Principles of Bovine Pharmacology

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Abstract

Certain considerations must be taken into account whenever one decides to administer a drug to a food animal. Some issues are relevant to drug use in any species, while others are specific for drug use in food animals. General principles of drug use in food animals are discussed, including withholding time, appropriateness of drug choice, and the potential for adverse effects. Some specific drug classes and compounds are discussed in order to provide examples of the factors that go into therapeutic decision-making.

Introduction

Although most of the drugs we use to treat cattle are also used in other species, there are special considerations for drug use in cattle that may not apply to other species. When treating cattle one must always bear in mind their potential to become food. Dairy cows, of course, also produce food in the form of milk. We must take particular care when deciding which drugs we use and how we use them when treating any type of food animal.

This paper will address some general considerations when treating cattle. Then two of the drug classes commonly used in food animals, anti-inflammatory drugs and antimicrobial drugs, will be examined in more detail in order to provide specific examples of factors affecting treatment decisions in cattle practice.

Labeling and Drug Use in Food Animals

Some drugs have an approved label for use in cattle. Approved drug labels are specific for a dosing regimen, species and disease. Labels may further specify a subset of animals, such as lactating dairy cows, and/or a specific disease agent, such as a bacterial pathogen. Drugs that are approved for use in food animals have information on their labels describing how to use them in a way that will prevent adulteration of the human food supply. The key information in this regard is the withholding time. Withholding time, also called withdrawal or hold out, is the specified amount of time following the administration of a drug during which a particular animal or its milk cannot enter the food chain.

Withholding times given on a drug label are calculated:

- for the specific drug,
- at a specific dose
- using a specific route of administration
- for a stated duration of treatment
- in a particular species
- sometimes for a particular class of animal (age or use).

These withholding times are calculated to insure that if the drug is used according to label directions, the animal and/or its milk will be safe to enter the food supply at the end of the withholding period. If a drug container does not have this information on it, the drug is not approved for use in food animals. Some drugs have more than one formulation; for example, there are products containing amoxicillin labeled for use in cattle, dogs and cats. The product approved for use in cats is not the same as the product approved for use in cattle. Use of an amoxicillin product labeled for cats in a cow is not an approved use, because the withholding time for cattle has not been calculated for the product that is approved for use in cats.

'Extra-label' use of a drug means to use the drug in a manner inconsistent with the approved dose, duration of use, route of administration, disease(s), species or class of animal described on the label. The United States Food and Drug Administration prohibits extra-label use of some drugs in food producing animals. For most drugs approved for use in food animals, however, extra-label use is permitted, provided certain conditions are met. These conditions are specified in the regulations that codify the Animal Medicinal Drug Use Clarification Act (AMDUCA). The AMDUCA regulations expressly prohibit extra-label drug use if it results in a violative residue (higher than the defined maximum amounts of the drug in a food animal or its products) or in any residue which may present a risk to public health. The AMDUCA regulations also require an extended withholding time following any extra-label use of a drug

in a food animal. A useful resource for deciding the withholding time to prescribe following extra-label drug use is the Food Animal Residue Avoidance Database (FARAD). FARAD can be contacted by telephone at 1-888-US-FARAD or online at www.farad.org. Using available data on the behavior of drugs in cattle or other species, they will recommend an appropriate withholding time based on the planned regimen of extra-label drug use.

Classes of Drugs Used in Food Animals

Many different classes of drugs are used in food animals, including hormones, vitamins, electrolytes, local anesthetics, general anesthetics, sedatives, steroidal anti-inflammatory drugs, non-steroidal anti-inflammatory drugs (NSAIDs), anthelminthics, parasiticides, antihistamines, diuretics and antimicrobial drugs (including antibiotics). Covering the main issues involved in the use of all of these classes of drugs would take quite a while. Because of limited time, we use as examples two commonly used classes of drugs: the anti-inflammatory drugs and antimicrobial drugs. We will discuss what they do, what they are used for, precautions to take when using them and selected specific agents in each group.

Anti-Inflammatory Drugs

There are two major classes of anti-inflammatory drugs, the steroids and the non-steroidal anti-inflammatory drugs (NSAIDs).

Steroid Drugs

Steroid drugs used for their anti-inflammatory properties are called glucocorticoids. The first member of this class of drugs to be developed was hydrocortisone, which is still commonly used in human topical anti-itch preparations. It was originally derived from Mexican yams. Chemical changes made to the original hydrocortisone molecule have led to the creation of new glucocorticoid drugs with more anti-inflammatory potency and fewer effects on electrolyte balance in the body (known as mineralocorticoid effects). Some of the newer glucocorticoid drugs, listed in order of increasing potency, are prednisone, prednisolone, isoflupredone, dexamethasone, and flumethasone.

Inflammation is marked by swelling, heat, pain, redness, and sometimes loss of function of the affected area. Glucocorticoid drugs have been used to treat inflammation in cattle from many causes, including but not limited to mastitis, injury, or being a "downer" cow.

In addition to anti-inflammatory action, glucocorticoids have many other effects, reflected in the wide variety of conditions they are employed in treating.[4,6] Glucocorticoids are used to counteract the effects of shock in many species of animals including humans. They tend to stimulate appetite in humans and small animals and may also do so in cattle. Glucocorticoids influence metabolism to increase the generation of glucose in the liver, which can help to resolve ketosis, a common problem in dairy cows.

Some glucocorticoid effects may not always be desirable. Repeated doses of glucocorticoid drugs can suppress an animal's immune system, increasing the likelihood of treatment failure or disease recurrence when the disease being treated is infectious in nature. In the case of an animal with severe illness or shock due to infectious disease, however, a single dose of a glucocorticoid drug may provide enough immediate benefit to outweigh the risk of immune suppression. The immune suppression caused by glucocorticoids can sometimes be beneficial, too, as it can mitigate allergic reactions such as hives.

When given to cows in later pregnancy, most glucocorticoid drugs will cause the animal to begin parturition or abortion within 48 hours. This effect may be desirable if the animal's due date is near or past and she is at risk (for example, if she is carrying a very large calf). For an animal that has not completed all but two weeks of gestation, however, the consequences of glucocorticoid administration can be catastrophic for the fetus that is born too early.

Glucocoticoid drugs also have the potential to contribute to the development and maintenance of stomach or abomasal ulcers, and they can reduce the absorption of calcium from the diet and increase the elimination of calcium in the urine.

When administering any drug, it important to consider all the effects of the drug, not only those that might be beneficial. Glucocorticoids are no exception to this rule. For example, if a newly dry cow is afflicted with lameness or other inflammation, one should not treat her with dexamethasone, as it will cause her to abort her calf. Giving a glucocorticoid drug once to an animal with an infectious disease may be safe, but the possibility of immune system suppression must be evaluated on a case-by-case basis, and it is generally not indicated to give more than one dose of a glucocorticoid drug to a food animal with an infectious disease.

Glucocorticoid drugs can be useful for relieving the pain and inflammation associated with a cow being "down", but when one is using glucocorticoid drugs for this condition, it is important to remember that they cause increased elimination of calcium from the body. Milk fever, which is caused by insufficient calcium in the cow's blood, is frequently all or part of the reason a cow is "down". Therefore, when administering glucocorticoid drugs to a down cow, the drug may decrease the cow's blood calcium even more; thus, steps must be taken

to compensate for the calcium wasting effect of the drug. "Down" cows may also be suffering from infectious disease, and this, too, should be considered when deciding whether to administer a glucocorticoid drug.

The glucocorticoid drugs most commonly used in cattle include dexamethasone and isoflupredone. Dexamethasone has many brand names. The brand name for isoflupredone is Predef 2x®. Dexamethasone is a potent anti-inflammatory drug with a long half life of 24 hours or more. Isoflupredone is less potent by about a third, and has a half-life that is probably less than 12 hours. The high potency and long half-life of dexamethasone as compared to other steroids may increase its efficacy as an anti-inflammatory drug, but may also contribute to an increased risk of side effects such as immune system suppression, decreased blood calcium, or gastric ulceration. Isoflupredone is an unusual steroidal drug due to its lack of abortion-inducing activity. When 48 cows in various stages of gestation were given repeated doses of isoflupredone, all of them continued to carry their calves until gestation was complete.[3]

Glucocorticoids are a powerful class of drugs that can be useful in veterinary practice. By becoming familiar with their major effects, we can use glucocorticoids in a way that will provide maximum benefit and minimal risk to our bovine patients.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs have been around for a very long time. The oldest member of this drug class, aspirin, has been used for its anti-inflammatory and fever-reducing properties since the 5th century BC, when Hippocrates used extracts of willow bark (containing the active ingredient in aspirin, acetylsalicylic acid) to treat pain and fever.[1] In fact, the name acetylsalicylic acid is derived from the latin name for the willow tree, Salix. Since then, numerous other NSAID drugs have been developed for human and animal use, including ibuprofen, phenylbutazone, ketoprofen, and one of the most commonly used NSAIDs in cattle practice, flunixin meglumine.

Like glucocorticoids, NSAIDs are commonly used to treat local signs of pain and inflammation from injury or illness. NSAIDs are also potent fever-reducing drugs, and they have commonly been used for this purpose, although there has lately been some debate about the benefit of reducing fever when treating infectious disease. Also in common with glucocorticoids, NSAIDs are used at times to relieve the signs of shock. They are a generally safe class of drugs that can provide humane relief to animals in pain.

Like glucocorticoids, there are effects other than anti-inflammatory ones that must be taken into consideration when using NSAID drugs in food animals. The most common adverse effects of NSAID drugs are gastrointestinal. In food animals, this is apt to be manifested as ulceration of the abomasum (stomach). NSAIDs also impair the ability of platelets to form blood clots. This, combined with their effects on the stomach, can lead to the formation of bleeding ulcers. NSAID drugs can also cause damage to the kidneys. The risk of any of these adverse effects can be minimized by limiting the duration of NSAID therapy, and the risk of kidney damage can be further reduced by insuring that the patient is not dehydrated.

It is important to understand a particular risk posed by the NSAID drug phenylbutazone, which is sometimes called "bute" or by the brand name Butazolidin®. This drug can cause aplastic anemia, a complete and irreversible suppression of the bone marrow in human beings. This results in anemia or too few red blood cells, and leukopenia, or too few white blood cells. Anemia causes a decreased capacity of the blood to carry oxygen, and leukopenia causes increased susceptibility to infection. Either condition, if unresolved, will eventually result in death. Because of the possibility of severe consequences to humans, it is important to be sure that phenylbutazone does not enter the human food supply via the meat or milk of a treated animal. The effort is complicated by the fact that phenybutazone has a long half-life in cattle and takes a long time to be entirely cleared from the animal's body following treatment. Furthermore, there is no approved phenylbutazone label for cattle, so there is no federally mandated withholding time for the drug in cattle. For all of these reasons, the use of phenylbutazone in food animals is being heavily scrutinized at this time.

Flunixin meglumine is a potent NSAID drug approved for use in cattle. Its half-life is not nearly as long as that of phenybutazone. In addition to the adverse effects given above for the NSAID class, flunixin has the potential to cause tissue irritation at the site of intramuscular injection, which can lead to inflammation and even scarring. This effect can be avoided by only administering the drug intravenously.

The old standby aspirin is also available for use in cattle. It is not as potent as flunixin meglumine, but it may be useful for conditions such as mild lameness or injury.

Like the glucocorticoids, NSAIDs are a useful class of drugs in veterinary medicine. When properly administered, they can provide safe, humane relief for a variety of inflammatory conditions in cattle.

Antimicrobial Drugs

Antimicrobial drugs, also called antibiotics if the basic molecule is produced by a living organism, are commonly used to treat infectious disease in both humans and animals. There are many classes of antimicrobial

drugs, and they act by a variety of mechanisms to either kill bacteria or inhibit their growth. Antimicrobial drugs are a valuable weapon against infectious disease, but treatment with them is not always successful. By understanding how the various classes of antimicrobial drugs work, what their limitations are, and what susceptibility testing has to offer, then combining this knowledge with rational decision-making, we can maximize the likelihood of success when using antimicrobial drugs.

One of the first things to take into consideration when choosing an antimicrobial drug is the spectrum of activity, or what types of bacteria it can act against. For example, anaerobic bacteria are outside the spectrum of gentamicin, and gram negative organisms are outside the spectrum of pirlimycin. Use of antimicrobial drugs against bacteria outside their spectrum of activity is fruitless.

Antimicrobial susceptibility testing is used to measure the susceptibility of bacteria to antimicrobial drugs in specific cases. This is useful because even though a certain species of bacteria may be within the spectrum of action of a drug, not every member of the species is necessarily susceptible to the drug. Susceptibility testing is performed when a sample from an infected animal is sent into a diagnostic laboratory for bacterial culture and sensitivity testing. The first step, bacterial culture, identifies the type of bacteria that are infecting the sampled animal or animals.

The second step is bacterial susceptibility testing, which attempts to give some indication of whether the cultured bacteria are likely to respond to different antimicrobial drugs if they are administered to the infected animal. Many laboratories adhere to standard laboratory practices for susceptibility testing described by the National Committee for Clinical Laboratory Standards (NCCLS), which gives consistency to results from different laboratories.

There are two key concepts to understand in relation to bacterial susceptibility testing: minimum inhibitory concentration (frequently called MIC) and breakpoints. Minimum inhibitory concentration is the minimum concentration of an antimicrobial drug necessary to inhibit microbial growth in a laboratory setting. A breakpoint uses the MIC for a specific drug and bacterial species to make predictions about clinical outcome when the drug is given to an animal infected with the bacteria.

Susceptibilty testing using the microwell dilution method measures bacterial growth in a series of small wells containing the bacteria plus various concentrations of the drug or drugs being tested. We can use the drug ceftiofur as an example of how this testing works. The breakpoints for ceftiofur in bovine respiratory disease caused by *Pasteurella* or *Haemophilus* species of bacteria are 2, 4 and 8 μg/mL. This means that a bacterial strain prevented from growing in the laboratory by 2 μg/mL of the drug is considered "susceptible" to the drug. If it takes 4 μg/mL of drug to inhibit growth, the microbe is "intermediate" and if 8 μg/mL of drug are required, it is considered "resistant". These breakpoints are frequently abbreviated as "S", "I" and "R". If growth of a *Pasteurella* or *Haemophilus* species of bacteria is inhibited by a concentration of 2 μg/mL of ceftiofur in the laboratory, then we can expect that the drug is likely to be effective against a respiratory infection caused by that strain of bacteria in a bovine. If it takes 4 μg/mL to inhibit growth under the same conditions, the drug may or may not clear the infection from the tested animal or animals infected with the same strain of *Haemophilus* or *Pasteurella*. If it takes at least 8 μg/mL of ceftiofur to inhibit bacterial growth under standard laboratory conditions, the drug will probably not work for treatment of an infected animal.

Another method of antimicrobial susceptibility testing with which you may be familiar is the Kirby-Bauer method. Using the Kirby-Bauer method, bacteria are grown on agar plates instead of in broth wells, and inhibition of growth is assessed in terms of how close to an anti-microbial disk on the agar gel surface the bacteria are able to grow. In the Kirby-Bauer method, breakpoints are not based on specific drug concentrations as they are in the microwell dilution method described above. Instead, breakpoint interpretations are based on the size of the "zone of inhibition" around each antimicrobial disk. It is important to note that breakpoint zones are not the same for all antimicrobial disks. For example, using human breakpoints, a *Staphylococcus* bacteria that grows to within 20 millimeters of the standard tetracycline disk would be considered susceptible to the drug, whereas the same microbe growing to within 20 millimeters of the ampicillin disk would be designated as resistant to that drug. Because of these variations in Kirby-Bauer breakpoints, simply picking the disk with the biggest zone around it will not necessarily result in selection of the drug to which the microbe is most susceptible.

It is also important to note that breakpoints, like withholding times, are very specific. Validated breakpoints are defined for:

- a specific drug,
- at a specific dose,
- given at a specific frequency,
- using a specific route of administration,
- for a stated duration of treatment
- of a particular condition
- caused by specific bacteria
- in a particular species.

Any deviation from the specifics of the validated breakpoint should be considered when deciding whether

susceptibility testing results are valid. Susceptibility testing can be done for almost any drug against almost any bacteria, but it is important to remember that not every combination of drug, bacteria, disease and affected species has a validated breakpoint. If there is no validated veterinary breakpoint, the testing laboratory will generally use the closest thing it can find, which is sometimes not so close. For example, they may use a breakpoint for a different disease caused by the same organism in the same species, or they may use a breakpoint for a different disease caused by the same organism in a different species. Human breakpoints are commonly used in reporting the results of susceptibility testing done for veterinary species. For example, if a milk sample from a cow with mastitis due to infection with *E. coli* is sent into a lab for culture and susceptibility testing, the breakpoints used in reporting results will have been derived from human non-mastitis *E. coli* infections.

There are other factors that influence whether an antimicrobial drug will work in a particular case. Even infections caused by bacteria within the spectrum of activity, which are determined to be susceptible to a particular drug when susceptibility testing is done, may not be cured when the drug is actually given to the affected animal. There are a number of reasons this might happen. One common reason is that the drug cannot get to the bacteria. For example, if the infection is in some area of the body that has restricted access for drugs, such as the mammary gland, brain, or prostate gland, therapy is not likely to be successful. Abscessation of an infection can also limit the efficacy of an antimicrobial drug as it can make it difficult for the drug to reach the pathogen or, as is the case with sulfa drugs, the pus itself may inactivate the antimicrobial drug. Some drugs can overcome the problems posed by abscessation, but some cannot. Bacteria can also evade antimicrobial drugs by surviving inside the cells of the animal's immune system, where many antimicrobial drugs cannot penetrate.

Sometimes the infection has progressed too far to reverse. If the animal's immune system is completely overwhelmed and unable to assist in clearance of bacteria or their toxins, even the best antimicrobial drug will not succeed in curing the animal. Other physiological problems may also contribute to treatment failure. For example, a cow with kidney or liver failure may not be able to eliminate some drugs. This can lead to accumulation of the drug to toxic concentrations, which may cause more harm to the animal than the benefit gained by the antimicrobial properties of the drug. A good example of a situation with the potential for this type of complication would be the use of potentially kidney-damaging drugs such as gentamicin or flunixin in calves with severe diarrhea, where kidney function may already be compromised by dehydration and endotoxic shock.

Some Specific Antimicrobial Drugs: Oxytetracycline and Ceftiofur

We have discussed some of the general concepts regarding antimicrobial use. Now we will briefly review some specific aspects of two antimicrobial drugs commonly used in bovine practice.

Oxytetracycline

Oxytetracycline is approved for use in treating many diseases of cattle, including wooden tongue (*Actinobacillus* infection), scours (bacterial enteritis), calf diphtheria, footrot, metritis, pneumonia, wound infections, pinkeye (*Moraxella* infection), Leptospirosis, anaplasmosis and other bacterial infections.[5] These are the approved uses for therapeutic injectible preparations. There are also feed additive oxytetracycline preparations, used for prevention and treatment of several diseases, but they are beyond the range of this discussion.

Oxytetracycline preparations have many brand names, including Agrimycin® 200, Bio-mycin®, Duramycin, Liquamycin®, Maxim-200®, OT 200, Oxybiotic™, Oxycure™, Oxy-mycin® and Status™. Preparations for injection have concentrations of 50, 100 or 200 mg/mL.

Oxytetracycline is not used for susceptibility testing in most laboratories, although some laboratories using extended-dilution microwell dilution methods are using both oxytetracycline and chlortetracycline. In many laboratories, only tetracycline is used in laboratory susceptibility testing, and results are extrapolated to include oxytetracycline. Breakpoints used in susceptibility testing for the tetracyclines, even in veterinary laboratories, are those used in human testing; they are not derived from use in animal diseases. Therefore, when one receives susceptibility testing results for oxytetracycline from the laboratory, they are extrapolated from human breakpoints, and they are often obtained using a different drug from the same family.

Thanks to the label indication "other bacterial infections", technically there are not many unlabelled uses for oxytetracycline. It has been used systemically for treatment of mastitis, but concentrations in the mammary gland do not get as high as those in blood, so oxytetracycline may have limited efficacy for mammary gland infections. Perhaps due to its widespread use, there is also a fairly high level of bacterial resistance to oxytetracycline.

It is important to keep in mind possible adverse reactions when using oxytetracycline in cattle. Foremost, intramuscular injection of oxytetracycline preparations is very irritating to tissues and can cause serious tissue blemishes. It is recommended that oxytetracycline preparations be given either subcutaneously or intravenously to avoid painful and damaging inflammation of tissues. It is important to note that long-acting prepa-

rations, such as LA-200®, depend on slow absorption from the injection site for their long duration of action. Therefore, if they are given intravenously, they are no longer long-acting! Any oxytetracycline should be administrated slowly if given IV.

Oxytetracycline does have some risks to its use and precautions should be taken to minimize these risks. As mentioned above, intravenous administration should be done slowly as the propylene glycol carrier in some preparations may cause the animal to collapse if it is given quickly.

Another possible adverse effect of oxytetracycline is nephrotoxicy (damage to the kidneys). The risk of kidney damage with oxytetracycline is potentiated when higher than label doses are used, when the animal is dehydrated, or when other potentially nephrotoxic drugs such as NSAIDs are used at the same time.

Oxytetracycline is a very commonly used antimicrobial drug in bovine medicine, and its use can be beneficial. In order to maximize the likelihood of a good outcome when using oxytetracycline, it is important to consider the status of the patient, whether or not oxytetracycline is the best antimicrobial drug choice, and how to minimize the likelihood of adverse effects.

Ceftiofur

Ceftiofur is the antimicrobial drug contained in Naxcel® (ceftiofur sodium) and Excenel® (ceftiofur hydrochloride). Ceftiofur is a member of the cephalosporin class of beta-lactam drugs, so it is related to other beta-lactam drugs such as the penicillins. When ceftiofur is given by injection, cattle quickly process it into another compound, the active metabolite desfuroylceftiofur, which has antimicrobial activity. Naxcel® and Excenel® contain the same drug in different carriers. The oily carrier of Excenel® makes it stable for storage in suspension, whereas Naxcel® must be stored in powder form and resuspended just prior to use. Following reconstitution, Naxcel® has a limited shelf life unless it is frozen. The difference in carriers also causes Excenel® to be absorbed more slowly than Naxcel®, and achieve a lower peak concentration in the blood of the cow. This difference in peak concentration should not affect efficacy of the drug in most cases, and the two forms of ceftiofur are considered "therapeutically equivalent".

Both ceftiofur products are labeled for treatment of bovine respiratory disease caused by *Pasteurella* or *Haemophilus* bacteria, footrot caused by *Fusobacterium* and *Bacteriodes* bacteria, and metritis in cattle.[2] Veterinary breakpoints validated for swine and bovine respiratory disease are used for ceftiofur susceptibility testing in the laboratory. Ceftiofur products are used off-label for other infections in cattle, including but not limited to joint infections, wound infections and prevention of infection following surgery.

It is important to recognize that ceftiofur, like all antimicrobial drugs, has its limitations. One critical aspect of ceftiofur to remember is that when given by injection, it will not go into the mammary gland in high enough concentration to treat an infection there (mastitis). Because only a tiny amount of the drug gets into the milk when it is injected systemically, there is no milk withholding required when ceftiofur is given by injection to a dairy cow. This is not the case if ceftiofur is administered directly into the mammary gland. Direct administration of ceftiofur into the mammary gland can easily result in concentrations high enough to cause a violative residue that can be detected at the milk processing plant if a proper withdrawal time is not observed. This is especially true if the oily Excenel® formulation is used.

Ceftiofur is generally considered a "safe" drug. At typical doses there is little likelihood of toxicity. Like its cousin penicillin, ceftiofur has the potential to cause an allergic reaction, and people or animals with penicillin allergy may be more prone to allergy to ceftiofur.

Conclusions

There are many drugs available for use to treat a variety of conditions in both beef and dairy cattle, but certain considerations must be taken into account when one decides to use any drug in food animals. Some questions must be considered before using any drug in any species. Is the drug an appropriate choice for the condition being treated? Do the benefits of the drug outweigh the risks of an adverse effect of the drug? How can I minimize the risk of drug-related adverse effects in the animal I am treating? When using any drug in cattle, there is also another consideration that is paramount: how can I use this drug in this animal in a manner that will preserve the safety of the human food supply? Some drugs are considered too risky to be used under any circumstance in food animals. These drugs have no label for food animal use and their extra label use is prohibited. Other drugs are approved for some uses in food animals, but may not be used in any way other than that described on the label. Drugs approved for use in food animals have labeled indications for which a dosing regimen and meat and milk withholding times are prescribed. The great majority of drugs with labeled indications in food animals may also be used in an "extra-label" fashion for diseases other than those listed on the label or at doses other than those given on the label, providing the conditions outlined in the AMDUCA regulations are met. One particularly important condition is that extra-label use requires an extended withholding time.

Two commonly used classes of drugs in food animals are anti-inflammatory drugs and antimicrobial

drugs. These drugs can be of great benefit in treating the diseases of cattle providing they are used appropriately and with regards to their limitations, benefits and risks.

References

1. Aspirin: Wonder drug of the 20th Century. Website at http://users.erols.com/blopatin/reference/aspirin/
2. Ceftiofur product labels, Pharmacia Animal Health, Kalamazoo, Michigan.
3. Mohammedsdegh M: Effect of isoflupredone acetate on pregnancy in cattle. *Vet Rec* 134:17, 453, 1994.
4. McDonald LE: *Veterinary Pharmacology and Therapeutics*, Ames, Iowa, Iowa State University Press, 1988, pp 616-634
5. Oxytetracycline product labels as listed in The Compendium of Veterinary Products, ed 5, Port Huron, Michigan, North American Compendiums, 1999, pp 507-513.
6. Upson, DW: *Handbook of Clinical Veterinary Pharmacology*, Manhattan, Kansas, Dan Upson Enterprises, 1988, pp 361-391.