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Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union

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Table of contents

CVMP Recommendations for action

'Off-label use' is defined in Article 1(16) of Directive 2001/82/EC (Official Journal of the European Communities, 2001) on the Community code relating to veterinary medicinal products (hereafter referred to as the 'Directive') as '*the use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics, including the misuse and serious abuse of the product'.* The cost of development of veterinary medicinal products (VMPs) inevitably leads to limited availability of products authorised for species and indications representing smaller market sectors. In addition, veterinary prescribing evolves rapidly, reflecting changing trends or advances in veterinary practice. Although it is preferable that VMPs are used in-line with the summary of product characteristics (SPC) as approved, the prescribing cascade is established under EU legislation to address this lack of authorised VMPs, with its use expected to be 'by way of exception' and in particular 'to avoid causing unacceptable suffering' (Articles 10 and 11 of Directive 2001/82/EC, as amended by Directive 2004/28/EC, (Official Journal of the European Communities, 2001; Official Journal of the European Union, 2004)). Not all off-label use practices are consistent with this requirement of the cascade.

Due to a lack of official data on the extent of off-label antimicrobial[1] use, and specific research on its impacts, it is only possible to speculate about the potential benefits and risks to animal and public health and acceptability of these practices based on general principles.

Responsible off-label use of antimicrobials includes a consideration of factors such as the availability of treatments for a minor species or indications not included on the SPC, changes to dosing regimens to accommodate the susceptibility of the target pathogen or the need to address a particular patient's physiological status or health disease characteristics. This may be seen as acceptable provided that potential additional impacts on public and animal health due to antimicrobial resistance (AMR) are taken into account and risk management measures are implemented (see recommendations below). Cascade use for groups of animals and use of human-only authorised antimicrobials in companion animals require careful consideration.

Some types of off-label antimicrobial use cannot be considered as cascade use and the potential associated risks cannot be justified. These include use of antimicrobials for practical or economic reasons alone, systematic preventive use in groups of animals, intentional under-dosing and concomitant use of two or more antimicrobials without proper diagnosis. Such practices are of high concern, in particular when they involve group treatments and/or use of critically important antimicrobials (CIAs).

The CVMP concludes that the following recommendations should be considered in relation to the off-label use of veterinary medicinal products containing antimicrobial substances:

1. Although the Directive makes provisions for cascade use, there is no official collection of data on the extent or nature of off-label use, or requirement for monitoring. There is therefore very little evidence on which to base an assessment of the risk due to AMR that off-label use actually poses to animal and public health.

   It is recognised that establishing a formal system to collect prescription data on off-label use in all countries could be burdensome on veterinarians and competent authorities. Hence, a limited,

[1] Antimicrobial agent: A naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms) at concentrations attainable *in vivo*. Antiparasitics and substances classed as disinfectants or antiseptics are excluded from this definition (OIE Terrestrial Animal Health Code definition). In the context of this reflection paper the focus is on compounds acting against bacteria.

research initiative sufficient to investigate the major off-label uses in the different species, particularly of antimicrobials that are currently only authorised for human use[2], is recommended. Knowledge of the extent and evolving nature of off-label use would be of value in identifying therapeutic gaps, and in further evaluating the potential risk to animal and public health due to AMR. In the longer term it could help in measuring the effectiveness of measures taken to manage the risks around off-label use.

Responsible body: Research institutes, government bodies with responsibility for policy-making and surveillance in the area of AMR.

2. Prescribing under the cascade should be limited to individual animals, if feasible, although it is recognised that this may not be applicable to all husbandry systems e.g fish, poultry or for minor species e.g. food rabbits. Off-label use, in particular that of antimicrobial substances/classes categorised as critically important with regard to their use in human and animal health (WHO, AMEG), should be supported by a full diagnostic investigation including bacterial culture and antimicrobial susceptibility testing (AST), where possible.

   Responsible body: Prescribing veterinarians, policy-makers.

3. When prescribing under the cascade, veterinarians should take into account the importance of the antimicrobial to human medicine and the risk for transmission of AMR from treated animals to humans. In particular, veterinarians should take these factors into account in the benefit-risk assessment before prescribing antimicrobials that are presently only authorised for use in human medicine[4] (AMEG Category 3) (EMA/AMEG, 2014), which are CIAs for use in human medicine as one of few alternatives to treat serious disease, and for which the AMEG considered the risk for spread of resistance to be high. This could be facilitated by use of treatment guidelines that have already considered these aspects (see below). Use of Category 3 antimicrobials should be kept to an absolute minimum.

   Responsible body: Prescribing veterinarians, professional bodies preparing treatment guidelines.

4. The development by regional professional bodies of evidence-based treatment guidelines is encouraged. Such guidelines can support responsible off-label use of antimicrobials by taking into account the local AMR situation and product availability in the Member State(s) in addition to the general clinical evidence base. Any off-label uses recommended in these guidelines, should be identified and comply with the conditions of articles 10 and 11 of the Directive (cascade). A One Health approach should be adopted so that the potential impact on public health is included in the risk assessment underlying this guidance. Guidelines should emphasise prudent use principles, especially in regards to CIAs. Guidelines should be regularly updated and veterinarians trained in their use and the use of SPCs through stewardship programmes. As articles and papers published in press and scientific journals are also important and influential in prescribing decisions made by veterinarians, it should be made clear in such publications when their recommendations are for off-label use and any conflicts of interest should be declared.

   Responsible body: Veterinary professional bodies, universities, veterinarians, journal editors.

5. Off-label use of antimicrobials for practical or economic reasons alone, systematic preventive use of antimicrobials in groups of animals, intentional under-dosing and concomitant use of two or

[2] antimicrobials that are currently only authorised for human use may not be used legally under the cascade in food-producing animals unless there is a Maximum Residue Limit for the active ingredient

more antimicrobials without proper diagnosis 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 criteria of Articles 10 and 11 of the Directive. With regard to the systematic preventive use detailed recommendations are given in the RONAFA report (EMA/EFSA, 2017).

Responsible body: Prescribing veterinarians, policy-makers, farmers and livestock associations.

6. As documented in the CVMP's strategy on antimicrobials 2016-2020 (EMA/CVMP, 2016), when conducting referral procedures and SPC harmonisation, further consideration should be given to developing methodologies to avoid the loss of indications from the SPCs of lower risk older antimicrobial veterinary medicinal products.

   Responsible body: CVMP

7. The pharmaceutical industry should be encouraged to develop and market VMPs containing Category 1 substances or other antimicrobials of lower risk for public health to address therapeutic gaps and broaden their indications, thereby reducing the need for off-label use. For Minor Uses and Minor Species (MUMS), this could largely be achieved through extensions to existing VMPs. It is also necessary for these products to be marketed across the EU.

   Responsible body: Pharmaceutical industry. It is also the responsibility of CVMP and competent authorities to provide scientific advice on the data requirements for MA applications.

8. Further research is needed into the impact on antimicrobial resistance selection of administration of antimicrobials by non-authorised routes for practical reasons to groups of animals, e.g. administration in liquid feed to pigs.

   Responsible body: Research organisations, livestock associations.

9. Veterinarians should be encouraged to report on the lack of efficacy in authorised antimicrobial VMPs when used either according to the label or off-label, via the pharmacovigilance system.

   Responsible body: prescribing veterinarians, regulatory authorites, MAHs.

1. Introduction

Medical treatments for animal diseases have evolved extensively over the last 100 years. A wide variety of pharmaceutical agents are marketed, but only a minority of these are authorised for use in animals, with specific indications. This relative paucity of approved veterinary medicinal products (VMPs) for the wide diversity of animal species and disorders, results in veterinarians using products outside of the authorised conditions of use detailed in their summaries of product characteristics (SPCs) in order to treat disease and alleviate suffering. This is known as 'off-label' use and is of particular relevance to minor species and/or minor indications, as defined in the CVMP guidance on the classification of veterinary medicinal products indicated for minor use minor species (MUMS)/limited market (EMA/CVMP, 2017). In these cases, the regulatory costs for the pharmaceutical industry associated with developing new medicines and maintaining them on the market are too great compared to the return on investment.

There are specific concerns relating to the off-label use of antimicrobials, for example administration when not indicated, use of incorrect doses or improper route of administration. These practices may lead to ineffective or unnecessary antimicrobial use and thereby pose an unjustified risk to animal and public health due to potential dissemination of antimicrobial resistance (AMR).

In the scientific literature, there are few references in which the off-label use of veterinary medicinal products has been investigated. Recently, a survey of practising veterinarians by the German Federal Office of Consumer Protection and Food Safety reported that, of the 146 veterinary practices taking part, 74% reported off-label use of systemic anti-infectives (Biedermann, 2014).

2. Scope

This document intends to define off-label use and provide relevant examples of off-label use of antimicrobials in animals and the underlying reasons for these practices. The circumstances when off-label use is compatible with responsible use of antimicrobials will be explored. The goal is to identify and focus on areas that may cause unacceptable public and animal health risks due to dissemination of antimicrobial resistance. Off-label antimicrobial use in companion animals and food-producing animals will be addressed.

This reflection should not be interpreted as promoting any therapeutic recommendations regarding off-label use of antimicrobials.

3. Definition and legal aspects of 'off-label' use

The Summary of Product Characteristics (SPC) is the regulatory document containing information on the approved uses of a medicinal product. In EU legislation it is considered implicit that, for authorised veterinary medicines, veterinarians should follow the conditions for use as set out in the SPC. Use outside of the SPC is commonly referred to as 'off-label' use and is defined in the European Directive 2001/82/EC:

"The use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics (SPC), including the misuse and serious abuse of the product."

Acknowledging that approved indications for veterinary medicinal products might not address all clinical needs and that product availability in MSs can vary considerably depending on their markets, legal provisions are in place to allow use outside of the approved conditions of use. Thus, it is

recognised that there are clinical situations in which off-label use of a product is necessary and appropriate. In EU legislation, the relevant legal text permitting such use is detailed in Articles 10 and 11 of the Directive, (known as 'the cascade'). The principle of the cascade is that if no suitable veterinary medicine is authorised in a member state to treat a condition, the veterinary surgeon responsible for the animal may, 'by way of exception' and 'in particular to avoid causing unacceptable suffering', treat the animal in accordance with the following sequence in descending order of priority:

- A VMP authorised in the member state for use in another animal species or for a different condition in the same species,
- if there is no such product, then either:
  - a medicine authorised for human use in the member state; or
  - a VMP authorised in another member state for use in the same species or another species;
- if there is no product referred to above, a VMP prepared extemporaneously.

AMR risk assessments are performed before approval of veterinary medicinal products and any identified risks are mitigated by specific warnings and/or restrictions in the SPC (EMA/CVMP, 2018). This includes establishment of a maximum residue limit (MRL) specific to the antimicrobial substance and a withdrawal period specific to the VMP to ensure that antimicrobial residues in food produce do not exceed levels that could impact the colonisation barrier or population of AMR bacteria in the colon of the consumer. In the interest of food safety, food-producing animals may only be treated under the cascade with medicines which contain substances listed in the Table of Allowed Substances included in the Annex to in Commission Regulation (EU) No 37/2010 (Official Journal of the European Union, 2010), i.e. for which MRLs have been established where needed. Where products are used in accordance with the cascade, minimum withdrawal periods are prescribed by law (Articles 11(2) of Directive 2001/82/EC, as amended by Directive 2004/28/EC, (Official Journal of the European Communities, 2001; Official Journal of the European Union, 2004)).

While much off-label use is to address the absence of authorised products (for a specific species or clinical indication), there are other factors that may result in off-label use of VMPs. For example, De Briyne et al. (2013) reported the results of a voluntary survey of veterinary practitioners on factors that influence antimicrobial prescribing habits. In this survey, which included 3004 responses from 25 European countries, respondents ranked training/literature as well as their own experience higher than SPCs as important sources of information influencing their prescribing behaviour. Of the respondents, 56% stated that they viewed the SPC only occasionally and/or seldom before treatment; a higher importance was associated with product labels and package leaflets, which should be consistent with the SPC although containing less detail.

Further, the authorisation of antimicrobial VMPs in accordance with current SPC guidance has the potential to lead to more off-label use. Previously, indications tended to be broad and were simply stated as, for example: 'for bacterial infections susceptible to [the concerned antimicrobial]', and thus only very few uses in the authorised target species would have been classified as off-label. Where 'older' lower risk antimicrobials have been the subject of a recent review, specific narrow indications against named target pathogens have been introduced (as specified in the revised EU guideline on the SPC for antimicrobial products) resulting in increasing examples of off-label use by veterinarians wishing to adhere to responsible use principles.

4. Collection of official data on off-label use

There are no official data on the volume of antimicrobials used off-label in the EU. The ESVAC project collects data on sales of antimicrobials within the EU but they are obtained mostly from wholesalers and Marketing Authorisation Holders, and detailed data on the conditions of use are not collected. In addition, no data on the sales of antimicrobial products used in animals but authorised for use in humans are collected (EMA/ESVAC, 2018).

In regards to use under the cascade, the use of the expressions, 'by way of exception', and 'in particular to avoid unacceptable suffering' allows legislators to indicate that off-label use is restricted. However, the implementation of the cascade legislation may differ between EU Member States. In a web-based survey conducted by the FVE and EMA to explore the reporting of adverse events (De Briyne et al., 2017), of the 2975 self-selected veterinarians who provided information on off-label use, 25 per cent reported that more than 10 per cent of their prescriptions related to off-label use, although this related to all types of veterinary medicines, not just to antimicrobials. Between the types of practice, off-label use in this survey was seen mostly in equine practice and the least in mixed practice and large variations were observed between the different countries. Data on off-label use of antimicrobials has been collected as part of surveys of their use in various member states (Biedermann, 2014; Cazeau et al., 2009; Gay et al., 2012) (see annex), but overall information on the extent and nature of off-label use of antimicrobials is limited. Consequently, it is only possible to speculate about the risks to animal and public health based on general principles.

5. Reasons for off-label antimicrobial use and associated risks

The choice to use an antimicrobial off-label is made by the prescribing veterinarian under their personal responsibility. Although all antimicrobial use carries an AMR risk, off-label use might be associated with additional risks for public and animal health, beyond those that have been established according to labelled use and are mitigated as far as possible with advice in the SPC. The additional risks that are especially important for antimicrobials include:

- Ineffective treatment due to incorrect choice of antimicrobial or dosing regimen for the target pathogen
- Selection and dissemination of antimicrobial resistance (AMR) in target pathogens, due to e.g.
  - Under-dosing (intentional or unintentional)
  - Inappropriate route of administration
  - Prolonged dosing for chronic conditions
- Selection and dissemination of antimicrobial resistance (AMR) in commensal bacteria and zoonotic pathogens of relevance to public health, due to e.g.
  - Prolonged treatment duration
  - Exposure to antimicrobials superfluous to animal health needs, especially when group treatments are involved
  - Use of human-only authorised CIAs

- Application of inadequate withdrawal periods resulting in antimicrobial residues in food produce which exceed the microbiological ADI (acceptable daily intake)

The occurrence of adverse events in the treated animal may be related to the off-label use of antimicrobials, as for off-label use of any medicine, and hence is not a focus in this reflection paper; although, some examples are given in the annex.

Some common reasons for off-label use of antimicrobials in veterinary medicine, together with consideration of the potential added risks and risk management, are discussed below.

5.1. Unmet medical need

Clinical practice is a dynamic environment, where not all bacterial indications are covered by authorised antimicrobial medicines. Some indications, although important, maybe too limited or too multifactorial in etiology for pharmaceutical companies to seek regulatory approval (e.g. septic arthritis, peritonitis, meningitis), and thus veterinarians will use antimicrobials off-label because of a medical need unmet by VMPs on the market ('minor uses'). In many instances this would entail use of an antimicrobial authorised for a different indication in the same species, but otherwise in accordance with the SPC. This should preferably be accompanied by isolation of the causative pathogen(s) and antimicrobial susceptibility testing, in accordance with responsible use principles. Considering that treatment is necessary, with appropriate clinical monitoring this practice would not be expected to increase the AMR risk beyond that associated with labelled use.

The AMEG report (EMA/AMEG, 2014) identified that a further primary area of concern regarding the availability of antimicrobial medicines was for minor species such as rabbits, game and minor fish species. Off-label use of antimicrobials in goats (and sheep) has been identified as relatively frequent (Gay et al, 2012; see annex). Antimicrobials are used under the cascade for the treatment of zoo and wild animals with data and knowledge on prescribing being shared through professional bodies such as the European College of Zoological Medicine and the European Association of Zoo and Wildlife Veterinarians. The validity of direct extrapolation of dose regimens from major to minor species may be impacted by differences in species pharmacokinetics and also differences in the susceptibility of the target pathogens to be treated (Toutain et al., 2010). In this case, care should be taken to ensure that the dose is effective by making use of published studies, where available. For food-producing animal species, adequate withdrawal periods should be applied in order to limit the AMR risk (see above).

In situations where availability of authorised antimicrobial treatment options are limited e.g. due to minor use / minor species, or due to the limited market in some countries, off-label use may allow a more prudent selection e.g. in terms of use of a less critically important antimicrobial; however, in this case the total evidence base (quality, safety, effectiveness) supporting the specific use must be considered.

Other unmet indications are more controversial.

The objective of surgical prophylaxis is to reduce postoperative infections, thereby reducing morbidity, mortality, and treatment costs. Based on experiences in human medicine, the benefit of prolonged antimicrobial therapy within the post-operative period has not been supported by the scientific literature (Classen et al., 1992; Mangram et al., 1999; Stone et al., 1976; Stratchounski et al., 2005), even for clean-contaminated surgeries (De Chiara et al., 2010). However, there is support in human medicine for prophylactic antimicrobial administration in the immediate peri-operative period, as documented in published guidelines (Bratzler et al., 2013). There are few studies investigating the use of surgical antimicrobial prophylaxis in veterinary medicine. Dumas et al. (2016) recommended that,

when considering the need for prophylactic antimicrobial use for abdominal surgery in periparturient cows, risk factors such as levels of wound contamination, potential pathogens, host immune status, surgical technique and duration of procedure should be evaluated by surgeons on a case-by-case basis.

Veterinarians may resort to antimicrobial treatment based on clinical signs that indicate a possible infection at an important body site/s (e.g. joint, eye, peritoneum, bone, septicaemia, endocarditis) without all clinical indicators or other evidence being present (e.g. bacterial culture and susceptibility testing). It is possible that a non-infectious cause could be driving clinical signs (e.g. trauma, immune-mediated). Treatment when there is a lack of clinical indicators could be due to the need for quick clinical intervention based on the serious nature of the condition or known poor accuracy (sensitivity/specificity) of culture (e.g. joint or blood culture). In human medicine, a reduction in application of these practices has been associated with either no negative clinical impact (Gonzalez et al., 2013; Mokart et al., 2014) or improved patient outcome, including for life-threatening conditions such as sepsis (Garnacho-Montero et al., 2014).

Use of antimicrobials only authorised for use in humans

There may be situations where AST reveals multi-drug resistant bacteria for which no authorised VMPs are available and the only remaining treatment option is to use antimicrobials only authorised for use in humans. Information on the extent of use of human-only authorised antimicrobials in animals is lacking; however, due to the absence of MRLs, their use is limited to non-food species only. The annex to this document includes examples of these substances and the indications for which they are used in companion animals. Substances include antimicrobials classed as CIAs for human health by the WHO (WHO, 2017) such as carbapenems, glycopeptides (vancomycin), oxazolidinones (linezolid) and rifamycins (rifampicin). It is noted that the emergence of multi-drug resistance in companion animal pathogens is a driver for their use, and the CVMP's reflection paper on the risk of antimicrobial resistance transfer from companion animals (EMA/CVMP, 2015) identified that several multi-drug resistant pathogenic bacteria are shared between companion animals and humans.

In 2014, the AMEG reviewed the off-label use of human-only authorised antimicrobials in veterinary medicine (EMA/AMEG, 2014). It was concluded that in the absence of data on the extent of use, the risk to public health could not be estimated; however, the AMEG recommended that the use of carbapenems and glycopeptides in veterinary medicine should be kept to a minimum and risk management options were suggested:

- To establish a list of diseases where off-label use would be possible;
- To require official declaration of use of carbapenems to the relevant authority.

An overarching recommendation was to include in future legislation flexible tools to allow prohibiting or limitation of off-label use in animals of certain antimicrobials/classes authorised only in human medicine following an unfavourable hazard characterisation or benefit-risk assessment.

5.2. Systematic group preventive use of antimicrobials

Routine preventive administration of broad spectrum antimicrobials to piglets immediately after birth, at the time of castration and at weaning, and to veal calves on arrival at farm (Jørgensen et al., 2007; Pardon et al., 2012; Timmerman et al., 2006) (see annex) have been reported. In these cases of systematic preventive treatment of piglets and veal calves at times of 'stress', antimicrobials are administered off-label as a management tool often to groups of animals (Callens et al., 2012).

Changes to management practices, e.g. improving biosecurity, hygiene and nutrition, minimizing transport as well as increasing the availability and use of vaccination could eliminate the need for this off-label antimicrobial use. This issue is discussed further in the RONAFA report (EMA/EFSA, 2017). Firm data on the extent of this use are not available, but some studies suggest that it may be prevalent in some member states (Callens et al., 2012; Moreno, 2014). It is especially of concern when such off-label use also relates to CIAs. The off-label preventive use of 3rd- and 4th-generation cephalosporins in day-old chicks has been associated with dissemination of resistance genes through the poultry production pyramid (Baron et al, 2014; see annex) and the occurrence of infections with resistant bacteria in humans (Dutil et al., 2010; see annex). In these cases the increased risk for AMR development cannot be justified. Following a European Commission Decision issued in 2012 (EMA/CVMP, 2012), the off-label use of 3rd- and 4th-generation cephalosporins in poultry has been contraindicated in SPCs.

Dysbacteriosis

Oral group medications for young food-producing animals account for a substantial amount of antimicrobial use. The most common reasons include gastrointestinal diseases (Pardon et al., 2012; Persoons et al., 2012; Timmerman et al., 2006). More recent evidence points to a cascade of physiological and farm management factors (diet composition, environmental stress, medication including antimicrobials (Larcombe et al., 2018) at the root of neonatal/weaning diarrhoea, creating a syndrome known as dysbacteriosis. Dysbacteriosis is a non-specific enteritis following from a disturbance in the equilibrium of the gut microbiota, similar to small intestinal bacterial overgrowth in human medicine (Abu-Shanab and Quigley, 2009). In veal calves, often *Escherichia coli* and *Clostridium perfringens* are the bacteria that overgrow the digestive tract (Pardon et al., 2012). In chickens (broilers), dysbacteriosis and necrotic enteritis are major indications for group antimicrobial treatments (Persoons et al., 2012). Dysbacteriosis is not included as an indication on the SPCs for antimicrobial medicines although antimicrobials are essentially used to treat or prevent the effects of dysbacteriosis.

Any off-label use of an antimicrobial VMP as a substitute for addressing underlying nutritional or management factors cannot be justified.

5.3. Alternative routes of administration

Certain clinical procedures and methods are becoming accepted as optimal treatment strategies. Among these are alternative routes of antimicrobial administration, especially those that are known to increase concentrations at sites of infection that are difficult to reach. These include intra-synovial antimicrobial injections, regional limb perfusion, and intra-osseous infusions (Cruz et al., 2006) (see annex). Some alternative routes are not well proven but commonly practised (e.g. inhalation, intrauterine, and intraperitoneal administration, guttural pouch instillation; see annex).

The impact of the route of administration on pharmacokinetics, and hence antimicrobial effectiveness and development of AMR in target pathogens, should always be considered when prescribing antimicrobials 'off-label'.

Where treatment of individual animals is concerned, the AMR public health impact will consequently be limited. However, there are other examples where antimicrobials are administered regularly by a non-authorised route for practical reasons to groups of animals. In northern European countries, it was estimated in 2008 that a significant proportion of grow-to-finish pig farms used liquid feed (WATTAgNet, 2009). Heller et al. (2016) (see annex) suggested that liquid feed containing

antimicrobials is a reservoir of antimicrobial resistant bacteria in swine production. The possible associated impact of such practices on animal and public health warrants further investigation.

5.4. Individual patient characteristics

The prescribing veterinarian may consider off-label treatment to address patient features such as breed, age or underlying conditions, e.g. renal or hepatic disease, or known hypersensitivity to a particular antimicrobial substance, which may limit the choice of authorised alternatives.

In neonates, differences in physiological characteristics and their rate of maturation may result in increased oral drug absorption, lower binding to plasma proteins (particularly albumin), differences in distribution of lipophilic and hydrophilic antimicrobials and differences in metabolism and elimination (Baggot and Giguère, 2013). These variations can make the prediction of dose and dosage intervals difficult or unreliable in neonates and antimicrobial dosing regimens that differ from those approved for adults are often recommended.

Where evidence-based, off-label use to address patient characteristics is aimed at improving target animal safety and effectiveness of treatment. Because such use mostly concerns individual animals, the impact on AMR selection is consequently reduced.

5.5. Use of combinations of antimicrobials

Complex medical conditions and those involving polymicrobial infections tend to attract broad spectrum antimicrobial coverage and combinations of antimicrobial treatments. Examples of recognized combination treatments include macrolides and rifampicin for treatment of *Rhodococcus equi* infections in foals (synergistic effect) and gentamicin and clindamycin for peritonitis after intestinal spillage (broad spectrum antimicrobial therapy) (Giguère et al., 2013). Possible drug interactions (both kinetic and dynamic) and susceptibility of the specific target pathogens need to be considered, and in many cases the information given in the individual SPCs is not sufficient to allow for an estimation of the benefits and risks associated with concomitant treatments.

Treatment with two or more different antimicrobials administered concomitantly may not be clearly regarded as off-label use; however, in many cases such use appears to be unnecessary and probably reflects a lack of proper diagnosis rather than a true need. On farrow-to-finish pig farms in Spain, it was found that combinations of colistin, amoxicillin and zinc oxide were used in feed preventively in the preweaning stage (Moreno, 2014). Pardon et al. (2012) found that for veal calves in Belgium, in 33.3% of oral group treatments a combination of two antimicrobial products was used, mostly for prevention on arrival at farm and treatment of respiratory disease.

Without proper diagnosis including culture and AST, circumstances where the use of combinations may be justified are limited (e.g. in an emergency situation with known risk factors). Unjustified combination antimicrobial treatment causes unnecessary exposure of both target pathogens and bacteria of relevance to public health.

5.6. Practical considerations

Availability of appropriate package sizes, strength, convenience of application, and costs may be considered important and as a rationale for off-label use by the prescriber, especially when dealing with exotic species. A European survey investigating the general antimicrobial prescribing behaviour of veterinary practitioners (De Briyne et al., 2013), found that economic factors were less important than

other (e.g. responsible use) factors in influencing prescribing decisions. However, Gibbons et al. (2013) found that costs, treatment frequency and shorter withdrawal periods were important considerations for cattle practitioners in Ireland. In a questionnaire survey carried out by the German Federal Office of Consumer Protection and Food Safety, a common reason stated by large animal practitioners for off-label antimicrobial use was the impracticality to stock their vehicles with all marketed antimicrobials for all indications (Biedermann, 2014). This suggests that at least some of the off-label use of systemic antibiotics in large animals could be based on practical reasons rather than the requirements of the specific disease (Biedermann, 2014).

Although treatment compliance is an important consideration when prescribing antimicrobials, practical or economic reasons alone cannot be seen as acceptable justification for off-label use.

5.7. Alternative dosing regimens (posologies)

Sometimes a veterinarian may consider that the effective treatment of a particular condition requires a different approach than that which appears in the SPC, either by increasing the dose or changing the dosing interval and/or duration. Lees and Shojaee Aliabadi (2002) indicate that treatment optimisation of a bacterial disease requires that antimicrobial doses are adapted to the susceptibility of the targeted microbe (i.e. minimum inhibitory concentration-MIC) and pharmacokinetic variability. Where there is evidence from clinical practice that authorised dosing regimens of old antimicrobials are no longer efficacious veterinarians are encouraged to report on potential lack of efficacy via the pharmacovigilance system. When treating food-producing species, changing the dosing regimen may impact on the withdrawal period (see section 4).

Dose changes may be common for some antimicrobials (e.g. beta-lactams) where there are limited concerns regarding the margin of safety. Veterinarians may increase doses for better penetration into difficult sites of infection (e.g. cerebrospinal fluid, tendons, bones). Furthermore, labelled doses are tailored to the indicated bacteria and may not reflect the requirements for other types of bacterial infections.

Canine pyoderma is an example of a chronic disease where treatment guidelines often suggest dosing regimens that exceed the dose and duration of treatment stated in the SPC (Beco et al., 2013) (see annex). Although chronic complex diseases requiring long-term antimicrobial treatment usually involve individual companion animals, they are associated with increased risk for selection of AMR and, where possible, use should be made of regular culture and susceptibility testing and evidence-based treatment guidelines, which may also provide guidance on reducing the zoonotic risk (Beco et al., 2013).

European surveys on antimicrobial use in cattle and pigs show that antimicrobials are frequently either over- or under-dosed (Gay et al., 2012; Pardon et al., 2012; Timmerman et al., 2006) (see annex) for reasons not always related to dose optimisation. In veal calves it was considered that under-dosing in oral group treatments may have been related to under-estimation of bodyweight (unintentional) or use of lower doses to treat dysbacteriosis (intentional). Under-dosing of oral group antimicrobial treatments was also commonly found on pig farms in Belgium (Callens et al., 2012; Timmerman et al., 2006) (see annex) where it was hypothesized to be related to confusion between dosing according to animal body weight or to the quantity of feed/water provided. In a survey of farrow-to-finish pig farms in Spain, long treatment durations of in-feed antimicrobials ranging up to 60 days during the growing phase were suggested as indicating discretionary use (Moreno, 2014).

In aquaculture it is speculated that unintentional under-dosing of antimicrobials may occur due to poor homogeneity of medicated feed as a result of on-farm mixing, and suppression of appetite which may be due to disease, palatability issues and/or changes in environmental temperature (FVE, 2014).

Sub-optimal dosing of antimicrobials carries the risk for ineffective treatment and selection of AMR in target pathogens (McKellar et al., 2004). Unintentional under-dosing may be more likely with group treatments, and should be avoided by weighing animals prior to treatment and providing clear dosing instructions. There is no justification for intentional under-dosing.

Use of dosing regimens exceeding those in the SPC presents a risk of exposure of consumers to antimicrobial residues unless withdrawal periods are suitably adjusted. Prolonged dosing for prevention of disease increases the risk of AMR selection in both bacteria of relevance to public health and potential target pathogens through collateral exposure; it cannot be justified and is a particular risk when it involves mass medication (see also 5.2).

5.8. Non-antibacterial purposes

Several antimicrobial agents have been found to have other effects on the body (e.g. anti-inflammatory, immunomodulatory or prokinetic properties) and are sometimes given for non-bacterial purposes (D'Agostino et al., 1998; Lester et al., 1998; Vos et al., 2012). For example, macrolides, doxycycline and metronidazole are known to modulate the immune response and the purpose of treatment may be to exploit this effect on the immune system. Tetracyclines can be used for their additional anti-inflammatory properties. Gentamicin is sometimes given as an intra-vitreal eye injection, in dogs and horses, to chemically ablate the ciliary body epithelium for treatment of uncontrollable glaucoma (König et al., 2003). Another non-bacterial effect of antimicrobials that is sometimes utilised is binding to bacterial endotoxins (e.g. polymyxin B) (see annex).

These types of treatments are likely to be used only for individual animals; however, possible impacts on AMR in commensal organisms and target pathogens should be considered.

5.9. Treatment guidelines

There is an increasing trend in veterinary medicine for the publication of treatment guidelines by veterinary associations, or veterinary specialist societies. By their nature, these guidelines often include off-label recommendations (e.g. different indications, doses, routes of administration), which may be based on veterinary specialists' advice, peer-reviewed publications or knowledge of changes in bacterial susceptibility patterns since the original approval of older antimicrobial products. Well researched treatment guidelines have a role to assist veterinarians if they take into account modern research findings (e.g. systematic reviews) as well as results of national or regional surveillance of antimicrobial resistance.

A concern about accepting treatment guidelines as defining 'appropriate' off-label antimicrobial use is that the basis for the recommendations may not be clear. For example, the priorities could relate solely to animal species-considerations (e.g. conservative broad spectrum antimicrobial use for individual companion animal medicine) without considerations for the 'one-health' public health perspectives of AMR. Also, such recommendations are not always 'in-concert' with national or EU surveillance programs that may monitor trends in regards to public health aspects of AMR. For example, not all species (e.g. companion animals, horses, aquaculture) are part of such surveillance programmes. When preparing treatment guidelines, the authors should give consideration to the impact of recommendations on off-label use on the risk to public health from AMR.

6. Reflections and conclusions on off-label antimicrobial use

As there is no organized collection of data on the volume of off-label antimicrobial use in the EU, and a limited number of mainly descriptive published studies devoted to the topic, it is only possible to speculate about the risks to animal and public health and acceptability of these practices based on general principles. Potential risks related to off-label use that are especially important for antimicrobials include lack of effectiveness and increased AMR risk to animal and public health.

According to the current EU legislation, use in compliance with the cascade is expected to be 'by way of exception'. Where an antimicrobial product is used in the intended target species for an unauthorised indication at the dose regimen detailed in the SPC, and if this use is supported by bacterial culture and susceptibility testing with appropriate clinical monitoring, then there is unlikely to be any additional risk to animal or public health due to AMR compared to authorised use.

Where an antimicrobial product is used under the cascade in an unauthorised species, by a different route of administration and/or there is an adjustment to the dosing regimen, then consideration should be given to potential risks for lack of effectiveness and increased selection pressure for AMR due to (i) a change in bacterial exposure to the antimicrobial in the animal, and (ii) possible antimicrobial residues in food produce. Measures to mitigate the potential risks include limiting such use to the treatment of individual animals, use of culture and susceptibility testing, attention to differences in pharmacokinetics and application of statutory minimum withdrawal periods.

Cascade use for groups of animals as compared to individuals requires particularly careful consideration because of the higher antimicrobial exposure. However, the cascade use of human-only authorised antimicrobials in individual companion animals should be kept to an absolute minimum following a careful benefit-risk assessment as these are often last-resort antimicrobials and close contact between humans and pets is a prime opportunity for exchange of multidrug resistant organisms.

The use of proper diagnosis coupled with bacterial culture and susceptibility testing (where possible) are paramount when applying the cascade. Treatment guidelines, SPC information (sections 5.1, 5.2), availability of veterinary clinical breakpoints and access to local AMR surveillance data can all further assist the veterinarian. Given that peer-reviewed scientific literature or veterinary conferences can be quoted as evidence for some off-label practices, editors could be encouraged to carefully consider the concepts of appropriate and inappropriate off-label antimicrobial uses in their journal scientific policy for the acceptance of manuscripts.

Some types of off-label antimicrobial use cannot be considered as cascade use and the associated risks cannot be justified. These include use of antimicrobials for practical or economic reasons alone, systematic preventive use in groups of animals, intentional under-dosing and concomitant use of two or more antimicrobials without proper diagnosis. Such practices are of high concern when they also involve group treatments and/or use of CIAs.

Annex

1. Examples of off-label use in different species

The summary below provides an overview of off-label use practices in the EU. The overview does not imply that the CVMP endorses all of these practices.

1.1. Ruminants

According to the findings of a questionnaire survey carried out by the German Federal Office of Consumer Protection and Food Safety, a greater proportion of veterinarians applied off-label use of systemic antibiotics for cattle or calves (30%) than for minor species (Biedermann, 2014). Up to 20% of off-label uses of systemic antibiotics were reported for sheep and goats. The majority of veterinarians reported that the off-label use concerned antimicrobial veterinary medicines already approved for ruminants but used for another indication or dose. Cattle was the species most frequently linked to reports of adverse effects involving off-label use of systemic antibiotics (Biedermann, 2014). Particularly notable were anaphylactic shock reactions after off-label use of penicillins and tetracyclines – often with a fatal outcomes. The reasons for the classification as off-label ranged from excessively low or (more frequently) excessively high dose to unapproved species, unapproved indication or application route.

In a publication describing the use of antibiotics in ruminants in France (Gay et al., 2012) data were collected from questionnaires sent to veterinarians. All the antibiotics used in bovines had a marketing authorisation for bovine use. Off-label use represented 13% of the prescriptions. The analysis of the posologies (combinations of the dose, frequency and length of administration) prescribed by the veterinarians were according to the SPC indications in 53% of the prescriptions, but in 31% of the cases the antibiotics were overdosed and in 16% of the cases were underdosed. Gay et al. (2012) also investigated the use of VMPs for sheep and goats, in which off-label use was relatively frequent; 16% of the prescriptions for ovines were for VMPs without an indication for the species and 43% of the prescriptions for caprines were without an indication for the species.

In another questionnaire to practitioners in France on the use of antibiotics in bovines (Cazeau et al., 2009), of 3001 prescriptions 184 (6%) were for an alternative route of administration to that recommended in the SPC. For example, of the 184 prescriptions, 56 (30.4%) were administered intraperitoneally when the approved route was for intramuscular or subcutaneous injection. Forty prescriptions (21.7%) were administered intramuscularly with VMPs intended for intravenous and/or subcutaneous injection. Twenty-seven prescriptions were administered intravenously with VMPs for intramuscular administration, and sixteen prescriptions (8.7%) were administered subcutaneously with VMPs intended for intramuscular injection. Also, out of 2986 prescriptions, 396 (13.3%) were for off-label indications (Table 1).

Table 1. Distribution of the classes of antimicrobials used for indications not included on the label of the VMP

Classes of antimicrobials	Number prescriptions	Frequency (%)
Cephalosporins (+ others)	131	33.1
Penicillins (+ others)	100	25.3
Fluoroquinolones	76	19.2
Tetracyclines (+ others)	30	7.6
Non-classified	23	5.8
Aminoglycosides	12	3.0
Phenicols	8	2.0
Penicillins + aminoglycosides	7	1.8
Macrolides (+ others)	6	1.5
Sulfamides (+ others)	2	0.5
Other	1	0.3
TOTAL	396	

In this same study the compliance to the SPC dose was calculated by comparing to the dose prescribed. Of 3048 prescriptions in 2004, 404 prescriptions (15.9%) were overdosed and 122 prescriptions (4%) were underdosed. Of 3010 prescriptions, 256 (8.5%) were administered at a frequency lower than the recommended frequency and 85 (2.8%) at a frequency higher than that recommended.

Pardon et al. (2012), studied antimicrobial use in veal calves in intensive systems in Belgium in 2007-2009. They identified that under-dosing occurred in 43.7% of group treatments – this was often related to use of oxytetracycline and tylosin to treat dysbacteriosis. Amoxicillin as preventive treatment on arrival at farm was over-dosed. An explanation was possible over-estimation of body weight at arrival, and under-estimation later in the production cycle at time of treatment of dysbacteriosis, although lower doses were often prescribed for dysbacterosis.

1.2. Pigs

In the questionnaire survey carried out by the German Federal Office of Consumer Protection and Food Safety, 15% of the off-label uses of systemic antibiotics reported by veterinarians treating food-producing animals were recorded in pigs (Biedermann, 2014). This is consistent with anecdoctal information that off-label use of antimicrobials is uncommon in pigs due to the larger range of VMP antimicrobials approved for this species. The majority of veterinarians reported that the off-label use concerned antimicrobial VMPs already approved for swine but used for another indication or dose. For example, some macrolides, pleuromutilins and florfenicol products are approved for respiratory diseases but used for sepsis indications. During the preparation of this paper short term high dose use as a disease elimination strategy was reported as one of the major off-label uses of antimicrobials in pigs (personal communication, Pig Veterinary Society, UK). Another example from a Danish survey involved the off-label use of ceftiofur. Despite the fact that ceftiofur is indicated for treatment of respiratory disease, this small survey found that it was used for other indications (e.g. systematic preventive treatment in one-day-old piglets, treatment of diarrhoea or arthritis) (Jørgensen et al., 2007). At the time of this survey, the data from the Danish programme for surveillance of antimicrobial resistance in bacteria from livestock, foods and humans (DANMAP) showed that consumption of ceftiofur in pig production had increased markedly over the previous five years and

that approximately 80% of the total amount prescribed for pigs in 2005 was used in sows/piglets. This strongly indicated that off-label use was common since bacterial respiratory diseases are relatively uncommon in sows and piglets compared with slaughter pigs. It should be noted that the Danish pig industry introduced a voluntary ban on the use of cephalosporins in 2010 and use reported to DANMAP in 2015 was extremely low at 1 kg (DANMAP, 2016). Callens et al. (2012) commented that the introduction of ceftiofur in a long-acting formulation in 2003 may have explained a shift towards its use on Belgian pig farms as it offered farmers a practical advantage over repeated administration of shorter acting formulations.

A Belgian survey which quantified antimicrobial drug consumption in pigs (Timmerman et al., 2006) found that off-label group treatments with injectable antimicrobial drugs were mostly administered immediately after birth and at the time of castration, mainly for prophylaxis, and included broad spectrum penicillins and cephalosporins. Group treatments for diarrhoea were mainly metaphylactic, using fluoroquinolones and aminoglycosides. Colistin was administered mainly to prevent postweaning diarrhoea. Dosing information was also calculated, revealing interesting differences between oral and injectable antimicrobials. For example, overall 50–75% of the oral formulations were underdosed. Of the four most frequently used antimicrobials, doxycycline was overdosed in 50–75% of the cases. On the other hand, trimethoprim-sulphonamides were underdosed in 50–75% of the cases. Amoxicillin and colistin were underdosed in 50 and 90% of the cases, respectively. It was proposed that underdosing of oral antimicrobials was probably caused by administering antimicrobials per 1000 kg feed or per 1000 L water, instead of per kilogram body weight, suggesting an unintentional off-label administration. Injectable formulations were almost always overdosed (>90%). This is probably due to the use of a standard therapy for young piglets, which is not based on a correct estimation of the body weight. Another possible reason might be the difficulty of administering small amounts (<0.5 ml) to piglets. Only the narrow spectrum injectable penicillins were underdosed. The same observations of under and overdosing were confirmed later in another Belgian study of fattening pigs (Callens et al., 2012). In that study 93% of the group treatments were for preventative reasons and often lacked a precise diagnosis. Although there was not a well-founded justification for the repeated use of preventive group treatments, farmers at large production facilities often considered the preventive use of antimicrobials, despite the associated cost, as a necessity to achieve less disease, lower mortality and better production results, as well as easier and less labour intensive to implement than treatment of clinically diseased animals after losses have occurred (Callens et al., 2012).

A significant number of swine farms are set up to deliver feed to pigs as liquid feed. Due to the design of such farms, it is not usually practical to medicate the pigs using dry medicated meal or pellets, or via the drinking water as intake may be reduced. Consequently, there are anecdotal reports of liquid fed pigs being medicated via the liquid feed, using products designed for medication via drinking water. Liquid feeding systems are coated with a biofilm. Heller et al. (2016) found that administration of antimicrobial premixes in liquid feed increased the number of feed samples containing tetracycline-resistant Enterobacteriaceae and the number of tetracycline-resistant Enterobacteriaceae per sample. It was suggested that liquid feed containing antimicrobials is a reservoir of antimicrobial resistant bacteria in swine production.

In the German questionnaire survey (Biedermann, 2014) the majority of the adverse event reports for pigs concerned macrolides, particularly products containing tildipirosin. The reasons for the off-label administration varied (e.g. indication not approved, use of a mixing syringe, overdosing, animal too young, etc.), but the reactions described were very similar. In most cases there were general allergic reactions, often resulting in death. The reporting of these reactions has led to the product literature being amended and appropriate warnings being included. Another focus of the reports was penicillins,

particularly benzylpenicillin in combination with the aminoglycoside dihydrostreptomycin. In most cases there was overdosing. The adverse signs described ranged from apathy, vomiting and diarrhoea to neurological signs and death.

1.3. Horses

A large postal questionnaire was conducted including 740 veterinarians that treat horses in the UK (Hughes et al., 2013), with a return rate of 38%. Less than 1% of practices had antimicrobial use guidelines. Trimethoprim-sulfonamides were most commonly prescribed in each clinical scenario. Eleven percent of prescriptions were for antimicrobial drugs not licensed for use in horses in the UK. Five percent of prescriptions for licensed antimicrobials were used at doses under the recommended dose rate and 56% over the recommended dose rate. Fluoroquinolones and 3rd- and 4th-generation cephalosporins accounted for 1 and 3% of prescriptions, respectively. Veterinary surgeons working at referral practices were more likely to prescribe 3rd- and 4th-generation cephalosporins and fluoroquinolones and antimicrobials off-label, whereas those working in first-opinion practices were more likely to prescribe potentiated sulfonamides.

Unmet medical need

Surveys have shown that up to 39-98% of equine surgeries, including elective procedures, are given perioperative prophylactic antimicrobials (Olds et al., 2006; Weese and Cruz, 2009). However, this heavy use of perioperative prophylactic antimicrobials is despite the fact that the incidence of post-operative infections is very low (0-0.9%) for common elective surgeries (e.g. carpal arthroscopy) (McIlwraith et al., 1987; Olds et al., 2006; Ridge, 2011; Weese and Cruz, 2009). Another study reported no association between antimicrobial use and infections associated with elective arthroscopic surgery in horses (Olds et al., 2006). In an American survey of 761 hospitalised horses, at total of 511 (67.2%) received an inappropriate amount of antimicrobial preoperatively (Dallap Schaer et al., 2012). The majority of these horses underwent colic surgery. Under-dosing was the most common inaccuracy observed. In addition to this, timing of antimicrobial administration was considered inadequate (e.g. more than one hour before surgery), with 88 (11.6%) of horses receiving the antimicrobial at the appropriate time (Dallap Schaer et al., 2012). In the majority of cases, antimicrobial therapy was continued for an average of 3.8 days. Out of the 761 horses followed, 680 received the combination of penicillin and gentamicin, 16 received ceftiofur and gentamicin and only 22 horses received a single antimicrobial.

Broad spectrum perioperative antimicrobial prophylaxis (e.g. combinations of penicillin and gentamicin) are also used commonly for equine colic surgeries (Traub-Dargatz et al., 2002), as well as cefquinome (Widmer et al., 2009). This practice of broad spectrum antimicrobial prophylaxis has been linked to high rates of faecal shedding of CTX-M producing *E. coli* in horses as well as nosocomial post-operative infections (Damborg et al., 2012).

Alternative routes of administration

Alternative routes of administration are common in equine medicine, including intra-synovial, regional limb perfusion, inhalation and intrauterine administration. Recommendations are available for antimicrobial impregnated beads for local administration into surgical sites, especially bone (Cruz et al., 2006). Additional antimicrobials are sometimes given during colic surgery, including by intra-operative abdominal lavage antimicrobials and/or placement along the incision during closure (Dallap Schaer et al., 2012).

Instillation of penicillin into the equine guttural pouches, following infections or carrier status with *Streptococcus equi*, has become common practice. This is believed to help eliminate the bacteria, as well as preventing horses from subsequently becoming carriers of strangles (Verheyen et al., 2000). However, the true efficacy of this practice has not been critically evaluated.

Individual patient characteristics

Due to the practicalities of handling horses, there is a bias towards use of oral antimicrobials (e.g. trimethoprim-sulfonamide) for ease-of-administrations. As horses are hindgut fermenters, there are very few safe options for oral antimicrobial medication. Doxycycline is regularly used off-label in equine practice because it can be given orally, in spite of poor oral bioavailability, to adult horses (Winther et al., 2011).

Neonates and foals are often treated with antimicrobials off-label. Some reasons for this include the fact that foals are not (yet) hindgut fermenters, and so antimicrobials that can cause severe colitis in mature horses do not carry the same risk in foals. In addition, antimicrobials that are cost prohibitive in mature horses can be chosen for foals. In neonatal foals the dosage given tends to be higher than that for adult horses. The higher incidence of bacterial infections in neonates has led to preventive administration of antimicrobials in the first days of life. A recent study found no difference in the incidence of infectious disease between neonatal foals treated with preventive antimicrobials and those that were not treated (Wohlfender et al., 2009). Further examples of off-label recommendations for foals and adults in the scientific literature are listed in Table 2.

Table 2. Examples of off-label antimicrobial use recommendations for foals

Antimicrobial	Reason for use	Examples
Ceftiofur	Higher doses:	4.4 mg/kg IM q12hrs, (Kol et al., 2005) 4.4 to 6 mg/kg IV q6-12 hrs, (Benedice, 2008) 5 mg/kg IV q6h, decreasing to q24hrs, (Butters, 2008) 10 mg/kg IV q6hrs (Wong et al., 2008) constant rate infusion at 1.5 mg/kg/hr - neonates (Corley and Hollis, 2009)
Ceftriaxone	Meningitis/septicemia	25 mg/kg IV every 12 hrs in foals, (Ringger et al., 1998)
Cefpodoxime protexil	Septicemia/diarrhea	10 mg/kg q6-12hrs *per os*, (Carrillo et al., 2005)
Penicillin (potassium or sodium)	Septicemia – human preparations for intravenous use	constant rate infusion: 22,000-44,000 IU/kg, q24 hrs, at a rate of 2,750-7,333 IU/kg/hr. (Corley and Hollis, 2009)
Amikacin	Septicemia/septic arthritis	20-25 mg/kg IV/intra-articular q24hrs. (Bucki et al., 2004; McKenzie and Furr, 2003)
Amoxycillin/clavulanic acid	Pneumonia/septicemia	30 mg/kg, q6-8hrs *per os* (Love et al., 1981)
Doxycycline hyclate	Omphalophlebitis *Lawsonia intracellularis* *Rhodococcus equi*	10 mg/kg *per os* BID twice daily, (Sampieri et al., 2006; Womble et al., 2007)

Antimicrobial	Reason for use	Examples
Ticarcillin-clavulate	Septicaemia by Gram negative bacteria resistant to aminoglycosides, or compromised renal function	50-100 mg/kg IV QID, (Wilson et al., 1991); (Sweeney et al., 1988) Constant rate infusion, at 8-16 mg/kg/h (Corley and Hollis, 2009).
Marbofloxacin	Septicemia	(Corley and Hollis, 2009)
Chloramphenicol / Florfenicol	Foals < 4months Septicemia, meningitis, osteomyelitis	20mg/kg IM q24-48hrs (Corley and Hollis, 2009)
Metronidazole	*Clostridium difficile* Diarrhea	15-25 mg/kg q8hrs PO 46, or 25 mg/kg q12hrs, (Giguère, 2009; Sweeney et al., 1986)
Clindamycin	Osteomyelitis caused by Gram positive bacteria and other sensitive organisms	(Corley and Hollis, 2009)
Imipenem	Septicemia	Adults: 10-20 mg/kg IV q6hrs, advocated as the dosing regimen of choice, (Orsini et al., 2005a) Foals: 10-15 mg/kg IV q6-12 hrs. Constant rate infusion at 0.4-0.8 mg/kg/hr, (Corley and Hollis, 2009)
Vancomycin	MRSA Septic arthritis/osteomyelitis *Clostridium difficile* macrolide-resistant *Rhodococcus equi* in foals	7.5 mg/kg IV q12h (Giguère et al., 2008; Orsini et al., 2005b), 300 mg in 60 ml of saline [0.9% NaCl] solution, (Rubio-Martinez et al., 2006)

Unavailability of medicines

There is a perceived lack of effective veterinary antimicrobials approved for *Rhodococcus equi* infection in young foals. Drugs of first-choice for the treatment of *Rhodococcus equi* infection are the combination of human medicinal product macrolides (e.g. erythromycin, azithromycin, clarithromycin) and rifampicin (Giguère, 2001; Giguère et al., 2004), for a minimum of four weeks. Azithromycin and rifampicin is endorsed currently for *Rhodococcus equi* infections by the CVMP in the 'Essential substances for Horses' updated list (Official Journal of the European Union, 2013). Other antimicrobials sometimes used include tulathromycin (Venner et al., 2013b) and doxycycline (Venner et al., 2013a). Preventive azithromycin for the first two weeks of life reduced the incidence of *Rhodococcus equi* from approximately 20% to 5% in one randomized study (Chaffin et al., 2008); however, the benefit/s of preventive antimicrobials are not supported by others (Venner et al., 2012). The cumulative incidence of macrolide and rifampin resistance in *Rhodococcus equi* has been increasing over the past 10 years and foals infected with resistant isolates are more likely to die than foals infected with susceptible isolates (Giguère et al., 2010).

Another example of an unmet need is clostridial diseases (e.g. *C. difficile*, *C. perfringens*) associated with colitis (e.g. colitis X, duodenitis-jejunitis syndrome, antimicrobial-associated diarrhoea) which is being increasingly recognised. As in human medicine, *Clostridium difficile* diarrhoea carries a grave

prognosis without treatment (Cohen and Woods, 1999; Magdesian et al., 2002). There are no approved medicines for this condition, and thus many horses are treated with metronidazole, as the drug-of-choice. However, up to 43% of metronidazole-resistant *C. difficile* isolates from horses have been reported in certain geographic locations (Jang et al., 1997; Magdesian et al., 2002).

Other examples where there is a lack of authorised antimicrobial treatments include the indications of anaplasmosis (*Anaplasma phagocytophila*), mycoplasma (*M. felis, M. equirhinis*), contagious equine metritis (*Taylorella equigenitalis*), Lyme's disease (*Borrelia burgdorferi*), proliferative enteropathy in foals (*Lawsonia intracellularis*), dermatophilosis (*Dermatophilus congolensis*), *Pneumocystis carinii* in foals and leptosporosis in horses (*L. hardjo*, *L. pomona*, *L. bratislava*, *L. ichterohaemorrhagicae*).

Other recommendations endorsed by the CVMP in the 'Essential substances for Horses' updated list (Official Journal of the European Union, 2013) include ticarcillin for *Klebsiella spp*., as well as amikacin for septic arthritis specifically for foals. When prescribing under the cascade, veterinarians should take into account the importance of the antimicrobial to human medicine and the risk for transmission of AMR from treated animals to humans.

Antimicrobial use for non-antimicrobial indications in horses

It is common practice to inject neonatal foals born with contracted tendons with one or two high doses of oxytetracycline (40–60 mg/kg) (Kasper et al., 1995). This disease is not related to any bacterial infection. The use of oxytetracycline for this purpose in foals is due to a unique side-effect that causes temporary tendon relaxation, possibly related to calcium chelation.

Polymyxin B is used for the treatment of endotoxemia in horses, due to its unique property of binding to non-specific endotoxins in the blood (Morresey and Mackay, 2006). Endotoxins (free-floating) are produced commonly in the equine gastrointestinal tract and can be absorbed systemically secondary to a gastrointestinal disease, or due to a bacterial infection. Recently, human medicine has a renewed interest in polymyxins (colistin) for the treatment of patients with multi-resistant bacterial infections, and it is now regarded as a CIA class. Recently, doxycycline has been promoted as a treatment for equine osteoarthritis (Maher et al., 2014). Low-dose, low-frequency off-label oral administration of doxycycline can attain *in vivo* synovial fluid concentrations and has chondroprotective effects through reduction of matrix metalloproteinase (MMP)-13 activity, while remaining below MIC_{90} of most equine pathogens.

1.4. Poultry

There have been anecdotal reports of the administration of antimicrobials in poultry by *in ovo* injection, in some cases combined with vaccination. In this case antimicrobials are used to control the early mortality rate associated with *E. coli*, and automatically administered *in ovo* to broilers or by subcutaneous injection to 1-day-old future layers. Use of aminoglycosides (e.g. gentamicin) has also been described in automated systems by *in ovo* administration or injection to 1-day-old chicks for the control of omphalitis and *Salmonella spp.* (Ashraf et al., 2002; Bailey and Line, 2001). Once antimicrobial resistant bacteria are selected and established within the hatchery environment, grandparent and/or parent flocks, then these resistance genes can persist throughout the poultry production pyramid, leading to the dissemination to a large number of birds including subsequent generations on numerous farms in different countries (Baron et al., 2014). In other words, this vertical or horizontal transmission of resistant bacteria or genes can persist in the absence of antimicrobial selection pressure during the whole lifecycle of the flock (Baron et al., 2014). In the case of cephalosporins, especially 3rd- and 4th-generation, this is especially relevant as such use implies a high

risk for spread of ESBLs to humans via food. There are no MRLs established for use of cephalosporins in poultry in the EU, however use both *in ovo* and in one day chickens has been strongly suspected. Outside the EU such practice is common and treatment of one day-old chickens with ceftiofur is authorised in the United States (FDA, last accessed: 2018). Furthermore a correlation was shown between the occurrence of ceftiofur resistant *S. Heidelberg* in retail chicken meat and human infections caused by bacteria of the same serovar, both of which showed a sharp reduction following the voluntary withdrawl of *in ovo* use of ceftiofur use in hatcheries (Dutil et al., 2010).

In the EU, following an Article 35 referral on veterinary medicinal products containing 3rd- and 4th-generation cephalosporins, a recommendation for a contraindication of use was made as follows: 'Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans' (EMA/CVMP, 2012).

Within the EU, off-label antimicrobial treatments are thought to be relatively uncommon in modern poultry production. In part, this is due to the wide range of antimicrobial VMPs approved for chickens. The exception is for minor poultry species (e.g. turkeys, ducks, etc.). The EU statutory withdrawal periods (7 days for eggs, 28 days for meat from poultry) following off-label antimicrobial use are a disincentive for such practices due to the short production cycle for poultry.

Avian intestinal spirochaetosis, due to *Brachyspira pilosicoli*, has been highlighted as an important production disease in layers, both caged and free-range (Burch et al., 2006). For this indication, tiamulin has been widely used off-label.

In a Belgian study, quantification of antimicrobial drug use was assessed based on the defined daily doses and used daily doses (Persoons et al., 2012). Tylosin was underdosed in most of the administrations whereas amoxicillin and trimethoprim-sulfonamide were slightly overdosed in the average flock. The main off-label indication for antimicrobials was dysbacteriosis (non-specific bacterial enteritis). It was not always clear as to the farmer's interpretation of dysbacteriosis. It was defined separately from necrotic enteritis, and usually quite indefinitely as 'watery excrements'. It can be questioned whether treatment was always necessary in these cases, as mild digestive disturbances following change of feed or after vaccination of the birds might resolve without therapy.

1.5. Aquaculture

In Europe, more than 35 different species of fish and shellfish are produced in a variety of intensive (tanks) or extensive (natural) systems, encompassing diverse environmental needs. Although there has been a marked reduction in the therapeutic use of antibiotics in aquaculture in the EU since the 1990s - following the development of effective vaccines and improvements to husbandry methods (ACMSF, 1999; EMA/EFSA, 2017) - beyond the major fish species (salmon and trout), there is a lack of authorised medicines for the variety of diseases seen in the minor and newer species to aquaculture (Alderman and Hastings, 1998; FVE, 2017b). Cited examples include bacterial infections e.g. with *Aeromonas* in all species, *Flavobacterium* in trout and carp, hatchery infections in seabass and streptococcal infections in sturgeon and tilapia (FVE, 2017a) . The low availability of fish medicines is compounded by challenges associated with their development (Storey, 2005).

The FVE (2014) reported that only a few antimicrobials are authorised in different EU member states, especially those with a small aquaculture industry, leading to the frequent need for veterinarians to prescribe under the cascade. In this case, the statutory 500 degree day withdrawal period can be very long in cold water conditions, further limiting the choice of treatments close to harvest.

Antimicrobials are most commonly administered to farmed fish in feed. In many EU countries there is limited access to feed mills prepared to produce medicated feed for fish, especially in relatively small quantities. As a result, antimicrobials are often prepared at farm level by coating or top-dressing already pelleted feed in dedicated mixers (FVE, 2014). These mixers often do not achieve the same level of homogeneity of mixing as regulated feed mills. In addition, appetite suppression in diseased fish and due to changes in environmental temperature can make it difficult to achieve the desired dose rate and may lead to unintentional under-dosing.

Although the direct risk of transfer of AMR from farmed fish to humans appears to be low in the EU (Alderman, 1998), aquatic systems are a significant reservoir for environmental release and spread of AMR bacteria and resistance genes (Taylor et al., 2011).

The lack of availability of authorised medicines for ornamental fish is a specific issue. Dobiasova et al. (2014) found that 19% of isolates of *Aeromonas* spp. from koi carp bred in the Czech Republic and 24% of isolates from imported ornamental fish were harbouring plasmid-mediated quinolone resistance genes. Ornamental fish producers often administer antimicrobials to increase the survival of fish during shipment, commonly using nitrofurans, quinolones and oxytetracycline. Imported ornamental fish may be diseased by *Aeromonas* spp., *Pseudomonas* spp*., Staphylococcus* spp*., Acinetobacter* spp*., Flexibacter* spp*., Mycobacteria* spp., which have zoonotic potential. Antimicrobial resistance in *Aeromonas* spp. from imported ornamental fish and their carriage water was highlighted as a concern for public health (Verner-Jeffreys et al., 2009).

1.6. Companion animals (dogs and cats, etc.)

The extent of off-label use of antimicrobials in dogs and cats, especially critically important antimicrobials for human medicine, is an under-investigated area. Examples are shown in Table 3. Although many of the examples listed reflect off-label use due to the unavailability of authorised veterinary medicines, there are also several examples in which antimicrobials are used to treat non-infectious conditions (Bernstein, 2009; Jauernig et al., 2001; Rosenkrantz, 2004; Rothstein et al., 1997; White et al., 1992). In some cases certain antimicrobials are used off-label in parasitic infections, such as leishmaniosis (Bianciardi et al., 2004; Pennisi et al., 2005) or giardiasis (Zygner et al., 2008), although there is little scientific evidence to support such use. The use of human authorised products in dogs and cats is not restricted by considerations of food residues as in food-producing animals. Thus, the use of human approved antimicrobials, which do not have veterinary authorisation, is more common practice in companion animals. Moreover, although in some instances the dosing must be extrapolated from experience in human medicine, often data on pharmacokinetics and pharmacodynamics in companion animal species are available.

The extent of use of human approved antimicrobials in dogs and cats varies depending on country, antimicrobial class and species (Grave et al., 1992; Holso et al., 2005; Odensvik et al., 2001). In aforementioned surveys the proportion of human approved drugs in canine and feline antimicrobial prescriptions ranged from 13-80% by animal species and by country, likely reflecting the availability of veterinary medicines. This was in contrast to a UK survey performed in 2012, where only 2% of canine and feline prescriptions contained a drug which was not licensed for these species (Knights et al., 2012).

As in horses, antimicrobials are commonly used prophylactically in surgical procedures in companion animals (Knights et al., 2012; Rantala et al., 2004) . Although there is evidence that preoperative and/or perioperative use of antimicrobials is useful in reducing the risk of postoperative infections in many cases, the benefit of such use can be diminished due to suboptimal or improper timing or dosing

of drugs (Knights et al., 2012). Another example of the off-label use of antimicrobials is the administration to an animal which does not have clinical signs of infections but is considered at-risk due to impaired immunity because of a disease or medication (Chretin et al., 2007; Kohn et al., 2006). The use of antimicrobials as a part of supportive treatment is often recommended by the relevant veterinary textbooks even though there is very little or no evidence on efficacy of antimicrobials in such circumstances.

Chronic pyoderma in dogs is an example of a disease where peers' (experts') guidelines advocate the use antimicrobials that for many substances is not compliant with SPC directions (Beco et al., 2013). Recommended effective dose rates (especially for fluoroquinolones) and durations significantly exceed those that are documented in SPCs, and 'third-line' antimicrobials include substances such as rifampicin and tobramycin that are not currently authorised for use in animals. Based on a small study of 23 dogs, cefalexin as long term 'weekend therapy' was suggested as potentially beneficial in dogs with idiopathic recurrent pyoderma, reducing relapses (Carlotti et al., 2004).

Off-label antimicrobial use – like any drug use – may lead to adverse effects. According to a recent report regarding adverse event surveillance of veterinary medicines in the UK, approximately 7% of reported events were associated with the use of authorised products contrary to the SPC instructions (Davis et al., 2015). Of more than 5300 adverse event reports, 75% concerned dogs and cats. Only 0.8% of all reports were associated with human drugs (Davis et al., 2015). The majority of adverse events related to human drugs were due to intra-venous use of amoxicillin-clavulanic acid compounds. Another study reported that approximately 7% of suspected adverse events were related to the off-label use of antimicrobials in a ten year follow-up period (Diesel, 2011). In a German study, veterinarians reported that 90% of the off-label drug use was for dogs and cats (Kirsch, 2004). As in the UK study, most of the reported adverse events were from dogs due to off-label use of systemic amoxicillin with or without clavulanic acid (Biedermann, 2014).

One important driving force toward off-label use of antimicrobials, especially CIAs for human use, is the emergence of multi-drug resistance among pathogens of companion animals. Examples are meticillin resistant *Staphylococcus aureus* (MRSA) (Catry et al., 2010), meticillin resistant *Staphylococcus pseudintermedius* (MRSP) (van Duijkeren et al., 2011), and extended spectrum beta-lactamase or carbapenemase producing Gram-negative rods (ESBLs) (Abraham et al., 2014; Guerra et al., 2014). This has resulted in a potential pressure for veterinarians to use CIAs authorised for human medicine (Papich, 2012; Papich, 2013). Such drugs could constitute last resort alternatives not only for animals, but also for humans.

Table 3. Examples of the off-label use of antimicrobials in dogs and cats

Antimicrobial and off-label use	References
The use of enrofloxacin in brucellosis	Ledbetter et al. (2009) Wanke et al. (2006)
Local application of injectable ticarcillin for the treatment of otitis externa caused by pseudomonas in dogs	Nuttall (1998)
The use of linezolide for the treatment of canine MRSP bacteremia and discospondylitis	Foster et al. (2014)
The use of metronidazole and spiramycin for treating leismaniosis in dogs	Pennisi et al. (2005)
The use of enrofloxacin and metronidazole in leishmaniosis	Bianciardi et al. (2004)
The use of cefotaxime for the treatment of septicaemia in dogs	Sumano et al. (2004)

Antimicrobial and off-label use	References
Intra-articular administration of amikacin for the treatment of septic arthritis	Hewes and Macintire (2011)
The use of enrofloxacin/ metronidazole /doxycycline in treating babesiosis in dogs	Lin and Huang (2010)
The local use of various injectable antimicrobials for the treatment of canine otitis externa	Morris (2004)
The use of prophylactic antimicrobials perioperatively	Knights et al. (2012)
The administration of gentamicin as aerosol in dogs	Riviere et al. (1981)
The use of doxycycline for treating canine osteoarthritis	Jauernig et al. (2001)
The use of azithromycin for papillomatosis in dogs	Bernstein (2009)
The use of azithromycin for giardiosis in dogs	Zygner et al. (2008)
The use of doxycycline and ivermectin combination for treatment of dirofilariosis due to bacterial endosymbiot *Wolbachia*	Bazzocchi et al. (2008)
The use of tetracyclines for treating immune mediated skin diseases in dogs	Rosenkrantz (2004) White et al. (1992)
The use of erythromycin for treating gastric motility disorders	Hall and Washabau (1999)
The use of tetracycline in combination with niacinamide for treatment of sterile pyogranuloma/granuloma syndrome	Rothstein et al. (1997)
The use of minocycline in the treatment of canine hemangiosarcoma	Clifford et al. (2000)
The use of tetracyclines for variety of ophthalmic conditions (adopted for veterinary use)	Federici (2011)
The use of metronidazole as a part of treatment regimen for canine inflammatory bowel disease	Jergens et al. (2010)

For other types of companion animals, in total 72% of veterinarians reported that they used off-label administration of medicines weekly or even daily in the case of rabbits, guinea pigs and birds, from a recent German survey. The most frequent off-label uses of medicines for rabbits and guinea pigs were for the gastrointestinal tract and systemic infections. Almost 50% related to drugs for functional gastrointestinal disorders. Where off-label administration was concerned, 98% of veterinarians participating reported using a medicine approved for another animal species (Biedermann, 2014). The survey also uncovered that serious side effects, often resulting in death, have also been reported for off-label use of cefovecin, which is contraindicated from use in small herbivores such as rabbits and guinea pigs (Kirsch, 2004). The other reports concerned enrofloxacin, amoxicillin, oxytetracycline and sulphadoxine/trimethoprim.

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