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SOCIO-ECONOMIC ANALYSIS

Of the potential restriction of the per- and polyfluoroalkyl substances (PFAS) used in the manufacture (including packaging) of veterinary medicines

The viewpoint of animal health companies

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Of the potential restriction of the per- and polyfluoroalkyl substances (PFAS) used in the manufacture (including packaging) of veterinary medicines – *The viewpoint of animal health companies*

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CONTENTS

ABBREVIATIONS

AhE	AnimalhealthEurope
API	Active Pharmaceutical Ingredient
AoA	Analysis of Alternatives
CA	Competent Authority
CAGR	Compound Annual Growth Rate
CAPC	Companion Animal Parasite Council
CEESA	Centre Européen D'études Pour La Santé Animale
C-F	Carbon–Fluorine
CMO	Contract Manufacturing Organization
CRO	Contract Research Organisations
DCM	Dichloromethane
DMF	Drug Master File
EBIT	Earnings Before Interest and Taxes
EC	European Commission
ECHA	European Chemicals Agency
EEA	European Economic Area
EiF	Entry into Force
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ESCCAP	European Scientific Counsel Companion Animal Parasites
ETFE	Ethylene Tetrafluoroethylene
EU	European Union
EUR	Euro (currency)
FP	Fluoropolymers
FTE	Full-time Equivalent
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
HPLC	High-Performance Liquid Chromatography
LRTP	Long-Range Transportation Plan
MRL	Maximum Residue Level
MSCA	Member State Competent Authority
NPV	Net Present Value
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OECD	Organization for Economic Co-operation and Development
OTC	Over the Counter

PBT	Persistent, Bioaccumulative and Toxic
PCTFE	Polychlorotrifluoroethylene
PFAS	Per- and Polyfluoroalkyl Substances
PFBS	Perfluorobutane Sulfonate
PFOA	Perfluorooctanoic Acid
PMT	Persistent, Mobile and Toxic
PoC	Proof of Concept
PPC	Primary Packaging Component
PPORD	Product and Process Orientated Research & Development
PTFE	Polytetrafluoroethylene
PVC	Polyvinyl Chloride
PVDF	Polyvinylidene Fluoride
QC	Quality Control
R&D	Research and Development
RAC	Committee for Risk Assessment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
ROI	Return on Investment
SAGA	Suitable Alternative Generally Available
SEA	Socio-Economic Analysis
SEAC	Committee for Socio-Economic Analysis
SME	Small and Medium Enterprise
SVHC	Substance of Very High Concern
TFA	Trifluoroacetic Acid
TroCAP	Tropical Council for Companion Animal Parasites
VMP	Veterinary Medicinal Product
vP	Very Persistent
vPvM	Very Persistent and Very Mobile
WHO	World Health Organization

1. SUMMARY OF SOCIO-ECONOMIC ANALYSIS

On 13 January 2023, the Competent Authorities (CAs) of Germany, the Netherlands, Sweden, Denmark and Norway submitted a joint REACH restriction proposal for a broad group of fluorinated substances. The proposed restriction aims to limit the risks to the environment and human health from the manufacture and use of a wide range of PFAS in Annex XVII of the REACH.[1]

The submission proposal has been sent to ECHA, and both RAC and SEAC will provide an opinion. Once this phase is finalised, the proposal and the opinions of RAC and SEAC will be forwarded to the European Commission for decision-making with the Member States in the REACH committee. The entry into force of a potential restriction is currently anticipated to take place at the earliest in 2025.

PFAS is a group of more than 10,000 synthetic (i.e., man-made) chemicals that are ingredients in various consumer and industrial products. Many PFAS are efficient surfactants or surface protectors because of the perfluoroalkyl moiety's high chemical and thermal stability as well as its ability to repel water and oil. As a result, they have been produced in large quantities and used in a variety of industrial, commercial, and consumer applications since the late 1940s.[2, 3, 4]

The main concern of lead Member State Competent Authorities (MSCAs) regarding PFAS is their high environment persistence (P), significantly exceeding the very persistent (vP) threshold set out in Annex XIII of the REACH Regulation. Additional concerns emphasised by ECHA are mobility (M) of compounds and long-range transport potential (LRTP), accumulation in plants, and Global Warming Potential.

This socio-economic analysis (SEA) focuses on the value of PFAS used as active pharmaceutical ingredients (APIs)[5] in veterinary medicines as well as in the manufacturing process of virtually all veterinary medicines (pharmaceuticals with or without PFAS APIs, and vaccines) for the European market. It has been performed by EPPA[6] at the request of AnimalhealthEurope (AhE), the association representing companies researching, developing and manufacturing veterinary medicines in the EEA and the UK (hereafter 'animal health companies'). The intention of this SEA is to provide regulators with strong evidence-based findings on social and economic impacts that are expected to occur should veterinary medicines and/or their manufacturing be restricted under REACH.

[1] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

[2] Banks, R.E., Smart, B.E., Tatlow, J.C., 1994. Organofluorine chemistry: Principles and commercial applications. New York (NY): Plenum. ISBN 978-1-4899-1202-2.

[3] Kissa, E., 2001. Fluorinated Surfactants and Repellents, 2nd Edition, CRC Press. ISBN 9780824704728.

[4] Buck, R.C., Franklin, J., Berger, U., Conder, J.M., Cousins, I.T., De Voogt, P., Jensen, A.A., Kannan, K., Mabury, S.A. and van Leeuwen, S.P., 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. *Integrated environmental assessment and management*, *7*(4), pp.513-541.

[5] Active pharmaceutical ingredient (API) is a commonly used term that is synonymous to the term active substance used in the joint REACH restriction proposal.

[6] www.eppa.com

The assessment has been conducted in accordance with the existing official guidance from ECHA under REACH,[7] and it is based on information and data gathered from the animal health companies that use PFAS either as active substances or in their synthesis, and in the manufacture (including packaging) of virtually all veterinary medicines.

Major animal health companies have participated in the survey, covering a market share of approximately 75% of the EEA market. The assessment is, therefore, highly representative and can serve as a basis for defining the anticipated socio-economic impacts resulting from a restriction of PFAS chemicals for veterinary medicines.

This SEA gathers technical and economic information to describe ex-ante in both qualitative and (if feasible) quantitative terms the (orders of magnitude of) socio-economic impacts the animal health industry as well as the relevant EEA supply chain and society are expected to face as a result of a ban on PFAS. This SEA covers the function of PFAS APIs in veterinary medicines as well as the crucial importance of PFAS at the different stages of the manufacturing process of virtually all veterinary medicines (pharmaceuticals with or without PFAS APIs, and vaccines). It describes the (un)availability of technically suitable alternatives, the technical difficulties associated with the substitution of PFAS, the social and economic impacts from their restriction, and the broader impacts on society.

Main findings

This SEA-Analysis of Alternatives report concludes that:

- **A broad restriction of PFAS in the manufacturing of veterinary medicinal products, including, but not limited to, the synthesis of active pharmaceutical ingredients, will have disproportionate negative impacts on the European economy and society.**

- **The animal health sector agrees to phase out the use of PFAS wherever this is possible. This requires however the availability of technically and economically viable alternatives which are to date not readily available. Finding alternatives is not guaranteed, and substitution (if possible) is a time-consuming process due to the legal requirements for quality, safety and efficacy in the sectoral legislation and guidelines. This cannot be achieved in the proposed 18-month transition time.**

- **The analysis reasonably justifies the exclusion of the whole process of veterinary medicines manufacturing, not just APIs, from the scope of the upcoming REACH restriction proposal, to avoid important shortages of veterinary medicines, both pharmaceuticals and vaccines which would lead to a detrimental impact on animal health and welfare, food supply and even human health.**

- **A time-unlimited derogation of PFAS chemicals** as substances required for the manufacture of active pharmaceutical ingredients in veterinary medicinal products is justifiably needed,

[7] The ECHA Guideline for an SEA to be used in REACH Application for Authorisation is available at: https://echa.europa.eu/documents/10162/23036412/sea_authorisation_en.pdf/aadf96ec-fbfa-4bc7-9740-a3f6ceb68e6e

irrespective if the active substance itself is in scope of the PFAS definition or not, on their own, in mixtures or in an article, and **covering the following uses**:

i. **Starting materials**
ii. **Intermediates**
iii. **Process chemicals**
iv. **Solvents, reagents**
v. **Processing aids**
vi. **Single or multiple use materials**

- Equally, a time-unlimited derogation is needed for substances used for the purposes of scientific research and development (SRD) and product- and process-orientated research and development (PPORD).

- **A time-unlimited derogation for fluoropolymer containing packaging (such as e.g., PCTFE, PTFE and ETFE) for veterinary medicinal products, veterinary medical devices, including in-vitro diagnostic devices, and veterinary medical molecular diagnostics should be foreseen.** This would broaden the scope and the nature of the provisional derogation in Art. 6.l and is justified by the findings of this SEA

- Furthermore, **a time-unlimited derogation for fluoropolymers and perfluoropolyethers for the use in industrial (manufacturing) applications should be foreseen, as well as for spare and replacement parts for existing (currently used) machinery during their lifetime**. Two of such derogations are already foreseen in Art. 6.a and 6.f. but should also be granted for veterinary medicines sector and modify the nature of the derogation.

In theory, some of these derogations, e.g., for packaging materials or some elements in industrial equipment, could be time-limited, based on the possibility that these uses of PFAS might be able to be substituted with non-PFAS alternatives within a prolonged derogation period. Although the industry will endeavour to ensure that such substitution does take place, **there are currently no alternatives available** and the requirements from the relevant sectoral legislation (Regulation (EU) 2019/6 and associated acts) may be prohibitive. As downstream users, animal health companies heavily depend on their suppliers to develop alternatives in this particularly specialised sector. Also, the validity of any such alternatives would need to be confirmed, together with guaranteed availability and supply. It should be clear that the negative impacts described in this SEA would still occur if such time-limited derogations were to be allowed to expire before it had been possible to effect substitution. Accordingly, they should expire only after it has been confirmed that substitution has taken place and they are no longer required. It would be important that any time-limited restriction would include a requirement to review the proposed derogations before they expire, to assess their continued need, and to revise and/or extend them as necessary and appropriate.

All above-mentioned statements are reasonably founded on the following evidence-based results:

- **Many decades of scientific research and innovation have focused on finding the optimal safety and efficacy of APIs now suddenly qualifying as PFAS under the new OECD definition in veterinary medicines**. Due to their functional therapeutic benefits, such APIs have been increasingly used in the EEA animal health industry as the most suitable ingredients that provide a large spectrum of health benefits to pets and livestock. Because of their proven efficacy and safety (positive benefit-risk ratio), they have received regulatory approval either centrally at the level of the EU (via the European Medicines Agency and through the European Commission), or in the Member States.

- **The whole process of developing and manufacturing of veterinary medicinal products, independently of whether they contain PFAS APIs or not, heavily depends on a number of PFAS chemicals in a wide variety of applications.** Consequently, it can be expected that all veterinary medicines (including those that are not containing PFAS APIs) produced at manufacturing sites in the EEA are reliant on PFAS materials at a certain stage(s) of their manufacturing process.

- **There is no evidence of currently technically suitable alternatives readily available which can substitute PFAS chemicals across their uses in the manufacturing process and quality control (strict regulatory requirement)**. No single "drop in" replacement for PFAS APIs and their precursors exists, given that veterinary medicines are developed in a targeted manner for different diseases and animal species. Thus, **a one-to-one replacement is impossible.**

- Under normal circumstances, the time requirements for the discovery and development of a new veterinary medicine can typically vary greatly and range between a minimum of 10 to 15 years, followed by a 2-year regulatory authorisation process. **Even in the best-case scenario, substituting PFAS based veterinary medicines by a similar therapeutic alternative can take more than 17 years**, where a successful candidate (alternative) substance already exists, and would have significant associated costs, also including in terms of animal and human health, because of the sudden and important treatment gaps in the meantime coupled with an unknown probability of success.

- In addition, **substitution of chemicals** such as starting materials not incorporated into the API, solvents, reagents, PFAS-containing and -coated parts in auxiliaries and manufacturing equipment, and analytical method reagents and equipment for in-process control, starting material and product release**, also takes several steps and years, provided that alternatives are available. As downstream users, animal health companies will depend heavily on the capabilities of their global suppliers to offer suitable alternatives**.

- In addition, where PFAS are used in **packaging materials**, substitution of those will also easily take **more than a decade, provided that alternatives are available,** because of the sheer number of products involved. Apart from capacity constraints at the industry side, regulatory agencies such as the EMA also will be struggling with the vast number of applications filed to get the changes approved. Changes cannot be implemented without prior regulatory approval.

- **A potential broad restriction would have disproportionate socio-economic implications on the EEA animal health sector:**

- Overall, at the level of the animal health companies, the **total impact of a REACH restriction of PFAS APIs is monetised at over 10 billion EUR** (conservative estimates in net losses), consisting of: social impacts from unemployment in the EEA, substitution costs and economic impacts (EBIT loss) for animal health companies. **The estimates reported in this socio-economic analysis should be considered as a minimum (lower boundary) of the expected impacts.**

- **Even more severe would be the consequences without additional derogations for PFAS materials used in the manufacturing process. As virtually all veterinary medicines manufacturing, both pharmaceuticals and vaccines, within the EEA depends on the use of PFAS in machinery and equipment such as pipes, valves, gaskets, O-rings, the whole animal health industry will no longer be able to manufacture any vaccines, APIs (both, classifying as PFAS or non-PFAS APIs) or associated veterinary medicines in the EEA. The total impact of a REACH restriction of PFAS materials is monetised at over 17 billion EUR.**

- **Collectively, this threatens the survival of the industry as a whole and may put some companies operating predominantly within the EEA basically out of business.**

- From a broader perspective, the PFAS restriction as proposed is expected to have **severe impacts on animal and human health**. A sudden shortage of veterinary medicines in the EEA will reduce the number of available animal health drugs resulting in a higher likelihood and number of **zoonotic diseases, parasite infections, and disease outbreaks.** This risk would be even more serious and concrete in the event of a PFAS restriction for the entire production process of medicines including vaccines as this would affect nearly 100% of products. Consequently, veterinary healthcare would no longer be possible and this will impact the vast majority of veterinarians in the EEA. It would also threaten the food supply as only healthy animals can enter the food chain.

- **Human health is also at stake** because of the intrinsic link between the animal and human health, as widely demonstrated and indicated for a long time by the WHO One Health principle[8] and recognised by the European Commission. **Veterinary medicines can also indirectly protect owners against vector-borne pathogens and zoonotic pathogens**, such as Lyme disease and tick encephalitis. **Vaccines also play an important role**; if, for example, vaccination against rabies were hampered, this could re-introduce the disease which would also constitute a risk to the human population.

- From an EEA macroeconomic standpoint, the PFAS restriction in the EEA will have impacts on the competitiveness of the EEA markets, on the competition in the EEA, on innovation, and on the overall EU trade balance. **Non-EEA manufacturing facilities (e.g., also in the UK) would have a considerable advantage compared to EEA manufacturers both in European and international markets**. Indeed, they would not be subject to a restriction of PFAS used in the different stages of production, thus would be able to supply and place on the market a wider range of products, currently preferred and purchased by consumers without bearing any reformulation costs. As a result, **a loss of competitiveness of European manufacturing sites would be expected in a market that is facing consolidation, while the attractiveness of the EEA for investment in innovation and R&D would be jeopardised**. This would be in vast contradiction with the EU's stated aim of shortening supply chains and bringing production to the EU.

- **In conclusion, a broad restriction as currently proposed would have an extremely disproportionate impact on the animal health sector, veterinary healthcare, animal health and welfare and the food supply.**

[8] World Health Organization. (n.d.). *One Health*. World Health Organization. Retrieved March 28, 2023, from https://www.who.int/europe/initiatives/one-health#:~:text='One%20Health'%20is%20an%20approach,achieve%20better%20public%20health%20outcomes

2. AIMS AND SCOPE OF THE SEA

2.1 Purpose, scope and methodology of SEA under REACH

On 13 January 2023, the Competent Authorities (CAs) of Germany, the Netherlands, Sweden, Denmark, and Norway submitted a joint REACH restriction proposal to limit the risks to the environment and human health from the manufacture and use of a wide range of PFAS in Annex XVII of the REACH Regulation.[9] Given that medicinal products are not generally exempt from the restrictions under Title VIII of REACH, Active Pharmaceutical Ingredients (APIs) classified as PFAS, as well as the placing on the market of these APIs and medicines containing them, are potentially in the scope of the PFAS restriction. In fact, although in the current proposal active pharmaceutical ingredients are derogated indefinitely (time unlimited derogation), the proposed scope may change during the restriction process. Additionally, at present, no derogation is envisaged for other PFAS-containing materials used in the manufacturing of veterinary medicines, such as starting materials and chemical intermediates, solvents and processing aids, auxiliaries and production materials used for respective production equipment, synthetic and analytical reagents and fluoropolymer-containing primary packaging materials, which would then be effectively banned.

In the proposed restriction, PFAS (Per- and Polyfluoroalkyl Substances) are defined as any substance containing at least one fully fluorinated methyl (CF_3-) or methylene (-CF_2-) carbon atom (without any hydrogen, chlorine, bromine, or iodine attached to it). The definition is based on the OECD definition of PFAS published in 2021 and covers over 10,000 substances, including some fully degradable subgroups. However, these fully degradable subgroups, which are defined by their key structural elements and do not display the high persistence that is the main concern with PFAS, are excluded from the scope of the restriction proposal.

In the field of veterinary medicine, there are several fluorinated compounds that have been identified for treating inflammation, serious infections and parasite infestations that can cause zoonotic diseases in humans, and for providing general anaesthesia for surgical procedures. These compounds match the criteria set by the OECD for PFAS. However, these molecules are not technically considered polyfluorinated or perfluorinated (they mostly have only one or a few terminal fluorinated methyl groups added to a much larger molecule) and do not fall under the criteria of concern in a technical sense as outlined by the competent authorities proposing to regulate PFAS. [10, 11]

9 OJ L 396, 30.12.2006, p.1.

10 OECD, 2018. Toward a New Comprehensive Global Database of Per and Polyfluoroalkyl Substances (PFASs): Summary Report on Updating the OECD 2007 List of Per and Polyfluoralkyl Substances (PFASs). Environment Directorate, Series on Risk Management No.39.

11 EFPIA and AnimalhealthEurope, 2022. EFPIA (Representing European Pharmaceutical industry) and AnimalhealthEurope (representing Animal Health Industry) position on use and risk of "per- and Polyfluorinated alkyl substances", p. 3. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjNpemFsML6AhVZPuwKHa8GC1EQFnoECAsQAQ&url=https%3A%2F%2Fwww.efpia.eu%2Fmedia%2F636866%2Fpfas-position-_-efpia-and-animalhealtheurope-january-2022.pdf&usg=AOvVaw1dfpT_NrD7qlUK5eogvxTz (accessed in September 2022).

This *ex-ante* Socio-Economic Analysis (SEA) aims to identify and to assess in both qualitative and quantitative (when feasible) terms the socio-economic impacts that are expected to occur in case of a REACH restriction to this group of substances, covering the generalised use and importance of PFAS used at different stages of the manufacturing process and for packaging of veterinary medicines.

A survey has been conducted by providing a detailed questionnaire to gather information and data from animal health companies likely to be affected by a PFAS restriction in the EEA. The participating companies have provided socio-economic data in view of extrapolating (based on a large total market share) the impacts for the whole market in a conservative approach, as further detailed below. Based on the estimated total EEA market for VMPs, the market share covered by this survey represents approximately 75% of the EEA market and is thus highly representative. **The estimates reported in this socio-economic analysis should be considered as a minimum of the expected impacts (lower boundary).**

The assessment has been conducted in accordance with the existing official guidance on SEA from ECHA under REACH Restrictions.[12] ECHA has developed a solid methodology for conducting socioeconomic assessments in the context of the REACH Regulation, with the support of a dedicated committee (Socio-Economic Assessment Committee – SEAC). More specifically, this methodology is consistently applied for REACH applications for authorisation of substances of very high concern (SVHC), and REACH restrictions for certain hazardous substances with a view of forecasting through the SEA the impacts of the different regulatory options.

From a geographical perspective, this analysis focuses on the European Economic Area (EEA) territory, comprising the European Union (EU-27), Iceland, Liechtenstein, and Norway. For this study, it has been decided to use a 4-year time horizon to estimate the socio-economic impacts, which is the time period suggested by SEAC when there is no suitable alternative available in general (SAGA)[13, 14].

In other terms, the SEA accounts for the socio-economic costs of a complete ban (REACH restriction) starting from the year 2027 (proposed year of the entry into force of the proposed restriction plus 18 months of transition period).

Future monetary values have been estimated by using the concept of net present value (NPV), adopting a 3% annual discount rate, which is the standard discount rate, adopted by the European Commission and European agencies (e.g., ECHA) in impacts assessments.[15] All monetised values have been adjusted to a base year, assumed to be 2027. Information and data have been aggregated and anonymised. Statements and estimations from the participating companies are as close to real data or perception of future changes as possible.

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12 The ECHA Guideline for an SEA to be used in REACH Restrictions is available at: https://echa.europa.eu/documents/10162/2324906/sea_restrictions_en.pdf/2d7c8e06-b5dd-40fc-b646-3467b5082a9

13 https://echa.europa.eu/documents/10162/13637/ec_note_suitable_alternative_in_general.pdf/5d0f551b-92b5-3157-8fdf-f2507cf071c1

14 https://echa.europa.eu/documents/10162/0/afa_seac_surplus-loss_seac-52_en.pdf/5e24c796-d6fa-d8cc-882c-df887c6cf6be?t=1633422139138

15 European Commission, 2021. Better Regulation Guidelines and Toolbox. https://commission.europa.eu/document/download/9c8d2189-8abd-4f29-84e9-abc843cc68e0_en?filename=br_toolbox-nov_2021_en.pdf

2.2 Overview of veterinary medicinal products and their value chain

2.2.1 Value chain overview

AnimalhealthEurope member companies are marketing authorisation holders and manufacturers of veterinary medicinal products. Following regulatory approval, these products are distributed through a network of subsidiaries and distributors, to finally reach animal owners through veterinarians and pharmacies. The member companies perform research and development activities, manufacture, prepare and submit regulatory dossiers to receive marketing authorisation and then supply and sell VMPs in the EEA and non-EEA markets.

The animal health companies either directly produce the APIs and VMPs themselves in their own manufacturing sites, or these are produced and supplied by external contract manufacturers in the context of a global supply chain. Contract manufacturers are based inside and outside the EEA and work under long-term manufacturing and supply agreements. All manufacturing sites both within and outside of the EEA need to comply with EU Good Manufacturing Practices (GMP) requirements[16] and are subjected to regulatory inspection by European Member State Authorities.

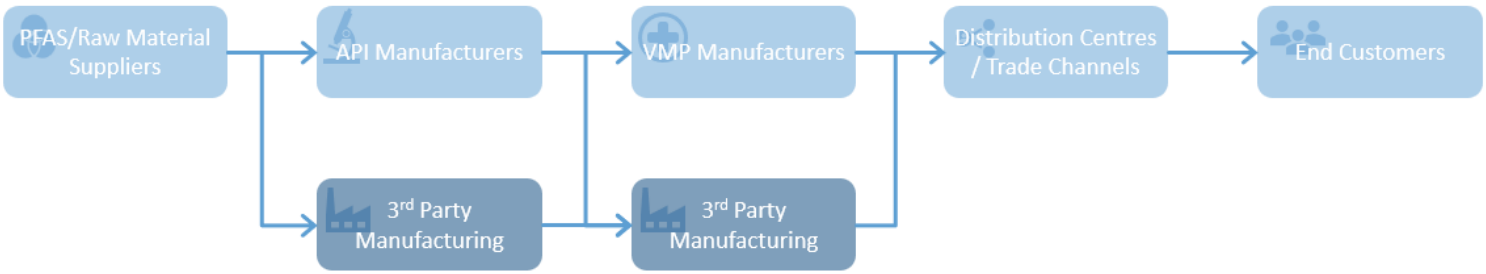
In practice, the VMP manufacturing sites are mainly located in the EEA, where they usually source the ingredients for the final VMPs such as the APIs, excipients, and packaging materials from third-party suppliers and/or contract manufacturers. Furthermore, all the equipment required to manufacture the final veterinary products such as production line machineries, solvents, reagents and laboratory equipment for quality control are commonly sourced from outside the VMP manufacturing site. The manufacturing sites ensure the legally required quality controls according to Quality Agreements between the entities, GMP and other regulations. The sites then manufacture the VMPs, including the packaging and labelling, ready for final use (finished products). This entire process must comply with the marketing authorisation granted for the product by the European Regulatory Authorities in accordance with Regulation (EU) 2019/6 (previously Directive 2001/82). If a VMP is imported from outside the EEA for use in the EEA, quality control of batches release by a Marketing Authorisation Holder located on EU soil is a legal requirement.

Veterinary medicinal products are sold to registered wholesale distributors and from there to pharmacies, veterinarians, or other retailers licenced according to national regulations of the MS where corresponding products are authorised. An important part of the products produced in EEA VMP manufacturing sites are for export outside the EU according to the product specification of the destination country.

The APIs used for the formulation of veterinary medicines may fall under the PFAS definition as may the starting materials, intermediates and process chemicals used for the actual synthesis of the API and manufacturing of veterinary medicines. This distinction and the relevance for the product portfolio of these companies is investigated in the subsequent chapters of this report.

16 https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

Accordingly, the typical supply chain for veterinary medicinal products is as follows:[17]



2.2.2 Market trends and developments

The global market for animal health was valued at 27 billion EUR in 2021. With an estimated share of 29%, Europe is the second largest veterinary medicines market worldwide. In 2022, the size of the EU animal health market was estimated at ~10 billion EUR.[18] The market is projected to grow at a CAGR of 6% between 2022 and 2027, reaching a value of 14 billion EUR by 2027.

European veterinary medicine market consists of two main categories: vaccines and (bio)pharmaceuticals. Important categories within the pharmaceuticals include parasiticides and antimicrobials. Vaccines and parasiticides each represent approximately one third of the European market, 32.9% and 28.3% respectively. They are followed by antimicrobials which represent approximately 12% of the market[19]

Broadly speaking, the European animal health market is expected to continue to grow steadily, in line with the market trends over the past ten years. The only exception is antimicrobials. This market segment has witnessed a decline in demand, as shown visually in Figure 1, and this is consistent with the responsible use efforts of the farming and animal health industry.

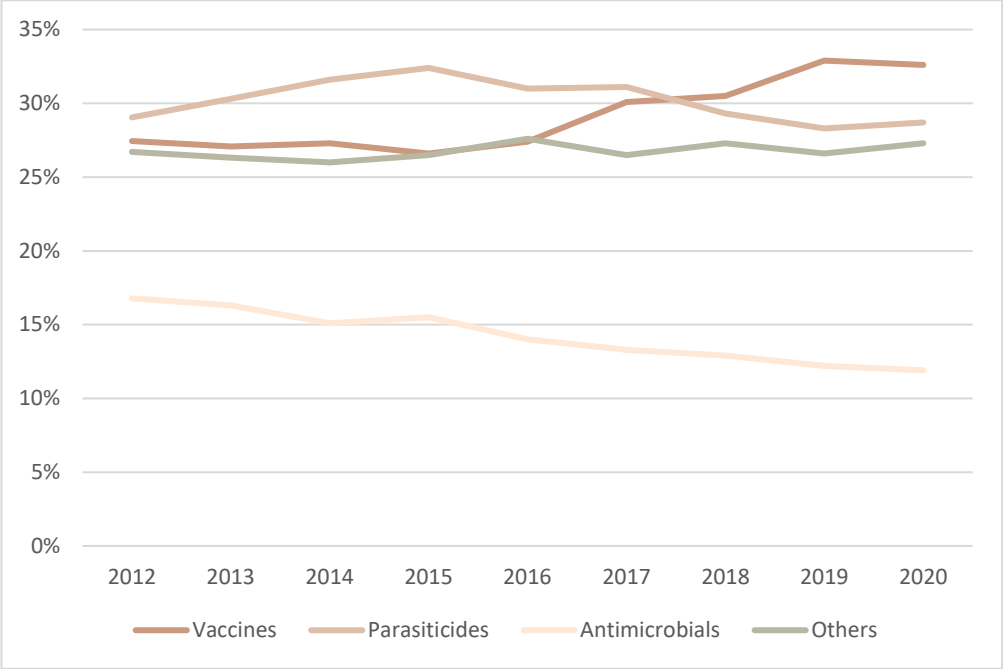
Figure 1. Evolution of the market proportion in percentage (%) [20]

[17] The graph serves only as an illustrative example. As such, it is a simplified illustration of the supply chain for the manufacture of veterinary products. It ought to be highlighted that the VMP manufacturing site is the bottleneck for many different materials needed for the VMP (e.g., ingredients for the VMP, including APIs), machines, equipment and reagents for quality control. These items may come from EU or from outside the EU.

[18] https://www.marketdataforecast.com/market-reports/eu-veterinary-healthcare-market

[19] Ibid.

[20] AnimalhealthEurope, 2021. https://figures.animalhealtheurope.eu/



Whether for livestock (raised to supply milk, eggs, fish and meat for consumers) or for companion animals (cats, dogs and horses), veterinary medicines are used to maintain or improve animal health and animal welfare. Veterinary medicinal products are supplied to a range of species (including exotic species and wild animals), and they cover a wide range of prophylactic and therapeutic purposes. According to the data gathered by AnimalhealthEurope and European Animal Health Study Centre (*Centre européen d'études pour la santé animale*, CEESA), pets account for over 41% of the demand for veterinary medicinal products in Europe, while medicines for livestock including poultry, aquaculture and horses are still covering the larger share of the EEA European market.[21]

Like human medicines, veterinary medicines are evaluated for efficacy, quality, and safety by the regulatory authorities prior to being granted marketing authorisation for placing them on the market.[22] Whilst veterinary medicines have existed for over 70 years, there has never been a more compelling need for such essential tools to manage and prevent disease in animals and safeguard animal welfare. The emergence of new diseases, climate change, the spread of existing diseases to new geographic areas, and other challenges call for greater availability of safe, efficient, high-quality veterinary medicines worldwide. These trends require ever-more-effective control of animal diseases. In addition, there are still therapeutic gaps and some diseases can still not be adequately treated, especially in so-called “minor species” such as sheep and goats, and in aquaculture (e.g., salmon).

Therefore, continued support is needed to create an environment that encourages investment and innovation in the creation of new medicines as well as support for those that have already been authorised.[23]

21 https://figures.animalhealtheurope.eu/

22 Regulation 2019/6 (previously Directive 2001/82/EC).

23 Vallat, B., 2010. Veterinary medicinal products. World Organization for Animal Health, Bulletin Editorial Committee. ISSN 1684-3770.

3. ANALYSIS OF ALTERNATIVES

This section provides a closer look at the **use, function, and requirements of PFAS for veterinary medicines in the manufacturing of VMPs, such as PFAS APIs, API starting materials and chemical intermediates, auxiliaries and production (e.g., process solvents) materials, synthetic and analytical reagents and fluoropolymer-containing primary packaging materials**. It covers the technical obstacles that prevent substitution via potential alternatives to PFAS, the challenges related to the development and launch of new APIs/VMPs, as well as the long timelines of a transition towards PFAS-free veterinary medicines. The analysis of alternatives concludes that **there are currently no available chemical alternatives** that could substitute PFAS-based veterinary medicines, neither as the API nor in the manufacturing process. **In the best-case scenario, substituting PFAS based veterinary medicines can take more than 17 years**, **provided successful candidate (alternative) substances are available.**

Unless clearly specified, all below information are sourced from participating companies' replies to the survey conducted in the context of this Socio-Economic Analysis.

3.1. Function and technical performance of PFAS in veterinary medicines

At present, active substances in veterinary medicinal products are out of the scope of the REACH restriction proposal, as currently worded. The derogation for veterinary active substances is justified in the restriction dossier because (i) the use of these substances is specifically regulated in the EU with extensive evaluations and approval processes by designated bodies; (ii) because of the importance for the protection of animals and humans from diseases and the welfare of animals; and (iii) to ensure the security of supply of veterinary medicines.

Nonetheless, as worded, this derogation does not achieve its very aim of allowing manufacturing of neither these active substances, which are considered PFAS, nor even of non-PFAS active substances and associated veterinary medicines in general in the EEA. None of the uses of PFAS chemicals shown below are currently listed as specific uses in the restriction dossier nor derogated under the current wording.

- To introduce fluorine into the API molecules, starting materials and chemical intermediates that qualify as PFAS are used, which are imported and/or manufactured, and these are not derogated.
- The same is true for processing aids and process chemicals, including solvents and reagents, which are used in the manufacturing and quality control of both PFAS APIs and non-PFAS APIs.
- In production of any veterinary medicines including vaccines, polyfluorinated polymers such as (e.g.,) polytetrafluoroethylene (PTFE) are often used as seals for chemical reactors, vials and in equipment such as membrane filters, gaskets, liners, O-rings, piping. Electronics are embedded in production equipment and are indispensable to correct functioning of any given production line.

- Likewise, polyfluorinated polymers are widely used in packaging materials (blisters, vial stoppers etc.) as they are extremely efficient in preventing interaction between product and packaging materials, which is a regulatory requirement.

The following paragraphs describe the function and technological advantages of PFAS for all these uses.

3.1.1 PFAS as an active pharmaceutical ingredient

In veterinary medicines, molecules that contain perfluoroalkyl substituents are used as active pharmaceutical ingredients (APIs).

Many decades of scientific research and innovation have focused on finding the optimal compatibility of all ingredients in a veterinary medicinal product. The benefits provided by the use of PFAS include (i) an extended biological half-life resulting in a significant reduction of the dosing frequency of VMPs; (ii) increasing permeability, binding affinity to the target and drug efflux; (iii) reducing undesired side effects.

Per- and polyfluoroalkyl substituents serve multiple purposes concerning molecular properties. A total of 16 different APIs have been identified as falling under the PFAS definition in the companies' VMPs portfolios.

One API can result in different products, either alone or in combination. As finished products can contain several combinations of different APIs, some of the veterinary medicines end up containing multiple APIs, both corresponding or not to the PFAS definition. Thus, the number of veterinary medicines impacted is much higher than the number of PFAS APIs.

PFAS continue to be a critical component in new drug developments for humans and animals. The extensive application of fluorine in drug research is related to the unique properties of this element. Many APIs used in human and veterinary medicine contain fluorine, an element of small size and strong electron withdrawing properties. It is widely used by medicinal chemists in the pharmaceutical and animal health industries to improve a molecule's potency and permeability, modulate its dissociation constant (pKa) and lipophilicity, reduce its rate of metabolism and clearance in the human or animal body, and control its structural conformation. Indeed, efficacy and safety of active ingredients depend on several key parameters, such as their physicochemical properties (e.g., solubility, lipophilicity, acidity/basicity). This is important for the compound to be optimally absorbed and distributed in the organism after administration, for their molecular geometry and ability to engage in effective interactions with their target receptors, and for their metabolic stability to ensure sufficient duration of efficacy.

To evolve a molecule into a potent and safe drug, all such parameters must be optimised simultaneously during the drug discovery process. In this context, fluoroalkylation of drug candidates is commonly used to exploit the unique properties of fluorine and to specifically alter key properties of the active ingredients. **The introduction of fluorine is often an essential part of achieving an optimally balanced profile.** Fluorine is comparably small in size. The size of a fluorine atom is

comparable to a hydrogen atom, but the stability of a C-F bond is greater than that a C-H bond. Moreover, fluorine has the highest electronegativity of all elements. The introduction of fluorine will change the lipophilicity and electron density distribution of the molecule.

The bioavailability and efficacy of APIs is often hampered by their rapid metabolism through liver or kidney enzymes. Alkyl groups in the molecules are preferred locations for such oxidative processes. Exploiting the unparalleled stability of C-F bonds, poly- or perfluorination of the alkyl groups has proven to be a very successful strategy to circumvent this issue and protect the reactive sites from metabolism.

In addition, fluorination is employed to modulate important physicochemical properties. Finetuning acidity and basicity of drug candidates may be crucial in the discovery process of novel APIs. The optimization of both its pharmacokinetic properties (i.e., the distribution of the molecule in the organism) and its binding efficiency to the molecular target depend on these properties. Since fluorine is the most electronegative atom, its ability to withdraw electron density from neighbouring functional groups and effect their physicochemical behaviour is unique. Thus, fluorination allows for targeted adjustment of their properties.

Another molecular parameter to be considered during the drug discovery process is the molecule's lipophilicity – its ability to be dissolved in fats, lipids, oils, and non-polar solvents. To improve the efficacy of an active ingredient the molecular structure often needs to exhibit areas of high lipophilicity that increase the binding affinity of the active ingredient to the target. However, increased lipophilicity may also result in low water solubility which might be associated with adverse properties. Replacing hydrogen by fluorine – on e.g., alkyl substituents – leads to a gradual increase in lipophilicity and offers a unique tool to balance this molecular property.

Fluoroalkyl substituents also influence the molecular geometry of bioactive molecules. Both size and electronegativity of fluorine can cause changes in the spatial orientation of substituents upon H/F replacement, that may result in improved interactions with the target receptor.

As mentioned before, fluoroalkyl substituents are uniquely equipped to improve the API´s affinity to its target receptor by modulation of physicochemical properties or an increase of lipophilic interactions. This regularly leads to an **increase of the drug's efficacy**. However, fluorine may also be involved in very specific polar interactions that cause an efficacy gain of the fluorinated drug compared to its non-fluorinated counterpart.

In conclusion, **the unique properties of the fluorine atom offer the possibility to influence and optimize key properties of APIs such as spatial conformation, physicochemical properties, intrinsic potency, membrane permeability, metabolic pathways, and pharmacokinetic properties**. This renders targeted introduction of (per- and poly) fluorinated substituents into drug candidates an unparalleled tool for drug design.

While replacement of a hydrogen by fluorine may not significantly change the size of a drug molecule, it will impact key properties required to make a drug efficacious and safe. The therapeutic effect, safety, application and toxicokinetic properties of any API are determined by the complete molecular

structure, i.e., any chemical modification changes essential properties. As mentioned before, a replacement will not only affect potency but can also lead to reduced clearance in the human or animal body, and enhanced permeability. Due to fluorine's electronegativity, introduction of fluorine will attract electrons, making a molecule more acidic or less basic (decreasing its pKa). This will subsequently impact key parameters required for a successful drug such as permeability, binding affinity to the target and drug efflux, and can reduce undesired side effects, thereby increasing the therapeutic index. Therefore, **chemical alternatives or technical replacements, such as substitution of per- and polyfluoroalkyl groups, are virtually impossible**.

Legally, substitution of an API in a veterinary medicine is not possible under Regulation 2019/6. The existing product will cease to exist and any new product with an altered API would be seen as a new product and would need to go through an entirely new product development cycle.

3.1.2 PFAS used in the manufacturing process

A PFAS restriction in the EEA would have also a severe impact on the industry manufacturing veterinary medicines since chemicals falling under the current definition of PFAS are used in the manufacturing process, in the packaging of veterinary medicines, and in the manufacturing equipment. The manufacture of APIs containing per- and polyfluorinated alkyl substituents requires starting materials and intermediates (the building blocks of the API molecules) that are now considered PFAS. However, independent of whether PFAS or non-PFAS APIs are produced, the manufacturing process will require PFAS chemicals as auxiliaries, solvents or reagents (e.g., trifluoroacetic acid, trifluoromethanesulfonic acid) to trigger specific chemical reactions during the synthesis of the APIs. In addition, PFAS polymers are equally essential for the manufacturing process as well as primary packaging of the finished VMP, independent from the nature of the API.

Simultaneously, there is also an impact on the development of (both PFAS and non-PFAS) APIs related to the use of PFAS materials at different stages of the manufacturing process of VMPs. From the early research phase to the later upscaling processes or during commercial production processes, a wide range of PFAS chemicals are utilised. Besides the direct materials for manufacturing (PFAS) APIs, **PFAS-containing materials are used as/in gaskets, tubes, inner layers of chemical reactors, tubes in analytical equipment, or tape used to build inert laboratory scale equipment**. More importantly for VMPs using APIs that do not contain PFAS (hereafter non-PFAS APIs), PFAS materials are widely used in the manufacturing environment for their specific properties as this group of substance exhibits an outstanding resistance and inertness against aggressive chemicals and mechanical impact and maintain these favourable material properties over a wide temperature range (e.g., from -30 °C up to +200 °C). In addition, they prevent interactions between the medicinal product and manufacturing equipment during formulation and production.

The whole process of developing and manufacturing veterinary medicinal products, independently if containing PFAS APIs or not, heavily depends on a number of PFAS chemicals in a wide variety of applications.

PFAS chemicals are also used to execute routine quality control testing activities and in packaging. The four main application scenarios identified by animal health companies are discussed below:

Starting material and chemical intermediates

Some PFAS starting materials and intermediates have been identified in the synthesis and production of APIs for veterinary medicines. The restriction proposal would no longer allow European pharmaceutical industry to use starting materials and intermediates now qualifying as PFAS under the new OECD definition and thus stop production of many APIs in Europe; while their import from areas outside of the EEA would not be guaranteed as some are not produced elsewhere. In order to keep the pharmaceutical industry in Europe, the use of PFAS chemicals for the production of APIs should not be restricted. The same applies to supplies of other materials and chemicals on which API manufacturers depend. Thus, the impacts could be substantial at the level of production capability but also on the availability and supply of veterinary medicines using these APIs.

Auxiliaries and production material, including solvents and processing aids

Examples of the unique properties of PFAS include chemical and physical inertness, chemical and physical stability, low permeability to gasses, heat-resistance, and low friction. These unique properties make PFAS excellent for use in production materials, where functions are required such as non-sticking of product to equipment, no reaction with the product, no leaching of substances to the product, no yield loss or clogging of membrane filters, maintaining form and function under stress (heat/pressure) to avoid leakages, and avoiding friction between product and equipment. PFAS used in the manufacturing sites as auxiliaries and production materials are a broad range of products required to achieve the desired quality during manufacture of both devices and chemicals, and which are not part of the final product.

In production lines, polyfluorinated polymers, such as polytetrafluoroethylene (PTFE), are often used as seals for chemical reactors, valves in production lines, vials and in devices (e.g., membrane filters, filters used in the transfer lines). Some examples have already been presented above and further include lubricants (containing PTFE and similar PFAS), replacements parts like gaskets (PTFE), single use disposables such as filters (PVDF), as well as PVDF membrane filters used for sterilising filtration of injectable drug products, PTFE coated stoppers used as primary contact material in injectable drug products, PTFE sprays, and PTFE seals used in valves and pipes. O-rings, fittings, pumps, lubricants, diaphragms, electronics, and other instrumentation used for pharmaceutical manufacturing also contain PFAS. In comparison to chemicals “consumed” in the manufacturing process, these production materials often have long lifetimes within machines or are replaced only with long maintenance intervals. Moreover, it ought to be noted that, even though the volume of PFAS used in these applications may be overall low, these are essential for the production of veterinary medicines.

A ban of using such equipment would mean that these materials could not be replaced at the end of their life span. **The usage of PFAS as auxiliaries and production materials is expected to occur along the whole manufacturing process of medicines in general, be it pharmaceuticals, biopharmaceuticals or vaccines.**

Synthetic and analytical reagents

Reagents are required in manufacturing, R&D and for analytical purposes in Quality Control (QC) laboratories. Per- and polyfluorinated reagents are effective in the manufacturing processes as both activating reagents and catalysts (e.g., Trifluoromethanesulfonic anhydride, and nonaflate). The R&D pipeline of the participating companies contain multiple non-PFAS APIs that utilise PFAS reagents in their synthesis. Examples of uses in laboratory and analytical equipment for executing quality control testing activities are trifluoroacetic acid (TFA) in analytical testing, gaskets in High Performance Liquid Chromatography (HPLC) equipment (due to the very good multi-resistance against chemicals, high temperatures, and high pressures), pipes and surfaces made with PFAS, valve blocks in analytical equipment, and the insulation of pipes, cables, and tubes (due to the high resistance against chemicals and extreme high or low temperatures).

During the R&D and production phase, the analysis of the produced APIs and finished veterinary medicinal product is a mandatory step. This can be done with different analytical methods, such as High Performance Liquid Chromatography, gas chromatography, nuclear magnetic resonance analysis to name but a few. The analytical detectors employed are extremely sensitive to impurities. Therefore, only PFAS materials are used to (e.g.,) seal samples, protect tubes, as these materials are very inert against other chemicals. Moreover, they do not wash-out during their lifetime. This bleeding process known from other materials would cause difficult interpretation of analytical results due to "background noise" coming from this wash-out effect.

Furthermore, PFAS materials such as TFA, hexafluoroisopropanol and trifluoro ethanol are indispensable in peptide synthesis. Additionally, the use of TFA is key in **vaccine production** as well as an essential reagent in numerous QC analytical procedures, such as high-performance liquid chromatography.

As a strictly regulated industry, companies have waste treatment procedures in place, often in form of incineration, to prevent emissions of substances that are not fully consumed in the production process. Specific examples are given in separate, confidential submissions as an addendum to the present SEA.

Fixed and consumable equipment made using PFAS chemicals

Equipment and consumables containing PFAS are a vital part of the production environment. This is particularly true for veterinary medicines manufacturing.

Manufacturers mostly rely on Teflon-coated equipment (e.g., in seals of reactors, valves, piping, just a few examples) to ensure integrity and purity of the veterinary medicines. Teflon used as described ensures coating on equipment preventing tablets from becoming compromised/dented/scratched and ensures water for injection systems remain at the highest purity required for pharmaceuticals. PFAS materials used for analytical or production equipment are extremely robust against temperature, with a much wider usable temperature range compared to other polymers. The same applies for mechanical or chemical robustness: this group of substances present a higher level of robustness than any metal against corrosion or other chemical degradation. Moreover, they are inert and do not react with the medicinal product – such interactions are not allowed as they would negatively affect the quality and safety of the medicine.

PFAS material can be used as thin coatings in equipment. For example, polypropylene ensures higher mechanical robustness over a wide temperature range. Accordingly, the lifetime of PFAS-covered equipment is much higher when using PFAS as it protects the underlying material much better than the alternatives. There is no need to adapt equipment to the next needed temperature range as PFAS is covering it already. Using non-PFAS materials would mean to replace, for example, seals or gaskets every time changes of production parameters or analytical parameters are done. This would result in high downtime losses and low efficiency of the equipment.

3.1.3 Packaging materials

For a number of injectable veterinary medicines, where products are particularly vulnerable to influences from chemicals in packaging materials, i.e., packaging in direct contact with the veterinary medicine, fluoro-coated stoppers are currently widely used across the animal health industry. The coated stoppers have been shown to be essential for the stability of the product. In addition, tablets use PFAS based 'blister' packaging to preserve and protect them from external factors and facilitate use.[24] Both stoppers and blister packaging using PFAS components have been assessed at length during the development of VMPs as they conferred the necessary stability to the product. The choice of packaging materials is directly linked to the properties of the medicine; some are extremely sensitive to external influences and for those, materials containing PFAS are currently the only option.

The benefits provided by the use of PFAS include: (i) moisture barrier film aiming to reduce or prevent water-based degradation processes and to meet the expected performance of the veterinary product in terms of stability; and (ii) prevent the risks of chemical or biological molecule absorption with the filter media or reduce the risk of extractables when the compositions require the use of non-aqueous solvents.

PFAS used during the manufacturing process and for packaging operations are fluoropolymers (FPs), especially PCTFE (polychlorotrifluoroethylene) and ethylene tetrafluoroethylene (ETFE) are among the materials used for 'thermoform' types of blisters. High density polyethylene (HDPE) containers used for storage of liquid materials may also have fluorinated compounds linings that are PFAS. In addition, stoppers for injectables, bottles, and syringe barrels and caps may contain PTFE as a coating material. A PTFE coating provides an effective barrier against organic and inorganic extractables and minimises interaction between the medicine and the primary packaging component.

Notably, PCTFE exhibits a combination of unique properties, such as zero moisture absorption and non-wetting, transparent, thermoformable, chemically very stable and inert, non-sticking, non-aging and sterilizable, which make it the **ideal solution for products that require a high level of protection, especially when used in stoppers or blisters**.[25]

Adding a layer of PCTFE gives technical advantages by increasing the stability of the medicine for a longer time period and thereby extending its shelf-life. ETFE or PTFE film coated elastomeric

[24] Pilchik, R., 2000. Pharmaceutical blister packaging, Part I. *Pharmaceutical technology, 24*(11), pp.68-68.

[25] An example is the PVC/Aclar films, made of a combination of PVC and PCTFE which are widely used.

components provide an effective barrier against organic and inorganic extractables that can leach into the drug product thus potentially affecting the drug product quality and efficacy and patient safety (toxicity), by minimising the interaction between the drug and the primary packaging components. Furthermore, ETFE or PTFE film reduces absorption and adsorption of the drug product. Elastomeric primary packaging components (PPC)'s also require a lubrication to prevent stickiness during storage and processing. A typical silicone lubricant could be used, but the silicone can be a source of particles in the drug product. The ETFE or PTFE film provides a particle free lubrication and prevents or reduces the use of silicone. All these PFAS materials are in direct contact with the drug product. As such, they are part of the drug product specifications (which must be met) and authorisation.

3.1.4 Conclusive remarks

Overall, the use of PFAS materials as preferred material in production is based on learnings from improvement processes in production and on regulatory requirements. PFAS materials are typically more expensive than other materials that could be used for the same purpose (e.g., in gaskets). Nonetheless, due to the specific material properties specified above, PFAS is commonly used as material of choice in production as much less maintenance is needed, thus resulting in higher performance in terms of reliability.

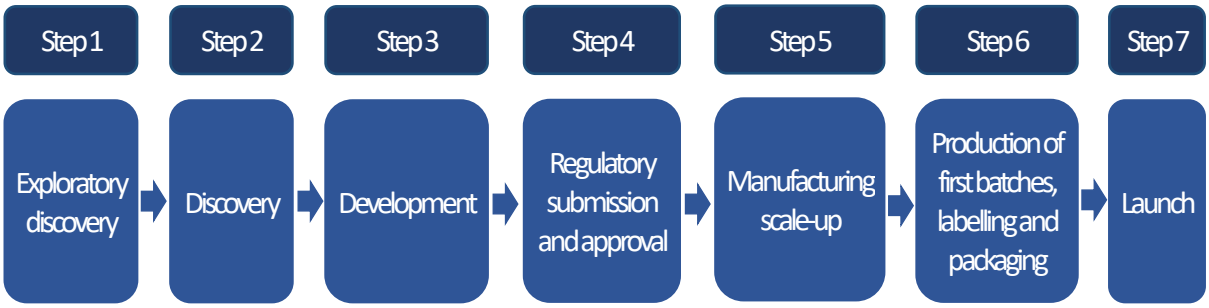
3.2. Challenges of substituting with alternatives

3.2.1 Typical innovation process and timing

New active substance and associated product(s)

To re-develop a new medicinal product, all the development steps for veterinary pharmaceutical development would need to be carried out. The rate of new substance/product introduction is rather low in the industry. This is due to the many obstacles and challenges faced by companies when trying to bring new products to market including very extensive and burdensome regulatory requirements. As a consequence, in general only one transformational innovation in a particular segment occurs approximately every 20 years in the veterinary sector.

The typical innovation cycle in the veterinary medicine sector consists of the main following steps:



The few products that pass the first four stages then have to be manufactured on an industrial scale and launched on the market.

Step 1. Exploratory discovery phase

The exploratory discovery phase is like that of human medicine and typically lasts between two to four years. The initial phase of drug discovery generally starts with the screening of potentially bioactive compounds against drug targets of interest.

Over decades, animal health companies have developed screening cascades that combine both target-based assays (i.e., testing of compounds for their efficacy on the target protein itself) and whole organism phenotypic screenings. While phenotypic testing takes place continuously, target-based approaches are typically run in campaigns. To increase the probability to find suitable starting points for drug development, the screening routinely starts with tens to hundreds of thousands of compounds, only few of which may initially pass. Both approaches are designed to identify individual molecules or larger sets of compounds showing initial potential that after optimization could result in the desired therapeutic effect, commonly known as '*hits*'. Subsequently, hit exploration and optimization is initiated to (i) validate and increase the often-weak effects; (ii) select the most promising compound classes (hit classes) for further optimization in the next research phase.

Step 2. Discovery phase

The second step is the discovery phase, where further chemical optimization within the selected classes will take place. Various laboratory trials (rarely on the field at this stage) are conducted during the discovery phase.

The iterative process of design, synthesis, and testing of new derivatives of the initial hits aims at identifying active molecule(s) with pharmaceutical-like properties (leads). Detailed lead profiling is performed to find the optimal combination of biological efficacy as well as human, target animal, and environmental safety. This evaluation is centred around determining if a viable strategy leading to an API usable in practice can be found, through proof of principle and proof of concept testing. Rigorous candidate selection during the lengthy process results in high attrition rates, as most lead compounds do not meet the required characteristics. Thus, pre-development work is only initiated on very few/single compounds: Preliminary formulation work is started to enable pilot experiments in animals, explore API stability and behaviour in various formulations, determine preferable route of administration, potential effective dose, and begin to characterize the API hazard profile. Further work includes initial chemical process development and pilot manufacturing set up. Ultimately, only one API is subsequently progressed through the development stage.

Generally, various steps are performed at this stage of the process, including a) assay method finalization for API, b) animal studies to establish absorption, distribution, metabolism, excretion and toxicity, c) animal studies to establish proof of concept (PoC) to ensure the product's safety for animals, humans, and the environment, as well as d) its dose-efficacy correlation and finally e) development of laboratory scale manufacturing and development of a formulation ready for further studies. Overall, the whole phase can last up to five years.

Step 3. Development

The development phase concerns animal, user and environmental safety, as well as all the pivotal and required studies. At this point, a final formulation will be developed and testing for regulatory purposes will begin, together with the full development and validation of the manufacturing process of both the API and the finished product. The time needed for this step is partly dependent on the number of studies required (e.g., chronic toxicity studies) to obtain marketing authorisation.[26] The ultimate objectives of these studies are to demonstrate the quality, safety and efficacy of the final veterinary medicinal product and requires extensive research in the following areas:

- **Quality documentation** which includes detailed description of the composition and general characteristics of the product, the manufacturing method and its validation, the active ingredient and its properties, the packaging, including tests on potential interactions with the product, as well as detailed documentation on stability testing of both the API and the finished VMP under various climatic conditions (up to five year stability testing to be provided on full batches), control tests, including microbiological control tests, batch to batch consistency (requiring several test batches to be produced and analysed) and other tests inherent to the type of product.

- **Safety documentation** to establish safety for the target animal, the user, including safety tests and residue tests (for products used in food-producing animals to ensure consumer safety). Precisely, detailed lead profiling is performed when developing a new veterinary medicinal product. This is done to derive the optimal biological efficacy of a product, but also to assess human, animal, and environmental safety. Various safety assessments establish the safety of the product for animals, humans, and the environment. These include:

    - Pharmacology studies (pharmacokinetic, pharmacodynamic).
    - Toxicology studies (mutagenicity, repeated dose and chronic tests, carcinogenicity, teratogenicity, reproductive toxicology).
    - Observations in humans.
    - Development of resistance (parasiticides, antibiotics).
    - Environmental risk assessment (environmental fate and effects studies for terrestrial and aquatic environments, PBT-screening).

- **Efficacy documentation** which refers to preclinical and clinical studies, including the results of clinical trials under real-life conditions farms or small animal veterinary practices.

[26] A full listing of regulatory requirements to be fulfilled for authorisation can be found in Annex II of Regulation 2019/6, Commission Regulation 2021/805 of 8 March 2021 (https://eur-lex.europa.eu/eli/reg_del/2021/805/oj).

Overall, a large amount of documentation describing this phase must be submitted to the regulatory authorities.[27] As such, given the body of work required for regulatory compliance, this phase is the most cost intensive and time-consuming. Even in this third stage, compounds may fail, usually on efficacy or safety issues. Thus, it typically lasts up to eight years and diverts important resources from companies.

The overall process may take several failed innovation cycles before a true replacement can be found, increasing timelines accordingly. It may happen that repeated failure results in a stop of the activities, a loss of all corresponding investments and with the consequence that a replacement cannot be identified.

Step 4. Regulatory submission and approval

Once, all the aforementioned studies are completed and a regulatory dossier has been produced and compiled, the authorisation process starts. On average, this process takes approximately from 14 months to two years.[28]

As specified by the participating companies, and in accordance with the provisions set out in the Veterinary Medicinal Products Regulation (Regulation (EU) 2019/6),[29] and the detailed guidance developed by the EMA,[30] the information about the manufacturing process for an active substance and the final product is part of the product authorisation and must include details about the process itself and the materials used, their quality control, and how they meet appropriate standards. Additionally, quality control tests and acceptance criteria at each critical step, information about intermediates and process validation studies, as well as validation data for analytical methods must be provided. Information about predictable and observed impurities, as well as their safety, must also be included. A retest period and storage conditions for the active substance must be specified except when the manufacturer of the finished product fully retests the active substance immediately before its use in the manufacture of the finished product. Further, stability data must be provided to demonstrate how the quality of the active substance changes over time and to support the retest period and storage conditions. Safety of the active substance must be demonstrated through toxicological data.

27 The EMA has an extensive list of detailed studies required to complete this documentation. https://www.ema.europa.eu/en/veterinary-regulatory/research-development/scientific-guidelines-veterinary-medicines

28 A full listing of regulatory requirements to be fulfilled for authorisation can be found in Annex II of Regulation 2019/6, Commission Regulation 2021/805 of the 8th of March 2021: https://eur-lex.europa.eu/eli/reg_del/2021/805/oj

29 https://eur-lex.europa.eu/eli/reg/2019/6/oj

30 https://www.ema.europa.eu/en/veterinary-regulatory/research-development/scientific-guidelines/quality-guidelines

A medicinal product cannot be marketed without a marketing authorisation. The granting of such an authorisation indicates that the product complies with the required standards of quality, safety, and efficacy. It is the responsibility of companies marketing medicinal products to comply with the relevant legislation and to ensure that such products are only marketed in accordance with legislation. The European Medicines Agency (EMA) evaluates applications for centralised marketing authorisation within the European Union (EU). This authorisation process enables pharmaceutical companies to apply for a single marketing authorisation with EMA, allowing them to market and distribute their medicine to veterinarians and pharmacies throughout the EEA with a single authorisation.

Environmental regulatory considerations

The possible environmental impact of veterinary medicinal products is evaluated. The Environmental Risk Assessment (ERA) of an API is required at the time of regulatory submission of a marketing authorisation application for veterinary medicinal products as of 1992 (Directive 92/18/EEC) and subsequently by Directive 2001/82/EC; as of January 2022, this continues to be regulated by Regulation 2019/6.[31]

Any application for marketing of veterinary medicines must include an ERA that specifies any potential risk posed to the environment. Any veterinary medicine that does not fulfil the requirements of the ERA will be denied authorisation for use. An independent and robust evaluation and authorisation process for animal medicines therefore means that, before reaching the market, the safety, efficacy, and quality of such medicines is evaluated as part of a benefit-risk evaluation. Therefore, animal medicines have a built-in One Health approach as they are tested for animal, user and consumer, and environmental safety.[32]

The manufacturing of APIs and veterinary medicines is also subject to the provisions of the Industrial Emissions Directive 2010/75/EU33, with the Member States being responsible for granting environmental permits to manufacturing sites and for ensuring compliance with emission limits.

Steps 5 to 7. Manufacturing scale up, labelling, packaging, and launch

As noted above, innovation in the veterinary medicines market is hindered by the many obstacles and challenges faced by companies when trying to bring new products to market. Regulatory compliance contributes to these challenges.

31 EFPIA and AnimalhealthEurope, 2022. EFPIA (Representing European Pharmaceutical industry) and AnimalhealthEurope (representing Animal Health Industry) position on use and risk of "per- and Polyfluorinated alkyl substances", p. 3. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjNpemFsML6AhVZPuwKHa8GC1EQFnoECAsQAQ&url=https%3A%2F%2Fwww.efpia.eu%2Fmedia%2F636866%2Fpfas-position-_-efpia-and-animalhealtheurope-january-2022.pdf&usg=AOvVaw1dfpT_NrD7qlUK5eogvxTz (accessed in September 2022).

32 https://animalhealtheurope.eu/focus-areas/one-health/

33 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32010L0075

Once a new substance is authorised, the manufacturing can start. These steps include the manufacturing scale-up, production of first batches, labelling and packaging, and launch. The manufacturing scale-up usually parallels the regulatory submission. Once the approval is received, three to six months are needed before the launch.

Alternative: moving production of an API

As indicated above, APIs cannot be substituted and if there is no derogation for starting materials and/or intermediates, that leaves the choice of either abandoning the products completely or relocating API production out of the EEA.

From experience, **the estimated timeline to transfer an API process out of the EEA is at least five to seven years for a drug product that is in liquid form, and at least six to eight years for a drug product that is in solid form.** This includes one year for enabling activities, two to three years for tech transfer, and up to three years for regulatory approvals worldwide.

These can be considered as a best-case scenario, but timelines can be longer. The steps integral in making these changes to an API manufacturing process are included hereunder:

Transfer Process out of the EEA	Typical Timelines	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Supplier Identification & Evaluation	6m								
Source Change Approval	3m								
Project Plan & Kick-off	3m								
Tech Transfer (Lab/AMTE/Docs)	9m								
Validation Campaign	~ 6-9m (varies)								
Analysis & Documentation	3m								
API Stability	6-24m								
DP Qualification	~ 3-6m (varies)								
DP Stability (std)	6-24m								
Regulatory Approval (Major markets) - *Solution*	35m								
Regulatory Approval (Major markets) - *Solid*	35m								

Timelines for regulatory approvals that are required with these process changes are dependent on the regulatory status of the manufacturing site, complexity of the process changes, scope of regulatory markets, prioritization of submission activities, and supply transition plans.

The estimated costs to make an API process transfer are in the range of 1.9 and 2.2 million EUR per API. These costs include project expenses such as (i) transfer costs (e.g., familiarization of the process

by the new site, lab scale trials, analytical methods transfer, stability studies, validation); and (ii) qualification expenses (e.g., analytical methods development, stability studies, scale-up/pilot and qualification batches). Costs also include the internal (personnel) resources that are needed on a full-time and part-time basis to ensure a successful and timely transfer.

It is unlikely that all API manufacturing processes could be transferred out of the EEA simultaneously due to logistics, costs, manpower, and regulatory considerations. If regulation prohibits all PFAS from being manufactured and/or used in the EEA, the timing to move all affected API processes outside of the EEA will take decades and will result in loss of veterinary medicines on the market.

Starting material, intermediates and process chemicals

The estimated timeline to modify an API process manufactured in the EEA to remove a PFAS substance that is used in the process (but not incorporated into, and does not become part of the API molecule) **is at least seven to nine years** for a drug product that is a solution. This includes up to three years of process development, two years for commercialization, and up to three years for worldwide regulatory approvals.

The steps integral in making these changes to an API process are included hereunder:

Modify and Scale-Up Process w/o PFAS	Typical Timelines	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
Concept Development	3m								
Project Approval	3m								
Project Plan & Kick-off	3m								
Process & Analytical Development	24-36 (varies)								
Tech Transfer (Lab/AMTE/Docs)	6-9m (varies)								
Validation Campaign	6-9m (varies)								
Analysis & Documentation	3m								
API Stability	6-24m								
DP Qualification	3-6m (varies)								
DP Stability (std)	6-24m								
Regulatory Approval (Major markets) - Solution	36m								

Timelines for regulatory approvals that are required with these process changes are dependent on the regulatory status of the manufacturing site, complexity of the process changes, scope of regulatory markets, prioritization of submission activities, and supply transition plans.

Modifying multiple non-PFAS API processes simultaneously would be challenging due to limited staff and competing processes, and less research funding because of revenue loss as a consequence of product withdrawal due to PFAS regulation. This could mean triple the amount of time to successfully change all components in these non-PFAS API processes, leading to decades of essential products not on the EEA market.

In order to modify an existing API process to remove PFAS process chemicals from the process (excluding those PFAS incorporated into, and become part of, the API), the estimated development costs are 1.5 million EUR per API in addition to the activities listed above for a process transfer (costing 1.9 to 2.2 million EUR), which is subsequently required to commercially implement the process. This 1.5 million EUR includes internal colleagues working on this modification, both on a full-time and part-time basis, and external expenses.

Auxiliaries and production equipment material

If suppliers can supply suitable alternatives, any substantial changes in equipment in a production line require re-validation of the line and depending on the change, regulatory inspection may be required. The suitability of alternatives would have to be tested first, which may require production of several test batches (but those cannot be marketed due to lack of regulatory approval).

For all these materials, it is likely that a transition period of 18 months will not be feasible for suppliers to the manufacturing of pharmaceuticals to make the changes required by the restriction (as currently worded). Any potential and sudden bans of these materials may seriously compromise manufacturing of veterinary medicines in the EU/EEA altogether.

Overall, **the estimated timeline to replace PFAS-containing and PFAS-coated parts in auxiliaries and manufacturing equipment – and associated regulatory approvals – depends on the required substitution, and the commercial availability of technically feasible alternatives. Provided alternatives are available, substitution will take years. As downstream users, animal health companies will depend heavily on the capabilities of their suppliers to offer suitable alternatives**, in the context of a complex and global supply chain.

Considering only synthetic and analytical reagents, the estimated timelines for substitution are in the range of four to ten years, including worldwide regulatory approvals.

Overall conclusion on innovation timelines to transition to suitable alternatives for APIs (PFAS and non-PFAS)

When a new active ingredient is sought in a certain therapeutic area – which is the case if one needs to substitute several products that would be banned under a PFAS restriction – that process will need to start with the very first step. The duration of the first three innovation phases is variable and depends on the intended therapeutic indication and studies required. In each phase, compounds fail the process, and several iterations may be required, prolonging the duration of the cycle, as also extensively documented in the literature.[34]

For all products containing the new API, quality, safety (user, target animal, consumer and environmental safety) and efficacy need to be demonstrated in a vast number of studies required by law and by additional guidance from the EMA. Since consumer safety is not an issue for products used in companion animals, development times may be shorter compared to products for use in food-producing species, where a number of additional and lengthy studies are required (Regulation 470/2009/EC).[35] Some products, such as parasiticides also require extra and lengthy environmental studies (e.g., the effects on dung fauna, field monitoring).

Overall, when all these steps are considered, including the discovery, development and authorisation of a new veterinary medicine, the **timelines for successful innovation cycles can vary greatly and range between a minimum of 10 and 15 years, and up to 17 years**. This is the case assuming that a technical feasible alternative exists.

The animal health companies who participated in the survey and contributed to this submission highlighted that, in the case of a PFAS restriction, the timelines could be longer, if we also take into considerations the time to re-adapt all production processes that rely on PFAS. Contextually, substitution of PFAS-containing and PFAS-coated parts in auxiliaries and manufacturing equipment, including analytical method equipment for in-process control, starting material release, product release and primary packaging equipment**, also takes several steps and years**, provided suitable alternatives would be found. As downstream users, animal health companies heavily depend on the capabilities of suppliers to offer suitable alternatives.

In the meantime, however, **the alternative veterinary medicines remaining on the market will not be able to match the performance and the large palette of functions of those based on PFAS APIs**. The consequent difference in performance would have both direct and indirect negative health impacts in the EEA.

3.2.2 Alternatives to PFAS used as an active ingredient

As discussed in the previous section, the development of existing alternatives to veterinary medicines is not a straightforward or rapid process. Any alternative to existing compounds requires:

[34] See, for example, Selzer, P.M. and Epe, C., 2021. Antiparasitics in animal health: Quo Vadis?. *Trends in parasitology*, *37*(1), pp.77-89.

[35] For example, prior to authorisation a maximum residue limit (MRL) needs to be established. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32009R0470&qid=1618469583877

- The availability and identification of a suitable alternative substance. In veterinary medicine development, thousands of compounds are tested to find just one that is both efficacious and safe for use in the patient and with no unacceptable environmental impact.

- A full new development process and regulatory approval under Regulation EU 2019/6, a process which can take up to 17 years, as shown in the previous section.

All participating companies indicated that there are currently no suitable alternatives to PFAS APIs that contribute to the same extent to the health of animals (and humans). More broadly, animal health companies stressed that, given the inherent properties of PFAS, alternatives for PFAS APIs in veterinary medicines mean the development of a totally different, and possibly not as effective, veterinary medicinal product.

As mentioned before, fluorine is important in pharmaceutical compounds, both for existing drugs as well as for an increasing number of hopeful future candidates. The importance of fluorine and its properties makes it a challenging element to substitute.

In the veterinary field, a number of fluorinated compounds for the treatment of life-threatening infections and parasite infestations have been identified. The unique properties of fluorine, which have been discussed above, are related to its extensive application in drug research, and mean that a direct replacement is not possible today.

The parasiticides being developed today have optimized safety and efficacy profiles. They have been and continue to be actively researched to ensure they meet and exceed rigorous requirements for registration. The few fluorinated carbons in their structures are deemed necessary for achieving this profile. To intentionally remove these would compromise their efficacy and safety, likely lead to more product use in quantity of product applied and frequency of application, and lead to inferior rather than improved product profiles, all without improving human or environmental health risk. The new broadest definition of PFAS does not differentiate these safe and efficacious molecules from the legacy large chain PFAS known to persist and bioaccumulate.

There are other electron withdrawing groups similar to $-CF_2-$ or $-CF_3$ such as carboxylic esters, amides, nitro, or cyano-groups, but they differ in their stability, toxicity, and permeability. The replacement of fluoroalkyl by other haloalkyl groups such as chloroalkyl can lead to reactive agents with serious toxicity issues.

Thus, a restriction that applies to the use of API containing perfluoro alkyl groups would remove these molecules from the EEA market. This would have severe consequences for animal health. **Even if PFAS APIs coexist with non-fluorinated drugs in the same therapeutic class, these APIs are not interchangeable. Limiting the options in a therapeutic class would have a large impact on the ability to treat animals with the safest and most efficacious medicine**.[36]

[36] For example, prior to authorisation a maximum residue limit (MRL) needs to be established. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32009R0470&qid=1618469583877

More generally, a lower number of substance classes available to the therapeutic arsenal will increase the risk of resistance development to the remaining substances; reduced options for well tolerated substances in certain target animals (example: permethrin in cats); reduced/no treatment options for diseases with high economic and zoonotic potential.

In this context, vaccination has the potential to be a sustainable form of control for parasitic disease in animals. However, despite decades (more than half century) of research **only a handful of vaccines against parasites are available across both human and veterinary medicine**. Until recently, the few vaccines available against parasitic disease relied on the use of attenuated live parasites or inactivation by irradiation. The need to harvest parasites from animal hosts poses challenges for animal welfare, standardisation, quality control, shelf life, and manufacturing costs.[37]

The biological complexity of parasites, including their life cycle, compared to bacteria and viruses poses difficult challenges for vaccine development:

- Lack of in-vitro culture methods for parasites hampers research and also manufacturing;
- Ability of parasites to interfere with host immune responses;
- Host-parasite interactions that mediate robust immunity are poorly understood;
- Lack of in-vitro or biochemical assays to predict the immunoprotective capacity of vaccines against parasitic diseases.

In addition, for ectoparasites, the often-short period of exposure makes it very difficult to develop effective vaccines against this group of parasites.

Another area that would be severely affected is that of general anaesthesia to allow surgical procedures to take place in a safe and sustainable manner in both humans and animals. Currently, this has been made possible using inhalation anaesthetics, but all of these now qualify as PFAS under the OECD definition. These substances are used for induction and maintenance of general anaesthesia in dogs, cats and horses and allow complex (e.g., orthopaedic) surgery to take place, even if the anaesthesia has to remain in place for several hours. They are also indispensable in horses, where anaesthesia for periods longer than 45-60 minutes is typically maintained with inhalation agents.[38] This cannot be achieved by injectable (pre)anaesthetics and removing these products from the market would mean an end to surgical procedures requiring more time than can be covered with the use of injectable anaesthetics. They have been used for decades and there are no alternatives available. Since they covered this therapeutic area in a safe and satisfactory manner, there have been no research activities to try and replace them.

3.2.3 Alternatives to PFAS used in the manufacturing process

[37] See, for example, Torgerson, P.R. and Macpherson, C.N., 2011. The socioeconomic burden of parasitic zoonoses: global trends. *Veterinary parasitology*, *182*(1), 79-95.

[38] Bettschart-Wolfensberger R (2021). Sevoflurane versus isoflurane –which agent leads to better recovery from anaesthesia in horses? Veterinary Record, Research Comment, August 2021.

The animal health companies who participated to the survey highlighted the complete lack of alternatives for the wide range of applications of PFAS used in the manufacturing process.

Starting material and chemical intermediates

No alternatives are available. To manufacture API molecules that contain such chemical building blocks, time un-limited derogations for starting materials and intermediates which are within the definition of PFAS used in the current restriction proposal are required. Replacing the necessary synthetic building blocks to build the final API with alternatives (other chemical building blocks) outside of the scope of the restriction proposal is therefore not possible, as it would result in a different API molecule and this would have to go through the lengthy development cycle again. The initial API would cease to exist.

Auxiliaries and production material

Auxiliary and production equipment materials are outside of the animal health companies' control and a responsibility of their third-party suppliers. However, one participating company made an analysis of PFAS-containing materials in equipment used for one single injectable product formulation line, which yielded the following outcome (outlined in the table hereunder):

Area	Component	Material Used
Formulation	Solvent Transfer Line (gaskets, liners)	Teflon, Kalrez®, Viton™, FKM
Formulation	Gaskets / valve membranes in contact with DP	Teflon, Kalrez®, Viton™ , FKM
Formulation	DP Phase Filter Media	PTFE
Formulation	DP Phase Vent Filters	PTFE
Formulation	DP Peristaltic Pump Hose Insert	PFL
Formulation	CP Phase & Excipient Filters	PVDF
Formulation	HFF Filter Membranes	PVDF (mesh)
Formulation	Membrane protecting net on HFF	PFA
Formulation	Gaskets in contact with solvent waste	Teflon, Kalrez®, Viton™, FKM
Formulation	Gaskets in contact with CIP	Teflon, Kalrez®, Viton™, FKM
WFI System	Gaskets / Valve membranes	Teflon with EPDM backing
Clean Steam System	Gaskets / Valve membranes	Teflon with EPDM backing
Filling	Glass vial stoppers	PTFE coating
Lyo	Gaskets & valve membranes within/at sterile boundary	Teflon with EPDM backing
QC Lab	PVDF filters	PVDF

This example illustrates to what extent PFAS are present in equipment materials used in pharmaceutical production, and the magnitude of the task of finding alternatives. In this case, substitution depends on suppliers. The impact of this is expected to be spread over multiple years and may be acute, particularly when a part containing PFAS may need to be replaced, or when new or

replacement equipment needs to have equivalent inert or durable properties. This is also an issue for all sectors (including research institutes) using analytical instruments such as HPLC where PFAS-coated tubes, PTFE seals and tapes and other parts will be present.

At present, there is no full inventory for every production line where PFAS are used in production equipment which is produced by external suppliers. Once suppliers would be able to propose alternatives, it would require years to investigate the suitability of alternatives with similar functional specifications. It would mean extensive testing and a long period of validation and subsequent approval of the production line by the regulatory authorities, with no guarantee that current product quality levels can be maintained.

If there will be no derogation for Teflon, for example, in manufacturing equipment parts, this will result in sudden failure of production lines and supply interruptions for all products currently manufactured in the EEA which may last for years. The only mitigation possible will be to fully relocate all manufacturing out of the EEA (see section 3.2.1), a process that will easily take decades given the number of products involved and the fact that the whole sector would be impacted.

Process chemicals and analytical reagents

PFAS-containing reagents are usually several orders of magnitude more reactive towards target structures, be it in PFAS or non-PFAS API synthesis and production. Replacing these would significantly hamper functionality and may even be impossible. Companies have provided examples for specific substances.[39]

Replacement of analytical reagents may be possible in the long-run, however, this will require substantial research and validation work, and subsequent approval from regulatory authorities, as explained in section 3.2.1.

3.2.4 Alternatives to PFAS used in packaging materials of VMPs

It is not yet clear if technically suitable alternatives can be found and supplied in sufficient quantities for packaging applications of PFAS. Some potential alternatives have been identified:

- For blisters applications, **Aluminium Cold** form blister is potentially a technically suitable alternative. Nevertheless, it brings other environmental concerns and cannot be considered as a viable and sustainable alternative.
- Additionally, **Polyvinyl chloride (PVC)** is an available alternative to PCTFE in blisters; however, it does not have the same technical advantages for medicines that require a higher level of protection.
- The use of uncoated stoppers can give rise to unknown consequences with a potential high risk for patient safety due to the extractables and leachables profile (highly drug product specific). There is a risk to exceed toxicological thresholds and/or influence drug

[39] This information is confidential and will be submitted by the companies in an addendum to this SEA.

product purity and stability (e.g., induction of particle generation due to extractables and leachables cannot be excluded and needs to be investigated at the finished product level).

In general, according to the companies who have participated in this submission, extractable and leachable studies as well as stability and safety studies will be required for each product for which an alternative would be available and in which the replacements would be used. Once more, as downstream users, animal health companies heavily rely on their suppliers to provide suitable alternatives. Timing to implement changes like this range from 18 – 36 months and costs will be in the order of magnitude of more than 100,000 EUR for each product presentation impacted. In addition, regulatory approval will be required before this change can be implemented. Further eight to nine months will be required.

3.3. Overall conclusion on the suitability and availability of alternatives

In conclusion, the analysis of alternatives shows that there are no appropriate chemical alternatives to PFAS in the different manufacturing phases of VMPs in general.

The entire process of manufacturing and developing veterinary medicinal products heavily depends on PFAS chemicals in a wide variety of applications. Consequently, it can be expected that most of the veterinary APIs and veterinary medicines manufactured in the EEA are reliant on PFAS materials at a certain stage of the production.

Therefore, **losing these uses of PFASs in veterinary medicines and their manufacturing would result in the lack of effective treatment or prevention for a majority of companion and farm animal conditions over the longer term**. The lack of effective treatments and vaccines would have severe impacts on animal health and welfare, as well as on the European farming sector, and severely impact veterinarians in their work as discussed later in the document.

The table below lists the substitution activities that can take place together with the minimum time required to execute them **once an alternative has been identified. The time to find alternatives is unpredictable and will vary greatly. Some uses are highly dependent on suppliers and their capability of substitution;** for some uses, no alternatives may be possible**.** These substitution activities would be necessary for a number of APIs and VMPs and cannot be done all at once **but need to be staged** and together can **take decades**; therefore, longer transition times than those stated in the table would be required.

PFAS Use Application	Substitution Activity	Substitution Timeline *(i.e., minimum time after alternative has been identified)*
API discovery/development	Developing a new API to substitute PFAS APIs and/or to substitute PFAS incorporated into an API	12-17 years, including regulatory approval
Starting materials, intermediates, and process chemicals*	Substituting a material or chemical used in API synthesis that is not incorporated into the API	At least 7-9 years, including regulatory approval[§]

PFAS Use Application	Substitution Activity	Substitution Timeline *(i.e., minimum time after alternative has been identified)*
API manufacturing	Transferring an API production process out of EEA	5-8 years, including regulatory approval[§]
Auxiliaries and production equipment material	Replacing PFAS-containing and -coated parts in auxiliaries and manufacturing equipment	Minimum 13.5 years[§]
Synthetic and analytical reagents	Substitution of reagents	4-10 years, including regulatory approval
Packaging materials of VMPs	Replacing packaging material for VMPs	2-4 years, including regulatory approval[§]

[§] ***Needs to be staged, impossible to do all at once***

* Replacement of PFAS containing API or starting materials / intermediates that are incorporated in the API might not be possible

4. ANALYSIS OF IMPACTS

The sections below provide a general overview of the social and economic impacts, considering business impacts (at different stages of the value chain), market impacts (on the product market), substitution costs, and broader EU macroeconomic consequences resulting from a potential REACH restriction of PFAS used for veterinary medicines.

4.1 Economic impacts on animal health companies

4.1.1 PFAS as an active ingredient

A survey of AhE members was utilised in the preparation of this report. **Major animal health companies contributed to the data**. The participating companies are among the biggest producers in the EEA animal health market. The market share covered by this questionnaire is approximately 75% of the whole EEA veterinary medicines market. The assessment is, therefore, representative. This fairly large share can be used to obtain reliable estimates for the EU market via extrapolation, as detailed below for the assessment of the economic impacts.

The core business of these companies is the production of veterinary medicinal products for companion and farm animals. Nevertheless, some of these companies are also active at different level of the value chain (vertically integrated) and directly produce the active pharmaceutical ingredients used in the development of veterinary medicines. In total, these companies employ approximately 20,000 workers for the production of drug products in the EEA. Almost half of these employees, i.e., 10,000 workers are directly or indirectly engaged in the manufacturing, R&D and supply chain of veterinary medicines for which PFAS are used across the EEA.

The derogation in the current restriction proposal does exclude APIs. However, API manufacturers located in the EEA use PFAS chemicals to process them to PFAS-APIs. As only the API is exempted from the PFAS restriction but not PFAS chemicals used for synthesis of the APIs, corresponding PFAS-APIs cannot be produced by and supplied from European manufacturers.

The APIs utilised in veterinary medicines can be either PFAS or not (based on the OECD definition). PFAS APIs represent a smaller fraction of the API portfolios of products of animal health companies, approximately 4%,[40] for a total of about 40 PFAS APIs out of aggregated portfolios of more than 1,000 APIs. Note that these figures are the aggregation of the API portfolios of manufacturers and that the same API (formula) can be produced by different companies. In other words, 40 APIs is not equal to 40 different formulas. Companies estimated approximately 16 different single PFAS APIs marketed in the EEA.

[40] Weighted average based on market shares.

This is equal to approximately 160 tons of PFAS APIs produced every year by these companies (or their contract manufacturers). However, these relatively small volumes underpin much larger turnovers when considering the veterinary medical products containing different combinations of PFAS and non-PFAS APIs. Namely, approximately 22.3% of the turnover of these companies in the EEA would be affected by a REACH restriction of PFAS APIs.

Hence, the participating companies utilize PFAS APIs to manufacture veterinary medicinal products for companion and farm animals. On aggregate, during 2022, **the sales of veterinary medicines containing PFAS APIs in the EEA amounted to nearly 600 million EUR**. These data were taken from a typical sales year and the volumes are considered representative for annual volumes.

In the business-as-usual scenario (i.e., assuming no PFAS restriction), the demand for veterinary medicines, which would fall within the scope of a restriction, is growing consistently. **The annual sales of PFAS based veterinary medicines products are projected to grow at an annual rate of 6-8% by 2027**. Precisely, the companion animal parasiticides market has the largest growth potential with expected high single digit volume growth over the next five years.

Therefore, a broad restriction of PFASs in the EEA would have significant impacts on the business of the VMP manufacturers and, most importantly, to their customers. In the EEA, the majority of the above mentioned PFAS-products are only available against prescription by a veterinarian and will be supplied to animal owners through their veterinarians or through a pharmacy following a prescription. Some of these products are administered directly by the veterinarian (e.g., inhalation anaesthetics, NSAIDs). It is difficult for the surveyed companies to estimate the number of animal owners (companion animals and livestock animals) being supplied through these channels. As an estimate, the companies which participated to the survey, which represent approximately 75% of the animal health industry, are supplying the vast majority of veterinary practices in the EEA: approximately 310,000.[41]

The expected income generated through the sale of veterinary medicinal products containing PFAS API in 2027 (year of the entry into force of the proposed restriction plus 18 months of transition period), **likely to be affected by a REACH restriction of PFAS used as an active pharmaceutical ingredient, is estimated at approximately 933 million EUR/year** (rounded). Future values are expected to grow at the same CAGR of 6-8%.

The direct cost of a PFAS restriction is represented by the loss of the contribution to the EEA economy of the Earnings Before Interest and Taxes (EBIT) generated by VMP manufacturers using PFAS chemicals and PFAS-based products, such as it is the case. The relevant economic measure to quantify this economic impact is given by EBIT. The monetization (net present value, NPV, with 3% discount rate)[42] of this economic impact (lost EBIT) is reported below.

41 https://figures.animalhealtheurope.eu/

42 In accordance with European Commission, 2021. Better Regulation Guidelines and Toolbox. https://commission.europa.eu/document/download/9c8d2189-8abd-4f29-84e9-abc843cc68e0_en?filename=br_toolbox-nov_2021_en.pdf

If the PFAS restriction proposal were to materialize, and PFAS APIs were to be restricted from use in veterinary medicines (assuming a derogation for the manufacturing only),[43] it would be estimated that **animal health companies would experience a net EBIT loss of approximately 427 million EUR/year** (rounded). Over four years, **the total impact amounts approximately to 1.59 billion EUR** (rounded; NPV, 3% d.r.) **for participating companies (animal health companies)**.[44]

As mentioned before, the survey does not cover the whole EEA animal health market. The market share covered by this survey represents approximately 75% of the whole EEA veterinary medicinal market. One can use the market share of the animal health companies which participated to the survey to extrapolate **the total economic impact in the EEA across the whole EEA veterinary medicines industry** (1.59 billion EUR / 0.75 = **2.1 billion EUR**).

Accordingly, the economic fallout of a REACH restriction of PFAS APIs in the EEA would be therefore equal to 2.1 billion EUR. Because the REACH restrictions would affect equally the whole EEA animal health industry, the corresponding loss in value added (i.e., loss in EBIT) can be considered as a net impact (EEA industry-wide impact).[45]

4.1.2 PFAS used in the manufacturing process and in packaging materials

It is important to note that also veterinary medicines which do not contain PFAS APIs rely on PFAS as process chemicals, in equipment and in packaging and quality control in the manufacturing process. Precisely, as outlined above (Section 3.1.2), beyond the use as an active ingredient, PFAS can also be used as starting materials and chemical intermediates, as auxiliaries and production materials, including processing aids and process chemicals, such as solvents and reagents, in fixed and consumable equipment, including single or multiple use materials, in medical devices, in machinery used for the production of medicines, and ultimately in packaging components.

Veterinary medicines, including vaccines, which rely on PFAS in the manufacturing process account for approximately 100% of the animal health companies' product portfolios. Basically, all products that are not imported from outside of the EEA, which is the vast majority of products, would be impacted by a REACH restriction of PFAS in the EEA. The impact of the proposed PFAS restriction on these medicines is largely caused by the production equipment used for API and product manufacturing, packaging materials as well as by analytical equipment and reagents used for starting materials and finished product testing.

Given the broader definition of PFAS, and under the assumption that all PFAS uses would be eventually restricted in the EEA, it is estimated that the vast majority of the overall company turnover in the EEA depends on activities where PFAS are used in manufacturing process, equipment and packaging and quality control.

[43] Companies were asked to project lost sales and EBIT under the assumption that a PFAS restriction were to be fully adopted as of 2027.

[44] Using the Excel function =PV(3%,4,-463000000,0,0).

[45] In other words, we are assuming that the companies that may benefit from a negative regulatory outcome for PFAS are competitors based outside the EEA (where the REACH requirements, especially in the manufacturing process, do not apply).

It is complicated for animal health companies to make an accurate estimate as they currently do not have a complete visibility from their supply chain of all PFAS which are used in their production facilities and throughout the supply chain of drug products (one is talking about more than 10,000 distinct PFAS substances potentially in scope of a broad restriction in the EEA if we consider the OECD definition).

It can be expected that close to 100% of the veterinary medicines manufactured at formulation sites in the EEA (including those VMPs not containing any PFAS APIs and vaccines) are reliant on PFAS materials at a certain stage of the production.

Thus, virtually, all veterinary medicines manufacturing within the EEA currently relies on the use of PFAS. The expected loss in income generated through the sale of these veterinary medicinal products is estimated at approximately 3.1 billion EUR/year (rounded). Future values are expected to grow at the same CAGR of 6-8%.

The direct cost of a PFAS restriction is represented by the loss of the contribution to the EEA economy of the Earnings Before Interest and Taxes (EBIT) generated by manufacturers using PFAS chemicals and PFAS-based products, such as it is the case. The relevant economic measure to quantify this economic impact is given by EBIT. The monetization (net present value, NPV, with 3% discount rate)[46] of this economic impact (lost EBIT) is reported below.

If the PFAS restriction proposal would materialize, and PFAS were to be restricted from use in the different stages of the manufacturing process of veterinary medicines,[47] it is estimated that **animal health companies would experience a net EBIT loss of approximately 1.61 billion EUR/year** (rounded), which is close to **100% of the current EEA production.**

Over four years, the total impact amounts approximately to 6 billion EUR (NPV, 3% d.r.) **for the EEA industry**.[48]

As mentioned before, the survey does not cover the whole EEA animal health market. The market share covered by this survey represents approximately 75% of the whole EEA veterinary medicinal market. One can use the market share of the manufacturer companies which participated to the survey to extrapolate **the total economic impact in the EEA across the whole EEA veterinary medicines industry** (6 billion EUR / 0.75 = **8 billion EUR**).

Without additional derogations, the whole Animal Health Industry will no longer be able to manufacture any APIs (both, classifying as PFAS or non-PFAS APIs) or associated veterinary medicines in the EEA. This would necessitate moving production out of the EEA as the only option, which would require years in itself, plus years of regulatory inspections and approvals. As a result, the

46 In accordance with European Commission, 2021. Better Regulation Guidelines and Toolbox. https://commission.europa.eu/document/download/9c8d2189-8abd-4f29-84e9-abc843cc68e0_en?filename=br_toolbox-nov_2021_en.pdf

47 Companies were asked to project lost sales and EBIT under the assumption that a PFAS restriction were to be fully adopted as of 2027.

48 Using the Excel function =PV(3%,4,-1618848731,0,0).

supply and availability of veterinary medicines in the EEA will be substantially impacted even in the longer term with new and extensive dependencies on non-EEA manufacturing and important shortages and therapeutic gaps in the field of veterinary medicine.

Accordingly, the economic fallout of a REACH restriction of PFASs in the EEA would be therefore equal to more than 8 billion EUR for the veterinary medicines manufacturing (lower bound estimate).

4.1.3 Substitution costs

The main challenge that has been raised by participating companies is the fact that deadlines provided by authorities (i.e., 18 months transition time) are considered too tight for business adaptability and to develop alternative products. There are various challenges associated with substitution. As outlined in the previous sections, a transition towards "PFAS free" API and manufacturing process would involve various steps to redevelop a new veterinary medicinal product (see Section 3.2.1 where the typical innovation timelines are described in details).

Given the importance of PFAS for these companies' portfolios, considering PFAS as process chemicals, implementing new manufacturing processes and replacing equipment in manufacturing and quality control, plus the associated regulatory submissions and approvals, it is clear that animal health companies require longer timelines to phase out PFAS - wherever possible - from both the portfolio and the production of APIs and VMPs. This will come at significant costs as detailed in section 3.2.1.

The Animal health industry is highly innovative, in the sense that innovation focuses on development of new veterinary medicinal products rather than on trying to adapt currently available drug products – which is not even practically or legally possible in the case of PFAS APIs or PFAS used in the synthesis of non-PFAS APIs. On average, the animal medicines industry spends 7.8% of annual turnover on their R&D budget for developing new veterinary medicinal products for use in animal patients, on par with the technology hardware and equipment industry.[49]

The search for alternatives to PFAS has so far borne no fruit, neither with regard to the API nor to the re-design of synthesis and production processes. On the other hand, development of brand-new APIs and medicines together with a redesign of manufacturing processes and equipment for the entire product portfolio of these companies would not only divert significant resources from R&D, but also entail considerable costs for the companies in terms of resources, without having the guarantee that veterinary medicines of equivalent efficacy and safety compared to today's product portfolio would be the outcome. Moreover, since revenues would be substantially and immediately impacted in a negative way, so will be the budget remaining available for R&D as this is a percentage of annual revenue.

[49] https://figures.animalhealtheurope.eu/

The additional investments in manufacturing processes include "developmental costs" to identify suitable alternatives, costs for redesigning manufacturing processes and quality assurance, costs for replacing manufacturing equipment and costs for the transition to a full-scale production using the alternatives. In addition, regulatory fees will have to be paid to obtain and maintain approvals under Reg 2019/6. These additional costs will only be partly transferred to customers over the next few years after the potential restriction. However, since animal owners pay the entire cost for medicines used for their animals, there are substantial limitations to this transfer of costs since otherwise, medicines would become unaffordable. Animal health companies would therefore have to absorb most of these costs.

Average costs for one successful innovation cycle vary between 50-60 million EUR, up to 100 million EUR.[50] In the case of PFAS, given the vital importance for companies' product portfolios, participating companies anticipated that a substitution will easily require 525 million EUR per API (in aggregate terms).

As mentioned above, companies reported that collectively 16 APIs in their portfolios qualify as PFAS. Thus, on aggregate, **the substitution costs to switch to an alternative API and associated products can be conservatively estimated to be approximately 8.4 billion EUR** (rounded),[51] not even taking into account PFAS APIs that are currently still in the pipeline and for which development has to stop irrespective of R&D costs already incurred, and assuming that the innovation cycle for all APIs would be successful, which is highly unlikely. Real costs including cost of failures would be substantially higher.

This is only part of the real substitution cost. For non-PFAS APIs and associated products, and for vaccines, costs will vary depending on the substitutions required. **For all products, replacement of manufacturing equipment coated with PFAS would be necessary**. For some, **additional changes in the manufacturing process** would be required (substituting process chemicals, reagents, solvents etc.). **For the vast majority, analytical equipment and reagents used in quality control** would be needed. For others, **alternative packaging materials** would need to be found. For all of these changes, **high regulatory fees** will need to be paid as well.

Collectively, this threatens the survival of the industry as a whole and may put some companies operating predominantly within the EEA basically out of business. Companies will look to move production out of the EEA to the extent possible; but this also comes at a significant cost and would require decades.

[50] See, for example, https://ahi.org/approval-and-regulation-of-animal-medicines/

[51] Result of 525 million EUR times 16 identified APIs identified by the companies which contributed to the survey.

4.2 Social impacts: unemployment

The restriction of PFAS will have a direct impact on the headcount of the manufacturer companies. However, to what extent these impacts will be felt on the employment is difficult to predict for surveyed companies. Indeed, all participating companies highlighted that the unemployment effect of a PFAS ban on sales will likely depend on the adaption of the supply chain to non-PFAS based materials required for the development and manufacture of veterinary medicinal products or imports of PFAS-containing medicines from outside of the EEA. Obviously, lack of additional derogations and/or a transition period of only 18 months would abruptly grind the sector to a halt, which would then affect the majority of its employees.

In general, it is difficult to estimate the unemployment because this also depends on whether the end user market can be addressed in the future with different veterinary medicines that do not rely on PFAS and if that transition is capable of retaining veterinary medicinal products of equivalent safety, efficacy and quality. It will also depend on capacity of production outside of the EEA to continue producing products during any transition time and to which extend companies can retain supporting and commercial staff in the EEA to distribute those medicines.

Animal health companies which participated in the survey declared that a PFAS restriction would very likely lead to unemployment within the companies – it would definitely be the case if the current draft proposal remained unchanged. If there were no specific derogations assigned to all critical applications which included the ability to continue manufacturing the products with the EEA, the amount of revenue at risk could force the closure of EU based manufacturing sites and relocation to non-EU based locations where the product could be imported under derogation, otherwise distributed globally.

4.2.1 PFAS as an active ingredient

With the loss of business, action would be deemed necessary to reduce workforce. It is estimated that, assuming a PFAS restriction is implemented on PFAS APIs *and* assuming that equipment and other uses of PFAS in production of veterinary medicines containing non-PFAS APIs could continue unaltered, approximately 1,500 workers in the companies participating in the survey will face layoff in the EEA. Here we report the monetization of the likely social costs of unemployment for these workers.

The average annual salary across these European workers (including the employer's social security contributions) is approximately 68,000 EUR.

A well-known guideline in monetising the social impact of unemployment has been developed by the European Chemicals Agency (ECHA) for evaluating such impact in different regulatory processes.

Estimates have been made in accordance with the ECHA document on the evaluation of unemployment (SEAC/32/2016/04)[52] and the paper of Dubourg (2016)[53] endorsed by ECHA. Therefore:

- Using Table A7 (column G, considering the gross wages including the employer's social security contributions) in Dubourg's paper, the total social cost of unemployment in EU is equal to 2.16 times the annual gross salary.[54]
- Table 1 presents the statistics from Eurostat (data for 2022-Q1) on the average duration of unemployment for both men and women in the age of 15-64 years in EU-27.[55]
- Only 75% of the average duration of employment is considered, to reflect the fact that some affected workers are highly skilled and could find employment sooner.

Table 1. Duration of unemployment in EU-27

Duration Grouping	Thousand units	Proportion (A)	Assumed duration (B)	Weighted average (A*B)
Less than 1 month	1643.2	0.121421710	0.5	0.060710855
From 1 to 2 months	2424.4	0.179147270	1.5	0.268720904
From 3 to 5 months	2126.5	0.157134412	4.5	0.707104855
From 6 to 11 months	1890.1	0.139666002	8.5	1.187161014
From 12 to 17 months	1441.2	0.106495234	14.5	1.544180891
From 18 to 23 months	830.8	0.061390675	20.5	1.258508830
From 24 to 47 months	1601.0	0.118303406	35.5	4.199770930
48 months or over	1575.8	0.116441292	48	5.589182000
Total	13533.0	1		**14.815340279**

The social costs of unemployment would therefore be equal to:

68,000 EUR x 1,500 people x 2.16 x 14.826475584/12 x 75% = 204 million EUR.

Although companies along the supply chain would face a reduction in sales over the years, we assume for simplicity that the entire workforce will continue working for the other three years. Therefore, one discounts the monetised impact derived above by three years due to the assumed delay in the layoff, using discount rate of 3% per year, as follows: 204 million EUR x $(1 + 0.03)^{-3}$ = 187 million EUR (rounded).

[52] ECHA (2016). The Social Cost of Unemployment. Available at: https://echa.europa.eu/documents/10162/13555/seac_unemployment_evaluation_en.pdf/af3a487e-65e5-49bb-84a3-2c1bcbc35d25

[53] Richard Dubourg, 2016. Valuing the Social Costs of Job Losses in Applications for Authorisation. The Economics Interface Limited.

[54] This value is greater than one (1) because it considers the following components: lost wage, costs of job searching, recruitment costs, the impact of unemployment status on future wages (scarring effect) and employment possibilities, and leisure time (which is a benefit and therefore subtracted from the previous components).

[55] Data extracted from https://ec.europa.eu/eurostat/web/products-datasets/-/lfsq_ugad

One can use the market share to extrapolate the total social impact of the unemployment in the EEA across all VMPs manufacturers: 187 million EUR / 0.75 = 245 million EUR (rounded).

At the level of animal health companies, the total impact from unemployment in the EEA is estimated at 245 million EUR. Nevertheless, there is a high likelihood that the total social impact of a restriction of PFAS *along the whole supply chain* would be much larger than this, once all other economic operators having business linked to veterinary medicinal products are considered (including distributors, pharmacies and veterinary practices and clinics which will no longer be able to function).

Other workers would be likely impacted, even though the AnimalhealthEurope member companies are not in a position today to quantify the unemployment effect.

Due to the impact on turnover, R&D capabilities would be reduced as well, since the R&D budget is a rather fixed percentage of annual sales and will not be increased because of the restriction; the opposite will happen also in terms of employment. Moreover, no derogation for PPORD is foreseen in the restriction dossier.

In addition, as a progressive result and due to the expected reduction in sales**, job creation is also expected to be negatively affected**. Manufacturers anticipated that eventually they would inevitably reduce new recruitment as all manufacturing and R&D activities would relocate outside the EEA.

4.2.2 PFAS used in the manufacturing process

As mentioned before, it can be expected that close to 100% of the veterinary medicines manufactured at formulation sites in the EEA (including those VMPs which do not contain any PFAS APIs and vaccines) are reliant on PFAS materials at a certain stage of the production.

Without additional derogations, the whole Animal Health Industry will no longer be able to manufacture any APIs (both classifying as PFAS and non-PFAS APIs) or associated veterinary medicines or vaccines in the EEA. Thus, the production will have to be moved out of the EEA wherever possible to maintain at least some continuity of supply, although this will be challenging even in the longer term.

Accordingly, with the relocation outside of the EEA, action would be deemed necessary to reduce workforce, especially for those directly or indirectly engaged in the manufacturing of veterinary medicines at formulation sites in the EEA.

Conservatively, it is estimated that, assuming a PFAS restriction is implemented on PFASs, even if with derogation for veterinary active substances, but assuming that equipment and other uses of PFAS in production of veterinary medicines containing non-PFAS APIs are no longer allowed as of 2027 (year of the entry into force of the proposed restriction plus 18 months of transition period), approximately 5,600 workers in the companies participating in the survey will face layoff in the EEA. Here we report the monetization of the likely social costs of unemployment for these workers.

The social costs of unemployment would therefore be equal to:

68,000 EUR x 5,600 people x 2.16 x 14.826475584/12 x 75% = 761 million EU (rounded).

Similarly, although companies along the supply chain would face a reduction in sales over the years, we assume for simplicity that the entire workforce will continue working for the other three years. Therefore, one discounts the monetised impact derived above by three years due to the assumed delay in the layoff, using discount rate of 3% per year, as follows: 761 million EUR x $(1 + 0.03)^{-3}$ = 697 million EUR (rounded).

One can use the market share to extrapolate the total social impact of the unemployment in the EEA across all VMPs manufacturers: 697 million EUR / 0.75 = 929 million EUR (rounded).

At the level of animal health companies who contributed to the data, the total impact from unemployment in the EEA is estimated at 929 million EUR. Nevertheless, there is a high likelihood that the total social impact of a restriction of PFAS *along the entire supply chain* would be much larger than this, once all other economic operators having business linked to veterinary medicinal products are considered. Veterinary practices and clinics cannot function without veterinary medicines and vaccines. There would be an impact on farmers and the food supply chain as well.

Due to the impact on turnover, R&D capabilities would be reduced as well, since the R&D budget is a rather fixed percentage of sales and will not be increased because of the restriction, but the contrary will happen also in terms of employment.

4.3 Wider economic impacts

It is also important to consider the wider macroeconomic impacts and consequences on the EU society at large, by focusing on the expected consequences for the EEA market. In particular, there are concerns on the overall EU trade balance (increase of imported veterinary medicines) and on the competitiveness of the EEA market.

Impacts on society – Animal and human health

A restriction of PFAS would have serious consequences on both animal and human health. Globally, there is a clear recommendation from leading scientists compiled for animal (pet) owners and veterinarians (ESCCAP, CAPC & TroCAP) on the importance of regular use of parasiticides to treat cats and dogs against internal and external parasites.[56] Veterinary medicines based on PFAS APIs and PFAS starting materials/intermediates are necessary products in this recommendation. More generally, the use of parasiticides supports animal health and welfare as infections with heartworm, lungworm, mite, and other parasites can be very serious and sometimes fatal. **Without these products, the health of companion animals would be critically endangered**.

[56] See, for example, http://www.esccap.org/uploads/docs/ogu35t0w_esccapgl3ectoguidelines.pdf

A restriction on PFAS APIs would also impact the availability of anaesthetics for use in surgery. At present, inhalation anaesthetics are the gold standard in both human and veterinary medicines. Injectable alternatives exist; however, they are not suitable for (complex) surgery taking more than an hour. This would mean the end of (e.g.,) orthopaedic surgery in companion animals and horses, increasing animal suffering and resulting in, in fact, unnecessary euthanasia in many cases that at present can be treated satisfactorily.

More broadly, if we consider the broad restriction of PFAS uses in the manufacturing of veterinary medicines (out of the scope of the derogation proposals, as currently worded), restrictions on starting materials or intermediates, auxiliaries, and other production materials used in the manufacturing process will significantly affect the production of close to 100% of VMPs that are currently used to treat a wide range of diseases. It would also impact vaccine production, a very important tool in the prevention of disease. **A sudden discontinuation of supply of these critical materials will affect production and result in severe shortages of medicines in the EEA and abroad, with serious knock-on effects on veterinary practices and clinics throughout the region, which cannot function without medicines and vaccines**. A whole sector may be affected especially if there are no derogations for manufacturing equipment. This would result in massive unemployment in a highly specialised sector with impact on animal and human health.

Even if we consider that PFAS-free products can be produced outside the EEA and imported, the removal of products containing PFAS substances (as defined by OECD) would make ectoparasite control of pets very complicated, as a large majority of active ingredients that protect against ectoparasites are concerned.

This leaves an important gap and will make treatment much more complicated (if not impossible) potentially less effective and more costly. Overall, this may result in reduced compliance and lower control of ecto- and endo-parasites as well as lower prevention of vector borne diseases. A decrease in parasite control capacity would lead to higher infestation rates, higher clinical observation rates of ectoparasitoses and vector borne diseases, and higher rates of transmission to humans, as widely studied in the literature.[57]

Overall, the ban and shortage of PFAS containing and/or PFAS based veterinary medicinal products in the EEA will dramatically reduce the number of available VMPs resulting in a high likelihood and number of **parasitic infections and outbreaks of diseases in animals, animal suffering and death**, as well as **zoonotic diseases in humans**. The supply of tools to protect animal health and welfare, to support veterinarians in their work with all the different animal species, to keep companion animals healthy and to support farmers with the care of their livestock will be heavily impacted long-term.

Animal health and welfare are closely linked to human health. In line with the 'One Health' concept developed in 2004 by the Wildlife Conservation Society, the World Health Organization (WHO) and

[57] See, for example, Otranto, D., Dantas-Torres, F., Fourie, J.J., Lorusso, V., Varloud, M., Gradoni, L., Drake, J., Geurden, T., Kaminsky, R., Heckeroth, A.R. and Schunack, B., 2021. World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines for studies evaluating the efficacy of parasiticides in reducing the risk of vector-borne pathogen transmission in dogs and cats. *Veterinary Parasitology*, 290, p.109369.

the European Commission recognised in 2008 the intrinsic connections between human health, animal health and the environment.[58]

For instance, some ectoparasites (mainly ticks, mosquitoes, sandflies and fleas) are important vectors of infectious pathogen agents, including viruses (e.g., encephalitis virus), bacteriae (e.g., *Rickettsia spp.* the spotted fever agents, *Borrelia spp*. the Lyme disease agents, *Ehrlichia spp.*, *Anaplasma spp.*, *Bartonella spp.*), protozoans (e.g., *Babesia* causing babesiosis, *Leishmania* causing leishmaniosis), filarial worms (*Dirofilaria immitis*, agent of Dirofilariosis), tapeworm (*Dipylidium caninum*).[59] As an example, veterinary medicines by preventing ticks in dogs indirectly protect owners against vector-borne zoonotic pathogens such as such as Lyme disease and tick encephalitis.

Ultimately, a REACH restriction of PFAS in the EEA would also force the use of older and less effective molecules, creating treatment gaps and possibly increasing the use of other over the counter (OTC) products that generally have a narrower spectrum of coverage. In addition, **veterinarians may need to prescribe more antibiotics for secondary bacterial infections with the associated risk of emergence of antibiotic-resistant bacteria**.[60]

A case in point is the importance of anticoccidial veterinary medicines (which are based on a PFAS API) for the treatment and control of coccidia in different farm animal species and in piglets. There are currently no effective alternative medicines available to manage and control coccidiosis in swine specifically. A ban of PFAS, with consequent likely withdrawal of these unique veterinary medicines, would inevitably increase the antibiotic consumption due to secondary infections, particularly in the swine industry.

The development of resistance against existing products is one of the major threats for parasiticides. In farm animals, most ectoparasiticides and anthelmintics have shown reduced efficacy or have completely lost their activity against many genera, and the search for new alternatives has not been successful to date despite the urgency, illustrating that innovation in veterinary medicine is a slow process. Although the situation in pets is less acute, the sporadic documentation of lack of efficacy in fleas and other parasites indicates that resistance development may be a question of time.[61] Therefore, a limited spectrum of insecticide/acaricide-classes will increase the risk of development and spread of resistance, and thus will reduce the number of available antiparasitic formulations.

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[58] World Health Organization (WHO), One Health, September 2017: https://www.who.int/features/qa/one-health/en/. One Health was endorsed in 2008 by several leading international organisations including the WHO, the World Bank and the European Commission, and was subsequently quoted in several official EU publications such as the 2017 EU Action Plan against Antimicrobial Resistance and the 2020 EU Biodiversity Strategy.

[59] See, for example, Colella, V., Nguyen, V.L., Tan, D.Y., Lu, N., Fang, F., Zhijuan, Y., Wang, J., Liu, X., Chen, X., Dong, J. and Nurcahyo, W., 2020. Zoonotic vectorborne pathogens and ectoparasites of dogs and cats in Eastern and Southeast Asia. *Emerging Infectious Diseases*, 26(6), p.1221.

[60] https://www.who.int/news/item/07-11-2017-stop-using-antibiotics-in-healthy-animals-to-prevent-the-spread-of-antibiotic-resistance

[61] See, for example, Rust, M.K., Vetter, R., Denholm, I., Blagburn, B., Williamson, M.S., Kopp, S., Coleman, G., Hostetler, J., Davis, W., Mencke, N. and Rees, R., 2015. Susceptibility of adult cat fleas (Siphonaptera: Pulicidae) to insecticides and status of insecticide resistance mutations at the Rdl and knockdown resistance loci. *Parasitology Research*, 114, pp.7-18.

Another example would be rabies, which is currently well under control in the EU thanks to mandatory vaccination of cats and dogs, but is likely to resurge and threaten human health when vaccination would no longer be possible. This is just one example out of many, where vaccines currently safeguard both animal and human health.

In conclusion, the lack of veterinary medicines and vaccines would mean that diseases of livestock and pets can no longer be treated or prevented with vaccines, which also has consequences for human health.

Impacts on society – Animal owners

Veterinary medicines play a vital role in maintaining the health and well-being of pets and animals, as well as supporting the livelihoods of their owners. The EEA is currently home to a significant number of farmers, pet owners, and other animal-related businesses that rely on continued access to veterinary medicines to maintain their animals' health. A REACH restriction of PFAS could have significant economic impacts on these groups.

As mentioned, the survey covers only the upstream level of the animal health supply chain but it is clear that the largest impacts would be suffered downstream in the chain, at the level of farmers, pet owners, and animal-related businesses, which would face a lack of medicines to treat their animals. In fact, the socio-economic impacts typically follow a magnification effect along the supply chain so that the downstream users are expected to have larger impacts.

For farmers, shortages in the supply of veterinary medicines in the EEA could lead to increased costs and decreased productivity. Farmers rely on veterinary medicines including vaccines to keep their livestock healthy and prevent the spread of disease, and any restriction on their access to these medicines could have severe consequences. This could lead to decreased yields, lower quality products, and ultimately, lower profits and threat to their livelihoods.

Similarly, pet owners would also be impacted. The cost of veterinary care is already high, and limiting access to medicines could result in even higher costs for pet owners. This and the lack of suitable medicines that were previously readily available could lead to increased cases of unnecessary euthanasia of pets, which is known to cause a high emotional burden.

In addition, as mentioned before, there would be other spill-over effects on veterinary practices. These businesses rely on medicines and vaccines to operate, and any restriction on access to veterinary medicines could impact their ability to provide quality care and services, and in fact this is an **existential threat** to the entire profession.

Impacts on the market – Competitiveness and competition

Because REACH Restrictions apply to all Animal health companies equally when placing veterinary medicines on the EEA market, **a potential broad restriction of PFAS would disadvantage the animal health companies with EEA-based manufacturing versus non-EEA one**. **Non-EEA manufacturing sites for APIs and VMPs would have a considerable advantage compared to EEA manufacturing both in European and international markets**. Indeed, some of the veterinary medicines that are currently completely produced outside the EEA would not be subject to any restrictions. Namely, those veterinary medicines which are produced with PFAS based materials and equipment but that do not contain any PFAS in the product itself nor in its packaging.

As such, if manufacturing of APIs and VMPS occur fully outside the EEA, they would be able to supply and place on the market a wider range of products, currently preferred and purchased by consumers without bearing any redevelopment costs, while animal health companies manufacturing their APIs and VMPs in the EEA risk a sudden and brutal halt to their capability to produce any veterinary medicine, largely due to PFAS in manufacturing equipment.

The risk of a market concentration in the EEA as a consequence of a restriction, has also been raised by the surveyed companies. **A loss of competitiveness of European manufacturing would be expected in a market that is already facing consolidation**.

In the short term, veterinary medicinal companies might even decide to **move outside of the EEA,** or at least move the manufacturing, in case of a negative regulatory decision and export to Europe non-PFAS containing drugs, with long-term consequences. [62] This scenario has been depicted as the most likely option rather than re-working their portfolios and manufacturing processes, with uncertain outcomes and costly investments, to produce region-specific products (viz., REACH compliant veterinary medicinal products that would serve the EEA market only, an option that is not viable). Furthermore, if PFAS uses in the overall production chain for all APIs would not be derogated, relocating as quickly as possible would be the only solution. **Should the industry move out of the EEA to service the rest of the world, it would result in a significant downsize for medicines manufacturing in Europe**,[63] **and contrary to the EU's objective to rehome production and reduce their dependence on third country manufacturing.**[64]

Impacts on the market – Trade

A broad restriction of PFAS would disadvantage European-based manufacturing facilities in their trade with the rest of the world. Indeed, just as the production of veterinary medicines would turn to non-EEA markets in the short to medium-term, exports of these products would decrease considerably – possibly cease entirely. On the other hand, imports are projected to grow in importance. If the use of PFAS in production (e.g., equipment) will be restricted, the EU animal health industries will have to source finished products from outside of the EU. This will increase the technological and manufacturing dependency of the EU on Asian and other countries and thereby also

62 This option would still be permitted by law as long as PFAS are only used in the production process and no traces of PFAS remain in the final products exported to the EEA.

63 As mentioned before, the animal health industry makes up 3% of the EU pharmaceutical industry.

64 A pharmaceutical strategy for Europe (europa.eu)

affect EU export and import flows. As a result, the **overall EEA trade balance would be adversely impacted**.

Impacts on the market – Innovation and R&D

R&D investments by VMPs manufacturers have been made as a function of both new market technology opportunities and the companies' financial health. **R&D budgets are proportional to revenue, therefore the loss of sales to the EEA market will have an inevitable negative impact on R&D investments and spending**. In a broader context, the current geopolitical situation, supply chain disruptions, and inflated cost of materials have already taken a toll on R&D funding.

In case of a restriction of PFAS APIs, the **current R&D efforts and resources would inevitably be redirected towards researching and developing entirely new APIs and products adapting production processes, re-qualifying, and re-certifying the portfolio of the participating companies**. This will require already reduced R&D resources to be used carefully, as the loss of the PFAS APIs would set therapeutic options back some 30 years in time for a number of therapeutic areas like parasite control and anaesthesia. Choices will have to be made to refill the treatment gaps created this way, versus looking at innovative solutions directed at the future.

A large proportion of ongoing and future research projects relies on PFAS chemicals in a variety of uses in API synthesis, highlighting the importance of poly- and perfluorinated substituents in R&D activities for new APIs. These include the large ongoing investments dedicated to address tomorrow's pathologies and zoonoses. In addition to chemicals for synthesis, analytical lab equipment also relies on materials that fall within the PFAS definition (e.g., seals, tubing in HPLC equipment). **Overall R&D activities for product manufacturing would therefore be largely affected by the current restriction proposal.**

During manufacturing, there are several points where quality control testing is required by sectoral legislation and guidelines. This implies the use of analytical instruments such as HPLC, which contain PFAS, and for which often reagents now qualifying as PFAS are needed. If these uses are not derogated, it will be impossible to even import veterinary medicines into the EEA as such testing must be conducted in the EEA.

The restriction proposal does not contain a derogation for **PPORD** (product and process orientated research and development). This will result in a barrier for R&D in the EEA. It is common for EU pharmaceutical sites to undertake late-stage testing of PFAS APIs with >1 t/y of the API and its isolated PFAS intermediates. This and other R&D activities would no longer be possible if not derogated.

Several of the participating companies have indicated that other pharmaceutical compounds for various therapeutic indications are in various stages of the development pipeline and may now qualify as PFAS. With a broad PFAS-restriction, investments already made in the development of these molecules would be wasted. This would further impact the resources available for innovation.

Several of the key manufacturing sites of the participating companies located in the EEA have been designated as sites which also perform late-stage process development activities, in advance of product filing and launch (both API and drug product manufacturing sites). Key to the mission of these sites is being adaptable and flexible to accommodate the development needs of a dynamic and evolving product pipeline and being able to supply initial launch quantities of medicines for global markets. **If these sites were unable to use PFAS materials during manufacturing, this would significantly reduce their flexibility, and therefore reduce the usefulness of these sites in accommodating a dynamic development pipeline.** As a result, the associated development and manufacturing activities performed by these sites would be shifted to non-EEA locations.

More generally, **broad regulatory restrictions outside of sectoral legislation such as the PFAS proposal, have a negative impact on the attractiveness of the EEA for investment**, including investments in innovation and R&D. Typically, innovation is made for global markets, including EEA, and not for specific regions. The general return on investment (ROI) for research and innovation for VMPs for EEA only is rather limited and the development costs too expensive, lengthy and complex for one single region. The reason is that unlike human medicine, veterinary medicine has to take care of a large variety of species which each require dedicated medicines. Therefore, the market is very fragmented and the market potential for any given VMP is much more limited than it is for human medicine which deals only with one species and this, together with any lack of state subsidies to animal owners for the cost of medicines, is affecting the ROI. **The EEA risks to jeopardize an important field of innovation.**

A ban on PFAS chemicals would impact discovery research activities in the EEA and slow down drug discovery timelines, and potentially lead to less-than-ideal drug candidates if they cannot contain or use PFAS chemicals. This would put EEA research groups at a major disadvantage relative to non-EEA research and drug discovery chemistry sites and will therefore likely lead to decreased investments in these activities in the EEA relative to other regions in the world. The participating companies have also noted that the proposed restriction would have a negative impact on clinical supply production activities and on the ability to run clinical trials of new medicines that contain PFAS in the EEA, which are currently quite substantial. These trends would decrease the level of investment in innovation in the region as R&D activities in the medicines industry would likely shift from EEA locations to non-EEA locations.

Impacts on the market – Sub-contractors

Various **sub-contractors and suppliers, such as contract manufacturing organisations (CMOs) and contract research organisations (CROs), will be negatively affected in the restriction scenario**. The participating companies have noted that these market players perform a variety of functions related to the production of the veterinary medicines according to companies' specifications. CMOs are contracted to produce the (PFAS) API itself in which PFAS starting materials/intermediates are used. These are essential to lead to the final API. Furthermore, some CMOs manufacture the final product formulation, package the final product formulation, 'tablet' a drug product into its final form, and/or conduct product specification testing of the final production.

Thus, a PFAS restriction would lead to **income losses in both the short- and long-term for sub-contractors** and could also lead to the **stop of some CMO API production in the EEA**. This also conflicts with EU strategies to reduce dependency on supply chains located mainly outside of the EU.

Accordingly, as an indirect result of such consequences for subcontractors, a **restriction would affect API development processes, resulting in longer production cycles, inefficiencies, and higher prices for the whole supply chain if not relocated out of the EEA.**

CROs help companies with the conduct of the mandatory quality, safety, toxicology and efficacy studies as animal health companies usually do not have these capabilities and animal facilities in house, or prefer to outsource large clinical field studies required for the authorisation dossier. Those CROs are very specialised and many of them would lose their viability if animal (and human) health companies would no longer place these studies in the EEA, which would inevitably be the case should the restriction proposal remain unchanged.

5. CONCLUSION

This SEA identifies the main potential negative consequences that the EU society at large would face due to the potential REACH restriction of PFAS used in the production of veterinary medicines. It has been performed in line with existing ECHA guidance under REACH and the results are based on a survey focused on the EU animal health industry, with an expected market share coverage of approximately 75% of the EU veterinary medicinal market. It therefore provides sufficiently reliable data for a representative extrapolation to the entire EU market.

The evidence-based findings of this report reasonably justify the exclusion of the whole process of veterinary medicines manufacturing from the scope of the upcoming REACH restriction proposal, on the basis that a broad restriction of PFASs in the manufacturing of veterinary medicinal products will have disproportionate negative impacts on the European economy and society, impacting the security of supply of all veterinary medicines and the future of veterinary medicine in the EEA.

The above statement is founded on the following:

- **The entire process of developing and manufacturing veterinary medicinal products, independently if containing PFAS APIs or not, heavily depends on a number of PFAS chemicals in a wide variety of applications.**

- **A one-to-one replacement is inherently impossible** because a large range of veterinary medicines are developed in a targeted manner for different diseases and species. **There is no evidence of currently technically suitable alternatives** readily available which can substitute PFAS chemicals across their uses as APIs and in the manufacturing process.

- **In the best-case scenario, substituting every PFAS-API-based veterinary medicine can take more than 17 years for each medicine**, when a successful candidate (alternative) has been identified, and would have significant associated costs, including in terms of animal and human health because of the sudden and important treatment gaps in the meantime coupled with an unknown probability of success. Contextually, **substitution of chemicals** such as starting materials not incorporated into the API, solvents, reagents, PFAS-containing and -coated parts in auxiliaries and manufacturing equipment, and analytical method reagents and equipment for in-process control, starting material and product release**, also takes several steps and years, provided that alternatives are available. As downstream users, animal health companies will depend heavily on the capabilities of their global suppliers to offer suitable alternatives**. In addition, where PFAS are used in **packaging materials**, substitution of those will also easily take **more than a decade, provided that alternatives are available,** because of the sheer number of products involved. Apart from capacity constraints at the industry side, regulatory agencies such as the EMA also will be struggling with the vast number of applications filed to get the changes approved. Changes cannot be implemented without prior regulatory approval.

- **In the case of a restriction of PFAS APIs, the total impact is monetised as more than 10 billion EUR,** including social impacts from unemployment in the EEA, substitution costs and economic impacts (EBIT loss) for animal health companies.

- **Even more severe would be the consequences without additional derogations for PFAS materials used in the manufacturing process.** The **total impact of a REACH restriction of PFAS materials is monetised as more than 17 billion EUR.** This is a conservative estimate (lower boundary), on the understanding this is not the sole impact likely to be suffered in the EU.

- **Non-EEA manufacturers would have a considerable competitive advantage compared to EEA manufacturers.** Hence, a PFAS restriction in the EEA will have impacts on the competitiveness of the EEA markets, on the competition in the EEA, on innovation, and on the overall EU trade balance, as EEA companies will be forced to relocate production out of Europe.

Based on the above evidence-based considerations, this report concludes that a broad restriction of PFASs for veterinary medicines manufacturing would not be warranted as their benefits outweigh their risk and such a restriction will have disproportionate negative impacts on the European economy and society.

The use of veterinary medicines is highly regulated in the EU with extensive generation of data and regulatory oversight required along with evaluations and approval processes by European Regulatory Authorities. **The analysis supports the proposed time unlimited derogation for active substances in veterinary medicinal products** on the basis of the importance for the protection of animals and humans from diseases, the welfare of animals and the supply of livestock products for food.

Without additional derogations, the entire Animal Health Industry will no longer be able to manufacture any API (both, classifying as PFAS and non-PFAS APIs) or associated veterinary medicines in the EEA. This would necessitate moving production out of the EEA as the only option, which would require years in itself, plus years of regulatory inspections and approvals. As a result, the supply and availability of veterinary medicines in the EEA will be substantially impacted even in the longer term with new and extensive dependencies on non-EEA manufacturing. In fact, such a situation risk to put some companies entirely **out of business as they would no longer be economically viable.**

Thus, the analysis reasonably justifies the introduction of a time-unlimited derogation of PFAS chemicals as substances required for the manufacture of active pharmaceutical ingredients in veterinary medicinal products, irrespective if the active substance itself is within scope of the PFAS definition or not, on their own, in mixtures or in an article, and covering the following uses:

i. **Starting materials**
ii. **Intermediates**
iii. **Process chemicals**
iv. **Solvents, reagents**
v. **Processing aids**

vi. **Single or multiple use materials**

Equally, a time-unlimited derogation is needed for substances used for the purposes of **scientific research and development (SRD) and product- and process-orientated research and development (PPORD).**

A time-unlimited derogation for fluoropolymer containing packaging (such as e.g., PCTFE, PTFE and ETFE) for veterinary medicinal products, veterinary medical devices, including in-vitro diagnostic devices, and veterinary medical molecular diagnostics should be foreseen. This would broaden the scope and the nature of the provisional derogation in Art. 6.l and is justified by the findings of this SEA

Furthermore, a time-unlimited derogation for fluoropolymers and perfluoropolyethers for the use in industrial (manufacturing) applications should be foreseen, as well as for spare and replacement parts for existing (currently used) machinery during their lifetime. Two of such derogations are already foreseen in Art. 6.a and 6.f. but should also be granted for veterinary medicines sector and modify the nature of the derogation.

In theory, some of these derogations, e.g., for packaging materials or some elements in industrial equipment, could be time-limited, based on the possibility that these uses of PFAS might be able to be substituted with non-PFAS alternatives within a prolonged derogation period. Although the industry will endeavour to ensure that such substitution does take place, **there are currently no alternatives available** and the requirements from the relevant sectoral legislation (Regulation (EU) 2019/6 and associated acts) may be prohibitive. As downstream users, animal health companies heavily depend on their suppliers to develop alternatives in this particularly specialised sector. Also, the validity of any such alternatives would need to be confirmed, together with guaranteed availability and supply. It should be clear that the negative impacts described in this SEA would still occur if such time-limited derogations were to be allowed to expire before it had been possible to effect substitution. Accordingly, they should expire only after it has been confirmed that substitution has taken place and they are no longer required. It would be important that any time-limited restriction would include a requirement to review the proposed derogations before they expire, to assess their continued need, and to revise and/or extend them as necessary and appropriate.

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