (level 4)	Substance name	2018	2019	2020	2021	2022
N04BA	Dopa and dopa derivatives	38.205	39.436	40.000	40.398	41.798
D06BB	Antivirals	41.948	42.957	41.398	40.720	41.197
L02AE	Gonadotropin releasing hormone analogues	30.494	32.395	34.373	36.448	38.600
L02BG	Aromatase inhibitors	31.442	32.705	33.530	35.153	37.546
N03AF	Carboxamide derivatives	41.034	39.610	38.064	36.768	35.863
N02AE	Oripavine derivatives	38.391	36.325	34.833	35.122	34.787
M05BX	Other drugs affecting bone structure and mineralization	30.466	31.534	31.618	32.633	34.531
A02BX	Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	33.549	34.901	36.917	37.641	33.166
L04AA	Selective immunosuppressants	25.713	27.132	27.726	29.081	30.951
C07AG	Alpha and beta blocking agents	33.081	32.397	29.537	29.586	29.683
L02BA	Anti-estrogens	32.144	31.440	30.483	29.806	29.509
A10AC	Insulins and analogues for injection, intermediate-acting	27.156	27.828	28.191	29.082	28.738
C01BD	Antiarrhythmics, class III	27.578	27.396	26.595	27.227	27.673
A12BA	Potassium	29.757	27.331	27.950	27.446	26.872
G03AC	Progestogens	23.269	20.984	20.320	25.007	26.061
A07EA	Corticosteroids acting locally	22.011	23.440	23.924	24.568	25.597
N03AE	Benzodiazepine derivatives	28.880	27.844	26.563	25.294	25.428
G03BA	3-oxoandrosten (4) derivatives	19.157	20.010	20.951	22.166	24.155
J05AR	Antivirals for treatment of HIV infections, combinations	21.762	23.037	22.868	22.928	23.649
G03FA	Progestogens and estrogens, fixed combinations	17.649	19.424	19.998	20.499	23.098
D11AX	Other dermatologicals	12.190	14.075	17.469	19.642	23.086
A07DA	Antipropulsives	29.687	25.296	23.226	22.922	22.325
H03BB	Sulfur-containing imidazole derivatives	21.370	21.100	21.089	21.540	22.246
A09AA	Enzyme preparations	16.375	17.766	18.739	19.726	20.882
N02CX	Other antimigraine preparations	25.291	23.895	21.914	21.618	20.011
D06BA	Sulfonamides	32.490	27.026	22.915	20.920	20.008
L04AD	Calcineurin inhibitors	18.012	18.645	18.764	19.272	19.909
N06DA	Anticholinesterases	20.281	19.355	18.628	18.267	18.321
C07BB	Beta blocking agents, selective, and thiazides	28.200	25.774	22.963	20.202	18.219
G03FB	Progestogens and estrogens, sequential preparations	13.566	15.311	15.457	16.715	17.663
A05AA	Bile acids and derivatives	15.493	16.121	15.769	15.979	17.279
N07BC	Drugs used in opioid dependence	14.992	15.888	16.053	16.487	16.657
N01BX	Other local anesthetics	13.135	13.939	13.385	15.358	15.916
A01AD	Other agents for local oral treatment	16.254	17.723	15.130	16.267	15.079
S01EA	Sympathomimetics in glaucoma therapy	20.342	13.171	12.851	14.426	14.964

ATC code (level 4)	Substance name	2018	2019	2020	2021	2022
N07BB	Drugs used in alcohol dependence	16.421	15.631	14.496	14.183	14.384
G02BA	Intrauterine contraceptives	11.443	12.252	13.328	15.100	13.978
A04AD	Other antiemetics	16.018	14.218	11.605	12.420	13.599
C03EA	Low-ceiling diuretics and potassium-sparing agents	41.064	36.370	32.214	24.273	13.229
B02BA	Vitamin K	22.399	17.720	15.448	15.500	12.927
C01EB	Other cardiac preparations	10.934	11.288	11.914	12.618	12.851
H01BA	Vasopressin and analogues	16.654	16.278	13.398	12.828	12.836
C09DB	Angiotensin II receptor blockers (ARBs) and calcium channel blockers	12.195	12.046	12.008	12.031	12.248
J01DD	Third-generation cephalosporins	7.927	10.072	10.519	10.131	11.757
A02BB	Prostaglandins	9.463	10.268	10.776	11.459	11.423
A10BD	Combinations of oral blood glucose lowering drugs	10.951	11.060	10.710	10.505	10.225
C09BB	ACE inhibitors and calcium channel blockers	9.291	9.705	9.691	9.772	10.123
L02BB	Anti-androgens	11.947	11.697	10.977	10.425	10.052
N05AF	Thioxanthene derivatives	11.525	11.010	10.534	10.052	9.641
G03DB	Pregnadien derivatives	4.854	5.947	5.718	6.787	8.616
A01AC	Corticosteroids for local oral treatment	5.207	6.090	6.530	7.407	7.998
C02AC	Imidazoline receptor agonists	3.663	4.202	4.256	4.395	7.987
M03AC	Other quaternary ammonium compounds	4.436	4.637	5.274	5.605	6.263
G03CX	Other estrogens	9.286	8.484	7.712	6.746	5.977
H01BB	Oxytocin and analogues	5.893	5.888	5.101	5.571	5.306
N03AA	Barbiturates and derivatives	5.601	5.255	5.052	4.723	4.527
H01CB	Somatostatin and analogues	3.793	3.930	3.946	3.964	3.980
G03HA	Antiandrogens, plain	5.001	5.026	4.723	4.270	3.964
N02CD	Calcitonin gene-related peptide (CGRP) antagonists	.	.	.	1.587	3.938
A06AX	Other drugs for constipation	1.740	2.253	2.624	3.154	3.826
A06AC	Bulk-forming laxatives	1.740	2.253	2.624	3.154	3.826
A06AG	Enemas	1.740	2.253	2.624	3.154	3.826
N03AB	Hydantoin derivatives	5.839	5.327	4.759	3.903	3.665
G01AA	Antibiotics	3.339	3.659	3.634	3.474	3.650
N05AL	Benzamides	2.371	2.550	2.703	3.200	3.634
N02BA	Salicylic acid and derivatives	5.474	4.932	4.416	4.043	3.617
N04BB	Adamantane derivatives	4.324	4.141	3.810	3.612	3.611
B01AX	Other antithrombotic agents	4.596	3.705	2.829	3.043	3.389
R06AB	Substituted alkylamines	6.624	4.722	3.775	3.664	3.389
C01DX	Other vasodilators used in cardiac diseases	955	1.230	1.708	2.359	3.083
L03AB	Interferons	3.320	3.092	2.947	2.946	2.986

ATC code (level 4)	Substance name	2018	2019	2020	2021	2022
J01DC	Second-generation cephalosporins	4.744	4.396	2.912	2.654	2.888
B05XA	Electrolyte solutions	1.573	2.169	2.218	2.082	2.515
B05BA	Solutions for parenteral nutrition	1.573	2.169	2.218	2.082	2.515
H05AA	Parathyroid hormones and analogues	1.855	2.260	2.403	2.513	2.454
J06BD	Antiviral monoclonal antibodies	2.747	2.764	2.663	2.541	2.442
C09BX	ACE inhibitors, other combinations	969	1.298	1.464	1.737	1.967
N04BX	Other dopaminergic agents	1.828	1.748	1.831	1.823	1.950
N05BE	Azaspirodecanedione derivatives	2.333	2.142	2.012	2.021	1.873
J04AM	Combinations of drugs for treatment of tuberculosis	2.440	2.238	1.880	1.952	1.867
G04BE	Drugs used in erectile dysfunction	1.481	1.563	1.647	1.658	1.785
G03AB	Progestogens and estrogens, sequential preparations	3.731	3.400	2.966	2.234	1.744
C02KX	Antihypertensives for pulmonary arterial hypertension	1.398	1.454	1.505	1.599	1.634
L01EX	Other protein kinase inhibitors	564	662	752	1.171	1.483
A11DA	Vitamin B1, plain	1.536	1.363	1.586	1.400	1.427
B02BX	Other systemic hemostatics	699	849	1.005	1.203	1.404
J01GB	Other aminoglycosides	1.145	1.238	1.199	1.289	1.332
R07AX	Other respiratory system products	659	776	761	854	1.308
C01BA	Antiarrhythmics, class Ia	1.299	1.217	1.173	1.135	1.171
J05AE	Protease inhibitors	2.687	2.027	1.603	1.359	1.143
J04BA	Drugs for treatment of lepra	1.222	1.192	1.114	1.075	1.076
C04AD	Purine derivatives	1.443	1.383	1.263	1.176	1.050
N01AH	Opioid anesthetics	1.449	1.412	1.061	1.025	1.045
R05CB	Mucolytics	962	962	947	921	810
J01DB	First-generation cephalosporins	782	776	790	691	787
A10BF	Alpha glucosidase inhibitors	1.400	1.235	900	780	782
N06DX	Other anti-dementia drugs	1.645	1.306	1.070	916	774
N06BX	Other psychostimulants and nootropics	1.171	1.028	902	792	753
M01AX	Other antiinflammatory and antirheumatic agents, non-steroids	1.536	1.353	1.139	968	742
N06AG	Monoamine oxidase A inhibitors	1.022	951	852	759	728
L02BX	Other hormone antagonists and related agents	779	710	664	680	699
C08GA	Calcium channel blockers and diuretics	513	628	590	619	638
A10BX	Other blood glucose lowering drugs, excl. insulins	697	700	703	660	612
N01AX	Other general anesthetics	425	602	557	516	528
A16AX	Various alimentary tract and metabolism products	406	444	469	496	520
A08AA	Centrally acting antiobesity products					462
J01XA	Glycopeptide antibacterials	298	302	319	409	421

ATC code (level 4)	Substance name	2018	2019	2020	2021	2022
J05AP	Antivirals for treatment of HCV infections	1.063	895	571	477	403
B05AX	Other blood products	1.185	1.153	1.140	434	386
N05AB	Phenothiazines with piperazine structure	1.502	822	451	398	357
J05AX	Other antivirals	110	113	151	181	311
B06AC	Drugs used in hereditary angioedema	165	173	185	201	217
V03AH	Drugs for treatment of hypoglycemia	137	156	145	147	189
M03AX	Other muscle relaxants, peripherally acting agents	153	134	142	136	170
N02BB	Pyrazolones	6	15	23	54	156
J02AA	Antibiotics	79	102	90	84	77
A14AB	Estren derivatives	120	118	93	85	74
G02AB	Ergot alkaloids	36	56	67	63	70
P01BC	Methanolquinolines	91	117	65	67	68
A11GA	Ascorbic acid (vitamin C), plain	24	36	39	26	39
H05BA	Calcitonin preparations	40	42	42	42	34
D08AC	Biguanides and amidines	34	25	37	19	14
B05AA	Blood substitutes and plasma protein fractions	12	12	16	15	12
A11HA	Other plain vitamin preparations	7	16	1	11	11
H01CC	Anti-gonadotropin-releasing hormones					9
L01BA	Folic acid analogues	34	6	15	8	8
G03CC	Estrogens, combinations with other drugs	96	128	112	2	5
B01AD	Enzymes	2	.	3	2	4
J05AD	Phosphonic acid derivatives	6	4	1	2	2
A16AB	Enzymes	67	66	68	2	1
V03AB	Antidotes	3	1	1	1	1

Infographic 1



How is an Active Pharmaceutical Ingredient produced?

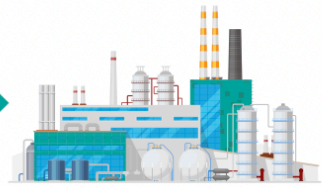
APIs are produced according to Good Manufacturing Practices (GMP) defined by regulatory authorities. The entire system is controlled by very strict regulatory procedures.

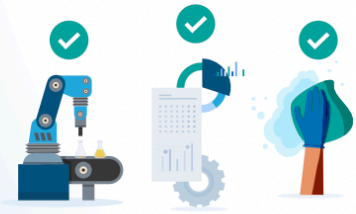
A license to manufacture, certifying that the company works **in accordance** with the requirements of the **EU legislation** on GMP.

A plant that has the **adequately trained personnel, premises and equipment** for the production and the conservation of each and every product.

Quality systems and **processes** that guarantee the proper functioning of the equipment and the **consistency and quality** of the APIs produced.

It is crucial for the API manufacturer to have a **cutting-edge Research & Development (R&D) facility,** enabling the **transition from laboratory scale** to **pilot plant** and then **to full industrial scale.** To achieve this an **excellent level of technology is needed.**





GMP standards require from manufacturers, inter alia, the **validation of their equipment, processes, analytical methods and cleaning methods.**

Strict **environmental, health and safety (EHS) standards** are required to operate manufacturing plants.

"Gold standards" are applied to meet excellence in **industrial safety, environmental protection and health & safety at work.**

At the expiry of its patent the **active ingredient can be used for the production of generic and biosimilar drugs,**

allowing **access to affordable healthcare** to **a wider patient population**, including in lower-income countries,

and **reducing the cost for health services** and insurers thus **freeing up resources for innovative therapies.**

efcg EUROPEAN FINE CHEMICALS GROUP

https://efcg.cefic.org

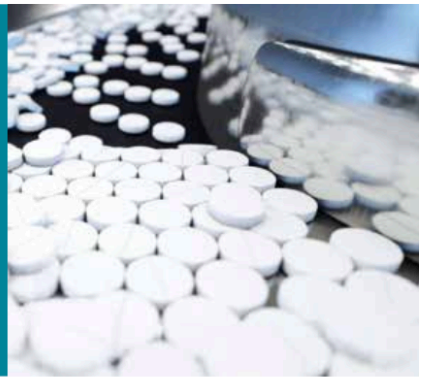
Infographic 2

Delivering treatments to patients: The medicines manufacturing journey

efpia

Manufacturing includes all the operations and the quality controls that are required to produce and distribute an Active Pharmaceutical Ingredient (API) and medicinal product. It is a highly regulated process: at each step, quality assurance confirmation ensures that the product has been manufactured and tested in accordance with marketing authorisation applications, regulations and commitments. Once all requirements are met, a final certification can be given to release the product for wholesale distribution.

Manufacturing facilities must operate to strict standards and are regularly inspected by competent authorities. Besides the unproductive time during cleaning, each facility is often shut down for 2-8 weeks each year to ensure maintenance, equipment qualifications and the implementation of innovations, e.g. for sustainability. Local regulatory requirements are part of the global manufacturing process. This means that the same manufacturing process delivers the same product to patients living in different parts of the World.



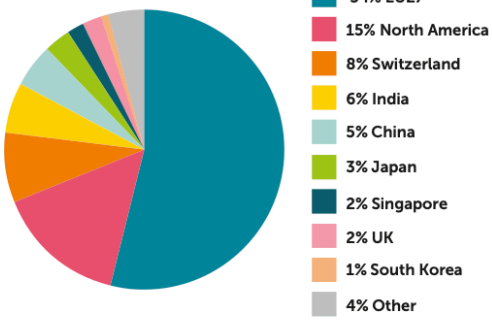
European manufacturing by the research-based pharmaceutical industry in figures

Today, the EU-27 is a leading location for the manufacturing of innovative medicines and related active ingredients, contributing to a trade surplus of 175 million euros in 2022[1] and continued supply to patients. The changing policy environment may put this contribution at risk.

€324 billion (EFPIA total): The value of pharmaceutical production in Europe in 2021[2]

€175 million: Trade surplus of medicinal and pharmaceutical products in 2022[3]

64% of APIs are manufactured in Europe (EU-27, Switzerland, UK)[4]



Innovative manufacturing is key to continue to meet patients' needs

Manufacturing enables access to medicines

The research-based pharmaceutical industry is constantly making investments in innovative manufacturing technologies such as continuous processing, automation, modular/mobile manufacturing for all medicines including vaccines, biologics, and advanced therapy medicines.

These innovations help improve supply reliability, meet regulatory requirements, as well as facilitating the green and digital transitions.

1,2,3 EFPIA, The Pharmaceutical Industry in Figures, 2023, https://www.efpia.eu/media/rm4kzdlx/the-pharmaceutical-industry-in-figures-2023.pdf
4 EFPIA survey conducted in April 2021. Number of APIs (biological and chemical) sourced or manufactured per region of origin (irrespective of value/volume). A total of 16 EFPIA member companies submitted their input to the survey referring to in-patent and off-patent medicines
5 Deoxyribonucleic Acid
6 Physical separation of a chemical substance of interest from foreign or contaminating substances
7 Bulk materials include any materials that are dry, granular, powdery, or lumpy in nature

The Manufacturing process: Continuously optimised by implementing innovations

efpia

Our Commitment

Developing and manufacturing **high quality** and **greener medicines**.

Ensuring a stronger **European voice** while being at the forefront of developing and implementing **innovative products and processes**.

Defining a strategic vision to **proactively prevent medicines shortages** caused by disruptions to global manufacturing and supply chains.

Raw materials:

These are usually commercially available and sourced from plants, organic and inorganic compounds, oil, or DNA[5]. Many are sourced from the bulk chemical industry from suppliers all over the world, with the pharmaceutical industry representing a minor customer.

Starting material:
(12–28 weeks)

Some API starting materials may be commercially available; others may be manufactured/ modified for the specific use and require complex chemical transformations. For biotech products, a working cell bank is created from the master cell bank.

API manufacturing:
(1–10 weeks)

Manufacturing of the Active Pharmaceutical ingredient (API) from API starting materials is conducted in a carefully controlled manner which is critical to the production of high quality, safe, and efficacious medicinal product. API manufacturing may require many chemical and purification[6] steps. Each of these steps may be performed in a dedicated facility, and in a continuous or batch manufacturing mode. For many products, especially biological, manufacture may be in a sterile environment. Cleaning is necessary after each manufacturing cycle and may take additional 1-3 weeks.

Excipients, containers, and packaging materials added:

Usually commercially available from the chemical or food industry. They can also be designed and manufactured specifically for pharmaceuticals. Quality is controlled by adherence to pharmacopoeia or internal standards. Major changes in demand may take between 1–12 months to implement.

Pharmaceutical products:
(1–10 weeks)

These are manufactured from the API with excipients towards 'bulk'[7] material and further processed into containers or devices. Conditions to ensure sterility are applied when required (e.g., for injectable products).

Devices used:
(as applicable)

Devices (e.g., inhalers, pre-filled syringes, on-body injectors) may be used for better patient experience. Where medical devices are required, they are manufactured and controlled to predefined specifications.

Medicinal product:
(1–2 weeks)

The packaging step prepares the final drug product to be delivered to patients. This step is applied to comply to country specific rules, including labels, packaging, and specific content for each country, including leaflets. Repackaging might occur, e.g., if the product is needed in another country or there is a change in the leaflet.

Distribution to patients:
(1–4 weeks)

The finished product gets delivered to different owners (e.g., distributors, wholesalers, pharmacies or directly to local health authorities), ensuring all Good Distribution Practices are respected. The distribution chain of medicinal products needs careful maintenance to ensure their quality, potency, and purity.

Call to action

Promote a **policy environment that fosters R&D in Europe** – the first step to locating advanced manufacturing in the bloc.

Streamline and harmonize **regulatory requirements** to support innovation.

Build a collaborative, best-practice led approach to **sustainable manufacturing** to address environmental challenges.

Engaging Associations

www.aesgp.eu

https://efcg.cefic.org/

www.efpia.eu

www.medicinesforeurope.com

www.vaccineseurope.eu