AnimalhealthEurope

Contribution
to the consultation of the Annex XV restriction dossier for per- and polyfluoroalkyl substances (PFAS)

Information in support of a time-unlimited derogation of veterinary active substances from the universal PFAS-restriction

Addendum to Submission 5390

S O C I O - E C O N O M I C A N A L Y S I S

Of the potential restriction of the per- and polyfluoroalkyl substances (PFAS) used in the production of veterinary medicines
The viewpoint of the manufacturers of veterinary medicines

As prepared by **EPPA SA/NV**

Information in support of a time-unlimited derogation of veterinary active substances from the universal PFAS-restriction

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1 About AnimalhealthEurope

AnimalhealthEurope represents companies that **research, develop and manufacture veterinary medicines** and other health products in Europe. The 12 companies and 17 national associations who are members of the association cover **more than 90% of the market**.[a] By protecting the health and welfare of more than 1 billion animals across Europe, the veterinary sector contributes to improve both animal and public health, to the production of safe, affordable and sustainable food and to a sustainable environment. The sector represents more than 50,000 direct jobs in Europe. The product portfolio includes vaccines, parasiticides, specialty medicines targeting specific diseases, anti-inflammatory agents, antimicrobials, diagnostics and other health products.

2 Executive summary

The definition of per- and polyfluoroalkyl substances (PFAS) applied within this restriction proposal is very broad which may lead to unintended and potentially far-reaching consequences. Not only does it include raw materials, intermediates and process chemicals used to manufacture veterinary medicinal products (VMPs)– certain active pharmaceutical ingredients (APIs) in these VMPs would also be considered as PFAS since they contain fluorine and match the new definition of PFAS.

These raw materials, intermediates and process chemicals, and/or APIs are critical to certain veterinary medicinal products, and due to the unique properties of fluorine, a direct replacement is virtually impossible. Consequently, restrictions or bans of any of these substances would remove essential disease-treating and life-saving veterinary medicines from the European market. In addition, it would prevent any new such medicines from being introduced to the European market in the future. This would have a major impact on animal health and welfare. **Socio-economic and technical information to support this has been provided in submissions 5390 and 5384**.

Moreover, it would also have a serious impact on public health as some of the conditions that are treated by medicines containing PFAS APIs are zoonotic, which means they can impact human health if the animals are left insufficiently treated, or even untreated. **The present submission provides more details about impacts on animal and human health in support of the proposed time-unlimited derogation for APIs**.

While VMPs are essential for animal and public health, **the volumes of PFAS-APIs used in Europe are low (52T/year)** in comparison to high-volume PFAS uses in other sectors. For example, 45 to 80 thousand tonnes of PFAS are consumed in the textiles sector alone.[b] This limited use (which doesn't equal emissions) results in negligible environmental exposure compared to other compounds and uses.

VMPs are already subject to a thorough and rigorous **regulatory review** under their respective legislations. They can only enter the market after successful completion of a scientific assessment and approval by the competent authorities. The **requirements are similar to or even stricter than those of REACH**, as extensive safety data have to be generated for every API and final VMP regardless of tonnages. This is also the reason why, in principle, VMPS are exempt from certain provisions of REACH. A PBT-assessment of the API is also part of the evaluation prior to market entry. An overview of requirements is presented in **Annex 1** of this submission for easy reference.

[a] Our members - AnimalhealthEurope

[b] https://echa.europa.eu/documents/10162/17233/pfas_in_textiles_final_report_en.pdf/0a3b1c60-3427-5327-4a19-4d98ee06f041?t=1619596551696

As it is critical for animal health and public health that substances used in or for veterinary medicines remain exempt from restrictions, we call on the competent authorities to fully derogate veterinary medicines and their manufacturing from the universal PFAS-restriction.

3 Introduction

The definition of PFAS as a chemical class introduced by the OECD in 2021 and used in the draft restriction dossier results in a number of active pharmaceutical ingredients used in human and veterinary medicine being classified as PFAS, which was not the case with the previously used definition (Buck et al, 2011).[1] The reason for this is that these APIs, being relatively large molecules contain one or a few terminal fully fluorinated carbon atom(s).

Therapeutic areas in veterinary medicine affected by this classification and a potential ban are the following:

- Parasiticides (treating parasitic disease/indirectly preventing pathogen transmission) for use in companion animals and livestock, with companion animal medicines most severely impacted;
- Inhalation anaesthetics used to perform surgical procedures in companion animals and horses;
- Non-steroidal anti-inflammatory drugs (NSAIDS) treating inflammation/pain management in companion animals, horses, and livestock.

The dossier submitters have proposed a time-unlimited derogation for these APIs, referring to **sectoral legislation** regulating the authorisation: Regulation 2019/6 replacing Directive 2001/82. **Other justifications** cited by the dossier submitters are the importance for the protection of animals and humans from diseases, the welfare of animals and the supply of food, and the fact that a general PFAS restriction for these applications could impact the security of supply of veterinary medicines. These three initial justifications have been elaborated further in **submissions 5390 and 5384** to the present consultation. Submissions 5390 and 5384 also contain detailed information on the data requirements pivotal for authorisation, including human, animal, and environmental safety. To note is that Regulation 2019/6 also contains a provision allowing **refusal of marketing authorisation for PBT-substances** (Art 37.j)**.**

However, AnimalhealthEurope was informed that SEAC has indicated that these justifications are not deemed sufficient to justify this derogation and therefore, the present submission provides **clarity regarding tonnages used and emissions of veterinary APIs. Also, the importance and benefits of these veterinary medicines to both animal and human health are described in more detail**.

4 Tonnages used and emissions of veterinary APIs

In the response to the call for evidence by the dossier submitters launched in July 2021, the industry association AnimalhealthEurope has provided information on emissions, as requested by the dossier submitters in their questionnaire:

In the tables presented on this page and the following, '?' in the cells show that the authorities do not have any information available. Input to fill these gaps is highly appreciated.

Sub-Use	Tonnage (tonnes/PFAS) per year in the EEA	Expected trend (--/-/0/+/++)[1]	Emissions/year in EEA[2] (tonnes/PFAS)
Medicines (human pharmaceuticals)	> 500[3]	+	> 500[3]
Medicines (veterinary pharmaceuticals)	?	?	?
Pharmaceutical intermediates[3]	8,200 (ECHA)	?	?

[1] -- = strong decrease, - = decrease, + = increase, ++ = strong increase, 0 = neutral

This information, which was submitted within the proposed time frame of the call, was however not included in the draft restriction dossier. Under Part V- Section B of the questionnaire, the association provided the **aggregated tonnage for these APIs, which amounted to 52 tonnes**, based on a survey within the membership:[c]

> No figures were provided during the first call for evidence. AnimalhealthEurope has conducted a survey within our membership and the results of that survey are: 52T
> It should be noted that these tonnages cannot be directly compared to some other categories of PFAS. In general, just a fraction of the molecules qualifying as PFAS and used in veterinary medicines is fluorinated (i.e. 1 to 3 C-F2 or C-F3 groups attached to the rather large rest of the molecule), making some of these substances only marginally qualifying as PFAS under the broad definition used for this call.

To note is that this is based on the **entire molecule**, and the tonnages relate to **production and use** in the EEA. As part of larger molecules, the fluorinated methyl-group attracts electrons which is used to optimize potency, permeability, and binding affinity of the veterinary medicines. None of the APIs used in VMPs is fully fluorinated. When considering only the PFAS moiety (one to maximum three -CF3 groups on a much larger molecule), **actual emissions of fully fluorinated methyl groups are only a fraction of mentioned total API tonnage**. For example, the molecular weight of substances in the API-group with the highest tonnage ranges between 365.4 and 596.8 g/mol versus the molecular weight of trifluoromethyl radical of 69 g/mol.

5 Data requirements under sectoral legislation Reg. 2019/6

A detailed overview has been presented in submissions 5390 and 5384; this information is included once more in Annex 1, Section 11 of this submission for easy reference.

6 The connection between animal and human health

While the role of livestock in the food chain is obvious and (bio)sanitary measures have been introduced to manage foodborne disease and food safety, the human relationship with companion animals has evolved during the last decades.[2] **The role of pets** has changed from work animals (protecting houses, catching mice) to **animals with a social function**, providing companionship. Pet ownership, or just being in the presence of a companion animal, can have a positive effect on individuals' mental and physiologic health status. Most research addressing **health benefits of pet ownership** focuses on reductions in distress and anxiety, decreases in loneliness and depression, and increases in exercise;[3] the positive effects of pets on persons with cancer, heart disease, and autism spectrum disorder and the economic benefits of companion animals including horses and other species have also been demonstrated.[4] In addition, dogs are increasingly used to assist people with impaired view and other disabilities.

[c] Our members - AnimalhealthEurope

Over the last couple of years, the **"One Health" concept** has been launched, which is defined by the WHO as "an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems. It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are **closely linked and interdependent**.".[d]

Pets undoubtedly have a positive effect on human health, while owners are increasingly aware of their pet's health and welfare. The human-animal bond has therefore been defined as "the dynamic relationship between people and animals such that each influences the psychological and physiological state of the other".[4] For the human however, there may be a **higher risk of transmission of zoonotic infections** (animal pathogens infecting humans) due to trends such as sleeping with pets, allowing pets to lick the face or wounds, bite accidents, keeping exotic animals, the importation of rescue dogs, travelling abroad together with dogs and indirect soil contact.

Close physical contact between owners and their pets is common and poses an increased risk. A study in the Netherlands found that 50% of owners allow pets to lick their faces. Sixty percent of the pets visit the bedroom; 45–60% (dogs–cats) are allowed on the bed, and 18–30% (dogs–cats) sleep with their owner in bed. Six percent of pets always sleep in the bedroom. Of the cats, 45% are allowed to jump onto the kitchen sink.[5] This allows for an **increased risk for animal owners to become infected by parasites and the diseases they may carry**. In addition to parasites, other pathogens such as bacteria, viruses, and fungi can also be transmitted from animals to humans, and vice-versa – often facilitated by arthropod vectors. Not every infected person will become ill, but young children (age < 5 years), the elderly (age > 65 years), patients with an impaired immunity, and pregnant women that carry a fragile foetus are at more than average risk of becoming ill after an infection.[2] Many of these pathogens are not reportable and presumably underdiagnosed or not recognized as such by family doctors due to the often-unspecific nature of mostly flu-like symptoms. Therefore, any reported frequency of such infections is likely underestimated.[2]

Most of the APIs now qualifying as PFAS under the OECD definition are parasiticides, predominantly used in companion animal medicine. Section 7 of this submission provides more detail on parasitic diseases and the risk to human health.

7 Companion animal parasiticides

7.1 Definition and importance of parasites in animal health[6]

Parasitoses are diseases caused by parasitic infection/infestations. Parasites are defined as eukaryotes needing one or several mandatory vertebrate or invertebrate hosts for their development (feeding, evolution, reproduction) and survival. Parasites can be unicellular eukaryotes (i.e. protozoans) or multicellular eukaryotes (i.e. helminths (worms): nematodes, cestodes, trematodes, or arthropods (insects: e.g. fleas, mosquitoes or acarians: e.g. ticks, mites)).

Parasites can have a superficial location on their host (ectoparasites) or an internal location in the intestinal tract, tissues, organs, and/or blood (endoparasites). Some parasites can infect/infest both animals and humans therefore being responsible for so-called "**zoonotic diseases**", diseases which are caused by agents that can be spread between animals and people. Some parasites, in particular parasitic arthropods like ticks and mosquitoes, are major vectors of disease-causing agents, including viruses, bacteria, protozoans, worms.

[d] https://www.who.int/health-topics/one-health#tab=tab_1

Parasitoses are very common infectious diseases affecting all animal species and humans worldwide and can have **significant health and welfare consequences**. Parasites have simple to very complex life cycles that may involve one or several hosts, and in-host only or free phases in the environment.
Ectoparasites live on animals' surface, such as the skin (e.g. fleas, ticks), ear canal (ear mites), hair follicles or epidermis layers (mange mites (scabies), *Demodex* mites), or hairs (lice). Ectoparasites can be permanent parasites (e.g. fleas, lice, mites), temporary parasites (e.g. ticks) or intermittent parasites (e.g. mosquitoes, sandflies).
Endoparasites live in animals' tissues and organs, such as the intestine (roundworms, tapeworms, hookworms, protozoans *Giardia* and *Coccidia*), the heart (heartworms), lungs (lungworms), blood (piroplasms), but many other organs can also be affected by other parasite species, such as urinary bladder, oesophagus, liver, kidney, eye, brain, etc. Some parasites may have a wide tissue distribution like *Leishmania*, *Toxoplasma.*

Parasites may harm their host by spoliation (taking away resources), mechanical (causing tissue damage) and/or immune effect, or by disease transmission.

- Spoliation depends on the number of parasites and the duration of the infestation. For example, an important flea or tick infestation may cause anaemia, as a consequence of an important blood feeding severely weakening the host. The common *Toxocara* ascarids (gastro-intestinal roundworm) may induce deficiency in nutrients such as vitamins, minerals, or amino acids.
- Harmful mechanical effects are caused by the parasite numbers and locations. For example, heartworms positioned in the pulmonary artery may cause venous and right heart hypertension, tapeworms or roundworms may cause intestinal impairment and obstruction, lungworms located in pulmonary arterioles cause alveolar necrosis by infarction. Mechanical damages may also be caused by the tissue migration of endoparasites, for example ascarid larvae that migrate through the liver. Mechanical damages may be induced during the feeding activity of the parasite, for example *Ancylostoma* hookworms that blood feed through the intestinal membrane.
- Protozoan parasites within the gastrointestinal tract (*Eimeria*, *Isospora* or *Cystoisospora*) cause disease especially in young animals (kitten and puppies as well as e.g. rabbits) with severe diarrhoea, anorexia leading to impaired growth.
- In many cases, local and general immune reactions are caused by the parasite's presence and activity with clinical consequences, such as flea allergy dermatitis consequent to flea bites, immune complexes consequent to heartworm antigens released in the blood stream, kidney failure during leishmaniosis, immune hemolysis during babesiosis/piroplasmosis, etc.
- Some ectoparasites (mainly ticks, mosquitoes, sandflies and fleas) are important vectors of infectious disease agents, including viruses (e.g. encephalitis virus), bacteria (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 immiti*s agent of Dirofilariosis), tapeworm (*Dipylidium caninum*) (Colella et al., 2020;[7] Skotarczak, 2018;[8] Steinbrink et al., 2022[9])
- Some parasites are zoonotic (Colella et al., 2020[7]), meaning that they may also harm humans, such as *Ancylostoma*, *Toxocara*, *Dirofilaria repens*, *Echinococcus granulosus and Echinococus multilocularis, Leishmania infantum, Toxoplasma gondii* and others, with sometimes severe or even fatal consequences.

The importance of parasite control in animals to protect both human and animal health is illustrated in the following table.

Summary table: why control parasites in companion animals?[6, 10, 11]

Parasitic diseases can be severe and deadly, at minimum they induce clinical symptoms	
Ectoparasites	
	Fleas 1- directly: responsible for skin irritation caused by the bites and flea allergy dermatitis (itching, hair loss, excessive discharge of sebum (an oily excretion from the skin), secondary skin infections) 2- indirectly: vector of disease agents (Bacteria: *Mycoplasma, Bartonella, Rickettsia,* and the tapeworm *Dipylidium*)
	Ticks 1- directly: responsible for anaemia, paralysis 2- indirectly: vector of disease agents inducing very severe, often deadly disease (Virusses: tick encephalitis; Bacteria: Lyme disease, *Ehrlichia, Anaplasma, Rickettsia;* Protozoans: *babesia, Cytauxzoon, Hepatozoon*; worms: *Filariae*)
	Others: mite agents of scabies (severe disease), demodicosis (severe disease), ear mange (severe disease), cheyletielliosis (cat scratch disease in humans); lice agents…
Endoparasites	
	Nematodes: - **causing mild disease**: roundworms, hookworms, whipworms, eyeworms, - **causing severe disease**: lungworms, heartworms…
	Cestodes: - **causing mild disease (to the pet)**: tapeworms including *Dipylidium*, *Taenia*, *Echinococcus*
	Protozoa: - **causing mild to severe disease:** Coccidia
Protecting pets to protect humans	
Severe zoonotic disease risks from pets	i. Larva migrans (worm larvae entering the human body and migrating to several organs including the brain and causing disease) due to ingestion of roundworm eggs: reservoir of roundworms are dogs (*Toxocara canis*) and cats (*Toxocara cati*) ii. Larva migrans due to infection by hookworm larvae: reservoir of hookworms are dogs and cats (*Ancylostoma caninum, Ancylostoma tubaeforme, Ancylostoma braziliense, Ancylostoma ceylanicum*, +/- *Uncinaria stenocephala*) iii. Echinococcosis (disease caused by tapeworms) due to ingestion of *Echinococcus* eggs. Dogs are definitive hosts for *E. granulosus* and *E. multilocularis*. Cats may be infected by *E. multilocularis*. Dogs and cats may contaminate the environment with tapeworm segments and eggs.
Mild zoonotic disease risks from pets	i. Flea bites inducing itching, papules; pets are natural hosts of fleas ii. Cat scratch disease (*Bartonella* spp. infection): normal cycle between cats and fleas iii. Flea borne spotted fever in human: *Rickettsia feli*s vectored by fleas iv. Mite infection (*Cheyletiella, Sarcoptes*) inducing itching, papules

Particular case = Ticks and Tick-borne diseases (TBD)	
Dogs, cats, and humans are equally victims. Reservoir of ticks and tick-transmitted pathogens are mainly the wild fauna (deer, rabbits, hares,…) with some exception like the brown dog tick *Rhipicephalus sanguineus* where dogs are the reservoir.	
	- Lyme disease is vectored by *Ixodes* forest ticks, reservoirs are rodents and deers - Tick borne encephalitis: reservoirs are rodents, again vector are forest ticks *Ixodes* - Risk related to dogs: Mediterranean spotted fever (*Rickettsia conorii*) vectored by *Rhipicephalus sanguineus*.

7.2 Are ectoparasitoses and vector borne diseases common in animals and humans?

Fleas are the most common ectoparasite found on dogs and cats, with prevalence of infestation ranging from 5% to 50% in the pet population in Europe and USA, at any time around the year, depending on their mode of life and history of treatment (Beugnet et al., 2013).[10] Fleas are vectors of various pathogens including zoonotic agents (Spitalska et al., 2022).[12] Around 4-20% of these fleas are infected with Bartonella (the agent of human cat scratch disease), 10-40% are infected with Rickettsia spp. (including the agents of human flea spotted fever), and 4% are infected with Dipylidium tapeworm larvae (Abdulla et al., 2019;[13] Beugnet et al., 2014;[14] Beugnet et al. 2018[15]). Flea Allergy Dermatitis is the most common allergy diagnosed in dogs and cats, and the first reason for dermatological consultation in dogs and cats, approximately 1% of dogs and cats are affected with this allergy (Guaguère et Beugnet, 2008[16]).

Ticks are observed on dogs at a prevalence of around 10-15% at any time and 2 to 7% in cats. *Ixodes*, *Dermacentor* and *Rhipicephalus* are the 3 major tick genera in order of frequency in western Europe (Beugnet et al., 2014;[14] Geurden et al.,[17] 2018; Schäffer et al., 2019[18]). *Rhipicephalus* being the most common in the Mediterranean area. Ticks are major vectors of various pathogen agents (viruses, bacteria, Rickettsia, protozoans and helminths), many of these being zoonotic agents (Hansford et al., 2022;[19] Steinbrink et al., 2022[9]). Around 5-30% of Ixodes are infected by Borrelia (Lyme disease), 5% by Anaplasma, up to 20% by Rickettsia. Around 5-10% of Dermacentor ticks are infected by *Babesia canis*, agent of the deadly piroplasmosis in dogs. Around 2-10% of Rhipicephalus ticks are infected by Ehrlichia/Anaplasma, 5-10% by Rickettsia and 2-4% by *Babesia vogeli*, another agent of piroplasmosis in dogs (Dantas-Torres et al., 2019;[20] Nguyen et al., 2020[21]).

Mites:
Globally, the prevalence of *Sarcoptes scabiei* in pet dog, the zoonotic agent of scabies (skin mange) is estimated to be 1.2% (Chen et al., 2014[22]).
In Europe and USA, the prevalence of *Otodectes cynotis* (the agent of ear mange) ranges from 10 to 50% in cats, 5 to 10% in dogs (Beugnet et al., 2014;[14] Beugnet et al., 2018[6]).
In Europe and USA, the prevalence of *Demodex canis* ranges from 30 to 50% in pet dogs, fortunately only 1% would develop severe clinical demodicosis (Rahman et al., 2021[23]).

The current climate changes, with a decrease of winter periods and negative temperatures, are introducing epidemiological changes in ectoparasitoses and vector borne diseases (Beugnet et Marié, 2009;[24] Carlson et al., 2017;[25] Ogden et al., 2016[26]). The Mediterranean tick, Rhipicephalus, is expanding to the north of Europe (Beugnet et al., 2009[24]). The same geoexpansion is observed from south to north and east for mosquitoes and sandflies. It creates a geoexpansion of severe vector borne diseases like cardiovascular dirofilariosis (heartworm disease), leishmaniosis, and canine monocytic ehrlichiosis in Europe (Mendoza-Roldan et al., 2020[27]). The best and most recent available ectoparasiticidal products are important to control these increasing risks.

7.3 Current availability of companion animal ectoparasiticides and impacts of a ban

There are a number of classes of parasiticides that can be used in companion animals, however, a ban on PFAS using the OECD 2021 definition would eliminate the most modern active substances used in the treatment and control of external parasites in cats and dogs.

Please refer to the confidential part of this submission for a detailed overview.

Given the variety of species, individual intolerances, and some breed-related sensitivities, it is important for veterinarians to have sufficient treatment options available. Some examples to illustrate the practical complexity beyond the primary goal of providing effective treatment and prevention against ectoparasites include:

- A cat may not tolerate administration of tablets, thus for this cat, a spot-on or collar may be a better option.
- Certain breeds have genetic hypersensitivity to specific classes (e.g. macrocyclic lactones), which may result in mortality when used.
- A dog may be allergic to some flavours used in certain tablets and therefore "non-oral" formulation types may be preferred.
- An owner may have personal preferences and may not be able (e.g., for cost reason) or wanting to afford certain "modern" ectoparasiticides so might prefer, e.g., a generic product containing well known active ingredients launched 20 years ago.
- Specific and unique properties of individual product classes are needed (e.g. to prevent biting/blood uptake and pathogen transmission by flying vectors via repellent activities of topical products).
- Some owners may prefer tablets over spot-ons or collars.
- Certain feline/canine individuals may not support the smell of certain products.

All these factors can impact parasite control, with consequences for animal health and increased risks to owner's health. Therefore, it is important to have a broader set of products and formulations available.

Removal of products containing PFAS substances (as defined by OECD, 2021) would make ectoparasite control of pets more complicated. It also must be noted that molecules now qualifying as PFAS are part of a considerable number of fixed combination products treating both external and internal parasites, which would need to be withdrawn from the market as well. **This leaves an important gap and will make treatment more complicated, less effective, and more costly**. Overall, this may result in substantially reduced treatment options, compliance and lower control of ecto- & endoparasites as well as lower prevention of vector borne diseases, increasing the risk to human health.

In addition, **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 parasites. 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 (Rust et al., 2015[28]). A relevant parameter for resistance development is selection pressure on parasites. The alternate use of molecules belonging to different classes with different modes of action is one important element in the reduction of resistance selection (Obaid et al., 2022[29]). Therefore, as a consequence of a potential PFAS ban, **having only a limited spectrum of remaining insecticide/acaricide-classes to treat animals will increase the risk of development and spread of resistance**, and thus will reduce the number of available antiparasitic formulations even further.

In summary, the current spectrum of ectoparasiticide application forms in pets includes topical administrations (spot-on), collars, oral administrations (tablets, chewable tablets) and injections. Their modes of action are insecticidal, acaricidal, repellent or by inhibition of insect growth. All of them have their advantages and, as detailed above, may be preferred for individual reasons. Reducing the choice due to PFAS-bans of whole molecular classes will **considerably impact the ectoparasite control options in pets** and the animal owner's treatment behaviour. With a ban, the newest, widely used and highly important ectoparasiticides with rapid onset of activity and favourable safety profile will disappear from the market. Available alternatives may not suit in all cases and may lead to non-compliance or complete stop of recommended treatment protocols. This would increase the risk of transmission of vector-borne pathogens, even to humans, and - in the former case - of resistance development.

7.4 Impact on innovation

The innovation cycle has been described in full detail in submissions 5384 and 5390 and is also illustrated in a peer-reviewed publication by Selzer and Epe (2021).[30]

The confidential part of this submission contains more detailed information on evolution and specific impacts.

Restricted availability of modern endectocides will mean multiple different products (up to 4) must be prescribed to achieve the same parasite coverage - likely leading to significantly lower compliance on the part of the pet owner and increased lapse in protection against zoonoses and potentially deadly diseases. Veterinarians would likely need to procure multiple, older products outside of typical vendor relationships in order to provide products that have the appropriate coverage for their patient needs.

Other scenarios or arguments are conceivable but lead to the same conclusion: any ban on PFAS APIs will considerably reduce the freedom of choice, especially, while not only, in the pet ectoparasiticide-segment. This will require a laborious effort of the veterinary community to avoid a **negative impact on animal-welfare, but also on human health due to the increased risk of zoonotic parasite and pathogen transmission**.

In summary, a ban of PFAS APIs will remove the most recent innovative medicines off the market, while an innovation cycle for a new parasiticide takes **up to 17 years** (+ up to 2 years for regulatory review and approval), especially for parasiticides, for a successful candidate substance. When looking to replace a product with certain therapeutic indications (as would be the case here), in practice, **it may take several failed innovation cycles (and many more years or even decades) before a true replacement can be found. In the worst case, despite all efforts, an adequate replacement may not be found.**

8 Livestock parasiticides

A restriction banning veterinary APIs would also have consequences for livestock health and welfare. In swine, ruminants and poultry production, a single PFAS API (in prescription only medicines for veterinary use) plays a pivotal role for the treatment of coccidiosis. **This would take away the only veterinary medicines available to treat protozoal disease caused by Cryptosporidium, Eimeria, and Cystoisospora.**

Coccidiosis is a protozoal disease caused by Eimeria species that affects the small intestine and causes scour in suckling piglets. It is characterised by severe diarrhoea that can significantly increase

the mortality rate within a herd. Pigs that are infected shed oocysts (coccidia 'eggs') that contaminate farms. Piglets are infected during the first week of life following the ingestion of oocysts that have sporulated in their environment.

There is currently no vaccine and no approved treatment alternative for coccidiosis in pigs on the market. Coccidiocides are effective for the control of infection. These are medicines that impede the development and shedding of coccidia. Metaphylactic administration of a coccidiocide, has also shown to improve performance. This is due to its positive effect on subclinical infections. The timing of the treatment intervention is significant in order to disrupt the development cycle of parasites. That is the reason why early intervention is more effective.

It is known that coccidiosis disease can facilitate the growth of bacteria such as Clostridium perfringens and can lead to sudden proliferation and bacterial-induced diarrhoea (Mengel et al. 2012[31]).

Apart from causing animal suffering and mortality, coccidiosis is a costly disease for the pig industry and can cause significant economic losses for pig farmers. The results of Western-European studies have shown that coccidiosis is prevalent on 75-76% of pig farms, with 40-100% of piglets on a farm being infected regardless of the farm's level of hygiene. As coccidiosis can cause diarrhoea, damage to the intestinal mucosa, and decreased weight gain in affected pigs, this leads to losses of up to 1,000 grams by weaning age and extending the fattening period. It also increases feed costs, mortality rates, and antibiotic use. The associated estimated cost of production per piglet at weaning is 1-3 EUR and can reach 3-7 EUR per pig at the end of the fattening period. Without treatment, the potential losses for the swine industry in the EU would be around 12-36 M EUR per year for weaned piglets and 12-84 M EUR per year for all slaughtered pigs. [e]

Coccidiosis in ruminants is a disease of lambs and calves mainly. Intestinal colonisation by pathogenic Eimeria in ruminants (*E. oviniodalis, E. crandallis in lambs and E. bovis, E. zuernii, E. alabamemsis* in calves) can lead to symptomatic disease (colic and pain, diarrhoea) or, more frequently, to subclinical cases leading to animal suffering and reduced weight gain.

In addition, **PFAS-APIs for deworming** in sheep play a significant role in terms of fighting anthelmintic resistant nematodes (i.e. alternating treatment regimes).

Finally, **another PFAS-API is used to treat poultry red mite** (*Dermanyssus gallinae*) infestation in chickens. Poultry red mite is a parasite that feeds on the blood; infestations can cause irritation and restlessness of the bird, feather pecking and anaemia (low red blood cell counts). Egg production may also be affected. For the treatment of poultry red mite infestation this PFAS-API represents the only viable alternative to the extensive use of biocides, which are even not approved in all member states.

9 Inhalation anaesthetics

The Member State report on medicinal products identifies desflurane, isoflurane and sevoflurane as PFAS-APIs (Table 1, page 4). These (and e.g., enflurane) are inhalation anaesthetic agents used for induction and maintenance of general anaesthesia during (complex) surgical procedures in veterinary practices and clinics. They are used in dogs, cats and horses, and in humans[f]. Especially isoflurane and sevoflurane are used in human and veterinary medicine.

[e] Ózsvári L. Production impact of parasitism and coccidiosis in swine. J Dairy Vet Anim Res. 2018;7(5):217–222. DOI: 10.15406/jdvar.2018

[f] Sevoflurane: Uses, Interactions, Mechanism of Action | DrugBank Online

The anesthetics are used under controlled conditions in veterinary surgeries in limited circumstances. As such, environmental exposure would be negligible.

Neither isoflurane nor sevoflurane are metabolized to any major extent in dogs and would be excreted unchanged.

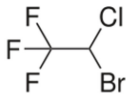
There would not be any unused medicine, as the products would be used on various patients until depletion of the containers. The latter are disposed of or refilled if still suitable in specialized facilities.

Benefits

Isoflurane and sevoflurane provide adequate anaesthesia, they give a rapid induction and recovery, and provide adequate analgesia.[32] Like other anaesthetics such as halothane, they cause dose-dependent cardiopulmonary depression but at minimal alveolar concentration and at an acceptable level. Relative speed of induction is faster for sevoflurane than isoflurane, and all a great deal faster than halothane was; whilst in recovery from prolonged anaesthesia, the difference between isoflurane and sevoflurane is not as great. These substances 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.[33] This cannot be achieved by injectable (pre)anaesthetics.

Potential alternatives

An alternative, the use of which has been largely abandoned in both human and veterinary medicine, is halothane[32]. However, halothane also qualifies as a PFAS:



Other potential alternatives include injectable opioids, ketamine, propofol and combinations thereof. However, these can only be used for very short surgical procedures. These products are actually used as pre-anaesthetics before intubation and use of inhalation anaesthesia.

Conclusion

Isoflurane and sevoflurane are **essential** to allow surgical procedures in dogs, cats and horses. All possible inhalation alternatives also qualify as PFAS. 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. This would be devastating for animal health and welfare. They are also used in human medicine. In addition, they are already regulated by the EU legislation under the supervision of the EMA and National Competent Authorities in the Member States.

Veterinarians would have to resort to injectable anaesthetics for complex surgery which entails more risk for the patients as any adverse reaction while under anaesthesia cannot be rapidly reverted, unlike with the inhalation anaesthetics. Because of this, veterinarians would be reluctant to perform some of this surgery (e.g., hip replacements, quite common in dogs), resulting in reduced treatment options for a variety of conditions in the EU, whereas these will still be available elsewhere, including in the UK. It is therefore not unlikely that some pet owners would seek treatment for their pets in that country or elsewhere.

10 Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, including long-term pain caused by arthritis, reduce inflammation, and bring down a high temperature.

Prostaglandins that promote inflammation, pain, and fever are produced within the body's cells by the enzyme cyclooxygenase (COX). There are two COX enzymes, COX-1 and COX-2. However, only COX-1 produces prostaglandins that support platelets and protect the stomach.
NSAIDs block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support platelets and blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding.

Although NSAIDs are commonly used, not every NSAID is suitable for every individual and side effects may occur. They have been increasingly used in human and veterinary medicine though to replace corticosteroids such as prednisolone and cortisone, as these are known to have more and more serious side effects.

While several NSAIDs are available for use in humans, the arsenal in veterinary medicine is much more limited. Here again, different tolerance is observed depending on species, breed, and individuals and therefore, a wider choice of products is required to ensure adequate treatment options to treat inflammation, pain and fever in companion animals as well as livestock.

NSAIDs are not used as a mass medication to treat multiple animals in a flock or herd; they are used only in individual animals and after careful consideration of product deemed suitable for that individual.

Some of these APIs now qualify as PFAS and, given the limited number of alternatives available for veterinary medicine in this class, a ban would create treatment gaps in this therapeutic area and considerable animal welfare issues.

Please refer to the confidential part of this submission for specific examples.

11 Annex 1: data requirements under Regulation 2019/6

***Development phase*:** At this point in the innovation cycle, 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. 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 (EUR-Lex - 32021R0805 - EN - EUR-Lex (europa.eu)). The ultimate objectives of these studies are to demonstrate the quality, safety and efficacy of the final veterinary medicinal product and requires research in the following areas:

- Quality documentation:
  - Composition and general characteristics of the product
  - Detailed description of the manufacturing method and its validation
  - Detailed description of the active ingredient and its properties
  - Detailed description of the packaging, including tests on potential interactions with the product
  - Development and validation of assays for the actives and other ingredients of the product
  - Control tests on the actives, intermediates, and finished product
  - Microbiological control tests
  - Batch to batch consistency (requiring several test batches to be produced and analysed)
  - Stability testing of both the active ingredient and the finished product under various climatic conditions – up to 5-year stability testing to be provided on full batches
  - Other tests inherent to the type of product
- Safety documentation:
  a) Safety tests:
  - Pharmacology (pharmacokinetic and pharmacodynamic studies)
  - **Toxicology** (acute, repeated dose and chronic tests, mutagenicity, carcinogenicity, teratogenicity, reproductive toxicology)
  - Other safety studies (special studies, observations in humans, development of resistance (antibiotics, parasiticides) and related risks in humans
  - **User safety assessment** (safety for the person administering the product, including sensitisation, dermal and ocular irritation, accidental self-injection etc)
  - **Environmental risk assessment** (PBT-screening, environmental fate and effects studies (terrestrial and aquatic))

  b) Residue tests (for products used in food-producing animals to ensure consumer safety)
  - Absorption, distribution, metabolism and excretion of residues
  - Depletion of residues from the various tissues over time
  - Development and validation of **analytical methods** for each of the tissues for control of residues
- Efficacy documentation:
  - Preclinical studies:
    - Pharmacology (pharmacokinetics, pharmacodynamics)
    - Development of resistance and related risk in animals
    - Dose determination and confirmation
    - Tolerance in the target animal species (testing of overdoses, potential adverse effects, safety margin)
  - Clinical studies
    - Results of pre-clinical studies (usually lab-based studies)
    - Results of clinical trials (experiments in the field under real-life conditions in farms or small animal veterinary practices

The EMA has an extensive list of detailed studies required to complete this documentation: Scientific guidelines for veterinary medicines | European Medicines Agency (europa.eu).

Even in this third stage, compounds may fail, usually on efficacy or safety issues.

***Authorisation*:** this process starts when all the studies listed in the development phase are completed and a regulatory dossier has been written and compiled (6 months – requirements according to Commission Regulation 2021/805). The procedures that can be used to obtain a marketing authorisation are described in detail in Regulation 2019/6 (https://eur-lex.europa.eu/eli/reg/2019/6/oj). This process takes 1.5 to 2 years on average. For food-producing animals, prior to authorisation, a maximum residue limit (MRL) needs to be established (EUR-Lex - 32009R0470 - EN - EUR-Lex (europa.eu)) and this process also takes 1.5-2 years, but may be started once the required documentation is ready, and prior to the product authorisation process.

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