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Reflection paper on prophylactic use of antimicrobials in animals in the context of Article 107(3) of Regulation (EU) 2019/6

Draft

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Executive summary

Promoting the responsible use of antimicrobials in animals is one of the main aims of Regulation (EU) 2019/6 on veterinary medicinal products (VMPs) [1]. Amongst the measures introduced are restrictions on the use of antimicrobial medicinal products for prophylaxis, so that they may only be used in exceptional cases, in an individual or a restricted number of animals, when the risk of infection is very high and the consequences are likely to be severe (Article 107(3)). For antibiotics specifically, prophylaxis is limited to administration to an individual animal only.

According to Article 4(12) antimicrobials comprise antibiotic, antifungal, antiprotozoal and antiviral, substances. Currently, there are no veterinary marketing authorisations for antiviral substances.

The purpose of this reflection paper is (i) to establish an understanding of the term 'prophylaxis' as defined in Article 4(16) of the Regulation and (ii) to develop high level principles to guide the implementation of the restrictions on prophylactic use as required by the provisions of Article 107(3). The definition and restrictions are applicable whether prophylaxis is applied in accordance with an authorised indication for a VMP, or for any other antimicrobial use e.g. outside the terms of the marketing authorisation under the 'cascade' (Articles 112, 113 and 114).

Whilst preparing these reflections, the CVMP has also considered alternative management strategies and recommendations for reducing the need for antimicrobial prophylaxis as documented by previous reviewers and international organisations (e.g. RONAFA, OIE, FAO). However, it should be recognised that the principles established in this reflection paper are based upon the specific legislative provisions set out in the EU Regulation.

In order to understand the need for and practices relating to prophylactic use of antimicrobials in animals in the EU, short literature reviews were undertaken for antibiotics, antiprotozoals, antivirals and antifungals. The reviews aimed to identify publications from the last decade that have investigated the effectiveness of prophylactic use of antimicrobials in several major domestic species. It is important to note the limitations of the reviews in respect of their conduct and findings. No or very few studies were found relating to prophylactic use of antifungals and antivirals. As the effectiveness of antimicrobial prophylaxis has been investigated for few indications or circumstances, it was difficult to determine how far the findings could be generalised. In most cases, the findings were often inconclusive. It should also be noted that owing to the scope of the reviews, study endpoints did not investigate the impact of prophylaxis on AMR (antimicrobial resistance) development although this is an important part of the benefit-risk assessment for responsible use. Observations drawn from the review do not prejudice the claims for authorised VMPs, which are based on data provided according to current regulatory requirements.

The high-level principles below have been developed to provide an explanation of CVMP's understanding of the definition of 'prophylaxis' provided in Article 4(16) and the application of the associated risk management measures set out in Article 107(3).

Taking into account these principles, it will be necessary to review the marketing authorisations of authorised antimicrobial veterinary medicinal products to ensure that pharmaceutical forms, routes of administration and the phrasing of claims and guidance on usage are consistent with the Regulation. The review of existing products for compliance with Article 107(3) will be conducted following finalisation of this reflection paper. The approach to that work and the precise regulatory mechanism to implement changes required to individual marketing authorisations, if any, will be defined as part of the follow-on activity.

The risk management measures provided in Article 107(3) may have implications in particular for intramammary antibiotics administered at the start of the dry period and for anticoccidials.

A review of authorised VMPs containing antimicrobials suggests that very few have authorised claims that potentially align with prophylaxis as defined in the Regulation. Other than for antiprotozoals, this suggests that prophylactic use in many cases will occur under the 'cascade'. The high-level principles below can be applied to both authorised and 'cascade' use.

CVMP Recommendations

The 'high level principles' below have been developed from the CVMP's reflections on the definition of 'prophylaxis' (Article 4(16)) and the associated risk management measures set out in Article 107(3) of Regulation (EU) 2019/6.

Principle 1: 'Prophylaxis' is defined in Art 4(16) of Regulation (EU) 2019/6 as "administration of a medicinal product to an animal or group of animals before clinical signs of a disease, in order to prevent the occurrence of disease or infection".

Essentially this is understood by CVMP to correspond in timing to the administration of an antimicrobial at any time point before micro-organisms have invaded tissues and started to cause tissue damage or dysfunction.

Implications

The CVMP and national competent authorities (NCAs) should ensure that the term 'prophylaxis' is applied correctly in the product literature of authorised products, taking account of the supporting data provided in the application dossier (e.g. circumstances of the clinical trials in relation to initiation of treatment).

Veterinarians should consider if their intended antimicrobial use aligns with the Article 4 definition of prophylaxis. In practice, this relates to administration to a healthy animal without disease and without clinical signs. Once clinical signs have developed, or laboratory tests show evidence of tissue invasion and damage or dysfunction due to the infection, then the disease is present and the administration is no longer 'prophylaxis'.

When using an antimicrobial for prophylactic use outside the terms of the marketing authorisation ('cascade' use), the strength of evidence to support the effectiveness of proposed prophylactic use should be considered (see also Principle 2).

Principle 2: Consideration of regulatory risk management requirements for prophylaxis under Article 107(3): Antimicrobial medicinal products shall not be used for prophylaxis other than in exceptional cases, for the administration to an individual animal (antibiotics) or a restricted number of animals (antiprotozoals, antivirals, antifungals) when the risk of an infection or of an infectious disease is very high and the consequences are likely to be severe.

The stated terms are understood by CVMP as follows:

(a) 'administration to an individual animal' means that the decision to use an antimicrobial agent is made on the basis of the risk factors pertinent to a specific individual animal.

(b) a 'restricted number of animals' means administering an antimicrobial agent (except antibiotics) only to those animals per group/herd that are at the same time subjected to the same risk factor(s) that warrant the intervention.

(c) the 'risk of an infection' is dependent on the probability of the infection/disease to occur taking into account the related risk factors (e.g. contagiousness, host susceptibility, virulence factors, mechanism of transmission and spread, epidemiology of the disease, possible herd health control measures, etc.).

To fully characterise the risk, the probability of the infection/disease to occur should be considered with the associated consequences resulting from these infections/diseases.

(d) the 'consequences of infection' are dependent inter alia on the anticipated level of morbidity and mortality and the acuteness of disease onset all of which can impact on animal health and welfare, on public health and livestock production, though purely economic consequences should be disregarded

Implications

The CVMP and responsible NCAs should ensure that the pharmaceutical form/route of administration of the authorised VMP and disease indication, together with the summary of product characteristics (SPC) guidance and warnings, are in agreement with the requirements of Article 107(3). Likewise, when using an antimicrobial for prophylactic use under the 'cascade', the pharmaceutical form/route of administration of the VMP should be appropriate to the requirements of Article 107(3).

In both cases, the prescribing veterinarian should ensure for the specific 'animal(s) under their care' that the circumstances, risk factors impacting on the probability of diseases to occur and resulting consequences thereof are compliant with the requirements for Art 107(3) (see also Principle 1).

Principle 3: Antimicrobials should not be used for prophylaxis in place of alternative treatments to antimicrobials or management strategies that have shown to be effective in preventing (the) infection/disease. These measures and strategies have been laid out by OIE, RONAFA and in the EU Guidelines for the prudent use of antimicrobials in veterinary medicine (2015/C 299/04). They include, amongst others, use of vaccination, improved biosecurity, hygiene, husbandry systems and nutrition.

Principle 4: When prescribing antimicrobials for prophylaxis, the veterinarian should have a good knowledge of the causative pathogen(s) of the concerned disease(s), its epidemiology and the farm/clinic history, supported through e.g. recent aetiological diagnosis of an infection at the unit and susceptibility testing. Selection of antimicrobials should be based on these factors and also considering AMEG categorisation (for antibiotics) and recommendations on route of administration. SPC guidance and warnings should be followed. Antimicrobials should only be prescribed for the duration necessary to cover the period of very high risk, no longer than what is advised in the SPC, and the use should be justified and documented.

Taking into account these principles:

1. Prevention/prophylaxis claims for antimicrobial VMPs intended for incorporation into feed ('premixes') are not compliant with legislation since their use for prophylaxis is prohibited according to Regulation (EU) 2019/4 (Article 17(3)). For these products, prevention claims cannot be retained; however, it should be determined if the claims may in fact be consistent with 'metaphylaxis' as defined in Article 4(15) of Regulation (EU) 2019/6. This is considered likely when the wording of the indications contains a condition such as 'when the disease has been diagnosed/established in the herd/flock before treatment'. In these cases, revisions of the SPC for related products would be needed.

2. For authorised products other than 'premixes' having 'prevention' claims, it should be considered if the conditions of the supporting clinical trials and use of the product as presented in the dossier are consistent with the definition of 'prophylaxis' or with 'metaphylaxis' (as defined by Regulation (EU) 2019/6). Accordingly, revisions of the claims of the corresponding products would be required.

3. If the claim falls within the definition of prophylaxis, it should comply with the requirements in Article 107(3):

- it is clear from the product presentation/information that such use will be limited to an individual animal (in the case of antibiotics) or a restricted number of animals (in the case of other AMs), and
- in relation with the indication:
  - the probability of infection/infectious disease is high, and
  - the infection/infectious disease has the potential to be life-threatening or irreversibly progressive or otherwise cause severe harm to animal and public health (including negative impact on disease control programmes or threaten sustainability of livestock production), and
  - data are available to confirm a benefit of prophylactic administration for the proposed indication

These conditions under which a prophylactic claim could be accepted for existing products apply also to future marketing authorisations and related guidelines will be updated accordingly.

1. Introduction

1.1. Background information

Antimicrobial resistance is recognised as an increasing major threat to human and animal health, as highlighted by international health organisations and addressed in the CVMP's strategy on antimicrobials 2021-2025 and the European Medicines Network Strategy to 2025. With respect to veterinary medicines, controlling the risks of AMR arising from the use of antimicrobials, particularly from non-prudent use, is one of the highest priorities addressed in Regulation (EU) 2019/6 on veterinary medicinal products, hereafter referred to as 'the Regulation', that entered in force in January 2019 [1].

Amongst the measures on AMR introduced in the Regulation are restrictions on the use of antimicrobial medicinal products for prophylaxis, so that they may only be used in exceptional cases, in individual or restricted numbers of animals, when the risk of infection is very high and the consequences are likely to be severe (Article 107(3)). Hence the CVMP work plan for 2021 mandates the Antimicrobials Working Party (AWP) and Efficacy Working Party (EWP) jointly to develop guidance/criteria for determining when antimicrobial administration for prophylaxis would be accepted and to elaborate a procedure for reviewing indications for existing products.

1.2. Scope of the reflection paper

The purpose of this reflection paper is

(i) to establish an understanding of the term 'prophylaxis' as defined in Article 4(16) of the Regulation and

(ii) to develop high level principles to guide the implementation of the restrictions on prophylactic use as required by the provisions of Article 107(3).

According to the Regulation, the recitals and articles that are related to prophylactic use of antimicrobials do not specifically refer to the marketing authorisation status. Thus, the reflections presented in this document will be applicable to both authorised antimicrobial VMPs that are used in

accordance with the SPC and to antimicrobials which are used outside the terms of the marketing authorisation ('cascade' use), as well as to new marketing authorisation applications.

According to Article 4(12), antimicrobials comprise antibiotic, antifungal, antiprotozoal and antiviral substances. The reflections and recommendations developed in this paper depend on the data and information available and are provided separately by type of antimicrobial.

The Regulation defines specific conditions governing the prophylactic use of antimicrobials in veterinary medicine. **Article 107**, states:

'(3) Antimicrobial medicinal products shall not be used for prophylaxis other than in **exceptional cases**, for the administration to an **individual animal or a restricted number of animals** when the **risk of an infection or of an infectious disease is very high** and **the consequences are likely to be severe.**

In such cases, the use of **antibiotic medicinal products** for prophylaxis shall be **limited to** the administration to **an individual animal only**, under the conditions laid down in the first subparagraph.

(4) Antimicrobial medicinal products shall be used for metaphylaxis only when the **risk of spread of an infection or of an infectious disease in the group of animals is high** and where **no other appropriate alternatives are available**. Member States may provide guidance regarding such other appropriate alternatives and shall actively support the development and application of guidelines which promote the understanding of risk factors associated with metaphylaxis and include criteria for its initiation.'

2. Considerations on prophylactic use of antimicrobials in the context of Article 107(3)

2.1. Legal background and interpretation of terms

Article 4 provides new definitions in relation to antimicrobials and their use:

(15) '**metaphylaxis'** means the administration of a medicinal product to a group of animals **after a diagnosis** of clinical disease in part of the group has been established, with the aim of treating the clinically sick animals and controlling the spread of the disease to animals in close contact and at risk and which may already be subclinically infected;

(16) '**prophylaxis'** means the administration of a medicinal product to an animal or group of animals **before clinical signs** of a disease, in order to prevent the occurrence of disease or infection.

Within this reflection paper, the verbs 'to control' and 'to prevent' are used corresponding to the administration of metaphylaxis and prophylaxis, respectively. This is intended to reflect the wording used in the legal definitions above.

The concept of 'treatment' is not defined in the Regulation. According to CVMP's Guideline on the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1) claims relating to this term are associated with administration of a VMP **after the onset of clinical signs** of disease, and in reference to group administration, where only clinically affected animals are to be treated.

Interpretations of terms

While the general wording of Articles 4(16) and 107(3) relating to prophylaxis is comprehensible, it was judged necessary to provide clear interpretation of specific terms employed in these Articles. Thus, in

order to avoid misinterpretation, the CVMP has agreed on an understanding of how to interpret the wording used in the definition of prophylaxis in Article 4 and on the risk mitigation measures on prophylactic use in Article 107(3) which are presented hereafter.

'Prevention' and 'prophylaxis'

The Regulation makes use of the terms, 'prevention' and 'prophylaxis'. While 'prophylaxis' is explicitly defined in Article 4(16), the Regulation does not include a definition of 'prevention'.

The definition of prophylaxis as such covers the administration of a medicinal product to an individual animal or group of animals 'before clinical signs of a disease, in order to prevent the occurrence of disease or infection', indicating that prevention of disease or infection is the purpose of prophylaxis. Thus, in the context of the Regulation the terms prophylaxis and prevention can be deemed very similar. However, detached from the Regulation's definition of prophylaxis, the concept of disease prevention is considered wider covering vaccination, use of alternative products (e.g. pre/probiotics…) and hygiene/biosecurity measures at farm level.

Of note, the term 'prevention' is defined in the current Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances [2] as 'administration of a VMP to healthy animals to prevent infection, if the risk for infection is very high and the consequences severe'. This definition of prevention is similar but not identical to the definition of prophylaxis in the Regulation. Alignment of the wording and definition in current and future guideline(s) should be sought to avoid confusion.

As regards existing products with 'prevention' claims, reviews of the underlying data presented in their dossiers are necessary in order to decide if 'prevention' can be substituted by 'prophylaxis', 'metaphylaxis' or can no longer be maintained (please refer for more details to chapter 4.)

'Clinical signs'

The definition of 'prophylaxis' in Article 4(16) of the Regulation states that this refers to '*administration… before clinical signs of a disease*.' The most relevant definition of 'clinical' provided in the Merriam-Webster dictionary states: *of, relating to, based on, or characterised by observable and diagnosable symptoms of disease'*, with 'symptoms' being further defined as '*subjective evidence of disease or physical disturbance*'. Black's Veterinary Dictionary [3], states that a 'clinical sign' is '*an abnormal appearance in an animal indicating illness. The synonym in man is 'symptom'*.'[i] Hence it can be understood that prophylaxis relates to administration of a medicine before signs of disease can be observed in an animal.

Following exposure to a pathogen, an animal host may progress through some or all of the (non-discrete) states shown below, according to the host-microbe interaction (based on historical definitions provided by Casadevall and Pirofski [4]):

Infection and disease status	**1.** **At risk of colonisation or infection.** **No disease**	**2.** **'Colonised', Not infected.** **No disease**	**3.** **Infected.** **No disease**	**4.** **Infected.** **Sub-clinical disease**	**5.** **Infected.** **Clinical disease**
Microbial status and host interactions	Negative	Colonised – presence of non-commensal microbe in the host without, or evading,	**Infected,** i.e. interaction between host + microorganism resulting in **tissue**	Infected and disease present i.e. interaction between host + microorganism resulting in tissue invasion and **tissue**	Infected and disease present i.e. interaction between host + microorganism resulting in tissue invasion and tissue

		immune response Or presence of commensals that have potential to become pathogens ('opportunists') **Not infected: no tissue invasion**	**invasion. Initiation of immune response.**	**damage/dysfunction.** Immune response.	damage/dysfunction. Immune response.
Diagnostic test status	Microbiology tests negative Other laboratory medical tests* negative	Microbiology tests may be positive Other laboratory medical tests* negative	Microbiology tests and serology may be positive. Other laboratory medical tests* negative	Microbiology tests and serology may be positive **Other laboratory medical tests* may be positive**	Microbiology tests and serology may be positive Other laboratory medical tests* may be positive
Clinical status	Healthy animal – no clinical signs.	Healthy animal – no clinical signs.	Healthy animal – no clinical signs.	No observable clinical signs of disease i.e. sub-clinical disease.	**Observable clinical signs of disease.**

*Other laboratory medical tests refer to those that are associated with identification of tissue damage or dysfunction, e.g. somatic cell counts, haematology, clinical chemistry, histopathology

The definition of prophylaxis, as given in Article 4(16), further states that the purpose is 'to prevent the occurrence of disease or infection.' As infection precedes an infectious disease, the term prophylaxis can best be understood to apply when antimicrobials are administered at any stage before development of disease, which for the current purpose is understood to be an abnormal status associated with the occurrence of tissue damage or dysfunction. Prophylaxis therefore relates to administration at any of the stages represented in the blue columns 1 to 3 of the table above whereas columns 4 and 5 represent stages of subclinical or clinical diseased animals in that antimicrobials are administered therapeutically, if needed.

It should also be noted that the definition of 'metaphylaxis' provided in Article 4(15) does not relate to infection/disease status alone, but also includes the concept of controlling the spread of disease from clinically sick animals to those in the group that are in close contact and at risk.

Therefore, the terms defined in the Regulation, which are associated with the risk management provisions included in the legislation, do not address all scenarios when administration of antimicrobials may be considered (e.g. the treatment of sub-clinical mastitis in individual cows).

'Individual animal/restricted number of animals'

Article 107(3) refers to the administration of antimicrobial VMPs to an individual animal or a restricted number of animals. The Regulation, however, does not provide definitions for what is understood as 'individual' or 'a restricted number' of animals.

The term '**individual** animal' is used in several other Directives and guidelines, e.g. Directive 2010/63/EU or Regulation (EU) 2016/429, again without definition [5, 6]. Considering parallels to human medicine the term 'individual patient' likewise is not defined in any Regulation. This term however is repeatedly used in the context of a customized treatment for each individual patient.

Following this explanation, it is the understanding of the CVMP that within the scope of Article 107(3) of the Regulation 'administration to an individual animal' means that the prophylactic administration of an antimicrobial to an animal is customised to its special needs and background situation. Therefore,

the need to administer a product to an individual animal is decided by the responsible veterinarian considering the unique risk factors and consequences for infection/disease in this specific individual animal, although the animal may belong to a group/herd.

A **'restricted** number' of animals is understood as administering an antimicrobial (except antibiotics) only to those animals per group/herd which are subjected to the same risk factors that warrant an intervention. Defining the restricted group eligible for the administration needs to be justified by the responsible veterinarian. A targeted administration customised for this restricted group is required.

In view of the CVMP the difference between 'individual animal' and 'restricted number of animals' in the context of Article 107(3) is that albeit the administration of the antimicrobial is customised and targeted, the decision made by the veterinarian is either based on unique risk factors that affect one single animal or is based on risk factors that are comparable for several animals in a group/herd at the same time and thus, a consistent approach for all eligible animals is warranted.

'the risk of infection/infectious disease is very high'

The definition for risk in the context of the risk assessment process, as expressed by several international institutions, focuses on the probability or likelihood of the (adverse) event considered and its impact.

According to CVMP, **risk** can be defined as 'the probability of an adverse effect and the severity of that effect, consequential to exposure to a hazard' [7]. For interpreting the risk in the context of prophylaxis, the infection or infectious disease is the surrogate for the (adverse) event.

To rank the probability of infection or infectious disease in animals the following scale from the guideline quoted above can be considered:

- Very low – very low probability to occur (plausible, but very unlikely)
- Low – low probability to occur
- Medium – medium probability to occur (likely, probable)
- High – significant probability to occur (very likely, certain)

Although the term '**very high**' does not appear in this scale, it can be considered to occur at the further end of the 'high' categorisation.

Depending on the nature of the disease and the pathogenicity of the specific microorganism involved, the clinical picture, the contagiousness and the spreading ability of the infection will differ greatly.

Although it is not straightforward to measure the probability of infection/infectious disease at individual/group level, since there are so many factors implicated, it is important to consider when this risk can be ranked 'very high' for a pathogen/disease that can be prevented effectively with antimicrobials and alternatives are not available. Literature and international guidelines from FAO and OIE provide methodologies and examples of such assessment, but most of them are applied at national or regional level and cannot be easily adapted to the individual/group level.

In case a condition of 'very high' risk is established, the time-period of persistence of such condition should be clearly defined and the prophylactic use should be limited to that period, i.e. prophylactic use should be as brief as possible and not longer than treatment periods approved in SPCs. In the assessment it is also important to identify the risk components related to biosecurity and management, to ensure that the measures in place are effective and the prophylactic administration is not a replacement for any alternative management strategies.

When prophylactic intervention is considered, the **probability of infection/infectious disease** of individual animals/restricted number of animals can be assessed 'very high' taking into account individual risk factors (and farm risk factors, if applicable) such as host susceptibility (e.g.

physiological, pathological and immunological status of the animals), in combination with factors related to the pathogens, such as:

- Mechanism of transmission e.g. by direct (animal to animal contact, droplets or aerosol) and/or vertical (from infected animals to their offspring) transmission
- Introduction into a herd/farm through infected asymptomatic animals (carriers) or animals incubating the disease
- Endemicity of the pathogen and history of previous infections on the farm/clinic
- Persistence of the pathogen in the environment including facilities and equipment
- Capacity of the pathogen to adapt to multiple species and to persist under different conditions e.g. climate, environment

In conclusion, when interpreting the 'risk of infection/infectious disease is very high' the probability of the infection/disease to occur has to be taken into account. However, to fully characterise the risk, a 'high probability' should be considered alongside the associated consequences resulting from these infections/diseases.

'the consequences are likely to be severe'

It is noted that the provisions of the Regulation do not specify the aspects related to infection or disease outcomes where 'the consequences are likely to be severe', i.e. it is not clear whether consequences to animal and/or public health, welfare and/or impacts on farming and aquaculture are covered.

Taking into account the EMA guidance document 'Criteria for classification of critical medicinal products for human and veterinary use' [8], the consequences may be considered likely to be **severe**:

- where prophylactic use of an antimicrobial is an integral part for prevention of a disease, which is life-threatening or irreversibly progressive, or without which the public and animal health could be severely harmed. This could be in acute situations (e.g. emergency situations), or chronic situations/maintenance of stable conditions, or disease with a fatal outcome where prophylactic use of the antimicrobial has been shown to affect the progression of the disease or survival.
- where omission of prophylactic use may have a negative impact on disease control programs or threaten sustainability of livestock production.

Different types of disease might pose different **'consequences'** to single animals (pain, discomfort, death, permanent impairment, etc.) and on a broader level to groups of animals (morbidity, mortality, etc.) at varying scales (e.g. individual animal, farm level, geographic area etc…), which impacts not only on animal health and welfare but also on public health and livestock production. Nevertheless, it is understood that the provisions of Article 107(3) do not cover purely economic consequences.

The severity of the consequences should always be evaluated together with the risk factors, as different combination of these two components might result in the same situation which may warrant a prophylactic intervention.

'exceptional cases'

With regards to the interpretations made on the terms used in Article 107(3), emphasis should be put on the fact that exceptional cases where prophylaxis could be accepted should fulfil **all** the **conditions** described above **at the same time**, namely:

- administration to an individual animal only, or to a restricted number of animals;
- the risk of infection/infectious disease is very high;
- the consequences are likely to be severe.

2.2. International recommendations

International organisations such as WHO, OIE, FAO, Codex Alimentarius have implemented prudent use recommendations for antimicrobials mainly focusing on antibiotics, especially those considered of highest importance for public health. Even if at international level the definitions of 'prophylaxis', 'prevention' and 'metaphylaxis' may differ from those of the EU Regulation, a common point shared by all these institutions is the need to avoid as much as possible the preventive use of antimicrobials (mainly antibiotics) in animals. Apart from that, and depending on the organisation, varying recommendations are stated e.g., a complete restriction of all antibiotic classes for preventive use in food-producing animals; to apply preventive use of antibiotics under defined exceptional situations, only; in general, to avoid preventive group use; not to use fluoroquinolones, 3rd and 4th generation cephalosporins, and colistin as preventive administrations by feed and water in food-producing animals. Moreover, it is recommended to implement and establish good management practices and effective biosecurity, as well as more specific disease preventive measures.

Generally, the prudent use recommendations for antimicrobials that have been implemented at international level are high-level recommendations and mainly focused on most critically important antibiotics. These recommendations are supported and consistent with the interpretation made in this reflection paper, but are not directly relevant for implementation of the EU regulation, considering notably the heterogeneity in antimicrobial use worldwide.

At European level, the RONAFA opinion includes specific recommendations in regard to preventive use of **antibiotics** in food-producing animals [9].

The measures that have been included in this joint opinion largely concur with the content of the article 107(3) and are in line with the interpretation of the terms of the CVMP. Most of these specific recommendations are still relevant and are up to date. The recommendations must serve as a basis for concrete actions to restrict preventive use only to exceptional situations where no other solutions are available. As examples extracted from the above mentioned RONAFA report, the following measures can be reiterated:

- There should be an aim at national and farm level to phase out preventive use of antimicrobials. This should be based on a structured review of such use at national or regional level by livestock sector professionals with the knowledge of local endemic disease epidemiology, underlying risk factors for disease and local husbandry systems. Related disease-specific guidance should be developed.
- In exceptional cases, if preventive use of antimicrobials can be justified, either to groups of animals or individuals, the following principles should apply (not all are applicable for individual animals):
  - Clear risk factors should be identified for a contagious bacterial infection that has serious disease consequences.
  - There should be a recent aetiological diagnosis on the farm of the potential pathogens involved and their antimicrobial susceptibility.
  - The prescribing veterinarian should have a good knowledge of the epidemiology of disease on the farm (e.g., virulence of organisms) and the risk factors for infection associated with the group, e.g., the immune status, management factors.

- In the veterinarian's judgement, the alternative of waiting to initiate metaphylaxis would negatively affect the outcome (especially mortality).
- Antimicrobials should be prescribed for a limited duration to cover the period of risk and there should be documented justification for such use.
- Prevention should not be used systematically if the underlying risk factors could be controlled by recognised alternative measures (e.g., vaccination, nutrition, hygiene,).
- Specific principles for the main sectors/diseases should be developed at national or regional level with assistance from livestock sector experts.
- When preventive use of an antimicrobials is applied to groups of animals, this should be focused on the animals at highest risk.

2.3. Current scientific literature

A literature review on antimicrobials used for prophylaxis was carried out to find any evidence of the efficacy of prophylactic use of antibiotics, antiprotozoals, antifungals and antivirals by animal species, production type and disease, and to complement and update the references of the RONAFA report with any additional prophylactic use of antibiotics in animals. Clinical trials, meta-analysis, systematic reviews, randomised controlled trials published between 2011/01/01 and 2021/02/22 in PubMed were included.

Several limitations have been noted in respect of this review (see annex section 1.3.); therefore, the examples listed under the following subchapters on 'findings' are based on a high level of uncertainty. In addition, studies investigating the efficacy of prophylaxis rarely also investigate its impact on AMR development, although this is an important part of the benefit-risk assessment for responsible use. Nevertheless, these publications can be a valuable tool, supporting regulatory decisions relating to Article 107(3) and being a source of information for veterinarians making prescribing decisions under the 'cascade'.

The detailed literature review can be found in the Annex Section 1.

NOTE: The examples below do not supersede decisions that have been (or will be) made in respect of approved claims for prophylaxis for authorised VMPs, which are based on the findings of randomised clinical trials and additional data submitted and assessed in line with regulatory requirements.

2.3.1. Findings on products containing antibiotics

Companion animals

1. Use of perioperative antibiotic prophylaxis in high-risk surgical cases (e.g. clean/contaminated surgery, use of implants) is customary practice in veterinary medicine and likely to be justified based on human evidence. Although inconsistent, in general the evidence does not support a benefit of continuation of antibiotic administration into the post-operative period.

(This finding is based on a limited number of prospective randomised controlled trials (RCTs) and retrospective observational studies).

Cattle

1. For intramammary infection at dry-off:

- the use of an internal teat sealant was significantly protective against the development of new intramammary infections (IMI) during the dry period. There was no additional effect of adding any category of intramammary antimicrobial to the teat sealant, and so for cows without existing

IMI, there did not appear to be an additional benefit of these added strategies to prevent new IMIs at calving.

(numerous scientific reviews, meta-analysis and clinical trial studies)

- One systematic review and meta-analysis evaluate the efficacy of Selective Dry Cow Treatment (SDCT) compared to Blanket Dry Cow Treatment (BCDT) in dairy cows. The indicators for the comparison were risk of intramammary infection (IMI) after calving, risk of new IMI after calving, relative risk of cure during the dry period, and a reduction in antibiotic use at drying-off. No significant difference was observed when BCDT and SCDT were compared, apart from antibiotic use, that was reduced by about 50% with SDCT in comparison with BDCT [10].

(One Meta-analysis of RCTs and non-RCTs)

2. Concerning prophylaxis for digestive infections or dysbacteriosis, several reviews have been identified relating to neonatal dairy calf diarrhoea. Results of these studies suggest that calves receiving prophylactic antibiotics in their milk during the first 2 weeks of life have a 28% greater risk for diarrhoea compared to calves receiving no antibiotics. Since, alternative strategies exist to limit the resort to oral antibiotic group use, such as fluid therapy and correct colostrum administration, the benefit of prophylactic antibiotic administration for neonatal calf diarrhoea is questionable.

(Scientific reviews and multi-center clinical trial studies)

3. One systematic review and meta-analysis of RCTs have been identified related to prevention of respiratory infections. From this meta-analysis of RCT, a relative risk reduction in Bovine Respiratory Disease (BRD) related morbidity could be demonstrated after antibiotic prophylaxis and metaphylaxis. The adjusted relative risk estimates revealed that metaphylaxis performed equally to prophylaxis in reducing BRD morbidity (metaphylaxis=RR, 95% CI = 0.53, 0.43–0.64; prophylaxis RR, 95% CI = 0.52, 0.47–0.57). Furthermore, the majority of randomized clinical trials reported zero mortality in control groups based on a 'treatment-only' strategy of visual BRD cases. However, the outcome on the relative risk reduction was highly variable and dependent on the antibiotic classes used, BRD attack rates and duration of the RCTs. Thus, no clear conclusions could be drawn from these investigations.
(One meta-analysis of RCTs)

4. While prophylactic use of antibiotics has been shown to reduce the risk of surgical site infections (SSI) in other species, no studies have investigated the relative risk in cattle surgeries with and without prophylactic antibiotics under various surgical conditions (hospital vs field, routine vs emergency etc.). Thus, from the literature there is no evidence on pros or cons of prophylactic antibiotic administration on SSI in cattle.

(No prospective RCT and retrospective observational studies)

Pigs

No studies could be identified clearly supporting either the efficacy or lack of efficacy of prophylactic antibiotic administration in the prevention of any specific bacterial swine disease. Thus, within the scope of the literature review no specific conditions could be identified that could be considered 'exceptional cases' where prophylaxis would be acceptable for swine.

Poultry

The prophylactic use of antibiotics in poultry to prevent bacterial diseases does not have strong scientific evidence of efficacy from the literature, but the low number and poor quality of clinical trials published was also highlighted. A review on the efficacy of antibiotics to prevent or control colibacillosis in broiler chickens did not provide evidence either in favour or against the use of antibiotics. Thus,

within the scope of the literature review no specific conditions could be identified that could be considered 'exceptional cases' where prophylaxis would be acceptable for poultry.

2.3.2. Findings on products containing antiprotozoals

The most common protozoal disease related to the prophylactic use of antimicrobials is coccidiosis.

Coccidial infections cause diarrhoea, with a high level of morbidity and mortality of up to 50% in young animals of different species, e.g. cattle, sheep, goats, pigs, rabbits and poultry.

Due to the high tenacity of oocytes, eradication of the disease in a flock or herd is hardly feasible, therefore the prophylactic use of antiprotozoal compounds, especially where vaccination is not feasible, is common. The majority of antiprotozoals in the EU is used as zootechnical feed additives under Regulation 1831/2003/EC in poultry and rabbits [11]. Those products are used to suppress any development and multiplication of coccidia by supplying anticoccidials often over the whole lifetime of an animal. This long-term administration is outside the jurisdiction of Article 107(3) of Regulation (EU) 2019/6 and will not be covered by this reflection paper.

In contrast, the prophylactic administration of anticoccidials with a marketing authorization according to Regulation (EU) 2019/6 is only short time and at a strategic point in the life cycle of the coccidia and the related target species.

Considering that the prophylactic usage of anticoccidials is a well-established practice since the 1970s, the number of recent publications eligible for the literature review is limited.

Nevertheless, available studies demonstrate the efficacy of a prophylactic use of halofuginone lactate, decoquinate, diclazuril and toltrazuril in calves, lambs and piglets with a reduced morbidity and mortality, faster recovery and reduced oocyte shedding.

For poultry, there is only little evidence found in the literature on the prophylactic use in the scope of Art. 107(3). One paper, however, underlines that while toltrazuril is efficient in preventing infection with *Eimeria*, a wider use of toltrazuril may be associated with a faster development of resistances towards this compound.

Concerning horses and companion animals only a few publications are available, which cannot be used to draw any well-founded conclusions.

2.3.3. Findings on products containing antifungals/antivirals

The literature research on the prophylactic use of antiviral and antifungal agents in animals has yielded scarce results. There are only few experimental uses, showing that in theory antiviral prophylaxis might provide protection against certain viral diseases (e.g. foot-and-mouth disease, classical swine fever, swine influenza viruses, bovine viral diarrhoea virus, aquatic rhabdoviruses). Antifungals are generally not used for prophylaxis at present in the veterinary practice.

2.4. Eligibility of route of administration/pharmaceutical form for prophylactic administration

Considering the terms of Article 107(3) of the Regulation and the interpretation above, it is suggested that only pharmaceutical formulations suitable to treat individual animals (antibiotics) or a restricted number of animals (other type of antimicrobials) should be used for prophylactic purposes.

The AMEG advice [12] suggests a list of routes of administration and types of formulation ranked in order from those expected to have a lower impact on the selection of AMR to those that would be

expected to have a higher impact on the development of resistance. These conclusions based on a scientific literature review should be generally taken into account when prescribing **antibiotics**. This ranking together with the AMEG categorisation of antibiotics should also be applied when antimicrobials are used for prophylaxis.

By taking into account the AMEG list [12], considerations on potential prophylactic use in individuals or a restricted number of animals are presented below.

- **Individual local administration** (e.g. intramammary formulation, eye or ear drops): *for use in individual animals, acceptable for prophylactic administration*
- **Individual parenteral administration** (e.g. intravenously, intramuscularly, subcutaneously): *for use in individual animals, acceptable for prophylactic administration*
- **Individual oral administration** (e.g. tablets): *For use in individual animals, acceptable for prophylactic administration*
- **Group medication via drinking water/milk replacer** (e.g. oral solutions, granules for oral use): *formulations intended for group administration, but may be acceptable for individual use*
- **Group medication via feed** (e.g. oral powders, granules): *formulations intended for group administration (via liquid feed), but may be acceptable for individual administration* (via liquid and solid feed)
- **Group medication via VMPs intended for incorporation into feed** (previously referred to as premix): *intended for group administration, not allowed for prophylactic use according to Regulation 2019/4 on Medicated Feed [13].*

The CVMP in its advice to ensure a safe and efficient administration of oral veterinary medicinal products via routes other than medicated feed [14] recommended that 'in veterinary medicine the use of **oral powders, granules** or similar pharmaceutical forms administered to terrestrial animals **via solid** feed shall be **restricted to use in individual animals** only. This includes veterinary medicinal products administered via top dressing'. This advice also recommended that 'for orally administered veterinary medicinal products only pack sizes considered appropriate for the number of animals to be treated, the recommended posology and the characteristics of the target population shall be authorised'.

Injectables and intramammary preparations are by essence pharmaceutical forms for individual administration, but some practices can lead to their administration to a large number of animals in a herd/flock (e.g. injectable group medication for metaphylaxis, intramammary dry cow therapy). Although some routes of administration and pharmaceutical forms suggest that they are applicable specifically for individual or group use, they cannot be directly applied as sole criterion for prophylactic use in individual or restricted number of animals.

3. Alternative strategies to reduce a prophylactic use of antimicrobials

The need to use antimicrobials can be substantially reduced through the application of good farm management and husbandry practices for terrestrial and aquatic animals by reducing the introduction and spread of microorganisms within and between farms or by using alternative treatments to antimicrobials. These approaches are considered crucial to avoid unnecessary use of antimicrobials including their prophylactic use.

For example, the OIE provide standards describing biosecurity procedures in different animal species. According to the OIE definition, biosecurity means a set of management and physical measures designed to reduce the risk of introduction, establishment and spread of animal diseases, infections or infestations to, from and within an animal population. Specific OIE guidance on biosafety and biosecurity in veterinary laboratories and animal facilities related to disease prevention and control is outlined in the Terrestrial Animal Health Code [15].

The FAO provided general guidance on biosecurity. According to the FAO, biosecurity is a strategic and integrated approach that encompasses the policy and regulatory frameworks (including instruments and activities) for analysing and managing relevant risks to human, animal and plant life and health, and associated risks to the environment [16]. At farm level, biosecurity has three major components: 1. Isolation 2. Traffic Control 3. Sanitation.

According to the RONAFA [9], on-farm management and husbandry procedures should be optimised for disease prevention, (i) to limit the entry of pathogens onto a premises, with particular attention to biosecurity and other relevant measures, (ii) to reduce within-farm transmission, including internal biosecurity measures and adequate cleaning and disinfection procedures and (iii) to increase animal robustness and the ability of an animal's immune system to respond to an infection, including use of efficacious vaccines and the promotion of husbandry conditions beneficial for health and welfare.

The EU has an active animal health policy and funds Member State veterinary programmes to eradicate, control, and monitor certain animal diseases and zoonoses under the first pillar of the Animal Health Strategy. In line with the RONAFA report, recommendations on disease eradication programs, notably on endemic pathogens should be implemented in future EU strategies. This is pertinent for both the purpose to reduce the need of therapeutic as well as prophylactic antibiotic administration. In particular, eradication can be successfully achieved in poultry production systems, as "all-in-all-out" production facilitates a clean break between flocks. For diseases where the risk of transmission between herds is high, control/eradication should preferably be done on an area/region/country level [17]. In contrast to bacteriological and viral disease, so far, no eradication, control or monitoring programs for coccidiosis are funded within the EU.

From all the above-identified recommendations, it is clear that some alternative management strategies exist and have shown to be effective at farm level in order to reduce the need to use certain antimicrobials and particularly their prophylactic use. European agencies and international organisations provided concrete measures that have been already taken in order to reduce the need for antimicrobials. All together, these approaches are considered crucial to avoid unnecessary use of antimicrobials including their prophylactic use.

4. Consequences of Article 107(3) for authorised products and future marketing authorisations

General considerations

Currently there are several antimicrobial products on the market with indications containing the term 'prevention'. As this term is not defined in Regulation (EU) 2019/6, a revision of those SPCs is considered necessary to ensure consistency with the legal definitions provided.

In the context of SPCs for antimicrobial VMPs, the CVMP previously published a question and answer document [18] in order to clarify the meaning and circumstances of 'treatment', 'metaphylaxis' and 'prevention'. In the Q&A it was stated that the word 'prevention' in combination with 'treatment' in any new assessments of antimicrobial VMPs should be replaced by the word 'metaphylaxis' (i.e. treatment and metaphylaxis). Whereas 'prevention' as a single and separate claim, would refer to the administration of an antimicrobial VMP to an individual healthy animal to prevent infection. These circumstances were taken into account for the purpose of revising SPCs, but should now be reviewed for consistency with the Regulation.

Prevention/prophylaxis claims for antimicrobial VMPs intended for incorporation into feed ('premixes') are not compliant with legislation since their use for prophylaxis is prohibited according to Regulation (EU) 2019/4 (Article 17(3)). For these products, prevention claims cannot be retained; however, it

should be determined if the claims may in fact be consistent with 'metaphylaxis' as defined in Article 4(15) of Regulation (EU) 2019/6. This is considered likely when the wording of the indications contains a condition such as *'when the disease has been diagnosed/established in the herd/flock before treatment'*. In these cases, revisions of the SPC for related products would be needed.

For authorised products other than 'premixes' having 'prevention' claims, it should be considered, if the conditions of the supporting clinical trials and use of the product as presented in the dossier are consistent with the definition of 'prophylaxis' or with 'metaphylaxis' (as defined by Regulation (EU) 2019/6); Accordingly, revisions of the claims of the corresponding products would be required.

However, other amendment or deletion may be needed.

If the claim falls within the definition of prophylaxis, it should comply with the requirements in Article 107(3):

- For antibiotics, the conditions for administration should be relevant for individual animals, only.
- For other antimicrobials, the conditions for administration should be relevant for individual or a restricted number of animals, only.
- The risk of an infection or of an infectious disease is very high and the consequences are likely to be severe.

The same conditions under which a prophylactic claim could be accepted for existing products likewise apply to future marketing authorisations, together with data available to confirm a benefit of efficacious prophylactic administration for the proposed indication.

4.1. Currently authorised products containing antimicrobials with a potential prophylactic claim

4.1.1. Findings on products containing antibiotics

A search for the terms 'prophylaxis', 'prevention' and 'control' occurring in the indications of centrally (CAPs) and nationally authorised products (NAPs) containing antibiotics failed to identify any products with 'prophylaxis' claims (as defined by the Regulation). To the contrary, 'prevention' claims have been accepted for both CAPs and NAPs containing antibiotics.

The screening of authorised antibiotic products suggests that the vast majority of authorised 'prevention' claims are likely to be consistent with metaphylaxis as defined in the Regulation. However, a change from 'prevention' to 'metaphylaxis' would need to be done at product level. Only few potential 'prophylaxis' claims were identified e.g. an injectable product authorised for the prevention of surgical infections in dogs and cats, an intrauterine tablet formulation that is authorised for the treatment and prevention of post parturient disorders in cattle and severe obstetrical procedures and intra-mammary products indicated for prevention of new infections during the dry period. These indications are considered to be consistent with the definitions of prophylaxis and a revision of the wording 'prevention' to 'prophylaxis' is suggested.

With regard to mastitis in general and more specifically to the claim '**prevention of new intramammary infections during the dry period**' the following is noted:

The claim 'prevention of new intramammary infections' mostly refers to antibiotic dry cow products.

Those products might be administered at the time of dry-off to cows with no evidence of clinical or subclinical mastitis in order to reduce the risk of new intramammary infections occurring during the dry

period and to prevent disease (i.e. clinical or subclinical mastitis) occurring during the dry and periparturient period.

In addition to a prophylactic dry cow administration, the majority of those antibiotic dry cow products are further indicated for the curative treatment of subclinical mastitis acquired during the previous lactation period.

While treatment of subclinical mastitis is done in the absence of observable clinical signs as per definition of Article 4 of the Regulation, both infection and disease are already present, i.e. an abnormal status associated with the occurrence of tissue damage or dysfunction has already developed which can be demonstrated by diagnostic tests (e.g. somatic cell count (SSC), bacteriological tests). Thus, treatment of subclinical mastitis is considered as therapeutic treatment rather than prophylaxis and does therefore, not fall under the definition of Article 4(16).

The preventive aspect of dry cow therapy (DCT), however, needs to be considered as prophylaxis falling under the scope of Article 107(3). Thus, prophylactic DCT is only allowed in individual animals, if the risk of infection is very high and the consequences are likely to be severe. Both the risk of infection and the severity of consequences of an infection depend on several factors. While the spectrum of pathogens on a farm contributes to the risk profile of all cows in a herd, there are also individual factors (e.g., history of previous infection, age, teat abnormalities etc.) defining the risk of infection/the severity of disease and related consequences.

In current dry cow management two different approaches are followed.

In **selective** DCT, the decision to treat cows with subclinical mastitis or administer antibiotics prophylactically is based on those risk factors related to the farm, the individual cow and in some cases the individual quarter. Thus, selective dry cow administration for prophylaxis of new intramammary infection of individual animals, may be consistent with the definition of prophylaxis and with provisions of Article 107(3), where the risk of infection/disease and severity of consequences are sufficiently substantiated on an animal basis by the responsible veterinarian.

In **blanket** DCT, however, antibiotics are administered to all 4 quarters in all cows eligible for dry-off based on herd-level risk factors alone, irrespective of the health status of an individual animal or related risk factors. Although administration is to individual animals, this use is systematic and considering administration to cows without subclinical mastitis, the risk of infection/disease has not been assessed on an individual animal basis; therefore, this type of administration would not be consistent with the requirements of Article 107(3) and consequently would not be acceptable for authorised products or future marketing authorisations.

4.1.2. Findings on products containing antiprotozoals

Based on a search for the terms 'prophylaxis' or 'prevention' occurring in the indications of centrally (CAPs) and nationally authorised products (NAPs) containing antiprotozoals, no product with a 'prophylaxis' claim (as defined by the Regulation) was identified, but several CAPs as well as NAPs with a 'prevention' claim are authorised within the EU.

Those products are authorised in cattle, pigs and/or sheep for the prevention of coccidiosis/cryptosporidiosis or to prevent clinical symptoms of those diseases. As preventive use is mostly based on disease history and initiated before a disease outbreak in the group/herd or flock, those products fall under the scope of Article 107(3).

While prophylaxis is warranted, it needs to be ensured that the legal framework and the conditions laid down by Article 107(3) of the Regulation are met. As a consequence, there might be necessary

changes considering the wording of the indication, inclusion of potential warnings or advice for the prophylactic use. SPCs of concerned products may need to be revised at individual product level.

With regard to the **prophylaxis claim for anticoccidials**, the following is noted:
Due to high tenacity of oocytes in the environment, a rapid spreading of the disease within a group and nearly simultaneous onset of clinical signs in all animals, combined with a very low treatment efficacy, if clinical signs occurred, management of the disease highly depends on an on-time treatment of animals in the prepatent (subclinical) stage of disease or prophylaxis of animals at risk of infection. Thus, most products containing anticoccidials are not authorised for the treatment of coccidiosis, but for either the prevention of coccidiosis or the prevention of clinical signs of coccidiosis, e.g. diarrhoea.

The administration of an antimicrobial to animals at risk of infection due to a history of disease in a herd/flock before outbreak of the disease (i.e. before infection and development of clinical signs), has to be considered as prophylaxis according to Article 4(16) and falls under the provisions of Article 107(3) of Regulation (EU) 2019/6.

It is agreed that in a farm with a history of coccidiosis, the risk of infection/disease is high with a morbidity of up to 100% and the consequences are severe with a mortality of acute coccidiosis cases ranging between 0 and 50% and severe impact on livestock production in subclinical or chronic coccidiosis cases with reduced weight gains and lower feed conversion ratios.

While alternative preventive measures often lack efficacy in controlling the disease under field conditions, prophylaxis of animals at risk for coccidial infections with antimicrobials should be considered an exceptional case in a restricted number of animals. This restricted number may be defined e.g. by age, as young animals in a certain age group are most susceptible for infections.

In order to underline the provisions of Article 107 (3) and to support the prudent use of anticoccidials, related warnings and advices may need to be included in the product literature of anticoccidials with a prophylactic claim.

A scenario with metaphylactic administration for coccidiosis is seldomly seen in the field as spreading of the disease is rapid and onset of clinical signs within a group occurs within a short period of time. Furthermore, as treatment efficacy is low, coccidiosis management regimens target a prevention of any clinical outbreaks. Thus, metaphylactic administration is largely limited to outbreaks following an initial introduction of the pathogen to a farm or a clinical outbreak facilitated by co-factors like reduced immunocompetence or faulty hygiene measures, and is used in order to limit further spreading within the herd. Efficacy of metaphylaxis, if animals within the herd already show clinical signs, may be reduced.

It is important to highlight that, although associated with poor efficacy, administration of anticoccidials to animals with clinical as well as subclinical (chronic) coccidiosis does **not** fall under the scope of Article 107(3).

4.1.3. Findings on products containing antifungals/antivirals

Based on a search for the terms ‘prophylaxis’ and ‘prevention’ in relation to centrally (CAPs) and nationally authorised products (NAPs) containing antifungal no product with a ‘prophylaxis’, ‘prevention’ or ‘control’ claim was identified. No antiviral products have yet been authorised for veterinary medicine.

4.2. Examples of existing mitigation measures in authorised VMPs

Certain warnings related to prophylactic use have been introduced particularly in SPCs of VMPs containing **antibiotics** after referral procedures e.g. 'Do not use for prophylaxis' was added to all products containing enrofloxacin administered via the drinking water to chickens and/or turkeys [19]. Other restrictions or recommendations on prophylactic use have been included in SPCs following product specific assessments of national authorisations. Some of these warnings are superseded by the Regulation (EU) 2019/6.

The revised guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances [20] has taken the new provisions on prophylactic use of antimicrobials into account. The guideline will come into effect on 28 January 2022 and has addressed risk mitigation measures arising from product-specific assessment of antimicrobials that may be necessary where prophylactic use is not deemed justified in view of the definitions of the Regulation (EU) 2019/6 and is associated with a high risk to public health. In such situations warning(s): *"Not for use for <prophylaxis>"* or *"Not for use for prophylaxis in case of …"* should be inserted in the product literature.

With regard to certain bacterial species e.g. *Mycoplasma* and *Brachyspira* ssp., SPCs of authorised products specify that these organisms can only be reduced but complete elimination may not be achieved by antibacterial treatment. Therefore, in the product literature of such VMPs it is mentioned e.g. in the case of swine dysentery: 'that a targeted early eradication programme of the disease should be considered', or related to respiratory infection caused by *Mycoplasma gallisepticum* in chickens when in ovum infection is likely: 'efforts should be made to develop a strategy to eliminate the pathogen from the parent generation'.

In contrast, comparable warnings for the prophylactic use of VMPs containing **antiprotozoals** are rarely found in related SPCs of authorised products.

It needs to be considered that most antiprotozoals are indicated for the prevention of coccidial infections or the prevention of clinical signs of coccidiosis and efficacy of treating coccidiosis highly depends on a timely administration of anticoccidials within the prepatent phase or before the infection. Thus, warnings mostly relate to an effective prophylactic use of those anticoccidials. For products containing toltrazuril, e.g. it is stated that 'To obtain maximum benefit, animals should be treated before the expected onset of clinical signs'. Furthermore, administration to all animals within a pen is recommended in order to reduce the infection pressure and assure a better epidemiological control of the infection. Additionally, for most anticoccidials a concomitant improvement of hygienic conditions is recommended in order to reduce the infection pressure.

5. Use outside the terms of the marketing authorisation - 'cascade use'

The CVMP's Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union [21] makes a distinction between 'off-label use' – the use of a veterinary medicinal product that is not in accordance with the summary of product characteristics, including the misuse and serious abuse of the product – and 'cascade' use, which falls within the narrower definition of the legal derogations. However, the Regulation does not make use of the terms 'cascade' or 'off-label use', instead the wording 'use of medicinal products outside the terms of the marketing authorisation' is applied. The purpose of the related Articles 112-114 is to facilitate treatment of diseases and animal species for which authorised VMPs are not available, in order to **avoid unacceptable suffering**.

According to the provisions of the Regulation, administration to animals under the cascade should, however, be **exceptional**.

Of note that the reflection paper states that off-label use of antimicrobials for systematic preventive use in groups of animals is not considered to be compatible with the principles of the 'cascade' and should not take place. Such use is considered not to be in line with the provisions of the Directive 2001/82/EC and this still holds for the provisions of Regulation (EU) 2019/6.

Sales or consumption data on antimicrobials that are used in the field for prophylactic purposes are not collected systematically in the EU. Thus, there is no official information to what extent antimicrobials are used, what kind of medicinal products or which classes of antimicrobials are used as prophylaxis.

The review of authorised products containing **antibiotics** has revealed that only few products were identified with a potential prophylaxis claim. It is therefore, presumed that prophylactic administration of antibiotics is in most cases 'cascade' or off-label use.

Since almost all **antiprotozoals** are indicated for the prevention of coccidial infections or the prevention of clinical signs of coccidiosis, it is assumed that those products largely are used according to their authorised indication. Off-label prophylactic use of antiprotozoals authorized within the EU should be limited to exceptional cases, as protozoal disease other than coccidiosis, e.g. theileriosis, trypanosomiasis or anaplasmosis are rare. 'Cascade' use, however, needs to be assumed as e.g. no VMPs are authorized in some E.U. countries for the prevention of diarrhoea caused by cryptosporidiosis in lambs. Thus, halofuginon, authorised for the preventive administration in calves is mostly used.

Following January 2022, SPCs of anticoccidials might need to be updated in agreement with the provisions of Regulation (EU) 2019/6 related to prophylactic use of antimicrobials in order to ensure that products can be used according to their SPC.

Since there is no authorised **antiviral** veterinary medicinal product in the EU and no **antifungal** veterinary medicinal product is authorised with a prophylactic indication, it is clear that the rare prophylactic administration of any antiviral and the infrequent prophylactic administration of antifungals are always 'cascade' or off-label use.

When **antimicrobials** are used under outside the terms of the marketing authorisation for prophylaxis, the prescribing veterinarian should ensure that their use is justified according to the definitions in Article 4, the legal framework on 'cascade' use in Articles 112-114, and the conditions laid down by Article 107(3) of the Regulation.

In addition, SPC guidance and responsible use of antimicrobials should be followed, i.e. the veterinarian should have a good knowledge of the epidemiology and the causative pathogens of the concerned diseases on the farm/clinic supported through e.g. recent aetiological diagnosis of an infection at the unit and susceptibility testing. When antimicrobials are used under the 'cascade', the duration of treatment should be limited to cover the period of high risk and their use should be justified and documented. Further to this, selection of the antimicrobial administration should also consider best possible AMEG categorisation (antibiotics) and recommendations on route of administration.

Any conditions on prophylactic use of certain antimicrobials as established under Article 107(6) of the Regulation must be applied.

6. Conclusions

It is important to achieve a consistent understanding of the term prophylaxis in line with the definition in the Regulation (EU) 2019/6. The interpretation of Article 107(3) predominately depends on the

clarification of the terms 'prophylaxis', 'risk of infection', 'consequences', 'individual animal' and 'restricted number of animals'. From the interpretation of the terms as described in this reflection paper, the following conclusions can be drawn:

- It is vital to underline that 'exceptional cases' where prophylaxis could be accepted need to fulfil all given prerequisites from Article 107(3) at the same time. In that context all three aspects - the number of animals, the risk of infection and related consequences - need to be carefully evaluated in order to conclude if a prophylactic administration of antimicrobials is consistent with the Regulation.
- Even if all prerequisites of Article 107(3) are fulfilled, accurately defined recommendations can only be suggested for situations where there is evidence for an efficacious prophylactic administration of antimicrobials, and no alternatives are available. A literature review was conducted but found few published studies investigating the effectiveness of prophylactic use.
- A defined list of indications that would be in alignment with Art 107(3) and thus acceptable for prophylactic use of antimicrobials cannot be provided due to the multiple risk factors involved (e.g. variability of circumstances and pathogens/disease involved). Thus, a decision if prophylactic use is justifiable can only be made by the responsible veterinarian.
- Although some routes of administration and pharmaceutical forms suggest that they are applicable specifically for individual or group administration, neither pharmaceutical form, nor route of administration shall be applied as sole criterion to decide, if a product is eligible for prophylactic use in individual or a restricted number of animals (except for VMPs intended for incorporation into feed which are not allowed for prophylactic use according to Regulation (EU) 2019/4 on Medicated Feed [13]).

In addition, the new definitions introduced in the Regulation 2019/6 as well as the provisions in Article 107(3), as interpreted by the CVMP, will have direct consequences on authorised VMPs, future marketing authorisations as well as valid and future guidelines. Thus, there will be a need for revisions of certain SPCs of VMPs and guidelines to align them with the definitions and risk mitigations measures. From the review of authorised products and approved indications, the following conclusions can be drawn:

- Currently there are several antimicrobial products on the market with indications containing the term 'prevention'. As this term is not defined in Regulation (EU) 2019/6, a revision of those SPCs is considered necessary to ensure consistency with the legal definitions provided.
- For authorised products other than 'premixes' having 'prevention' claims and future marketing authorisations, it should be considered, if the conditions of the supporting clinical trials and use of the product as presented in the dossier are consistent with the definition of 'prophylaxis' or with 'metaphylaxis'. Accordingly, revisions of the claims of the corresponding products would be required.

In should be noted that the review of authorised products containing antibiotics identified only few products with a potential prophylaxis claim, implying that prophylactic administration of antibiotics is in most cases outside the terms of the marketing authorisation. To the contrary, almost all antiprotozoals are indicated for the prevention of coccidial infections/clinical signs of coccidiosis suggesting that those products are largely used according to their indication. Since no antiviral VMPs are authorised in the EU and no antifungal VMPs are authorised with a prophylactic indication, prophylactic administration of antivirals or antifungals is always 'cascade' or off-label use.

- Thus, when antimicrobials are used outside the terms of the marketing authorisation for prophylaxis, the prescribing veterinarian should ensure that their use is justified according to

the relevant provisions of the Regulation, responsible use principles are respected and AMEG recommendations are followed as much as possible.

High-level recommendations for antimicrobials that have been implemented at international level are mostly consistent with the interpretation made in this reflection paper. Particularly specific recommendations in regard to preventive use of antibiotics in food-producing animals made on an EU level (RONAFA report) [9], which concur with the provisions of Article 107(3). These recommendations are still highly relevant and should serve as a basis for concrete actions to restrict prophylactic use only to exceptional situations where no other solutions are available.

Although not directly within the scope of this reflection paper, alternative strategies have highest importance in order to reduce the use of antimicrobials particularly for prophylaxis purposes. Thus, it is crucial to consider that the need to use antimicrobials in animal husbandry can be substantially reduced through the application of good farm management and husbandry practices or by using alternative therapeutic approaches. To this end, guidance on biosafety and biosecurity related to disease prevention and control must be followed in order to reduce the introduction and spread of microorganisms within and between farms.

Annex

1. Literature review on antibiotics used for prophylaxis

1.1. Introduction

Prophylactic use of antimicrobials in veterinary medicine in the EU for herd-health purposes has been based generally on traditional farm practices or attitudes; reduced labour costs since less monitoring of animals is needed; previous history of herd outbreaks; herd management practices (grouping of animals); high stocking densities (i.e. increased 'risk' of disease); scheduled events in the production animal cycle (e.g. dry-off cow period, before transport); stressful events (e.g. weaning, castration, dehorning, viral outbreaks) [9, 22].

Surgical procedures in animals are another common reason for antimicrobial prophylaxis. The relative risk for surgical site infections is often assumed to be higher in farm animals than in human or companion animal surgery, because of the unsanitary operating environment in the field, depressed patient immune function in the periparturient period and the high probability of post-operative wound contamination [23].

1.2. Search methodology for literature review on antibiotics used for prophylaxis

A literature review on antibiotics used for prophylaxis was carried out to find any evidence of the efficacy of prophylactic use of antibiotics by animal species, production type and disease, and to complement and update the references of the RONAFA report with any additional prophylactic use of antibiotics in animals. A search strategy was developed to ensure a broad and standardized approach using the Medical Subject Headings (MeSH) thesaurus, a controlled and hierarchically-organised vocabulary produced by the National Library of Medicine.

The selection criteria included clinical trials, meta-analysis, systematic review, randomised controlled trials published from **2011/01/01** to **2021/02/22** in PubMed. Letters, editorials, case studies and commentaries were excluded. Reviews were included in the fourth search string to ensure the highest detection probability of relevant papers. The selected references were divided by animal species and country.

Details on the keywords used and on the search strategies:

STRING SEARCH 1:

("Antibiotic Prophylaxis/classification"[Mesh] OR "Antibiotic Prophylaxis/methods"[Mesh] OR "Antibiotic Prophylaxis/organization and administration"[Mesh] OR "Antibiotic Prophylaxis/statistics and numerical data"[Mesh] OR "Antibiotic Prophylaxis/therapeutic us e"[Mesh] OR "Antibiotic Prophylaxis/veterinary"[Mesh])

STRING SEARCH 2:

("Antibiotic Prophylaxis/classification"[Mesh] OR "Antibiotic Prophylaxis/epidemiology"[Mesh] OR "Antibiotic Prophylaxis/methods"[Mesh] OR "Antibiotic Prophylaxis/organization and administration"[Mesh] OR "Antibiotic Prophylaxis/pharmacology"[Mesh] OR "Antibiotic Prophylaxis/statistics and numerical data"[Mesh] OR "Antibiotic Prophylaxis/therapeutic use"[Mesh] OR "Antibiotic Prophylaxis/therapy"[Mesh])) AND "Antibiotic Prophylaxis/veterinary"[Mesh]

STRING SEARCH 3:

("prevention and control" [Subheading]) AND "veterinary" [Subheading]

STRING SEARCH 4:

("prevention and control" [Subheading]) AND "veterinary" [Subheading]

The duplicated references were discarded, and the remaining references were checked for relevance and selected according to these additional criteria: availability of quantitative information on the prophylactic use of antibiotics and data about animal species included in the scope of this paper (laboratory animals, wildlife and humans were excluded). Studies conducted in an European country were preferred, but since many of the selected articles were systematic reviews and meta-analyses, this aspect was not a selection criterion. This step was performed by checking title and abstract of each individual reference. After this step the selected references were divided by animal species and country.

1.3. Conclusions on literature search by animal species

When drawing conclusions from the literature in order to derive recommendations on antibiotic prophylaxis use it is important to highlight the limitations related to the literature search.

- Search methodology focused mainly on systematic reviews and metanalyses, to identify the evidence of efficacy from such type of studies. Studies with examples of prophylactic use of antimicrobials were not considered, since their inclusion would have required quality and comparability assessments, not feasible in the framework of this reflection paper. Moreover, although an articulated search strategy was implemented, some limitations in completeness and some biases were possible, and such limitations were not assessed due to time constrains.
- Very few scenarios of prophylactic use in veterinary medicine have been investigated and published as systematic reviews or meta-analyses (respiratory diseases in cattle and pigs, dry-off in dairy cows and ewes, surgery in companion animals are the most common). In addition to this, most of the literature concerned studies conducted in non-EU countries, posing the issue of the comparability of the outcomes (different husbandry systems, animal species and breeds, etc) and the extrapolation of general conclusions.
- Studies identified did not clearly define "prophylactic use" of the antimicrobial(s) considered. The use for "prophylaxis and control" of the infection/disease was, on the other hand, often reported, creating ambiguity on the real use of the drug(s).
- Several authors pointed out the poor quality of the studies included in their analyses, in particular concerning the design of the studies, the considered endpoints and the overall quality. This aspect was reflected in the cumulative results of many systematic reviews, often inconclusive concerning the comparative prophylactic efficacy of the antimicrobials tested. In particular, the endpoints considered in the studies never included the occurrence of AMR, but only production and/or health-related parameters.
- For some animal species no reference was found, in particular for fishes, goats, poultry other than chickens, companion animals other than dogs.

It should be highlighted that the evidence that would be identified and the associated conclusions do not supersede decisions that have been (or will be) made in respect of efficacy for authorised VMPs, which are based on the findings of randomised clinical trials and additional data submitted and assessed in line with regulatory requirements.

Although it is recognised that the information will only cover a limited number of scenarios conclusions may be used to support **regulatory** decisions relating to Article 107(3) and as a source of information for veterinarians making prescribing decisions under the 'cascade'.

1.3.1. Cattle

Summary from the RONAFA report for prophylactic/preventive use in cattle

Prophylactic group treatment against respiratory or digestive infections represents high use of antibiotics in cattle, e.g. in Belgium, approximately 13.0 % of antibiotics were reported for preventive use (immediately after arrival on farm) and 87.0 % for metaphylactic use or as a curative measure in veal calves [24]. It was suggested that this may be due to the organisation of the veal industry in Belgium in which young calves are sourced from multiple farms and comingled after the stress of recent transportation, increasing disease risk of infection.

Antibiotic dry cow therapy (ADCT) was often administered to the whole herd as a blanket treatment. In a survey of drying-off practices on dairy farms in northern Germany [25], 79.6% of participating farms practised blanket ADCT. Since the prevalence of contagious mastitis pathogens has now decreased and due to concerns on AMR, this approach is now under question [26]. The RONAFA report further highlights that in the Netherlands the preventive use of antibiotics has been prohibited for dry cow treatment since 2011. A survey of Dutch dairy farms conducted in 2013 found that udder health had not deteriorated compared to that seen in previous studies where herds were smaller and before the restriction in antibiotic use [27].

Further national actions were presented such as in Belgium, where the AMCRA (Antimicrobial Consumption and Resistance in Animals) recommends that there should be no preventive use of antibiotics, except those associated with perioperative use and for dry cow management. Similarly, in France, the ANSES provided an expert opinion in 2014 on the risk of emergence of AMR associated with modes of antibiotic use in animal health [28]. This report reviewed use of antibiotics with the objective to identify 'at-risk practices' (i.e. those resulting in significant selection of resistant bacteria). In regards to use of preventive treatments, it was concluded that in many cases antibiotic use (e.g. 'preventive group treatment of neonatal diarrhoea/respiratory infections and intramammary treatment at dry-off) could be abandoned either immediately, or over a period of time to allow the introduction of recognised alternative measures.

Summary from the literature review for prophylactic/preventive use in cattle

Dry cow therapy:

Antimicrobial dry cow therapy was often administered to the whole herd as a blanket treatment. A survey of Dutch dairy farms conducted in 2013 found that udder health had not deteriorated compared to that seen in previous studies where herds were smaller and before the restriction in antimicrobial use [27].

The different efficacy of selective dry-cow antimicrobial therapy compared to blanket therapy (all quarters/all cows) is questionable. Risk of intramammary infection (IMI) at calving in selectively treated cows was higher than blanket therapy but substantial heterogeneity was present, although subgroup analysis revealed that for trials where all cows received an internal teat sealant (bismuth subnitrate), the frequency was not significantly different between selective therapy and blanket therapy [29].

The comparison of efficacy for IMI risk after calving and cure risk between Selective Dry Cow Treatment (SDCT) and Blanket Dry Cow Treatment (BDCT) did not differ significantly. Only a limited number of studies were included in this meta-analysis. From this analysis, there was no statistical

difference on the effect of SDCT in comparison to BDCT on IMI risk after calving, new IMI risk after calving, and cure risk during the dry period, but the use of antibiotics was reduced of about 50% with SDCT in comparison with BDCT [10].

Non-antimicrobial internal teat sealant (ITS)-based dry-off approaches are efficient for preventing new IMI during the dry period when compared with no treatment. Moreover, bismuth subnitrate-based ITS performed better than an antimicrobial for preventing new IMI during the dry period. An ITS-based approach would only slightly or not at all reduce the prevalence of IMI at calving compared with untreated quarters [30].

Internal teat sealants (bismuth subnitrate) provided significant protection against developing new IMI at calving compared to NTCs. No significant additional benefit of the provision of any antimicrobial group in addition to the use of an internal teat sealant. However, the authors identified a lack of replication of interventions and thus cannot reach a definitive conclusion of the efficacy of additional antimicrobial administration, nor if differences exist between antimicrobial groups [31].

Calves diarrhoea:

Several reviews related to prophylaxis/prevention of neonatal dairy calf diarrhoea were identified but there is insufficient evidence to draw firm recommendations. Prophylactic antibiotic treatments in calves for the first 2 weeks of life have a 28% greater risk for diarrhoea compared with calves receiving no prophylactic AB in their milk. Also, alternatives strategies exist to limit the resort to oral group treatment such as fluid therapy and correct colostrum administration [32]. Also, a prospective multi-centre study found an association between antimicrobial consumption data and the occurrence of antimicrobial resistance profiles in the bovine digestive (*E. coli*) and upper respiratory tract (Pasteurellaceae) [33]. A high population density combined with cross-infection and co-selection are suspected to increase the risk for the spread and persistence of antimicrobial resistance, as seen in human medicine for intensive care units.

No specific alternative prophylaxis/preventive treatments were identified. Alternatives options include essentially good herd practices notably correct administration of colostrum that appears to be the best preventive practices.

Respiratory infections:

One systematic review and meta-analysis of randomised controlled clinical trials (RCTs) for naturally occurring BRD investigating antimicrobial prophylaxis/metaphylaxis to prevent morbidity/mortality where identified [22]. From this meta-analysis of RCT a relative risk reduction in BRD related morbidity could be demonstrated after antibiotic prophylaxis and metaphylaxis. However, the outcome on the relative risk reduction was highly variable and dependent on the antibiotic class used, BRD outbreak rates and duration of the RCTs. Best relative risk reductions were from broad-spectrum critically important antimicrobials, or combinations. No specific alternative prophylaxis/preventive treatments were identified. Alternatives options include essentially good herd practices and increased biosecurity measures

Surgery:

From a questionnaire sent to veterinary surgeons, 100% of the respondents reported the use of prophylactic antibiotics in caesarean section, and 72% of the respondents reported prophylactic antibiotic use for left displaced abomasum correction. Most of the respondents answered to selected broad-spectrum antibiotic for surgical prophylaxis, although procaine benzylpenicillin accounted for 20 to 50% of the chosen antibiotic [34]. Also, from a survey among Belgian veterinarians on the use of antibiotics in caesarean section penicillin has been identified as the first drug of choice, but as second or third choice amoxicillin, oxytetracycline or lincomycin-spectinomycin have been also identified [35].

From this survey, it appears that there is also simultaneous use of molecules from different antibiotic classes. The duration of the antibiotic treatment is mainly 1 day. Concerning the route of administration, frequent use of intraperitoneal injection route is cited, which is not registered. There is no evidence that this route of administration has any additional effect on top of pre-operative prophylaxis and should therefore require adjusted withdrawal period [34]. Also, it has been identified that the dosage of antibiotics varies enormously and excessive injection volumes are common, especially when multiple injection routes are combined with no additional benefit and leading to overdose and unnecessary use of antimicrobials; increases expenses and withdrawal times adjustments [35].

Conclusions from recent literature research

Concerning prophylaxis for intramammary infection (IMI) at dry-off period, several studies from literature are available including scientific review, meta-analysis and clinical trial. From these studies:

- the comparison of efficacy on IMI after calving and cure risk at dry period between SDCT and BDCT did not differ significantly. Antibiotic use was reduced by about 50% with SDCT in comparison to BDCT.
- the use of an internal teat sealant (bismuth subnitrate) was significantly protective for the development of new IMI at calving, compared to non-treated animals. There was no additional effect of adding any category of intramammary antimicrobial to the teat sealant, and so for cows without existing IMI, there did not appear to be an additional benefit of these added strategies to prevent new IMIs at calving.

Concerning prophylaxis for digestive infections or dysbacteriosis, several reviews have been identified relating to neonatal dairy calf diarrhoea. Results of these studies suggest that calves receiving prophylactic antibiotics in their milk during the first 2 weeks of life have a 28% greater risk for diarrhoea compared to calves receiving no antibiotics. Since, alternative strategies exist to limit the resort to oral antibiotic group treatment, such as fluid therapy and correct colostrum administration, the need for prophylactic antibiotic treatment of neonatal calf diarrhoea should be carefully reviewed.

One systematic review and a meta-analysis of randomised controlled clinical trials (RCTs) have also been identified related to prevention of respiratory infections. From this meta-analysis of RCT, a relative risk reduction in BRD related morbidity could be demonstrated after antibiotic prophylaxis and metaphylaxis. However, the outcome on the relative risk reduction was highly variable and dependent on the antibiotic classes used, BRD outbreak rates and duration of the RCTs. Thus, no clear conclusions could be drawn from these investigations.

While prophylactic use of antibiotics has been shown to reduce the risk of surgical site infections (SSI) in other species, no studies have investigated the relative risk in cattle surgeries with and without prophylactic antibiotics under various surgical conditions (hospital vs field, routine vs emergency etc.). Thus, from the literature there is no evidence on pros or cons on prophylactic antibiotic SSI in cattle.

1.3.2. Pigs

Summary from the RONAFA report for prophylactic/preventive use in pigs

Digestive and respiratory disorders were reported being the most common indications for preventive treatments. In farrow-to-finish farms antimicrobial consumption for prophylaxis use decreased from the pre-weaning and growing to the fattening phase. Preventive antimicrobial consumption in fattening pigs was higher on farms which only finished pigs and this was attributed to a high turnover of animals coming from multiple sources.

Group treatments via oral administration accounted for higher antimicrobial exposure than via injectable administration. The most frequently used antimicrobials at oral group level were colistin, mainly to prevent post-weaning *E. coli* infections, and amoxicillin as prevention against streptococcal infections. Of concern was a shift from oral group treatments with doxycycline and potentiated sulfonamides towards use of long-acting injectable formulations, some of which included 3rd- and 4th-generation cephalosporins.

Injectable antimicrobial drugs were found to be mainly administered for prophylaxis at birth and castration and included broad spectrum penicillins, cephalosporins and fluoroquinolones.

The RONAFA lists examples of identified 'at-risk practices' (source: ANSES [28]) for those preventive treatments administered to lactating sows to prevent digestive problems in suckling piglets should be abandoned without delay. The preventive use of polypeptides and aminoglycosides for post-weaning diarrhoea, preventive use of antimicrobials to control *Mycoplasma hyopneumoniae* and *Actinobacillus pleuropneumoniae* in nucleus/breeder herds, and for disease control of swine dysentery (*Brachyspira hyodysenteriae*) should be abandoned over time.

The RONAFA furthermore gives examples of contagious bacterial diseases in swine that could justify antimicrobial use for prevention i.e. *Streptococcus suis* and certain virulent forms of *Actinobacillus pleuropneumoniae*.

Summary from the literature review for prophylactic/preventive use in swine

Respiratory disorders

A systematic review of the efficacy of antibiotics for the prophylaxis/prevention of swine respiratory disease was conducted by inclusion of controlled studies performed world-wide [36]. The trials evaluated prophylactic antibiotic use in nursery and grower pigs based on clinical morbidity and mortality. 44 eligible trials from 36 publications showed heterogeneity in the antibiotic interventions and comparisons as well as concerns related to statistical non-independence and quality of reporting were noted. Thus, there was **insufficient evidence to allow quantification of the efficacy, or relative efficacy of antibiotic interventions**.

Digestive disorders

Based on a systematic review (SR) and meta-analysis (MA) of the efficacy and quality of evidence for *Salmonella* reduction in grow-finish swine produced in Canada ranking of intervention efficacy was found: feeding meal>inclusion of acids in ration, feeder pen disinfection or *Salmonella* spp. vaccination>in-feed tetracyclines [37]. MA of the dataset investigating inclusion of **in-feed tetracyclines** yielded significant odds ratio (OR) **indicating a potential harmful effect**, measuring faecal culture, (OR Range: 14 (1.9, 108); 1.0 (0.43, 2.5)) with significant heterogeneity (P=0.003, I2=82%) across studies, suggesting some potential for withdrawal of in-feed tetracyclines to reduce *Salmonella* shedding. Although the authors concluded that SR-MA was useful for ranking efficacy, the a**pproach was limited by the small number of comparable studies available**.

In an Italian study 50 pigs weaned at 24 d were divided into 5 groups: control (CO), CO + colistin (AB), CO + 5 x 10^{10} cfu of *Saccharomyces cerevisiae* (SCC)/kg feed, from d 0 to 21 (PR), CO + 5 x 10^{10} cfu of SCC/kg feed from d 7 to 11 (CM), and CO + 1 shot of 2 x 10^{11} cfu of SCC when the first diarrhoea appeared (CU). On d 7 post weaning, all the pigs were orally challenged with 10^{8} cfu of ETEC. Growth performance did not differ between the treatments. **Mortality was reduced in the AB group** (P< 0.01) and, marginally, in the PR group (P = 0.089) when compared to the CO group. **ETEC-specific IgA concentration was lower in the AB group** than in CO (P = 0.04) at d 12 [38].

A Chinese study evaluated the effects of dietary *E. faecalis* LAB31 on the growth performance, diarrhoea incidence, blood parameters, faecal bacterial and *Lactobacillus* communities in weaned piglets. A total of 360 piglets weaned at 26±2 days of age were randomly allotted to 5 groups for a trial of 28 days: group N (negative control, without antibiotics or probiotics); group P (neomycin sulphate, 100 mg/kg feed); groups L, M and H (supplemented with *E. faecalis* LAB31 0.5 x 10^9, 1.0 x 109, and 2.5 x 10^9 CFU/kg feed, respectively). Average daily weight gain and feed conversion efficiency were found to be higher in group H than in group N, and showed significant differences between group H and group P (P0 < 0.05). Furthermore, groups H and **P had a lower diarrhoea index** than the other three groups (P0 < 0.05) [39].

General performance, animal health

An Irish study investigated the effect of removing prophylactic in-feed AB on health and welfare indicators in weaner pigs [40]. At group level, pigs having received sulfadiazine-trimethoprim (AB) were more likely to have tail (OR = 1.70; P = 0.05) but less likely to have ear lesions than pigs of the control group (CG) (OR = 0.46; P<0.05). The number of ear bites (21.4±2.15 vs. 17.3±1.61; P<0.05) and fights (6.91±0.91 vs. 5.58±0.72; P = 0.09) was higher in AB than in CG. There was no effect of treatment on health deviations and the frequency of these was low. **Removing AB from the feed of weaner pigs had minimal effects on health and welfare indicators**.

In another study conducted in Ireland in-feed antibiotics (sulfadiazine-trimethoprim) were not added to the feed for half of the pigs (NOI) and were added in the other half (ABI) within each batch for the whole weaner stage [41]. Individual pigs in both treatments were treated with parenteral administrations if and when detected as ill or lame. **ABI pigs showed higher growth (P = 0.018) and feed intake** (P = 0.048) than NOI pigs in the first weaner stage **but feed efficiency was not affected** (NOI = 1.48 vs. ABI = 1.52). Despite an initial reduction in performance, NOI pigs had similar performance in finisher stage (ADG: NOI = 865.4 vs. ABI = 882.2) and minimal effects on health compared to ABI pigs. **No difference between treatments** was found at the abattoir for the percentage of pigs affected by pneumonia, pleurisy, pleuropneumonia and abscesses (P > 0.05). Mortality rate was not affected by treatment during the weaner stage (P = 0.806) although it tended to be slightly higher in NOI than ABI pigs during the finisher stage (P = 0.099). Parenteral treatments were more frequent in NOI pigs during the weaner stage (P < 0.001) while no difference was recorded during the finisher stage (P = 0.406). These data suggest that the **removal of prophylactic in-feed antibiotics is possible with only minor reductions in productive performance and health** which can be addressed by improved husbandry and use of parenteral antibiotics.

In 164 randomly selected Swiss piglet production farms and 101 fattening farms, the indication for antibiotic use in 2012/2013 was recorded and an animal treatment index (TBI) was calculated for each age group [42]. In sows, antibiotics were used prophylactically on 22.6% of the treatment days, in suckling piglets on 50.5%, in weaners on 86.1% and in fattening pigs on 79.0% of the treatment days. A **prophylactic oral antibiotic group therapy did not have a significant positive effect on daily weight gain** of fattening pigs, **nor was it able to reduce the number of individual or group therapies.** In farms with prophylactic oral group therapy, the **mortality rate during the first two fattening weeks even tended to be higher** (p=0.06) than in farms without oral group therapy.

Conclusions from recent literature research

Systematic reviews including meta-analyses and studies were found investigating the efficacy of antibiotics for prophylaxis of respiratory, digestive disorders as well as their impact on productive performance and animal health and welfare indicators.

In some studies, positive effects after prophylactic antibiotic treatments were observed such as reduced mortality, lower diarrhoea index, and higher growth and feed index. To the contrary, other

study results have shown no to minimal effects (e.g. on feed efficiency, performance, mortality rate, need for subsequent antibiotic treatments) or even indicated negative effects (e.g. higher bacterial shedding, lower IgA concentration, higher number of ear bites) resulting from prophylaxis.

Nevertheless, no studies could be identified clearly supporting either the efficacy or lack of efficacy of prophylactic antibiotic treatment in the prevention of any specific swine disease. Thus, no specific conditions that can be considered 'exceptional cases' where prophylaxis would be acceptable. This includes also the examples given in the RONAFA report, i.e. infectious diseases caused by *Streptococcus suis* and certain virulent forms of *Actinobacillus pleuropneumoniae,* for that likewise no scientific evidence was found that would either prove or disprove a sound justification for a defined recommendation.

1.3.3. Poultry

Summary from the RONAFA report for prophylactic/preventive use in poultry

Routine group medication in poultry often occurs immediately before or after transport of day-old chicks or possibly to address perceived potential losses of productivity, but the RONAFA report does not provide a clear distinction between prophylactic and metaphylactic/therapeutic treatments.

From other sources [17, 43], in Canada the prophylaxis/prevention use of antimicrobials in poultry is primarily intended to prevent necrotic enteritis caused by *Clostridium perfringens* and coccidiosis. Sargeant, Bergevin [44] described also antibiotic use for Avian pathogenic *E. coli* (APEC), either in flocks where the birds are not diseased but may be at risk of illness in order to prevent illness (prophylaxis) or in flocks where some birds are already ill with the intention to prevent further illness or mortality (metaphylaxis).

The RONAFA report provides examples of antimicrobial use in poultry in the UK, where the use of antimicrobials in broilers was for therapy (42.4% of the farms), for prophylaxis/prevention (54%) and 24% for both reasons [45]. Pokludová [17] described the figures of Canada in 2014, where 81% of the antimicrobials used on broiler farms were for prevention purposes, from which part administered in the feed was 84%. Updated figures of antimicrobials use for prophylaxis/prevention in poultry are not available, and the abovementioned examples probably do not adequately represent the differences among poultry productions and countries.

Summary from the literature review for prophylactic/preventive use in poultry

The reason why prophylactic use of antibiotics for colibacillosis in poultry is considered is the great diversity among APEC strains that limits the possibilities of vaccination, and vaccines are not used on a large scale. Several vaccines based on killed or attenuated strains have been tested experimentally. In general, they give sufficient protection against infection with homologous strains, but protection against heterologous strains is less efficient.

The result of a systematic review on the efficacy of antibiotics to prevent or control colibacillosis in broiler chickens are the following. Sargeant, Bergevin [44] conducted a systematic review on controlled trials in broilers that evaluated an antibiotic intervention, with at least one of the following outcomes: mortality, feed conversion ratio (FCR), condemnations at slaughter, or total antibiotic use. Seven trials allowed data extraction; all reported results for FCR and one also reported mortality. Due to the heterogeneity in the interventions and outcomes evaluated, it was not feasible to conduct meta-analysis. Qualitatively, for FCR, comparisons between an antibiotic and an alternative product did not show a significant benefit for either. Some of the comparisons between an antibiotic and a no-treatment placebo showed a numerical benefit to antibiotics, but with wide confidence intervals. The risk-of-bias assessment revealed concerns with reporting of key trial features.

The results of their review did not provide compelling evidence for or against the efficacy of antibiotics for the control of colibacillosis.

A clinical trial on the development of resistance in *Escherichia coli*, *Enterococcus faecicum* and *Staphylococcus aureus* isolates from turkeys after treatment with paromomycin sulfate for prevention of blackhead (Histomoniasis) showed a higher frequency of resistance in isolates from treated flocks vs non treated, and resistance was not only against paromomycin, but also to other antibiotics [46].

Conclusions from recent literature research

The prophylactic use of antibiotics in poultry, although quite common, doesn't have strong scientific evidence of efficacy from the literature. However, this lack of evidence is mainly due to the poor number and quality of clinical trials set for the assessment of the efficacy of prophylaxis in the different poultry species for the main infectious diseases. Indeed, there is a need of good clinical trials to compare the efficacy of different antibiotic treatments and alternatives to antibiotics, to guide the appropriate use of antibiotics in poultry.

The efficacy of antibiotics to prevent or control colibacillosis in broiler chickens was assessed by [44]. However, results of this review did not provide compelling evidence for or against the efficacy of antibiotics for the control of colibacillosis.

1.3.4. Companion animals

The review of literature in companion animals relating to research consistent with the definition of prophylaxis given in the Regulation identified studies that mainly addressed administration of antibiotics in the perioperative period for surgical prophylaxis.

Dogs

There is limited specific evidence in veterinary medicine relating to peri-operative use of antibiotics in dogs. Current recommendations in terms of the needs, antibiotic selection, timing and duration of treatment have been extrapolated from human guidelines; however, these may not be fully applicable due to differences in veterinary post-operative care and the patient environment [47, 48].

Antimicrobial prophylaxis is usually not recommended in small animal practice for clean procedures but is indicated in procedures classified as clean-contaminated or contaminated because of the risk of surgical site infection (SSI). In elective orthopaedic procedures, peri-operative antimicrobial prophylaxis has been shown to decrease SSI [49] and has been adopted particularly for procedures involving use of implants e.g. TPLO, total hip replacement, where SSI can lead to serious consequences [47].

Several studies have been conducted to investigate the protective effect of post-operative antibiotic administration against development of SSI in dogs undergoing clean orthopaedic surgery involving metal implants. In most studies, no benefit could be shown over peri-operative administration alon [50-55]; although findings are inconsistent and further prospective randomized controlled trials may be warranted.

There has also been debate over use of antibiotics for decolonization of methicillin-resistant *Staphylococcus* spp. (MRS) carriers prior surgery. A limited number of studies have shown that MRSP carriage can persist for a year after systemic treatment and clinical resolution of pyoderma [56, 57], suggesting it is unlikely to be effective for decolonization; whereas decolonization using topical treatments may be effective for short periods [58]. The WAVD recommendations on treatment of MRS

[59] conclude that there is currently insufficient evidence to recommend antibiotic use for routine decolonization of MRS carrier animals that pose a risk to susceptible in-contact people and animals. However, in respect of screening of patients prior to high risk surgery, MRSP carriage in dogs has been shown to pre-dispose to SSI in dogs undergoing TPLO [54], and WAVD suggests that screening could be considered in this population, allowing peri-operative antimicrobial use to be guided by susceptibility testing for MRSP carriers.

Horses

A retrospective review of 113 horses that underwent surgical treatment for colic found that 43% developed post-operative infection; however, the infection rate was not higher in those that received antibiotics for < 36 h compared to those receiving longer courses [60]. Horses undergoing exploratory coeliotomy at two referral hospitals were randomised to receive either 72 hours (n=42) or 120 hours (n=50) of peri-operative antimicrobial therapy. The overall incisional complication rate was 42.2 per cent, and no significant difference in the number of incisional complications in the two groups was identified (p=0.3) [61]. Reviews have identified that peri-operative use of antimicrobials is standard practice prior to laparotomy in horses, but the best timing in relation to dosing and duration of administration require further evidence, and compliance with published recommendations is poor [62, 63].

A retrospective study investigated the use of post-operative antibiotics in addition to peri-operative administration alone in 516 horses that underwent elective synovial endoscopy at a teaching hospital [64]. No horses developed septic synovitis, but administration of post-operative antimicrobials (beyond the time of surgery) was associated with increased risk of complications, which were predominantly gastrointestinal.

The traditional practice of prophylactic use of antibiotics to prevent infectious disease in newborn foals was investigated in a retrospective study that examined the records of > 1000 Thoroughbred foals born on stud farms in the UK. No significant difference was found in the 30 day incidence or prevalence of various infectious diseases between foals treated or not treated with antibiotics [65]. The authors concluded that the practice of prophylaxis could not be supported, but noted that the nature of the evidence was not the strongest possible, and that equine management had improved since practice was first introduced.

Conclusions from recent literature research

The review of recent literature in companion animals relating to research consistent with the definition of prophylaxis given in the Regulation identified studies that mainly addressed administration of antibiotics in the perioperative period for surgical prophylaxis.

Recommendations around peri-operative use of antimicrobials in companion animals have been extrapolated from evidence-based human treatment guidelines. Considering this guidance, the need for prophylactic administration in animals undergoing clean procedures (e.g. equine arthroscopy) could be questioned. The difficulty in extrapolation from human to animal surgical scenarios should be acknowledged and more research is needed in this area; although noting potential ethical implications.

It appears that use of perioperative antimicrobial prophylaxis in high-risk surgical cases (e.g. clean/contaminated surgery, use of implants) is customary practice and likely to be justified based on human evidence; however, although inconsistent, in general evidence does not support benefit of continuation into the post-operative period. Further research under specific circumstances is warranted. In addition, the risk of complications e.g. gastrointestinal upset in some species, due to prolonged antibiotic administration should be considered.

2. Literature review on prophylactic use of antiprotozoals

2.1. Introduction

In the EU, most infections with protozoa are caused by flagellates or coccidia spp.

The most common protozoal disease related to the prophylactic use of antimicrobials is coccidiosis.

Coccidial infections, typically causing diarrhoea, occur in all age groups. In clinical form, however, it predominately occurs in young animals of different species, e.g., cattle, sheep, goats, pigs, rabbits and poultry. Especially, under high stocking conditions morbidity is up to 100%. While acute mortality is highly variable and ranging between 0 and 50%, financial losses are mostly associated with subclinical or chronic coccidiosis, due to loss in weight gain and reduced feed conversion ratio. Albeit coccidial infections occur in a wide range of target animals, individual coccidial species are mostly species-specific and only a few have an increased zoonotic potential leading mostly to gastro-intestinal disease.

The two mayor driving factors for disease outbreaks in a herd/flock are the hygienic status and stress leading to an impaired immune system.

Due to high tenacity of oocytes, eradication of the disease in a flock or herd is hardly feasible. Therefore, control measures aim on reduction of the infection pressure by means of hygiene measures, disinfection, on strengthening the immune system (e.g. by vaccination) and improving the resilience. Nevertheless, those measures often lack efficacy under field conditions and the prevalence of coccidiosis especially in intensive cattle, pig and poultry farming systems varies between 40 and 90%.

Therefore, the prophylactic use of antiprotozoal compounds, especially where a vaccination is not feasible, is common. The majority of antiprotozoals in the EU are, however, used as zootechnical feed additives under Regulation (EC) No 1831/2003 in poultry and rabbits and, therefore, fall not under the jurisdiction of Article 107(3).

2.2. Search methodology on antiprotozoal prophylactic use (2011 – 2021)

A literature review on the use of antiprotozoal prophylactic use was carried out to find any evidence of the efficacy of prophylactic uses of antiprotozoals by animal species, production type and disease. A search strategy was developed to ensure a broad and standardized approach using the Medical Subject Headings (MeSH) thesaurus, a controlled and hierarchically-organized vocabulary produced by the National Library of Medicine.

The selection criteria included clinical trials, meta-analysis, systematic review, randomized controlled trials published from 2011/1/1 to 2021/3/1 in PubMed. Letters, editorials, case studies and commentaries were excluded.

Details on the keywords used and on the search strategies are provided below.

STRING SEARCH 1:

("Antiprotozoal Agents/pharmacology"[Mesh] OR "Antiprotozoal Agents/physiology"[Mesh] OR "Antiprotozoal Agents/prevention and control"[Mesh] OR "Antiprotozoal Agents/therapeutic use"[Mesh] OR "Antiprotozoal Agents/therapy"[Mesh]) AND "veterinary" [Subheading]

STRING SEARCH 2:

("Antiprotozoal Agents/pharmacology"[Mesh] OR "Antiprotozoal Agents/physiology"[Mesh] OR "Antiprotozoal Agents/prevention and control"[Mesh] OR "Antiprotozoal Agents/therapeutic use"[Mesh]

OR "Antiprotozoal Agents/therapy"[Mesh]) AND "veterinary" [Subheading] AND "prevention and control" [Subheading]

The duplicated references were discarded, and the remaining references were checked for relevance and selected according to these additional criteria: availability of quantitative information on the prophylactic use of antiprotozoals, investigation of pharmacologicals (exclusion of vaccines, and herbal, fruit, plant additives) and data about animal species included in the scope of this paper (exclusion of laboratory animals, wildlife and humans). Studies not conducted in a European country were included, if study conditions, animal species, pathogen and treatment were comparable to conditions known in the EU. On the other hand, studies investigating prevention of arthropode-born protozoal disease by means of repellent effects were excluded.

Those steps were performed by checking title and abstract of each individual reference and, if necessary, assessing the whole paper. After this step, the selected references were divided by animal species and active substances. An overall table on the evidences collected is provided in annex II.

2.3. Conclusions on literature search by animal species

2.3.1. Cattle

Marketing Authorisations of VMPs with 'prevention' claims:

In the EU several VMPs containing halofuginon base are authorised for the prevention of diarrhoea caused by *Cryptosporidium parvum*. Moreover, VMPs containing diclazuril, toltrazuril or decoquinate are authorised for the prevention of clinical signs of coccidiosis or just coccidiosis caused e.g., by *Eimeria bovis* and *Eimeria zuernii*. All of those marketing authorisations require a confirmed history of cryptosporidiosis or coccidiosis on farm. Nevertheless, as animals may be treated only based on disease history and without the requirement of a diagnosis of clinical disease in part of the group has been established, this preventive treatment needs to be considered as prophylactic and falls under the jurisdiction of Article 107/3.

Summary from recent literature research:

Considering the nature of a coccidiosis outbreak with a rapid spreading of the disease within a group and nearly simultaneous onset of clinical signs in all animals, combined with a very low treatment efficacy, if clinical signs occurred, control of the disease highly depends on prophylaxis of animals at risk of infection.

The efficacy of prophylaxis is underlined by study results published by Trotz-Williams, Jarvie [66], who found that calves treated with halofuginone lactate for the first 7 days following birth showed improved growth measurements, a reduced mortality and a reduced shedding of oocytes. Various studies reported a delayed onset and reduced intensity of diarrhoea after halofuginone treatment, albeit incidence of diarrhoea was not affected in all studies

Another study by Zechner, Bauer [67] compared the efficacy of diclazuril and toltrazuril in calves aged between 3 and 7 wks. While calves treated with an anticoccidial showed a reduced shedding of oocytes and a lower number of days of diarrhoea, the authors further underlined that the inclusion of a small number of untreated control calves in the study design may have led to higher levels of oocyst challenge and recommended that all calves in a group of a similar age be treated at the same time.

2.3.2. Pigs

Marketing Authorisations of VMPs with 'prevention' claims:

In the EU several VMPs containing toltrazuril are authorized for the prevention of clinical signs of coccidiosis caused by *Isospora suis*, the most common pathogen causing diarrhea in neonatal pigs [68]. All of those marketing authorisations require a confirmed history of coccidiosis on farm. Nevertheless, as animals may be treated only based on disease history and without the requirement of a diagnosis of clinical disease in part of the group has been established, this preventive treatment needs to be considered as prophylactic and falls under the jurisdiction of Article 107/3.

Summary from recent literature research:

While older studies [69] demonstrated a reduction of coccidiosis in litters treated prophylactically with toltrazuril from 71 to 22%, only one study on prophylactic use of antiprotozoals in piglets has been published within the time period relevant for this literature research. This study, however, did not investigate the efficacy of anticoccidials in preventing infections or disease against a negative control but investigated the efficacy of a combined toltrazuril and iron product against the separate administration of both compounds [70]. In conclusion, oocysts count as well as the development of bodyweight and the number of dead piglets did not differ between groups.

2.3.3. Sheep

Marketing Authorisations of VMPs with 'prevention' claims:

In the EU several VMPs containing diclazuril, toltrazuril or decoquinate are authorized for the prevention of clinical signs of coccidiosis or just coccidiosis caused e.g., by *Eimeria crandallis* or *Eimeria ovinoidalis*. Furthermore, decoquinate is used for the prevention of toxoplasmosis and associated clinical signs. All of those marketing authorisations require a confirmed history of coccidiosis on farm. Nevertheless, as animals may be treated only based on disease history and without the requirement of a diagnosis of clinical disease in part of the group has been established, this preventive treatment needs to be considered as prophylactic and falls under the jurisdiction of Article 107/3.

Summary from recent literature research:

A study published in 2011 investigated the efficacy of administering decoquinate added to mineral salt for controlling eimeriosis in lambs. While the route of administration and the unreflected administration of an anticoccidial to all lambs is not in agreement with the provisions of Regulation (EU) 2019/6, results of this study support the assumption that a prophylactic and metaphylactic administration of decoquinate is effective in preventing eimeriosis outbreaks in lambs.

2.3.4. Poultry

Marketing Authorisations of VMPs with 'prevention' claims:

No VMPs are authorized for the prevention/prophylaxis of protozoal disease in poultry. Toltrazuril and amprolium are authorized but only with a treatment claim.

The ionophores salinomycin, narasin, monensin, lasalocid, maduramicin, and semduramicin and the chemical anticoccidial drugs robenidine, decoquinate, halofuginone, nicarbazin, and diclazuril are licensed in the EU as zootechnical feed additives under Regulation (EC) No 1831/2003 in species [11], where coccidiosis is systematic for biological and zootechnical reasons, which is the case for poultry and rabbits. Systematic means that in these species, diagnosis of coccidiosis is not required and therefore, no prescription is necessary. Consequently, those compounds are not authorized as veterinary medicinal products and do not fall under the jurisdiction of Article 107(3).

Summary from recent literature research:

Only a small number of active compounds with an antiprotozoal effect falls under the jurisdiction of EU 2019/6 as most ionophores and chemical anticoccidial drugs are licensed as feed additives under EU 2003/1831. Currently, only toltrazuril, amprolium and some sulfamides are authorized as VMPs for the treatment of coccidiosis in the EU.

While there is a study demonstrating the efficacy of toltrazuril in preventing infection with Eimeria tenella and Eimeria brunetti in a challenge model [71], a general prophylactic usage of this compound is not supported. In contrast to ionophores, a wider use of toltrazuril is associated with a faster development of resistances towards this compound.

2.3.5. Horses

Marketing Authorisations of VMPs with 'prevention' claims:

No VMPs are authorized for the treatment or prevention/prophylaxis of protozoal disease in horses.

Summary from recent literature research:

While coccidiosis is known in horses and especially foals as well, clinical signs like diarrhoea occur seldom and only in cases of massive infestation. Due to housing and breeding conditions in the EU, hygiene measures and treatment of infected animals mostly suffices to control outbreaks. A preventive treatment with antiprotozoal VMPs is neither suggested in the literature nor is there any evidence that antiprotozoals are used for prevention of infections within the EU.

Infections with *Sarcocystis neurona*, however, are more in the focus of preventive measures. *Sarcocystis neurona* is the primary etiologic agent of equine protozoal myeloencephalitis (EPM). While this parasite is endemic in North America, so far within the EU, the pathogen was only detected in horses, which were imported from North America. Therefore, as of yet, there is no need for a preventive use of antiprotozoal VMPs to prevent new infections with *Sarcocystis neurona*. Nevertheless, a study conducted by Pusterla, Packham [72], suggests that a low daily dose of diclazuril (i.e., 0.5mg/kg) successfully reduces *S. neurona* infections in foals.

2.3.6. Companion animals

Marketing Authorisations of VMPs with 'prevention' claims:

No VMPs are authorized for the prevention/prophylaxis of protozoal disease in companion animals.

Summary from recent literature research:

The literature research according to the specifications explained above did not yield any publications on prophylactic use of antiprotozoal substances for the prevention of infections in companion animals. There is, however, a publication investigating the efficacy of emodepside plus toltrazuril suspension against *Isospora canis* and *Isospora ohioensis*-complex. If puppies were treated during the prepatent phase, oocyst counts were reduced by 90-100% and the number of days with diarrhoea was lower [73].

Protozoal disease found in dogs and cats in the EU are *Giardia intestinalis*, *Tritrichomonas fœtus*, *Isospora* spp., *Cryptosporidium* spp., *Toxoplasma gondii*, *Neospora caninum*, *Hammondia* spp. and *Sarcosystis* spp.

As those infections are often subclinical and self-limitating and the risk of infection is generally low, preventive treatment is not recommended. In case of infections in types of housing with high stocking density (animal shelter, breeding kennels, animal boarding houses) hygiene and disinfection measures are commonly suitable to reduce the risk of infection together with treatment of infected animals [74].

3. Literature review on prophylactic use of antivirals

At present there are no authorized antiviral veterinary medicinal products in the EU. Authorized human products may be used in animals by 'cascade', but the use of antiviral agents (e.g. amantadine, rimantadine, nucleoside analogues, foscarnet, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, neuraminidase inhibitors, fusion inhibitors, ribavirin) in veterinary medicine, whether for prevention or treatment, is limited due to a number of factors. These are, for example, the narrow spectrum, the short duration of therapeutic effect, the cost of drugs or the food safety aspects. The antiviral substances most of the time only reduce viral replication, and in many cases, the symptoms of the disease are not directly attributable to the virus, but to the immune response. Due to the difficulties and limitations of antiviral drug therapy, the fight against viral animal diseases is mostly fought by products that work by influencing the host's immune system (e.g. vaccines, antibodies, interferons).

The literature research on the prophylactic use of antiviral agents in animals has yielded scarce results. There are only few experimental uses, showing that in theory antiviral prophylaxis might provide protection against certain viral diseases (e.g. foot-and-mouth disease, classical swine fever, swine influenza viruses, bovine viral diarrhea virus, aquatic rhabdoviruses).

According to Article 107(3), antiviral group prophylaxis in a restricted number of animals – e.g. water-immersion antiviral prophylaxis in aquaculture or prophylaxis against swine influenza viruses in pigs– can be considered as acceptable, if the risk of an infection is very high and the consequences are likely to be severe. This can happen for example, if there are no effective vaccines or other alternatives against the viral disease in question.

Antiviral individual prophylaxis might also have a narrow field of application in non-food horses (e.g. equine influenza) or in companion animals (e.g. feline infectious peritonitis) if the risk of an infection is very high, the consequences are likely to be severe and other suitable alternatives are not available.

4. Literature review on prophylactic use of antifungals

No antifungal veterinary medicinal product is authorized in the EU with a prophylactic indication. Products authorized for human or veterinary use may be used for prophylaxis in animals by 'cascade'. The literature search did not reveal any relevant information of the present prophylactic veterinary use of antifungal substances (azoles, griseofulvin, allylamines, benzylamines, polyenes, flucytosine, echinocandin). Due to their nature, prevention of fungal infections in animals are primarily ensured by appropriate animal husbandry, hygienic and feeding conditions, as well as by vaccination if vaccines are available.

Although on the basis of the literature search it can be concluded that antifungals are generally not used for prophylaxis at present in the veterinary practice, it is realistic, especially with companion animals, that a healthy animal, in close contact with a fungal infected person or animal is treated with an antifungal drug off-label or by the 'cascade' to prevent the spread of infection. This practice is considered as acceptable on the basis of Article 107(3), if the risk of infection is very high and the consequences are likely to be severe.

5. References

1. Official Journal of the European Union, *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*. 2019: https://eur-lex.europa.eu/eli/reg/2019/6/oj.
2. EMA/CVMP, *Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1)*. 2016: https://www.ema.europa.eu/en/demonstration-efficacy-veterinary-medicinal-products-containing-antimicrobial-substances.
3. Boden, E. and A. Andrews, *Black's veterinary dictionary*. 2015: Bloomsbury Publishing.
4. Casadevall, A. and L.-a. Pirofski, *Host-pathogen interactions: basic concepts of microbial commensalism, colonization, infection, and disease.* Infection and immunity, 2000. **68**(12): p. 6511-6518.
5. Official Journal of the European Union, *Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes*. 2010: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32010L0063.
6. Official Journal of the European Union, *Regulation (EU) 2016/429 of the European Parliament and of the Council of 9 March 2016 on transmissible animal diseases and amending and repealing certain acts in the area of animal health ('Animal Health Law')*. 2016: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32016R0429.
7. EMA/CVMP/AWP, *Draft guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals (EMA/CVMP/AWP/706442/2013)*. 2015: https://www.ema.europa.eu/en/assessment-risk-public-health-antimicrobial-resistance-due-use-antimicrobial-veterinary-medicinal.
8. EMA/IHMP, *Criteria for classification of critical medicinal products for human and veterinary use. Shortages due to GMP non-compliance/quality defects (EMA/24304/2016)*. 2016: https://www.ema.europa.eu/en/documents/other/criteria-classification-critical-medicinal-products_en.pdf.
9. EMA/EFSA, *Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA)*, in *EFSA Journal*. 2017: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/advice-impacts-using-antimicrobials-animals/reducing-use-antimicrobial-agents-animal-husbandry.
10. Weber, J., et al., *Effects of Selective Dry Cow Treatment on Intramammary Infection Risk after Calving, Cure Risk during the Dry Period, and Antibiotic Use at Drying-Off: A Systematic Review and Meta-Analysis of Current Literature (2000–2021).* Animals, 2021. **11**(12): p. 3403.
11. Official Journal of the European Union, *Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition*. 2003: https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32003R1831.
12. EMA/CVMP/CHMP, *Categorisation of antibiotics in the European Union (EMA/CVMP/CHMP/682198/2017)*. 2019: https://www.ema.europa.eu/en/documents/report/categorisation-antibiotics-european-union-answer-request-european-commission-updating-scientific_en.pdf.
13. Official Journal of the European Union, *Regulation (EU) 2019/4 of the European Parliament and of the Council of 11 December 2018 on the manufacture, placing on the market and use of medicated feed, amending Regulation (EC) No 183/2005 of the European Parliament and of the Council and repealing Council Directive 90/167/EEC* 2019: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32019R0004.
14. EMA/CVMP, *Advice on implementing measures under Article 106 (6) of Regulation (EU) 2019/6 on veterinary medicinal products – scientific problem analysis and recommendations to ensure a safe and efficient administration of oral veterinary medicinal products via routes other than medicated feed (EMA/CVMP/508559/2019)*. 2020: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/advice-implementing-measures-under-article-106-6-regulation-eu-2019/6-veterinary-medicinal-products-scientific-problem-analysis-recommendations-ensure-safe-efficient_en.pdf.
15. OIE, *Terrestrial Animal Health Code*. 2019: https://rr-europe.oie.int/wp-content/uploads/2020/08/oie-terrestrial-code-1_2019_en.pdf.
16. FAO, *FAO Biosecurity Toolkit*. 2007: https://www.fao.org/3/a1140e/a1140e00.htm.
17. Pokludová, L., *Antimicrobials in Livestock 1: Regulation, Science, Practice: A European Perspective*. 2020: Springer.

18. EMA/CVMP, *Question and answer on the CVMP guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005)*. 2014: https://www.ema.europa.eu/en/documents/other/question-answer-cvmp-guideline-summary-product-characteristics-antimicrobial-products_en.pdf.
19. European Commission, *Commission Implementing Decision of 28.2.2014 concerning, in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for veterinary medicinal products containing "enrofloxacin" to be administered via the drinking water to chickens and/or turkeys. C(2014) 1484 final* 2014: https://ec.europa.eu/health/documents/community-register/2014/20140228127398/dec_127398_en.pdf.
20. EMA/CVMP, *Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/383441/2005-Rev.1)*. 2021: https://www.ema.europa.eu/en/guideline-summary-product-characteristics-spc-veterinary-medicinal-products-containing-antimicrobial.
21. EMA/CVMP/AWP, *Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union (EMA/CVMP/AWP/237294/2017)*. 2018: https://www.ema.europa.eu/en/off-label-use-antimicrobials-veterinary-medicine-european-union.
22. Baptiste, K.E. and N.C. Kyvsgaard, *Do antimicrobial mass medications work? A systematic review and meta-analysis of randomised clinical trials investigating antimicrobial prophylaxis or metaphylaxis against naturally occurring bovine respiratory disease.* Pathogens and disease, 2017. **75**(7).
23. Dumas, S., et al., *Judicious use of prophylactic antimicrobials to reduce abdominal surgical site infections in periparturient cows: part 1-a risk factor review.* The Veterinary record, 2016. **178**(26): p. 654.
24. Pardon, B., et al., *Prospective study on quantitative and qualitative antimicrobial and anti-inflammatory drug use in white veal calves.* J Antimicrob Chemother, 2012. **67**(4): p. 1027-38.
25. Bertulat, S., C. Fischer-Tenhagen, and W. Heuwieser, *A survey of drying-off practices on commercial dairy farms in northern Germany and a comparison to science-based recommendations.* Veterinary Record Open, 2015. **2**(1): p. e000068.
26. Biggs, A., et al., *Antibiotic dry cow therapy: where next?* Veterinary Record, 2016. **178**(4): p. 93-94.
27. Santman-Berends, I., et al., *Evaluation of udder health parameters and risk factors for clinical mastitis in Dutch dairy herds in the context of a restricted antimicrobial usage policy.* Journal of Dairy Science, 2016. **99**(4): p. 2930-2939.
28. ANSES, *Assessment of the risks of emergence of antimicrobial resistance associated with modes of antibiotic use in the field of animal health*. 2014: https://www.anses.fr/en/system/files/SANT2011sa0071Ra.pdf.
29. Winder, C., et al., *Comparative efficacy of blanket versus selective dry-cow therapy: A systematic review and pairwise meta-analysis.* Animal health research reviews, 2019. **20**(2): p. 217-228.
30. Dufour, S., et al., *Non-antimicrobial approaches at drying-off for treating and preventing intramammary infections in dairy cows. Part 1. Meta-analyses of efficacy of using an internal teat sealant without a concomitant antimicrobial treatment.* Animal health research reviews, 2019. **20**(1): p. 86-97.
31. Winder, C., et al., *Comparative efficacy of teat sealants given prepartum for prevention of intramammary infections and clinical mastitis: a systematic review and network meta-analysis.* Animal health research reviews, 2019. **20**(2): p. 182-198.
32. Meganck, V., G. Hoflack, and G. Opsomer, *Advances in prevention and therapy of neonatal dairy calf diarrhoea: a systematical review with emphasis on colostrum management and fluid therapy.* Acta Veterinaria Scandinavica, 2014. **56**(1): p. 75.
33. Catry, B., et al., *Effect of Antimicrobial Consumption and Production Type on Antibacterial Resistance in the Bovine Respiratory and Digestive Tract.* PLoS One, 2016. **11**(1): p. e0146488.
34. Jorritsma, R., A. Van der Heide, and I. Van Geijlswijk, *Survey of veterinarians in the Netherlands on antimicrobial use for surgical prophylaxis in dairy practice.* Journal of Dairy Science, 2021.
35. Djebala, S., et al., *Prophylactic antibiotic usage by Belgian veterinarians during elective caesarean section in Belgian blue cattle.* Preventive veterinary medicine, 2019. **172**: p. 104785.
36. Sargeant, J.M., et al., *A systematic review of the efficacy of antibiotics for the prevention of swine respiratory disease.* Animal health research reviews, 2019. **20**(2): p. 291-304.

37. Wilhelm, B., et al., *Assessment of the efficacy and quality of evidence for five on-farm interventions for Salmonella reduction in grow-finish swine: a systematic review and meta-analysis.* Preventive veterinary medicine, 2012. **107**(1-2): p. 1-20.
38. Trevisi, P., et al., *Comparison of three patterns of feed supplementation with live Saccharomyces cerevisiae yeast on postweaning diarrhea, health status, and blood metabolic profile of susceptible weaning pigs orally challenged with Escherichia coli F4ac.* Journal of animal science, 2015. **93**(5): p. 2225-2233.
39. Hu, Y., et al., *Dietary Enterococcus faecalis LAB31 improves growth performance, reduces diarrhea, and increases fecal Lactobacillus number of weaned piglets.* PLoS One, 2015. **10**(1): p. e0116635.
40. Diana, A., et al., *Do weaner pigs need in-feed antibiotics to ensure good health and welfare?* PloS one, 2017. **12**(10): p. e0185622.
41. Diana, A., et al., *Removing prophylactic antibiotics from pig feed: how does it affect their performance and health?* BMC veterinary research, 2019. **15**(1): p. 1-8.
42. Hartmann, S., et al., *Antibiotikaeinsatz in Schweizer Ferkelerzeugungs-und Mastbetrieben.* Schweizer Archiv für Tierheilkunde, 2019. **161**(12): p. 797-808.
43. Public Health Agency of Canada, *Canadian Antimicrobial Resistance Surveillance System Report 2016*. 2016: https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-report-2016.html.
44. Sargeant, J.M., et al., *The efficacy of antibiotics to control colibacillosis in broiler poultry: a systematic review.* Animal health research reviews, 2019. **20**(2): p. 263-273.
45. Hughes, L., P. Hermans, and K. Morgan, *Risk factors for the use of prescription antibiotics on UK broiler farms.* Journal of antimicrobial chemotherapy, 2008. **61**(4): p. 947-952.
46. Kempf, I., et al., *Effect of in-feed paromomycin supplementation on antimicrobial resistance of enteric bacteria in turkeys.* The Veterinary Journal, 2013. **198**(2): p. 398-403.
47. Verwilghen, D. and A. Singh, *Fighting surgical site infections in small animals: are we getting anywhere?* Veterinary Clinics: Small Animal Practice, 2015. **45**(2): p. 243-276.
48. Anderson, M., M. Wimmers, and J. Weese, *Infection Prevention and Control Best Practices for Small Animal Veterinary Clinics, 2nd ed. Guelph: Ontario Animal Health Network*. 2019: https://www.oahn.ca/wp-content/uploads/2021/04/OAHN-IPC-Guide-SB-Final-Jan0820_All_tagged.pdf.
49. Whittem, T.L., et al., *Effect of perioperative prophylactic antimicrobial treatment in dogs undergoing elective orthopedic surgery.* Journal of the American Veterinary Medical Association, 1999. **215**(2): p. 212-216.
50. Pratesi, A., et al., *Efficacy of postoperative antimicrobial use for clean orthopedic implant surgery in dogs: a prospective randomized study in 100 consecutive cases.* Veterinary Surgery, 2015. **44**(5): p. 653-660.
51. Yap, F., et al., *Perioperative risk factors for surgical site infection in tibial tuberosity advancement: 224 stifles.* Veterinary and Comparative Orthopaedics and Traumatology, 2015. **28**(03): p. 199-206.
52. Aiken, M.J., et al., *Prospective, randomized comparison of the effect of two antimicrobial regimes on surgical site infection rate in dogs undergoing orthopedic implant surgery.* Veterinary Surgery, 2015. **44**(5): p. 661-667.
53. Spencer, D.D. and R.M. Daye, *A prospective, randomized, double‐blinded, placebo‐controlled clinical study on postoperative antibiotherapy in 150 arthroscopy‐assisted tibial plateau leveling osteotomies in dogs.* Veterinary Surgery, 2018. **47**(8): p. E79-E87.
54. Nazarali, A., et al., *Association between methicillin-resistant Staphylococcus pseudintermedius carriage and the development of surgical site infections following tibial plateau leveling osteotomy in dogs.* Journal of the American Veterinary Medical Association, 2015. **247**(8): p. 909-916.
55. Clark, A.C., J.J. Greco, and P.J. Bergman, *Influence of administration of antimicrobial medications after tibial plateau leveling osteotomy on surgical site infections: A retrospective study of 308 dogs.* Veterinary Surgery, 2020. **49**(1): p. 106-113.
56. Beck, K.M., et al., *Prevalence of meticillin‐resistant Staphylococcus pseudintermedius (MRSP) from skin and carriage sites of dogs after treatment of their meticillin‐resistant or meticillin‐sensitive staphylococcal pyoderma.* Veterinary dermatology, 2012. **23**(4): p. 369-e67.
57. Windahl, U., et al., *Carriage of methicillin-resistant Staphylococcus pseudintermedius in dogs--a longitudinal study.* BMC veterinary research, 2012. **8**(1): p. 1-8.
58. Saijonmaa‐Koulumies, L., E. Parsons, and D. Lloyd, *Elimination of Staphylococcus intermedins in healthy dogs by topical treatment with fusidic acid.* Journal of Small Animal Practice, 1998. **39**(7): p. 341-347.
59. Morris, D.O., et al., *Recommendations for approaches to meticillin‐resistant staphylococcal infections of small animals: diagnosis, therapeutic considerations and preventative measures.*

Clinical Consensus Guidelines of the World Association for Veterinary Dermatology. Veterinary dermatology, 2017. **28**(3): p. 304-e69.
60. Freeman, K., et al., *Post operative infection, pyrexia and perioperative antimicrobial drug use in surgical colic patients.* Equine veterinary journal, 2012. **44**(4): p. 476-481.
61. Durward - Akhurst, S., et al., *Comparison of two antimicrobial regimens on the prevalence of incisional infections after colic surgery.* Veterinary Record, 2013. **172**(11): p. 287-287.
62. Salem, S., C. Proudman, and D. Archer, *Prevention of post operative complications following surgical treatment of equine colic: current evidence.* Equine Veterinary Journal, 2016. **48**(2): p. 143-151.
63. Dallap Schaer, B., J. Linton, and H. Aceto, *Antimicrobial use in horses undergoing colic surgery.* Journal of veterinary internal medicine, 2012. **26**(6): p. 1449-1456.
64. Pezzanite, L.M., et al., *Intra - articular administration of antibiotics in horses: Justifications, risks, reconsideration of use and outcomes.* Equine Veterinary Journal, 2022. **54**(1): p. 24-38.
65. Wohlfender, F.D., et al., *Diseases in neonatal foals. Part 1: the 30 day incidence of disease and the effect of prophylactic antimicrobial drug treatment during the first three days post partum.* Equine Vet J, 2009. **41**(2): p. 179-85.
66. Trotz - Williams, L., et al., *Efficacy of halofuginone lactate in the prevention of cryptosporidiosis in dairy calves.* Veterinary Record, 2011. **168**(19): p. 509-509.
67. Zechner, G., et al., *Efficacy of diclazuril and toltrazuril in the prevention of coccidiosis in dairy calves under field conditions.* Veterinary Record, 2015. **176**(5): p. 126-126.
68. Driesen, S., P. Carland, and V. Fahy, *Studies on preweaning piglet diarrhoea.* Australian veterinary journal, 1993. **70**(7): p. 259-263.
69. Driesen, S., V. Fahy, and P. Carland, *The use of toltrazuril for the prevention of coccidiosis in piglets before weaning.* Australian Veterinary Journal, 1995. **72**(4): p. 139-141.
70. Streyl, K., et al., *Field evaluation of the effectiveness of an oral toltrazuril and iron combination (Baycox® Iron) in maintaining weaning weight by preventing coccidiosis and anaemia in neonatal piglets.* Parasitology research, 2015. **114**(1): p. 193-200.
71. Alnassan, A.A., et al., *Efficacy of early treatment with toltrazuril in prevention of coccidiosis and necrotic enteritis in chickens.* Avian Pathology, 2013. **42**(5): p. 482-490.
72. Pusterla, N., et al., *Daily feeding of diclazuril top dress pellets in foals reduces seroconversion to Sarcocystis neurona.* The Veterinary Journal, 2015. **206**(2): p. 236-238.
73. Altreuther, G., et al., *Efficacy of emodepside plus toltrazuril suspension (Procox® oral suspension for dogs) against prepatent and patent infection with Isospora canis and Isospora ohioensis-complex in dogs.* Parasitology research, 2011. **109**(1): p. 9-20.
74. ESCCAP, *Guideline 6: Control of Intestinal Protozoa 6 in Dogs and Cats*. 2018: https://www.esccap.org/guidelines/gl6/.