CURRENT DRUG THERAPY for
SMALL ANIMAL PRACTICE

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STRATEGIES FOR SELECTING ANTIMICROBIAL AGENTS
FOR SMALL ANIMALS:
Empirical Antimicrobial Drug Choices

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Antibiotic therapy has made many advances that has given veterinary medicine a large number of effective drugs and provided pharmacokinetic and pharmacodynamic information to guide dosing. Improved techniques for bacterial identification and susceptibility testing have helped to provide information for the most appropriate drug selection.

BACTERIAL SUSCEPTIBILITY
If the bacteria are accurately identified, or predicted based on historical reference, antibiotic selection is simplified because the susceptibility pattern of many organisms is predictable.

Examples for Selecting Antibiotics Based on Identification:
What are the most predictable bacteria?
- *Streptococcus* (but not *Enterococcus*): susceptible to penicillin and penicillin derivatives.
- *Pasteurella multocida*: Common in wound and respiratory infections. Susceptible to most common antibiotics (penicillins, tetracyclines, trimethoprim-sulfonamides, cephalosporins).
- *Staphylococcus* species: Common in skin infections. Susceptible to $\beta$-lactamase resistant $\beta$-lactams (eg, a cephalosporin), or a drug combined with a $\beta$-lactamase inhibitor (eg, Clavamox).
- Anaerobic Bacteria: Common in penetrating wounds, dental infections, or abdominal infections. If the bacteria is an anaerobe, such as *Clostridium, Peptostreptococcus, Actinomyces, Fusobacterium, or Bacteroides* (including those of the *Bacteroides fragilis* group), predictable results can be attained by administering the following antibiotics: amoxicillin + $\beta$-lactamase inhibitor (Clavamox), chloramphenicol, metronidazole (Flagyl), clindamycin (Antirobe), or a second-generation cephalosporin: cefoxitin (Mefoxin). (*Not effective* against anaerobes are aminoglycosides, most fluoroquinolones, and trimethoprim-sulfonamides.)

What are the problem bacteria (susceptibility not predictable and a susceptibility test advised)?
- *Pseudomonas aeruginosa*
- Enterobacteriaceae (*E. coli, Klebsiella, Enterobacter, Proteus*)
- Methicillin-resistant *Staphylococcus* (eg, MRSP, MRSA)
- enterococci (*Enterococcus faecium, Enterococcus faecalis*)

Therapy for the gram-negative enteric bacterial infections can be initiated with a fluoroquinolone (enrofloxacin, ciprofloxacin, marbofloxacin, pradofloxacin, or orbifloxacin), an extended-spectrum cephalosporin (ceftiofur, ceftazidime, cefotaxime, cefpodoxime proxetil), or
an aminoglycoside (gentamicin, amikacin). However, if initial treatment is not effective, guidance from a susceptibility test is advised. For *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus*, or *Enterococcus* spp, a susceptibility test is always advised because susceptibility is unpredictable. Always use CLSI standards for susceptibility testing (CLSI, 2013, 2015).

**Observations Regarding *Staphylococcus* in Small Animals:**

*Staphylococcus* isolated from small animals is most likely to be *S. pseudintermedius* rather than *S. aureus*. Note that previously identified *Staph intermedium* probably have been misidentified and are now referred to as *S. pseudintermedius* by many laboratories. This species of *Staphylococcus* will usually have a predictable susceptibility to β-lactamase resistant β-lactam antibiotics such as amoxicillin combined with a β-lactamase inhibitor (Clavamox), or first-generation cephalosporin such as cephalexin or cefadroxil, or the third-generation cephalosporins, cefovecin (Convenia) and cefpodoxime (Simpecif). *Staphylococcus* also is susceptible to oxacillin and dicloxacillin but these are not used as commonly in small animal medicine. Most *staphylococci* are also sensitive to fluoroquinolones. The majority of staphylococci are sensitive to lincomamides (clindamycin, lincomycin), trimethoprim-sulfonamides, or erythromycin, but resistance can occur in as high as 25% of the cases. Emergence of methicillin-resistant *Staphylococcus* in companion animals has complicated treatment because this strain is now encountered with more frequency (Bond & Loeffler, 2012; Frank & Loeffler, 2012; Papich 2012; Kadlec & Schwarz, 2012).

**Problem, or Resistant Bacteria**

If the organism is *Pseudomonas aeruginosa*, *Enterobacter*, *Klebsiella*, *Escherichia coli*, or *Proteus*, resistance against many common antibiotics is possible and a susceptibility test is advised. For example, bacteria of the Enterobacteriaceae (eg, *E. coli*) are resistant to commonly used agents such as 1st generation cephalosporins, aminopenicillins, amoxicillin-clavulanate, and tetracyclines. Based on data from surveillance studies, for initial therapy we usually expect the gram-negative enteric bacteria to be susceptible to fluoroquinolones and aminoglycosides. If the organism is from a urine culture, higher breakpoints may be used and these isolates may be susceptible to cephalexin or amoxicillin-clavulanate. An extended-spectrum cephalosporin (second- or third-generation cephalosporin) usually is active against enteric-gram negative bacteria, but will not be active against *Pseudomonas aeruginosa*. If the organism is a *Pseudomonas aeruginosa*, inherent resistance against many drugs is common, but it may be susceptible to fluoroquinolones, aminoglycosides, or extended-spectrum penicillin such as piperacillin-tazobactam. When administering a fluoroquinolone to treat *Pseudomonas aeruginosa* the high-end of the dose range is suggested. Of the currently available fluoroquinolones, (human or veterinary drugs) ciprofloxacin is the most active against *Pseudomonas aeruginosa*, followed by marbofloxacin, enrofloxacin, and orbifloxacin (Rubin et al, 2008).

**PENETRATION TO THE SITE OF INFECTION**

For most tissues, antibiotic drug concentrations in the serum or plasma approximate the drug concentration in the extracellular space (interstitial fluid). This is because there is no barrier that impedes drug diffusion from the vascular compartment to extracellular tissue fluid (Nix et al, 1991). There is really no such thing as “good penetration” and “poor penetration”
when referring to antibiotics in most tissues. Pores (fenestrations) or microchannels in the endothelium of capillaries are large enough to allow drug molecules to pass through unless the drug is restricted by protein binding in the blood. If adequate drug concentrations can be achieved in plasma, it is unlikely that a barrier in the tissue will prevent drug diffusion to the site of infection as long as the tissue has an adequate blood supply. Drug diffusion into an abscess or granulation tissue is sometimes a problem because in these conditions drug penetration relies on simple diffusion and the site of infection lacks adequate blood supply.

In some tissues a lipid membrane (such as tight junctions on capillaries) presents a barrier to drug diffusion. In these instances, a drug must be sufficiently lipid-soluble, or be actively transported across the membrane in order to reach effective concentrations in tissues. These tissues include: the central nervous system, eye, and prostate. A functional membrane pump (p-glycoprotein) also contributes to the barrier. There also is a barrier between plasma and bronchial epithelium (blood:bronchus barrier). This limits drug concentrations of some drugs in the bronchial secretions and epithelial fluid of the airways. Lipophilic drugs may be more likely to diffuse through the blood-bronchus barrier and reach effective drug concentrations in bronchial secretions.

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<tr>
<th>Tissue</th>
<th>Barrier</th>
<th>Drugs that will penetrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Blood-Brain Barrier</td>
<td>Fluoroquinolones (minimal), Chloramphenicol (minimal), trimethoprim, 3rd-generation cephalosporins (some), metronidazole.</td>
</tr>
<tr>
<td>Eye</td>
<td>Blood-Ocular Barrier</td>
<td>Tetracyclines, Fluoroquinolones, Chloramphenicol</td>
</tr>
<tr>
<td>Prostate</td>
<td>Blood-Prostate Barrier</td>
<td>Trimethoprim, Fluoroquinolones, Macrolides* (*macrolides have a narrow spectrum that may not be effective)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Blood-Bronchus Barrier (epithelial lining fluid)</td>
<td>Macrolides, tetracyclines, fluoroquinolones, chloramphenicol</td>
</tr>
<tr>
<td>Intracellular</td>
<td>Intracellular sites</td>
<td>Tetracyclines, azithromycin, fluoroquinolones</td>
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</table>

**LOCAL FACTORS THAT AFFECT ANTIBIOTIC EFFECTIVENESS**

Local tissue factors may decrease antimicrobial effectiveness. For example, pus and necrotic debris may bind and inactivate vancomycin or aminoglycoside antibiotics (gentamicin or amikacin), causing them to be ineffective. Cellular material also can decrease the activity of topical agents such as polymyxin B. Foreign material in a wound (such as material surgically implanted) can protect bacteria from antibiotics and phagocytosis by forming a biofilm (glycocalyx) at the site of infection (Habash & Reid, 1999; Smith 2005). Cellular debris and infected tissue can inhibit the action of trimethoprim-sulfonamide combinations through the secretion of thymidine and PABA, both known to be inhibitors of the action of these drugs. This may explain why trimethoprim-sulfonamide combinations have not been effective in some infected tissues. Cations can adversely affect the activity of antimicrobials at the site of infection. Two important drug groups diminished in activity by cations such as Mg++, Al³⁺, Fe³⁺, and Ca²⁺ are fluoroquinolones and aminoglycosides. (Cations such as magnesium, iron, and aluminum also can inhibit oral absorption of fluoroquinolones.)

An acidic environment of infected tissue may decrease the effectiveness of clindamycin, erythromycin, fluoroquinolones, and aminoglycosides. Penicillins and tetracycline activity is not
affected as much by tissue pH, but hemoglobin at the site of infection will decrease the activity of these drugs. An anaerobic environment decreases the effectiveness of aminoglycosides because oxygen is necessary for drug penetration into bacteria. As mentioned previously, an adequate blood flow is necessary to deliver an antibiotic to the site of infection. Effective antibacterial drug concentrations may not be attained in tissues that are poorly vascularized (eg, extremities during shock, sequestered bone fragments, and endocardial valves).

PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) OPTIMIZATION OF DOSES

To achieve a cure, the drug concentration in plasma, serum, or tissue fluid should be maintained above the minimum inhibitory concentration (MIC), or some multiple of the MIC, for at least a portion of the dose interval. Pharmacokinetic-pharmacodynamic (PK-PD) relationships of antibiotics explain how these factors can correlate with clinical outcome (Drusano 2007). The parameters that define antibacterial activity are taken from the shape of the plasma concentration vs time profile. The $C_{\text{MAX}}$ is simply the maximum plasma concentration attained during a dosing interval. The $C_{\text{MAX}}$ is related to the MIC by the $C_{\text{MAX}}: \text{MIC}$ ratio. The AUC is the total area-under-the-curve. The AUC for a 24 hour period is related to the MIC value by the AUC:MIC ratio. The time-above-MIC is the relationship of time to MIC measured in hours ($T > \text{MIC}$).

Rather than bacteriostatic or bactericidal, drugs are now more frequently grouped as either concentration-dependent or time-dependent in its action. If concentration-dependent, one should administer a high enough dose to maximize the $C_{\text{MAX}}: \text{MIC}$ ratio or AUC:MIC ratio. If time-dependent, the drug should be administered frequently enough to maximize the $T > \text{MIC}$. For some of these drugs the AUC/MIC also predicts clinical success. Examples of how these relationships affect drug regimens are described below:

Aminoglycosides

Aminoglycosides (eg, gentamicin, or amikacin) are concentration-dependent bactericidal drugs, therefore the higher the drug concentration, the greater the bactericidal effect. An optimal bactericidal effect occurs if a high enough dose is administered to produce a peak of 8-10x the MIC. This can be accomplished by administering a single dose once daily (Drusano et al, 2007). This regimen is as effective and less nephrotoxic, than lower doses administered more frequently. Our current regimens in small animals employ this strategy. For example, a once daily dose for gentamicin is 5-8 mg/kg for cats, and 10-14 mg/kg for dogs, once daily.

Fluoroquinolones

For the fluoroquinolone antimicrobials, as reviewed by Wright et al (2000) and Papich & Riviere (2009) investigators have shown that either the peak plasma concentration above
bacterial minimum inhibitory concentration (MIC), also known as the C_{MAX}:MIC ratio, or the total AUC above the MIC (also known as the AUC:MIC ratio), may predict clinical cure in studies of laboratory animals, and in a limited number human clinical studies. There are no published studies involving dogs or cats that indicate which of these parameters are the best predictor of clinical cure, or what the respective target ratios might be. Therefore, the optimum value for these surrogate markers has not been determined for infections in dogs or cats. However, derived from other studies, a C_{MAX}:MIC of 8-10, or a AUC:MIC of greater than 100-125 have been associated with a cure. As reviewed by Wright et al (2000), for some clinical situations AUC:MIC ratios as low as 30-55 for a clinical cure, because the studies that determined higher ratios involved critically ill human patients or immunosuppressed animals. This difference may also be organism specific.

Wild-type strains of many bacteria from small animals are expected to have an MIC for fluoroquinolones in the range of 0.125 mg/mL, (+/− one dilution). Using this value for MIC, the administration of the lowest label dose of any of the currently available fluoroquinolones usually meets the goal of a C_{MAX}:MIC ratio or a AUC:MIC ratio in the range cited above. To take advantage of the wide range of safe doses for fluoroquinolones, low doses have been administered to treat susceptible organisms with low MIC, such as *E. coli* or *Pasteurella*. But, for bacteria with a higher MIC, (for example gram-positive cocci) a slightly larger dose can be used. To achieve the necessary peak concentration for a bacteria such as *Pseudomonas aeruginosa* that usually has the highest MIC among susceptible bacteria, the highest dose within a safe range is recommended. Bacteria such as streptococci and anaerobes are more resistant and even at high doses, a sufficient peak concentration or AUC:MIC ratio will be difficult to achieve.

**Beta-lactam antibiotics**

β-lactam antibiotics such as penicillins, potentiated-aminopenicillins, and cephalosporins are slowly bactericidal. Their concentration should be kept above the MIC throughout most of the dosing interval (long T>MIC) for the optimal bactericidal effect (Turnidge 1998). Dosage regimens for the β-lactam antibiotics should consider these pharmacodynamic relationships. Therefore, for treating serious infections particularly those caused by gram-negative bacteria, a regimen administered frequently (3 to 4 times per day) is more effective than administration less frequently. Some long-acting formulations have been developed to prolong plasma concentrations. Some of the third-generation cephalosporins have long half-lives and less frequent regimens have been used for some of these drugs (for example cepodoxime proxetil, cefovecin [Convenia], and ceftiofur). Gram-positive organisms are more susceptible to the β-lactams than are gram-negative bacteria and lower doses and longer intervals are possible when treating these bacteria. Additionally, because antibacterial effects occur at concentrations below the MIC (post antibiotic effect or PAE) for *Staphylococcus*, longer dose intervals may be possible for staphylococcal infections. For example, cephalixin or amoxicillin-clavulanate have been used successfully to treat staphylococcal infections when administered just twice-daily. Cefpodoxime proxetil (Simplicef) is effective for once-daily administration, which is due to both high activity (low MIC values) and a longer half-life compared to other cephalosporins. Cefovecin (Convenia) has a very long half-life of 5-7 days in dogs and cats and has been successfully administered as a single dose, or once every 14 days (8 mg/kg SC).

**Other Time-Dependent Drugs**

The drugs such as tetracyclines, macrolides (erythromycin derivatives), sulfonamides,
Lincosamides (lincomycin and clindamycin), and chloramphenicol derivatives act in a time-dependent manner against most bacteria. Either time above MIC (T>MIC) or total drug exposure, measured as AUC/MIC, has been used to predict clinical success for these drugs.

The time-dependent activity is demonstrated by studies in which effectiveness is highest when the drug concentrations are maintained above the MIC throughout the dosing interval. Drugs in this group should be administered frequently to achieve this goal. However, a property of some is that they persistent in tissues for a prolonged time, which allows infrequent dosing intervals. The macrolide derivative azithromycin (Zithromax) has shown tissue half-lives as long as 70-90 hours in cats and dogs, permitting infrequent dosing. Tissue concentrations of trimethoprim-sulfonamides persist long enough to allow once-daily dosing for some infections. Most published dosage regimens are designed to take the pharmacokinetic properties of these drugs into account.

**SUGGESTED EMPIRICAL TREATMENT BASED ON TISSUE SITE**

On the following table is a list that includes some (but not all) possible choices for common infections encountered in veterinary medicine. In this list the “first choice” is a drug with a high likelihood of success, low expense and few risks. If the first choice has not been effective, or if patient factors preclude using the first choice (eg, allergy) the alternate choice should be considered.

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<th>First choice drugs</th>
<th>Alternate choice drugs</th>
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<tr>
<td>Skin: pyoderma or other skin infection</td>
<td>Amoxicillin-clavulanate Cephalosporin</td>
<td>Trimethoprim-sulfonamides Fluoroquinolone Clindamycin</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Cephalosporin Amoxicillin / Ampicillin Amoxicillin-clavulanate</td>
<td>Trimethoprim-sulfonamides Fluoroquinolone Tetracycline</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Amoxicillin-clavulanate Fluoroquinolone Cephalosporin</td>
<td>Macrolide (erythromycin, azithromycin) Tetracycline (doxycycline, minocycline) Aminoglycosides (amikacin, gentamicin) Chloramphenicol Trimethoprim-sulfonamide (for some organisms) Extended-spectrum cephalosporin #</td>
</tr>
<tr>
<td>Septicemia</td>
<td>Amoxicillin-clavulanate Cephalosporin Fluoroquinolone</td>
<td>Aminoglycoside Extended-spectrum cephalosporin Piperacillin-tazobactam</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>Cephalosporins Amoxicillin-clavulanate</td>
<td>Trimethoprim-sulfonamides Clindamycin Extended spectrum cephalosporins Fluoroquinolones</td>
</tr>
</tbody>
</table>

+ Fluoroquinolone = enrofloxacin, difloxacin, marbofloxacin or orbifloxacin

# Extended spectrum cephalosporin = 2nd – or 3rd-generation drugs (eg, cefotetan, cefotaxime, cefpodoxime).
REFERENCES CITED AND ADDITIONAL READING


ANTIBIOTIC THERAPY
TREATING AND MANAGING ANTIMICROBIAL RESISTANT INFECTIONS

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*STAPHYLOCOCCUS SPECIES IN SMALL ANIMALS*

Staphylococcus isolated from small animals is most likely to be *S. pseudintermedius* rather than *S. aureus*. (Note that previously identified *Staph intermedius* probably have been misidentified and are now referred to as *S. pseudintermedius* by many laboratories. Other *Staphylococcus* species have also been reported – some of these being coagulase-negative *Staphylococcus*. When infection is caused by a typical wild-type strain, *Staphylococcus pseudintermedius* has a predictable susceptibility to β-lactamase resistant β-lactam antibiotics such as amoxicillin combined with a β-lactamase inhibitor (Clavamox), a first-generation cephalosporin such as cephalaxin or cefadroxil, or the third-generation cephalosporins, cefovecin (Convenia) and cefpodoxime (Simplicef). Susceptible strains of *Staphylococcus* also are susceptible to oxacillin and dicloxacillin but these are not used as commonly in small animal medicine. Historically, *Staphylococcus pseudintermedius* retained susceptibility to commonly available drugs (Lloyd, et al, 1996; Pinchbeck et al, 2007). In addition to the β-lactamase stable β-lactam antibiotics listed above (cephalosporins and amoxicillin-clavulanate), most wild type strains are also susceptible (*in vitro*) to fluoroquinolones, lincosamides (clindamycin, lincomycin), trimethoprim-sulfonamides, or macrolides (erythromycin).

However, the incidence of methicillin-resistance among *S. pseudintermedius* has dramatically increased. The methicillin-resistant *Staphylococcus* spp. (including *Staph. pseudintermedius*) are isolated with increased frequency from animals with skin infections (Perreten et al, 2010; Bond & Loeffler, 2012; Weese, 2005; Weese & van Duijkeren, 2010). These infections are not confined to dermatology. Orthopedic surgeons have also encountered these strains as a cause of post-surgical orthopedic infections.

*Methicillin-Resistant Staphylococcus*

The most important resistance mechanism for *Staphylococcus* is methicillin-resistance. Methicillin-resistance presents a problem for veterinarians because, in addition to resistance to β-lactam antibiotics, most of these bacteria are also multi-drug resistant. The increased emergence of methicillin-resistant *Staphylococcus* in animals has been discussed in several publications and review articles (Bond & Loeffler, 2012; van Duijkeren, et al, 2011). The presence of the mecA gene and methicillin resistance appears to be increasing in veterinary medicine based on the number of reports in the last several years. Methicillin-resistant *Staphylococcus aureus* (MRSA) in human hospitals and in the community has reached alarming rates.

Staphylococcal methicillin resistance is caused by acquisition of the mecA gene, which encodes an altered penicillin-binding protein (PBP-2a). Although oxacillin is used as the surrogate for testing, these are referred to as methicillin-resistant staphylococci – MRS (Gortel et al, 1999; Deresinski 2005; Jones et al, 2007; Bemis et al, 2006). Methicillin has replaced oxacillin for testing in laboratories and resistance to oxacillin is equivalent to methicillin-resistance. If the pathogen is *Staphylococcus aureus* the term methicillin-resistant *S. aureus* (MRSA) can be applied. But *S. aureus* is an infrequent pathogen in dogs, and occasionally in cats.

If staphylococci are resistant to oxacillin or methicillin, they should be considered resistant to all other β-lactams, including cephalosporins and amoxicillin-clavulanate (eg, Clavamox), regardless of the susceptibility test result. Adding a β-lactamase inhibitor will not overcome methicillin resistance. Unfortunately, these bacteria often carry co-resistance to many other non-β-lactam drugs, including lincosamides (clindamycin, lincomycin), fluoroquinolones, macrolides (erythromycin), tetracyclines, and trimethoprim-sulfonamides. In the report by Bemis et al (2009), more than 90% of the methicillin-
resistant isolates of *S. pseudintermedius* also were resistant to > 4 other drugs. The cause of the increased frequency of resistance has not been identified with certainty. Use of fluoroquinolones and cephalosporins has been linked to emergence of resistance of methicillin-resistant staphylococci in people (Dancer, 2008; Harbarth & Samore, 2008). In small animals, use of specific drugs have not been associated with methicillin-resistance, but administration of any antimicrobial within 30 days of prior to infection was identified as a risk factor in one study (Weese, et al, 2012). Dogs can carry these resistant strains for a long time after resolution of a clinical infection (Windahl, et al, 2012).

**ANTIBIOTIC CHOICES FOR METHICILLIN-RESISTANT STAPHYLOCOCCUS**

Because susceptibility to non-β-lactam antibiotics is unpredictable, a susceptibility test is needed to identify the most appropriate drug to administer for these infections. Susceptibility testing should always use CLSI standards (CLSI, 2013, 2015). Chloramphenicol, tetracyclines, aminoglycosides (gentamicin) and rifampin, are drugs to consider for these infections if a susceptibility test can confirm activity. These drugs are discussed in more detail below, but not all of these drugs are allowed in some countries, or there may be limitations on availability. Unlike the human strains of community-acquired *Staphylococcus aureus* (CA-MRSA), the veterinary strains of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) are usually not susceptible to trimethoprim-sulfonamides, clindamycin, or fluoroquinolones (Perreten et al, 2010; Bemis et al, 2009). However, a susceptibility test should always be used to confirm whether or not these drugs may have activity against isolates from animals. Topical drugs also should be considered for treatment of localized infections and shampoos and other topical treatment can be used to limit the need for antibiotics.

**Rifampin (Rifampicin)**

Rifampin, also known in some countries as rifampicin, is an older antibiotic that has seen recent interest because of its activity against methicillin-resistant *Staphylococcus*. Equine practitioners have been familiar with rifampin for many years because of its use for treating infections caused by *Rhodococcus equi*. Now, small animal veterinarians are becoming more familiar with this antibiotic because of its activity against methicillin-resistant *Staphylococcus*. This antibiotic may be new to small animal veterinarians, but was originally discovered in the pine forests of France in the 1950s and was introduced into clinical medicine in the 1960s. Rifampin is the USP official name, and Rifampicin is the INN and BAN name; both names are synonymous. Rifamycin and rifabutin are structurally similar antibiotics — all in the group of rifamycins – but are not identical.

Rifampin is a bactericidal antibiotic that acts by inhibiting bacterial RNA polymerase. It is highly lipophilic, with a high volume of distribution and good absorption in practically all animal species studied. The intracellular penetration has made this drug valuable for treating intracellular bacteria in people and animals, including *Mycobacterium* and *Rhodococcus equi*. Rifampin is active against most strains of methicillin-resistant *Staphylococcus pseudintermedius*, (Perrepet et al, 2010), although resistance among canine isolates has been identified (Kadlec et al, 2011). Rifampin has been effective for treatment of canine pyoderma caused by *Staphylococcus pseudintermedius* at a dose of 5 mg/kg once daily for 10 days (Senturk et al, 2005). Another study had success with 5-11 mg/kg twice daily (DeLuria, et al, 2012). A dose of 10 mg/kg per day, usually split into two doses, 12 hours apart has been recommended (Papich 2016). Higher doses recommended in some veterinary formularies are discouraged.

Resistance occurs through mutations and clonal spread of a resistant strain. To reduce rate of mutation, combination therapy with other agents has usually been recommended in human guidelines (Liu et al, 2011), as was the recommendation from a veterinary study (Kadelec et al 2011). However, in a review of the evidence from clinical trials of eradication of *S. aureus* in humans, rifampin was an effective agent for eradication of *S. aureus*, whether administered as monotherapy or as a combination (Falagas et al, 2007). Addition of a second antibiotic did not seem to confer additional effectiveness to rifampin monotherapy for eradication of methicillin-resistant *Staphylococcus*. As the authors pointed out, “…the decrease in the development of resistance to rifampin with the use of combination therapy has
been mainly validated in clinical situations in which long-term therapy with rifampin was necessary (eg, tuberculosis) and may not be the same for short-term treatment for \textit{S. aureus} carriage eradication”.

Rifampin is a strong inducer of drug metabolizing enzymes (Reitman et al, 2011). Induction can significantly increase the metabolism and clearance of other co-administered drugs that are affected by these proteins. The consequence of induction is diminished effect of the co-administered drug and may require a higher dose or more frequent administration. For example, rifampin co-administration significantly affects the exposure to prednisolone (Lee, et al, 1993). In people 4 weeks is required for full recovery of the rifampin effect after discontinuation (Reitman et al, 2011). Rifamin may also have dual effects in which it can be an inhibitor of intestinal transport, as well as an inducer of other proteins.

Adverse effects, which are associated with high doses, include liver injury and GI disturbance. A study reported in 2012 indicated that among dogs treated with 5-11 mg/kg twice daily, there were elevations in liver enzymes in most dogs, and GI and hepatic abnormalities in some dogs (De Lucia et al, 2012). In a study (Bajwa et al, 2013) 16% of dogs had adverse events associated with rifampin, and 26% had elevations in liver enzymes. In dogs, hepatotoxicosis is the most common adverse reaction and 20%-25% of dogs receiving 5-10 mg/kg develop increases in liver enzymes and some develop hepatitis. To avoid adverse effects, it is recommended not to exceed a dose of 10 mg/kg per day. Rifampin has an unpalatable taste. It also may produce a discoloration (orange-red color) to the urine, tears, and sclera. Owners should be warned of this possibility.

**Tetracyclines (Doxycycline, Minocycline)**

Occasionally, some methicillin-resistant \textit{Staphylococcus pseudintermedius} are susceptible to tetracyclines (Maaland et al, 2013; Hnot et al, 2015). Because the choices of oral tetracyclines are limited for small animals, either doxycycline or minocycline should be used. The human susceptibility testing breakpoint of \( \leq 4 \mu g/mL \) is too high for testing bacteria from animals. The doxycycline breakpoint has been revised for animals and is now \( \leq 0.12 \mu g/mL \) for testing doxycycline, and is \( \leq 0.5 \mu g/mL \) for testing minocycline (CLSI, 2015).

Doxycycline administration to small animals is usually accomplished with tablets (50, 75, 100 mg) or oral suspension (5 mg/mL suspension and 10 mg/mL syrup) at doses of 5 mg/kg twice daily. When compounded in a suspension in a more concentrated form (either 33.3 mg/mL or 167 mg/mL) in an aqueous-based vehicle, the formulation was stable for 7 days, but declined to only 20% of the initial potency at 14 days.

Adverse effects from doxycycline have been rare. Renal injury, intestinal disturbances, or hepatic injury is uncommon. Unlike other tetracyclines, it has little affinity for calcium and does not cause the dental enamel discoloration known for other tetracyclines, and does not chelate with calcium-containing oral products. It has been mixed with chocolate milk for administration to children with no interference with absorption.

Minocycline also should be considered when a susceptibility test indicates that the \textit{Staphylococcus} is susceptible to a tetracycline, and especially when the test shows a MIC \( \leq 0.5 \mu g/mL \). Minocycline is a reasonable substitute for doxycycline and a dose of 5 mg/kg oral, twice daily will reach therapeutic targets. Toxicology studies have indicated a good safety profile and was well tolerated at doses recommended for clinical use. Recent studies in dogs indicate that some MRSP isolates may be susceptible to minocycline, yet resistant to other tetracyclines (ie, those that carry the \textit{TetK} resistance). If used in cats, the dose of 8.8 mg/kg once daily (or 50 mg per cat once daily) will reach therapeutic targets.

**Chloramphenicol**

Chloramphenicol was discovered in 1947. It was in popular use decades ago, but gradually replaced by safer alternatives. The small animal formulation is approved by the FDA (Chloromycetin) but is not actively marketed. The use of chloramphenicol diminished in the 1970s and 80s because other active and safer drugs became available. Chloramphenicol has the disadvantage of a narrow margin of safety in dogs and cats, and necessity of frequent administration in dogs to maintain adequate concentrations (three or four times daily oral administration). These disadvantages still exist, but the
activity of chloramphenicol against bacteria that are resistant to other oral drugs (eg, staphylococci and enterococci) has created increased use of chloramphenicol in recent years.

Chloramphenicol has FDA approval in the U.S. for use in dogs as 100, 250, and 500 mg tablets (Chloromycetin). The oral suspension of chloramphenicol palmitate is rarely available. Although chloramphenicol is poorly soluble (< 5 mg/mL), the poor solubility does not interfere with oral absorption. Chloramphenicol is absorbed orally with- or without food (except some formulations in cats). Tablets and capsules have similar oral absorption in dogs.

Plasma concentrations of chloramphenicol were published in several studies. Using Monte Carlo Simulations and the pharmacokinetic parameters listed above, at a dose of 50 mg/kg PO to dogs, every 8 hours there is a 90% probability that the plasma concentrations are above the MIC of 8 µg/mL for 25% of the dosing interval. Because this dose appears to have clinical efficacy in dogs, plasma concentrations may need to be above the MIC for only a short time during the dosing interval to be effective, or chloramphenicol may be more bactericidal against \textit{Staphylococcus} than previously thought.

Significant disadvantages of chloramphenicol are adverse effects and drug interactions. As cited above, chloramphenicol has a narrow margin of safety. High doses easily produce toxicity in dogs (Clark, 1978). Gastrointestinal disturbances are rather common. A decrease in protein synthesis in the bone marrow may be associated with chronic treatment. This effect is most prominent in cats, but can occur in any animals. Idiosyncratic aplastic anemia has been described only in humans. The incidence is rare but the consequences are severe because it is irreversible. Because exposure to humans can potentially produce severe consequences, veterinarians should caution pet owners about handling the medications, and to ensure that accidental exposure does not occur at home (eg, to young children).

An important adverse effect that has emerged with recent experience treating dogs is a syndrome of ataxia, and hind-limb weakness that has been attributed to a peripheral neuropathy. This problem appears to be more common in large breed dogs. It is reversible if the medication is discontinued.

Chloramphenicol is notorious for producing drug interactions. Chloramphenicol is a Cytochrome P450 - CYP2B11 inhibitor, and possibly other enzymes, in dogs (Aidasani et al, 2008; KuKanich et al 2011). Therefore, chloramphenicol can decrease the clearance of other drugs that are metabolized by the same metabolic enzymes. Chloramphenicol will inhibit the metabolism of opiates, barbiturates, propofol, phenytoin, salicylate, and perhaps other drugs (KuKanich et al, 2011; Akesson & Linero PEM, 1982; Sanders et al, 1979; Adams & Dixit 1970).

\textbf{Aminoglycosides (Gentamicin)}

Aminoglycosides – specifically gentamicin and amikacin – have \textit{in vitro} activity against \textit{Staphylococcus}, including methicillin-resistant strains of \textit{Staphylococcus pseudintermedius}. Amikacin also has good activity, but it is less available commercially, is more expensive, and clinical advantages over gentamicin for \textit{Staphylococcus} spp. treatment are not apparent, even though some strains may show \textit{in vitro} susceptibility to amikacin but resistant to gentamicin (Gold et al, 2014). The disadvantage of gentamicin administration is the need for daily injection, the potential for kidney injury in animals with prolonged use, or high risk of toxicity if animals have evidence of kidney disease.

Gentamicin sulfate has been administered IV, IM, or SC. Because it is a water-soluble formulation, it is well absorbed from SC and IM injection sites, although these routes may produce pain in some patients. In-hospital the route is usually IV, but owners have been trained to administer SC or IM injections at home.

Once-daily regimens are used based on pharmacokinetic-pharmacodynamic principles (Drusano \textit{et al}, 2007) that presume that treatment is aimed at gram-negative bacilli. Aminoglycosides have rapid bactericidal activity against gram-negative bacilli because they act to disrupt the outer membrane of these organisms. Gram-positive cocci lack this feature; therefore, aminoglycosides are not considered as effective for treating \textit{Staphylococcus} species as compared to gram-negative bacilli (Llanos-Paez., \textit{et al.} 2017). More frequent administration may be needed for optimum efficacy. Because efficacy has not been confirmed with clinical studies using aminoglycosides to treat pyoderma, this property of their action should be considered before selecting an aminoglycoside for treatment.
The MIC values for *Staphylococcus* spp. are usually below 2 µg/mL. The current CLSI breakpoint for susceptible bacteria (CLSI 2015) is ≤ 2 µg/mL. This breakpoint assumes a dose of 10 mg/kg, q24h, IM in dogs, but higher dose or IV use would produce higher plasma concentrations for which this breakpoint also would apply. Activity of aminoglycosides is diminished in the presence of pus and cellular debris (Konig et al 1998). This may be important for some skin infections. These conditions may decrease the usefulness of gentamicin for the treatment of wound and ear infections.

The most serious adverse effect associated with aminoglycoside therapy is nephrotoxicity. Toxicity initially affects the renal proximal tubules because of active uptake in these cells. Eventually, the entire nephron can be affected. Animals that are dehydrated, have electrolyte imbalances (for example low Na⁺ or K⁺), septicemic, or have existing renal disease are at a higher risk for toxicity than healthy animals. Nephrotoxicity is related to persistent drug levels (especially high trough concentrations). Therefore, extended dosing intervals will decrease risk of nephrotoxicosis (Drusano et al, 2007). To decrease the risk of drug-induced nephrotoxicosis, therapeutic drug monitoring and careful evaluation of renal function during its use is recommended.

**Glycopeptides (Vancomycin)**

Of the glycopeptides, vancomycin is the only one used in veterinary medicine, but is restricted from use in some countries. Vancomycin is not a new drug – although it may be new to many veterinarians. It is difficult to administer to small animals because of the need to administer IV. Therefore, its use is rare and will probably remain so. Despite its long history of use, resistance to vancomycin among *Staphylococcus aureus* is extremely rare with only a few cases described worldwide.

Vancomycin is slowly bactericidal for staphylococci by inhibiting the cell wall in a time-dependent manner. Vancomycin is poorly absorbed orally and this route should not be used except to treat intestinal infections. Intramuscular administration is painful and irritating to tissues. The usual dosage for small animals is 15 mg/kg q8h, IV, via slow infusion. Therapeutic drug monitoring (TDM) can be performed to ensure that trough concentrations are maintained above 10 µg/mL for skin, soft-tissue infections.

If vancomycin is administered according to the recommended dosing rates, adverse reactions are rare. Early formulations of vancomycin were associated with a high incidence of adverse effects. Most of these effects resulted from rapid IV administration, which induced flushing of the skin, pruritus, tachycardia and other signs attributed to histamine release. Nephrotoxicity and ototoxicity also was reported. Newer formulations are safer because impurities have been removed.

**What about new drugs?**

In response to the emergence of resistant gram-positive bacteria in humans – primarily methicillin-resistant *Staphylococcus* and drug-resistant *Enterococcus* spp. – the pharmaceutical industry has responded with new antibiotics. These drugs are generally expensive, and most of them must be administered by the intravenous route, in some cases via a central vein. They have primarily a gram-positive spectrum, but in some instances can be used for bacteria other than *Staphylococcus* or *Enterococcus*. Because of the expense, or the difficult administration, the use of these drugs has not been described in clinical veterinary patients. These drugs include streptogramins (combination of 30:70 quinupristin:dalfopristin called Synercid); daptomycin (Cubicin), a cyclic lipopeptide antibiotic; telavancin, another glycopeptide; tigecycline (Tygacil), a unique tetracycline; linezolid (Zyvox), the first in the class of oxazolidinones, telithromycin (Ketek), the first of a class of drugs called ketolides (currently restricted because of toxicity risk in humans); and a new generation of cephalosporins, ceftaroline fosamil (Tefero) and ceftobiprole. The only one of these agents that has been used in veterinary patients, to the author’s knowledge, is linezolid, which is discussed briefly below.

**Oxazolidinones**

Linezolid (Zyvox) is the first in the class of oxazolidinones to be used in human medicine. It is currently being used in people to treat methicillin-resistant *Staphylococcus* and vancomycin resistant
gram-positive infections caused by enterococci and streptococci. It has excellent activity against staphylococci and enterococci. Resistance can occur, but several sequential mutations are needed for development of resistance because of the redundant nature of the 23S rRNA gene, which codes for the target of this drug. Consequently, resistance has been rare in human patients and not documented in veterinary patients.

Linezolid is absorbed orally and also is administered IV. Oral absorption is practically 100% in all animals tested (Slatter et al, 2002), and is not affected by food. Linezolid is metabolized similarly across species (Slatter et al, 2002) and pharmacokinetic parameters scale allometrically across species, allowing accurate prediction of doses for both dogs and cats of approximately 10 mg/kg twice daily (Bhamidipati et al, 2004).

Because of the high expense, linezolid has been used very infrequently in veterinary medicine. The brand-name tablets may cost over $120 per tablet in retail pharmacies. However, the availability of a generic tablet may reduce this cost by approximately 10-fold less. The use at this time has only been reported in unpublished anecdotal canine and feline cases, which have responded with good outcomes.

Toxicokinetic studies in dogs at high doses showed that linezolid was well tolerated and did not accumulate (Slatter et al, 2002). Linezolid is a mild, reversible inhibitor on monoamine oxidases A and B. In the 10 years of clinical use of linezolid in people, these theoretical interactions with adrenergic agents have not been significant. Whether or not linezolid will produce interactions in dogs administered adrenergic agents (eg, phenylpropanolamine, selegiline), or other drugs metabolized by monoamine oxidases (eg, serotonin reuptake inhibitors or tricyclic antidepressants) has not been studied. Long-term use (>14 days) can cause bone marrow suppression (eg, thrombocytopenia) in people, but this has not been reported in dogs or cats. If it occurs, myelosuppression is mild and reversible.

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ANTIBIOTIC THERAPY
MANAGING PATIENTS WITH ANTIMICROBIAL RESISTANCE

Resistant Gram-Negative Infections

After a susceptibility report is available, one may find that the only antimicrobials to which some gram-negative bacilli are sensitive, including *Pseudomonas aeruginosa*, are extended-spectrum cephalosporins, penems (carbapenems), piperacillin-tazobactam, amikacin, or tobramycin.

Cephalosporins

Cefpodoxime is more active than many other third-generation cephalosporins against *Staphylococcus*, and pharmacokinetic properties allow for once-daily dosing (Papich et al, 2010). However, it is not active against *Pseudomonas aeruginosa*, *Enterococcus*, or methicillin-resistant *Staphylococcus*.

In the spring of 2008 cefovecin (Convenia) was approved was registered by the FDA-CVM for use in dogs and cats for treatment of skin infections. In December of 2006 cefovecin (Convenia) was introduced to small animal medicine in Europe and in Canada in October 2007. There have also been pharmacokinetic studies (Stegemann et al, 2006ab) published for dogs and cats, pharmacodynamic studies published (Stegemann et al, 2006c), and clinical efficacy studies in dogs and cats (Stegemann et al, 2007ab; Passmore et al, 2007; Six et al, 2008). In the clinical studies, cefovecin was compared to another active antimicrobial (cefadroxil, cephalexin, or amoxicillin-clavulanate) and non-inferior to these other drugs.

In dogs and cats, cefovecin is registered in Europe and Canada for treatment of skin infections. In dogs it is also registered for urinary tract infections. In Europe, but not Canada, it is also registered for urinary tract infections in cats. The approved label dose in these countries is 8 mg/kg SC, once every 14 days. The studies published show efficacy with a 14 day interval for administration. The injection may be repeated for infections that require longer than 14 days for a cure (eg, canine pyoderma). The approval for the United States lists treatment of skin infections in dogs and cats and therapeutic concentrations are maintained for an interval of 7 days, but drug concentrations persist long enough for a 14 day interval for some indications.

There are currently not any CLSI approved standards for susceptibility testing established for cefovecin (CLSI 2013). Based on the distribution of organisms reported (Stegemann et al, 2006c) ≤ 2.0 µg/mL should be considered. It has equal or greater activity against *Staphylococcus* spp. isolates and gram-negative bacteria of the Enterobacteriaceae (eg, *E. coli*, *Klebsiella*). However, activity against *Pseudomonas aeruginosa* is poor and it will not be effective against methicillin-resistant staphylococci.

Cefovecin is a third-generation cephalosporin and is more active with lower MIC values than first generation cephalosporins. This was demonstrated for pathogens from Europe and the United States (Stegemann et al, 2006c, Six et al, 2008). Cefovecin MIC₉₀ values were 0.25 µg/mL for *Staphylococcus intermedius* compared to 2 µg/mL for cephalexin and cefadroxil. As a 3rd-generation cephalosporin, it is expected to have even greater activity against gram-negative bacteria as was demonstrated by the MIC₉₀ values of 1 µg/mL compared to 16 µg/mL for cephalexin and cefadroxil (Six et al, 2008). Other MIC comparisons are provided in the tables in the paper by Stegemann et al (2006c).

Although cefovecin and cefpodoxime are technically considered 3rd-generation
cephalosporins, the activity of cephalosporins within these arbitrary “generations” are not always similar. Cefovecin and cefpodoxime are not as active against gram-negative bacteria compared to injectable 3rd-generation cephalosporins used in human medicine, such as ceftazidime or cefotaxime. When other injectable cephalosporins are considered for small animals, the most often used are cefotaxime and ceftazidime, although individual veterinary hospitals have utilized others in this group. These drugs are injectable, and must be administered frequently. Of the cephalosporins, only the 3rd-generation cephalosporins, ceftazidime (Fortaz, Tazidime), cefoperazone (Cefobid), or cefepime (Maxipime), a 4th-generation cephalosporin, have predictable activity against *Pseudomonas aeruginosa*. Ceftazidime has greater activity than cefoperazone and is the one used most often in veterinary medicine. These drugs must all be injected, and are usually given IV, although SC, and IM routes have been used.

**Carbapenems:**

The β-lactam antibiotics with greatest activity against resistant strains of the *Enterobacteriaceae* (*E. coli*, *Klebsiella*, etc.) and *Pseudomonas aeruginosa* are the carbapenems. The carbapenems are β-lactam antibiotics that include imipenem-cilastatin sodium (Primaxin), meropenem (Merrem), ertapenem (Invanz) and most recently, doripenem (Doribax). All drugs in this group have activity against the enteric gram-negative bacilli. ertapenem does not have anti-*Pseudomonas* activity. Resistance (carbapenemases) among veterinary isolates has been very rare. Imipenem is administered with cilastatin to decrease renal tubular metabolism. Imipenem has become a valuable antibiotic because it has a broad spectrum that includes many bacteria resistant to other drugs. Imipenem is not active against methicillin-resistant staphylococci or resistant strains of *Enterococcus faecium*. The high activity of imipenem is attributed to its stability against most of the β-lactamases (including ESBL) and ability to penetrate porin channels that usually exclude other drugs (Livermore 2001). The carbapenems are more rapidly bactericidal than the cephalosporins and less likely to induce release of endotoxin in an animal from gram-negative sepsis.

Some disadvantages of imipenem are the inconvenience of administration, short shelf-life after reconstitution, and high cost. It must be diluted in fluids prior to administration. Meropenem, a more recent generation carbapenem (some experts consider it a 2nd–generation penem) and has antibacterial activity greater than imipenem against some isolates. One important advantage over imipenem is that it is more soluble and can be administered in less fluid volume and more rapidly. For example, small volumes can be administered subcutaneously with almost complete absorption. There also is a lower incidence of adverse effects to the central nervous system, such as seizures. Based on pharmacokinetic experiments in our laboratory (Bidgood & Papich, 2002), the recommended dose for *Enterobacteriaceae* and other sensitive organisms in dogs is 8.5 mg/kg SC every 12 hr, or 24 mg/kg IV every 12 hr. For infections caused by *Pseudomonas aeruginosa*, or other similar organisms that may have MIC values as high as 1.0 mg/mL: 12 mg/kg q8h, SC, or 25 mg/kg q8h, IV. For sensitive organisms in the urinary tract, 8 mg/kg, SC, every 12 hours can be used. In our experience, these doses have been well-tolerated except for slight hair loss over some of the SC dosing sites. For cats, published studies recommend 10 mg/kg IM, SC, or IV (SC is easiest) every 12 hours.

**Penicillin Drugs**

Penicillin G and the amino-derivatives ampicillin and amoxicillin have little activity on gram-negative bacteria. This is true also for ampicillin-sulbactam (Unasyn) and amoxicillin-
clavulanate (Clavamox) combinations. When resistance is encountered among Enterobacteriaceae, *Pseudomonas aeruginosa*, and other gram-negative bacteria, other penicillins can sometimes be useful.

This group includes the ureidopenicillins (mezlocillin, azlocillin, piperacillin) and the carboxylic derivatives of penicillin (carbencillin, ticarcillin). Ticarcillin and ticarcillin-clavulanate (Timentin) was once popular for use in many veterinary hospitals. However, this product has been removed from the market and is no longer available. The most consistently available drug, and one for which we have pharmacokinetic and susceptibility data to support the use is piperacillin-tazobactam (Piperacil, or “Pip-Taz”). This is a very active drug against a broad spectrum of bacteria, including ESBL. However, it has a very short half-life in dogs and must be given frequently (e.g., 50 mg/kg every 6 hours IV) or via constant rate infusion (4 mg/kg IV loading dose, followed by 3.2 mg/kg per hour CRI). There are no orally effective formulations in this class.

**Aminoglycosides**

Aminoglycosides, discussed in a previous section, are active against most wild-type strains of *Pseudomonas aeruginosa*. Against resistant isolates, amikacin and tobramycin are more active than gentamicin, and resistance is less likely to these drugs (Petersen et al, 2002). For *Pseudomonas aeruginosa*, tobramycin can be used as an alternative. Aminoglycosides are valuable for treating gram-negative bacilli that are resistant to other drugs. They are rapidly bactericidal, less expensive than injectable drugs listed above, and can be administered once-daily. Among these, amikacin and tobramycin are the most active and the first choice in small animal medicine when resistant or refractory infections are encountered. Both drugs are administered once-daily IV, IM, or SC. Important disadvantages to systemic use of aminoglycosides are the adverse effects (primarily kidney injury) that increase if treatment must extend for at least two weeks or longer. Risk of nephrotoxicosis is greater with longer duration of treatment. To decrease the risk of drug-induced nephrotoxicosis, therapeutic drug monitoring and careful evaluation of renal function during its use is recommended. Activity of aminoglycosides is diminished in the presence of pus and cellular debris (Konig et al 1998). This may decrease their usefulness for the treatment of wound and ear infections caused by *Pseudomonas aeruginosa*.

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Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

There are many nonsteroidal anti-inflammatory drugs (NSAIDs) available that have been used to treat osteoarthritis and pain. Many are registered for use in people (but we use them in animals also) and several are approved for use specifically for animals, particularly dogs. There has been a tremendous amount of information published on NSAIDs in the last 10 years (see references at end of this section). A review of clinical trials for treating osteoarthritis may be found in the paper by Aragon et al (2007). Comprehensive references on this topic were provided in the Veterinary Clinics of North America (July 2000, Vol. 30(4); and November 2008 Vol. 38). The last review by this author was in 2015 (Papich & Messenger, 2015) which was an update from earlier manuscripts (Papich, 2008 and 2000). A description of the chemistry, mechanism of action, and clinical use of the COXIB class of NSAIDs was provided in a thorough review (Bergh & Budsberg, 2005). Pharmacokinetics and pharmacodynamics of NSAIDs were reviewed extensively by Lees et al (2004b). A general summary (Lascelles 2005), guidelines for clinical use in dogs (Lascelles et al, 2005) and cats (Lascelles et al, 2007; Carroll and Simonson, 2005); Taylor & Robertson (Part 1, 2004) and Robertson & Taylor (Part 2 2004; Sparkes et al, 2010) are available in excellent reviews. The paper by Sparkes et al (2010) provides a current consensus of use in cats. A discussion of the physiologic characteristics of cyclooxygenase products can be found in the reference by Jones & Budsberg (2000). For a comparison on how osteoarthritis is treated in people, consult the review by Steinmeyer & Konttinen (2006).

Pharmacology of NSAIDs

It has been accepted since Dr. Vane's work of the early 1970's that the most important mechanism of action of NSAID is inhibition of the cyclo-oxygenase enzyme (Abramson, et al, 1988, 1985), and the inhibition of prostaglandin synthesis. Tepoxalin (Zubrin; no longer available) is only veterinary NSAID for which there is evidence that it also inhibits the lipoxygenase cascade (inhibition of leukotriene synthesis). Other drugs that are inhibitors of the lipo-oxygenase enzyme, or that block leukotrienes, are only used to treat asthma in people.

The non-steroidal anti-inflammatory drugs (NSAIDs) have provided many choices for veterinarians to treat canine patients (cats discussed separately below). Several agents in this class have come and gone. One of the oldest agents, carprofen (Rimadyl, and generic) is still popular today. Newer additions include deracoxib (Deramaxx), firocoxib (Previcox), robenacoxib (Onsior), meloxicam (Metacam), and grapiprant (Galliprant), which acts through a different mechanism, but is still an NSAID. In other countries, additional drugs are available, such as tolfenamic acid (Tolfedine), mavacoxib (Trocoxil), nimesulide, and ketoprofen (Anafran).

The pharmacologic action of the nonsteroidal anti-inflammatory drugs (NSAID) has been reviewed in the references cited above. These drugs act to inhibit the isoenzymes of cyclo-oxygenase (COX). Cyclo-oxygenase 1 (COX 1) is a constitutive enzyme expressed in
tissues (Meade et al 1994). Prostaglandins, prostacyclin, and thromboxane synthesized by this enzyme are responsible for normal physiological functions. Cyclo-oxygenase 2 (COX-2), on the other hand, is inducible and synthesized by macrophages and inflammatory cells after stimulation by cytokines and other mediators of inflammation. In some tissues, COX-2 may be constitutive, or may be induced to maintain favorable conditions in healthy tissue. The target of recently-developed NSAID has been COX-2, with the goal of producing analgesia and suppressing inflammation without inhibiting physiologically important prostanoids (Laneuville et al, 1994; Bergh & Budsberg, 2005). Whether or not selective inhibition of COX-2 is the safest and most effective approach for animal treatment has yet to be established in dogs and cats.

### COX-2 Selective Drugs vs Non-selective Drugs

The evidence for superior efficacy for selective COX-2 inhibitors is lacking. In people, they may be safer for the GI tract, but not necessarily more effective than older drugs (Peterson and Cryer 1999; Laine, 2003). However, the studies demonstrating safety of COX-2 inhibitors in people have been criticized (Malhotra et al, 2004). Some skeptics have proposed that selective COX-2 inhibitors may not be appropriate for all patients because COX-2 enzyme

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<th>NSAIDs Used in Dogs</th>
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<tr>
<td>Aspirin a</td>
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<tr>
<td>Phenylbutazone b</td>
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<tr>
<td>Carprofen (Rimadyl, and generic) e</td>
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<tr>
<td>Etodolac (EtoGesic)</td>
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<tr>
<td>Meloxicam (Metacam) c, e</td>
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<tr>
<td>Ketoprofen (Anafen) d</td>
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<tr>
<td>Deracoxib (Deramaxx)</td>
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<tr>
<td>Firocoxib (Previcox)</td>
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<tr>
<td>Meclofenamic acid (Arquel) b</td>
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<tr>
<td>Robenacoxib (Onsior) e</td>
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<tr>
<td>Grapiprant (Galliprant)</td>
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<tr>
<td>Tepronaxin (Ziprin) b</td>
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<tr>
<td>Mavacoxib (Trocoxil) f</td>
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<tr>
<td>Tolfenamic acid (Tolfedine) d, e</td>
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<tr>
<th>NSAIDs Used in Cats</th>
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<tr>
<td>Aspirin</td>
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<tr>
<td>Meloxicam c</td>
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<td>Carprofen f</td>
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<td>Robenacoxib</td>
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<td>Ketoprofen d, f</td>
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a Aspirin is not FDA-approved for dogs, cats or horses, but some forms are marketed for dogs as if there was FDA-approval. There is an approved combination with methylprednisolone (Cortaba tablets, 0.5 milligram of methylprednisolone and 300 milligrams of aspirin).
b Approved for dogs, but not actively marketed.
c Approved for cats also as a single dose.
d Approved in Canada
e Also available as an injectable as well as oral, the others are all available in oral forms.
f Approved for this use in other countries, but not the U.S.
products may be involved in actions other than inflammation. For example, COX-2 products may be biologically important for angiogenesis, renal function, regulation of bone resorption, reproductive function, and healing of gastroduodenal ulcers (Wolfe et al 1999). There are high endogenous levels of COX-1 in the stomach, which is subject to high acid levels and shear forces. Inhibition of COX-1 in the stomach increases the risk of gastric ulceration. On the other hand, in the duodenum, COX-2 may be induced as a result of other treatments or injury to the duodenal mucosa (Wooten et al, 2008; Wooten et al, 2010). Injury and perforations that have been observed in the duodenum of dogs treated with COX-2 inhibitors (Lascelles et al, 2005; Case et al, 2010) may provide evidence that some patients have a requirement for upregulation of COX-2 in the duodenum. If the risk of mucosal injury to the duodenum is high, and the COX-2 inhibited by selective drugs, there is the possibility of it may produce serious ulcers. COX-2 selective drugs also may cause a higher risk of cardiovascular problems in people because it preserves COX-1 which may promote platelet aggregation and vasoconstriction (Mukherjee et al, 2001). High COX-2 selectivity may increase risk of cardiovascular events (Topol 2004) which led to the removal of the approved drugs rofecoxib (Vioxx) and valdecoxib (Bextra) from human medicine in 2004. There is only one human COX-2 selective inhibitor on the market (celecoxib).

Newest NSAID for Dogs: Grapiprant (Galliprant®)

Grapiprant is a new class called “pirants”. This is the first from this group approved for any animal or human. For dogs it is approved for daily administration to treat osteoarthritis. Grapiprant is considered an NSAID, but acts through a different mechanism than traditional NSAIDs. Grapiprant is a non-cyclooxygenase (COX) inhibiting agent. It is instead, a prostaglandin receptor antagonist. It has a unique mechanism of action by antagonizing the prostaglandin E₂ (PGE₂) EP4 receptor. PGE₂, is one of the mediators of pain and inflammation after prostaglandins are synthesized. There are also other receptors: EP1, EP2, EP3 and EP4. The EP4 receptor has been identified as the primary receptor responsible for mediating pain and inflammation associated with osteoarthritis. Grapiprant acts to selectively block the EP4 receptor, thus blocking PGE2 elicited pain and inflammation. The approved dose is 2 mg/kg once daily. Adverse reactions in dogs are typical as for traditional NSAIDs and may include vomiting, diarrhea and decreased appetite.

Adverse Effects of NSAIDs:

Gastrointestinal (GI) Tract Injury

The gastrointestinal effects of NSAIDs are by far the most common. These events can range from mild gastritis and vomiting, to severe gastrointestinal ulceration, bleeding and even deaths. Vomiting, anorexia, nausea, and diarrhea are by far the most common events. There are two forms GI injury that can occur as a result of NSAID administration (Wolfe et al 1999): (a) a direct effect caused by exposure of the lining of the stomach and intestine to the drug, and (b) injury caused by prostaglandin inhibition.

NSAID can directly injure the lining of the stomach because of direct irritation of an oral medication. This is common from aspirin. It usually is not serious, but can cause stomach discomfort, dyspepsia, and nausea. The other NSAIDs can directly injure the intestinal villi via exposure from the intestinal lumen. Drugs that enter the lumen via the bile perhaps have a higher risk for injury, which presents a greater problem for the NSAIDs that undergo
enterohepatic recycling and produce high biliary concentrations. These effects may not result in a perforation, but can be an important cause for the nausea, vomiting, and diarrhea observed in animals following administration of NSAIDs. The drugs that we administer to prevent stomach problems from NSAIDs may actually increase problems in the intestine. The use of proton pump inhibitors such as omeprazole is considered to be an independent risk factor associated with NSAID-associated enteropathy (Marlicz, et al, 2014).

A more serious form of GI injury occurs because prostaglandins are responsible for a healthy GI tract. When these prostaglandins are inhibited by NSAID, gastritis, GI ulcers, GI bleeding, perforations, diarrhea, and protein losing enteropathy have all been described in animals. Gastrointestinal toxicity may be exacerbated by co-administration with high doses of corticosteroids in dogs. In horses, GI ulcers are also an important problem as well, but most ulcers in horses occur from administering doses that are too high. The most severe ulcers in horses occur in the glandular mucosa because this is the region where prostaglandin inhibition plays the most important role.

**Kidney injury:**

COX-1 and COX-2 products play an important role in renal vascular tone (perfusion) and tubular function (natriuretic effect). Both COX-1 and COX-2 enzymes synthesize prostaglandins important for renal tubular function and blood perfusion during hypovolemia, hypotension, and salt depletion (Jones & Budsberg, 2000). COX-2 may be inducible in the kidneys to prevent kidney injury. These effects of renal prostaglandins are particularly important during times of stress. NSAIDs are not inherently nephrotoxic, but in animals with decreased renal perfusion, NSAIDs may cause ischemic nephropathy. Accurate (safe) doses and keeping animals well-hydrated is important to avoid kidney injury. Even in older cats with kidney disease, NSAIDs can be used safely as long as low doses are administered and the animal does not become dehydrated.

**Pharmacokinetic Features**

For most of the NSAID there is adequate pharmacokinetic data for dogs and horses, some for cats and cattle, but more limited for other animals (eg, exotic animals). Most of the traditional drugs in this group are weak acids that are highly protein bound and most of them have a small volume of distribution. Some new drugs are an exception because they have higher volumes of distribution than expected.

The NSAIDs are excreted at varying rates, depending on the species, metabolic pathway, and extent of enterohepatic circulation. There are tremendous species differences in drug elimination among the NSAIDs. For some drugs the enterohepatic cycling may slow the clearance and increase the risk of toxicosis because the local effects of the drug may be focused on the intestinal mucosa through repeated cycling through the biliary system.

Although the drug distribution, half-life, and clearance, have been characterized for most NSAIDs used in animals, this information has not always been of use for predicting safe and effective dosage regimens. For example, NSAIDs such as ibuprofen and indomethacin easily cause toxicity in dogs even though they have short half-lives. On the other hand, naproxen and piroxicam have long half-lives of 74 hours and 40 hours, respectively, but have been used safely when dosed carefully (eg, piroxicam at a low dose given once-daily or once every other day to dogs). Among the small animal NSAIDs, half-lives do not correlate with the frequency of administration. Most currently-used NSAIDs are given once a day, but half-lives vary widely.
An important feature of the NSAID pharmacokinetics is that anti-inflammatory and analgesic effects persist longer than the plasma half-lives would predict. In dogs, several NSAID have half-lives of 24 hours or less, (aspirin carprofen, 8 hours ; phenylbutazone 6 hours; flunixin: 3.7 hours; meloxicam: 10-24 hours; etodolac, 8-12 hours; robenacoxib, 1 hour), but have been administered once every 24 hours with effective results. For example, robenacoxib has a very short half-life (1-2 hours) in plasma, but effective half-life in tissues that is much longer. These drugs persist in tissues, and particularly inflamed tissues, longer than they persist in plasma.

### Pharmacokinetic data for NSAIDs at the dosages tested in dogs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life in dogs</th>
<th>Test Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>8 hours</td>
<td>10-20 mg/kg q8-12h, oral</td>
</tr>
<tr>
<td>Carprofen</td>
<td>8 hours (range 4.5-10)</td>
<td>4.4 mg/kg q24h, or 2.2 mg/kg q12h, oral</td>
</tr>
<tr>
<td>Deracoxib</td>
<td>3 hr at 2-3 mg/kg; 19 hr @ 20 mg/kg</td>
<td>3-4 mg/kg q24h, oral</td>
</tr>
<tr>
<td>Etodolac</td>
<td>7.7 hrs fasted; 12 hr non fasted</td>
<td>10-15 mg/kg q24h, oral</td>
</tr>
<tr>
<td>Flunixin</td>
<td>3.7 hr</td>
<td>1 mg/kg, oral or IM, once.</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>12-36 hours</td>
<td>0.2 mg/kg initial, then 0.1 mg/kg q24h, oral</td>
</tr>
<tr>
<td>Naproxen</td>
<td>74 hr</td>
<td>5 mg/kg initial, then 2 mg/kg q48h, oral</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>6 hours</td>
<td>15-22 mg/kg q12h, oral</td>
</tr>
<tr>
<td>Robenacoxib</td>
<td>1 hour</td>
<td>1-2 mg/kg q24h</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>40 hours</td>
<td>0.3 mg/kg, q24h, or q48h, oral</td>
</tr>
<tr>
<td>Tevoxalin</td>
<td>1.6 hrs parent drug; 13 hr for active metabolite</td>
<td>20 mg/kg initial; then 10 mg/kg q24h, oral</td>
</tr>
<tr>
<td>Firocoxib</td>
<td>7.8 hours</td>
<td>5 mg/kg q24h, oral</td>
</tr>
</tbody>
</table>

### DRUG SELECTION

When selecting a drug for treatment in animals, there are several choices (see table). Veterinarians should not allow unsubstantiated claims affect the decision of selecting one drug over another. When selecting an NSAID, we really don’t know which NSAID is the best one. Each has advantages and disadvantages. There are different dosage forms that include injectable, oral liquid, regular tablets, oral mucosal, and chewable tablets. The preference of each of these depends on the clinical situation and animal/owner preference. There are veterinary generic formulations of popular drugs and there are some human-labeled drugs used off-label (eg, piroxicam).
Consistent features of NSAIDs
1. All NSAIDs, regardless of COX-1/COX-2 specificity are capable of producing gastrointestinal lesions, particularly at high doses.
2. All NSAIDs (selective or non-selective) can produce other gastrointestinal signs, including vomiting, diarrhea, decreased appetite, without producing ulceration.
3. All NSAIDs have potential for producing hepatic injury. Susceptibility appears to be idiosyncratic and unpredictable.
4. All NSAIDs have the potential for producing renal injury. Previous renal disease, salt depletion, dehydration will increase the risk.
5. No NSAID is consistently more clinically effective than another.

NSAIDs for Dogs:
For acute pain, such as perioperative use, there is evidence published showing that oral and injectable formulations are effective. NSAIDs have been used for this indication for short-term of 1-3 days to decrease fever, pain, and discomfort from surgery or trauma. Preoperative injections of carprofen to dogs were shown to be beneficial to decrease post-operative pain in dogs after ovariohysterectomy (Lascelles et al 1998). Meloxicam has been evaluated in two published studies for perioperative use, and was shown to be superior to butorphanol in some of the pain assessments that were measured.

For chronic administration, such as treatment of myositis, arthritis, and osteoarthritis, drugs that have been administered in the U.S. to small animals were listed previously. Review papers have also summarized these choices (KuKanich, et al, 2012). Veterinarians also have used human-label drugs such as aspirin, piroxicam, and naproxen. If these human-label drugs are considered, consult appropriate references for accurate dosing because it may differ from the human dose schedule. For long-term use to treat osteoarthritis, there are no controlled studies to indicate which drugs is the safest and most effective. When drugs are compared to one another, it is difficult, using subjective measurements, to demonstrate differences between among the drugs when evaluating them for efficacy or safety. Without a very large number of patients, the statistical power to detect differences among drugs in clinical veterinary studies is difficult. It is a rational approach to consider a rotating schedule of two or more drugs to identify which drug is better tolerated, effective, and easier to administer in each patient.

NSAIDs for Cats:
For a review of NSAID drug selection for cats, consult the references cited earlier (Lascelles et al, 2007; Sparkes et al, 2010; Carroll and Simonson, [2005]; Taylor & Robertson [Part 1, 2004] and Robertson & Taylor [Part 2 2004]). Meloxicam is commonly used in cats because it can be injected for the initial use, and follow-up is possible with oral treatment. The oral solution has been palatable for cats, but the dose should be reduced compared to the canine dose. Robenacoxib also is approved for cats and there is good evidence for its safety and efficacy. Part of the explanation for robencoxib’s safety is a short half-life; thus, short exposure in the highly perfused tissues, but longer persistence in the inflammatory sites such as joints and soft tissues. Other drugs such as ketoprofen, aspirin (at an extended interval), and occasionally other drugs listed for dogs have been used off-label in cats. For short-term use, carprofen, deracoxib, and flunixin have been used.
ALTERNATIVES TO NSAIDs IN SMALL ANIMALS

What are the alternatives to nonsteroidal anti-inflammatory drugs (NSAIDs) for dogs and cats? Although NSAIDs are important agents for acute and chronic treatment of pain, and are particularly useful for osteoarthritis, some patients cannot tolerate NSAIDs. In other cases, NSAIDs alone are not enough and other agents are considered as add-on treatment. What are those options?

Tramadol

Tramadol is a unique oral analgesic drug that recently was changed to a DEA-Controlled Substance (Schedule IV). The generic formulation is inexpensive and widely available. The exact mechanism of action for tramadol is uncertain but there is probably more than one mechanism that contributes to its clinical effects. Tramadol has some mu-opioid receptor action, and it inhibits the reuptake of norepinephrine (NE), and serotonin (5-HT). One of the isomers has greater effect on serotonin reuptake and greater affinity for mu-opiate receptors. The other isomer is more potent for norepinephrine reuptake and less active for inhibiting serotonin reuptake. Taken together, the effects of tramadol may be explained via inhibition of serotonin reuptake (similar mechanism as fluoxetine and other antidepressant drugs), action on alpha-2 receptors (similar mechanism as dexmedetomidine), and activity for opiate mu-receptors (similar mechanism as morphine). Although tramadol is a weak opioid compared to morphine, the metabolite (desmethyltramadol, also called M1) may have greater opiate effects than the parent drug (for example, 200x in opiate receptor binding).

There have been several pharmacokinetic studies on dogs, horses, cats, and some exotic animals. Tramadol is moderately well-absorbed orally in dogs and was well-tolerated. However, dogs produce low and inconsistent concentrations of the metabolite (M1) which is the metabolite that contributes to analgesic effects in people. Clearance is higher than in people, which necessitates a higher dose for dogs. Note that the dose in humans is less than 1 mg/kg, but in dogs we routinely administer 5 and 10x this dose without much effect. Although safety and efficacy studies have not been sufficient to provide clinical dosing recommendations, based on pharmacokinetic studies, doses of 5-10 mg/kg every 6 to 8 hours orally are administered to dogs.

Is Tramadol Effective?

Combinations of tramadol with other drugs – particularly NSAIDs – have been reported to be effective for some conditions in dogs (for example, Flôr et al, 2013); but there are no conclusive studies that have shown efficacy when tramadol was used alone. Some studies have shown effects for acute pain, such as peri-operative analgesia when administered by injection. But injectable forms are not available in the U.S. The few studies on efficacy thus far have not provided convincing evidence that tramadol is efficacious for chronic or post-operative pain. Moreover, there is evidence that clearance increases, and plasma concentrations decline, with repeated administration. Nevertheless, many clinicians believe that it is a useful alternative when NSAIDs alone are not effective.

In cats the clearance and metabolism are much different than in dogs. The efficacy of tramadol as an analgesic in cats is consistent with opioid-mediated analgesia. The clearance of the desmethylmetabolite (M1), which is conjugated to glucuronic acid for elimination in other animals, is much slower in cats. Because the M1 metabolite is associated with greater opiate-mediated effects than the parent drug, opiate effects have been observed more often in cats than
dogs. Dosage recommendations for cats have been in a range of 2-4 mg/kg PO q 12 hours, but a dose of 4 mg/kg orally produced some dysphoria and mydriasis in some of the experimental cats. Further work is necessary to determine the optimum dose and frequency in cats.

**Gabapentin**

Gabapentin (Neurontin) is ordinarily used as an anticonvulsant but may have analgesic properties as well. Gabapentin is a structural analogue of gamma aminobutyric acid (GABA). Although it is structurally related to GABA, it does not interfere with sodium-dependent channels or exhibit affinity for other neurotransmitter receptors, such as those affected by benzodiazepines (i.e., glutamate, dopamine, NMDA).

Gabapentin inhibits the alpha2-delta subunit of the N-type voltage-dependent calcium channel on neurons. After binding to this subunit, it reduces the calcium influx needed for release of neurotransmitters – specifically excitatory amino acids – from presynaptic neurons. This channel becomes up-regulated when nerves are stimulated, such as in epileptic or neuropathologic conditions. Blocking the channels has little effect on normal neurons, but appears to suppress stimulated neurons; therefore, gabapentin is associated with few adverse effects in dogs except for sedation.

Gabapentin and a related drug, pregabalin (Lyrica), have been used in humans to treat many pain states, including fibromyalgia, inflammatory pain, diabetic neuropathy, malignant pain, central pain, complex regional pain syndrome, and trigeminal neuralgia. These types of pain may occur in animals, but the existence has not been confirmed.

Gabapentin is available in 100-, 300-, and 400-mg capsules; 100-, 300-, 400-, 600-, and 800-mg scored tablets; and a 50-mg/ml oral solution. The oral solution contains xylitol, which is toxic to dogs if administered at high concentrations. Gabapentin pharmacokinetic have been reported for dogs (KuKanich & Cohen, 2011). It is excreted via renal mechanisms and thus has no hepatic interactions. The half-life is approximately 3-3.5 hours, necessitating a dose interval of at least every 8 hours. The suggested dose is 10-20 mg/kg. Pregabalin (Lyrica) is not as commonly used. It is more expensive and is a controlled drug.

For rescue analgesia (when other drugs have not been effective), gabapentin has been administered in both dogs and cats (and a case-report in horses); however, the dose range is wide. The lower end of the recommended dose is used initially, and the dose may be increased gradually. Sedation is more likely as the dose increases. Despite the anecdotal references to the use of gabapentin in animals, there are no studies in dogs or cats available to demonstrate convincing efficacy. In dogs, it was not effective for relieving pain from amputation surgery. When administered to dogs for control of pain after intervertebral disc surgery (10 mg/kg every 12 hours) there was no detectable reduction in pain behavior compared to the other drugs (Aghighi et al, 2012). In cats, at doses of 5, 10, or 30 mg/kg, it did not affect thermal threshold anti-nociception in cats (Pypendop et al, 2010), and did not provide thermal antinociception. Patients need to be weaned from gabapentin over 2 to 3 weeks to prevent seizures (reported in humans) and a rebound pain phenomenon.

**Amantadine**

Amantadine is an antiviral drug that has also been used to treat some pain syndromes. The proposed mechanism of action for treating pain in animals is via NMDA-receptor antagonism. Oral absorption of amantadine is good, but the precise duration of action and dosing regimens have not been fully investigated in animals. In a study from NCSU (Lascelles et al,
2008), it was used in combination with NSAIDs for treatment of pain in dogs. At a dose of 3 to 5 mg/kg PO administered once daily with meloxicam, dogs responded better than if meloxicam were given alone. Other doses that have been cited for pain are 2 to 10 mg/kg PO q 8 to 12 hr in dogs and 2 mg/kg orally q 24 hr in cats. Amantadine is available in a 100-mg capsule or in a foul-tasting 10-mg/ml liquid. For rescue analgesia, amantadine is often given with other drugs and may take days to weeks to reach full effect.

**Oral Opioids**

Hycodan bitartrate is formulated as 5 mg of hydrocodone + 1.5 mg homatropine. Hydrocodone (5 mg) + acetaminophen (500 mg) is combined in a tablet and used for analgesia (Vicodin, and generic). Because of the acetaminophen in these products, they should **never** be administered to cats. In dogs, high acetaminophen exposure may result from the high doses necessary. There is new FDA approved product (Zohydro ER) that contains only hydrocodone in an extended-release oral formulation. The use of this product has not been reported in animals. Recently, hydrocodone was rescheduled by the DEA from Schedule III, to Schedule II because of high abuse of this drug in people. This restricts prescribing for animal use (written prescription only), and in some states the duration of use may be limited.

There are no studies that have documented analgesic efficacy from oral hydrocodone in dogs. There is limited evidence that dogs produce the active metabolite from oral dosing (hydromorphone), but it is possible that other metabolites may have activity.

Oral morphine is available as syrup, tablets, and prolonged-release oral medication. Despite the advantages of oral morphine formulations, pharmacokinetic studies to demonstrate effective levels are lacking. Dogs do not appear to produce the active metabolite (M6G) after oral administration and studies at NCSU in which a specific assay was used indicated negligible oral absorption (Kukanich et al 2005). Therefore, the efficacy of oral morphine in dogs is questionable due to high clearance and poor oral absorption.

**Dietary Supplements**

**N-6/N-3 Fatty Acids:** A 2012 study (Vandeweerd et al, 2012) provided a systematic review of efficacy of dietary supplements to alleviate clinical signs of osteoarthritis. They found that although there was conflicting evidence for the efficacy of glucosamine-chondroitin sulfate, the highest global efficacy score was from administration of omega-3 fatty acids.

Some of the studies (especially old studies) should be interpreted with caution because the design may have been uncontrolled. Furthermore, some trials did not control for the diets the animals may have consumed. The n-6 and n-3 fatty acid content of commercial pet foods can vary tremendously (Roudebush, 2001). Levels of n-6 and n-3 fatty acids consumed in some foods often exceeded levels that are provided by commercial dietary supplements. Without controlling the amounts of n-6 and n-3 fatty acids in the diet, the results of published clinical trials of these dietary supplements are difficult to interpret.

The optimum dose has been debated as well as the optimum ratio of n-3 to n-6 fatty acids (Harvey 1999). Most supplement contain both n-3 and n-6 fatty acids in a variety of ratios. One of the problems in evaluating the effects of the administration of dietary supplements containing n3/n6-fatty acids is that available products containing these compounds vary considerably in potency and dose. In dogs that were fed experimental diets containing various ratios of n-6/n-3 fatty acids, the diets containing the highest proportion of n-3 fatty acid (eg, EPA, DHA) resulted in less inflammatory leukotriene synthesis compared to other diets, and lower n-6/n-3 fatty acid
ratios in blood and blood cells (Vaughn, et al, 1994; LeBlanc et al, 2008; Filburn & Griffin, 2005). Therefore, there may be more benefit from the n-3 component than n-6 and some studies have shown better results from supplements that contain the highest ratios of n-3 to n-6 fatty acids, especially if the source of n-3 was fish oil.

Glucosamine / Chondroitin Sulfate: Glucosamine, a complex sugar (amino monosaccharide), is a dietary supplement that has been promoted for treatment of osteoarthritis. Dietary supplements are not regulated by the FDA in the same way as drugs. Therefore, therapeutic claims of efficacy are more difficult to establish. Nevertheless, the combination of glucosamine-chondroitin sulfate is commonly administered to patients with osteoarthritis.

Since glucosamine is one of the precursors for proteoglycan synthesis, supplementation to the diet is believed to stimulate glycosaminoglycan, proteoglycan synthesis, and collagen synthesis in cartilage and other connective tissue. Glucosamine also may have some anti-inflammatory activity or inhibit enzymes that degrade articular cartilage.

Chondroitin sulfate is a much larger molecule and is one of the major glycosaminoglycans found in articular cartilage. It may be a building block for the synthesis of cartilage matrix, or to inhibit enzymes that degrade articular cartilage (Neil, et al, 2005). Although these compounds – usually used in combination – are often administered as a dietary supplement to animals with arthritis, there is no evidence that animals with arthritis are nutritionally deprived of these “building blocks”.

Results from clinical studies are controversial. A European study found that glucosamine may decrease progression of osteoarthritis in humans by as much as 50%. This finding led the Arthritis Foundation to declare supplementation of glucosamine as an “appropriate treatment” for humans with osteoarthritis. On the other hand, a study in people (Cless et al 2006) with osteoarthritis concluded that, “we did not identify significant benefits associated with the use of glucosamine or chondroitin sulfate alone”. The placebo effect in this study was 60%.

Controlled critical evaluations have been more limited in animals. In some studies, there has been a benefit; in other studies, there has been no benefit. Some of these studies are summarized in the review by Neil et al (2005). In one study (Canapp et al, 1999) dogs were given glucosamine-chondroitin before induction of synovitis, and there was a better response to treatment compared to a control. However, if they received glucosamine-chondroitin after induction of synovitis, there was no benefit. In horses, problems with study design and evaluation have produced results that are not conclusive on the beneficial effects of glucosamine/chondroitin sulfate supplements. A 2012 paper (Vandeweerd et al, 2012) provided a systematic review of efficacy of nutraceuticals to alleviate clinical signs of osteoarthritis. They found that glucosamine-chondroitin sulfate may provide some prophylactic benefit for synovitis. Otherwise, the results were contradictory with some evidence of efficacy and some showing no benefits.

Glucosamine and chondroitin sulfate are marketed, usually as a combination product, in capsules which are administered to animals for at least 30 days. Oral absorption can be low and variable. Glucosamine absorption has ranged from 12% in dogs to only 2.5% in horses. Components of glucosamine freely diffuses into organs and tissues after oral administration, but it is not known if this molecule is intact. Chondroitin absorption from oral administration is also low and variable. In horses it has been reported to be 20-30%, but as low as 5% in dogs. There have been some questions about whether or not the chondroitin molecule is absorbed intact. If degradation products are absorbed, it is not known if they are equally effective as intact
chondroitin. Other references contain more detailed information on the pharmacology and action of glucosamine/chondroitin sulfate in animals (Neil et al, 2005).

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Compounding for veterinary patients has received a lot of attention in the past few years. Because of problems with compounded preparations for human patients, there have been calls for more regulations on compounding. The recent problems that resulted from some human compounded formulations, including 74 human deaths, were highly publicized in the press. Subsequently, the U.S. Congress held hearings and proceeded with legislation to help prevent problems in the future. This act, named the “The Drug Quality and Security Act” was signed into law on November 27, 2013. It was intended to ensure better quality of compounded products. Unfortunately – or fortunately, depending on one’s perspective – regulation of veterinary compounding was not included in the federal legislation that resulted from this action. The new federal legislation is somewhat limited in its scope and is intended to primarily improve quality of sterile compounded products. Some critics of the legislation suggest that it comes up short of ensuring safety and quality of compounded products. According to one perspective of the act, (Outterson, 2014) “Traditional compounders can now operate without fear of federal enforcement”. Because of concerns with veterinary compounding – particularly compounding from bulk chemical substances – the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) have initiated a new Guidance for veterinary compounding (GFI #230).

Where Do We Stand With Veterinary Compounding?

Until recently, veterinary drug compounding was covered in Food and Drug Administration (FDA) Guidance issued in 2003. This guidance, called “Compounding of Drugs for Use in Animals, or Guidance 608.400” (http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074656.htm), addressed the areas in which the FDA would use regulatory discretion to enforce the Federal Food, Drug, and Cosmetic Act. However, many parts of the guidance, particularly those involving the use of bulk chemicals (bulk powder) were not actively enforced. This guidance has now been withdrawn and the agency is preparing to implement the new Guidance #230, which is described here: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm447159.htm

The basis of the new guidance is that even though compounding from bulk chemicals is not allowed under the current law. But the FDA recognizes that there are limited circumstances when an animal drug compounded from bulk drug substances may be necessary. This new guidance, called GFI #230 outlines specific conditions under which the agency generally does not intend to take action against state-licensed pharmacies or veterinarians when drugs are compounded for animals from bulk drug substances. The guidance has not yet been finalized by the FDA. They requested comments until November 2015 and a final version was scheduled after comments were reviewed. It is anticipated that the final version will limit compounding for animals to FDA-approved products, or bulk chemicals when no other reasonable option exists. According the FDA, “there are circumstances where there is no approved drug that can be used or modified through compounding to treat a particular animal with a particular condition. In those limited situations, an animal drug compounded from bulk drug substances may be an appropriate treatment option”.
Compounding, defined by the United States Pharmacopeia (USP) as “the preparation, mixing, and assembling, packaging, and labeling of a drug or device in accordance with a licensed practitioner’s [the veterinarian] prescription of medication or under an initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice.” Drug compounding has always been a part of veterinary medicine. Historically, veterinarians have been known for preparing concoctions, mixtures, and remedies for their patients because there were few approved formulations on the market for animals. Now, there are more available drugs for animals, and a better understanding of the risks of drug instability and incompatible mixtures. Questions concerning this widespread practice have been raised, particularly with respect to the drug’s stability, purity, and potency when the original dose form is altered, or when compounding is performed from the bulk drugs. “Bulk chemicals” or “Bulk drugs” are defined as the active pharmaceutical ingredient (referred to as the API) used in the manufacture of finished dosage forms of the drug. Bulk API does not contain excipients, which are the inactive ingredients added as a preservatives, stabilizers, buffers, or to enhance solubility.

Compounding is performed for the purpose of ease of administration or because the original dosage form is unsuitable for the purpose intended. Compounding does not include the preparation of a drug by reconstitution or mixing that is according the manufacturer’s instructions on an approved human or veterinary drug product. (For example, preparing a vial for injection.)

Veterinary medicine has been debating the practice and regulation of compounding for over 20 years. In 1993, a symposium on Compounding in Veterinary Medicine was held by the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT) (JAVMA, 1994). This symposium had representatives from AVMA, FDA/CVM, pharmacology and pharmacy groups, and USP. The symposium heard various views from practitioners, pharmacologists, regulatory officials, pharmacists, and lawyers. This symposium issued a Task Force Report that summarized the presentations and resulted in the Compliance Policy Guide published in 1996 (FDA 1996). The proceedings from this symposium are very informative and contained 115 pages of presentations, which cannot be adequately summarized here. The FDA followed several years later with a revised Compliance Policy Guide (CPG) of 2003 for compounding drugs that was cited above.

The FDA recognizes the importance of compounding in veterinary practice, but also must ensure that compounded drugs do not cause harm to the treated animals, produce ineffective potency, or residues in food animals. FDA regulations permit the compounding of formulations from approved animal or human drugs under the current federal code: 21 CFR 530.13. The FDA is concerned that allowance of some compounding on a patient-by-patient basis has gone over the limits intended in the original federal regulation and has been expanded to result in large-scale production and labeling of some products that may constitute manufacturing and distributing of new animal drugs.

The Need for Compounded Drugs in Veterinary Medicine

The palatability, ease of administration, and dispensing factors are among the considerations when formulating drugs for animals. Drugs intended specifically for animals are designed with great care. Pastes and dosage syringes are available for some drugs used in horses. Flavored tablets are used commonly in dogs for tablets that are given by pet owners. Transdermal medications are available for dogs and cats to avoid the necessity of frequent administration to a pet that may be difficult to medicate. Sometimes compounding is a necessity. Despite the advances in new drugs available for animals, many needs are still not met. Therefore, many drugs are crossed over from one animal species to another, or are human drugs administered to animals. Some drugs require compounding simply because no
approved form of the drug exists in the U.S. Drugs that are often compounded for veterinary medicine because approved forms are not available include: potassium bromide, metronidazole benzoate suspension, methimazole transdermal, diethylstilbestrol, cisapride, various antidotes, and other products that have either been discontinued in human medicine, or because of shortages in availability.

Are There Concerns from Compounded Veterinary Formulations?

There are many compounded formulations that are compounded by reputable pharmacies that result in high quality medications with assurances of potency, stability, and beyond-use-dates (BUD). However, there are also concerns. Beyond-use-dates are provided in the USP general chapter on compounding (USP <795>). The BUD for aqueous (water-containing) oral formulations stored at controlled cold temperatures is 14 days to maintain the potency within 90-110% of the nominal formulation strength (+/- 10% is the USP standard for strength of formulations). But compounding pharmacies sometimes go beyond this date without studies to support their claim. There is evidence from published articles that some drugs are not suitable for compounding because they result in rapid inactivation or loss of potency, or lack of systemic absorption when administered to an animal. We now have evidence that administration of antibiotics from some compounded formulations are sub-therapeutic and can increase the risk of bacterial drug resistance, which is a risk both to the pet and animal owner. In some cases the compounded products may actually contain levels well above the labeled amount which presents a risk of toxicity for the pet, as well as the animal owner handling the medication.

Examples of potential problems

There are several relevant published examples in which drug stability and efficacy has been compromised through compounding. When protective coatings are disrupted, and the vehicles altered, the stability of the product may be compromised. When the formulation is prepared from the bulk API without excipients or preservatives added to maintain stability, strength, or to maintain a desired pH, the quality and strength of the drug may be compromised. In some instances, only a slight alteration of pH can affect the drug. According to the USP-NF, “improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug. A drug solution or suspension may be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes the pH, it degrades in minutes or days. It is possible that a pH change of only one unit could decrease drug stability by a factor of ten or greater.” Addition of a water-based solution to a product to make a liquid solution or suspension can hydrolyze some drugs (beta-lactams, esters). Some drugs undergo epimerization (steric rearrangement) when exposed to a pH range higher than what is optimum for the drug (for example this occurs with tetracycline at a pH higher than 3). Other drugs are oxidized, catalyzed by high pH, which renders the drug inactive. Drugs most likely to be subject to oxidation are those with hydroxyl group bonded to an aromatic ring structure. Oxidation may occur from exposure to light and oxygen during reformulation and mixing. Oxidation is catalyzed by high pH and usually leads to drug inactivation.

For example, when omeprazole was compounded for oral use in horses, it was not as effective for treating gastric ulcers as the commercial formulation registered for horses (Gastroguard). Omeprazole is known for its instability unless administered in the original formulation intended for horses or people. Itraconazole is notorious for its instability and variable oral absorption. When the brand name itraconazole (Sporanox) and generic itraconazole were compared in research dogs, they produced similar plasma concentrations. But by comparison, the plasma concentrations from a compounded product were negligible.
Plasma concentrations from compounded itraconazole administered to cats was barely detectable compared to concentrations produced from the brand name capsule or solution. When doxycycline hyclate was examined in a compounded aqueous formulation made from crushed tablets, strength of the preparation depleted drastically after 7 days. Other compounded formulations known to produce formulations of poor strength and quality are pergolide, trilostane, pimobendan, clenbuterol, boldenone, amikacin, minocycline, and ketoprofen.

On the other hand, some compounded formulations made from extemporaneous preparations have been shown to retain their strength for storage times of at least 28 days and longer. These include enrofloxacin, carprofen, meloxicam, potassium bromide, sodium bromide, and metronidazole benzoate. Despite the problems cited above for compounded omeprazole, if one starts with the FDA-approved equine formulation of GastroGard and compounds it with corn oil to a concentration of 10 or 40 mg/mL (appropriate for cat and dogs) it retained the original strength for 6 months.

Veterinarians and pharmacists are obligated to be cognizant of the potential for interactions and interferences with stability. Oxidation is often visible through a color change (color change to pink or amber for example). Loss of solubility may be observed through precipitation. Some drugs are prone to hydrolysis from moisture. A rule-of-thumb for veterinarians is that if a drug is packaged in blister packs or moisture proof barrier, it is probably subject to loss of stability and potency if mixed with aqueous vehicles. If compounded formulations of solid dose forms show cracking or “caking”, or swelling, the formulation has probably accumulated moisture and may have lost potency. Another rule-of-thumb is that if the original packaging of a drug is in a light-protected or amber container it is probably prone to inactivation by light. Vitamins, cardiovascular drugs, tetracyclines, and phenothiazines are labile to oxidation from light during compounding. Also, as a general rule, if an antibiotic is available in a powder that must be reconstituted in a vial or oral dispensing bottle prior to administration, it should not be mixed with other drugs.

Many drugs intended for one species (or humans) are frequently compounded for another veterinary species. In these instances, it is not only the compounding practice that may affect drug absorption, but also the species differences. Although one assumes that absorption may be similar, differences can exist that may result in poor efficacy. Grass & Sinko concluded that there is no apparent relationship when comparing bioavailability of orally-administered drugs, between humans, dogs, primates, and rodents (Grass & Sinko, 2002). Therefore, for drugs administered orally, it is very difficult to broadly extrapolate from studies performed in people to veterinary species. Specific studies are usually needed, unless it is known that the drug is highly stable, soluble, and well absorbed under a variety of conditions.

The problem with compounded transdermal gels

Several published studies, or studies presented at conferences in abstracts have demonstrated poor or unreliable systemic absorption from transdermal gels. To the author’s knowledge, only two drugs have been shown to produce therapeutic effects when compounded into a transdermal gel and applied to the ear of cats: methimazole for feline hyperthyroidism, and amlodipine for feline hypertension. The skin is an efficient barrier and it is very difficult to facilitate the absorption of most drugs through the skin. Drugs have been combined with penetration enhancers to facilitate transdermal absorption. One popular example of a penetration enhancer, is pleuronic lecithin organogel (PLO), which is lecithin (derived from eggs or soybeans) mixed with isopropyl palmitate and a poloxamer (Pluronic). The ingredients in PLO are intended to act as surfactants, emulsifiers, and solubilizing agents. Although the use of PLO is popular among the veterinary compounding pharmacies, there are
no successful commercial formulations that have combined PLO with systemic drugs.

The list of drugs that have been shown to be absorbed poorly or highly inconsistently in this form includes: cyclosporine, atenolol, glipizide, dexamethasone, buspirone, amitriptyline, fentanyl, morphine, fluoxetine, diltiazem, and enrofloxacin. Despite the lack of assurance of systemic absorption from transdermal gels, some veterinary compounding pharmacies advertise and promote transdermal gels on their websites. One compounding pharmacy lists over 10 pages of compounded transdermal gels for cats. Development of transdermal technology in animals is very difficult and assurance of stability, potency, and systemic absorption for the vast majority of these products has not been demonstrated. Most compounded transdernals for animals are at best placebos. Because of the lack of effective absorption when these products are applied to the ears of cats, it presents a risk of exposure to the family of these pets, especially children. It is a common habit of cats to rub their ears against their owners and on furniture and bedding.

Can Compounding Pharmacies Provide Assurances?

The FDA-CVM will use regulatory discretion to allow veterinary drug compounding within the scope of clinical veterinary practice through the GFI #230 mentioned above. However, there are still some restrictions that apply, and each state may have more restrictive requirements than Federal Law. The source of the drug should be a USP or an NF grade substance. Drugs must be compounded from the original formulation, if an approved product exists. Compounding from bulk drugs will not be allowed if a proprietary approved formulation is available that meets therapeutic needs. Therefore, if a veterinary pharmacy is in the practice of compounding drugs from a bulk source for the purpose of producing a cheaper product, it will be subject to FDA regulatory enforcement. If bulk drugs are used because there is no other available form, the pharmacist should use bulk substances registered with FDA, and accompanied by a valid certificate of analysis.

It is the responsibility of the veterinarian and pharmacist to ensure that regulations and guidelines are being followed for confidence in the compounded medication. The USP-NF lists specific standards in the General Chapter on Pharmaceutical Compounding <795> and <797>, (USP-NF, http://www.usp.org). Often overlooked in compounding practices is the guideline to ensure that the compounded formulation is not less than 90.0% and not more than 110% of the theoretically calculated and labeled quantity of active ingredient per unit weight or volume. There are also guidelines available for Quality Assurance in Pharmaceutical Compounding (USP <1163>).

Compounding pharmacies have a responsibility to provide veterinarians and their clients with assurances that their formulations meet compendial standards and are stable and potent for the specified beyond-use-date. Pharmacies can be accredited by the Pharmacy Compounding Accreditation Board (PCAB). This is a voluntary program for improving the quality of compounding operations and preparations. An accredited pharmacy that adheres to USP compounding standards provided in General Chapters <795> and <797> will have significant checks in place to ensure that compounded products meet a high standard of quality. On the other hand, some pharmacies may not follow these standards and instead, provide veterinarians and their clients with misleading information on the quality of their products. For example, some products may be promoted as meeting “stability standards” for 30, 60, 90, or 180 days after preparation. But, there is a difference between stability testing and potency testing (Kupiec, et al, 2008). True stability testing of products is extremely expensive and more than likely a stability-indicating method has not been used. According to the FDA, a stability indicating method is “a validated quantitative analytical procedure that can detect the changes with time in the pertinent properties of the drug substance and drug product. A stability-indicating method accurately measures the active ingredients, without
interference from degradation products, process impurities, excipients, or other potential impurities.” As described in the USP General Chapter <1191> there are five types of stability: chemical, physical, microbiological, therapeutic, and toxicological. Stability-indicating methods include forced degradation tests, high heat and humidity, UV radiation, acid exposure, base exposure, and peroxide exposure. This is much different from a simple HPLC assay that measures strength based on a peak response.

Summary

Compounding for veterinary patients has not changed with the recent federal legislation, but may be affected by implementation of the new Guidance #230. It is not known at this time how closely the new Guidance will be enforced. Until now, compounding for veterinary patients has largely unregulated and without federal enforcement. Changes can also be enacted by specific states that could restrict some forms of compounding for animals. In the meantime, veterinarians are encouraged to be skeptical of broad claims of stability, quality, and systemic absorption from compounded products unless the pharmacy can provide some assurances based on studies conducted, or adherence to compendial standards.

References Cited

2. FDA-CVM. GFI #230. Found at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm447159.htm
4. JAVMA. Symposium on Compounding in Veterinary Medicine. Journal of the American Veterinary Medical Association 205: 189-303, 1994. (This issue of the Journal contains several individual papers addressing compounding in veterinary medicine.)