1.8. Concomitant use of biocides and medicated water

Recommendation

Potential interactions between commonly used biocides and veterinary medicinal products administered via drinking water should be assessed and appropriate guidance regarding interactions and incompatibilities should be provided in the product information.

Rationale:

At farm level, biocides may be used to reduce microbial contamination of drinking water. However, concomitant administration of biocides and veterinary medicinal products in drinking water may affect the veterinary medicinal product. Studies have demonstrated that biocides may decrease the stability of certain antibiotics administered via drinking water, which may result in treatment failures and/or increase the risk of development of resistance. Biocides may also adversely affect the viability of bacteria/viruses included in live vaccines leading to a reduced efficacy.

2. General considerations

Two regulations were published in 2019 related to medication of animals. These were Regulation (EU) 2019/6 on veterinary medicinal products and Regulation (EU) 2019/4 on medicated feed. Both regulations came into force in January 2019 and will apply as of 28 January 2022. Regulation (EU) 2019/4 introduced – among others - rules on the preparation and administration of medicated feed. Regulation (EU) 2019/6 regulates veterinary medicinal products and – among others - mandates the European Commission to adopt delegated acts in order to supplement Article 106, as necessary, to establish the rules on appropriate measures to ensure the effective and safe use of veterinary medicinal products authorised and prescribed for oral administration via routes other than medicated feed.

The scope of this advice is therefore to provide a scientific problem analysis and recommendations to the European Commission in the context of Article 106(6) of Regulation (EU) 2019/6 in order to ensure consistent requirements, as appropriate, between both Regulations.

The scientific problem analysis in this document mainly focuses on oral routes of administration of veterinary medicinal products to groups of food-producing animals via (mixing veterinary medicinal products with) feed, drinking water or milk, as these are the most commonly used oral routes of administration, and which are also considered the most likely alternatives to the use of medicated feed. In particular, instructions for mixing antimicrobial veterinary medicinal products into feed and/or drinking water and cleaning the equipment used for administration of those products have been reviewed so that cross-contamination, and in the case of antimicrobials the potential for antimicrobial resistance development, can be reduced and to ensure that the requirements do not deviate from Regulation (EU) 2019/4. As a result of the problem analysis, recommendations have been made to the European Commission.

A marketing authorisation dossier for a veterinary medicinal product must address the pharmaceutical quality, the safety and the efficacy of the product, and the particular benefits and risks of the veterinary medicinal product which will be evaluated during the regulatory assessment. Different types of veterinary medicinal products (e.g. antimicrobials, antiparasitics, vaccines etc) have different risks when used in the field (e.g. resistance development), which will form part of the veterinary medicinal product's assessment. This report will consider factors that have the potential to impact on the safety and efficacy of veterinary medicinal products administered by the oral route under field conditions and,

based on those considerations, propose recommendations for the appropriate use of such products with the specific purpose of reducing any potential risks associated with inappropriate use.

The decision by a veterinarian on whether to prescribe a veterinary medicinal product or medicated feed for the group treatment of food-producing animals will depend on several factors, some of which are outside the scope of this report, e.g. the distance to the nearest feed mill or economic considerations. Other aspects like rules relating to prescriptions as defined in national legislation might vary, which might result in differences between Member States regarding the choice of using medicated feed versus a veterinary medicinal product. However, it should be emphasised that the use of a veterinary medicinal product is considered essential for animal health and welfare, and that all the available pharmaceutical forms and routes of administration of a veterinary medicinal product are considered useful and should be taken into account within a certain production system. Thus, the choice of the most appropriate administration method to be used in any given situation should remain with the prescribing veterinarian, who has knowledge of the particular farm concerned, of its equipment and of the possible therapeutic alternatives.

2.1. Methodology

In this report, veterinary medicinal products were grouped into different categories by analysing all the currently available oral pharmaceutical forms and routes and methods of administration as defined by the European Directorate for the Quality of Medicines and healthcare (EDQM: https://www.edqm.eu/en). Veterinary medicinal products administered orally via routes other than medicated feed were then categorised based on their ability to be administered with a reasonable degree of precision at the recommended dosage.

Some methods and routes of administration, which may result in gastrointestinal absorption, but do not fall under the EDQM definition for oral use, have not been included in this report, as they were not covered by the request for advice from the European Commission. Such routes would include e.g. oculonasal administration, which is mainly used in poultry. Also, the (unintended) oral uptake by animals in contact with topically treated animals, e.g. by licking is also not addressed in this advice.

Veterinary medicinal products to be used in individual animals are generally considered suitable to be administered at the recommended dosage *(see section 5, oral formulation for individual use)*.

However, for group treatment, some pharmaceutical forms/routes of administration could not guarantee that all the animals would receive the recommended dosage. The main routes of oral administration of veterinary medicinal products containing antimicrobials for food-producing animals are "in-feed use" and "in-drinking water use" (see the reports by the European Surveillance of Veterinary Antimicrobial Consumption on the "sales of antimicrobial agents in 31 European countries 2010 – 2017", ESVAC reports: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/european-surveillance-veterinary-antimicrobial-consumption-esvac#). This also applies to other classes of veterinary medicinal products for oral group treatment, and the focus of this report is therefore mainly on two routes of administration for group treatment of food-producing animals: in-feed use (including liquid feed) and in-drinking water use *(see sections 3 and 4)*. The different pharmaceutical forms available for these routes of administration are defined by EDQM. In addition, some specific practices in target species or formulations are also addressed, as appropriate. (Note: In-drinking water use in the report would also include its use in milk or milk replacer. Also, the terms "oral powder" and "oral solution" in this report could also refer to granules, lyophilisates, powders, suspensions and similar pharmaceutical forms, unless specified).

2.2. Use of oral medication

Oral medication of animals is a commonly used, non-invasive and well-established way for professional and non-professional animal owners to medicate individual animals or groups of animals, and veterinary medicines for oral administration cover a wide range of product types (e.g. chemicals, immunologicals), active substances, indications, target species, pharmaceutical forms and routes of administration.

In general, medicines authorised for food-producing animals require a prescription. There are some differences in the requirements for veterinary prescriptions between Regulation (EU) 2019/4 and Regulation (EU) 2019/6 (e.g. need for diagnosis, number of treatments per prescription, full adherence to SPC recommendations), but these differences were considered appropriate taking into account the different purposes and target animal populations treated with medicated feed *versus* other routes of oral medication.

2.3. Commonly used classes of oral medication

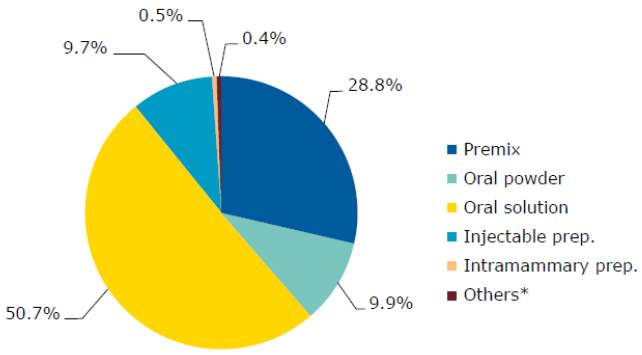
The most commonly used veterinary medicinal products administered orally for the group treatment of food-producing animals are antimicrobials, antiparasitics and immunologicals (vaccines).

2.3.1. Antimicrobials

According to the ESVAC Interactive Database (https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/european-surveillance-veterinary-antimicrobial-consumption-esvac), in 2017 the most commonly used antimicrobials in food-producing animals were tetracyclines and penicillins, which were mostly administered directly as veterinary medicinal products (approximately 56 and 61%, respectively) and to a lesser extent as veterinary medicinal products incorporated into medicated feed (approximately 39 and 23%, respectively).
For fluoroquinolones, approximately 76% were administered as an oral solution, and for polymyxins (colistin) 45% were administered as an oral solution, 38% as an oral powder and 16% as a premix for medicated feedingstuff. The high percentage of these veterinary medicinal products used for group treatment is notable, given that these classes of antimicrobials are categorised by the EMA under the category "Restrict" (EMA, 2019), and by the WHO as Highest Priority Critically Important Antimicrobials (WHO, 2019).

According to the ESVAC report (2017 data), the most commonly used classes of antimicrobials in food-producing animals were administered via the oral route (approximately 90%), either as medicated feed (listed in the ESVAC reports as "premix", approximately 29% of total use) or as veterinary medicinal products administered via feed or drinking water (listed in the ESVAC reports as "oral powder" and "oral solution", approximately 10% and 51% respectively of total use). These data show that about two thirds of the sales of antimicrobials for group treatment for food-producing animals are in the form of veterinary medicinal products (oral powders or solutions), see ESVAC figure 1 below.

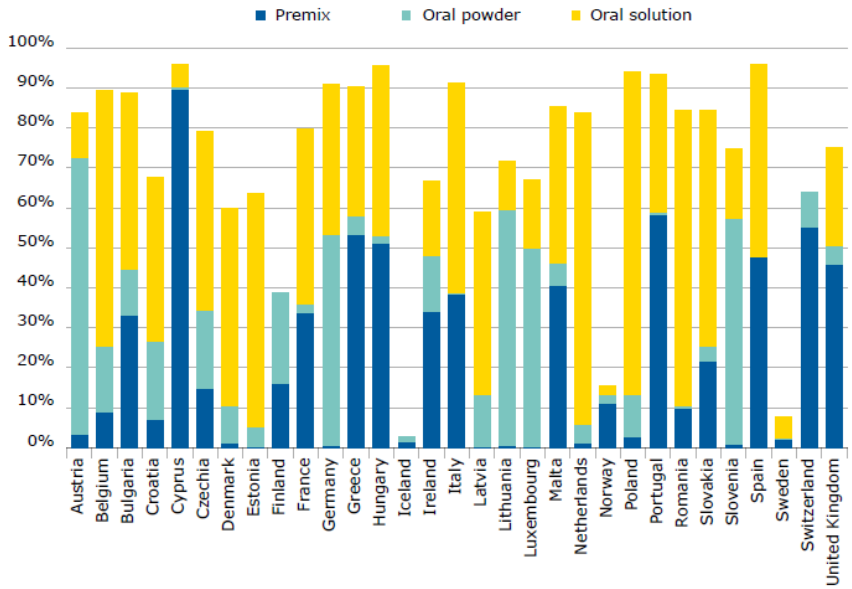
Figure 1: Distribution of sales, in mg/PCU, of the various pharmaceutical forms of veterinary antimicrobial agents for food-producing animals, aggregated by the 31 European countries, for 2017 (ESVAC, 2017)



* Oral pastes, boluses and intrauterine preparations.

The same ESVAC report also shows how the use of the different pharmaceutical forms can vary greatly between countries, with some countries having a small percentage of the sales of antimicrobials as premixes for medicated feed, oral powders or oral solutions, whilst others have most of their sales as one of the mentioned pharmaceutical forms. There is also an important variability in the percentage of the above-mentioned pharmaceutical forms for oral use between the countries (see ESVAC figure 2, below). Note: in the ESVAC reports the terms "oral powder" and "oral solution" are generally used to describe the routes of administration (in-feed or in-drinking water use), rather than strictly using the EDQM standard term of the pharmaceutical forms. The terms "oral powder" and "oral solution" in this report could therefore also include the use of granules, lyophilisates, powders, suspensions and similar pharmaceutical forms.

Figure 2: Oral solutions (includes powders for administration in-drinking water), oral powders and premixes as percentages of total sales, in mg per population correction unit (mg/PCU), of veterinary antimicrobial agents for food-producing animals, in 31 European countries, for 2017 (ESVAC, 2017)



Specific target animal species considerations

Poultry

Antimicrobials are mainly prescribed for group treatment of broilers and turkeys, and to a far lesser extent for the treatment of pullets, breeders and layers, or other poultry species (ducks, pheasants, etc.). In the vast majority, antimicrobials are to be administered via drinking water or medicated feed.

Ruminants

Due to their specific gastro-intestinal anatomy, oral antimicrobials are usually only used in young, i.e. pre-ruminant animals. For ruminants in conventional farming systems (adults, new-borns and replacement animals for dairy and suckler cattle, dairy and suckler sheep and goats), the oral administration of veterinary medicinal products is mainly used for the treatment of individual animals (e.g. with tablets or oral pastes), and principally for curative purposes.
Animals fattened in groups (veal calves, growing fattening cattle, growing fattening kids and lambs), in which digestive and respiratory infections remain highly prevalent, may receive collective metaphylactic treatments, orally via milk or milk replacer or in the form of medicated feed (Anses, 2014; Murphy et al., 2016). According to a longitudinal study conducted by Catry et al., 2016, it appears that an increased consumption of antibiotics, especially when administered orally, has an undeniable effect on the development of resistance to antimicrobials in digestive tract *E. coli* and respiratory tract *Pasteurellaceae* in cattle.

Antimicrobial group treatment is generally justified by the epidemiology of diseases, as animals are often gathered from diverse origins and have different age, health and immune statuses. They might have been transported for varying lengths of time and then grouped together under variable biosecurity, hygiene and stress conditions. Often, they are subject to repeat this cycle many times until slaughter with variations of diet, behaviour, environment and microbial pressure. These factors combined contribute to weakening of their immune status, and thus increasing infectious risk (Baptiste and Kyvsgaard, 2017; Ives and Richeson, 2015).

Pigs

In pigs, antimicrobials are usually administered orally to groups of animals. Based on the data collected from 180 farms from nine EU countries (Belgium, Bulgaria, Denmark, France, Germany, Italy, Poland, Spain and the Netherlands), although variations existed between the countries, the vast majority of antimicrobial treatments of pigs were administered via the oral route (Sarrazin et al., 2019). The results from a study by Callens et al. (2012) in Belgian pig farms, show that antimicrobial treatments administered to groups of pigs via the oral route represent the most common way of antimicrobial administration to these species in this country, in terms of treatment incidence. Also, Postma et al. (2015), having collected data from Belgium, France, Germany and Sweden, identified that licensed antimicrobial products for pigs are mostly administered orally, via the feed or water, compared to other routes of administration. In different studies (Callens et al., 2012; Sarrazin et al., 2019), it has been observed that the majority of antimicrobial group treatments are administered to weaners.

Fish

In fish, antimicrobials are only administered orally to groups, except for brood fish which may be treated individually by injection.

The most commonly used antimicrobials in fish are tetracyclines, enrofloxacin, florfenicol, flumequine, oxolinic acid, sulphonamide and trimethoprim, and amoxicillin.

The main target species of fish for which antimicrobial veterinary medicinal products have been authorised are Atlantic salmon, rainbow trout and carp, and to a lesser extent other fish species (such as sea bass, sea bream, other salmonids including Pacific salmon, turbot, eel, catfish, aquarium fish, etc.). However, since there are only a limited number of veterinary medicinal products authorised for each fish species and pathogen, the use of the so called 'cascade' in fish is fairly common.

Although outside the scope of this advice, a general issue in aquaculture is the potential for residues in the environment from administering antimicrobials orally. It is noted that fish farmers try to keep the environmental impact low by feeding treated fish smaller portions to ensure that as much food is taken up as possible. For treatment with antimicrobials, sub-therapeutic concentrations of antibiotics in the water, or accumulated in sediments in ponds or under net-pens, can result in an increase in the prevalence of bacterial strains housing antibacterial resistance genes in the environment (Buschmann et al. 2012; Di Cesare et al. 2013; Piotrowska et al. 2017). In addition, antimicrobials might have an impact on cyanobacteria, and also a risk for *algae* cannot be ruled out (as some antimicrobials have shown a high toxicity for terrestrial plants).

The CVMP is currently reflecting on the possible effects of antimicrobial resistance in the environment (CVMP draft reflection paper on antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products, EMA/CVMP/ERA/632109/2014). The draft conclusions of this document acknowledge that the emission of antimicrobials to the environment contribute to environmental reservoirs of resistance. Nevertheless, at the current time, it is not possible to disentangle the contribution of human and veterinary inputs. Additionally, it is recognized that there are currently no methodologies available to make an environmental risk assessment in relation to the resistance in the environment.

Considerations for the safe and efficacious use of oral antimicrobials

In order to ensure the effective and safe use of antimicrobials, the assessment of the veterinary medicinal product takes into consideration the specific risks that antimicrobials might cause to human and animal health and the environment. For food-producing animals, this includes an assessment of the impact of residues of the antimicrobials in food produce on the development of resistance in the gut flora of human consumers. In addition, consideration is given to the potential for the emergence of resistance in target pathogens in the animal and in zoonotic and commensal organisms that could be a risk to public health. The product information carries detailed warnings in regard to the veterinary medicinal product, as necessary.

Oral administration is of particular concern in terms of potential to promote the development of antimicrobial resistance due to the high exposure of gastrointestinal commensal bacteria, although parenterally administered antimicrobials that undergo biliary excretion may have a similar effect. For practical reasons, premix formulations have historically been used more often for the prevention or metaphylaxis of diseases, as they are easy to administer over longer periods of time, while formulations for administration via drinking water tend to be administered for more acute stages of clinical diseases, and also for shorter durations.

For most indications, the veterinarian will make a presumptive diagnosis of the infectious disease and use methodology available to confirm the diagnosis and test the susceptibility of target bacteria. Guidance from the CVMP is available on the specific dossier requirements and also on relevant prudent use warnings that should be included on the labelling for antimicrobials (CVMP guideline on the SPC for antimicrobials, EMEA/CVMP/SAGAM/383441/2005; CVMP guideline on the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances, EMA/CVMP/627/2001 Rev. 1). Both the revised medicated feed (i.e. Regulation (EU) 2019/4) and the veterinary medicinal product (i.e. Regulation (EU) 2019/6) regulations have introduced stricter requirements for the use of antimicrobials, in particular for metaphylactic and prophylactic use. With Regulation (EU) 2019/6, the preventive use of antibiotics is restricted to single, individual animals only, and will be allowed only when justified by a veterinarian and where there is a high infection risk. 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 (Article 107(4) Regulation (EU) 2019/6), following the diagnosis of the infectious disease by a veterinarian, and after appropriate justification from a veterinarian. As a consequence of the new veterinary medicinal product legislation, indications for the preventive and/or metaphylactic use of authorised antimicrobials may need to be reviewed, and existing marketing authorisations may need to be amended accordingly. In line with Article 152 (2) of Regulation (EU) 2019/6, veterinary medicinal products placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004 may still continue to be made available until 29 January 2027, even if they are not in compliance with Regulation (EU) 2019/6 (this does not apply to marketing authorisations for antimicrobial veterinary medicinal products containing antimicrobials, which have been reserved for treatment in humans; see separate implementing act referred to in Article 37(5) Regulation (EU) 2019/6).

It is noted that the definitions for "metaphylaxis"[1] and "prevention/prophylaxis""[2] differ between Regulation (EU) 2019/6 and the current definition used by veterinary medicinal product regulatory authorities in the CVMP guideline on the Demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001 Rev. 1), which came into effect in August 2016. Prior to this, there was no harmonised definition established EU-wide for indications in marketing authorisation for the terms "prevention/prophylaxis" and "treatment", and the term "metaphylaxis" was not used in all Member States.

Appropriate pack sizes should be made available, especially for oral products containing antimicrobials, in line with the requirements outlined in the "Question and Answer document on the CVMP Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/414812/2011-Rev.2)". Pack sizes should reflect the intended use.

Antimicrobials can only be used following a veterinary prescription, and the prescription of antimicrobials should follow the SPC and product literature, as well as other treatment guidelines, where available, establishing e.g. 1st, 2nd and 3rd line treatment, taking into account amongst other factors the risk categorisation of the class of antimicrobials in line with AMEG scientific advice (EMA, 2019; AMEG categorisation, see EMA/CVMP/CHMP/682198/2017). It is noted that the AMEG advice also includes a list of preferred routes of administration with respect to selection of antimicrobial resistance. Article 105(1) of Regulation (EU) 2019/6 requires a veterinary diagnosis prior to the prescription of antimicrobials for metaphylaxis, which ideally should follow a farm visit by a veterinarian who will assess which treatment will be the most suitable. Article 16(9) of Regulation (EU) 2019/4 states that the veterinarian shall not prescribe medicated feed with more than one veterinary medicinal product containing antimicrobial. A specific requirement that only a single antimicrobial veterinary medicinal product should be prescribed at a given time is not included in Regulation (EU) 2019/6.
Occasionally, an animal suffers from more than one infection at the same time, in some cases, therefore, it may exceptionally be necessary to treat an animal with more than one antimicrobial

[1] Definition **Metaphylaxis:**
Article 4(15) Regulation (EU) 2019/6 (metaphylaxis): "*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"*.
CVMP guideline: "*Group treatment of all clinically healthy (but presumably infected) animals kept in close contact with animals showing clinical signs of a contagious disease. Metaphylaxis is always combined with the treatment of the diseased individuals and consequently a metaphylaxis claim will only be accepted in conjunction with a treatment claim"*
[2] Definition **Prophylaxis/prevention:**
Article 4(16) Regulation (EU) 2019/6 (prophylaxis): "*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*".
CVMP guideline (prevention): "*Administration of a VMP to healthy animals to prevent infection if the risk for infection is very high and the consequences severe*. "

veterinary medicinal product at the same time. It is acknowledged that treatment with more than one antimicrobial veterinary medicinal product might increase the risk of developing antimicrobial resistance. Additionally, the possibility of prescribing more than one antimicrobial veterinary medicinal product might potentially be an incentive for veterinarians to favour prescribing veterinary medicinal products rather than medicated feed (which, in accordance with Regulation 2019/4, can include only one antimicrobial veterinary medicinal product). For products administered orally, the veterinarian should therefore only prescribe more than one veterinary medicinal product containing an antibiotic agent when the treatments are duly justified on the basis of a full diagnostic investigation, including bacterial culture and antimicrobial susceptibility testing**.**

2.3.2. Antiparasitics

Regulation (EU) 2019/6 (Article 4(13) defines antiparasitic as a "*substance that kills or interrupts the development of parasites, used for the purpose of treating or preventing an infection, infestation or disease caused or transmitted by parasites, including substances with a repelling activity*".

In general, antiparasitics used in food-producing animals are prescription only medicines. For companion animals, some antiparasitic veterinary medicinal products may be supplied without the need for a prescription.

Usually, a prescription requires a veterinary diagnosis; however, for antiparasitics used in medicated feed, Regulation (EU) 2019/4, Article 16 (4), allows that "if it is not possible to confirm the presence of a diagnosed disease, a veterinary prescription for medicated feed containing antiparasitics without antimicrobial effects may be issued based on the knowledge of the parasite infestation status in the animal or group of animals". In the recitals of the medicated feed legislation (Regulation (EU) 2019/4), it is also considered that, in certain cases for the management of parasite infections using medicated feed, prophylaxis should be allowed, as regards medicated feed containing antiparasitics (recital 27) and that a diagnosis prior to prescription is not necessary when diseases, which can be transmitted to humans, should be prevented (recital 28). Likewise, for veterinary medicinal products, Regulation (EU) 2019/6 does not specifically mention the need for a veterinary diagnosis prior to prescription or prophylactic indications for antiparasitics. On this point, it is noted that a diagnosis in advance of treatment may not be feasible for all claimed indications for certain antiparasitic products.

Specific target animal species considerations

Pigs, poultry

Antiparasitics for pigs and poultry, such as flubendazole, fenbendazole or fluralaner, are usually administered as a group treatment, either via medicated feed or using a veterinary medicinal product via their drinking water. However, there are also some antiparasitic veterinary medicinal products authorised as oral powders or granules for in-feed medication, which are mixed into the feed by the farmer or administered as top-dressing use.

Ruminants

In ruminants, antiparasitic veterinary medicinal products are mainly administered individually to the animals (e.g. by drench or bolus), although this is often done for each animal in the whole group, and often not based on individual diagnosis. Oral powders containing antiparasitic substances administered in feed might be used to treat "indoor parasitism" in calves/lambs (e.g. *Strongyloides papillosus*) or "outdoor parasitism" in grazing cattle/sheep (young or adult).

Fish

An issue of concern in aquaculture are potential residues in the environment. Antiparasitic veterinary medicinal products administered to fish may be emitted into the surrounding water, which can have detrimental effects on non-target aquatic organisms. For instance, amongst the veterinary medicinal product used against salmon louse are benzoylureas (e.g. teflubenzuron). Their mechanism of action is to impair chitin synthesis in the crustacean salmon louse; however, toxic effects have been reported in non-target crustaceans with a chitin cuticula, like shrimps and lobsters. It is also noted that these substances are usually persistent, and can build up in sediment, where detritivorous crustaceans feed.

Considerations for the safe and efficacious use of oral antiparasitics

In order to ensure the effective and safe use of antiparasitic veterinary medicinal products, a large number of guidance documents are available (VICH and CVMP guidelines), which detail the dossier requirements for certain antiparasitic classes and/or target species.

The assessment of the veterinary medicinal product takes into consideration the risks of these products, in particular in regard to the impact of these substances on the environment, and in regard to resistance development.

By their very nature, antiparasitics will not only affect those parasites for which they are indicated, but might also impact on insects, worms and other species in the environment. The environmental risk is considered during the initial evaluation, and the product information will carry appropriate warnings, as needed.

Antiparasitic resistance is a growing concern, in particular in regard to helminths in small ruminants, but also in worms of horses and cattle. In addition, resistance of red mites to several ectoparasitics has been observed in poultry houses. There is less information available in regard to antiparasitic resistance compared to antimicrobial resistance, but potential risk factors associated with antiparasitics are underdosing, e.g. due to errors in the administration (*see section 6.1 - dose*) and/or inappropriate/non-homogeneous administration (*e.g. section 3.3.1-top-dressing, section 3.2-oral powders*).

The CVMP has published guidance on the prudent use for anthelmintics (see CVMP guidance on the Summary of product characteristics for anthelmintics, EMEA/CVMP/EWP/170208/2005) and the SPCs and product literature of antiparasitic veterinary medicinal products should include such warnings, as appropriate. Regulation (EU) 2019/6 has also taken the importance of antiparasitic resistance into consideration by:

- Requiring that the product information include relevant warnings on appropriate use in *order to limit the risk of development of resistance"* (Article 35 (1) c Xii);
- Permitting a decision for refusal of a marketing authorisation where the risk to *public health in case of development of antiparasitic resistance outweighs the benefits of the veterinary medicinal product to animal health* (Article 37 (2)f), and
- Incentivising the submission of variations to a marketing authorisation that will result in *a reduction in antiparasitic resistance*" (Article 40 (5) a).

2.3.3. Immunologicals

The use of medicated feed containing immunological veterinary medicinal products is foreseen in Regulation (EU) 2019/4. However, so far, it seems that no immunological veterinary medicinal products (including vaccines and other immunological products) have yet been authorised in the EU as a premix for medicated feeding stuff.

In contrast, the administration of vaccines via the oral route is common in veterinary medicine. The oral vaccination route is most widely used in poultry; it is less common in pigs and fish, and very limited in other species, e.g. cattle, companion animals.

Most of the vaccines currently authorised for use via the oral route are live attenuated vaccines presented as lyophilisates for suspension. The methods of administration used to deliver oral vaccines vary in the different target species and include in-drinking water use, spray (nebulisation), and in-feed use.

Special considerations for target species

Poultry

Oral vaccination is used very widely in poultry (chickens). Most of the currently authorised vaccines for oral use in poultry are live attenuated vaccines against viral (e.g. infectious bursal disease, Newcastle disease, infectious bronchitis, infectious laryngotracheitis), bacterial (e.g. *Salmonella*) or protozoal (e.g. coccidia) pathogens. The most common methods of oral administration in poultry are via their drinking water and spray (nebulisation) on the birds.

Administration in-drinking water:
Live attenuated vaccines are presented most frequently as lyophilisates for suspension (some as effervescent tablets) that are reconstituted with cool, clean water free from traces of chlorine, or other disinfectants. Instructions for the calculation of the necessary doses, reconstitution, dilution of the vaccine and administration to birds are given in the SPC and product literature, which usually also includes directions to ensure appropriate intake of the vaccine (e.g. withdrawal of drinking water prior to vaccination, provision of food during vaccination, temperature, light).

To ensure successful vaccination, many parameters must be considered *(see also section 4 - in-drinking water use)*:

- Viability of live vaccines: in-use shelf life
- Water quality (cool, fresh, distilled water free from minerals or chlorine, use of stabilisers)
- Equipment (drinkers, pumps)
- Vaccinator experience (adequate training)
- Environmental conditions (light, temperature).

Administration via spray (on birds)
Spray administration is very commonly used for birds at an early age. Usually, one-day-old birds are vaccinated at the hatchery, or at the receiving farm, in vaccination chambers (manually operated), or using automatic sprayers which spray the vaccine evenly onto the birds (typically groups of 80-150 birds) placed in crates on a moving conveyor belt. The vaccine is delivered in vaccine droplets typically 100-300 µm in diameter, i.e. a coarse spray. Some vaccine droplets will reach the birds through their ocular mucosa, but most will be taken in orally as the vaccine droplets on the surface of the birds are ingested by pecking or preening. Administration by coarse spray is also used in older birds.

Instructions to ensure the appropriate delivery of such vaccines are given in their SPC and product literature (e.g. reconstitution in distilled water or clean chlorine-free water, volume of water necessary that will vary according to the spray equipment, distance of sprayers to birds, droplet size, cleanliness of equipment, light). Factors affecting successful vaccination via spray:

- Droplet size (spray pressure, nozzle size, volume applied, compressed air quality)
- Water quality (cool, fresh, distilled water free of minerals and chlorine, use of stabilisers)
- Equipment (calibration of automatic sprayers, cleanliness, etc.)
- Vaccinator experience (adequate training)
- Environmental conditions (light, temperature, ventilation, etc.).

Administration via spray (on feed)
Some vaccines against coccidia are authorised for administration via spray on feed, where the vaccine suspension is diluted in water and then sprayed evenly onto the surface of feed using a coarse spray. This method of administration is not much used anymore due to practical limitations and the potential risk of desiccation of coccidia oocysts and the consequential detrimental effect on their viability, and thus the efficacy of the vaccine.

Pigs

There is a limited number of vaccines currently authorised for oral administration to pigs. All of them are live attenuated vaccines against bacterial pathogens (e.g. *Escherichia coli, Salmonella spp., Lawsonia intracellularis)* which are generally administered by either drench application (to individual animals) or in-drinking water (group treatment). The most common pharmaceutical form is a lyophilisate for oral suspension. Similar to other live attenuated vaccines, the lyophilisate is to be reconstituted in clean water, free from residues of antimicrobials, detergents or disinfectants. The amount of vaccine is calculated based on the expected water intake of the pigs, which will vary according to their weight, the temperature, etc. For some of these vaccines, the use of stabilisers (e.g. skimmed milk) at a defined concentration is recommended in the SPC and product literature. The water containing the vaccine should be consumed within the specified time (i.e. in-use shelf life), typically 4 hours.

One EU authorised vaccine can also be administered mixed into liquid feed. The preparation of the vaccine in this case is as described above, except that the reconstituted vaccine is then mixed homogenously with the liquid feed. During the assessment of the marketing authorisation application, the stability of the vaccine in different types of liquid feed is evaluated. For this route of administration, warnings may be added to restrict the use with certain types of liquid feed, or to specify types of feed that were not tested (e.g. feed with controlled fermentation or feed containing formaldehyde).

Fish

There is a limited number of vaccines currently authorised in the EU for oral use for fish due to the challenges that this route of administration poses for vaccine development (e.g. relatively poor efficacy, degradation of vaccine antigens in the intestinal tract, limited duration of immune response).

In contrast to other species, all the authorised oral fish vaccines are inactivated vaccines against bacterial pathogens (e.g. *Yersinia ruckeri, Vibrio anguillarum, Vibrio ordalii, Photobacterium damselae subsp. piscicida*). The most common pharmaceutical form of these vaccines is "oral emulsion" and these vaccines are intended to be administered by adding them to the feed (e.g. the vaccine emulsion is slowly sprayed by the farmer directly onto the feed pellets, which are then mixed using different types of devices and left for soaking prior to feeding).

Considerations for the safe and efficacious use of oral vaccines

In order to ensure the effective and safe use of vaccines administered via the oral route, some general considerations should be made regarding:

- the nature of the active substance of the vaccine: vaccines are classically divided into two types, inactivated vaccines and live attenuated vaccines,
- the target species,
- the method of administration: vaccine preparation (e.g. calculation of doses, water/feed consumption, mixing of the vaccine and delivery),
- the husbandry practices on the farm (e.g. biosecurity, hygiene, cleaning of equipment, devices).

The potential risks in each case will therefore be influenced not only by the characteristics of the vaccine itself, but also by how the vaccine is administered to the target species and the husbandry practices in place.

Inactivated vaccines do not raise particular concerns when administered by the oral route. Live attenuated vaccines have, however, by their nature, additional risks associated with them, which are mainly related to their level of attenuation (e.g. a virus can be sufficiently attenuated for one species, but not for another one) and recombination of vaccine strains with field strains (or other vaccine strains). All these risks, inherent to the nature of live attenuated vaccines, are evaluated during the authorisation process, but also need to be taken into account when considering the safe and efficacious administration of oral vaccines in the field, since inappropriate administration may increase those inherent risks.

The efficacy of live attenuated vaccines depends on the viability of the microorganisms included in the vaccine which naturally have a limited lifespan once the vaccine container is first broached. Therefore, it is essential that these vaccines are prepared (e.g. reconstituted, diluted) and administered within the short period of time defined in the SPC and product literature (i.e. in-use shelf life; typically no more than 3-4 hours).
Furthermore, live vaccine microorganisms are susceptible to disinfectants, detergents or other substances with biocidal properties commonly used for cleaning farm equipment (pipelines, dosing devices, pumps, etc.) and for treatment of the drinking water (e.g. chlorine). Therefore, it is of paramount importance to ensure that the vaccine microorganisms do not come into contact with disinfectants, chlorinated water or water-sanitising materials commonly used on farms. The addition of skimmed milk powder to water used to prepare the vaccine suspension is frequently used to overcome the detrimental effects of chlorine. Use of skimmed milk in the preparation or administration of vaccines can build up in, and block, delivery systems and be favourable to bacterial growth.

In order to ensure correct administration, it is important that the vaccines are correctly prepared.

Vaccines are prescription only medicines but are typically administered by farmers and farm personnel. Lack of adequate knowledge and/or training on the correct preparation and administration of vaccines via the oral route, including the use of the necessary equipment, devices, etc. (e.g. settings, cleaning, maintenance) may result in their incorrect administration, with consequences for the safety (adverse events) and/or efficacy (lack of efficacy) of the product.

To ensure the safe and effective use of vaccines, appropriate information on preparation and dispensing should be included in the product information. In addition, a good practice guide should be developed for farmers on the use of veterinary medicinal products administered orally other than via medicated feed, with recommendations on the correct preparation and administration of oral vaccines, including the use, maintenance and cleaning of equipment and/or dosing devices, e.g. in a similar way as it has been done for feed (see feed hygiene legislation (Regulation 183/2005), Annex I, part B, Art 20)***.***

3. In-feed use

Veterinary pharmaceutical forms for in-feed use in food-producing animals are mostly premixes for medicated feed or oral powders (or similar forms, e.g. granules). The differences between premixes for medicated feed and powders/granules for oral use or use in-drinking water are described in the CVMP position paper on "Premixes for medicated feeding stuffs for veterinary use versus powders/granules for oral use or use in-drinking water" (EMEA/CVMP/199/97-FINAL), dated August 1998. The type of feed (e.g. powder, pellets, liquid) and feeding equipment used may vary between species. Commonly used in-feed medications administered to production animals include antimicrobials, anthelmintics, ectoparasitics, anticoccidials and vaccines (fish), see section 1 (general considerations). In general, medicated feed is currently used for group treatment only, whereas the in-feed use of a veterinary medicinal product is currently used for both group and individual animal treatments.

3.1. Premixes for medicated feeding stuff

A premix for medicated feedingstuff (also described as "premix for medicated feed") is defined by the EDQM as a "*veterinary medicinal product, which is exclusively to be used in the preparation of medicated feed and intermediate products*". This means that it is not dispensed directly to the end-user (farmer), but the premix must first be mixed into animal feed, only by an authorised farmer or by an authorised feed mill. The resulting product is "medicated feed", which is regulated under Regulation (EU) 2019/4. The medicated feed is ready-to-use, prescribed by a veterinarian and will be administered by the farmer to the animals as their main feed during treatment, and it should contain the correct dose for the intended treatment. Article 16(10)(c) of Regulation (EU) 2019/4 requires that the medicated feed containing the prescribed dosage of the veterinary medicinal product corresponds to at least 50% of the daily feed ration. As indicated under section 1.2.3 (immunologicals), Regulation (EU) 2019/4 also allows the use of immunological veterinary medicinal products in medicated feed. However, so far, it seems that no premix for medicated feed containing an immunological product has been authorised in the EU.

Upon delivery to the farm, the medicated feed is generally stored in a silo before it passes through the feed pipelines and into the feeding troughs.

In general, treatment via medicated feed is the recommended in-feed route of administration for group treatment, since it is a convenient way to treat a large group of animals, and the preparation allows the medicine to be mixed into the feed in a homogenous way, thus ensuring a safe and efficacious treatment with the correct dose. However, the use of medicated feed under field conditions also has some disadvantages or constraints in terms of management. For example, medicated feed might only be available in a larger batch size than required for the number of animals to be treated or manufacturing and logistical constraints might result in a certain delay between prescription and delivery of the medicated feed to the farm and, therefore, a delay in its administration.

Special considerations for the quality assessment

Although the current medicated feed legislation restricts the veterinary medicinal products that can be used in the preparation of medicated feed to premixes for medicated feed, Regulation (EU) 2019/6 no longer specifies the pharmaceutical form, and just refers to veterinary medicinal products "*authorised for the preparation of medicated feed*". Article 1(5) of Directive 2001/82 defines a premix for medicated feeding stuffs as *"Any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feeding stuffs".* The EDQM monograph (01/2014:1037) for "Premixes for medicated feeding stuffs for veterinary use" defines a premix as a pharmaceutical form to be "used exclusively in the preparation of medicated feed". However, there is no corresponding

restriction in the veterinary medicinal product legislation that would explicitly define those formulations that can be used in the preparation of medicated feed, and the PI of a veterinary medicinal product does currently not always clearly state that it is authorised to be used to prepare medicated feed. Also, the prescribing veterinarian should be able to clearly identify those veterinary medicinal products that can be prescribed to prepare medicated feed. The PI of a veterinary medicinal product that can be used in the preparation of medicated feed should therefore clearly indicate this use.

For premixes for medicated feeding stuff, a specific CVMP guideline entitled "Additional quality requirements for products intended for incorporation into animal feeding stuffs (medicated premixes)" (EMEA/CVMP/080/95-FINAL), July 1997, and a VICH guideline on the "Stability testing for medicated premixes" (VICH GL8, CVMP/VICH/836/99-Final) are available. .

Information should be available in the dossier about the type of animal feed that can be used for incorporating the premix for medicated feedingstuff, including information about any possible interactions with feed or feed additives. The above CVMP guideline (EMEA/CVMP/080/95) indicates clearly that the medicated premix should be compatible with feed. The purpose of the tests listed in the guideline is to provide information on which to propose a shelf-life for the medicated feedingstuff, to make recommendations to the feed compounder in respect of processing and compatibility, and to ensure that a homogeneous feedingstuff is produced. For premixes for medicated feed, the above guidelines also outline that an applicant must show during the authorisation procedure which kind of feed (dry feed, liquid feed, pellets) is suitable, and also to take into account the manufacturing conditions (humidity, temperature).

3.2. Oral Powders

An oral powder is a veterinary medicinal product, which may be added to, or mixed into, animal feed at the farm by the farmers themselves. There are also other pharmaceutical forms, such as granules, that can be used in a similar way; however, unless specifically stated otherwise, the same considerations as for "oral powders used in feed" will be applied to these, and the report will only make reference to "oral powders".

In order to correctly mix the veterinary medicinal product into the feed, special mixing equipment, dosing systems and/or the need to prepare a "pre-mixture" might be required. Alternatively, the powder can be sprinkled on top of the feed (top-dressing use), which is done with the intention to ensure that the complete dose of the medication is consumed by the animal *(see also section 3.3.2 on top-dressing).*

However, it is noted that the EDQM definition for an oral powder states it is a "*Single-dose or multidose preparation consisting of one or more particulate solids of varying degrees of fineness. Oral powders are intended for oral administration. They are generally administered in or with water or another suitable liquid but may also be swallowed directly*." This definition applies to both human and veterinary medicinal products. However, as a result of its rather general definition it is noted that veterinary medicines referred to as oral powders are also often administered in feed, or on feed, in some EU Member States. Therefore, it appears that different national competent authorities across the EU, are interpreting the term "oral powder" differently, that is, some Member States would consider the in-feed use of an oral powder as "off label". A revision of the EDQM standard terms to include a clear definition and harmonised view on the use of the term 'oral powder' for veterinary medicines would ensure the harmonised and correct use of the term in veterinary medicines across the European Union.

As a consequence of the current rather general definition of the term "oral powder", there also appears to be differences across Member States in the terminology used for their route of administration. Some

Member States describe the use of oral powders to be administered via animal feed as "in-feed use", whilst other Member States reserve the term "in-feed use" solely for premixes for medicated feeding stuffs (administered via medicated feed) and only allow the term "oral powder" when the product is to be administered via top-dressing use. Clarification on the EDQM standard term to define the route of administration for an oral powder via animal feed would facilitate the correct use of the products.

It is noted that "oral powders" are also used in-drinking water (see section 4 - in-drinking-water/milk use). However, for these the EDQM provides more detailed standard terms with definitions clearly indicating the method of preparation, e.g. "Powder for use in-drinking water" (or "…drinking water/milk"), or "Powder for oral solution", "…for oral suspension", etc.

When administering medicines mixed into animal feed for a group of animals, the mixture must be homogeneous to ensure that each animal receives the same dose in their feed. In view of the volume of the feed used for group treatment, as well as the large variety of animal feed and feeding systems used, it is not considered possible to achieve such homogeneous distribution of an oral powder in dry feed. The result of a non-homogeneous mixture could be over- or under-dosing of the animals. This is a particular concern if larger amounts of feed with a veterinary medicinal product are to be prepared for groups of animals that might also compete for the feed. It is therefore considered that the use of oral powders for in-feed use should be restricted to individual animals. If a number of animals are to be treated, the medication should be prepared and administered to each individual animal separately.

Special considerations for the quality assessment

The dossier requirements and data to be assessed for oral use formulations are detailed in Annex II of Regulation (EU) No 2019/6. Since reference to in-feed use is not included in the EDQM definition for an oral powder, there are currently no clear, specific requirements for this pharmaceutical form when used in feed. Consequently, the quality dossier for an oral powder might not include data on use in feed (as provided for premixes for medicated feeding stuff), and this might then result in insufficient information to ensure appropriate use of the product at the farm level.

Clearer guidance for applicants and assessors should therefore be provided on the quality dossier requirements of an oral powder when it is to be used in feed e.g. in regard to homogeneity and interactions/compatibility with feed. This could be addressed in guidance published by the Agency.

Special considerations for the safety and efficacy assessment

The result of a non-homogeneous mixture (see above, quality) could be over- or under-dosing of the animals; this is a particular concern, if large amounts of solid feed with a veterinary medicinal product are to be prepared for groups of animals that might also compete for the feed (see section 6.1 – dose). Therefore, for groups of animals, the use of an oral powder administered via solid feed, but not via medicated feed, is generally not considered to be appropriate. Instead, administration of veterinary medicinal products via medicated feed or drinking water or liquid feed should be the recommended routes of administration for the group treatment of animals**.**

The administration of an oral powder into solid feed is, however, considered to be acceptable for individual animals, as here the uptake of the feed with the medication can be better controlled, and the homogeneity of the mixture of the veterinary medicinal product (oral powder) and feed is of lesser concern, as the animal would be expected to take up all the allocated amount of medication. In regard to the treatment of small numbers of animals, it is understood that this concerns animals which could be fed individually (e.g. individual sows in farrowing units, or animals kept purely for non-commercial purposes). If a number of animals are to be treated, the medication should be prepared separately and administered to each individual animal. These animals could therefore still be able to be treated with

an oral powder via solid feed, e.g. mixed into their feed or via top-dressing use. However, exceptions from this general recommendation shall apply to the use of oral powders in solid feed administered to group treatment in regard to fish (*see section 3.4-special considerations for fish*), and in regard to oral powders administered via liquid feed (*see section 3.3.2-liquid feed*)***.***

As oral powders, granules or similar pharmaceutical forms are usually prepared and mixed by an animal owner, the product information should include clear mixing instructions, in accordance with the relevant guidelines published by the Agency***.***

3.3. Specific considerations for administration via feed

3.3.1. Administration via top-dressing

A specific route of administration via feed is top-dressing use, i.e. the administration of a veterinary medicinal product immediately prior to feeding by application onto the surface of the feed (and not by mixing into the feed). The intention of this route of administration is to ensure that the complete dose of a veterinary medicinal product is taken up by an animal, even if it would not eat its whole ration of feed. Top-dressing is a common route of administration of antimicrobials, particularly to sows. For instance, in a study in Belgium where 52 pig farms were visited (Vandael et al., 2019), it was observed that in 14 of these farms - at which in-feed medication was prepared at the farm - this medication was mostly administered by top-dressing (n=11). In the vast majority of these farms (n=9) top-dressing was used in individual animals, but it was also administered at the pen level (n= 1 farm). In addition, other veterinary medicinal products (e.g. altrenogest, flubendazole, fenbendazole) are also authorised as top-dressing use for individual sows.

When groups of animals (that compete for the feed) are treated via top-dressing, it cannot be ensured that all animals to be treated will actually receive the correct dose due to non-homogeneous distribution of the veterinary medicinal product and/or palatability issues, as animals might intentionally take up more or less of the medication depending on taste or appetite (see also section 6.1-dose). It is noted that some Member States have already taken measures to restrict the use of top-dressing in food-producing animals. For example, in France, ANSES considers top-dressing use of antimicrobials to be an inappropriate practice for the treatment of animals fed collectively and advises to avoid this method of administration in farming systems where the competition between animals for feed is not limited (Anses, 2012). Given the potential for incorrect dosing, and the associated risks, it is therefore considered that the use of top-dressing should be restricted to individual animals only. Implementation of this recommendation would require the amendment of the EDQM standard term for this route of administration accordingly.

When an oral powder is administered to animals via top-dressing, it should be spread over a small amount of feed first (not the whole ration), so that the animal is more likely to take up all the feed provided, which will include the correct dose. The product information should include appropriate information to the animal owner on how to correctly administer it, in accordance with the relevant guidelines published by the Agency. The pack size(s) should be consistent with the treatment of individual animals, in accordance with the recommendations of the SPC and product literature.

Spillage (environmental risk) and dust development (user risk) might cause specific additional concerns for this route of administration; however, this is generally assessed during the evaluation of the veterinary medicinal product, and the product information would therefore include appropriate warnings.

3.3.2. Administration via liquid feed

Oral powders for pigs and piglets may sometimes be used/mixed into liquid feed which is then administered via feeding pipelines. To note: "Milk" is in this report not considered "liquid feed" but addressed separately *(see section 4.2 – veterinary medicinal products used in milk*). Liquid feed is usually prepared at the farm level by a farmer, either by mixing all three ingredients together at the same time (feed, water, veterinary medicinal product) or by first mixing an oral powder with the feed and then adding water to prepare the liquid feed. Some veterinary medicinal products, e.g. vaccines authorised for administration via liquid feed are prepared according to the recommendations e.g. by first reconstituting the vaccine in the solvent provided and then mixing with the prepared liquid feed.

Currently, the specific use of oral powders to be incorporated into liquid feed (mixture of feed and water) has not been considered in the assessment of a veterinary medicinal product (see above, section 3.2 - oral powder), and this route of administration is not specifically addressed in the EDQM standard terms.

Most of the concerns considered above for the in-feed use of oral powders would also apply for the use of oral powders in liquid feed (e.g. homogeneity, compatibility). However, unlike oral powders used in dry feed, it is considered that homogeneity could be achieved in liquid feed, provided the following steps are taken: the veterinary medicinal product should first be mixed into the liquid base (e.g. into (drinking) water) used to prepare the liquid feed, and then mixed into the final feed.

Apart from considerations for in-feed use, the assessment of veterinary medicinal products used in liquid feed would therefore also need to consider aspects generally assessed for in-drinking water use, such as: solubility/insolubility in water (of different qualities), instability (in water), interactions with biocides/acids (e.g. chloride water)/biofilms and quality of water (see section *4.2 – Quality of water used*)). In addition, homogeneity, stability and solubility would impact on other aspects such as dosing and cross-contamination, cleaning of equipment, as addressed in other sections of this report. This could be addressed in guidance published by the Agency.

For oral powders, granules or similar pharmaceutical forms intended for administration via liquid feed, the product information must carry clear information about the preparation and mixing/dissolution of the veterinary medicinal product into liquid feed. Under these circumstances, it is considered that oral powders can still be used for group treatment via liquid feed; i.e. only oral powders administered via **solid** feed should be authorised for use in individual animals only (*see section 3.2 - oral powders*).

3.3.3. Concomitant use of feed-additives

It is stated in Article 5(2)(b) of Regulation (EU) 2019/4 that the feed used to prepare medicated feed must not contain coccidiostats or histomonostats, if the veterinary medicinal product used to prepare the medicated feed contains the same active substance. In addition, it is stipulated that in cases where the active substance of the veterinary medicinal product is the same as that of a contained feed additive, the total content of the active substance in the medicated feed must not exceed the maximum content indicated in the prescription (or product information in the case of anticipated production).

The presence of feed additives in the feed used to administer a veterinary medicinal product might also have an impact on its safe and effective use, e.g. feed containing coccidiostats might affect the efficacy or safety of anticoccidial veterinary medicinal products or could interact with some active substances. Any known interactions between a veterinary medicinal product and feed additives are considered during the assessment of the authorisation of a veterinary medicinal product, i.e. the product information would carry special warnings, if needed. In addition, it is good veterinary practice for a

veterinarian to consider possible feed additives in the feed of the animals for which a veterinary prescription is issued.

3.4. Specific considerations for fish

The oral administration of veterinary medicinal products to fish is mainly via their feed. Antibacterials, antiparasitics (for external and internal parasites), and vaccines can be administered orally to fish. Ornamental fish may also be treated with veterinary medicinal products mixed in their feed, i.e. antibacterials and antiparasitics.

The vast majority (approximately 90%) of commercial fish farms administer medicines via medicated feed, often in form of pellets. However, for smaller farms that would only need small batches of medicated feed (e.g. 100-200 kg), it can be difficult to obtain such small quantities. Also, in countries/regions where fish farming is very remote and scattered, e.g. small islands/offshore fish farms, ensuring the timely delivery of medicated fish feed might be problematic. It is also noted that some fish farmers use their own feed, which would not be available at a feed mill. In addition, the use of the cascade is often necessary since there are insufficient veterinary medicinal products available authorised to prepare medicated feed for all the fish species and all the indications. Finally, there are specific dosage forms which cannot be used to prepare medicated feed, e.g. live prey, which is sprayed with a veterinary medicinal product and then used as vehicle for the treatment of larvae.

Treatment via medicated drinking water, which is an alternative oral group treatment option for other species, is not suitable for fish. Therefore, the veterinarian might prescribe a veterinary medicinal product that is administered orally by the farmer. Such veterinary medicinal products are usually oral powders, but also may be liquid (e.g. solution). Mixing of the veterinary medicinal product into the feed is usually done during the production of the feed, normally by using a motorised mixer modified for such use (e.g. a cement mixer, or similar). If necessary, the feed will be moistened to enhance adhesion of the veterinary medicinal product. The preparation at farm level is generally taken into account when authorising veterinary medicinal products for use in fish, and the product information of most veterinary medicinal products authorised for this route carry appropriate information for the farmer to allow the safe and efficacious administration of the medicines in feed.

The environmental risks of veterinary medicinal products or medicated feed used for aquatic species are recognised, and there are currently ongoing activities at the European level (European Commission, 2019) to address these. As for the cascade rule, it should be noted that by January 2027 an implementing act should come into force which will establish a list of substances used in veterinary medicinal products authorised in the Union for food-producing terrestrial animal species or substances contained in a medicinal product for human use authorised in the Union in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004, for the use in food-producing aquatic species (Article 114(3) Regulation (EU) 2019/6). Such medicinal products may then be used in aquaculture if their active substance appears in the list of substances that will be established in the implementing act. Environmental risks and availability (or lack of availability) of alternative medicinal products are among the criteria to be taken into account when establishing the list of active substances.

It is noted that most medications used in fish are premixes for medicated feeding stuffs, and in principle, the use of medicated feed for the group treatment of food-producing animals should be the first option. However, in view of the above constraints, many fish farmers might not have easy access to medicated feed with batch sizes appropriate for their needs. In addition, it is noted that Regulation EU) 2019/4 harmonises at an EU level the requirements for preparing medicated feed at farm level and might, depending on the Member State, increase the requirements for fish farmers. As the use of premixes for medicated feeding stuffs at the farm level is not allowed for a farmer without the

necessary approval to prepare medicated feed on their farms ("on-farm mixer", Article 3 of Regulation 2019/4), a shift from medicated feed to the use of veterinary medicinal products not authorised for the preparation of medicated feed might therefore occur.

Whilst not within the mandate of this report to comment on the medicated feed legislation, it is noted that a specific approach regarding the approval for on-farm mixers for fish farmers might be considered to facilitate the use of medicated feed. In addition, Regulation (EU) 2019/4 will permit the production in advance and delivery of smaller batches of medicated feed, which could then be delivered to the fish farmers. Where possible, feed mills in regions with significant aquaculture production should therefore be encouraged to produce such smaller batches in advance. Likewise, in view of the limited availability of medicines for fish, Regulation (EU) 2019/6 considers fish as limited market, meaning that reduced data requirements could be applied, which might provide additional incentives for pharmaceutical companies to develop new medicines for use in fish. As outlined above, due to the particularities for the treatment of fish, the use of medicated feed is considered the best way to ensure safe and efficient administration of medicines, and pharmaceutical companies should be encouraged to develop medicines (premixes) for use in the preparation of medicated feed for fish.

3.4.1. Tolerance levels

For group treatment a homogeneous mixture of feed and veterinary medicinal product is required. In the feed ration for an animal, the actual amount of active substance incorporated in the feed (either via medicated feed or as veterinary medicinal product) might vary. Annex IV of Regulation (EU) 2019/4 sets tolerances allowed for discrepancies between the nominal content of an active substance of the veterinary medicinal product in a medicated feed and the actual content. These discrepancies are caused e.g. by technical limitations of the mixing process and the equipment used, by the nature of the feed ingredients (e.g. abrasive substances for pre-mixture), or by aggressive pelleting conditions such as high temperature. For antimicrobial active substances a tolerance of 10 % is applicable. For other active substances, permitted tolerances in the medicated feed are given of 10-20 % depending on the final concentration of the active substance in the feed, i.e. a minimum amount of 80 or 90 %, and a maximum amount of 110-120 % of the nominal content would be acceptable. Compliance with the tolerance levels are checked in the feed mill after manufacturing.

Tolerances and homogeneity in feed have to be evaluated in the dossier for the premix for medicated feed in the context of assessing mixing instructions, stability, segregation during transport etc. The same considerations could also apply for veterinary medicinal products administered in feed other than via medicated feed, when administered for group treatment (e.g. in fish treatment, where other routes of administration like in water use are not an option, and in group treatment via liquid feed). However, e.g. for oral powders mixed into feed, there is currently no clear guidance for applicants or assessors on tolerance levels or incompatibilities that are to be assessed, or information to be provided to the end user on dosing and mixing instructions, and subsequent handling of that feed, to ensure accurate dose delivery and, to the extent possible, that the recommended treatment dose is consumed by individuals in the treated group.

4. In-drinking-water/milk use

There is a large number of veterinary pharmaceutical forms for use in-drinking water/milk in production animals: granules *(for oral solution, for oral suspension, for use in-drinking water, coated granules)*, concentrates *(for oral spray (suspension), for oral solution, for oral suspension)*, lyophilisates *(for oculonasal suspension/use in-drinking water, for oral spray (suspension), for oral suspension, for use in-drinking water)*, oral powders, powders *(for oral solution, for oral suspension,*

for use in-drinking water, for use in-drinking water/milk oral solution), oral solutions/concentrates for nebuliser solution, oral sprays (suspension), oral suspensions, solutions for use in-drinking water, solutions for use in-drinking water/milk, and suspensions for use in-drinking water. The generic term "Oral solution", as used in the ESVAC reports, refers only to the final form that is administered to the animal, independent of the actual pharmaceutical form of the veterinary medicinal product, and this term is therefore also used in this report.

A description of the way in which medicated drinking water is prepared and administered is generally provided for the veterinary medicinal product. Medicated drinking water is always prepared on the farm. Depending on the drinking water supply system, the veterinary medicinal product is usually first mixed into a small amount of water, which is then added to a drinking water reservoir or to a bucket coupled to an electrical or mechanical dosing pump.

Administration of a veterinary medicinal product via drinking water is a common route of administration for food-producing animals because it is easy to administer by the farmer, the medicines will usually be taken even by severely diseased animals (that would no longer eat, or eat less, but still drink), and in addition the dose can be adjusted easily.

4.1. Quality requirements for the veterinary medicinal product

There are two specific CVMP guidance documents available that address the dossier requirements for the authorisation of veterinary medicinal products administered via drinking water: the CVMP guideline on "Quality aspects of pharmaceutical veterinary medicines for administration via drinking water" (EMEA/CVMP/540/03) from 2005 advises investigating the preparation of such veterinary medicinal products using two types of water - soft and hard – in order to test the solubility and the stability of such a veterinary medicinal product. The CVMP position paper on the "maximum in-use shelf life for medicated drinking water" (EMEA/CVMP/1090/02) from 2002 states that the shelf life of medicated drinking water should be defined on the basis of in-use stability studies and should not exceed 24 hours.

Certain active substances cannot be used with water due to stability and/or solubility reasons, for example, some products used in drinking water and containing trimethoprim/sulfadimethoxine (or sulfadiazine) or tylosin are poorly soluble in drinking water. Other examples are products that might sediment, which can also lead to under- or over-dosing depending on the length of time the animals take to drink the medicated water. Sometimes poor solubility can lead to obstructed drinking nipples or to sedimentation in pipelines, which might increase the risk of biofilms.

There are currently no defined active substance content limits for veterinary medicinal products administered via drinking water when already dissolved in the water. For oral powders administered via drinking water, generally, quality assessors would consider a range of 90 – 110% of active substance content in the medicated water satisfactory. However, there is currently no specific guidance for applicants and assessors on this, and so further guidance would be useful with tolerances aligned to those specified in the Regulation (EU) 2019/4. This could be addressed in guidance published by the Agency.

4.2. Quality of the water used

An important aspect for the efficacy of drinking water treatments is the quality of the water used to prepare medicated water, medicated milk replacer, or liquid feed. Water can be obtained either from a well or from a municipal water distribution system. Especially when obtained from a well, contamination with e.g. minerals from the ground or bacteria is possible, which might interact with the veterinary medicinal product. Drinking water quality depends on the source, filtration and water

treatment (e.g. acidification with organic acids to prevent infections by enteropathogenic bacteria), method of storage at the farm, water distribution pipelines (e.g. pipeline materials, cleaning and disinfection protocol) and the surrounding environment.

Management of the quality of water and knowledge of its physicochemical and microbiological properties is crucial for correct medication. Therefore, water quality should be regularly tested by the farmer, not only for the presence of bacteria (e.g. *E. coli*), yeasts and fungi, but also for chemicals and physico-chemical properties, and farmers should be aware of the need to monitor the water quality.

Existing guidelines require applicants submitting a dossier for veterinary medicinal products used in drinking water, to investigate incompatibilities of veterinary medicinal products, such as the hardness of water and the pH (e.g. precipitation of doxycycline may occur in alkaline water).

However, other aspects are currently not covered by current guidelines, such as the presence of polyvalent cations like Ca^{2+}, Mg^{2+}, Zn^{2+}, and Fe^{3+}, which might provoke the formation of complexes (e.g. which may reduce the absorption of tetracyclines), and appropriate warnings might therefore not be included in the product information. This could be addressed in guidance published by the Agency.

In the feed hygiene legislation, the development of "Community guides for good practice" for farmers is recommended (Regulation (EC) 183/2005, Article 20 and Annex I part B). Such guidance does however not address the use of veterinary medicinal products administered via drinking water (or milk, milk replacer or liquid feed). Developing similar guidance for farmers, including recommendations on the use of veterinary medicinal products administered via drinking water/milk, milk replacer or liquid feed would be considered useful.

4.3. Concomitant use of biocides

In some farms, water is not supplied from the tap, but for practical (availability) and economic reasons from drills or wells. As those sources of water can be contaminated with microbes, biocides might be added routinely by a farmer to the animals' drinking water to reduce such contamination (biocides type PT05 category: products used to disinfect drinking water for humans and animals). The most commonly used biocides used are active chlorine (chlorine dioxide ClO_2, sodium hypochlorite $NaClO_2$, sodium dichloroisocyanurate (also called sodium troclosene or NaDCC)) and hydrogen peroxide H_2O_2. Even if tap water is used, the use of biocides might still be needed, in order to avoid biofilms in the water pipes.

Some studies show that antibiotics such as penicillins and polypeptides are subject to degradation in the presence of biocides (impact of hardness, time, nature of the biocide and nature of the active substance). It has been demonstrated by Guichard et al. (2019) that biocides may decrease the stability of certain antibiotics administered in drinking water, leading to under-dosage in the treated animals, e.g. colistin is sensitive to chlorine, or amoxicillin might react with hydrogen peroxide. This finding can probably be extrapolated to antibiotics administered in milk replacer prepared with water containing biocides, although it has not been documented. That could lead to decreases of the expected nominal dose, and therefore, treatment failures and/or the development of resistance. Biocides may also adversely affect the viability of bacteria/viruses included in live vaccines leading to a reduced efficacy. Standard warnings are included in the product information of live vaccines intended for administration in drinking water addressing the issue.

Routine discontinuation of biocide use prior to treatment may have adverse /unintended consequences related to contamination/biofilm formation etc. The stability of medicated water in the presence of biocides should therefore be considered during the assessment of veterinary medicinal products administered via drinking water, milk or liquid feed. However, compatibility with biocides is currently

neither addressed nor requested, as it is not mentioned in the CVMP guideline on "Quality aspects of pharmaceutical veterinary medicines for administration via drinking water" (EMEA/CVMP/540/03 rev 01).

Potential interactions between commonly used biocides and veterinary medicinal products administered via drinking water should be investigated and assessed, and appropriate guidance regarding interactions and incompatibilities be provided in the product information.

4.4. Concomitant use of solubility enhancers

Some oral powders are poorly soluble in drinking water, and in order to achieve better homogeneity in the water, farmers or veterinarians might use solubility enhancers to improve the solubility of the veterinary medicinal product.

However, the use of solubility enhancers together with a veterinary medicinal product, which has not been tested and approved for such concomitant use, might affect the safe and/or effective use of the veterinary medicinal product, as e.g. the product information has no information about the suitability or dose of the solubility enhancer. Also, the solubility enhancer might have an impact on the bioavailability of the veterinary medicinal product, which could impact on e.g. its target animal safety or its withdrawal period, or on the stability of the veterinary medicinal product in the drinking water.

It is considered that the addition of solubility enhancers together with a veterinary medicinal product to animals' drinking water which have not been tested and approved, is not considered acceptable. The fact that a veterinary medicinal product needs to be used together with solubility enhancers seems to indicate an unsuitable formulation or insufficient pharmaceutical development, by not taking into account different types of waters (pH, hardness) that might have an impact on the solubility. Farmers should be made aware of this. Such information should be made available to farmers in a good practice guide on the use of orally administered veterinary medicinal products**.**

4.5. Veterinary medicinal products used in milk

Medicated milk/milk replacer is usually prepared by the farmer shortly before administration and given to calves at approximately 37-40°C, because calves prefer to drink warm milk.

However, in particular when using milk replacer (which needs to be dissolved in hot water), the medication at farm level is sometimes prepared with hot water exceeding 70°C.

This aspect is, however, not taken into account in the current guideline in regard to the investigations of the stability of the active substance and the solubility of the finished product. The fact that warm or hot water may be used in farms should therefore be considered in a future revision of the appropriate quality guideline (EMEA/CVMP/540/03).

The current guidance (EMEA/CVMP/540/03) specifies that the maximum in-use shelf life for medicated drinking water should be based on in-use stability data and the specification for medicated drinking water and should not exceed 24 hours. However, for medicated milk/milk replacer, no such considerations regarding preparation, stability and in-use shelf life of the medicated milk/milk replacer appear in European guidelines. This could be addressed in guidance published by the Agency.

5. Oral formulations for individual use

5.1. Pharmaceutical forms for individual use

Certain pharmaceutical forms, such as solid oral dosage forms (e.g. tablets, capsules) are mainly used in companion animals and are considered a low risk for dosing errors due to the fact that the required dose can be administered with a reasonable degree of precision. In species with large weight ranges (e.g. dogs), tablets are usually available in a variety of different strengths and/or carry break lines to facilitate their accurate splitting into halves and quarters and therefore allow accurate dosing.

It is noted that sometimes this route of administration can be inconvenient for the owner when the animal refuses to accept the tablet and, as a consequence, for example, an antimicrobial treatment might not be completed. This risk might be reduced by using specific formulations, coated tablets, palatable tablets or flavoured tablets.

In cattle, solid oral dosage forms (e.g. intra-ruminal device) are used. These pharmaceutical forms are entirely swallowed by the animal and are therefore considered a low risk in terms of dosing errors.

It is noted that Regulation (EU) 2019/4 now also considers the use of the medicated feed route to prepare and store medicated feed in advance, and to only dispense smaller batches of such medicated feed. This would therefore make the use of medicated feed more attractive for target groups previously not likely to receive medicated feed, e.g. pets and may lead to applications for premixes for medicated feed for companion animals.

5.2. Routes and methods of administration

A number of routes and methods of oral administration, as defined by the EDQM, are considered to be mainly for use in individual animals, these include beak dipping, oral pastes, buccal use, dental use, gastric use, gastroenteral use, gingival use, intraruminal use, oromucosal use, oropharyngeal use, and sublingual use. These oral routes and methods of administration are considered to be well controlled, as they are usually only used for individual animals, and they are also considered to enable accurate dosing.

6. Further considerations linked to oral administration of veterinary medicinal products

6.1. Dose

The administration of the prescribed dose at the frequency, and for the duration of time advised by the veterinarian (i.e. in accordance with the instructions of the product information), are the essential conditions for treatment success. This treatment is expected to be efficacious and safe for the treated animals, safe for the handler, safe for the consumer (in case of food-producing animals) and safe for the environment. Furthermore, during the assessment of the veterinary medicinal product, any recommendations and/or warnings would have been assessed based on the recommended treatment dose.

Incorrect administration of oral veterinary medicinal products may lead to over-dosing or under-dosing. The tolerance of exposure in the target animal to an overdose is usually assessed prior to the authorisation of the veterinary medicinal product, and appropriate warnings are included in the product information. An overdose might result in risks for the target animal, the user or the consumer (regarding the withdrawal period in case of food-producing animals). Treatment via feed resulting in

under-dosing may result in subtherapeutic doses, which may result in reduced efficacy or ineffective treatment and, in the case of antimicrobial or anti-parasitic products, might also promote the development of resistance.

It is therefore important to ensure that the administration of a veterinary medicinal product to groups of animals must be in a homogenous way, using suitable veterinary medicinal product formulations at the correct dose, for which quality aspects (e.g. regarding solubility, homogeneity) of the veterinary medicinal product have been adequately assessed (*see section 3.2 - Oral powders, and 3.3.1 – Top-dressing*).

Errors in the administration of the correct dose of the veterinary medicinal product may occur, and can be due to e.g. miscalculating the correct dose or the number of animals to be treated, or on insufficient information available to the person preparing the medication resulting in an incorrect mixing procedure to ensure adequate homogeneity in the dispersion/distribution of the veterinary medicinal product in the feed or drinking water. Clear information in the SPC and product literature is therefore essential for the correct administration of a veterinary medicinal product, and the legislation for both medicated feed and veterinary medicinal products require clear instructions for the preparation of the medicated feed or the use of veterinary medicinal product, respectively.

Oral dosage forms may be administered by non-professional users, and some types of veterinary medicinal products (or the equipment used to administer them) might need special knowledge or special instructions on how to use them (e.g. withdraw water for a period of time prior to vaccination/treatment via water; use of indicator substances in water; purge pipelines prior to dosing to ensure correct concentration, individual and herd water consumption; etc.). Depending on the type of product, detailed information should be included in the product information relating to the mixing of the veterinary medicinal product into (different types of) feed/drinking water, use of dosing equipment, and cleaning of the dosing equipment, taking into account risks raised elsewhere in the report.

Annex I to this advice gives an overview of factors related to animals to take into account when calculating the correct dose. In order to achieve the correct dose of veterinary medicinal products, special dosing/mixing devices are often used for larger groups of animals. Annex II to this advice provides further information about the use of measuring, dosing and mixing devices.

Any farmer administering veterinary medicinal products orally should be aware of the approach to calculating the correct dose, and when using a dosing pump and/or existing drinking/feeding pipelines should be familiar with the use and maintenance of these product delivery methods. It would therefore be recommended to develop a good practice guide for farmers with advice on doing so. The information in the annexes could be taken into consideration when developing such a guide.

It is noted that more research on aspects of animal husbandry systems that can influence the efficacy and safety of medicated drinking water would be useful; e.g. in regard to the amount of spillage from different water systems, biocides that can be used to clean pipelines after vaccination or antibiotic treatment, and the impact of antibiotic residues in the watering system on bacterial resistance development.

6.2. Cross-contamination

Cross-contamination at the farm level can have a negative impact on animal or human health. The type of feed and the type of veterinary medicinal product play a great role in the level of cross-contamination. The 2019 report from the joint FAO/WHO meeting on "*carryover in feed and transfer from feed to food of unavoidable and unintended residues of approved veterinary drugs*", gives information on cross-contamination and its consequence for public health.

Residues in the feeding system from treatment with a veterinary medicinal product or medicated feed, or in the feeding/drinking system or mixing/dosing equipment following treatment with a veterinary medicinal product, carry the risk of cross-contamination (e.g. Filippitzi et al., 2016). Good farming hygiene practices (e.g. regular cleaning of equipment, good maintenance of pipelines) should therefore be followed thoroughly on the farm.

Cross-contamination may lead to traces of an active substance from a veterinary medicinal product in non-target populations, which might increase the risk of resistance selection in bacteria and parasites (e.g. Filippitzi et al. 2018). Cross-contamination of supposedly non-medicated feed with residues of antimicrobial compounds may cause an animal and public health concern associated with the potential for selection and dissemination of resistance in commensal bacteria (e.g. *Enterobacteriaceae*, *Enterococcus* spp) and potentially zoonotic bacteria (e.g. *Campylobacter* spp) (*e.g.* Peeters et al., 2017). The consumption of cross-contaminated feed in animals may theoretically lead to presence of residues in animal products intended for human consumption; however, such cross-contamination is generally expected to be at too low concentrations to result in residue levels with adverse effects to human health.

It is noted that EFSA, in collaboration with EMA, is drafting a scientific opinion as regards maximum levels of cross-contamination for 24 antimicrobial active substances in non-target feed, which will be published in 2021. The opinion should provide further clarification on the amounts of residues of antimicrobials in feed below which there would be no effect on the selection for resistance in bacteria in food-producing animals. However, the opinion considers cross-contamination at feed mill level (and not at farm level).

Feed hygiene legislation - Cleaning of feeding equipment / watering system

The feeding and watering of commercially kept production animals, in particular pigs and poultry, is usually achieved by using feeding/watering systems/pipelines, which should be regularly cleaned. Annex III of the feed hygiene legislation (Regulation (EC) 183/2005) requires that feeding equipment and watering systems must be designed, constructed and placed in such a way that contamination of feed and water is minimised. Watering systems shall be cleaned and maintained regularly, where possible.

However, under field conditions, adequate regular cleaning might not always be undertaken (Vandael et al. 2019), and it might also not be possible to fully avoid residual feed in the pipelines, whilst animals are still present during the cleaning of the pipelines. Residues of feed, in particular feed containing a veterinary medicinal product, in the feeding system/feeding pipelines after treatment may lead to possible cross-contamination of the next feed batch.

Administration of veterinary medicines via drinking water, milk, milk replacer and liquid feed (e.g. antibiotics or vaccines given together with skimmed milk or other stabilisers) may result in the formation of sediment in the pipelines, and this could potentially cause the formation of biofilms (bacteria) or residual traces of antibiotics. Limited information is available on the extent of this problem, such as the length of time residues of veterinary medicinal products are present in water (cross-contamination), and if there is a potential for development of resistant bacteria. Bacteria can also develop resistance to biocides, which might co-select for antimicrobial resistance in the environment.

A pilot study (unpublished, undertaken by the Dutch ministry of agriculture, still on-going) investigating residues of different antimicrobials in water using a miniature drinking water system, indicated differences in the persistence of different types of antibiotics. Some classes of antimicrobials

appeared to be rather persistent, despite the drinking water systems being flushed several times with hydrogen peroxide and peracetic acid.

In poultry, live vaccines are commonly administered via their drinking water together with stabilisers such as skimmed milk. Skimmed milk might coagulate when biocides with a low pH are used for the cleaning of pipelines, and thus form a suitable growing medium for bacteria (Marchand et al, 2012).

In calves, medicated milk replacer/milk may be fed using nipple bottles, individual nipple buckets, multi-feeder buckets (with nipples), milk lines with nipple bars, or automated feeders. A lack of proper cleaning of lines, reservoirs, nipples and surfaces both around and below nipples could lead to the persistence of residues of veterinary medicinal products, and the formation of biofilms, slimes and moulds.

The feed hygiene legislation (Regulation (EC) 183/2005) makes the regular cleaning of watering systems mandatory, but it does not specify the cleaning of the system after using it to administer veterinary medicinal products. However, it is important that systems used to administer veterinary medicinal products orally are cleaned after use with appropriate products and methods, where possible. Also, this requirement does not specifically apply for systems used to administer milk, milk replacer or liquid feed.

Similar requirements as outlined in Annex III of Regulation (EC) 183/2005 in regard to the cleaning and maintenance of feeding equipment or watering systems and use of automated dosing devices should be considered for veterinary medicinal products that are administered by a farmer via the animals' feed or drinking water, as applicable.

It is therefore recommended to make the cleaning of any watering/feeding systems mandatory, after it was used to administer veterinary medicinal products orally.

Feed hygiene legislation – good practice guide for farmers

Farmers should apply good feed hygiene and cleaning practices, in particular when using feed containing medication or drinking systems, after using them for the administration of a veterinary medicinal product. Proper use of biocides according to a well-defined method is required, and farmers should be aware of the proper cleaning methods, e.g. biocides (PT4 or PT5 category[3]) that are authorised for such purposes and appropriate for use in the vicinity of animals.

However, in view of the many feeding/watering systems available, the product information of veterinary medicinal products does generally not contain much information on how to clean the water system after treatment. Also, most authorised biocides do not provide information about their suitability for cleaning a water system after medication with veterinary medicinal products.

In the feed hygiene legislation, the development of "Community guides for good practice" for farmers is recommended (Regulation (EC) 183/2005, Article 20 and Annex I part B). Such guidance does not address the use of veterinary medicinal products administered via feed or drinking water/milk, milk replacer or liquid feed. It is therefore recommended to develop similar guidance for farmers, including recommendations on the handling and cleaning of feeding and drinking pipelines and any equipment used to administer veterinary medicinal products. Such guidance should take into account the cleaning materials to be used and the appropriate timing for the cleaning.

[3] According to Annex V of the Biocidal Products Regulation (EU) 528/2012, biocidal products are classified into 22 biocidal product-types; PT 4 and PT 5 are disinfectants for food and feed area (PT4) and drinking water (PT5).

6.3. Other responsibilities

Regulation (EU) 2019/4 gives clear responsibilities to an animal owner to adhere with the prescription issued by the veterinarian. In particular, Article 17(2) states that animal keepers shall use medicated feed in accordance with the prescription, taking measures to avoid cross-contamination. Animal keepers must also ensure that only the identified animals in the veterinary prescription for medicated feed are administered with the medicated feed, and that expired medicated feed is not used.

Whilst appropriate warnings on these (and other) issues are included in the product literature for a veterinary medicinal product, the veterinary medicinal product legislation does not have equivalent requirements explicitly stating the responsibility of an owner/keeper of a treated animal when using oral medicinal products. It is important that the animal owner is not only aware of the risks associated with their use (as stated in the package leaflet) but is also given the responsibility to comply with the treatment as outlined in the veterinary prescription.

The need for the animal owner to use medicines in accordance with the prescription and comply with the other requirements listed above does not only apply to those veterinary medicinal products administered orally but to all. However, since the majority of veterinary medicinal products used by animal owners/keepers are products authorised for oral administration, and as the risks associated with their use may be similar, or even higher than those associated with the use of medicated feed (please also refer to section 5.2 on cross-contamination), it seems relevant to introduce similar rules on the use of oral veterinary medicinal products. Such rules could contribute to ensuring the safe and efficient use of veterinary medicinal products for oral administration.

6.4. Pack sizes

Article 105(6) Regulation (EU) 2019/6 states that *"The quantity of the medicinal products prescribed shall be limited to the amount required for the treatment or therapy concerned. As regards antimicrobial medicinal products for metaphylaxis or prophylaxis, they shall be prescribed only for a limited duration to cover the period of risk".* Veterinary medicinal products for food-producing animals are generally prescription-only, and pack sizes should therefore allow to fulfil this requirement. The suitability of a pack size is usually addressed during the initial assessment of a veterinary medicinal product, although there is currently no clear legal requirement to restrict a proposed pack size. There should be a clear requirement, so that the pack size of a veterinary medicinal product complies with its recommended posology, route of administration and target species, in particular for those containing antimicrobial (active) substances. It is noted though that in Regulation (EU) 2019/6 (Annex II, quality requirements, product development), it is stated that "*The proposed pack sizes shall be justified in relation to the proposed route of administration, the posology and the target species in particular for antimicrobial (active) substances*". This provision refers to data requirements, but it is important to extend the provision to the granting of a marketing authorisation, e.g. to allow the refusal or request modification of an unsuitable pack size during the marketing authorisation procedure.

The main concerns associated with an unsuitable pack size are the inappropriate disposal of unused product and its impact on the environment, in particular for products that are to be administered orally as these are usually handled by an animal owner who might not be aware of the appropriate disposal methods. "Unsuitable" pack sizes could be either too small (i.e. not suitable for the full course of treatment) or too large, resulting in unused product. There is a risk that larger amounts of unused medicines might be given to non-target animals, or unused but already opened medicines might be kept for later use (and potentially not comply with the recommended in-use shelf life or storage conditions).

Specific guidance is currently provided for suitable pack sizes of veterinary medicinal products, but this applies to antimicrobial veterinary medicinal products only (see CVMP Question and answer document on the CVMP guideline on the SPC for antimicrobial products (EMA/CVMP/414812/2011-Rev.2). However, similar guidance might also be useful for other classes of products, such as anthelmintics, in particular those that are administered orally, as these are the most commonly used type of medicines administered by animal owners themselves.

Considerations to take into account when assessing the pack size will mostly take into account compliance with the dosing instructions, i.e. the amount needed to treat a specific number of the intended target species for the recommended period of time.

6.5. User safety

Mixing of the medicines into animal feed may cause unintended exposure of the user to the medicine, e.g. via direct contact or inhalation. However, this risk is usually evaluated during the assessment of the medicines, and the product information carries appropriate warnings, if necessary (e.g. to use protective clothing). Therefore, no recommendations are considered necessary related to this topic.

6.6. Environmental safety

The assessment of a veterinary medicinal product takes into consideration the impact of the product on the environment. This assessment includes calculations on potential quantities of the veterinary medicinal product that might appear in the environment, and also takes into account the particular use of the veterinary medicinal product in the target species (e.g. pasture *versus* housed animals). The product information carries detailed warnings concerning the proper use of that veterinary medicinal product, and in case of specific risks for the environment, additional warnings are added, as necessary; e.g. for substances that can be toxic for aquatic life, a warning could be added not to allow treated animals near watercourses.

Both, Regulation (EU) 2019/4 and Regulation (EU) 2019/6 require information on the label about the disposal of the product. For veterinary medicinal products, Article 117 of Regulation (EU) 2019/6 requests that "*Member States shall ensure that appropriate systems are in place for the collection and disposal of waste of veterinary medicinal products", and the* product literature includes a section on "Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products". For medicated feed, Regulation (EU) 2019/4 states that "*Member States shall ensure that appropriate collection or discard systems are in place for medicated feed and intermediate products that are expired or in case the animal keeper has received a bigger quantity of medicated feed than he actually used for the treatment referred to in the veterinary prescription for medicated feed. MS shall also take measures to ensure that relevant persons are aware of the location of collection or discard points*."

However, for medicated feed it is required that the label include the following statement: *"inappropriate disposal of medicated feed poses serious threats to the environment and may, where relevant, contribute to antimicrobial resistance"*. A similar warning in regard to unused product/waste from veterinary medicinal product is currently not included in the product information for veterinary medicinal products. However, a warning should be added to the product information of veterinary medicinal products intended to be administered orally for group treatment, in particular in regard to antimicrobials used in feed or drinking water for herd treatment (likely to be larger amounts) that the "*inappropriate disposal of feed or water containing a veterinary medicinal product might pose a threat to the environment and may, where relevant, contribute to antimicrobial resistance"*.

6.7. Labelling requirements

Since oral medication is commonly administered by both professional and non-professional users (animal owners), clear instructions on how to use the medication is pivotal. Both, Regulation (EU) 2019/4 and Regulation (EU) 2019/6 contain labelling requirements, which should be easily understood by the end user. In general, the requirements of both regulations complement each other, and the information available for the veterinary medicinal product authorised to prepare medicated feed should provide the feed-mill with all the appropriate information to prepare the medicated feed, and then to label the medicated feed accordingly (in line with Article 9 and Annex III of Regulation (EU) 2019/4).

For veterinary medicinal products, Articles 10-14 Regulation (EU) 2019/6 outline the requirements for the "product literature", which includes the outer packaging (e.g. cardboard box), the immediate container (e.g. bag with powder, blister with tablets) and the package leaflet. In addition, a "summary of product characteristics" (SPC) is prepared which includes more detailed information and is addressed to healthcare professionals.

Templates are available from the NCAs/EMA to provide applicants and assessors with guidance on the text/wording that should be used for the information required in these documents ("QRD documents").

For veterinary medicinal products including antimicrobial or antiparasitic substances, additional guidance is provided (e.g. "SPC guideline for antimicrobials"); in addition, various other CVMP guidelines and guidance documents may also address specific text/standard terms required in the product information, such as the storage conditions. The wording of the product literature is part of the marketing authorisation, and the product information (i.e. the SPC, packaging, labelling and package leaflet) of the veterinary medicinal product put on the market must reflect the wording agreed with relevant competent authority.

There are some areas where guidance on labelling requirements (e.g. QRD template guidance, SPC guidelines) could be updated, as outlined in various sections within this report, e.g. mixing and cleaning instructions (see above sections 6.1-dose, 6.2 cross-contamination, 6.6 - environmental safety).

Definitions

Product information

The information provided by the marketing authorisation holder on the veterinary medicinal product, including the summary of product characteristics (a document mainly addressed to health care professionals), and the product literature (i.e. the labelling and the package leaflet) of the veterinary medicinal product.

Watering system:

Any equipment used by a farmer to administer drinking water, including pipelines, buckets, troughs, as well as dosing pumps, and water tanks.

European Directorate for the Quality of Medicines and healthcare (EDQM):

In-drinking water/milk use:
Administration of a veterinary medicinal product by incorporation into the animal drinking water, milk or milk replacer.

In-feed use:
Administration of a veterinary medicinal product by incorporation into the animal feed.

Oral use:
Taking a medicinal product by means of swallowing.

Oral powder:
Single-dose or multidose preparation consisting of one or more particulate solids of varying degrees of fineness. Oral powders are intended for oral administration. They are generally administered in or with water or another suitable liquid but may also be swallowed directly.

Oral solution:
Liquid single-dose or multidose preparation consisting of a solution intended for oral use. Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume, generally 5 mL or multiples thereof.

Powder for use in drinking water/milk:
Solid preparation for veterinary use consisting of one or more powders, including freeze-dried powders, intended to be dissolved in the animal drinking water, milk or milk replacer. If alternative methods of administration to individual animals are also authorised, the method of administration is clearly described in the product information.

Premix for medicated feeding stuff:
Liquid, semi-solid or solid preparation intended to facilitate oral administration of active substances to animals. Premixes for medicated feed are used exclusively in the preparation of medicated feed. Used as powders or granules, they are free-flowing and homogeneous. Used in liquid form, they are homogeneous suspensions or solutions which may be obtained from thixotropic gels or structured liquids. The particle size and other properties are such as to ensure uniform distribution of the active substance(s) in the final feed.
(Note: An alternative and recently more commonly used term is "premix for medicated feed").

Suspension for use in-drinking water:
Liquid preparation for veterinary use consisting of a suspension intended for administration by incorporation into the animal drinking water. If direct oral administration to individual animals is also

authorised, the method of administration, including any necessary dilution, is clearly described in the product information.

Top-dressing use:
Administration of a veterinary medicinal product by application onto the surface of the feed immediately prior to feeding.

Regulation (EU) 2019/4 on medicated feed: Article 3:

Cross-contamination:
Contamination of a non-target feed with an active substance originating from the previous use of the facilities or equipment.

Feed business operator:
Any natural or legal person responsible for ensuring that the requirements of this Regulation are met within the feed business under that person's control.

Intermediate product:
Feed, which is not ready to be directly fed to animals without further processing, consisting of a homogenous mixture of one or more veterinary medicinal products with feed materials or compound feed, exclusively intended to be used for the manufacture of medicated feed.

Medicated feed:
A feed, which is ready to be directly fed to animals without further processing, consisting of a homogenous mixture of one or more veterinary medicinal products or intermediate products with feed materials or compound feed.

Non-target feed:
Feed, whether medicated or not, which is not intended to contain a specific active substance.

On-farm mixer:
A feed business operator manufacturing medicated feed for the exclusive use on its farm.

Veterinary prescription for medicated feed:
A document issued by a veterinarian for a medicated feed.

Regulation (EU) 2019/6 (Veterinary medicinal products); Article 4:

Active substance
means any substance or mixture of substances intended to be used in the manufacture of a veterinary medicinal product that, when used in its production, becomes an active ingredient of that product.

Antibiotic
means any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases.

Antimicrobial resistance
means the ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species.

Antimicrobial
means any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals.

Antiparasitic
means a substance that kills or interrupts the development of parasites, used for the purpose of treating or preventing an infection, infestation or disease caused or transmitted by parasites, including substances with a repelling activity.

Food-producing animals
means food-producing animals as defined in point (b) of Article 2 of Regulation (EC) No 470/2009.

Immediate packaging
means the container or any other form of packaging that is in direct contact with the veterinary medicinal product.

Labelling
means information on the immediate packaging or the outer packaging.

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.

Outer packaging
means packaging in which the immediate packaging is placed.

Package leaflet
means a documentation leaflet on a veterinary medicinal product which contains information to ensure its safe and efficacious use.

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.

Veterinary medicinal product
Any substance or combination of substances which fulfils at least one of the following conditions:
it is presented as having properties for treating or preventing disease in animals;
its purpose is
- to be used in, or administered to, animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;
- to be used in animals with a view to making a medical diagnosis;
- to be used for euthanasia of animals.

Veterinary prescription
means a document issued by a veterinarian for a veterinary medicinal product or a medicinal product for human use for its use in animals.

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Annex I

Factors to calculate the correct dose

Group treatment

- *Weight of the animals to be treated:* In general, the weight of the animals to be treated is estimated according to the experience of the farmer/veterinarian, responsible for administering the veterinary medicinal product. This might need to take into account (an estimate of) the number of animals per group, but also their expected daily weight gain. Overestimating the weight to be treated may lead to an overdose, while underestimating this weight would result in under-dosage.
- *Social rank:* Soraci et al. (2014) report a large variability in internal exposure to fosfomycin and conclude that oral treatment under rearing conditions, whether via water or feed, is clearly impacted by the social status of the animals. This finding corroborates those of other authors confirming the impact of social rank on eating habits in farm animals (Bøe and Færevik, 2003; Jensen, 2003; Keeling and Gonyou, 2001; Place et al., 1995).
- *Water/milk/feed consumption:* the level of consumption depends on a multitude of factors, including the health status of the animals, their housing conditions, environmental conditions such as temperature and humidity, breed, growth stage and expected performance, etc. Concerning the health status, for example, more severely diseased animals often have a reduced appetite or stop eating, resulting in less uptake of medication via their feed, and this can result in considerable variability in exposure to the veterinary medicinal product between animals (clinically ill pigs also tend to drink less). Williams (1996) reports a significant drop in levels of solid feed and water consumption in chickens suffering from coccidiosis. In addition, it seems that inter- and intra-individual variations in water consumption are observed in pigs (Massabie et al., 2014; Rousselière et al., 2016). In the product information of oral veterinary medicinal products authorised for group treatment, farmers are generally advised to record the animal consumption every day and to adjust the incorporation rate of the veterinary medicinal product on a daily basis. In case of a severe drop in water/milk/feed consumption, veterinarians are asked to consider an alternative treatment via another suitable route of administration.
- *Spillage*: Veterinary medicinal products administered orally, and in particular via drinking water, are considered to have a high risk of spillage into the animals' environment, partly due to the ability of water to drip on the floor during use, but also due to animals playing around with the equipment, bored pigs…). The amount of spillage will vary depending on the type of feeding/drinking system used, but also on the water pressure in the system. There is currently not much knowledge on the average amount of spillage per system or on possible mitigating measures to be taken when medicated water is used. For example, chickens can have access to drinking water via a nipple system, with or without drip cups, or via bell drinkers.
  Spilled medicated water will likely mix with the animal's litter, and residues of the veterinary medicinal product might then end up in the environment. This waste carries the risk of contamination of manure. However, environmental safety (and appropriate risk mitigation measures) are already assessed during the environmental risk assessment at the time of authorisation of the veterinary medicinal product, where an exposure of 100% of the dose of the active substance is estimated (and metabolites, if it is known that they are of higher concern/toxicity). However, where spillage is significant, this may pose a risk of under-dosing.

- *Palatability* of feed or water/milk, which includes a veterinary medicinal product, may result in a reduced/increased uptake of the feed/water/milk and therefore the medication by the treated animals. This could also happen under the cascade (species-differences in taste).
- *Preparation of oral solutions using water*: As outlined above *(see section 4 – in drinking water / milk use)*, the quality of the water used to prepare the oral solution, the chemical properties of the veterinary medicinal product, as well as the addition of any other substances (e.g. biocides, solubility enhancers) may impact the stability and/or solubility of the veterinary medicinal product in the final oral solution. This might then result in a decrease of the expected nominal dose and under-dosing.
- *Administration of the* veterinary medicinal product *via feeding/drinking pipelines:*
    - The flow rate of the drinkers should be adjusted correctly as: (1) a low flow rate will lead to under-consumption of water and an increase in social tensions in the group; (2) a high flow rate will waste the medicated water and the capacity of the dosing pump may be exceeded, and the potential for environmental contamination increased.
    - Pipelines should be cleaned both prior to use and after the use of any medication: non-purging of pipelines with clean water before treatment will otherwise delay the start of the consumption of medicated water, until the remaining non-medicated water is consumed. This will lead to an under-dosing.

Individual animals:

- *Regurgitation*: during the administration of an oral treatment (liquid or solid), it can happen that the animal refuses or regurgitates the medication, thus leading to an under-dosage. A rigorous monitoring of the animal's medication intake is necessary in order to ensure compliance with the prescribed dosage.
- *Ensure the uptake of the correct dose by the animal*: The weight of the animal to be treated should be determined as accurately as possible. For veterinary medicinal products to be administered via feed, it is generally recommended to present the veterinary medicinal product to the animal mixed into a small amount of palatable feed at the start of its meal, before the rest of the feed is given. In case of refusal, treatment using another pharmaceutical form or route of administration should be considered.
- *Availability of the correct dose:* due to the lack of a suitable range of strengths of some veterinary medicinal products for the treatment of certain animal species with a wide weight range (e.g. dogs, pigs), it is sometimes difficult to administer the precise dose specified in the product information of the veterinary medicinal product.

Annex II

Use of measuring/dosing/mixing devices

In order to achieve the correct dose of veterinary medicinal products, special dosing/mixing devices are often used for larger groups of animals.

In feed, such devices are often used for pigs, and usually installed at the beginning of the feeding system/pipeline (Filippitzi M, 2018). The feed is transported through the pipeline and in regular intervals (e.g. every second), a portion of veterinary medicinal product (e.g. oral powder) is spread over the feed (i.e. not homogeneously incorporated). Inappropriate mixing techniques, dosing systems or other equipment on the farm might, however, lead to inhomogeneity of the feed, resulting in under-/over-dosing of the animals. Likewise, insufficient maintenance and calibration of equipment might result in incorrect dosing. In addition, the use of mixing/dosing equipment to add a veterinary medicinal product (e.g. oral powder) into animal feed carries the risk of cross-contamination, if the same equipment is used to prepare a feed ratio of different types of feeding stuffs mixed together.

Medicated drinking water for group treatment is usually administered via the existing drinking water pipelines/system, and specially designed dosing equipment/pumps. A dosing pump dilutes the stock solution to a suitable concentration of the veterinary medicinal product in water so that the animals are dosed according to the product information. The increasing and widespread use of an automated dosing pump is often not taken into account in the requirements requested to applicants for a veterinary medicinal product. Indeed, the calculation of the maximum solubility of the veterinary medicinal product must be put in perspective together with the possible settings of the equipment (concentrated 1% (e.g. diluting 1:100), 5%, etc.). In case the pump is not well maintained or calibrated this might pose a risk of over- or under-dosing. Flow rate settings of the dosing pump should be adjusted according to the concentration of the stock solution and the water intake of the animals to be treated, whilst not exceeding the maximum solubility of the veterinary medicinal product. The maximum and minimum flow rates of water achievable by the pump must be compatible with the highest flow rate at peak watering times, and also when only one drinker is used. Otherwise, overworking or a non-triggering of the pump may take place leading to under-dosing. The water pressure in the pump is also an important factor, as pressure drops in the farm's water system during peaks of water use by the animals (e.g. if a large amount of water is used to clean the buildings) may hinder the triggering of the dosing pump.

The SPC and product literature should contain clear instructions on the mixing of the veterinary medicinal product into feed or drinking water, taking into account the bodyweight range of animals to be treated, dispensing machines, and on the information required for veterinary medicinal products likely to be administered using special dosing equipment. However, in view of the large variety of dosing / mixing as well as watering / feeding equipment available, there are limitations on the details that can be included in the product information. Dosing equipment, which cannot guarantee homogeneous mixing of feed and veterinary medicinal product should be avoided.