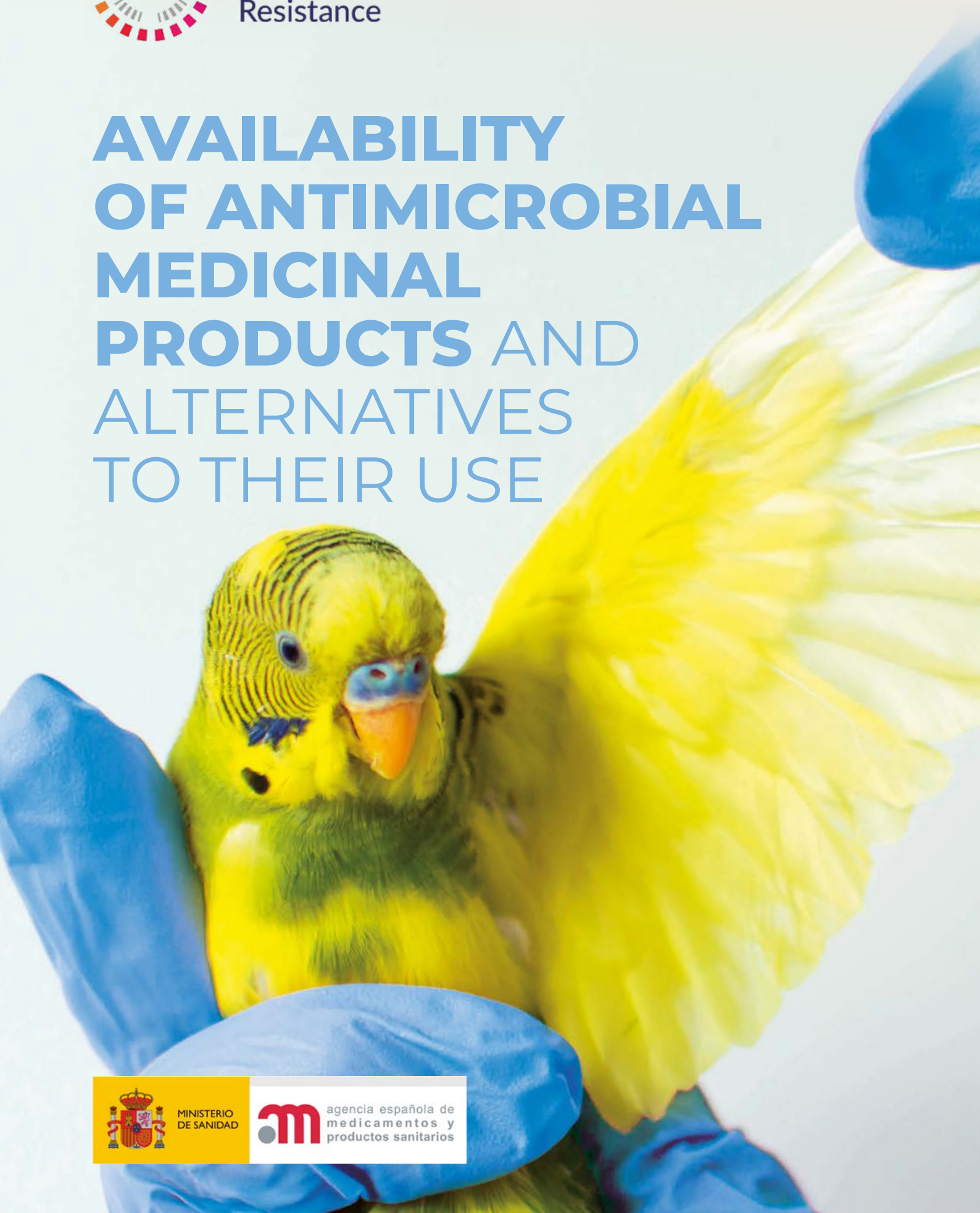




Spanish Action Plan
on Antibiotic
Resistance

AVAILABILITY OF ANTIMICROBIAL MEDICINAL PRODUCTS AND ALTERNATIVES TO THEIR USE



MINISTERIO
DE SANIDAD



agencia española de
medicamentos y
productos sanitarios

**Spanish Agency for Medicines
and Medical Devices (AEMPS)**

Calle Campezo, 1, Edificio 8 • E-28022 Madrid

<https://www.aemps.gob.es>

<https://resistenciaantibioticos.es>

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AUTHORS

SPANISH NATIONAL ACTION PLAN ON AMR (PRAN)

Cristina Muñoz Madero
Alejandro Platt Orzáez
Carmen Pastor Alcaide
Cristiana Teixeira Justo
Guillermo Cubillo Dapena
María J. Vilar Ares
Sagrario Muñoz Ronco
Sara Sacristán Álvarez

SPANISH AGENCY OF MEDICINE AND MEDICAL DEVICES (AEMPS)

Ramiro Casimiro Elena
Cristina Ballesteros Tercero
Marta Ayllón Morales

FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS (ANMV)

Christine Miras
Flore Demay
Justine Timonnier
Laetitia Leletty
Laure Baduel
Laurent Fabry
Sylvie Louet

PORTUGUESE DIRECTORATE GENERAL OF FOOD AND VETERINARY (DGAV)

Ana Avelar
Ana Paula Maças Caldeira Pinto
Andrea Cara D'Anjo
Inês Martins de Almeida
João Pedro Duarte Silva
José Manuel Costa

IRISH HEALTH PRODUCTS REGULATORY AUTHORITY (HPRA)

Juliana Camargo Teixeira

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ABBREVIATIONS

AEMPS	Spanish Agency of Medicine and Medical Devices
AFVAC	French Association of Veterinarians for Companion Animals
AM	Antimicrobial
AMR	Antimicrobial resistance
ANMV	French Agency for Veterinary Medicinal Products
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
API	Active Pharmaceutical Ingredients
ATAm	Alternatives to antimicrobials
ATU	Authorisations for temporary use
AVEF	French Association of Equine Veterinarians
CAPs	Centrally authorised products
CODI-VET	Committee on Availability of Veterinary Medicinal Products
CSMV	Veterinary medicinal products monitoring committee
CVMP	Committee for Medicinal Products for Veterinary Use
DAFM	Irish Department of Agriculture, Food and the Marine
DGAV	Portuguese Directorate General of Food and Veterinary
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
RFSA	French Animal Health Network
GMP	Good Manufacturing Practices
HPRA	Irish Health Products Regulatory Authority
HMPs	Human medicinal products
MA	Marketing authorisation
MAH	Marketing authorisation holder
MAPA	Ministry of Agriculture, Fisheries and Food
MS	Member State
MRL	Maximum residue limits
NCA's	National competent authorities
PRAN	Spanish National Plan against Antibiotic Resistance
PRESVET	Veterinary antibiotic prescriptions monitoring systems
SNCTV	National society of technical veterinarians group
SPC	Summary of Product characteristics

SPOC	Single Point of Contact
UPD	Union Product Database
VMP	Veterinary medicinal product

SUMMARY



SUMMARY

Antimicrobial resistance (AMR) is recognised as a major global threat to human, animal and environment health. The European Union (EU) One Health Action Plan against AMR published in 2017 highlighted the need to support the development of alternative and novel therapeutic approaches for the treatment or prevention of infectious diseases. Besides, the [European medicines agencies network strategy to 2025](#) emphasized the need to strengthen the availability of medicines and to optimise the path from development and evaluation to access for medicines. In addition, the veterinary medicinal products [Regulation \(EU\) 2019/6](#) provides incentives to stimulate innovation like veterinary limited markets, and incentives to increase the availability of veterinary medicinal products (VMPs), strengthens EU action to fight AMR through specific measures ensuring prudent and responsible use of antimicrobials in animals, including reserving certain antimicrobials for the treatment of infections in people. The Regulation improves the functioning of European internal market for veterinary medicines, not least by publishing information on the availability of VMPs in the [Union Product Database](#) (UPD) in collaboration with the EU Member States (MS) serving as a single source of information on all VMPs authorised within the Union.

Notwithstanding these initiatives, the veterinary sector has several challenges due to its peculiarities such as the vast diversity of animal species and breeds, the safety and environmental implications, the complexities of VMPs formulations, and the market characteristics, which is much more fragmented than the human sector.

All European countries share similar challenges in the veterinary sector, although each one with its own particularities. [The French Agency for Veterinary Medicinal Products](#) (ANMV) and the [Spanish Medicines and Medical Devices Agency](#) (AEMPS) had been working to identify therapeutic gaps and their causes and possible alternatives, and to define the priorities. Therefore, they created a working group on antibiotic availability together with the [Portuguese Directorate General of Food and Veterinary](#) (DGAV) and the [Irish Health Products Regulatory Authority](#) (HPRA) has showed interest in joining the group.

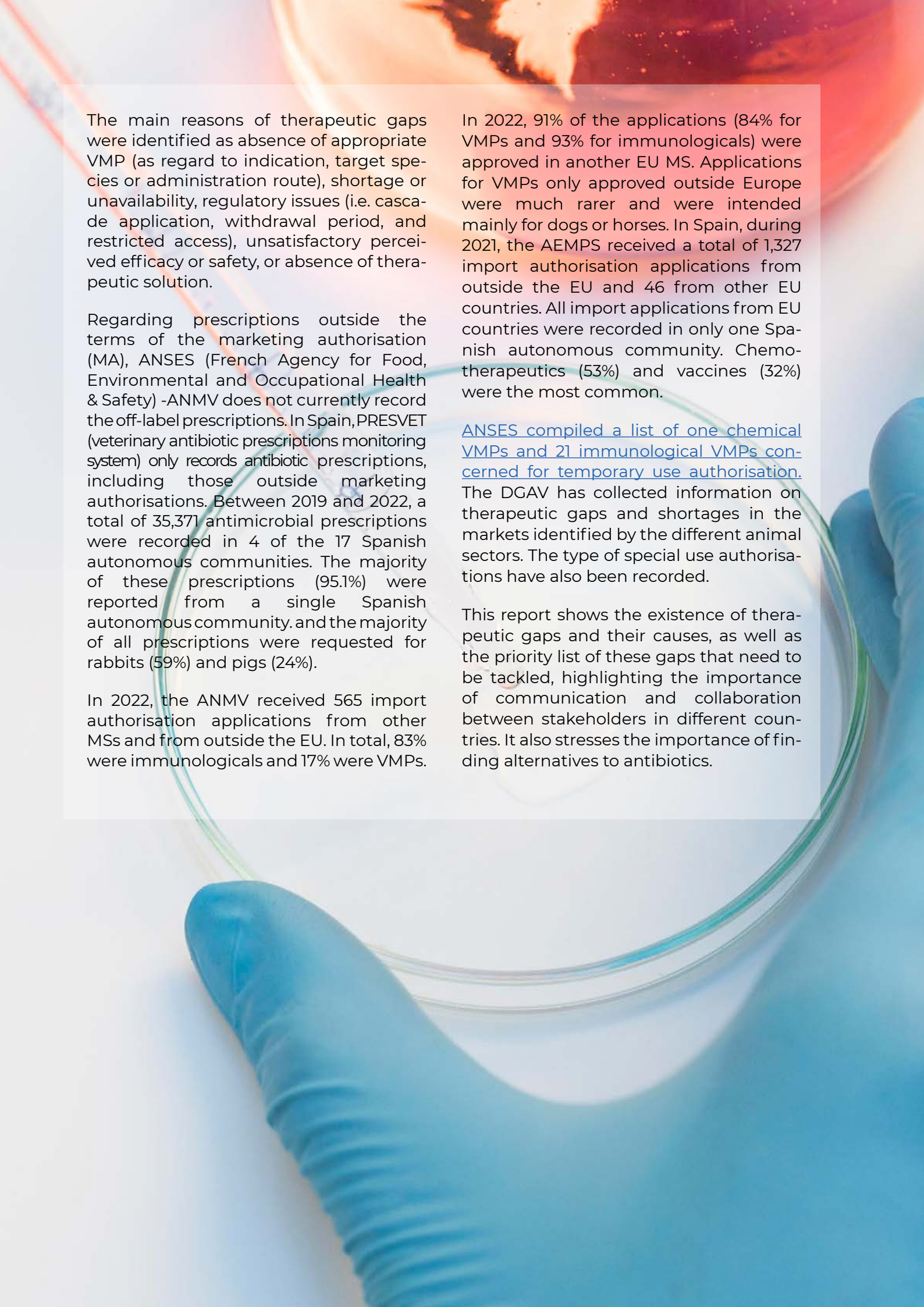
All European countries share similar challenges in the veterinary sector, although each one with its own particularities.

The objectives of the working group are to:

- Identify the therapeutic gaps and recognise the reasons for those gaps.
- List (prioritise) the therapeutic gaps based on their consequences for human, animal and environmental health, and for the economy and food safety.
- Establish ways of collaboration between countries to address common problems.

The ANMV, the Animal Health Network (RFSA) in France, the National Action Plan on AMR (PRAN) and the Committee on Availability of VMPs (CODI-VET) in Spain have met and worked with members of veterinary technical associations and other stakeholders. The main identified therapeutic gaps by sector were:

Sector	Therapeutic gaps	
	France	Spain
Bees	Varroosis	Varroosis
Cattle	Ocular infections and teat injury. Respiratory mycoplasmosis	Coccidiosis, respiratory infections and leptospirosis
Fish farming	Products for external parasitism	Products for external parasitism. Flavobacteriosis, furunculosis, pasteurelosis, tenacibaculosis vibriosis
Equine	Non-critical antibiotics for intravenous injection and chondroprotection	Theileriosis and sepsis
Goats and sheep		For cryptosporidiosis and mastitis, and absence of anti-inflammatory drugs
Goat	Respiratory pasteurellosis and mastitis by mycoplasma	Mycoplasmosis, coccidiosis and respiratory infections
Sheep	Gastrointestinal Strongylosis	Respiratory disease complex
Poultry	Fever and inflammation in viral infections in laying hens (absence of possible anti-pyretics in laying hens)	Respiratory infections, red mite and tapeworm infestations in laying birds Salmonella, enteric and respiratory infections, and haemorrhagic enteritis in broilers and turkeys
Swine	Neonatal diarrhoea due to enterococci or rotavirus, influenza Remarked disappearance of medicated feed and premixes	Diarrhoea by rotavirus in piglets, neonatal diarrhoea and post-weaning colibacillosis, and swine dysentery
Rabbit	Respiratory diseases due to pasteurella, mycoplasma and/or bordetella, coccidiosis (oral treatments), ringworm	Epizootic rabbit enteropathy, coccidiosis, staphylococcal mastitis, myxomatosis, respiratory infections and ringworm
Cats and dogs	FIP, non critical antibiotics for IV injection (intensive care)	Sepsis and viral and bacterial eye infections



The main reasons of therapeutic gaps were identified as absence of appropriate VMP (as regard to indication, target species or administration route), shortage or unavailability, regulatory issues (i.e. cascade application, withdrawal period, and restricted access), unsatisfactory perceived efficacy or safety, or absence of therapeutic solution.

Regarding prescriptions outside the terms of the marketing authorisation (MA), ANSES (French Agency for Food, Environmental and Occupational Health & Safety) -ANMV does not currently record the off-label prescriptions. In Spain, PRESVET (veterinary antibiotic prescriptions monitoring system) only records antibiotic prescriptions, including those outside marketing authorisations. Between 2019 and 2022, a total of 35,371 antimicrobial prescriptions were recorded in 4 of the 17 Spanish autonomous communities. The majority of these prescriptions (95.1%) were reported from a single Spanish autonomous community, and the majority of all prescriptions were requested for rabbits (59%) and pigs (24%).

In 2022, the ANMV received 565 import authorisation applications from other MSs and from outside the EU. In total, 83% were immunologicals and 17% were VMPs.

In 2022, 91% of the applications (84% for VMPs and 93% for immunologicals) were approved in another EU MS. Applications for VMPs only approved outside Europe were much rarer and were intended mainly for dogs or horses. In Spain, during 2021, the AEMPS received a total of 1,327 import authorisation applications from outside the EU and 46 from other EU countries. All import applications from EU countries were recorded in only one Spanish autonomous community. Chemotherapeutics (53%) and vaccines (32%) were the most common.

[ANSES compiled a list of one chemical VMPs and 21 immunological VMPs concerned for temporary use authorisation.](#)

The DGAV has collected information on therapeutic gaps and shortages in the markets identified by the different animal sectors. The type of special use authorisations have also been recorded.

This report shows the existence of therapeutic gaps and their causes, as well as the priority list of these gaps that need to be tackled, highlighting the importance of communication and collaboration between stakeholders in different countries. It also stresses the importance of finding alternatives to antibiotics.

1. INTRODUCTION



1. INTRODUCTION

Antimicrobial resistance (AMR) is recognised as a major global threat to humans, animals and environment health. AMR already represents a serious social and economic burden, and it also threatens the achievement of several of the United Nations sustainable development goals. Despite all efforts and actions against the rise of AMR, the incidence of antimicrobial (AM) resistant infections has increased in recent years. At the same time, the discovery, development, manufacture and commercialisation of new antimicrobials has slowed down significantly in the past 20 years ([A European One Health Action Plan against Antimicrobial Resistance](#)).

The European Union's One Health Action Plan against AMR, published in 2017, aims to address the AMR problem. This Plan highlights the need to support the development of alternative and novel therapeutic approaches for the treatment or prevention of infectious diseases. However, due to the challenges associated with development of new antibiotics, 'alternatives'¹ could have a relevant role in veterinary medicine, and support the overall objective of reducing antimicrobial use in animals reflected in the Farm-to-Fork strategy of the 'European Green Deal' ([EMA/CVMP/143258/2021](#)). The Committee for Medicinal Products for Veterinary Use (CVMP) ([EMA/CVMP/179874/2020](#)) strategy on antimicrobials 2021-2025 aims to encourage the development of new and existing antimicrobial VMPs and the development of alternatives to antimicrobials (ATAm) with some measures currently available. Besides, the [European medi-](#)

[cines agencies network strategy to 2025](#) emphasized the need to strengthen the availability of medicines and to optimise the path from development and evaluation to access for medicines. It has also listed its strategic goals to tackle antimicrobial resistance and other emerging health threats. In addition, the VMP [Regulation \(EU\) 2019/6](#) provides incentives to stimulate innovation, to increase the availability of VMPs, and establishes the [UPD](#) in collaboration with the EU MSs. The UPD is the first centralised database of all VMPs authorised in the EU and the European Economic Area (EEA), which went live on 28 January 2022, together with its multilingual public interface ([www.medicines-info.eu](#)) containing information on all authorised VMPs in the EU and EEA.

Notwithstanding these initiatives, the veterinary sector presents several challenges due to its peculiarities, such as the great diversity of animal species and breeds, the safety and environmental implications, the complexities of VMPs formulations, and the characteristics of the market, which is much more fragmented than the human sector. As a consequence, there are few or no AM/ATAm currently authorised for the so-called minor species (animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats). Therefore, the current situation regarding availability of antimicrobials in the EU is as follows:

- there is no AM or ATAm available on the market in a specific country, but it

¹Definition of alternatives to antimicrobials 'a veterinary medicinal product the use of which provides an alternative treatment approach to the use of antimicrobials in animals or that reduces the need for the use of antimicrobials by preventing or controlling infectious disease' ([Reflection paper on promoting the authorisation of alternatives to antimicrobial veterinary medicinal products in the EU \(europa.eu\)](#), accessed 3 July 2023)



could be available in other European countries.

- there is an AM or ATAm available on a market, but it is not authorised for the animal species or specific indications in question.
- there is an AM or ATAm available on a market and authorised for the specific animal species and indications in question, but the pharmaceutical form, dosage, duration of treatment or other specifications need to be updated.

All European countries share similar challenges in the veterinary sector, although each with its own particularities. [The French Agency for Veterinary Medicinal Products](#) (ANMV) presented the work they had been carrying out to identify therapeutic gaps, their causes and possible alternatives, and to define priorities during the Informal meeting of the Committee

for Veterinary Medicinal Products / Coordination Group for Mutual Recognition and Decentralised procedures for veterinary medicinal products (CVMP/CMDv) in June 2022. In parallel, [the Spanish Medicines and Medical Devices Agency](#) (AEMPS) had also been working on similar issues, so the AEMPS set up a working group on antibiotic availability with the ANMV and the Portuguese [Directorate General of Food and Veterinary](#) (DGAV) to discuss their situation and strengthen collaboration. The [Irish Health Products Regulatory Authority](#) has welcomed the [National Action Plan on AMR](#) (PRAN) initiative as a means to foster the development of needed VMPs and to cooperatively address shortage issues, especially in the case of veterinary medicines for food-producing animal species.

All these countries face common problems, particularly in certain sectors (dairy sheep and goats, rabbits, and fish) which correspond to limited markets. As per the



Regulation (EU) 2019/6, article 4 (29) defines a limited market as a market intended for the following medicinal product types:

1. VMPs for the treatment or prevention of diseases that occur infrequently or in limited geographical areas.
2. VMPs for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats.

Harmonisation of the therapeutic arsenal available in these different countries would make it possible, among other things, to limit the need for import applications or authorisations for temporary use (ATU) requests.

Its objectives are:

- To identify and communicate the therapeutic gaps identified in France, Ireland, Portugal, and Spain aiming at a

greater involvement of pharmaceutical companies.

- To list the applications for VMPs approved in one of our countries, in order to motivate marketing authorisation holders (MAH) to submit mutual recognition for those VMPs.
- To promote the interest of jointly defining some good practices on early declaration and anticipation of abandonment of any VMP, in order to better assess its possible negative impact and find some possible alternatives.
- To extend this initiative to other EU MSs and promote collaboration.



2.

METHODOLOGY

2. METHODOLOGY

2.1 Identification of therapeutic gaps

The identification and availability issues were assessed by the working groups during regular meetings. These groups were composed of representatives of the animal sector and the different authorities (ANMV and PRAN).

2.2 Reasons for the therapeutic gaps

The main reasons of therapeutic gaps were identified as absence of an appropriate VMP, shortage or lack of availability, regulatory problems i.e.: cascade application, withdrawal period, restricted access, unsatisfactory perceived efficacy or safety and absence of a therapeutic solution.

Data collection

Imports and temporary use authorisations for medicines authorised in other countries are key measures to address shortages and therapeutic gaps. Data were obtained from national reports on therapeutic gaps and other information sources, from datasets on prescriptions outside the terms of marketing authorisation (MA), and from import applications records from EU and non-EU countries (or third countries). The market for VMPs is usually not harmonised in the EU. Therefore, most VMPs cannot circulate freely in Europe and must be authorised to be placed on the market in the MS in which they are marketed.

2.3 A list (prioritisation) of therapeutic gaps

Three to five major priorities were identified based on the health and welfare consequences for humans and animals, as well as the economic consequences.

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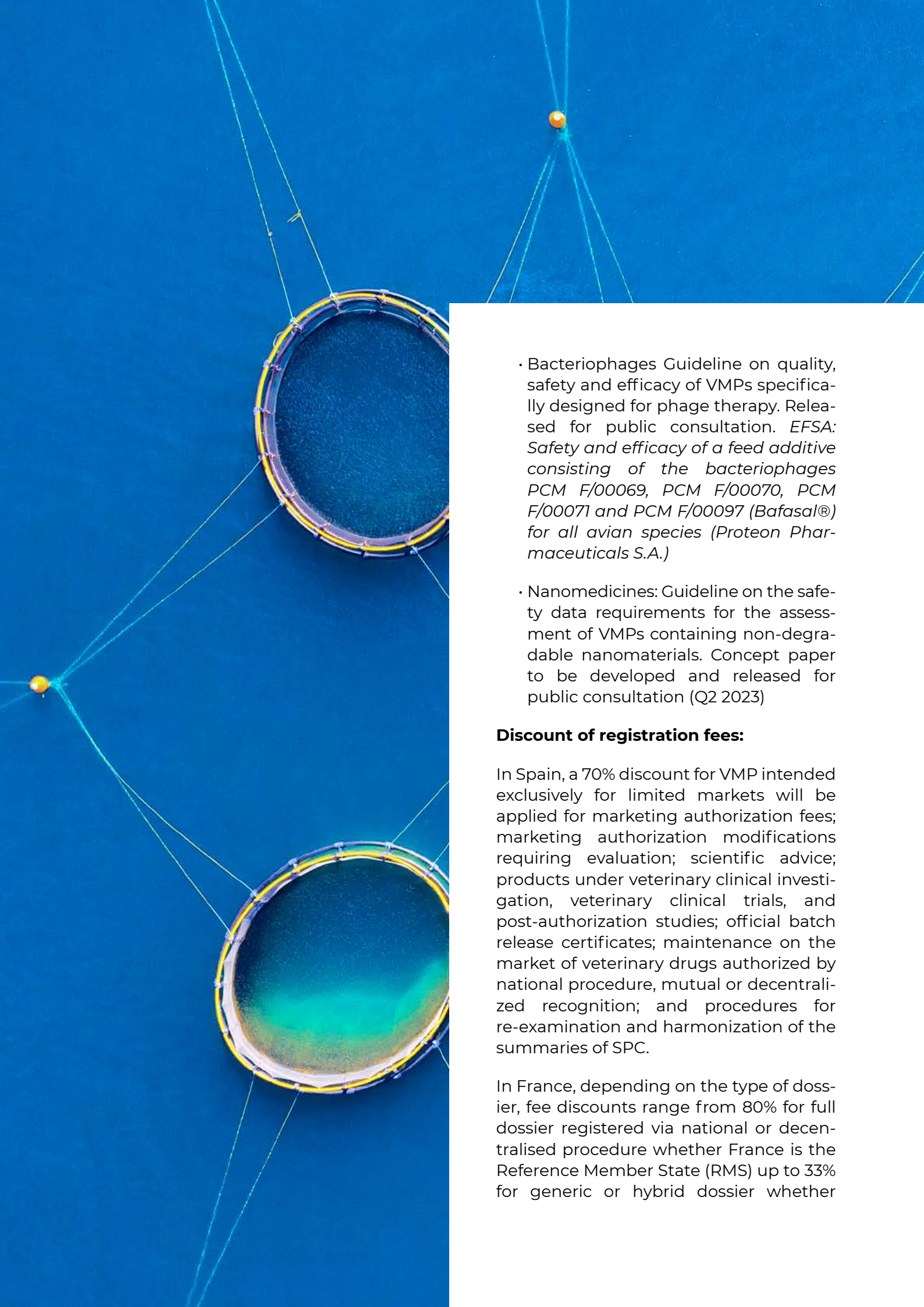
Some measures to address therapeutic gaps were listed:

Vaccines:

- Guideline on plasmid DNA vaccines for veterinary use (Released for public consultation)
- Guideline on data requirements for adjuvants in vaccines for veterinary use
- Guideline on data requirements for authorisation of immunological VMPs in exceptional circumstances - Scientific guideline: Replaced CVMP related guidelines for vaccines against bluetongue and avian influenza
- Guideline on data requirements for vaccine platform technology master files (vPTMF)

Novel Therapies


- Monoclonal antibodies: VICH Draft guideline on target animal safety evaluation for veterinary monoclonal antibody products. Completion date: December 2023 (to be determined)
- Cell therapies: Guideline on the development and data requirements of potency tests for cell-based veterinary therapy products and the relation to clinical efficacy. Completion date: Q2 2023

- 
- Bacteriophages Guideline on quality, safety and efficacy of VMPs specifically designed for phage therapy. Released for public consultation. *EFSA: Safety and efficacy of a feed additive consisting of the bacteriophages PCM F/00069, PCM F/00070, PCM F/00071 and PCM F/00097 (Bafasal®) for all avian species (Proteon Pharmaceuticals S.A.)*
 - Nanomedicines: Guideline on the safety data requirements for the assessment of VMPs containing non-degradable nanomaterials. Concept paper to be developed and released for public consultation (Q2 2023)

Discount of registration fees:

In Spain, a 70% discount for VMP intended exclusively for limited markets will be applied for marketing authorization fees; marketing authorization modifications requiring evaluation; scientific advice; products under veterinary clinical investigation, veterinary clinical trials, and post-authorization studies; official batch release certificates; maintenance on the market of veterinary drugs authorized by national procedure, mutual or decentralized recognition; and procedures for re-examination and harmonization of the summaries of SPC.

In France, depending on the type of dossier, fee discounts range from 80% for full dossier registered via national or decentralised procedure whether France is the Reference Member State (RMS) up to 33% for generic or hybrid dossier whether



France is a Concerned Member State (CMS).

2.4 Ways of collaboration

It is of high interest to seek ways of collaboration between countries to improve the availability of VMP. For example, by taking advantage of the marketing authorization in different countries, and thus promoting the availability of VMPs that have been evaluated and authorized in all other MS which may need them. Therefore, an action plan with possible channels of collaboration between France, Ireland, Spain, and Portugal has been drafted. It includes:

- Mutual recognition of national marketing authorisations.
- Identification of tools and mechanisms already in legislation that allow identified VMPs are available as priority.
- Promotion of new market authorisations or their extensions when therapeutic gaps are identified in several EU MS (i.e. dairy sheep and goats, fish and rabbits).
- Involvement of stakeholders (MAH).

3. RESULTS



3. RESULTS

3.1 FRANCE

The working group on availability of VMPs, whose members are ANMV and the French Animal Health Network (RFSA), has been working since 2014 as follows:

The ANMV organises biannual hearings with representatives of the veterinary profession, members of veterinary technical associations such as National Society of Veterinary Technical Groups (SNGTV), French Association of Equine Veterinarians (AVEF) or French Association of Veterinarians for Companion Animals (AFVAC), and of the VMP Monitoring Committee (CSMV). If necessary, representatives of veterinary education (national veterinary schools), research (ANSES) or other representatives of the sector are also invited. The aim of these hearings is to list the therapeutic gaps encountered in the field, identify their causes and possible alternatives, define the priorities, and initiate possible actions with the various actors involved.

Communication of this work is ensured by publishing the minutes of the meeting, in French and in English (since 2020), to the participants and on [RFSA website](#). The conclusions of the meetings are also presented to the RFSA steering committee and to the CSMV, which take place on a quarterly basis.

IDENTIFICATION OF THERAPEUTIC GAPS

During the last hearings, therapeutic gaps linked to absence or limited availability of suitable antibiotics or alternatives were identified in all sectors. The identified therapeutic gaps are shown in Figures in Appendix A and in Appendix B. Briefly,

these were the main recognised therapeutic gaps per animal sector:

- The beekeeping sector identified varroosis.
- The cattle sector mentioned the need of topical antibiotics for ocular and teat infections.
- The fish working group listed external parasitism products, treatments of bacteriosis, and prevention of virosis.
- The equine sector highlighted the absence of non-critical antibiotics for intravenous injection.
- The goat sector mentioned respiratory pasteurellosis, paratuberculosis and *Mycoplasma* mastitis, while sheep sector listed strongylosis with increased resistance to benzimidazoles, levamisole and eprinomectin, and cryptosporidiosis.
- The poultry working group identified lack of antipyretic or anti-inflammatory products for treatment of laying hens during viral infections, and product gaps for turkey histomonosis and aspergillosis. General remarks about the poultry sector were the absence of antipyretics, that it is a sector penalised by lack of maximum residue limits (MRLs), that turkeys are highly penalised by therapeutic gaps, that organic and alternative farming favours certain diseases, and the valuable use of autogenous vaccines.
- The swine sector recognised that the risk of disappearance of mediated feed and premixes has a critical impact for macrolides and betalactams, and that compliance with the

Summary Product Characteristics (SPC) can be problematic for old antibiotics with inadequate dosage. Several gaps were identified for indications such as neonatal diarrhoea due to enterococci or rotavirus, *Streptococcus suis* and *Brachyspira*.

- The rabbit sector identified respiratory diseases due to *Pasteurella*, *Mycoplasma* and/or *Bordetella*, coccidiosis and ringworm.

REASONS FOR THE THERAPEUTIC GAPS

The causes of therapeutic gaps can be of different nature (as shown in Figure 1). If VMPs with a valid MA are available for the target species and the indication in ques-

tion, the gap may be due to prolonged shortages or to insufficient perceived efficacy or safety. If VMPs are available, but without a valid MA for the target species or the indication concerned, the gap will generally be due to the application of articles 112, 113 and 114 of the VMP Regulation (EU) 2019/6, (the so-called “Cascade” provisions) being difficult (e.g. a too long withdrawal period for milk or eggs) or impossible (e.g. [MRL](#) with use restrictions meaning not possible for dairy or laying animals). The other cases are either due to the absence of appropriate VMPs or accessible human medicinal products (HMPs) for the disease in question, or to the absence of a therapeutic solution known to date.

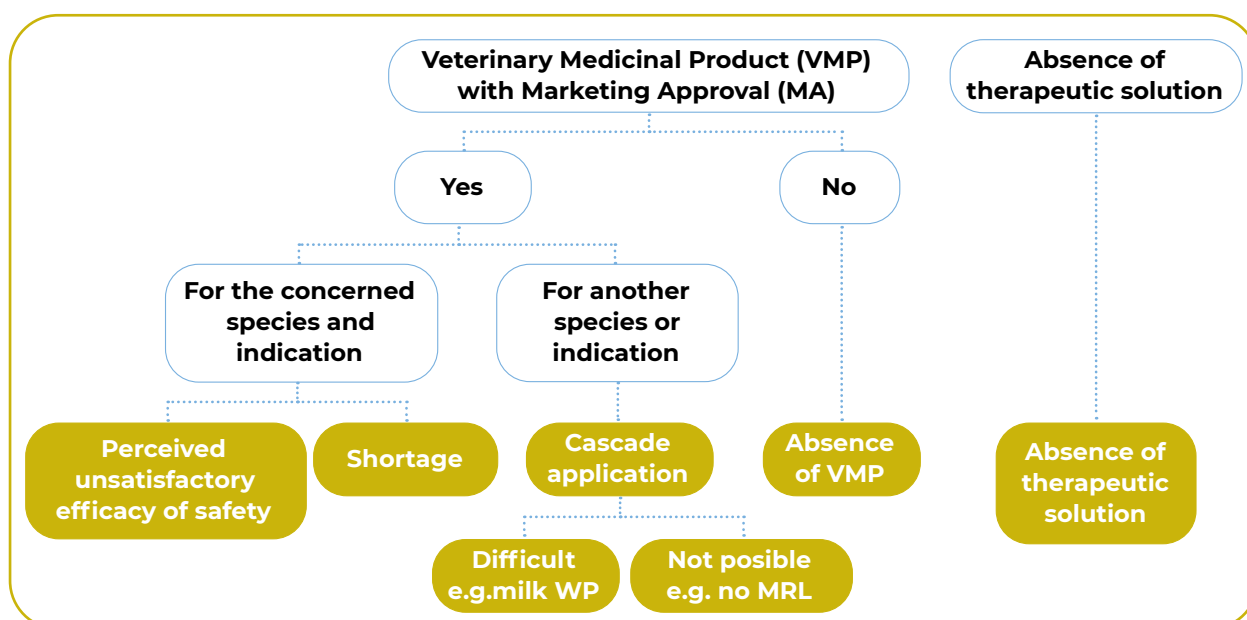


Figure 1. Identified reasons for therapeutic gaps

DATA COLLECTION

National reports about therapeutic gaps and other priorities

Shortages *sensu stricto* (temporary disruptions) are regularly monitored by the ANMV's post-MA surveillance department (ANSES 2022) and are the subject of regular communications (ANSES 2023a) and

reviews (ANSES 2023b, Orand, 2023). A shortage is defined as the impossibility for a customer to obtain a VMP in the national market.

The Market Surveillance and Pharmacovigilance unit has been monitoring and managing VMP shortages since 2014. To collect the relevant data, a specific declaration document² has been created,

²Declare a stock shortage of a veterinary medicinal product to the market ([Declare a stock shortage of a veterinary medicinal product to the market | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail](#). Accessed 6 July 2023)

which includes information on the product (target species, diseases concerned), the importance of its sales and market share, the duration of the disruption (return date) and possible alternatives. These data are used to establish a real-time monitoring table of all current shortages, until the market is correctly restocked with new batches of the VMP.

A stock shortage is assessed as critical when it is likely to induce a risk to animal

health and welfare or even indirectly to human health. Since June 2019, the most critical shortages are posted on the ANSES-ANMV website.

Shortage declarations since 2014 are shown in Figure 2. Briefly, the most common were vaccines (33%) and antibiotics (20%). Shortages for a specific antibiotic are not considered critical when alternatives are available (e.g. other antibiotics from the same or another family).

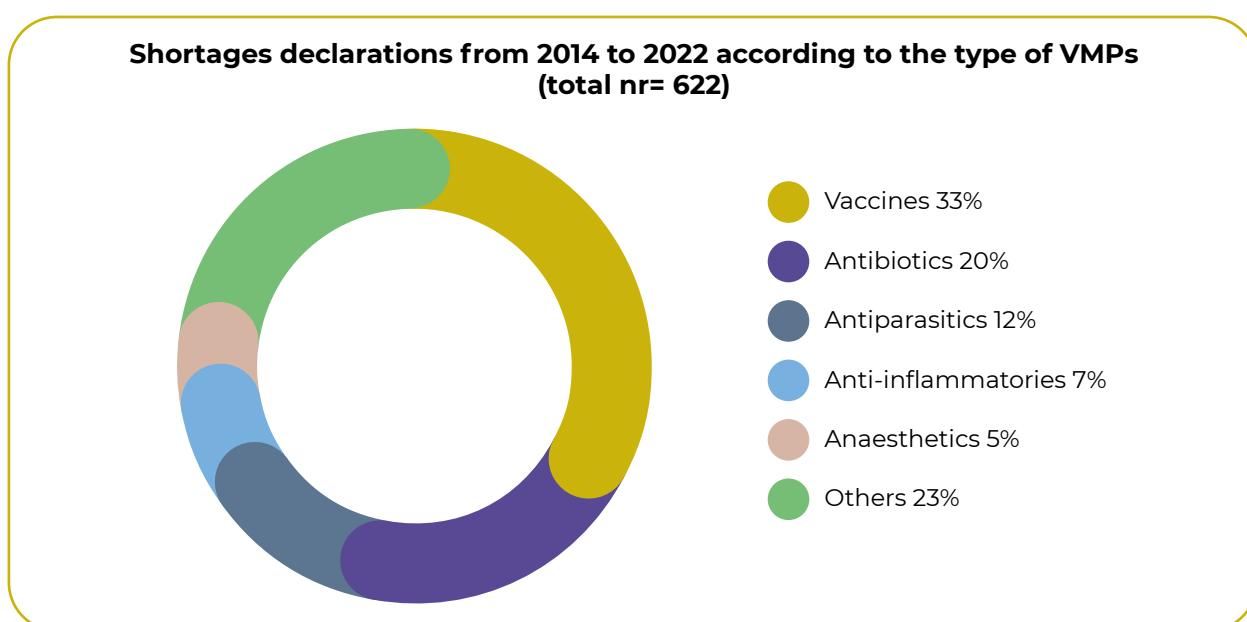


Figure 2. Percentage of shortages declarations by type of VMPs in France, all years (2014-2022).

The percentage of shortages concerning vaccines and antibiotics has increased since 2019 (see Figure 3). In 2021, vaccines, accounting for 27%, led the reported shortages, followed by anti-inflammatory drugs (17%) and antibiotics (15%). Vaccine shortages were mainly due to supply difficulties in the pet market, which has been growing sharply since 2020. Among anti-inflammatories, meloxicam-based medicinal products (in various forms) were particularly affected, while the main antibiotics affected were those based on amoxicillin (plus clavulanic acid). The number of shortages has risen by 20% by 2022, mainly because of numerous vaccines shortages.

The percentage of shortages concerning vaccines and antibiotics has increased since 2019

The shortage of antibiotics could be critical in case of scarcity of manufacturers related to the:

- limited number of Active Pharmaceutical Ingredients (API) manufacturers, almost all in China or India, with serious implications (GMP incident for benzylpenicilline in 2015, COVID-19 crisis and war in Ukraine more recently...), and
- small batches compared to human medicinal products

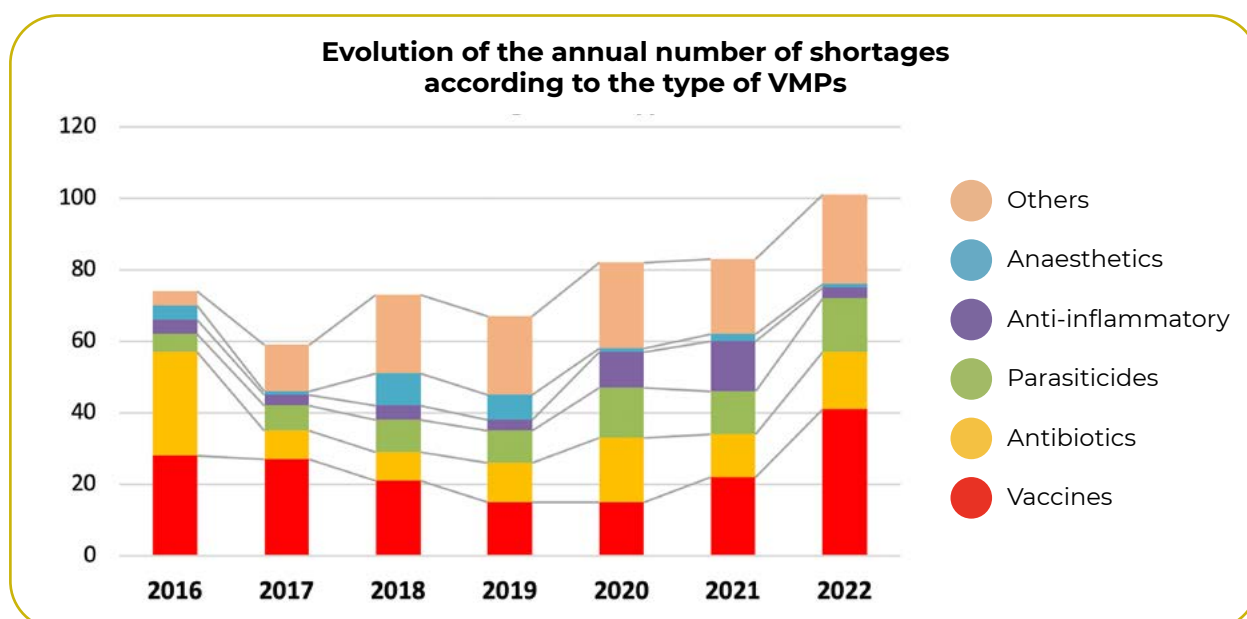


Figure 3. Percentage of shortages declarations in France by drug category over the last years

Prescriptions outside the terms of the marketing authorisation (off-label)

In France, ANSES-ANMV does not currently record the off-label prescriptions. New software implemented very recently for the collection and monitoring of antimicrobials use will make this possible in the near future.

Imports from other EU MSs and from outside the EU

In the absence of nationally VMPs authorised by ANSES in France or centrally authorised products (CAPs) by the European Commission and suitable for the intended treatment, a veterinarian may use a medicinal product authorised in another EU MS. This use requires import authorisation issued by the ANSES³.

There are two types of imports, depending on who requests for it:

- a. Import requested by a veterinarian. The veterinarian may prescribe, within the framework of Article L. 5143-4 of the Code de la Santé Publique⁴ (Therapeutic Cascade), VMPs

authorised in another MS or party to the Agreement on the EEA in the absence of a VMP suitable for the species or condition. This import is intended for therapeutic purposes. Under this article of the Code de la Santé Publique, the veterinarian can also prescribe HMP authorised in France. A veterinarian may not prescribe and request the importation of a HMP authorised in another MS or party to the EEA Agreement.

- b. Import requested by a pharmaceutical company.

The company can apply for an import authorisation for a clinical trial, a non-therapeutic use (physico-chemical analyses, preclinical studies on animals, etc.), or a transit in France followed by an export. The applicant must meet some conditions: either an authorisation to open as a manufacturing and/or import establishment; or an approval as an animal experimentation establishment; or an approval issued by the customs authorities for a national export warehouse referred to in article 277 A of the General Tax Code.

³<https://www.anses.fr/en/content/import-veterinary-medicinal-products>, Accessed 6 July 2023

⁴Public Health Code (https://www.legifrance.gouv.fr/codes/texte_lc/LEGITEXT000006072665/, Accessed 6 July 2023)

In 2022, the ANMV received a total of 565 requests for import authorisations, the most common concerning immunologicals (83%), and 16,8% were pharmaceutical products. These requests were accepted in 92,4% of cases, rejected in 2,3% and withdrawn by the applicant in 5,3% of cases. The majority of the requested vaccines were for *Mycobacterium paratuberculosis* vaccines to be used in for sheep/goats, followed by Aujeszky´s vaccines for hunting dogs. Figure 4 shows the number of requests of authorised imports of

vaccines by type of animal species and Figure 5 shows the number of requests for authorised imports of pharmaceutical products by product type. In 2022, 91% of applications (84% for pharmaceutical products and 93% for immunologicals) concern the import of approved VMPs in another EU MS. The need for VMPs only approved outside EU is much rarer and were mainly intended for dogs or horses.

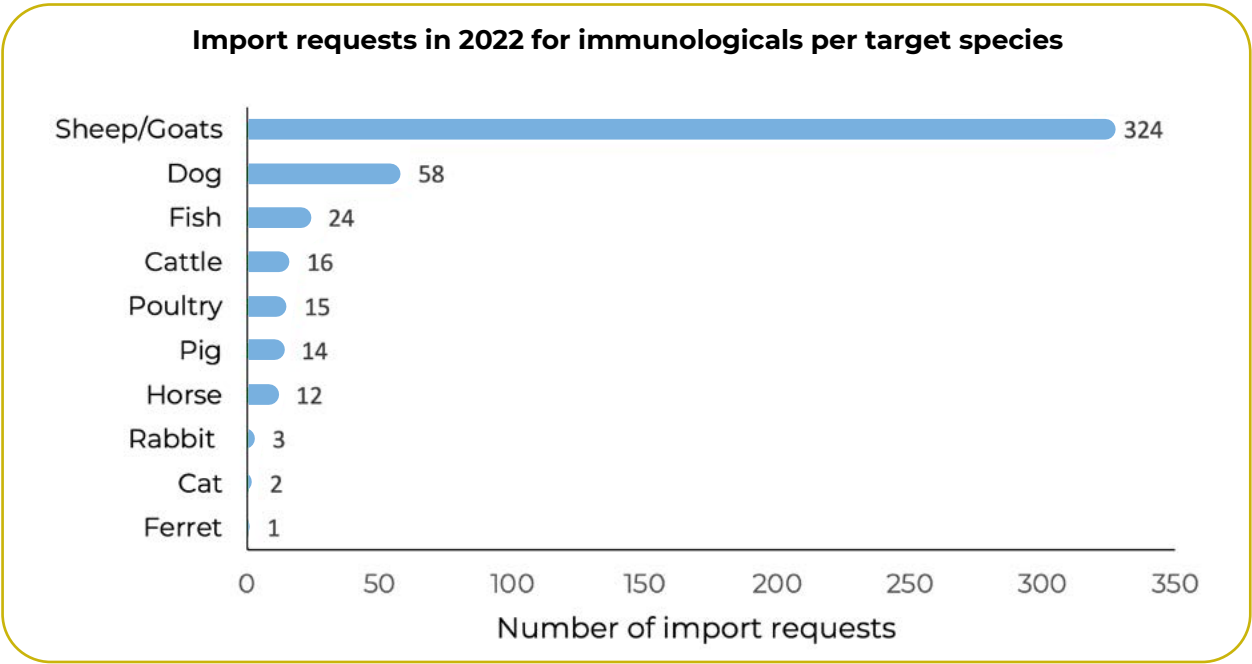


Figure 4. Number of requests to import vaccines by animal species in France, in 2022

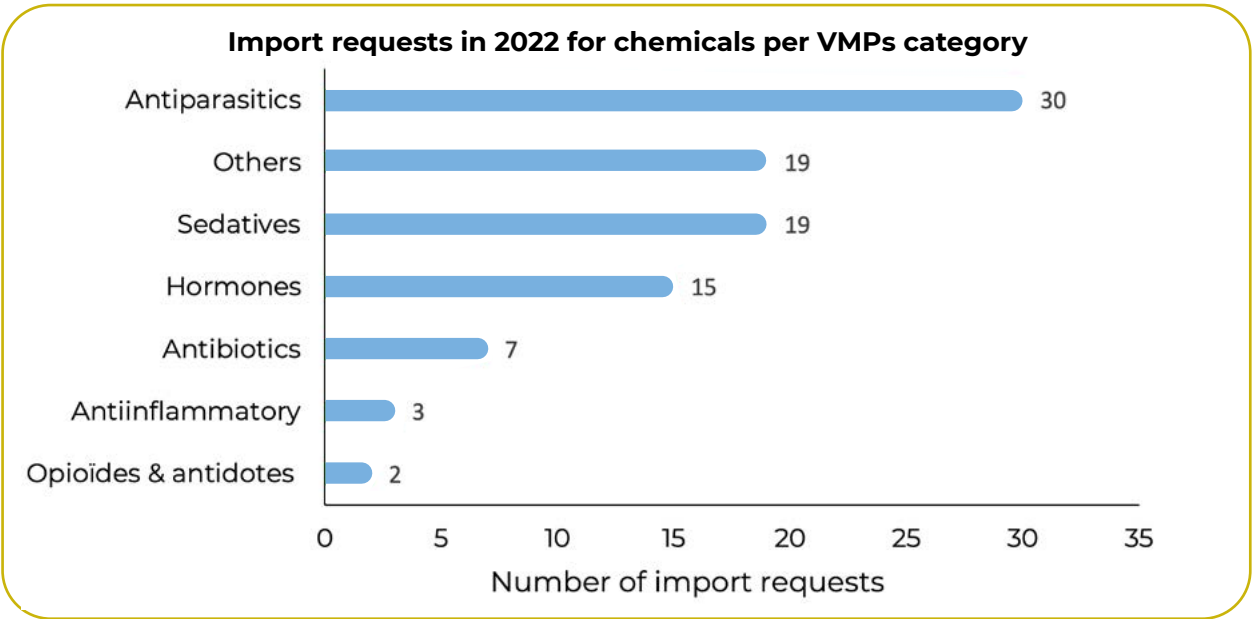


Figure 5. Number of requests to import pharmaceuticals VMPs by product type in France, in 2022



Temporary use authorisation

The procedure for ATU referred to in Article L. 5141-10 of the Code de la Santé Publique allows the use of VMPs that are not authorised for use in France, but are authorised in another MS, or third countries. It can also be used for medicinal products under development for which not all scientific data, including clinical data, are available. The ATU issued by the Director-General of ANSES is an exception to the prior MA procedure which allows, under certain conditions, the management of a particular health situation.

The applications correspond to a proven disease and a demonstrated absence of other authorised therapeutic alternatives. They mainly concern so-called minor species and/or minor pathologies. This procedure can be used for immunological or pharmaceutical medicinal products. The authorisation may be requested by a veterinary pharmaceutical establishment which will carry out import, storage and distribution operations to veterinarians when the medicinal product is marketed in third countries.

The list of ATU is published in [ANSES website](#) concerns a pharmaceutical medicinal product and 21 immunological ones.

LIST (PRIORITISATION) OF THERAPEUTIC GAPS

The prioritisation of gaps is established by consensus of the working group participants according to the perceived therapeutic, health or economic harms in the field. This prioritisation is not based on detailed quantitative criteria, but has the main objective of specifying the 3 to 5 major gaps and differentiating them from other "less major" or minor gaps. In this way, actions that provide solutions to these gaps can be proposed and prioritised.

Table in Appendix B shows the main priority therapeutic gaps identified for the animal sectors identified during the hearings conducted in 2021-2022. The main gaps concerning antimicrobials or their

alternatives, or antiparasitics, according to the hearings conducted in each sector were for: varroosis in bees; topical antibiotics for ocular infections with corneal lesions and teat injuries in cattle; external parasitism in fish; non critical injectable intravenous antibiotics for intensive care in horses; fever and inflammation control in case of viral infections in laying hens, and histomonosis and aspergillosis in turkeys; post-weaning colibacillosis and influenza in pigs; respiratory diseases due to *Pasteurella*, *Mycoplasma* and/or *Bordetella* in rabbits; gastrointestinal strongylosis in sheep and goats, neonatal colibacillosis and cryptosporidiosis in sheep, and respiratory pasteurellosis in goats.

ACTIONS / ACHIEVEMENTS

Absence of appropriate VMPs: search for alternatives e.g.: ATU of new drugs (e.g. inactivated vaccine PROTIVITY for bovine mycoplasmosis), import of VMPs with a MA in the EU or outside the EU (e.g. CRESS for fish), autogenous vaccines (*Streptococcus suis* for pigs, fish bacterial diseases etc.). Communication to industry, through the minutes of the hearings available on the RFSA website, about the wish for new medicines or for MA extensions.

Shortage: identification of causes and promotion of shortages declarations if not already declared, and searching for alternatives and information on possible supplies (e.g. via import authorisation demands).

Cascade application: clarification of MRL status (e.g. antipyretics, tenicide, antifungal for poultry, ophthalmic antibiotics, oral antipyretic and tranquilliser for cattle), precisions about possible access to medicines for horses or dogs (e.g. in case of restricted prescription of human medicines), need for residue depletion study in milk when not available while use is allowed by the MRL status, etc.

Efficacy or safety perceived as unsatisfactory: Reminders on the importance of pharmacovigilance declarations, reflections and drafting of specific recommen-

dations e.g. on declarations concerning VMPs for bees. Communication to industry, through the minutes of the hearings available on the RFSA website, of information concerning difficulties in using certain medicines or about the wish for new medicines.

Absence of therapeutic solution: identification of risks and impact, information on the existence of alternatives or need for research.

CONCLUSIONS

Since 2014, as part of its participation in the RFSA Working Group on the availability of medicines, the ANMV has developed an original approach to identify therapeutic gaps, by soliciting, during biannual hearings, vet practitioners for each animal sector.

The main benefits of these hearings are to promote exchanges between veterinarians and national competent authorities (NCAs), thus enabling a cross-sectional view of the problems encountered in the field at national level.

The identification of the causes, alternatives, risks and priorities related to these therapeutic gaps allows the implementation of actions to work together towards short-, medium- or long-term solutions. These actions are also in line with the main objectives of the European veterinary medicinal products-Regulation and enable the monitoring of its impact on improving the availability of veterinary medicinal products.

Good Practices for managing veterinary medicinal products shortages were established in 2018 with the different stakeholders (MAHs, Vets, Wholesalers and the ANMV). Updated in 2021, these good practices set out the definition of a critical shortage, the actions to be taken by each of the players (the ANMV, pharmaceutical industry, wholesalers and veterinarians) and the arrangements for exchanging information at national and European levels. ANMV has participated to the Avail-

lability Single Point of Contact (SPOC) network since 2020⁵.

3.2 SPAIN

The Spanish working group on availability of AMs and alternatives to their use is composed of the Spanish PRAN, the Committee for Availability of Veterinary Medicinal Products ("Comité de Disponibilidad de Medicamentos Veterinarios", CODI-VET), the Ministry of Agriculture, Fisheries and Food (MAPA), the Spanish regional authorities or autonomous communities, the associations of the pharmaceutical industry Veterindustria and Fundación Vet+i, and technical coordinators of different animal sectors (pig farming, beef and dairy cattle, poultry and turkey production, laying hens, small ruminants, fish and rabbit farming). Representatives of different animal sectors have been working with PRAN since 2016. This group aims to identify the therapeutic gaps encountered in the field, and to list the main priorities and urgent needs.

The Spanish legislation describes the aim and functions of the CODI-VET (article 25 of the Royal Decree 1275/2011)⁶. Its main objective is to promote the availability of VMPs when there are therapeutic gaps and/or in the case of limited markets. CODI-VET facilitates, encourages, and supports research, development, registration and commercialisation of VMPs of interest.

Representatives of different animal sectors have been working with PRAN since 2016

IDENTIFICATION OF THERAPEUTIC GAPS

CODI-VET and technical coordinators of the different animal sectors meet regularly to discuss the therapeutic gaps and the needs in the field. The main therapeutic

gaps are shown in Figures in Appendix C. Briefly, the animal sectors recognised the following therapeutic gaps:

- The beekeeping sector identified varroasis.
- The cattle working group recognised the need of treatments for coccidiosis, respiratory infections and leptospirosis.
- The fish working group identified the need of oxytetracycline via premix and treatments for ectoparasites.
- The horse sector listed theileriosis and sepsis.
- The goats and sheep working group identified therapeutic gaps for cryptosporidiosis and mastitis, and absence of anti-inflammatory drugs. In addition, the goat sector mentioned mycoplasmosis, coccidiosis and respiratory infections, while sheep sector listed the respiratory disease complex.
- The poultry working group listed Salmonella, enteric and respiratory infections, and haemorrhagic enteritis. The laying hens sector mentioned respiratory infections, and red mite and tapeworm infestations.
- The pig sector identified the absence of vaccines and treatments against diarrhoea by rotavirus in piglets, neonatal diarrhoea and post-weaning colibacillosis, and swine dysentery.
- The rabbit sector identified several therapeutic gaps for diseases such as epizootic rabbit enteropathy, coccidiosis, staphylococcal mastitis, myxomatosis, respiratory infections and ringworm.
- The cat and dog working group mentioned sepsis, viral and bacterial eye infections.

⁵EMA, Medicine Shortages Single Point of Contact (SPOC) Working party (<https://www.ema.europa.eu/en/committees/working-parties-other-groups/medicines-shortages-single-point-contact-spoc-working-party>, Accessed 6 July 2023)

⁶Real Decreto 1275/2011, de 16 de septiembre, por el que se crea la Agencia estatal "Agencia Española de Medicamentos y Productos Sanitarios" y se aprueba su Estatuto (<https://www.boe.es/buscar/doc.php?id=BOE-A-2011-15044>, Accessed 6 July 2023)

REASONS FOR THE THERAPEUTIC GAPS

Different reasons were identified as causes of therapeutic gaps: lack of ATAm; the low number of authorised antimicrobials (especially for use in so-called minor species), stock shortages, and the need to review and adjust indications, dosage and target species in the SPC of many VMPs containing antimicrobials.

The lack of ATAm to control and prevent high prevalent pathologies (e.g. cryptosporidiosis, coccidiosis, colibacillosis, salmonellosis and mycoplasmosis in cattle) is also a major constraint.

DATA COLLECTION

The identification of therapeutic gaps has been carried out using official data recorded on veterinary prescriptions outside MA, exceptional imports from other EU MS and non-EU countries (third countries).

Prescriptions outside the terms of the marketing authorisation (therapeutic gap and off-label)

In Spain, in accordance with Regulation (EU) 2019/6, it is allowed to treat animals with a VMP authorised for its use in the

same species for other indication or authorised for another species for the same (or other) indication, under the responsibility of the veterinarian.

The MAPA manages a database, [PRES-VET](#)⁷ (computerised system for central control of veterinary antibiotic prescriptions) which records only antibiotics prescriptions to monitor their use, but not the reason or clinical diagnosis. In addition, it does not include veterinary prescriptions for companion animals (non-food-producing animals), or data from VMPs other than antibiotics. Information on prescriptions of antibiotics outside the terms of the MA was extracted from PRES-VET. A total of 35,371 off-market prescriptions for antimicrobials were recorded from 2019 to 2022 in 4 out of 17 Spanish autonomous communities as shown in Figure 6. Most of these prescriptions (95.1%) were reported from a single autonomous community. The group Other included 2 ferrets, rodents, 2 reptiles and 2 alpacas, and other herbivores. It is worth to mention that the high number of prescriptions outside the market for the rabbit sector is due to two main reasons: the lack of needed antibiotics and the use of a premix to treat Mucoid enteropathy.

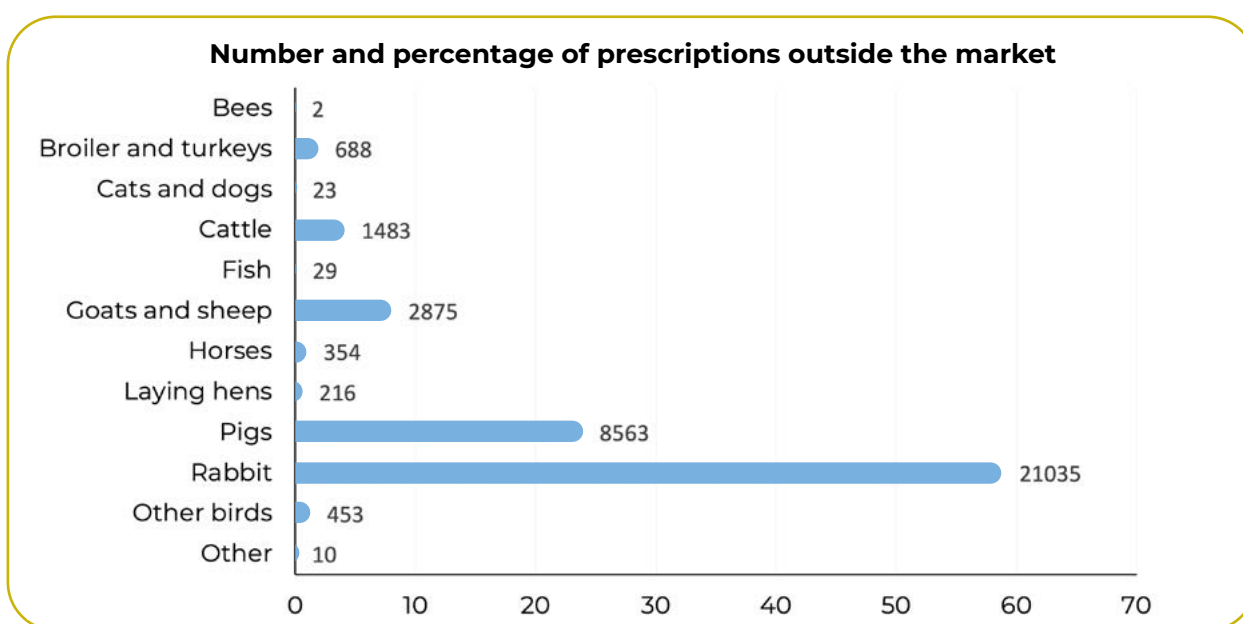


Figure 6. Prescriptions outside marketing authorisation in Spain, 2019 to 2022

⁷<https://servicio.mapama.gob.es/presvet/Account/Login?ReturnUrl=%2Fpresvet%2F>, accessed 23 August 2023

Imports from other EU MS and non-EU countries (third countries)

In case of therapeutic gap, shortages and/or distribution problems, a veterinarian may use a VMP imported from another EU MS or non-EU countries (third countries) if its use has been authorised in advance by the AEMPS or autonomous community. In 2021, the AEMPS received a

total of 1,327 import authorisation requests from non-EU countries and 46 from other EU MSs (Figure 7). All import requests from other EU MS were recorded in one autonomous community. Chemotherapeutic products (53.1%) and vaccines (31.9%) were the most commonly requested VMP. These requests were accepted in 91.3% of the cases, and rejected in 3.4%.

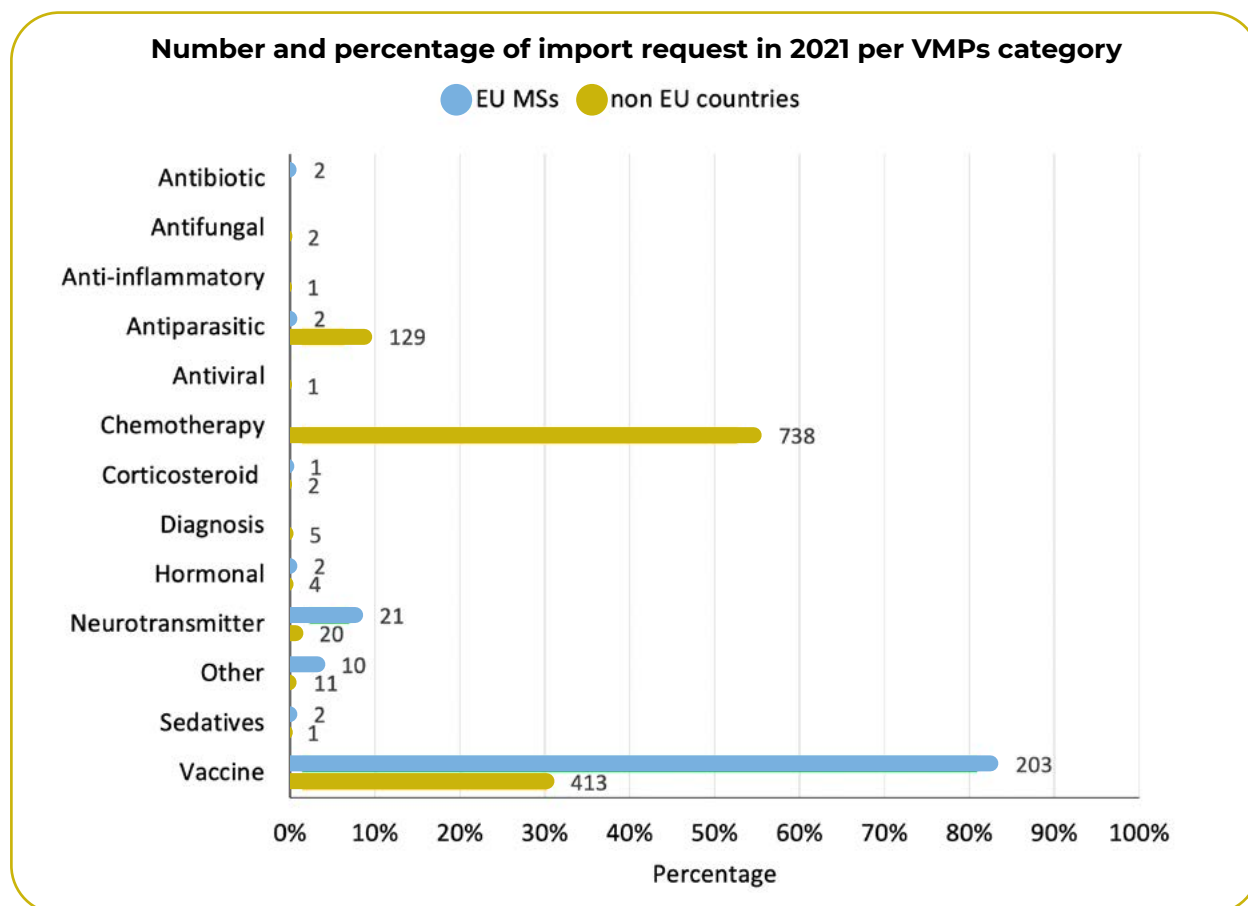


Figure 7. Import request by VMP category in Spain, 2021

LIST (PRIORITISATION) OF THERAPEUTIC GAPS

The prioritisation of gaps is established by consensus of the working group participants according to the therapeutic, health or economic harm perceived by the sector. This prioritisation is not based on detailed quantitative criteria, but enables actions to be proposed and prioritised in order to provide solutions to these gaps.

CODI-VET publishes an annual report that lists the therapeutic gaps and priority needs, which is available on the AEMPS website⁸. The results of this report are shown in Appendix C (in Spanish).

CONCLUSIONS

The results of this Spanish report show that the veterinary sector faces a challenge due to therapeutic gaps, especially the

⁸<https://www.aemps.gob.es/la-aemps/informe-del-comite-de-disponibilidad-de-medicamentos-veterinarios-codi-vet-sobre-vacios-terapeuticos-y-otras-necesidades-prioritarias-2/?lang=en>, accessed 22/10/2023

rabbit and pig sectors, which need to prescribe a large number of antimicrobials outside the terms of marketing authorisation. This could drive the emergence and dissemination of AMR.

One of the common comments received from the animal sectors was the concern about the restrictions that Regulation (EU) 2019/6 establishes on the use of VMPs outside the terms of the MA. As a result of such restrictions, there could be more limited access to VMPs, which would have negative consequences on animal welfare and health.

As a result of restrictions, there could be more limited access to VMPs, threatening animal health and welfare.

The prescription of VMPs outside the terms of MA (cascade application) was required to apply the VMP for several reasons:

1. An indication not specified in the SPC. This situation was commonly found in the pig sector, with prescriptions of florfenicol, currently approved for respiratory diseases, but very often used in gastrointestinal disorders, supported in the results of the antimicrobial susceptibility testing.
2. A different concerned animal specified in the SPC. As an example, the premix with sulfadiazine and trimethoprim, which approved species is “preruminant lamb”, but would be needed for sheep.
3. The outdated information specified in the SPC would lead to infradosification of some routinely used antimicrobials. For instance, premixes with chlortetracycline and tetracycline for cattle and small ruminants.

Some sectors have highlighted that research and innovation should be a priority to develop new medicinal tools, especially for diseases without therapeutic option available, such as some bacterial infections. Legal regulations should be also developed to tackle these problems.

3.3 PORTUGAL AND IRELAND

The Portuguese DGAV has collected information on therapeutic gaps (as shown in Appendix E Table 1) and shortages in markets (Appendix E Table 2) for different animal sectors. The type of special use authorisations has also been recorded (Appendix E Table 3).

In Ireland, the Irish [Department of Agriculture, Food and the Marine](#) (DAFM) is the national competent authority for special imports of veterinary medicines to address national shortages. In order to proactively address availability, the HPRA, as national competent authority for mainstream medicines, has long established incentives to help mainstream veterinary medicines that may have limited market potential.

The availability of VMPs is a long-standing issue in Ireland. The situation has become more challenging since the end of the Brexit transition period. Formerly, over 50% of VMPs marketed in Ireland shared a common label with the UK. However, divergent regulatory pathways between the EU and the UK challenge this paradigm, meaning that Ireland is more vulnerable to shortages of VMPs. To address the issue, Ireland is open to new possibilities to attract medicines that are already available in other EU markets.

A photograph of a flock of sheep in a lush green field. In the foreground, two sheep are standing and looking towards the camera. In the background, many other sheep are grazing or resting. Overlaid on the right side of the image is a large blue number '4' followed by a solid yellow circle.

4.

DISCUSSION AND CONCLUSIONS

4. DISCUSSION AND CONCLUSIONS

This report shows the existence of therapeutic gaps and their causes, as well as the priority list of these gaps that need to be tackled, highlighting the importance of communication and collaboration between stakeholders in different countries. It also stresses the importance of finding alternatives to antibiotics.

Both, ANMV and PRAN organise regular meetings, to share information, which is a key element to further update the list of therapeutic gaps and search for best solutions. On this same topic of therapeutic gaps, it is worth noting the existence of the European project [DISCONTTOOLS](#) (Research gaps for improving infectious disease control in animals), an open access database, created by a European public-private consortium and launched in 2014, to help private or public research to target therapeutic or diagnostic research efforts on identified diseases.

In addition, the VMP [Regulation \(EU\) 2019/6](#), in force since January 2022, aims to improve the availability of VMPs. It addresses in several articles the problem of therapeutic gaps: Article 23 (applications for limited markets), article 25 (applications in exceptional circumstances), article 40.5 (prolongation and additional periods of the protection of technical documentation), articles 112, 113 and 114 on the use of medicinal products outside the terms of the MA and article 115 (withdrawal periods for medicinal products used outside the terms of the MA in food-producing animal species). In addition, the actions implemented to limit therapeutic gaps meet the other main objectives of this regulation revision, in particular:

- to “mitigate the risk of the development of resistance to antimicrobials” and to “promote innovation” by identifying and stimulating the development of alternatives to antibiotics through the communication about wishes for new vaccines MAs or ATUs, for import authorisations or autovaccines;
- to “reduce the administrative burden” and “improve the functioning of the internal market of VMPs”, e.g. by stimulating the submission of MAs rather than increasing the number of applications for imports.

To address some of the identified problems, the [Medicine Shortages Single Point of Contact \(SPOC\) Working Party](#) is responsible for monitoring and reporting events that may affect the supply of medicines in the EU. It recommends to the EMA on the Executive Steering Group on Shortages and Safety of Medicinal Products on all matters related to the monitoring and management of medicines shortages and other medicine availability issues affecting human and veterinary medicinal products.

Moreover, some other tools are or will be available, as for example: the UPD where MAHs submit Volume of Sales Data since 2022, which can inform about the amount of VMP sold and the availability status of any VMP in EU MSs. There is an intention to further enrich the UPD by adding the therapeutic indication, as indicated in the business requirements catalogue. Another tool that can play an important role is the [European sales and use of antimicrobials for veterinary medicine working group](#) (ESUAvet), which collects and analyses data on sales volumes of veteri-

nary AM and the use of AM in animals. In order to achieve this, data quality is essential and therefore should be a priority among EU MS.

As previously highlighted, communication and collaboration between stakeholders in different countries is essential. An

example of success is the Quadripartite established by Spain, France, Ireland and Portugal. For instance, by using the procedure of mutual recognition of national authorisation, a vaccine for turkeys authorised in France is being used in Spain.

5

NEXT STEPS



5. NEXT STEPS

This report is the starting point to establish ways of collaboration between countries to address common problems related to the challenge of availability of AM and ATAm, as mutual recognition of national marketing authorisation and the involvement of stakeholders.

Some of the next steps include:

- Organize regular meetings of the working groups
- Organize regular meetings with stakeholders taking into account the concerned actions of CODI-VET
- Expand this initiative to other EU MSs and to foster collaboration between countries

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ORAND JP. 2023. Les ruptures de médicaments vétérinaires (Veterinary Medicinal Products Shortages). Bull. Acad. Vét. France. 1-8. Doi : 10.3406/bavf.2023.71017 (https://academie-veterinaire-defrance.org/fileadmin/user_upload/Publication/Bulletin-AVF/BAVF_2023/orand_ruptur_medic_vet_bavf_2023.pdf , Accessed 5 July 2023)

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02019R0006-20220128&qid=1688456656696>, Accessed 5 July 2023)

APPENDIX



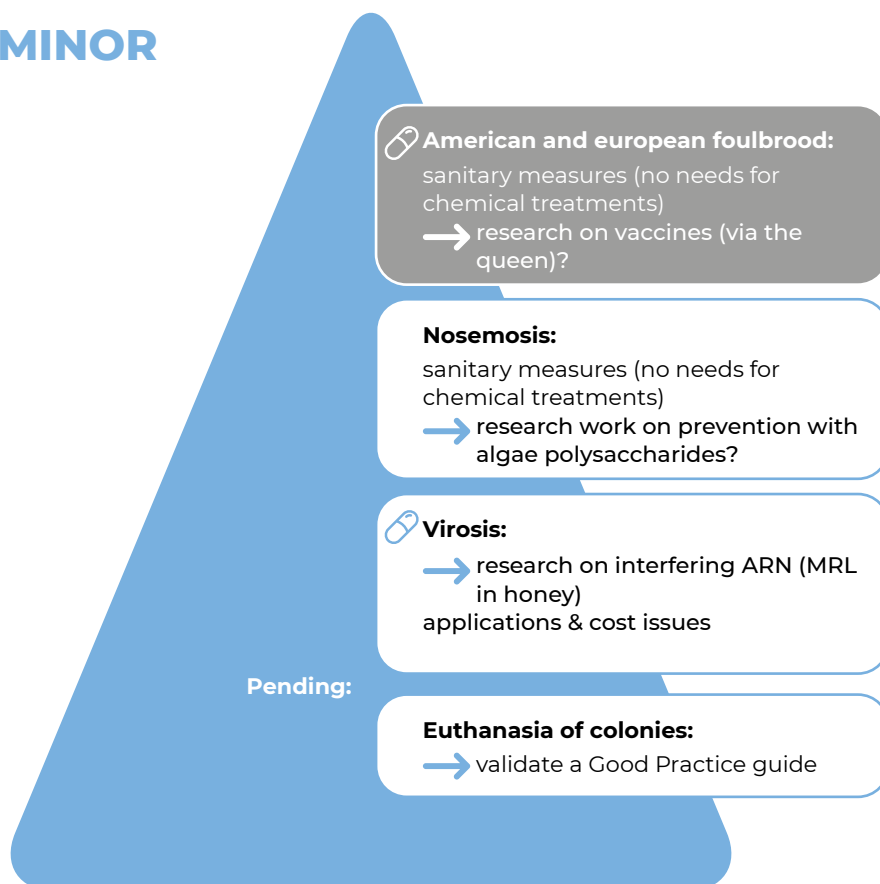
APPENDIX A – LIST OF THERAPEUTIC GAPS AND PRIORITIES IN FRANCE

GAPS IN BEE SECTOR

HEARING OF 15/10/21

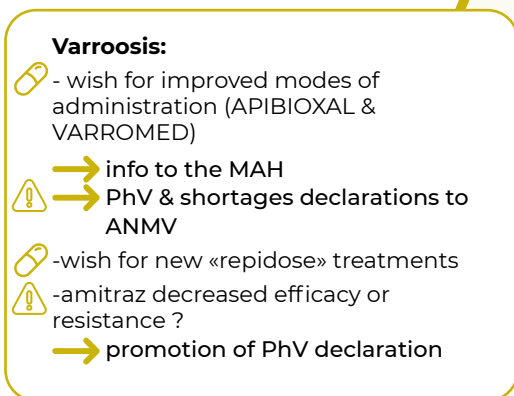


MINOR



MAJOR

N° 1



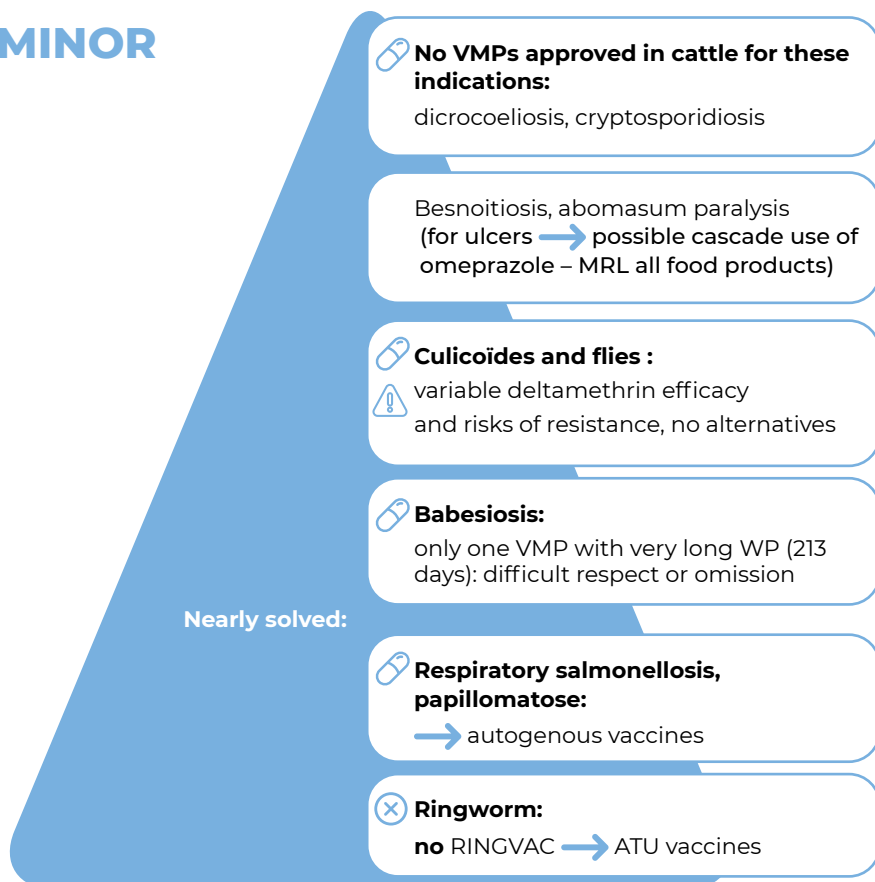
GAPS IN CATTLE SECTOR

HEARING OF 27/04/21



Impact on ATM use incl. absence or limited alternatives

MINOR



MAJOR

N° 1

No MA for topical treatments in cattle:
-for ocular infections:
→ possible cascade use of intra-mammary or of some ophtalmic ointments for horses or pets
-for teat injury

N° 2

Respiratory mycoplasmosis:
no vaccines → AMR risks

N° 3

Antipyretics per os:
no paracetamol per os for cattle
→ Possible use via cascade (MRL for pigs for all food products)

N° 4

Tranquilizers per os:
no LMR status for acepromazine
→ forbidden cascade use of oral VMPs available for horses

N° 5

Paramphistomosis:
no MA in cattle for this indication
→ need for specific studies to define the efficient dosage

GAPS IN FISH SECTOR

HEARING 13/12/21



Impact on ATM use incl. absence or limited alternatives

MINOR

Anesthesia for vaccination injection / eggs collection for consumption or for fertilisation / **weighing and sorting** (notably in perciforms farms)

- post-treatment rinse with :
 - tricaine (trouts) → import Spanish VMP
 - benzocaine (sea bass) → import Spanish VMP
 - eugenol & isoeugenol (extemp. preparation)
- wish for a VMP with WP nul for fish eggs or MR of Spanish VMPs

Other requests:

- **Pragmatic regulation for assessment of the fish treatments ecotoxicity**
 - CVMP GL project by 2024
- **Promote pharmacovigilance declarations**
 - define with SNGTV pragmatic criteria for serious cases declaration

N° 1

External parasitism

Treatment of cutaneous-branchial parasitosis by balneotherapy: therapeutic use of various products with biocidal activity but without MA for veterinary medicine

- case of formaldehyde (conditional import VMP from Spain)
- case of PYCEZE shortage & import of CRESS

Treatment of the most common bacteriosis: yersiniosis, furunculosis, vibriosis, lactococcosis

almost no more ATB available VMPs for fish:

- Médic'Eau project on ATB dosages in fish farming
- cascade use, import of premixes, auto-vaccines
- wish for yersiniosis + furunculosis bivalent vaccine (large trout) and furunculosis vaccine (char and brown trout)

N° 2

Control of less common bacteriosis or in « minor » species:

- Edwardsiellosis (turbot)** → import vaccine from Japan?
- Streptococcosis (sturgeon)** → research on vaccine
- Flavobacteriosis (rainbow trout juveniles)** → wished vaccine

N° 3

Prevention of virosis:

IPN (Infectious Pancreatic Necrosis - Togavirus)

- biosecurity, import of vaccines?

Emerging Virosis (reovirus)

- eradication policy: vaccines not required (unless for reproducers?)

MAJOR

GAPS IN HORSES SECTOR

HEARING OF 19/10/21



Impact on ATM use incl.
absence or limited
alternatives

MINOR



Leptospirosis:

controversial increase in seropositivity
(rare clinical expression – zoonosis)
vaccine exists in the US



Asthma:



difficult administration of ASERVO

→ PhV declarations to report «Real need for alternatives»



Induction of lactation:

domperidone ± efficient, cessation of injectable sulpiride for humans



Chemical castration:

IMPROVAC poorly tolerated and inadequate packaging

Botulism:

very rare. Import of ANTRAVAC, vaccine for cattle

Other requests:

Difficult veterinary use of products without MA in EU, not authorised as 1st-line products because of existing approved VMPs (human hyaluronic acid, sarapin, Arthramid vet US)

Sarcoids

difficult access to BCG in pharmacy
(reserved quota to humans)

MAJOR

N° 1



Absence of non critical ATB for IV injection (intensive care)



refused access to Clamoxyl for humans (why?)

N° 2



Chondroprotection:

→ wish for a single-dose VMP for intra-articular injection with triamcinolone, or hyaluronic acid (single-dose medical devices available for humans but forbidden for vet use, while well formulated and cheaper)

GAPS IN POULTRY SECTOR

HEARING OF 07/10/2022



Impact on ATM use incl. absence or limited alternatives

MINOR

🔗 **Colibacillosis in broilers:**
protection of Poulvac only for O78

⊗ **Candidosis in turkeys:**
risk of parconazole premix abandon (WP 1d thanks to NVR)

🔗 **Coccidiosis in turkeys & guinea fowls:**
upcoming in ovo vaccines only for Gallus

⊗ **Haemorrhagic enteritis Turkeys & pheasants:**
shortage of the unique vaccine i.e DINDORAL

Nearly solved:

🔗 **Colibacillosis in laying hens:**
Poulvac *E. coli*: **contra-indication removed. Autovaccines**

🔗 **Coccidiosis in standard broilers:**
upcoming in ovo vaccines (3 vaccines only for Gallus short productions)

IAHP
Sanitary policy & new vaccines to come

General remarks:

1. **Absence of antipyretics :**
economic impact +++
2. **Sector penalised by lack of MRLs** (paracetamol, praziquantel, enilconazole)
3. **Turkeys sector highly penalised** by therapeutic gaps
4. **Organic and alternative farming favours certain diseases** (e.g teniasis, histomonosis)
5. **Valuable use of autovaccines**, even if approved VMPs are available

N° 1 🔗 **Fever and inflammation control in viral infections in laying hens:**
no antipyretics without eggs downgrading
no MRL for eggs or poultry for:
paracetamol: cascade eggs WP ≥10 d
aspirin: forbidden in laying hens

N° 2 🔗 **Histomonosis in turkeys, guinea fowls, label and laying hens:**
no VMPs with MA (difficult development of live vaccines)

N° 3 🔗 **Aspergillosis in turkeys**
off-label enilconazole spraying in presence of animals
MA and MRL only for cattle & horses,
for topical use → « cascade » WP ≥ 1d

N° 4 🔗 **Teniasis in laying hens and breeders no MRL** of praziquantel in eggs, off-label use of benzimidazoles

N° 5 🔗 **Pain and welfare management for « convenience acts** (caponizing, guinea fowl wing jointing):
problems of immunocastration, no local anesthetics, neither ketoprofen MA

MAJOR

GAPS IN PIG SECTOR

HEARING OF 18/11/22



Impact on ATM use incl. absence or limited alternatives

MINOR

Post-weaning colibacillosis:

vaccination of sows without sufficient effect Window of deficiency of piglets immune protection → use of ATM

Neonatal diarrhoea due to *E. coli*:

vaccines ± effective → autogenous vaccines / ATB → risk of resistances

⊗ *Glaesserella parasuis*:

vaccines ± effective, import

Genital infections:

no local ATB with such MA

Nearly solved:

Neonatal diarrhoea due to *Clostridium*:
new vaccines

⊗ Post-partum:

HEMOGEN import, then **ATU 2022**

Actinobacillosis:

vaccines ± effective, autovaccines and ATB satisfactory

Existing solution:

Ileitis: new vaccine
(PORCILIS lawsonia – MA 2019)

Leptospirosis: new vaccine since 2019
(PORCILIS ERY+PARVO+LEPTO)

General remarks:

1. Risk of disappearance of medicated feed and pre-mixes: critical impact for macrolides & βactamines

2. Compliance with the SPC (Art 106 NVR) may be problematic for old antibiotics with inappropriate dosages

N° 1

⊗ Neonatal diarrhoea due to enterococci or rotavirus:
no vaccines available yet

N° 2

⚠ Influenza:
current vaccines ± effective,
interference with maternal immunity, evolution of strains. Risk of zoonosis

N° 3

⊗ Anesthetics for castration
⚠ the only recommended VMP not very effective and poorly tolerated

N° 4

⊗ *Streptococcus suis*:
no marketed vaccine
→ Autovaccines ± satisfactory or antibiotics (βactamines)

N° 5

⊗ *Brachyspira*:
no marketed vaccine
⚠ → use of macrolides
Brachy RB Porcs efficacy ? (new ATU)

MAJOR

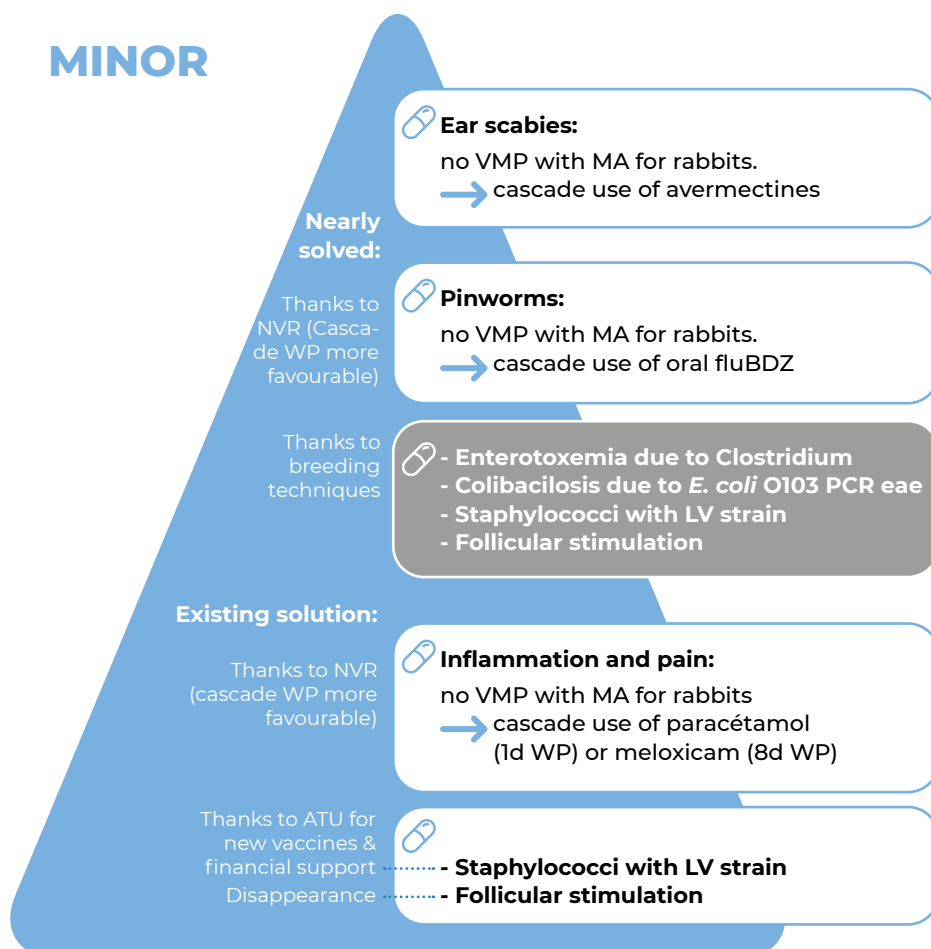
GAPS IN RABBIT SECTOR

HEARING OF 13/06/22



Impact on ATM use incl.
absence or limited
alternatives

MINOR



MAJOR

- N° 1** **Respiratory diseases due to pasteurella, mycoplasma and/or bordetella:**
no vaccines with MA for rabbits
ATB still widely used
WP issues (tilmicosin & oxyTC)
- N° 2** **Coccidiosis:**
residues concerns with WP of TMP-sulfa premix
limited efficacy of additives
wish for a rabbits' MA for other oral anticoccidials
- N° 3** **Ringworm (zoonosis)**
no VMP with MA for rabbits
→ import of BIOVETA vaccine or
→ cascade use of IMAVERAL

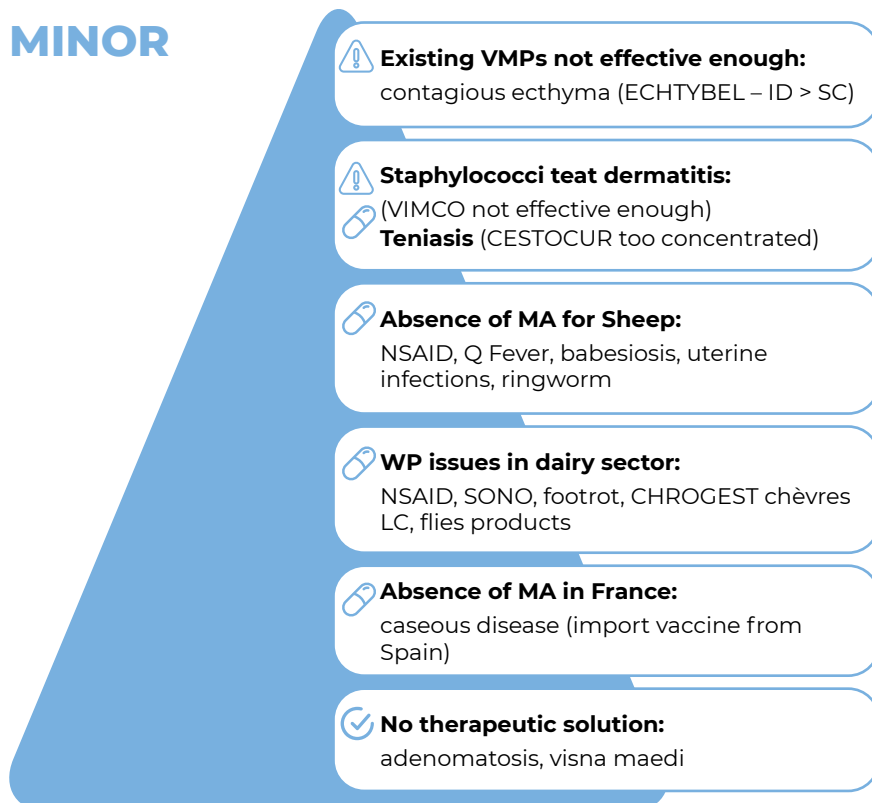
GAPS IN SHEEP/GOAT SECTOR

HEARING OF 16/04/21

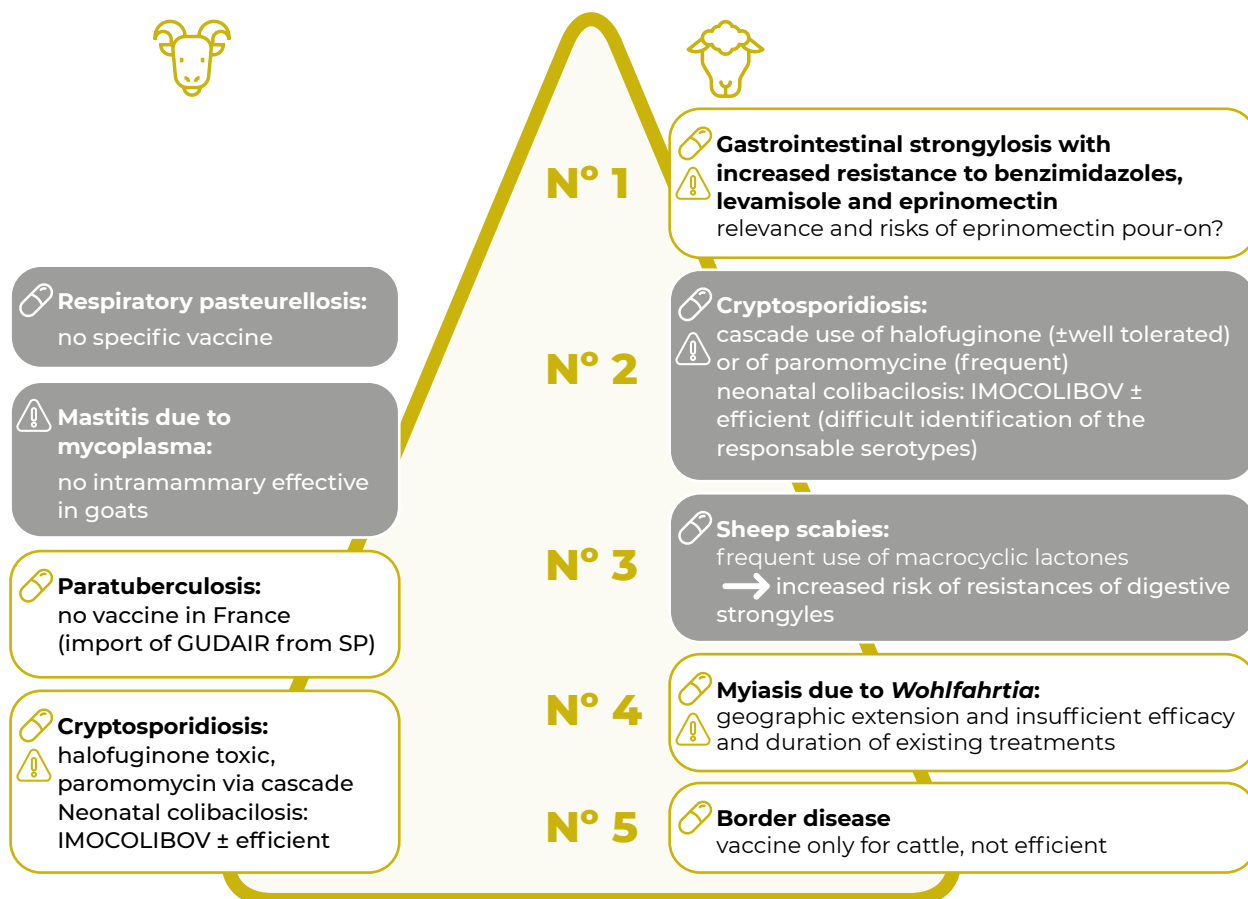


Impact on ATM use incl. absence or limited alternatives

MINOR



MAJOR



APPENDIX B – LIST OF MAJOR PRIORITY THERAPEUTIC GAPS IN FRANCE

Table 1. Main major priority therapeutic gaps recorded during the hearings conducted in 2021-2022 for the various animal sectors (except companion animals).

Sector	Therapeutic gaps				
	N°1	N°2	N°3	N°4	N°5
Bees	Varroosis (APIBIOXAL caramelisation when sublimation use and galenic problems for VARROMED)				
Cattle	Need for topical antibiotics in case of : ocular infections with corneal lesions and teat injuries	Respiratory mycoplasmosis	Oral antipyretics for calves	Oral tranquilisers	Paramphistomosis Dicrocoeliosis
Fish	External parasitism Balneotherapy of cutaneo-branchial parasites, mainly protozoa and monogenic worms	Most common bacteriosis treatment: yersiniosis, furunculosis, vibriosis, lactococcosis etc. Metaphylactic oral treatment of septicemic bacteriosis (after coating the premix onto the feed)	Prevention of virosis : • IPN (Infectious Pancreatic Necrosis - Togavirus) • Emerging virosis (reovirus)		
Horses	Non critical injectable antibiotics for IV route, in case of intensive care	Chondroprotection			
Poultry	Fever and inflammation control in case of viral infections Laying hens	Histomonosis Turkeys, Guinea fowl, volailles label and laying hens	Aspergillosis Turkeys	Teniasis (cestodes) Laying hens on ground & reproductive hens	Pain and welfare control for «convenience acts»: caponising, guinea fowls wing jointing
Pigs	Post-weaning colibacillosis	Influenza	Local anesthesia for castration	<i>Streptococcus suis</i>	<i>Brachyspira</i>
Rabbits	Respiratory diseases due to <i>pasteurella</i> , <i>mycoplasma</i> and/or <i>bordetella</i>	Coccidiosis	Ringworm		
Goats and Sheep	Gastrointestinal strongylosis, because of increasing resistance to benzimidazoles, levamisole and eprinomectin	Respiratory pasteurellosis Cryptosporidiosis Neonatal colibacillosis	Mastitis due to <i>Mycoplasma</i> Ovine scabies	Paratuberculosis Myiasis due to <i>Wohlfahrtia magnifica</i> and <i>Lucilia sericata</i>	Cryptosporidiosis Border disease

APPENDIX C – LIST OF MAJOR PRIORITY THERAPEUTIC GAPS IN SPAIN

PRIORITIES: BEES



Varroosis

Other VMPs available

PRIORITIES: CATTLE



Coccidiosis

Decoquinate for individual treatment



Respiratory infections

Pleuromutilins, injectable forms



Leptospirosis

Vaccines (*L. pomona*)

Other needs

- Tetracyclines: review and adjustment of the SPC
- Alternatives to group B antibiotics for dairy cattle. Options with shorter withdrawal time in milk from group C and D
- Topical antibiotic forms for ocular infections and teat injury

PRIORITIES: DOGS AND CATS



DISEASE	ACTIVE SUBSTANCE	ROUTE
Sepsis	ampicillin/amoxicillin	intravenous
	cefazoline	intravenous
	metronidazol	intravenous
Viral eye infections	ganciclovir	eye drops (cats) ⚠
Bacterial eye infections	chloramphenicol	eye drops
	ciprofloxacin	eye ointment

Other needs/issues

- VMPs for Keratoconjunctivitis sicca
- 'Reserved' List
- Antimicrobials for topic use

PRIORITIES: EQUINES



Theileriosis ⚠

Buparvacuone



Sepsis ⚠

Availability of antibiotics as intravenous forms, metronidazol and other antibiotics from group C and D

Other needs

- Ectoparasiticides: availability of other VMPs
- Antimicrobials for topic use

PRIORITIES: FISH FARMING








DISEASE	ACTIVE SUBSTANCE	ROUTE	SPECIES
External parasitosis	formaldehyde	bath	other species apart from gilthead and turbot
	others	bath	
Flavobacteriosis	oxytetracycline	premix	trout, rainbow trout
Furunculosis			gilthead, seabass, sole, trout, turbot
Pasteurellosis			gilthead, meagre, seabass
Tenacibaculosis			gilthead, seabass, seriola, sole, turbot
Vibriosis (not caused by <i>V. anguillarum</i>)			gilthead, meagre, seabass, seriola, sole, turbot

Other needs/issues

- Other antibiotics
- Polyvalent vaccines

PRIORITIES: PIG FARMING



-  **Diarrhoea in piglets caused by rotavirus** 
Vaccine
-  **Neonatal diarrhoea and post weaning colibacillosis** 
VMPs and vaccines
-  **Swine dysentery**
Bacitracin methylene salicylate
Vaccines

Other needs

- Tetracyclines and florfenicol: review and adjustment of the SPC

PRIORITIES: POULTRY



Broilers and Turkeys



Salmonella, different serotypes
In-ovo vaccines



Enteric and respiratory infections
Other antibiotics with shorter duration of treatments & withdrawal periods



Hemorrhagic enteritis (turkeys) ⚠️
Vaccine

Other needs

- VMPs against Histomoniasis & Aspergillosis
- In-ovo vaccines for other diseases



Laying birds



Respiratory infections ⚠️
• Vaccines

- Bronchodilators, mucolytics
- Anti-inflammatory drugs



Enteric and respiratory infections
• Vaccine
• Antiparasite drugs



Hemorrhagic enteritis (turkeys) ⚠️
• Vaccine



Epizootic rabbit enteropathy

- Avilamycin (oral, premix) or others antibiotics
- Enzymes complex as feed additive



Coccidiosis

Other VMPs available



Staphylococcal mastitis

Long-acting penicillins (parenteral)



Myxomatosis

Review and update of available vaccines



Respiratory infections

Vaccines



Ringworm

Vaccines and VMPs

PRIORITIES: SMALL RUMINANTS



**Sheep
& Goats**



Cryptosporidiosis

Other VMPs available



Mastitis

Intramammary VMPs such as cloxacillin ⚠



Anti-inflammatory drugs ⚠



Sheep



Ovine respiratory disease complex

Vaccine



Goats



Mycoplasmosis

- Marbofloxacin as injectable form
- VMPs for mastitis



Coccidiosis

- Diclazuril (oral forms)



Respiratory infections

- Vaccines

APPENDIX D – LIST OF THERAPEUTIC GAPS AND THERAPEUTIC NEEDS IN SPAIN

Information extracted from [CODI-VET 2022](#)

Table 1. Main major priority therapeutic gaps for bees.

Animal sector	Priority	VMP
Apicultura	1	<ol style="list-style-type: none"> 1. Medicamentos frente a la varroosis: nuevos medicamentos veterinarios que contengan sustancias activas diferentes a las autorizadas, que permitan realizar una rotación en los tratamientos. Asimismo, tengan otras formas o vías de administración en las colmenas (por ejemplo, a base de ácido oxálico en tiras) 2. Medicamentos frente a <i>Nosema spp</i>
	2	<ol style="list-style-type: none"> 1. Medicamentos frente a <i>Galleria spp</i>

Table 2. Main major priority therapeutic gaps for cats and dogs.

Animal sector	Priority	VMP
Gatos y perros	1	<ol style="list-style-type: none"> 1. Medicamentos para procesos oftalmológicos: <ul style="list-style-type: none"> • Antimicrobianos: tetraciclina, tobramicina y enrofloxacino • Antivirales: aciclovir, ganciclovir y remdesivir • Corticoides: dexametasona • Antiinflamatorios no esteroideos (AINE): diclofenaco y ketorolaco • Antiglaucomatosos: betaxolol, dorzolamida, timolol y latanoprost • Cicatrizantes: vitamina A • Midriáticos, ciclopléjicos: atropina, fenilefrina y ciclopentolato • Anestésicos locales: tetracaína y oxibuprocaina • Agentes para diagnóstico: fluoresceína, rosa bengala y verde lisamina • Colirios antibióticos y antifúngicos sin estar asociados a otras sustancias activas (p. ej. antiinflamatorios) • Inmunosupresor oral: tacrolimus 2. Medicamentos para procesos del aparato digestivo: <ul style="list-style-type: none"> • Antisecretores gástricos: ranitidina, famotidina, omeprazol • Antiulcerosos: sucralfato • Antiinflamatorios intestinales: mesalazina y sulfasalazina • Simpaticolíticos: prazosina • Antieméticos y procinéticos: metoclopramida (en formas farmacéuticas orales) y cisaprida • Estimulantes apetito: mirtazapina oral • Contrastes iodados, gastrografin y sulfato bario • Sistema Biliar: ácido ursodesoxicólico oral 3. Antineoplásicos: <ul style="list-style-type: none"> • Orales: ciclofosfamida, lomustina, metotrexato, clorambucilo, melfalan y temozolamida • Subcutáneos: asparaginasa y citarabina • Intravenosos: vincristina, vimblastina, ciclofosfamida, doxorubicina, citarabina, actinomicina B, mitoxantrona, cisplatino, carboplatino, estreptozocina, bleomicina, vinorelbina, dacarbacina y 5-fluorouracilo 4. Diuréticos: furosemida (en formas farmacéuticas inyectables) y manitol 5. Sustitutivos del plasma: expansores plasmáticos, isoplasmas, lipofundina, dextrano y albumina 6. Medicamentos para procesos del aparato reproductor: misoprostol, análogos de la gonadorelina e inhibidores de las contracciones uterinas y progesterona

Table 2. Main major priority therapeutic gaps for cats and dogs. (*Continuation*)

Animal sector	Priority	VMP
Gatos y perros	1 (Cont.)	<p>7. Medicamentos para enfermedades endocrinas:</p> <ul style="list-style-type: none"> • Enfermedad de Addison: fludrocortisona • Hiperadrenocorticismo: en concentraciones adecuadas para animales de pequeña masa corporal • Acromegalia e insulinooma: pasireotida (análogo de somatostatina), diazóxido y estreptozocina • Diagnósticos: hormona adrenocorticotropa (ACTH), tetracosactida <p>8. Medicamentos psicótrpos: midazolam, diazepam (en formas farmacéuticas orales) y lorazepam</p> <p>9. Medicamentos de uso en cardiología: dopamina, dobutamina, procainamida, amiodarona, fenilefrina, efedrina, isoprenalina, vasopresina, adrenalina, noradrenalina, atenolol, sotalol, mexiletina, digoxina, diltiacem, amiodarona, esmolol, lidocaína, sildenafil y terbutanilo</p> <p>10. Anestésicos locales: bupivacaína, mepivacaína y lidocaína</p> <p>11. Estupefacientes: morfina, petidina y dihidrocodeína</p> <p>12. Antimuscarínicos: atropina, escopolamina y glicopirrolato</p> <p>13. Antagonistas de la morfina: naloxona</p> <p>14. Antiepilépticos: valproato, levetiracepam y bromuro potásico</p> <p>15. Sangre y hemoderivados: antitrombóticos (heparina sódica), antiagregantes plaquetarios (ácido acetilsalicílico y clopidogrel), antifibrinolíticos (ácido tranexámico) otros antianémicos (darbepoetina) y activador plaminógeno tisular</p> <p>16. Antiasmáticos: salbutamol y teofilina, y corticoides en formas farmacéuticas inhalatorias o por nebulización</p> <p>17. Antihistamínicos</p> <p>18. Agentes para diagnóstico: lopromida y gadoteridol</p> <p>19. Antibióticos en formas farmacéuticas intravenosas: cefazolina, ampicilina y metronidazol (también en forma de jarabe)</p> <p>20. Antitusivos: codeína, dextrometorfano y butorfanol</p> <p>21. Vacunas frente a coronavirus</p> <p>22. Mucolíticos: acetilcisteína y bromhexina en formas farmacéuticas orales</p> <p>23. Antibióticos tópicos: sulfamidas, gentamicina, mupirocina</p> <p>24. Dermatológicos: inmunosupresores (micofenolato de mofetilo y azatioprina), DMSO en solución acuosa para tratamiento de la calcinosis cutis, imiquimod (en forma farmacéutica tópica), retinoides (sistémicos y tópicos), pentoxifilina, antifúngicos (terbinafina e itraconazol en formas farmacéuticas orales), antivirales (sistémicos y tópicos) y corticoides (prednisolona, prednisona, dexametasona y triamcinolona en formas farmacéuticas orales. Prednisolona en forma farmacéutica tópica)</p> <p>25. Inmunosupresores: tacrolimus y sirolimus</p> <p>26. Antifúngicos: sistémicos (fluconazol) y tópicos (en forma farmacéutica de pomada)</p>
	2	<p>1. Medicamentos para tratamientos de alergias cutáneas: antihistamínicos y corticoides en formas farmacéuticas tópicas</p> <p>2. Antiprotozoarios: buparvacuona para el tratamiento de la infección por Babesia microti-like (sin. <i>Theileria annae</i>)</p> <p>3. Laxantes de administración oral y por vía rectal: macrogol</p>

Table 2. Main major priority therapeutic gaps for cats and dogs. (*Continuation*)

Animal sector	Priority	VMP
Gatos y perros	2 (Cont.)	4. Anestésicos generales: etomidato
		5. Analgésicos no opioides: paracetamol y amantidina
		6. Analgésicos en procesos neuropáticos: gabapentina
		7. Psicotrópos para el manejo del “miedo”: benzodiacepinas (alprazolam, cloracepato), SARI (trazodona), agonistas α -2 adrenérgicos (clonidina) y antidepresivos tricíclicos (TCA) (amitriptilina), gabapentina, cloracepato, fluvoxamina y sertralina
		8. Células madre para tratamientos articulares y oculares
		9. Plasma rico en plaquetas para tratamientos articulares
		10. Vacunas frente a ectoparásitos (vectores de enfermedades infecciosas como garrapatas y pulgas)
		11. Antibióticos sistémicos (en formas farmacéuticas orales e inyectables): ácido fusídico, azitromicina, rifampicina, ticarcilina, amikacina e imipenem
		12. Antibióticos óticos: sulfamidas, tobramicina, kanamicina y vancomicina
		13. Alopurinol
		14. Antiepilépticos de administración rectal

Table 3. Main major priority therapeutic gaps for fish.

Animal sector	Priority	VMP
Acuicultura	1	1. Antiparasitarios internos frente a: <i>Uronema (philasterides)</i> , <i>Enterospora</i> , <i>Enteromyxum</i> , <i>Cryptosporidium</i> (apicomplexa: <i>C. molnari</i> , <i>C. scopthalmi</i>), <i>Myxo-zoos (enteromyxum)</i> – toltrazuril y triazinona) y coccidios (apicomplexa: <i>Eimeria</i> , <i>Goussia</i> – monensina, amprolio, salinomicina y decoquinato)
		2. Antiparasitarios externos frente a <i>Monogeneas</i> : praziquantel en formas farmacéuticas orales y para inmersión o baño, mebendazol en formas farmacéuticas orales y para inmersión o baño, y peróxido de hidrógeno
		3. Antiparasitarios externos frente artrópodos: deltametrina, azametifos, diflubenzuron y lufenuron
		4. Antimicrobianos: flumequina (para otras especies que no sea la trucha), ácido oxolínico, sulfamidas combinadas con otros antibacterianos, neomicina, amoxicilina y gentamicina, en formas farmacéuticas orales y para inmersión o baño, y oxitetraciclina en formas farmacéuticas para el baño
		5. Anestésicos generales (benzocaína – existe una autorizada, pero se precisa registrarla para otras especies)
		6. Tranquilizantes: isoeugenol y eugenol
		7. Vacunas frente a <i>Aeromonas salmonicida</i>
		8. Vacunas frente a nodavirus en doradas
		9. Vacunas frente a <i>Pseudomona anguilliseptica</i>
		10. Vacuna frente a <i>Flavobacterium psychrophilum</i>
		11. Vacunas frente a <i>Vibrio harveyi</i>
		12. Vacunas frente a <i>Tenacibaculum spp.</i>
		13. Hormonas: gonadotropina coriónica, GnRH, metiltestosterona, 17β estradiol y dietilestilbestrol

Table 3. Main major priority therapeutic gaps for fish. (*Continuation*)

Animal sector	Priority	VMP
Acuicultura	2	<ol style="list-style-type: none"> 1. Medicamentos farmacológicos con concentraciones de la/s sustancia/s activa/s mayores a las actuales 2. Medicamentos en forma de premezcla medicamentosa y en forma de inmersión o baño 3. Vacunas polivalentes (<i>Photobacterium damsela</i> subsp. <i>piscicida</i>; <i>Photobacterium damsela</i> subsp. <i>piscicida</i>, <i>Vibrio anguillarum</i> y <i>Aeromonas salmonicida</i> subsp. <i>Salmonicida</i> para lubina; <i>Lactococcus garvieae</i> y <i>Yersinia ruckeri</i> (biotipos 1 y 2) destinado a trucha arcoiris), en formas farmacéuticas orales, en particular, en forma de premezclas medicamentosas 4. Probióticos y postbióticos para la prevención y control de estas enfermedades en acuicultura (p.ej. para el tratamiento de <i>Mycobacteriosis</i>)

Table 4. Main major priority therapeutic gaps for goats and sheep.

Animal sector	Priority	VMP
Ovino-caprino	1	1. Antiparasitarios: ivermectina en forma de premezcla medicamentosa, ivermectina en forma farmacéutica inyectable para caprino y halofuginona en formas farmacéuticas orales
		2. Anticoccidiósicos en formas farmacéuticas orales: toltrazurilo y diclazurilo para caprino, amprolio para ovino y caprino
		3. Antimicrobianos para procesos respiratorios y procesos reproductivos en formas farmacéuticas orales: doxiciclina y enrofloxacino
		4. Antimicrobianos para el complejo respiratorio ovino (CRO) en ovino y caprino: tulatromicina en formas farmacéuticas inyectables
		5. Mucolíticos: bromhexina (en formas farmacéuticas orales)
		6. Antiinflamatorios: dexametasona (en formas farmacéuticas inyectables) y ketoprofeno (en formas farmacéuticas orales e inyectables)
		7. Vacunas frente al complejo respiratorio ovino (CRO) que incluyan los tres microorganismos principales (<i>Mannheimia haemolytica</i> , <i>Bibersteinia trehalosi</i> y <i>Pasteurella multocida</i>)
		8. Vacunas frente a ectoparásitos (vectores de enfermedades infecciosas)
	2	9. Medicamentos de uso oftálmico: antimicrobianos (tetraciclina, tobramicina y enrofloxacino) y corticoides (dexametasona y prednisolona)
		1. Antiparasitarios en premezcla medicamentosa: albendazol y fenbendazol
		2. Antiparasitarios frente a cisticercos
		3. Antiparasitarios frente a la sarna en ovino y caprino: eprinomectina (en formas farmacéuticas inyectable y <i>pour-on</i>)
		4. Antiparasitario frente a fasciola hepática en ovinos y caprinos: oxiclozanida (en formas farmacéuticas orales)
		5. Antifúngicos: enilconazol frente a dermatomicosis en ovino y caprino en formas farmacéuticas tópicas
		6. Anticoccidiósicos en formas farmacéuticas orales: sulfadimetoxina y sulfadimetoxina + ftalilsulfatiazol
		7. Antiinflamatorios con efectos antiinflamatorio, analgésico y antipirético para procesos respiratorios, mamarios y musculoesqueléticos: flunixin meglumina y ácido tolfenámico, ambas en formas farmacéuticas inyectables

Table 4. Main major priority therapeutic gaps for goats and sheep. (*Continuation*)

Animal sector	Priority	VMP
Ovino-caprino	2 (Cont.)	8. Antiinflamatorios en ovino y caprino: metilprednisolona en formas farmacéuticas inyectables
		9. Hormonales para sincronización del celo: prostaglandinas y flugestona y medroxiprogesterona en esponjas vaginales en caprino
		10. Antimicrobianos: tilosina (en formas farmacéuticas orales), lincomicina, lincomicina + espectinomicina (en premezclas medicamentosas), marbofloxacino (en formas farmacéuticas inyectables), oxitetraciclina (en comprimidos / bolos intrauterinos), cefalexina, cefapirina y rifaximina (para uso intramamario)
		11. Antimicrobianos para procesos respiratorios y procesos reproductivos: ceftiofur (en formas farmacéuticas inyectables)
		12. Anestésicos: xilacina y lidocaína
		13. Vacunas frente a <i>Clostridium botulinum</i> tipos C y D para ovino y caprino
		14. Vacunas polivalentes frente a pasteurellas para ovino y caprino
		15. Vacunas frente a toxoplasma en caprino
		16. Vacunas frente a <i>Coxiella burnetii</i> en ovino
		17. Vacunas frente a cisticercos en ovino y caprino
		18. Vacunas frente a pseudotuberculosis en ovino y caprino
		19. Vacunas frente a coccidios en ovino y caprino

Table 5. Main major priority therapeutic gaps for horses.

Animal sector	Priority	VMP
Équidos	1	1. Medicamentos para procesos articulares: glucosamina y condroitín sulfato, hidrogel de poliacrilamida
		2. Antimicrobianos: bencilpenicilina sódica, amoxicilina/clavulánico oral, ampicilina, amikacina, polimixina B, cefpodoxima, cefalexina, cefquinoma, ceftiofur sódico endovenoso, doxiciclina, azitromicina, claritromicina, eritromicina, enrofloxacin oral, rifampicina, ticarcilina, metronidazol (en formas farmacéuticas orales e intravenosa) y fosfomicina
		3. Antiinflamatorios: betametasona, ácido acetilsalicílico, dimetilsulfóxido, AINE COX 2, firocoxib en formas farmacéuticas orales, flunixin meglumina en formas farmacéuticas orales, dexametasona en formas farmacéuticas orales, beclometasona inhalada, fluticasona inhalada, budenosina inhalada
		4. Medicamentos para procesos del aparato reproductor: análogos de la gonadorelina en formas farmacéuticas inyectables, estrógeno cipionato y progestágenos-progesterona de acción retardada
		5. Anestésicos generales: propofol
		6. Miorrelajantes: guaifenesina, metocarbamol, dantroleno
		7. Anestésicos locales: bupivacaína
		8. Psicotrópos: diazepam, acetilpromazina en formas farmacéuticas orales, alprazolam, fluoxetina y midazolam
		9. Medicamentos para procesos digestivos: metoclopramida, sucralfato, subsalicilato de bismuto, Plantago ovata o psyllium, cimetidina, misoprostol, betanecol, lidocaína y omeprazol en formas farmacéuticas inyectables
		10. Anticoagulantes: heparina, nadroparina cálcica en formas farmacéuticas inyectables subcutánea, enoxaparina sódica, dalteparina sódica y clopidogrel

Table 5. Main major priority therapeutic gaps for horses. (*Continuation*)

Animal sector	Priority	VMP
Équidos	1 (Cont.)	11. Tratamiento de las hemorragias: ácido aminocaproico y ácido tranexámico
		12. Medicamentos para mejorar la perfusión tisular y como coadyuvante en el tratamiento de enterotoxemias: pentoxifilina en formas farmacéuticas oral e inyectable
		13. Medicamentos para tratar estados de hipovolemia: hidroxietilalmidón y cloruro de sodio, solución hipertónica 7,5%, glucosalino 5%, solución de Ringer, solución de Ringer lactato
		14. Antiprotzoarios: buparvacuona (frente a la teileriosis por <i>T. equi</i>)
		15. Diuréticos: furosemda, manitol intravenoso y acetazolamida
		16. Medicamentos para tratamientos musculares: sales selenio en formas inyectables y dantroleno sódico
		17. Agonistas adrenérgicos: salbutamol inhalado y adrenalina, dobutamina y fenilefrina en formas inyectables), medetomidina
		18. Antagonistas adrenérgicos: atipamezol hidrocloreto
		19. Electrolitos y derivados: cloruro potásico, sulfato de magnesio, cloruro cálcico en formas farmacéuticas inyectable y bicarbonato sódico en formas farmacéuticas inyectable y oral
		20. Antihistamínicos: hidroxizina en formas farmacéuticas orales
		21. Antineoplásicos: cisplatino en formas farmacéuticas inyectables y bolas retardo con aceite de sésamo, imiquimod crema, 5-fluorouracilo crema y mitomicina C
		22. Estimulantes respiratorios: cafeína y naloxona
		23. Antimuscarínico: Bromuro de ipratropio inhalado, atropina formas farmacéuticas inyectables, escopolamina formas farmacéuticas inyectables y glicopirrolato formas farmacéuticas inyectable e inhalado
		24. Vasopresores: vasopresina formas farmacéuticas inyectables
		25. Medicamentos para procesos cardíacos y antiarrítmicos: digoxina, verapamilo, quinidina formas farmacéuticas oral e inyectable, flecainida, propranolol, quinapril y amiodarona
		26. Hormonas tiroideas para suplementación: levotiroxina
		27. Derivados opioides: metadona formas farmacéuticas inyectable, fentanilo en parches cutáneos y morfina formas farmacéuticas inyectables
		28. Antivirales: valaciclovir y ganciclovir
		29. Medicamentos para procesos oftalmológicos: Antimicrobianos si estar en asociación (ciprofloxacino, cloranfenicol, enrofloxacin, gentamicina, tetraciclina y tobramicina), antivirales (aciclovir), antiinflamatorios esteroideos (dexametasona y prednisolona), antiinflamatorios no esteroideos (bromfenaco y diclofenaco), antiglaucomatosos (betaxolol y dorzolamida), antifúngicos (miconazol y voriconazol), cicatrizantes (vitamina A), agentes para diagnóstico (fluoresceína), atropina, ciclopentolato, tropicamida, tetracaína, pilocarpina, timolol, antiedema (NaCl hipertónico) y fenilefrina
		30. Anticolvulsionantes: fenobarbital y gabapentina
		31. Antídotos: flumazenil, carbón activado y naloxona
	2	1. Antidopaminérgicos: sulpirida y domperidona vía intravenosa
		2. Agentes dopaminérgicos: pergolida oral y dopamina inyectable
		3. Fluidos de uso en diálisis peritoneal

Table 5. Main major priority therapeutic gaps for horses. (*Continuation*)

Animal sector	Priority	VMP
Équidos	2 (Cont.)	4. Conjugado de proteína análogo del factor de liberación de la gonadotropina (GnRF) como alternativa a la castración física: flutamida
		5. Antioxidantes/nutrición: vitamina C y glutamina
		6. Plasma rico en plaquetas para tratamientos articulares
		7. Vacuna frente a la arteritis viral equina

Table 6. Main major priority therapeutic gaps for laying hens and poultry.

Animal sector	Priority	VMP
Aves de puesta	1	1. Antiparasitarios frente al ácaro rojo: foxima. Aun habiendo autorizado en España un medicamento a base de fluralaner, se considera una necesidad prioritaria tener a corto plazo medicamentos que contengan sustancias activas diferentes, que permitan realizar una rotación en los tratamientos
		2. Anticoccidiósicos en especies menores (p. ej. codornices) alternativos al amprolio
		3. Antimicrobianos frente a la colibacilosis que sean alternativas a la colistina, para gallinas ponedoras, codornices, patos, ocas, pavas reproductoras, etc.
		4. Vacunas frente a micoplasmas (<i>Mycoplasma gallisepticum</i> en otras especies como codornices y pavas reproductoras)
		5. Vacunas frente a <i>Mycoplasma synoviae</i> para pavas reproductoras
		6. Vacunas frente a <i>Ornithobacterium ryanotrichae</i> (ORT) para pavas reproductoras, gallinas reproductoras pesadas y otras especies
		7. Vacunas frente a coccidios en especies menores (codornices, pavas reproductoras, etc.)
		8. Vacunas frente a laringotraqueitis infecciosa en otras especies que no sean gallinas
		9. Vacunas frente a colibacilosis en gallinas ponedoras y en otras especies (p. ej. codornices)
		10. Antiparasitarios frente a histomonas (tanto en gallinas en sistemas de producción alternativos como en otras especies como pavas reproductoras, codornices, patos y ocas)
		11. Antimicrobianos en especies menores (p. ej. codornices, perdices, faisanes, ocas, patos, etc.): amoxicilina
		12. Vacunas frente a ectoparásitos
	2	1. Antiparasitarios frente a áscaris y heterakis: flubendazol (en formas orales), tanto para gallinas en sistemas sin jaula, pavas, codornices y otras especies
		2. Medicamentos frente a la enteritis necrótica, tanto en gallinas ponedoras como en otras especies (p. ej. codornices)
		3. Vacunas frente a enteritis necrótica (<i>Clostridium perfringens</i> tipo A), tanto para gallinas ponedoras como en otras especies (p. ej. codornices)
		4. Bacteriófagos para enfermedades de origen bacteriano como colibacilosis y salmonelosis en la cría de aves

Table 6. Main major priority therapeutic gaps for laying hens and poultry. (Continuation)

Animal sector	Priority	VMP
Aves de producción cárnica	1	1. Antiparasitarios frente a la histomoniasis de reproductoras pesadas y pavos
		2. Antiparasitarios frente al ácaro rojo en reproductoras para poder hacer rotaciones
		3. Medicamentos frente al escarabajo <i>Alphitobius</i>
		4. Antibióticos como alternativa a la colistina para el control intestinal del <i>E. coli</i>
		5. Vacunas frente a adenovirus que incluyan los serotipos 8b y 11
		6. Vacunas frente a la enteritis hemorrágica del pavo
		7. Vacunas vivas frente a salmonela de declaración y <i>Salmonella spp.</i> para la cría de pollos, pavos y otras especies aviares
		8. Vacunas inactivadas frente a salmonelas zoonóticas y <i>Salmonella spp.</i> para pollos, pavos y otras especies aviares
		9. Vacunas frente a <i>Mycoplasma gallisepticum</i> y <i>M. synoviae</i> para pavos de engorde
		10. Tratamientos y vacuna frente a pasteurellosis en pavos
		11. Tratamientos y vacunas frente a <i>Ornithobacterium ryantracheale</i> (ORT)
		12. Vacunas frente a coccidiosis en pavo de engorde
		13. Vacunas frente a <i>Clostridium perfringens</i> (enteritis necrótica) en pavo de engorde
		14. Vacunas frente a ectoparásitos (vectores de enfermedades infecciosas)
		15. Antimicrobianos en especies menores: amoxicilina
	2	1. Desarrollo de virus bacteriófagos frente a <i>E. coli</i> y <i>Salmonella</i>

Table 7. Main major priority therapeutic gaps for rabbits.

Animal sector	Priority	VMP
Conejos	1	1. Antimicrobianos: avilamicina, doxiciclina y sulfadiazina-trimetoprima (todas en forma de premezcla medicamentosa)
		2. Anticoccidiósicos: salinomina
	2	1. Antiparasitarios internos (frente a G° <i>Passalurus</i> y G° <i>Encephalitozoon</i>): flubendazol (en premezcla medicamentosa y en formas farmacéuticas solubles), fenbendazol y levamisol (en formas farmacéuticas orales solubles) e ivermectina (en formas farmacéuticas orales)
		2. Antiparasitarios externos: Ivermectina
		3. Anticoccidiósicos orales (solubles): amprolio, toltrazurilo y sulfamidas no absorbibles
		4. Acaricidas: foxima (en formas farmacéuticas tópicas), dimpilato, cipermetrina e ivermectina (en formas farmacéuticas orales e inyectables)
		5. Antifúngicos: enilconazol (en formas farmacéuticas tópicas)
		6. Antimicrobianos: penicilina y amoxicilina (en formas retardadas como penicilina G benzatina), oxitetraciclina (en formas farmacéuticas inyectables), espiramicina, tulatromicina y tilmicosina (en solución oral)
		7. Vacunas frente a coccidios
		8. Antimicrobianos inyectables para mastitis: oxitetraciclina y penicilinas de larga acción
		9. Vitaminas: complejos vitamínicos del grupo B y AD3E
		10. Suero fisiológico y suero glucosado

APPENDIX E – INFORMATION COLLECTED BY THE PORTUGUESE DIRECTORATE GENERAL OF FOOD AND VETERINARY (DGAV)

Table 1. Therapeutic gaps identified by different animal sectors and type of VMPs recorded by DGAV.

Animal sector	Type of VMP	Therapeutic gaps
Bovine	Biological	<ul style="list-style-type: none"> Passive immunisation against neonatal <i>Escherichia coli</i> infections by administration of the vaccine to pregnant cows or ewes. Reduction of diarrhoea and mortality caused by enterotoxigenic <i>E. coli</i> strains in both lambs and calves
	Pharmacological	<ul style="list-style-type: none"> Treatment and control of nematodes, gastrointestinal and lung cestodes and trematodes Pitomyxiosis is a recurrent disease, over the years, in cattle grazing during the summer months in the Azores (it also occurs in sheep and goats. It results from the contamination of pastures with <i>Pithomyces chartarum</i>. Pitomyxiosis induces clinical and subclinical secondary photosensitivity. In moderate and severe clinical cases, the white portion of the skin (in the case of Holstein-Frisian cattle, or sheep and goats) falls off. In severe cases, it can lead to the rejection or death of the animal. However, in mild clinical cases and in subclinical cases the signs are mild or not visible, there is extensive liver damage that affects animal health and welfare, production, as well as increasing the probability of culling due to loss of production Zinc oxide was administered to treat such disease
Fish	Pharmacological	<ul style="list-style-type: none"> Aquaculture premix containing emamectin benzoate - external parasites Hydrogen peroxide concentrate for solution for fish treatment Antibiotic indicated for the treatment of infections caused by microorganisms sensitive to flumequine
Pigs	Vaccine	<ul style="list-style-type: none"> Swine leptospirosis (<i>L. bratislava</i>, <i>L. canicola</i>, <i>L. grippotyphosa</i>, <i>L. hardjo</i>, <i>L. icterohaemorrhagiae</i>, <i>L. pomona</i>) <i>Streptococcus suis</i> serotype 9 Porcine epidemic diarrhoea (Coronavirus)
	Pharmacological	<ul style="list-style-type: none"> Swine dysentery (<i>Brachyspira hyodysenteriae</i>): bacitracin methylene disalicylate
Goats and Sheep	Vaccine	<ul style="list-style-type: none"> Ovine respiratory disease complex
	Pharmacological	<ul style="list-style-type: none"> Mastitis intramammary VMPs such as cloxacillin (group D) Anti-inflammatory drugs: dexamethasone, flunixin meglumine, meloxicam, carprofen More antibiotics (like marbofloxacin) Mycoplasmosis: marbofloxacin (group B) as injectable forms Coccidiosis: diclazuril (oral forms)

Table 2. Shortages in markets identified by different animal sectors and VMP and indication.

Animal sector	Type of VMP	Type of VMP
Cattle	Ampronium	Ectoparasiticide
Fish	Florfenicol	Antibiotic
Horses	Deltamethrin Ivermectin	Ectoparasiticide Ectoparasiticide
Pigs	Ivermectin Cypermethrin	Ectoparasiticide Ectoparasiticide
Rabbits	Oxytocin Tulathromycin Albendazol Acetylsalicylic acid	Obstetric use Antibiotic Gastrointestinal nematodes Antipyretic

Table 3. Special use authorisations recorded by DGAV by animal sector and type of VMP.

Animal sector	Type of VMP	Indication
Major needs		
Bovine	Vaccine	<i>Brucella abortus</i>
Broilers	Vaccine	<i>Haemophilus paragallinarum</i> serotypes A, B y C. Infectious laryngotracheitis virus <i>Mycoplasma gallisepticum</i>
Dogs	Pharmacological	Keratoconjunctivitis sicca
Fish	Vaccine	Tenacibaculose
Horses	Vaccine	Active immunisation against equine rhinopneumonia
Goats and sheep	Vaccine	Contagious ecthyma
Ban or limited by article 110 (Regulation (UE) 2019/6)		
Bovine	Vaccine	Immunisation against Leptospirosis (<i>L. Pomona</i>)
Pigs	Vaccine	Enterotoxemia and colibacillosis, and Swine epidemic diarrhoea virus

AVAILABILITY OF ANTIMICROBIAL MEDICINAL PRODUCTS AND ALTERNATIVES TO THEIR USE



Spanish Action Plan
on Antibiotic
Resistance



 agencia española de
medicamentos y
productos sanitarios