FDA Requests Public Comments on the Use of Antimicrobials in Companion Animals

Response to the FDA Request for Comments from the
American Academy of Veterinary Pharmacology and Therapeutics (AAVPT)

(Due date June 16, 2022)

To electronically submit comments to the docket, visit [www.regulations.gov](http://www.regulations.gov) and type FDA-2021-N-1305 in the search box. To submit comments to the docket by mail, use the following address. Be sure to include docket number FDA-2021-N-1305 on each page of your written comments.

Dockets Management Staff
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852
1. Please describe if antimicrobial use practices in companion animals have impacted the development of antimicrobial resistance in bacterial pathogens of companion animals. Please provide information, data, and/or references to support your response.

Antimicrobial treatment to companion animals has likely impacted the development of resistance in bacterial pathogens in companion animals, but the extent of this effect is unknown. It has been difficult to directly link specific antimicrobial prescribing practices in companion animals to emergence of resistant bacteria.

Shedding of resistant bacteria associated with antibiotic administration can easily be demonstrated in research animals, but it is more difficult to identify the cause of resistant bacteria in the natural population.

Resistant strains of fecal bacteria are found more frequently in animals that have been previously been hospitalized and/or treated with antibiotics (Ogeer-Gyles et al., 2006; Hamilton et al., 2013; Gibson et al., 2008; Gibson et al., 2011; Espinosa-Gongora et al., 2020; Belas et al., 2014). However, it is more difficult to associate this resistance with one particular agent or class of drugs. Oral administration of a fluoroquinolone may be more likely to select for antibiotic-resistant *Escherichia coli* shedding in dogs (Gibson et al., 2011; Trott et al., 2004; Moreno et al., 2008); but, in experimental dogs, all classes of antibiotics studied (amoxicillin, amoxicillin-clavulanate, cephalaxin, fluoroquinolones, cefovecin) were capable of increasing drug resistant bacteria (particularly *E. coli*) in fecal samples. Even common antibiotics such as amoxicillin can produce these effects. Gronvold et al. (2010) showed that amoxicillin administration to dogs increased shedding of antibiotic resistant *E. coli* in feces. Cephalexin, a first-generation cephalosporin, selected for extended-spectrum cephalosporin-resistant bacteria in the feces of healthy dogs (Kimura et al., 2017).

Thus, it can be assumed from these reports that any antibiotic administration to pets can – at least transiently – increase the shedding of drug-resistant fecal bacteria; but it is uncertain if one antimicrobial or certain class of antimicrobial is more likely to be more responsible for this risk.

Most of the focus on fecal shedding of antibiotic resistant bacteria has been on *E. coli*. However, identification of methicillin-resistant *Staphylococcus* spp. in dogs are also associated with antibiotic use. The most common drug-resistant *Staphylococcus* isolated from pets is methicillin-resistant *S. pseudintermedius* (MRSP) (In older publications, referred to as *S. intermedius*.) Methicillin-resistant staphylococci were identified with increasing frequency through the 1990s and 2000s (Perreten et al., 2010), and are common in veterinary referral hospitals that receive patients previously treated with antibiotics. As reviewed by Harbarth & Samore (2008), in people there is a relationship...
between antibiotic use and MRSA rates, and this likely occurs in companion animals for methicillin-resistant staphylococci (Perreten et al., 2010). The drugs most often cited for driving MRSA acquisition and transmission in humans is the use of cephalosporins and fluoroquinolones (Harbarth & Samore, 2008; Dancer, 2008), both of which are frequently prescribed in small animals (Guardabassi et al., 2008). In addition to these antibiotics, there is also evidence that any prior antibiotic administration is a contributing factor for selection of MRSP in dogs, but no specific drug class was implicated (Schwarz et al., 2017; Beck et al., 2012; Eckholm et al., 2013; Rota et al., 2012; McCarthy et al., 2014; Nienhoff et al., 2011; Weese et al., 2012).

This is a complex issue and other risk factors also contribute to identification of antibiotic resistant bacteria in dogs. In addition to prior antibiotic exposure, as described above, raw meat diets were a significant risk factor for the prevalence in dogs (van den Bunt et al., 2020; Nilsson et al., 2015), as was housing conditions. Dogs from shelter/breeders were approximately three times more likely to have an ESBL- or AmpC-producing *E. coli* than dogs from private owners (Belas et al., 2014).

2. **Please describe if antimicrobial use practices in companion animals, including extralabel use, have impacted the development of antimicrobial resistance in human bacterial pathogens. If possible, please describe whether the impact was the result of direct or indirect contact between humans and the treated companion animals. Are there specific concerns about the development of antimicrobial resistance in human bacterial pathogens when particular antimicrobial drugs or drug classes are used in companion animals? Please provide information, data, and/or references to support your response.**

The antimicrobial use practices in U.S. companion animals were summarized in a recent review article (Papich, 2021) and available from surveys and studies that have examined prescribing practices among U.S. veterinarians (Bloch et al., 2022; Goggs et al., 2021; Robbins et al., 2020; Taylor et al., 2022). These reports show that both FDA-approved and extralabel antimicrobial agents are administered to companion animals. Extralabel use is common because antibiotics approved for companion animals are often approved with a narrow label indication (often skin, soft-tissue infections) but are used for many other indications. There are many unmet needs for the currently approved antimicrobials used in companion animals, and extralabel use is often a necessity, particularly in horses and cats.

The risk of antibiotic-resistant bacteria transferred from pets to people has been reviewed by Schwarz et al., (2017), Pomba et al., (2017), Weese et al (2015), and Guardabassi et al. (2004), among others. These reviews agree that more information is needed before making conclusions about these risks, or before limiting or restricting certain antibiotic classes.
Citations listed above provide evidence from clinical and experimental studies that antibiotic administration can increase fecal shedding of drug-resistant bacteria in companion animals. But the extent to which these bacteria impact the development of resistance in people is unknown. It is uncertain if transfer of resistant bacteria is a large problem, or simply that identical resistant strains can be found in both populations. As one group summarized, “In conclusion, the opinion that animal ESBL-producing *E. coli* is a major source of human infections is oversimplified, and neglects a highly complex scenario” (Ewers et al., 2012). These authors studied multiple ESBL and AmpC *E. coli* resistance genes across a range of geographical areas and concluded that the most important transmission of these resistant bacteria is person-to-person rather than primarily from animals.

There is some evidence that humans and pets in the same household share *E. coli* and its virulence and resistance genes. Virulence genes were identified in fecal *E. coli* from healthy dogs and their owners (Stenske et al., 2009); however, it was unusual for both dogs and their owners to have the same bacterial genes. Analysis of paired samples from dogs and their owners in the same households in Japan showed that transfer of *E. coli* between owners and their dogs had occurred within just 3/34 (8.8%) households (Harada et al., 2012). In a Swedish study, identical ESBL producing strains of Enterobacteriaceae were found on only 2 of 22 households studied (Ljungquist et al., 2016), which is a similar rate (approximately 10%) as the sharing of *E. coli* types reported by Stenske et al. (2009). In one study, simply owning a dog was not a risk factor for transfer of antibiotic-resistant bacteria in the Netherlands (van den Bunt et al., 2019), but in other studies, pet ownership was a risk factor for colonization with ESBL-producing *E. coli* (Meyer et al., 2012). In a follow-up study by the same group (van den Bunt et al., 2020), in only 5% of the households studied was there a match of ESBL producing strains of Enterobacteriaceae between people and dogs. They found the prevalence of ESBL producing strains of Enterobacteriaceae higher in dogs than in humans, but co-carriage in the same household was uncommon (5 out of 550 households). Cats had a low prevalence.

In another study, the predominant *E. coli* was from a sequence type that is uncommon in people and the extended-spectrum β-lactamase-producing isolates of human origin were uncommon in canine isolates (LeCuyer et al., 2018). The authors concluded that, although not common, there is support for occasional cross-host-species sharing of strains of *E. coli*.

Some studies have suggested a higher risk (Johnson et al., 2008). In a Michigan study, fecal samples were analyzed from pets and humans in households to determine the within-household transmission of *E. coli*. They found that within household sharing of *E.
coli was common (68%). They also found that 50% of the fecal E. coli from pets exhibit virulence characteristics suggesting pathogenic potential.

The risk of human-to-animal transmission of resistant bacteria may be as important as animal-to-human transmission. In a comparison of the phylogenomics of antibiotic-resistant Klebsiella pneumoniae originating from companion animals and humans in France, the authors found that resistant clones circulated between humans and animals (Garcia-Fierro et al., 2022), and human-associated resistant clones have the capacity to infect companion animals. Carbapenem-resistant bacteria were identified, but because carbapenems are not administered to companion animals in France, the authors concluded that antibiotic administration to companion animals was not the source of the resistant bacteria. Likewise, in a study from Finland, carbapenemase-producing E. coli were identified in dogs, but because carbapenems are not allowed to be used in pets in Finland, the authors concluded that the transmission likely occurred from human to dog (Grönthal et al., 2018).

Other studies have suggested the potential for antibiotic-resistant bacteria of human origin to transfer to pets in the same household. In a Swedish study, (Ljunquist et al., 2016), they found that identical strains of ESBL-producing E. coli were found in dogs and humans in the same household, but these resistant strains were not found in dogs if there was not a human carrier in the same household. They could not conclude whether transmission of antibiotic resistant E. coli occurred from humans to dogs or vice versa, but their evidence pointed to the source of these bacteria in people as being from another person in the same house. In their discussion, they summarized a range of studies and concluded “these studies indicate that humans carrying extended-spectrum resistant Enterobacteriaceae are more likely to share the bacteria with other household members than with dogs.”

These studies and others cited in reviews (Schwarz et al 2017; Pomba et al., 2017, Guardabassi et al., 2004), suggest a potential for transfer of resistant fecal bacteria – particularly E. coli – from animals to humans in the same household, as well as transfer from humans to pets and these bacteria can potentially cause extra-intestinal infections. (Reeves et al., 2011; Ukah et al, 2018).

What is missing from these reports of potential transfer of antibiotic resistant bacteria between humans and companion animals is the association with antibiotic administration. Shedding of resistant bacteria is possible regardless of whether the animals (or humans) were exposed to antimicrobial agents. A history of antibiotic exposure to pets (approved antibiotics or extralabel) in these reports was not explored as the source of antibiotic-resistant bacteria or their genes.
Methicillin-resistant *Staphylococcus* spp. was not included in the studies cited above. Although it is possible for pets to transmit MRSP to humans, infection is unlikely. There may be rare cases of *S. pseudintermedius* infections in people, but these are isolated reports. Therefore, infection with *S. pseudintermedius* is not an important risk for humans (summarized in other reviews cited above). Methicillin-resistant *Staphylococcus aureus* (MRSA) is typically human origin. Pets may be transient carriers of MRSA, but the source is most likely from an infected human or human carrier in the household. Therefore, there is a consensus among the reviews cited above that occurrence of MRSA in pets is most likely of human origin, but pets can serve as transient carriers that can potentially affect humans.

3. **How should the human medical importance of particular antimicrobial drugs or drug classes be considered when deciding whether, or under what conditions, to use such drugs in companion animals?**

We see little evidence in the surveys available, or prescribing habits of veterinarians, that the classification of an antimicrobial according to human medical importance has a bearing on the prescribing practices of companion animal veterinarians in the U.S. Many general practitioners may not be aware of the classification, such as that provided by the WHO. Antimicrobial decision making by companion animal veterinarians in the U.S. is guided by antimicrobial agent availability and cost.

Resources used for selection of antimicrobial agents by companion animal veterinarians are textbook chapters, popular websites, and handbooks for veterinary practitioners (Papich, 2021). Frequently-cited guidelines are those produced by the International Society of Companion Animal Infectious Disease (www.ISCAID.org). (Lappin et al., 2017; Weese et al., 2019; Hillier et al., 2014). These papers were developed as consensus guidelines by an international team of experts from various medical disciplines. They are often cited as a guide by other organizations, including the American Veterinary Medical Association, with links to these documents provided on their website (https://www.avma.org/resources-tools/one-health/antimicrobial-use-and-antimicrobial-resistance/antimicrobial-use-veterinary-practice). Antibiotics listed as “first tier” or preferred choice antimicrobials in these guidelines are frequently in the “critically important” or “highly important” category used by the WHO. Therefore, the experts that developed these documents did not consider human importance of the antimicrobial agent as a factor for listing the highest category recommendations.

As cited above, there is certainly evidence that any antibiotic, regardless of class, can increase the fecal shedding of drug resistant bacteria in animals. This has been observed
regardless of the medical importance of the antimicrobial agent in people. The fluoroquinolones and 3rd generation cephalosporins are listed by the WHO as “Critically Important – highest priority”. As cited above, there is evidence in dogs that administration of enrofloxacin increases fecal shedding of antibiotic resistant bacteria in dogs. However, antibiotics in the lower tier of “high priority” category (aminopenicillins, aminopenicillins with beta lactamase inhibitors) also increase the shedding of antibiotic resistant bacteria, including ESBL-producing strains of *Escherichia coli* in dogs. Likewise, antibiotics in the “high priority” class – 1st generation cephalosporins – also can select for antibiotic resistant bacteria in dogs. Damborg et al. (2011) showed that the 1st-generation cephalosporin cephalexin increased *CMY-2* resistance in *E. coli* of dogs. Kimura et al. (2017) showed that cephalexin increased the broad-spectrum cephalosporin resistant strains of *E. coli* in feces of dogs within 3 days of administration. This resistance persisted for 2 weeks.

We also are aware that there are approved antimicrobial agents approved to be “safe and effective” by the FDA for companion animals that are in the WHO critically-important highest priority category. These include fluoroquinolones (enrofloxacin, marbofloxacin, orbifloxacin, and pradofloxacin), and third-generation cephalosporins (cefovecin, ceftiofur, and cepodoxime). Likewise there are other approved antimicrobial agents in the critically-important high priority category (aminopenicillins, aminopenicillins with beta-lactamase inhibitors). These agents are approved and meet the FDA requirements for safety and efficacy in companion animals. It is apparent that the agency has not used these medically important categories when approving antibiotics for routine use in common infections in companion animals.

4. **How can CVM best engage with our stakeholders on promoting antimicrobial stewardship for companion animals? Examples of stakeholders include other government agencies, the pharmaceutical industry, public health organizations (both public and private entities), veterinary professional organizations, veterinary schools, veterinarians, pet owners, and veterinary diagnostic laboratories.**

A variety of approaches were recently cited in the National Academies report on antimicrobial resistance ([https://doi.org/10.17226/26350](https://doi.org/10.17226/26350)). In their report, they cited several recommendations. Among the recommendations, they recommended that the CVM use better tracking of antimicrobial consumption in animals, and support the development of antimicrobial susceptibility testing breakpoints (including funding as listed in Recommendation 5-3).

Susceptibility testing breakpoints are developed by the Clinical and Laboratory Standards Institute (CLSI) subcommittee on Veterinary Antimicrobial Susceptibility Testing (VAST) ([www.CLSI.org](http://www.CLSI.org)). This is a volunteer organization funded solely by sales of
their documents, without regulatory agency or industry financial support. The CLSI-VAST is the only standard setting committee in the world that has approved antimicrobial susceptibility testing breakpoints for bacteria isolated from animals. New antimicrobials approved by FDA should consider the CLSI approved breakpoint for label decisions, and update the information when revisions are available. We encourage the FDA to maintain their active participation in CLSI activities, including serving as members, advisors, and engaging in the CLSI working groups.

The American Veterinary Medical Association has the Committee on Antibiotics (CoA). The FDA-CVM already has active participation on this committee, which is an example of a beneficial current stakeholder partnership. Continued participation is encouraged. The FDA-CVM should also actively engage with the Animal Health Institute (AHI) to facilitate responsible new antimicrobial agent approvals, antimicrobial stewardship, and surveillance.

Outreach with professional societies that sponsor scientific conferences such as the American Academy of Veterinary Pharmacology and Therapeutics would be an effective tool to engage key partners in academia, industry and regulatory agencies.

5. **How can CVM encourage the development of antimicrobial drugs consistent with the principles of antimicrobial stewardship for the treatment of infectious diseases in companion animals for which there are no FDA-approved animal drugs?**

Development of new antimicrobial drugs is urgently needed for companion animals. As described in the review article cited earlier (Papich, 2021), in the last 10 years, there have been only two new antimicrobial agents approved by the FDA-CVM for companion animals. (Excluding topical products for ear infections.) In the last 24 years, only 6 new antimicrobials were approved. This does not include generic drugs. The only new products on the market are generic antimicrobial drugs that have Abbreviated New Animal Drug Applications (ANADA) because they are simply duplicates of earlier-approved drugs. For species like the horse or the cat where annual sales are modest, development costs for new antimicrobials may be prohibitive which leaves these species to rely on extra-label use of canine or human products. This is also true for less common infections in the dog.

A review of the older FDA-approved antimicrobials for companion animals is needed in order to be consistent with antimicrobial stewardship and accepted clinical use practice. Many of the older approved products are outdated for use in small animals. For example, penicillin G is approved for dogs and cats, but there are very few indications that are relevant to current clinical practice. The label for procaine penicillin G in dogs says simply “Treatment of infections caused by penicillin-sensitive organisms.” There are
not any susceptibility testing breakpoints for dogs to identify “sensitive organisms”, and many bacteria encountered in dogs are inherently resistant.

Chloramphenicol is still listed as an approved drug (Chloromycetin®), but not marketed in all forms (for example injectable formulations are rarely available), and usually generic human versions are used. The approved chloramphenicol canine label states for the “Oral treatment of bacterial pulmonary infections, bacterial infections of the urinary tract, bacterial enteritis, and bacterial infections associated with canine distemper caused by susceptible organisms.” These indications may be outdated – which is common for many of the other older agents – and there are no susceptibility testing standards available to identify the “susceptible organisms”.

FDA-approved antimicrobial agents also includes irrational combinations. The indication listed for combination product containing prednisolone plus novobiocin and tetracycline (Delta Albaplex®) is outdated and the pathogens listed are rarely susceptible to the agents on the label.

Products containing oxytetracycline, lincomycin, tetracycline, or spectinomycin are still listed as approved products by the FDA for companion animals, but are no longer used in small animals, or these formulations are not available in small animal forms. Erythromycin is listed as an approved drug for dogs, “For the treatment of bacterial pneumonia, upper respiratory infections (tonsillitis, bronchitis, tracheitis, pharyngitis, pleurisy), endometritis and metritis, and bacterial wound infections caused by Staphylococcus species, Streptococcus species, and Corynebacterium species, sensitive to erythromycin.” But, it is rarely used because the formulations are not available for veterinary use, and administration to dogs causes a high incidence of vomiting.

This short summary of examples of approved FDA products for companion animals shows that many drug labels should be updated, or the product approval withdrawn.

a. What bacterial diseases affecting companion animals are most in need of an FDA-approved animal antimicrobial drug?

The unmet needs for companion animal veterinarians were described in a review paper (Papich, 2021) and demonstrated by the extent of extralabel use of human medications or formulations approved in other animal species. There are several bacteria encountered in companion animal practice for which there are no approved antibacterial agents. Without an FDA approval, there are no tests of safety or efficacy, except for limited clinical reports and anecdotal observations. These infections include:
• Methicillin-resistant *Staphylococcus* spp.
• ESBL-producing Enterobacterales
• *Pseudomonas aeruginosa*
• *Enterococcus* species
• Vector-borne organisms

Body site indications on current labels are often limited to skin and soft-tissue infections for dogs and occasionally cats. Missing from modern labels are other indications encountered in veterinary medicine. These indications include:

• Bacterial pneumonia
• Vector-transmitted (blood borne) infections
• Bone (osteomyelitis) and joint infections
• Urinary tract infections
• Abdominal infections
• Intestinal infections

b. What safety and effectiveness study design considerations present challenges for developing antimicrobial drugs to address specific infectious diseases in companion animals (e.g., Lyme disease, sepsis, or osteomyelitis)? Are there alternative study designs that would address these challenges? If not, what role(s) could the stakeholder groups identified in question 4 play in developing such alternative study designs?

Because most of the antimicrobial agents are common classes of antimicrobials, the safety information in laboratory species is often available and in some cases, it may be published. For approved human antimicrobial agents, canine toxicology studies were sometimes performed to support the human development program, and this information can be useful for an animal-specific approval. These studies can help inform drug development for animals, but current US regulations require terminal target animal safety studies to be done in target species using the final dosing formulation at multiples of the use dose. If the final formulation is not used for the pivotal target animal safety study, bridging pharmacokinetic studies are required. For many of the most common classes of antimicrobial agents there are also pharmacokinetic-pharmacodynamic (PK-PD) guidelines to derive optimum dosages to reach targets of susceptible bacteria. However, for novel classes, PK-PD relationships are often poorly understood during the drug development process.

For many antimicrobial agents not approved for companion animals, there are consensus guidelines from experts, and published clinical data demonstrating
safety and efficacy. Consensus guidelines by ISCAID, described earlier, are examples of these resources.

There is a precedent that has been used to establish extralabel uses and doses for unapproved antibiotics in companion animals. The rationale and approach to developing clinical breakpoints for these unapproved drugs were described for some of these agents in published papers (Madsen et al., 2019; Maaland et al., 2013; Maaland et al., 2014; Papich & Lindeman, 2018; KuKanich et al., 2021). The clinical breakpoints for testing and guidelines for developing these criteria are available from CLSI (CLSI, 2020). Because there are no approved labels for these antibiotics, the CLSI committee used a consensus-driven process and evaluated existing pharmacokinetic, pharmacodynamic, and clinical use data to determine the breakpoint and clinical dosage.

Pivotal studies for clinical effectiveness of some companion animal antimicrobials in the US have required that two bacteriological cultures be obtained to establish efficacy. For certain indications and for less common isolates, this can be a significant challenge and may be impractical or not feasible. We encourage FDA-CVM to accept alternative study designs to establish efficacy.

Approvals of antimicrobial agents for companion animals in Europe and other countries is an underutilized source of safety and efficacy information that could support a U.S. approval. Some of these products have been on the market for several years, with substantial safety and efficacy experience in animals. The FDA-CVM should allow sponsors a pathway for an abbreviated approval process if the antimicrobial agent is already approved in another country in which there has been adequate evaluation of safety and efficacy. This would have significant animal welfare benefits as well.

We encourage the FDA to accept these, and other prior data as evidence for considering approval for animal use. In human medicine, there is the “Animal Rule” (found at https://www.fda.gov/emergency-preparedness-and-response/mcm-regulatory-science/animal-rule-summary). The Animal Rule regulations (21 CFR 314.600) are used to approve antimicrobial agents for human use for unmet needs (Allio, 2016; Bergman, 2009). Under this rule, the FDA can rely on the data from animal studies to provide substantial evidence of the effectiveness of these products when pathophysiological mechanism of toxicity are well-recognized across animal species, the clinical response is expected based on well-designed animal models, and a clear clinical endpoint has been established for predicting the response in humans. If the animal study
endpoint is clearly related to the desired benefit in humans, this information is considered for approval of the agent in people. The animal rule provides that information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans, which is generally the enhancement of survival or prevention of major morbidity. It is accepted that PK-PD principles and therapeutic targets can be translated across species (Ambrose et al., 2007). Clinical pharmacologists assist in translating pharmacology information to support approval of new agents for emerging infections, under the FDA’s Animal Rule (Bergman, 2009). We encourage the FDA-CVM to explore adopting a similar rule that would apply to new approvals of antibiotics for animals. This would allow sponsors to consider data from across animal species, or from human medicine, to approve new antimicrobials and use for animals. Allowing this rule to apply to animal health approvals would also positively impact animal welfare as this could reduce unnecessary animal testing.

c. **Are there specific infectious diseases in companion animals for which topical formulations of antimicrobial drugs (e.g., medicated shampoos, rinses, or ointments) may be a better alternative than using systemic antimicrobial drugs from the perspective of antimicrobial stewardship? If so, what role(s) could the stakeholder groups identified in question 4 play toward fostering the use of such topical antimicrobial formulations?**

Topical agents are used often by veterinarians for specific infections. These are primarily dermatology cases, and more specifically, infections of the external ear canal (otitis externa). There are several commercial products approved for otitis externa. Multiple products are available as shampoos, rinses, sprays and topical formulations for treating infections of the skin. Antimicrobial stewardship guidelines (Hillier et al., 2014) have strongly encouraged the use of these products, when it is feasible, to avoid use of systemic agents.

Despite the popularity and common recommendations to encourage topical agents for treating bacterial infections in companion animals, we are aware that many of these are not regulated by the FDA. Safety to the animal and pet owner is also a concern. Any topical agent can be licked off by the pet, resulting in systemic exposure. Topical medications applied to pets can be transferred to furniture, bedding, the owner’s hands, and other pets in the household. Thus, safety of these products is an often overlooked concern.
Regarding the role of the stakeholder groups, the FDA-CVM could encourage and support efforts by the CLSI to develop antimicrobial susceptibility testing interpretive categories for topical agents.

6. Labeling:
   a. What information on currently approved animal drug labeling helps the veterinarian prescribe or use an antimicrobial drug in a manner consistent with the principles of antimicrobial stewardship?

The most important information for the currently approved medications is the dose, frequency, and duration of treatment. However, the duration of treatment is often not listed on the label, and the dose may be outdated and inconsistent with modern clinical practice or PK-PD principles.

The dose and dose frequency listed must be accurate and current. As illustrated above by the lack of new approvals, most antimicrobial labels for companion animals are 30-40 years (or more) old. These were developed before modern identification and susceptibility-testing methods were developed. In many instances the dose on the label is not accurate, but veterinarians have learned to use the agent in an extralabel manner by searching other published sources.

Two of the most commonly administered oral antibiotics for dogs and cats are amoxicillin trihydrate and amoxicillin trihydrate-clavulanate potassium (both available as tablets and oral suspension for dogs and cats). The approved label indication for amoxicillin includes *E. coli*, and *Proteus mirabilis* in skin, soft-tissue, respiratory, and genitourinary tract infections (11 mg/kg twice daily for all indications). However, at the currently approved CLSI breakpoint for dogs, which is ≤ 0.25 µg/mL (CLSI, 2022), all wild-type strains of *E. coli* and *Proteus* will test resistant to amoxicillin unless the infection located in the lower urinary tract (Ludwig et al., 2016; Moyaert et al., 2017). Likewise, treatment of skin and soft-tissue infections caused by *E. coli* is one of the approved labeled indications for amoxicillin-clavulanate, but all the wild-type strains are resistant unless located in the lower urinary tract.

For some of the older antimicrobial agents approved for dogs and cats, the label simply says “for treatment of susceptible bacteria in [dogs or cats].” In addition to the outdated indications, the doses listed for many of the approved agents are not consistent with current PK-PD principles (Martinez, et al. 2012; Papich, 2014). Pharmacokinetic-pharmacodynamic concepts that are common today
were not known, or well understood, at the time these drugs received regulatory approval 30 or 40 years ago.

We now have information that exposure relationships measured as the area-under-the-curve to MIC ratio (AUC/MIC) time above MIC (T>MIC), or peak concentration / MIC ratio (C\text{MAX}/MIC) can be used to optimize doses and improve outcome (Martinez et al., 2012; Ambrose et al., 2007). There is not a regulatory requirement for new approved animal drugs to meet PK-PD targets in the United States. For example, the principle of attaining a AUC/MIC target ratio was not known when the currently available fluoroquinolones were approved for dogs. Higher doses administered once daily to achieve the highest AUC/MIC ratio is the accepted use of fluoroquinolones in current practice. Likewise, the approved label dose of gentamicin for dogs is 4.4 mg/kg twice daily initially, then once daily thereafter. It is now recognized that a dose of 10 mg/kg once daily that produces the optimum exposure relationship for aminoglycosides peak concentration/MIC ratio (either C\text{MAX}/MIC ratio, or AUC/MIC ratio) is a more effective dosing regimen (Drusano & Louie, 2011; USCAST, 2019; https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-aminoglycosides-animals-european-union-development-resistance-impact-human_en.pdf).

We believe that the FDA-CVM should undertake a thorough review of the current labels for older approved companion animal antimicrobial agents with a goal of bringing these labels up to modern standards to improve antimicrobial stewardship. Where labeling is found to be outdated, the approval should be updated or withdrawn. But, sponsors should be offered an abbreviated path to updating a label, without re-opening the entire label.

An approved generic label, approved under an Abbreviated New Animal Drug Application (ANADA), although may have been recently approved, contains the same outdated label as the pioneer product. This problem was highlighted in a commentary by Toutain and Bousquet-Melou (2013), in which they stated that flooding the market with generic and “me too” branded drugs has increased overall antibiotic consumption correlating with the emergence and spread of bacterial resistance to antibiotics. These authors argue that because of these disincentives and burdens, the only “new” antibiotics entering the veterinary market are generic copies of older drugs that have unfavorable pharmacokinetics and insufficient activity to treat current problems.

b. What additional information could be added to the approved animal drug labeling to improve the veterinarian’s ability to prescribe or use an
antimicrobial drug in a manner consistent with the principles of antimicrobial stewardship?

An accurate dose and frequency, based on pharmacokinetic-pharmacodynamic (PK-PD) principles, standard of care and use, and susceptibility profile should be provided. An accurate list of susceptible bacteria, based on wild-type distributions, would help empirical antibiotic prescribing.

The most recently approved antimicrobials for companion animals (although infrequent) have narrow indications on the label. Commonly, the indications are limited to skin and soft-tissue infections in dogs and cats. When extralabel information is available from reasonable and reliable sources to treat other infections, the sponsor, working with the FDA-CVM, should be allowed a mechanism to make this information available to veterinarians without fear of regulatory action from FDA for making extralabel claims. The only mechanism currently available to veterinarians is to search these indications through internet queries, literature review, or published guidelines. A vetted, evidence-based, and fact-checked database (perhaps an internet link) of available resources provided by the FDA-CVM could make this information easily accessible to veterinarians.

c. Is there a need for materials containing labeling information and/or information about antimicrobial stewardship that veterinarians could provide to the client when they prescribe an antimicrobial drug (e.g., client information sheets or other educational handouts)?

We are not convinced that materials with current labeling information or antimicrobial stewardship provided by the FDA would be helpful. If current labels are not accurate, this effort would not advance antimicrobial stewardship.

However, there are existing informational materials (posters, handouts, etc.) already available from other sources, such as AAHA, and the AVMA (see: https://www.avma.org/antimicrobial-use-veterinary-practice).

7. With respect to the use of antimicrobial drugs in companion animals, what other actions should CVM consider taking to foster greater antimicrobial stewardship?

One of the problems, as cited above, is that many of the older antimicrobial drug labels approved by the FDA are not current and do not meet the needs of veterinary practitioners. As described above, a review of the older antibiotic labels is needed.
The second concern, as cited above, is that of antimicrobial drug availability. There are not enough approved antimicrobial agents available to meet the needs of companion animal veterinarians, particularly for cats and horses. Shortages and high expense of human-approved antibiotics exacerbate the problem of availability. Some suggestions and possible remedies for this problem are provided above.

References Cited:


Clinical and Laboratory Standards Institute (CLSI). Development of Quality Control Ranges for Antimicrobial Agents Used in Veterinary Medicine. 4th ed. CLSI guideline VET02. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2020

CLSI. Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals. 6th ed. CLSI supplement VET01S. Clinical and Laboratory Standards Institute; forthcoming in 2022.


